19
PART 1 of 4

REPOSITORY Oak Ridge Operations Office
COLLECTION Reading Room
BOX No. RHA Shipment 9162 Box 6 & 7
FOLDER New York Times FOIA Requests 88-91

707049

OFFICE OF CHIEF COUNSEL
FILE
No papers will be removed herefrom
without special authority

PART 1

1017583

TABLE 1

Nuclear Data

Radionuclide	^{52}Fe	^{55}Fe	^{59}Fe
Physical Half-Life	8.2h	2.6y	45d
Decay Constant			$0.0154d^{-1}$
Mode of Decay	E.C. & B^+	Elec. Cap.	Beta-Minus
Equilibrium Dose constant for Non-Penetrating Radiation (g-rad/μCi-h)			

Principle Photons:	Ei	ni	Ei	ni	Ei	ni
Ei, Energy (MeV)	0.165	0.942	0.0059	0.2339	0.1925	0.0278
Ni, Mean Number/Dis	0.511	1.13			1.095	0.560
					1.292	0.430

1017584

TABLE II

Fe-59 Dosimetry

Intercompartmental Rate Constants (fraction/day)

	Disease	Plasma to Marrow λ_1	Marrow to RBC λ_2	Plasma to Radid stores	Rapid stores to Slow Stores	Slow Stores to Rapid stores	Rapid Stores to Plasma
A	Hemochromatosis	30.0	0.30	12.0	0.10	0.12	0.82
B	Leukemia	9.6	0.17	6.2	3.0	0.005	0.10
C	Refractory Anemia	29.0	0.15	4.0	0.02	0.001	0.29
D	Follicular lymphoma	8.0	0.30	6.9	3.0	0.005	1.46
E	Intestinal bleeding	15.6	0.10	0.27	0.13	0.27	0.29
F	Sideroblastic anemia (marrow storage)	28.7	0.01	6.16	1.55	0.56	0.74
G	Refractory anemia (liver storage)	4.2	0.07	10.5	0.74	0.01	0.44
H	Refractory anemia	2.7	0.20	6.8	0.45	0.03	0.001
I	RCA(suspected)	6.2	0.13	3.2	0.53	0.04	0.29
J	RCA(remission)	3.8	0.35	3.9	0.37	0.001	0.31
K	Pure RCA	0.65	0.004	4.0	0.73	0.08	0.12
L	Refractory anemia	5.3	0.19	2.7	0.11	0.19	0.18
M	RCA(remission)	24.8	0.14	1.8	13.7	0.66	0.001
N	RCA(suspected)	5.0	0.18	5.0	0.61	0.09	0.001
O	Pure RCA	0.24	0.04	2.3	0.65	0.11	0.001
P	RCA(suspected)	3.78	0.03	4.3	13.7	0.001	12.4
Q	Normal	8.00	0.23	2.3	0.53	0.05	0.20

1017585

Table III

Fe-59

Dose Equivalent/Microcurie-day *

(rem/μCi-day)

S-Factor

SOURCE / TARGET	LIVER	SPLEEN	MARROW	TOTAL BODY
LIVER	8.13×10^{-3}	2.13×10^{-4}	2.01×10^{-4}	4.25×10^{-4}
SPLEEN	2.12×10^{-4}	5.77×10^{-2}	2.02×10^{-4}	4.11×10^{-4}
R. MARROW	1.97×10^{-4}	2.15×10^{-4}	4.74×10^{-3}	3.91×10^{-4}
OVARIES	1.73×10^{-4}	1.15×10^{-4}	5.81×10^{-4}	3.98×10^{-4}
TESTES	4.36×10^{-5}	2.42×10^{-5}	6.68×10^{-5}	4.14×10^{-4}
TOTAL BODY	4.13×10^{-4}	4.12×10^{-4}	3.94×10^{-4}	3.66×10^{-4}

* W.S. Snyder, et. al. ORNL Report No. 5000 "A Tabulation of Dose Equivalent per μCi-day for Source and Target Organs of an Adult for Various Radionuclides."

1017586

TABLE IV

Cumulative Activites Fe-59 Citrate

μCi · day/μCi administered

	A	B	C	D?	E	F	G	H	I	J	K	L	M	N	O	P	
ed Marrow	2.85	1.73	0.91	2.85	6.67	38.9	1.17	0.37	4.12	1.63	2.57	2.92	1.93	2.04	0.90	5.50	3
lood	55.5	19.0	8.83	[illegible]	43.3	5.1	5.32	4.82	34.8	37.2	0.67	36.0	17.5	23.9	2.34	10.7	5
iver	8.1	26.0	31.0	13.0	13.0	13.0	52.0	19.5	19.0	19.2	41.0	19.5	13.0	16.2	41.0	26.0	
pleen	2.6	13.0	13.0	22.0	2.6	13.0	5.2	4.6	2.8	2.6	3.9	2.6	5.2	3.9	5.2	3.9	

1017587

Table IV

Fe-59 Citrate Dose Estimates

for

Various Erythropoietic Diseases

(mrem/μCi)

DISEASE	LIVER	SPLEEN	RED MARROW	GONADS	*BLOOD	TOTAL BODY
Refractory Anemia	118 - 258	169 - 762	8 - 191	3 - 20	5 - 36	11 - 28
Hemachromotosis	91 - 426	175 - 313	19 - 37	5 - 23	5 - 53	25 - 36
Leukemia	223	763	24	9	10	24
Folicular Lymphoma	135	1296	43	28	53	35
Red Cell Plasia	114 - 335	169 - 310	14 - 32	2 - 25	1 - 37	15 - 25
Intestinal Bleeding	126	172	52	24	50	25
ormal	77	175	41	23	53	25

* non-penetrating dose only

1017588

References

1. J. D. Cook, H. E. Palmer, K.G. Pailthorp and C. A. Finch. The measurement of iron absorption by whole body counting. Phys. Med. Biol. 1970 15, 3, p 467-473.

2. L. C. McKee, Jr., R. Price, R. E. Johnston, R. M. Heyssel, L. E. Johnson and A. B. Brill. Long term studies of iron metabolism in normal males: comparison of red blood cell radioactivity with whole body counter data. J. N. Med, 1974, 15, 3, p 156-160.

3. T. Sargent, M. Pollycove, L. Carpe, and J. H. Lawrence: Dynamics of total body iron: gastrointestinal blood storage and "fixed" components. Clin. Res., 1962, 10:78.

4. M. Pollycove: Seminars—in hematology: iron metabolism and kinetics, 3, 4, October 1966.

5. M. Pollycove and M. Tono: Studies of the erythron. Seminars in Nuclear Medicine, 5, 1, January 1975.

6. R. R. Price, L. C. McKee, Jr., S. B. Krantz, and A. B. Brill: Estimation of slow dynamic function parameters in iron kinetics studies using quantitative measurements and compartmental modelling analysis; Proceedings of IAEA Symposium on "Dynamic Studies with Radioisotopes in Medicine - 1974."

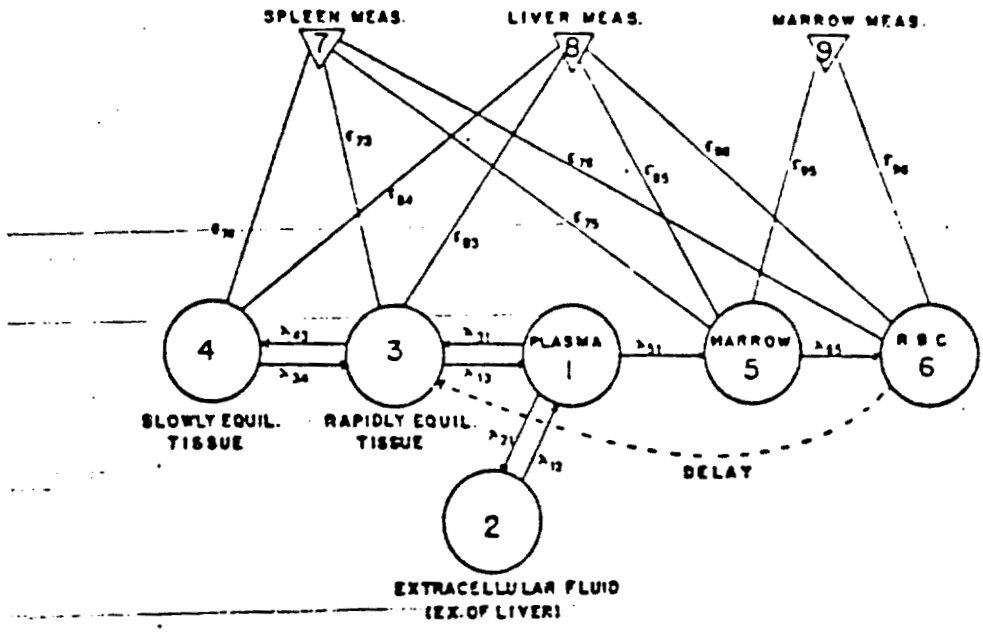
7. R. R. Price, R. E. Johnston, A. B. Brill, and J. R. Watts: Estimation of radioactive content of body organs by combining direct measurements and distribution models. Proceedings of IAEA Symposium on "Assessment of Radioactive Contamination in Man", 1972.

8. M. Berman: Compartmental Analysis in Kinetics, Ch. VII, Computers in Biomedical Research (Stacy, R.W., Waxman, B.D., eds.), New York, 1965.

1017589

Appendix I

Diagram of SAAM Compartmental Model for Fe-59 kinetics.



Model Input Data

1) Percent of administered activity in plasma
2) Percent of activity in circulating red blood cells
3) Percent of activity in liver from quantitative whole-body scan
4) Percent of activity in spleen from quantitative whole-body scan
5) Percent of activity in pelvis from quantitative whole-body scan
6) Fraction of circulating red blood cell pool in each region of the body (determined from ^{51}Cr-labelled red blood cell whole-body scan)

1017590

Appendix II

Absorbed dose tabulation Fe-59 citrate in abnormals (mrem/μCi)

* source in blood assumed to be equivalent to total body distributio

PATIENT

A

SOURCE / TARGET	RED MARROW	BLOOD *	LIVER	SPLEEN	TOTAL
LIVER	.6	23.6	65.9	.5	90.6
SPLEEN	.6	22.8	1.7	150.0	175.1
MARROW	13.5	21.7	1.6	.6	37.4
OVARIES	1.7	22.1	1.4	.3	25.4
TESTES	.2	23.0	.3	.1	23.6
TOTAL BODY	1.1	20.3	3.3	1.1	25.8

B

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.3	8.1	211.4	2.7	222.5
SPLEEN	.3	7.8	5.5	750.1	763.7
MARROW	8.2	7.4	5.2	2.8	23.6
OVARIES	1.0	7.6	4.4	1.5	14.5
TESTES	.1	7.9	1.0	.3	9.3
TOTAL BODY	.7	7.0	10.7	5.4	23.7

C

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.2	3.6	252.0	2.7	258.7
SPLEEN	.2	3.6	6.5	750.1	760.4
MARROW	4.3	3.5	6.2	2.8	16.8
OVARIES	.5	3.5	5.3	1.5	10.8
TESTES	.1	3.1	1.2	.3	5.3
TOTAL BODY	.4	3.2	12.7	5.4	21.7

D

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.6	23.6	105.7	4.6	134.5
SPLEEN	.6	22.8	2.7	1269.4	1295.5
MARROW	13.5	21.7	2.6	4.7	42.5
OVARIES	1.7	22.1	2.2	2.5	28.5
TESTES	.2	23.0	.5	.5	24.2
TOTAL BODY	1.1	20.3	5.3	9.1	35.8

E

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	1.3	18.4	105.7	.5	126.0
SPLEEN	1.3	17.8	2.7	150.0	171.9
MARROW	31.6	16.9	2.6	.6	51.7
OVARIES	3.9	17.2	2.2	.3	23.6
TESTES	.5	17.9	.5	.1	19.0
TOTAL BODY	2.6	15.8	5.3	1.1	24.9

10-1591

F

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	7•8	2•2	105•7	2•7	118•4
SPLEEN	7•9	2•1	2•7	750•1	762•8
MARROW	184•4	2•0	2•6	2•8	191•8
OVARIES	22•6	2•0	2•2	1•5	28•3
TESTES	2•7	2•1	•5	•3	5•6
TOTAL BODY	15•3	1•9	5•3	5•4	27•9

G

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	•2	2•3	422•8	1•1	426•3
SPLEEN	•2	2•2	10•9	300•0	313•4
MARROW	5•5	2•1	10•4	1•1	19•1
OVARIES	•7	2•1	8•8	•6	12•2
TESTES	•1	2•2	2•1	•1	4•5
TOTAL BODY	•5	1•9	21•3	2•1	25•9

H

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	•1	2•0	158•5	1•0	161•6
SPLEEN	•1	2•0	4•1	265•4	271•6
MARROW	1•8	1•9	3•9	1•0	8•5
OVARIES	•2	1•9	3•3	•5	6•0
TESTES	•0	2•0	•8	•1	2•9
TOTAL BODY	•1	1•8	8•0	1•9	11•8

I

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	•8	14•8	154•5	•6	170•7
SPLEEN	•8	14•3	4•0	161•6	180•7
MARROW	19•5	13•6	3•6	•6	37•5
OVARIES	2•4	13•9	3•2	•3	19•8
TESTES	•3	14•4	•8	•1	15•5
TOTAL BODY	1•6	12•7	7•8	1•2	23•3

J

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	•3	15•8	158•5	•5	175•2
SPLEEN	•3	15•3	4•1	150•0	169•7
MARROW	7•7	14•5	3•9	•6	26•7
OVARIES	•9	14•8	3•3	•3	19•4
TESTES	•1	15•4	•8	•1	16•4
TOTAL BODY	•6	13•6	8•0	1•1	23•3

PATIENT

K

SOURCE / TARGET	RE MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.5	.3	333.3	.8	334.9
SPLEEN	.5	.3	8.6	225.0	234.4
MARROW	12.2	.3	8.2	.8	21.5
OVARIES	1.5	.3	7.0	.4	9.2
TESTES	.2	.3	1.6	.1	2.2
TOTAL BODY	1.0	.2	16.8	1.6	19.7

L

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.6	15.3	158.5	.5	175.0
SPLEEN	.6	14.8	4.1	150.0	163.5
MARROW	13.8	14.1	3.9	.6	32.4
OVARIES	1.7	14.3	3.3	.3	19.6
TESTES	.2	14.9	.8	.1	15.9
TOTAL BODY	1.2	13.2	8.0	1.1	23.4

M

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.4	7.4	105.7	1.1	114.6
SPLEEN	.4	7.2	2.7	300.0	310.4
MARROW	9.1	6.8	2.6	1.1	19.7
OVARIES	1.1	7.0	2.2	.6	10.9
TESTES	.1	7.2	.5	.1	8.0
TOTAL BODY	.8	6.4	5.3	2.1	14.6

N

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.4	10.2	131.7	.8	143.1
SPLEEN	.4	9.8	3.4	225.0	238.7
MARROW	9.7	9.3	3.2	.8	23.1
OVARIES	1.2	9.5	2.8	.4	13.9
TESTES	.1	9.9	.6	.1	16.8
TOTAL BODY	.8	8.7	6.6	1.6	17.8

O

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	.2	1.0	333.3	1.1	335.6
SPLEEN	.2	1.0	8.6	300.0	309.8
MARROW	4.3	.9	8.2	1.1	14.5
OVARIES	.5	.9	7.0	.6	9.0
TESTES	.1	1.0	1.6	.1	2.8
TOTAL BODY	.4	.9	16.8	2.1	20.2

PATIENT

P

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	1•1	4•5	211•4	•8	217•9
SPLEEN	1•1	4•4	5•5	225•0	236•0
MARROW	26•1	4•2	5•2	•8	36•3
OVARIES	3•2	4•3	4•4	•4	12•3
TESTES	•4	4•4	1•0	•1	5•9
TOTAL BODY	2•2	3•9	10•7	1•6	18•3

Q
(NORMAL)

SOURCE / TARGET	RED MARROW	BLOOD	LIVER	SPLEEN	TOTAL
LIVER	•7	23•2	52•8	•5	77•4
SPLEEN	•7	22•5	1•4	150•0	174•6
MARROW	17•3	21•4	1•3	•6	40•6
OVARIES	2•1	21•0	1•1	•3	25•3
TESTES	•3	22•6	•3	•1	23•2
TOTAL BODY	1•4	20•0	2•7	1•1	25•2

Appendix III

Quantitation of Radioactivity For Irregular Geometric Shapes Using External Measurements

There have been several methods devised to estimate the activity of an in-vivo radioisotope distribution from external counting measurements. It is widely recognized that the combined effects of photon attenuation and body geometry can cause large errors. Therefore the scan data are usually collected and/or manipulated in some way that the detector system response depends upon these effects as little or as simply as possible. For example, in whole-body counting, spatial resolution is not required, which allows the counting of Compton-scattered photons and use of non-collimated detectors to minimize attenuation/geometry effects. But when multiple source organs are present, and the activity of each is required, the geometric mean of dual opposed detectors is commonly used to minimize the effects of source depth, although the geometric mean does depend upon body thickness. A point of concern is that the calibration of the detector system is frequently accomplished with homogeneous, constant thickness (water) phantoms - usually containing a "point" source - whereas the human body is heterogeneous, of irregular shape, and contains irregularly-shaped organs. If there is comparatively little attenuation, then the combined effects of attenuation and geometry are correspondingly small, but it is unclear whether or not this is true for lower energy emitters such as Tc-99m and Xe-133.

It will be assumed that a dual opposed detector system is used in the following formalism, and that a digitized image is obtained for each detector. It is also assumed that the source of interest is well-resolved from any other sources that may be present. The scan field is imagined to be composed of an array of rectangular cells, with the length and width of each corresponding to the area of an image point (i.e., with a scanning system, each cell length is the distance the detectors move in generating the counts for an image

0015995

point, and each cell width is the distance between adjacent scan lines). Within each cell j are a body thickness d_j, anterior source organ wall coordinate z_{2j}, posterior source organ wall coordinate z_{1j}, and hence source organ thickness t_j ($= z_{2j} - z_{1j}$). An activity A_j is contained in each cell, with a relative depth distribution function $g_j(z)$, which is normalized to unity so as to integrate to unity over the cell depth. Hence the array of cells is being used for a discrete approximation to the source and scattering medium structures in the scan field. The continuous variable z is being used to describe depth features within any given cell.

The counts in image point i due to the activity in cell j will be written in terms of calibration data obtained from scanning a "point" source in a constant thickness phantom. Define

$\Omega_{ij}(d,z)$ = counts in image point i/activity of point source in cell j (1)

to be the normalized point source image (note there will be several $\Omega_{ij} \neq 0$ when $i \neq j$, depending upon the spatial resolution of the imaging system). In order to characterize the calibration scan by a simpler function, the calibration scan counts are summed and divided by the source activity:

$$f(d,z) = \sum_i \Omega_{ij}(d,z), \tag{2}$$

with there being an f_T for the top detector and an f_B for the bottom one.

For the distributed source, the counts in image point i due to cell j is given by

$$C_{ij} = A_j \int_{z_{1j}}^{z_{2j}} g_j(z)\, \Omega_{ij}(d_j,z)\, dz . \tag{3}$$

The known quantities from the scan are the image counts C_i, which equal the sum of the C_{ij} over j. However, this sum is over the source elements, whereas the

4017596

sum in (2) is over the calibration image points i. This problem can be avoided by also summing over the image counts C_i to obtain

$$C = \sum_i C_i = \sum_i \sum_j C_{ij} = \sum_j A_j \int_{z_{1j}}^{z_{2j}} g_j(z)\, f(d_i, z)\, dz . \tag{4}$$

As before, there are sums of this form for each detector - C_T for top, and C_B for the bottom.

The activity estimate, A', comes from assuming that the distributed source is equivalent to a point source of the same activity located at an effective depth z_0 within the patient. Then A' is simply the ratio of the geometric mean of the patient counts to the geometric mean of the calibration data:

$$A' = \left(C_T C_B\right)^{1/2} \left(f_T(D, z_0)\, f_B(D, z_0)\right)^{-1/2} . \tag{5}$$

A problem with this expression is that a single effective patient thickness, D, is needed, as well as a single effective depth z_0. In highly symmetric geometries, D and z_0 are often suggested by the symmetry, but this is not true for patients. To investigate this matter, one can first substitute for C_T and C_B in (5) from (4):

$$A'/A = \left(\sum_j n_j T_j \sum_j n_j B_j\right)^{1/2} \cdot \left(f_T(D, z_0)\, f_B(D, z_0)\right)^{-1/2} \tag{6}$$

where

$$T_j = \int_{z_{1j}}^{z_{2j}} g_j(z)\, f_T(d_j, z)\, dz \tag{7a}$$

$$B_j = \int_{z_{1j}}^{z_{2j}} g_j(z)\, f_B(d_j, z)\, dz , \tag{7b}$$

and n_j is the fraction of the total source activity A contained in cell j. Equation (6) implies that the activity estimate A' will equal the true source activity A only if the right side of (6) is unity. However, the T_j and B_j are

101759

difficult to evaluate directly, because they require knowledge of the depth distribution of activity, the source size and depth, and the body thickness. In practice, one knows only the scan counts, body thickness (from a transmission scan), and perhaps the source organ thicknesses from an ultrasonic scan or computed tomography scan. Therefore approximations will be used to simplify (6) so that an activity estimate can be made from the known quantities. As will be shown, the validity of the approximations depends upon attenuation and geometry, and illustrates their importance.

The Schwarz Inequality for two sets of quantities X_j^2 and Y_j^2 is

$$\left(\sum_j X_j^2 \sum_j Y_j^2\right)^{1/2} = \sum_j X_j Y_j \quad \text{, if } X_j/Y_j \text{ is independent of } j \tag{8a}$$

$$\left(\sum_j X_j^2 \sum_j Y_j^2\right)^{1/2} > \sum_j X_j Y_j \quad \text{, otherwise.} \tag{8b}$$

By defining $X_j^2 = T_j$ and $Y_j^2 = B_j$, (6) becomes

$$A'/A = \left(\sum_j n_j (T_j B_j)^{1/2}\right) \cdot \left(f_T(D,z_0) f_B(D,z_0)\right)^{-1/2} \text{, if } T_j/B_j \text{ is independent of } j \tag{9a}$$

$A'/A >$ Same , otherwise. (9b)

As explained below, (9a) is more easily evaluated than (6) is. The condition for validity of (9a) is quite important, and depends upon attenuation and geometry. The less attenuation there is, the less the values of the ratio T_j/B_j vary from one cell to another. It can be shown that (8a) is insensitive to first order perturbations; that is, if the ratio X_j/Y_j varies by an amount ϵ_j from one cell to another, the Schwarz Inequality is still a strict equality to first order in ϵ_j . The inequality (8b) arises from terms of order ϵ_j^2 . So if the patient geometry is just right, or if there is absolutely no attenuation, (9a) is completely equivalent to (6). Neither case will generally occur, but if attenuation is not too great, or if the patient geometry is not too different from the "just right" geometry, (9a) will still be a very good approximation to

0017598

(6). At worst, the value of A deduced from (9a) will be an upper limit to the true source activity, as can be seen from (9b).

The numerator of the right side of (9a) involves a sum of geometric means, whereas (6) involves a geometric mean of sums. This fact makes (9a) easier to evaluate, because T_j and B_j vary in such a way that their geometric mean is essentially constant. This can best be illustrated by an example. Suppose that the source is a uniform source, and that the calibration data are described by

$$f_T(d_j,z) = a \exp(-\mu d_j + \mu z) \qquad f_B(z) = b \exp(-\mu z), \tag{10}$$

where a,b and μ are constants. For a uniform source, $g_j(z) = t_j^{-1}$ and $n_j = t_j / \sum_j t_j$ so that (7a) and (7b) become

$$T_j = a \exp\left[-\mu\left(d_j - t_j/2 - z_{ij}\right)\right] \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \tag{11a}$$

$$B_j = b \exp\left[-\mu\left(t_j/2 + z_{ij}\right)\right] \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}, \tag{11b}$$

and (6) becomes

$$A'/A = \exp(\mu D/2) \left\{\sum_j \exp\left[-\mu\left(d_j - t_j/2 - z_{ij}\right)\right] \sinh(\mu t_j/2)\right\}^{1/2} \cdot \left\{\sum_j \exp\left[-\mu\left(t_j/2 + z_{ij}\right)\right] \sinh(\mu t_j/2)\right\}^{1/2} \cdot \left(\sum_j \mu t_j/2\right)^{-1}, \tag{12}$$

and (9a) becomes

$$A'/A = \exp(\mu D/2) \left[\sum_j \exp(-\mu d_j/2) \sinh(\mu t_j/2)\right] \cdot \left[\sum_j \mu t_j/2\right]^{-1}. \tag{13}$$

The simplicity of (13), compared with (12), is evident. Note that z_0 does not

1011599

appear, as a consequence of (10). The form of (10) is used here because it is experimentally observed, at least over the range of depths that most organs occupy. However, at depths very near the anterior or posterior body wall, deviations from (10) may be observed. The remaining tasks with (13) are to investigate the condition for its validity, and to produce a scheme for evaluating D.

Equation (13) will be valid if the ratio T_j/B_j is independent of j. From (11a) and (11b), this ratio is equal to

$$R_j = (a/b)\ \exp(-\mu d_j + \mu t_j + 2\mu z_{1j}) ,$$

or since $t_j = z_{2j} - z_{1j}$,

$$R_j = (a/b)\ \exp(-\mu d_j + 2\mu z_{0j}) , \qquad (14)$$

where $z_{0j} = (z_{1j} + z_{2j})/2$. The ratio a/b is independent of j, but the argument of the exponential is not unless $\mu = 0$ (no attenuation), or $d_j - 2z_{0j}$ is equal to a constant (the "just right" geometry). To obtain a geometric interpretation of this latter condition, suppose that the cells are sufficiently small that d_j and z_{0j} can be given as $d(x,y)$ and $z_0(x,y)$, where x and y coordinates have replaced the j index. Then the differential of $d(x,y) - 2z_0(x,y)$ is

$$d\left[d(x,y) - 2z_0(x,y)\right] = \underline{\text{grad}}\ (d - 2z_0) \cdot \hat{u}\ ds. \qquad (15)$$

This implies that the quantity $d - 2z_0$ will be constant if its directional derivative is zero in an arbitrary direction in the x - y plane (scan plane) given by the unit vector $\hat{u}$. This condition will certainly not be met with all patients, if any at all, so (13) will be of use only when attenuation is small enough that the small μ will keep the R_j of (14) from varying too much.

The evaluation of D will be made from a consideration of (13). The first

0017600

summation in (13) can be written as

$$\sum_j \exp(-\mu d_j/2)\,\sinh(\mu t_j/2) = \sinh(\mu t'/2) \sum_j \exp(-\mu d_j/2) \quad , \tag{16}$$

where t' is somewhere between the minimum and maximum t_j values. Also in (13),

$$\sum_j (\mu t_j/2) = m\,\mu\bar{t}/2 \quad , \tag{17}$$

where m is the number of terms in the sum, and $\bar{t}$ is the average source thickness. Then (13) becomes

$$A'/A = \exp(\mu D/2) \left[m^{-1} \sum_j \exp(-\mu d_j/2) \right] \cdot \left[\sinh(\mu t'/2) / (\mu\bar{t}/2) \right] . \tag{18}$$

The quantities in brackets involving t' and $\bar{t}$ are weighted self-attenuation corrections, which suggests that D be defined as

$$\exp(-\mu D/2) = m^{-1} \sum_j \exp(-\mu d_j/2) \quad , \tag{19}$$

in which case (18) reduces to

$$A'/A = \sinh(\mu t'/2) \;/\; (\mu\bar{t}/2). \tag{20}$$

Although D is now defined, the parameter t' has been introduced. Its defining equation, (16), is generally difficult to evaluate because a set of correlated d_j and t_j values are needed. If these correlated data are available (e.g., a computed tomography scan), then D can be found from (19), t' from (16), $\bar{t}$ from (17), A' from (5), and finally A from (20). If not, t' must be approximated. One possible approximation comes from substituting (19) into (16):

$$m^{-1} \sum_j \exp(-\mu d_j/2 + \mu D/2)\,\sinh(\mu t_j/2) = \sinh(\mu t'/2) \quad . \tag{21}$$

By expanding the exponential in a power series, one has

$$m^{-1} \sum_j \sinh(\mu t_j/2) + (\mu D/2)\, m^{-1} \sum_j (1 - d_j/D) \sinh(\mu t_j/2) + \ldots = \sinh(\mu t'/2) \tag{22}$$

01 1601

and by retaining only the first term:

$$m^{-1} \sum_j \sinh(\mu t_j/2) \approx \sinh(\mu t'/2) \ . \tag{23}$$

How well (23) approximates (22) and (21) depends upon how much the $\exp(-\mu d_j/2)$ and the $\sinh(\mu t_j/2)$ vary. Each can be separately checked to see how large their standard deviation is, which means comparing

$$\left[m^{-1} \sum_j \exp(-\mu d_j) \right]^{1/2} \geq m^{-1} \sum_j \exp(-\mu d_j/2) \tag{24}$$

and

$$\left[m^{-1} \sum_j \sinh^2(\mu t_j/2) \right]^{1/2} \geq m^{-1} \sum_j \sinh(\mu t_j/2) \ . \tag{25}$$

If either (24) or (25) is near to equality and the other is not greatly different from equality, (23) will give acceptable results. As limiting cases, one can note that if all t_j are the same, then they equal t' and $\bar{t}$. If all d_j are the same, then (23) follows exactly from (21). Using transmission scan data and ultrasonic scan data, (24) and (25) have been evaluated for Tc-99m in the liver of several patients. The left side of (24) was found to exceed the right by only 4 %, and the left side of (25) exceeded the right by 14 %. Therefore (23) seemed adequate.

Regardless of the means used to estimate D and t', one should also check that (13) is a good approximation to (12). One way of doing this is to compute the standard deviation of the R_j values in (14), using either ultrasonic or computed tomography data. For the liver scan patients just mentioned, this standard deviation was found to be 5 %, so (13) was felt to be sufficiently accurate (recall that the Schwarz Inequality is insensitive to first order perturbations).

It must be remembered that equations (12) - (25) were derived for a uniform source and calibration data given by (10). They might not be applicable to

1011902

other source distributions or different calibration data forms. Despite this, the example given should be useful. The equation for D, (19), should apply whenever (10) can be used, because the $\exp(\mu D/2)$ was simply carried through the equations. For non-uniform activity distributions, T_j and B_j would clearly have different forms, depending upon the assumed activity distribution. In many cases, the activity distribution is not really known. It is simply assumed to be uniform based upon the general appearance of scan images, and/or lack of a better assumption. A general investigation of the importance of the assumed activity distribution is beyond the scope of this discussion, although some guidelines can be given.

1. The amount of self-attenuation is the crucial factor in evaluating the importance of the assumed activity distribution. The more self-attenuation, the more important is knowledge of the true activity distribution.
2. If one decides, by some criteria, that self-attenuation is negligible for his purposes, then the depth distribution of activity may be regarded as a point source , for which A and A' are equal. Even though source thickness is not needed, body thickness still is.
3. If one decides that self-attenuation is appreciable, but not great,then assumption of a uniform source is probably adequate.
4. If self-attenuation is great, then one has no choice but to somehow determine the true activity distribution.
5. If one is unsure whether case 3 or case 4 above applies, then the magnitude of the self-attenuation correction can be estimated for a uniform source. If this correction (the right hand side of (20)) is relatively small - say a 20 % correction deduced and 10 % accuracy required - then case 3 applies. Otherwise, case 4 applies.
6. If case 4 does apply, then one has a very difficult problem. The Schwarz Inequality will likely be a very strong inequality, so that (9a) will not be valid. Similarly, new expressions for D and other parameters will have

101603

to be derived.

A table has been given by Jones, Johnston, and Brill (Phys. Med. Biol.,20,3, 1975, Table 2, p. 461) which shows the upper limit of the size of the self-attenuation correction (called the overestimate) as a function of photon energy for a 15 cm thick uniform,unit density source. For photon energies of 100 keV and more, the correction does not exceed 30 %. At 50 keV, the correction has climbed to 55 %, and from there to 20 keV it rises sharply to 3,832 %. Because a 15 cm thickness encompasses most body organ sizes, a uniform distribution is probably adequate for energies of 100 keV and greater (until pair production predominates). It may be adequate in many cases for photon energies between 50 and 100 keV; however, this should be checked for each case. For lesser photon energies, the distribution assumed is very critical, as well as the accuracy of all measurements involved.

1017604

Appendix IV

Draft - Sect. 5, NCRP-65 (J. Jones 7/77)

IV. Dose Measurements

A. Introduction

The accuracy of any dose measurement system is dependent upon two major considerations. Clearly, the apparatus itself must perform reliably (e.g., it must be sensitive enough to accurately respond to the radiation levels of interest). Second, one must correctly deduce the dose of interest from the detector response. The specific methods involved under the first consideration depend upon the type of apparatus used, but generally reflect the rules of good laboratory technique (care in handling, electronic stability, and the minimization of any factors causing a spurious response). The methods involved under the second consideration are less apparatus-dependent; they depend upon the type and energy of radiation detected, upon what one wishes to infer from the measurement, and upon the accuracy to which this inference is to be made. Consequently, the second consideration may involve subtle points that are not appreciated until one thinks carefully and critically about his results. To call attention to these points, some general remarks will be given below. Remarks specific to given types of detectors will not be given, because thorough discussions can be found in Radiation Dosimetry and other instrumentation references.

B. General Remarks

The means used to infer radiation dose from detector response depends upon the detector size as compared to the range of secondary electrons produced within and around it, as pointed out by Burlin (Radiation Dosimetry, Ch. 8, Vol. 1). If the detector is very small compared to this range, then the energy it absorbs comes largely from electrons originating in the surrounding medium. Thus the detector response is interpreted in terms of the dose to the surrounding medium. This cavity chamber approach has been well-documented, and the Bragg-Gray theory (or a suitable modification) is well established. At the other extreme is a detector much larger than the electron range. Here the energy absorbed

1017605

in the detector is due largely to photon interactions within the detector itself. Under certain conditions one may be able to regard the detector as a sampler of the photon flux within the surrounding medium, whose presence does not appreciably alter the flux. If so, the dose to the medium is determined by mulitplying the detector dose by the ratio of energy absorption coefficients for the medium and detector, respectively, which is also a well-established procedure. If not, one should still know the detector dose, although further interpretation may be difficult. Between these size extremes, both electrons from the surrounding medium and photons make appreciable contributions to the detector response. Burlin has given an empirical technique for use in such cases, which may be used, or one can avoid detectors not of these size extremes.

Because of the relatively low photon energies emitted by isotopes used in Nuclear Medicine, along with the predominance of Compton interactions, some commonly used detectors (thermoluminescence detectors (TLD's), ionization probes) are larger than the electron ranges involved. Thus the conditions under which the detector samples the photon flux of the surrounding medium are of practical importance. They include that the detector be uniformly dosed, and that the detector be in charged particle equilibrium (as much kinetic energy is transported via charged particles into the sensitive volume of the detector as is transported out.) If charged particle equilibrium is not achieved, the detector will be between the extremes of size mentioned above, and the range of secondary electrons will have to be taken into account.

If the detector is too large to be uniformly dosed, then it may pertrub the photon flux of the surrounding medium. In addition, its response will be due to a weighted average dose within it, which may be difficult to determine.

Most detectors require a calibration exposure before use, and it is here that all factors affecting detector response come into play. It is imperative that the combined effects of these factors be the same (within the accuracy

1017606

required) in both the calibration exposure and that to the radiation field of interest. It frequently happens that the calibration exposure is made with a carefully calibrated "point" source in air, while the radiation field of interest is due to an irregularly-shaped, distributed source located in an irregularly-shaped, heterogeneous scattering medium. Even if the same isotope is used for both exposures, the detector will be exposed to different energy spectra incident from different directions, and a faulty calibration may result. For this reason, it is urged that a test exposure, using "bad geometry" phantoms, be run to check the calibration procedure and detector performace. Absorbed fraction information for various spheres, ellopsiods, and cylinders in MIRD Pamphlet No. 3 can be used for this purpose.

C. Human Dose Mesurements

The human radiation dose of greatest interest is that to internal organs, but the difficulty of making accurate, atraumatic, and noninvasive masurements has led to heavy reliance on dose calculations. In particular, the work of the MIRD committee and the table of S-factors in MIRD Phamphlet No.11 contain the most widely used dose estimation parameters. This discusion will center on measurements designed to evaluate the applicability of the calculated parameters to humans, since humans are of different sizes, shapes, and medical conditions. The problems of measurement for this are severe. Implantation of small detectors in body cavities or catheters is possible but the lack of extensive measurements within an organ and patient risks and discomfort compromise measurement accuracy. Implantation of detectors in cadavers is also possible, but there are problems in assuring that the distribution of activity is representative of in-vivo distributions, that the detectors can be properly psoitioned without excessive insult to cadaver organs, and in obtaining cadavers for several experiments. Use of animals is yet another possibility, but it is uncertain how to extrapolate animal dose measurements to humans. All these possibilities seem inordinately difficult for the purposes of dosimetry alone, but they should not be rejected because the risks, discomforts,

L0176O1

and or costs might be borne for other reasons, such as special clinical procedures. In such cases, useful dosimetric information may be obtained in conjunction with the primary purposes of the procedures, especially when the dosimeters are small and do not require constant attention, such as TLD's.

Far less complex, but more indirect, are two other approaches--to make measurements in special phantoms, and to make external measurements on humans. Both these approaches have been used in limited studies. Garry, Stansbury, and Poston have made measurements in a phantom (MR. ADAM) built according to the specifications given in MIRD Pamphlet No. 5. Two source organs and several target organs were used, with satisfactory agreement between measurements (made with an ionization detector) and calculations. However, the isotopes used were Co-60 and Cs-137, which are higher energy emitters than those commonly used in Nuclear Medicine, such as Tc-99m. Additional measurements using more source organs and lower energy emitters would be helpful in assessing the accuracy of the model calculations as well as in validating experimental measurement techniques.

Yamaguchi, Kato, and Shiragai have made measurements with LiF powder in a RANDO phanton of different size and shape than the MR. ADAM phantom. Again, two source organs were used with several target organs for Co-60. The authors also devised a scaling technique to account for the different size of their phantom. The results, when scaled, are in good agreement. It may be noted that before scaling, the measured values were almost twice as large as the calculated values, which is not negligible when it is realized that discrepancies would be larger for lower energy emitters, and both phantoms are intended to represent typical human size.

External measurements on human subjects have been made for Tc-99m sulfur colloid by Jones, Wagner, and Brill. The source organs were liver and spleen, and the target region was a 5 cmX 5cm X 0.89cm thick slab of LiF located on the skin, anterior to and overlaying the liver. On humans, this slab was simulated with an array of LiF TLD's of the same thickness. Again reasonable agreement

1017608

between measurements and calculations was found, although body size had an effect and discrepancies up to a factor of two were noted.

The indirect approaches of phantom measurements and external human measurements have distinct disadvantages, however. The application of phantom measurements to humans depends upon how well the phantom represents humans--something not well known. External measurements on human subjects do not give direct information on internal organ dose, although the accuracy of external calculations does give some indication of the accuracy of internal dose calculations. Another disadvantage at present is the need for a special computer run to make the external target calculations. Also, the external target region should be fairly samll, to assure uniform dosage, which tends to increase the computer time needed to make the calculations. But perhaps the most serious limitations of external measurements are the small doses which must be measured, and accounting for the biokinetics of the radiopharmaceutical. Ideally, it would quickly concentrate in a single organ and stay there for several isotope half-lives. Then the external target region would be chosen close to the source organ, and TLD's or other suitable dosimeters exposed until an acceptably large dose was accumulated (probably several half-lives). However, few radiopharmaceuticals localize in this fashion. Radiocolloids (liver, spleen) and microspheres (lungs) concentrate well, and several radiopharmaceuticals concentrate in the bladder. There also some that concentrate well initially, but are quickly removed, such as iodohippurate (kidneys) and inhaled xenon gas (lungs). Finally, free iodide is concentrated by the thyriod. But to make a realistic test of the model calculations, fairly low energy emitters, such as Tc-99m or Xe-133, should be favored because the effects of attenuation and geometry are more pronounced than with I-131, for example.

The small doses to be measured are indicated by the fact that Jones, et. al. found the eternity dose to their target region overlaying the liver to be approximately 55 mrad per millicurie in the liver. For other radiopharmaceuticals, the lack of single organ concentration implies that still smaller doses will be

1011609

encountered, in addition to the difficult problem of deducting the cumulated activity for each source organ. This latter problem could be somewhat reduced by restricting the dose measurements to short time intervals, so that the isotope distribution will have changed little, but this will lead to yet smaller doses to measure.

Therefore, it appears that human dose measurements will be in the range of 100 mrad and less--perhaps much less. (This will be especially true for Nuclear Medicine patients where exposure time is lost because of routine X-ray procedures.) This dose level is near the lower limit for accurate measurement with LiF TLD's and many other detectors. More sensitive detectors usually have higher atomic number (such as CaF_2), which can introduce ambiguities such as photon energy dependence of the response.

Most of these problems of external measurement can be avoided by using spectrometry systems to measure photon spectra. Sodium iodide and germanium detectors are commonly used to collect spectra from low activity samples, so their sensitivity should be adequate to allow human spectrum collection in a relatively short period of time. Then using standard spectrum analysis techniques, one can compare the patient spectra to those calculated with the model. However, one should be aware that measured spectra are photon energy absorption spectra within the detector, whereas model calculations would be of energy spectra incident upon the detector. These spectra are different, and proper data analysis would be needed to allow comparison between them.

At present there are no model spectra to compare human spectra against. If model spectra could be determined and published for standard target areas, commonly used radionuclides, and common source organs, a large body of human data could be generated quickly. This data would help show how well the model calculations apply to humans of widely different sizes, shapes, and medical conditions, including children. The principal limitation of external measurements is that the geometric relationship between various internal organs cannot be checked; but body size, shape, heterogeneity, depth of source organ within the

0017610

the body, and the spatial distribution of activity within the organ will all affect the spectra.

1017611

Appendix V

SAAM SEMINAR - WORKSHOP
INSTITUTE OF ENERGY ANALYSIS
OAK RIDGE ASSOCIATED UNIVERSITIES
OAK RIDGE, TENNESSEE
April 28-31, 1977

Sponsored by: National Cancer Institute, National Inst. of Health
Division of Nuclear Medicine, Vanderbilt Univ. Health Center
Training Division, Oak Ridge Associated Universities
Biomedical Computing Technology Information Center (BCTIC)

P R O G R A M

April 28

8:00 am - 9:00	Registration	
9:00	Introduction	M. Berman
9:15	SAAM Features.	M. Weiss
	(a) SAAM Architecture	
	(b) Algorithms	
9:45	Coffee Break	
10:15	Models and SAAM Equivalences . . .	M. Berman
11:15	Lunch	
1:00 pm	Modeling	M. Berman
2:00	Automation of Modeling and Simulation	M. Berman
2:30	Coffee Break	
3:00	Conversational SAAM.	R. McGuire
4:00	Computer Support.	L. Zech
7:00	Task Group: Problem Definitions	

April 29

9:00 am	Presentation of Group Problems
12:00	Lunch
1:30	Panel Discussion
2:30	Hands-on Computer Activity

April 30

9:00 am	Hands-on Computer Activity

1017612

LIST OF PEOPLE REGISTERED

Bruce Struthers
University of Rochester
School of Medicine & Dentistry
Rochester, New York 14642

Dr. Robert Kilpper
University of Rochester
School of Medicine & Dentistry
Rochester, New York 14642

Salvador Bozzo, M.D.
Applied Science Div.
Brookhaven National Lab.
Upton, Long Island, N.Y. 11973

John E. Wolff
Ruakura Agric. Research Center
Hamilton
New Zealand

Vijay K. Batra
3 Secora Rd., Apt. #D1
Monsey, NY 10952
(Lederle Laboratories)

David W. A. Bourne
College of Pharmacy
University of Kentucky
Lexington, KY

Peter B. Bright
2462 Coolidge Ave.
Los Angeles, CA 90064
(Consultant to UCLA)

A. B. Brill
Div. of Nuclear Medicine
Vanderbilt Univ.
Nashville, TN 37232

R. N. Bubar
Univ. of Ill.
College of Vet Med.
Urbana, Ill. 61801

Walter Crackel
University of Ill.
College of Vet Med
Urbana, Ill. 61801

Patrick Cahill
New York Hospital
Cornell Medical Center
535 68th St.
New York, NY 10021

Dr. Richard P. Gural
Food and Drug Admin.
HFD-525 Rm 1662
5600 Fishers Lane
Rockville, Md. 20857

Mr. John D. Haynes
Lederle Laboratories, Bldg. 2
Pearl River, NY 10965

Gary D. Koritz, OhD, DDM
College of Vet Med.
Univ. of Ill
Urbana, Ill. 61801

Jane Madden, Ph.D.
VA Hospital
151
Wood, WI 53193

P. Todd Makler, Jr.
Temple Univ. Hospital
960 Meeting House Rd.
Rydal, PA 19046

James H. Matis
Inst. of Statistics
Texas A & M Univ.
College Station
Texas 77843

Steven H. Quarfordt, M.D.
Duke Univ. Medical Center
Box 3902
Durham, North Carolina 27710

David M. Shames, M.D.
Dept. of Radiology
Univ. of California
San Francisco, Calif. 94143

George A. Smith, Ph.D.
Veterans Admin. Center
VAC-151
Wood, WI 53193

1017613

Randall B. Smith
College of Pharmacy
Univ. of Kentucky
Lexington, Kentucky 40506

Benjamin M.W. Tsui
Univ. of Chicago
Box 420
950 East 59th St.
Chicago, Ill. 60637

Dr. G. Wilkinson
Dept. of Pharmacology
Vanderbilt University
Nashville, TN 37232

James H. Bernard
Institute of Respiratory Diseases
Kettering Medical Center
Kettering, Ohio

Betty F. maskewitz
BCTIC - ORNL
P. . O. Box X
Oak Ridge, Tenn. 37830

W. J. McClain
CSD - BCTIC
P. O. Box X
Oak Ridge, Tenn. 37830

Hemma Comolander
BCTIC
ORNL
P. O. Box X
Oak Ridge, Tenn. 37830

Frances Alsmiller
ORNL
P. O. Box X
Oak Ridge, Tenn. 37830

Jerry Jones
Vanderbilt University
Nashville, Tennessee

Ron Price
Vanderbilt University
Nashville, Tennessee

Monas Berman
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

David Foster
National Cancer Institute
National Institutes of Health
Bethesda , Maryland

Marjory Weiss
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Ajit Thakur
National Cancer Institute
National Institutes of Health
Bethesda , Maryland

Betty N. McGuire
National Cancer Institute
National Institutes of Health
Bethesda , Maryland

Robert McGuire
National Cancer Institute
National Institutes of Health
Bethesda , Maryland

Anita Babcock
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Loren Zech
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Edward Purich
Lederle Labs
Pearl River, New York 10965

1017614

ERDA

Progress Report

Radioiostope Studies Utilizing a Low Level Whole Body Counter

and

Clinical Application of Activation Analysis

January 16, 1980

Prinicpal Investigator

A. B. Brill, M.D., Ph.D.
Ronald R. Price, Ph.D.

Vanderbilt University

Medical Center

Nashville, TN 37232

SDI 6/24/80

1017615

TABLE OF CONTENTS

		Page
A.	Task Description	1
B.	Publications	2
C.	Purpose	4
D.	Background	4
E.	Technical Progress	
	1. Specific Dosimetry Projects	5
	a. Iron-59 Dosimetry in Abnormal Human Subjects	
	b. NCRP Report on Radiation Protection in Nuclear Medicine	
	2. Radiation Sensitivity of the Thyroid During I-131 Therapy	
	3. Instrumentation Projects	
	a. Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies.	
	b. Microprocessor Controlled Whole-Body Scanner for Human Dosimetry Studies.	

Appendices

A. Fe-59 Dosimetry in Abnormal Subjects - Draft Manuscript

B. Changes in Thyroid Iodine Content Following I-131 Therapy

1017616

A. TASK DESCRIPTION (Approach, relation to work package, in 200 words or less)

The main emphasis of these studies is the development of methods (hardware and software) for the quantitation of body and specific organ burdens of radioactivity. Current work is directed toward the evaluation of radiation dose distributions in human beings from new radioactive tracers and new procedures used in nuclear medicine. Dosimetry and clinical studies will be carried out on patients using new radiopharmaceuticals where dosimetry data are lacking.

Future efforts will be directed toward the development of systems that will facilitate the collection of dosimetry data using less specialized facilities. The availability of instrumentation and analytic techniques that provide clinical images as well as dosimetry data should enhance the rate of collection of data on human exposures in medicine and assist in the optimization of diagnostic strategies.

In parallel with these efforts, we are developing a new computer assisted technique for diagnostic decision making. The basic aim is to utilize efficiently all the available data to maximize information gain while minimizing cost factors.

1017617

B. Publications.

1. Fiscal Year 1978

Price, R. R., Touya, J. J., Branch, R., Goddard, J. and Brill, A.B. Validation of renal transit-time calculations using compartmental models and direct measurements, A Review of Information Processing Medical Imaging. Proceedings of the Fifth International Conference, A. B. Brill and R. R. Price, Editors, pp. 536-554, Vanderbilt University, Nashville, 1978.

Efron, U., Kedem, Dan, Kedem, Drora, Smith, C. W., Erickson, J., Price, R. R., Nelson, J. H. and Brill, A. B. New methods for pulsatile blood flow measurement using cine-densitometry, A Review of Information Processing in Medical Imaging. Proceedings of the Fifth International Conference, A. B. Brill and R. R. Price, Editors, pp. 68-84, Vanderbilt University, Nashville, 1978.

Brill, A. B. and Price, R.R., Editors, A Review of Information Processing in Medical Imaging. Proceedings of the Fifth International Conference held at Vanderbilt University, Nashville, 1978.

Brill, A.B. and Erickson, J. J. Display systems in nuclear medicine. Semin. Nucl. Med. 8, No. 2, 155-61 (1978).

Kedem, Dan, Kedem, Drora, Smith, C. W., Dean, R. H. and Brill, A.B. Velocity distribution and blood flow measurements using videodensitometric methods. Invest. Radiol. 13, 46-56 (1978).

Price, R. R., Erickson, J. J., Patton, J. A., Jones, J. P., Lagen, J. E. and Rollo, F.D. Practical clinical applications of the computer in nuclear medicine. 25th Annual Meeting of Society of Nuclear Medicine, Anaheim, CA, June 26-7, 1978.

Larson, K.H. Measurement of regional and total body bone mineral content in vivo using transmission scanning and neutron activation analysis. Ph.D. thesis, Vanderbilt University, (unpublished), 1978.

Brill, A. B., Lindstrom, D. P., Nelson, J. H., Rhea, T. C., Kedem, Dan, Kedem, Drora, Price, R. R., Erickson, J. J., Graham, T. P. and Smith, C. W. A versatile digital densitometry system for cardiovascular studies. Roentgen-Video Techniques, D. H. Heintzen and J. H. Bursch, Editors, pp. 12-4, George Thieme Publishers, 1978.

1017618

Publications (Cont'd.)

Price, R. R., Branch, R., Ramage, A. A., Touya, J. J. and Brill, A. B. Deconvolution analysis of transplant renograms. Med. Imaging, 2, No. 2, 46-7 (1978).

Brill, A. B., Erickson, J., Goddard, J., Patton, J. A., Price, R. R., Rollo, F. D. and Touya, J. J. Computer applications in nuclear medicine. Textbook of Nuclear Medicine: Basic Science, A. F. C. Rocha and J. C. Harbert, Editors, Lea and Febiger, 1978.

Erickson, J. and Brill, A. B. Scintillation cameras. Textbook of Nuclear Medicine: Basic Science, A. F. C. Rocha and J. C. Harbert, Editors, Lea and Febiger, 1978.

Lee, C. S., Patton, J. A. and Brill, A. B. Serial thyroid iodide content in hyperthyroid patients treated with radioiodine. J. Nucl. Med. 19, No. 6, 742 (1978).

Patton, J. A. and Brill, A. B. X-ray fluorescence techniques for thyroid imaging, methods and results. Radioaktive Isotope in Klinik urd Forschung, Vol. 13, R. Hofer and H. Bergmann, Editors, pp. 287-98, Verlag H. Egermann, 1978.

Patton, J. A., Price, R. R., Rollo, F. D., Brill, A. B. and Phel, R. H. Clinical and experimental results with a nine element high purity germanium array. IEEE Trans. Nucl. Sci.,NS-25, No. 1, 653-56 (1978).

Wibulyachainunt, S., Price, R., Brill, A.B. and Krantz, S. B. Studies on red-cell aplasia: IX. Ferrokinetics during remission of the disease. Am.J.Hemat. 4, 233-44 (1978).

2. Fiscal Year 1979

Price, R. R., Larsen, K. H., Patton, J. A. and Brill, A. B. A digital system for imaging bone mineral mass. 31st Annual Conference on Engineering in Medicine and Biology Proceedings, 20, Oct. 21-25, Atlanta, 1978.

Erickson, J. J. and Price, R. R. Factors influencing the performance of nuclear medicine computer systems. Proceedings of 19th Annual Meeting and Continuing Education Lectures, Functional Studies in Nuclear Medicine, Southeastern Chapter of Society of Nuclear Medicine, November 1-4, 1978, Birmingham, Alabama, CS 6-1-6-9.

Askins, B. A., Brill, A. B., Rao, C. U. V. and Novak, G. Autoradiographic enhancement of mammograms. Radiol. 130, 103-07 (1979).

Publications (Cont'd)

Touya, J. J., Price, R. R., Patton, J. A., Erickson, J. J., Jones, J.P. and Rollo, F.D. Gated regional spirometry. J.Nucl.Med. 20, 620 (1979).

Price, R. R., et al. Comparison of differential renal function determination by ^{99m}Tc DMSA, ^{99m}Tc DTPA, ^{131}I-Hippuran and ureteral catheterization. J. Nucl. Med. 20, 631 (1979).

Pickens, D., Patton, J. A., Pearse, D., Price, R. R. and Brill, A. B. Simultaneous multiplane deconvolution in focal plane tomography. J. Nucl. Med. 20, 666 (1979).

Patton, J. A., Gibbs, S. J., Price, R. R. and Brill, A. B. Identification of radiopaque material in the maxillary sinus by x-ray fluorescence. J.Nucl. Med. 19, 1337-38 (1979).

C. Purpose

1. Development of methods (analytical and instrumental) for quantitation of body and specific organ contents of stable and radioactive tracers; and

2. Application of these techniques to obtain information on:

   A. Pathophysiologic status of patients receiving established and new radiopharmaceuticals; and

   B. Dosimetry.

3. Development of analytic techniques for efficient extraction of information from images (features), for diagnostic and therapeutic decisions.

D. Background

This contract was originally directed toward the development of low level whole body counters for assessment of fallout fission fragments from weapons testing in the late 1950's. In the late 1960's, we redesigned the data collection systems for assessment of radiation dose from radiopharmaceuticals used in nuclear medicine diagnosis and therapy. In the 1970's, high resolution solid state detectors (GeLi) were added for stable tracer studies using neutron activation analysis to obtain information without patient radiation dose. These studies involved collaboration with scientists at ORNL. X-ray fluorescence (SiLi) detectors were developed for analysis of thyroid iodine content, and high resolution emission mapping (HPGe mosaic array) investigated in collaboration with LBL and FMI.

These investigations have required quantitative measurement and analysis techniques in which computers have played a major role. We have attempted to demonstrate the advantages to be derived from the use of the CAMAC standard in nuclear medicine. These efforts have involved collaborations with LASL, FNAL, and AERE (Harwell).

The previous program will be divided into two parts:

1. An extension of the past work, emphasizing the development and application of new concepts in instrumentation and analysis to nuclear medicine and focused on assessment of the impact of new energy sources on health. This work will be conducted at BNL and is described in this document.

2. A transfer of the BCTIC operation from ORNL to Vanderbilt.

E. Progress in FY 1979

1. Dosimetry

a. Radio-iron Dosimetry

A draft manuscript has been submitted to the MIRD Committee summarizing the data we have collected and analyzed. The key tables resulting from these computations follow (Tables VI, VII, VIII), and a draft manuscript has been prepared. (Appendix A)

b. NCRP Report on Radiation Protection in Nuclear Medicine (Scientific Committee 32)

The initial review by the prime reviewers has been obtained, their comments and suggestions incorporated and the revised manuscript returned to NCRP staff for final typing and distribution to the council. The report includes tabulations of organ dose estimates from commonly employed radiopharmaceuticals based on calculations made by W. Snyder and M.R. Ford (ORNL) using biokinetic data reviewd by the committee and using MIRD data, where available. The report should be approved and published in mid 1980.

1017621

Table VI

Average Radiation Absorbed Dose in Normal Subjects from Radioiron (rads/mCi)

Target Organ	Source Organ: Liver	Spleen	Red Marrow	RBC*	Total
		$^{52}Fe + {}^{52m}Mn$			
Liver	2.68	0.03	0.14	0.04	2.89
Spleen	0.03	16.11	0.12	0.04	16.30
Red Marrow	0.03	0.02	8.96	0.03	9.05
Ovaries	0.01	0.02	0.48	0.04	0.55
Testes	0.00	0.00	0.05	0.04	0.09
Total body	0.10	0.07	0.47	0.03	0.67
		^{55}Fe			
Liver	60.2	0	0	3.8	64
Spleen	0	267	0	4.0	271
Red marrow	0	0	6.0	3.8	9.8
Ovaries	0	0	0	4.0	4.0
Testes	0	0	0	3.8	3.8
Total body	1.5	0.7	0.1	3.8	6.1
		^{59}Fe			
Liver	127	1.7	0.8	15.9	145
Spleen	3.3	463	0.8	15.0	482
Red marrow	3.1	1.7	18.5	14.1	37
Ovaries	2.7	0.9	2.2	15.0	21
Testes	0.7	0.2	0.3	15.0	16
Total body	6.3	3.3	1.5	13.2	24

* Dose from RBC activity outside of the liver and spleen. Total body "S" values used.

1017622

Table VII

Average Radiation Absorbed Dose in Abnormal Subjects from Radioiron (rads/mCi)

(self-irradiation dose only)

	^{52}Fe + ^{52}Mn		^{55}Fe		^{59}Fe	
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Liver	12.4(G)	0.397(D)	161(O)	33.7(A)	351(O)	58.9(A)
Spleen	69.0(D)	0.840(B)	1120(H)	567(F)	1720(H)	86.0(F)
Red marrow	13.3(M)	0.652(N)	151(F)	1.98(H)	176(F)	6.3(H)

1017623

Table VIII

Comparison of ^{59}Fe Dose Estimates (rad/mCi)

	(1)	(2)	(3)	(4)	(5)
Liver	83	150	100	27	145
Spleen		230	140	57	482
Red marrow	46	140	50	65	37
Ovaries	26				21
Testes	22				16
Blood			75-100	77	
Skeleton			13		
Kidneys		90			
Total body	23	30	5-35	23	24

(1) Feller PA, Grossman LW, Sodd VJ, Kereiakes JG: Dosimetry of Fe-52 and Fe-59. To be published (1979)

(2) Hine GJ, Johnston RE: Absorbed dose from radionuclides. J. Nucl. Med. 11, 468-469, 1970 (letter)

(3) Garby L, Nosslin B: Radiation Doses from Radioactive Substances in Substances in Medical Use. Stockholm, Swedish National Institute of Radiation Protection, 1969 (a compilation)

(4) Cloutier RJ, Edwards CL, Snyder, WS: Radiation doses from radionuclides in the blood. In CONF-691212, 1970, pp. 325-345

(5) This article

1017624

2. Prediction of Radiation Sensitivity of the Thyroid During I-131 Therapy

Information of iodine uptake, the effective half-time of its retention in the thyroid and thyroid mass are used in calculating the amount of I-131 to be administered to patients in the treatment of hyperthyroidism. A major variable, however, which we have not yet learned how to assess and use in planning therapy is radiation sensitivity of the thyroid.

In previous work on iodine kinetics, we evaluated iodine metabolism in large numbers of patients during treatment of thyrotoxicosis and have determined model parameters which are reasonable predictors of absorbed radiation dose to the thyroid, given knowledge of thyroid gland size.

To evaluate thyroid sensitivity, we sought to find and measure a parameter that reflects damage to the thyroid. The rate of loss of iodine from the gland immediately following therapy is due to altered rates of release from the gland and by diminution of uptake. We have now measured the iodine content of the gland after therapy by means of x-ray fluorescence scanning in a large number of patients in an attempt to determine if the later incidence of hypothyroidism can be predicted from early changes in iodine content after therapy. We measured iodine content and other thyroid function parameters in 52 patients who received radioiodine therapy. These patients were studied at monthly intervals following I-131 therapy with serial, quantitative fluorescent scans and radioimmunoassays. All patients showed a steep decline in iodine content between the second and third month post-therapy.

The major finding of interest from these studies is that those patients who were destined to become hypothyroid had lower iodine content values at the 2-3 month interval than other groups. From inspection of the data, we chose a value of 2 mg as the level for making predictions on the outcome of therapy. Applying this separation criterion to the 43 patients in whom adequate follow-up information was available (as of June 1978) some interesting observations can be made as shown in the lower section of Table V. Of the 21 patients who had iodine contents of 2 mg or greater at the 2-3 month interval, only 3 became hypothyroid within 12 months. The remaining 18 either remained euthyroid or relapsed into hyperthyroidism within 12 months. On the other hand, of the 22 who had iodine contents of less than 2 mg at 2-3 months post-therapy with I-131, 18 became hypothyroid. Thus, this is a clue deserving further study to determine whether this predisposes the patient to develop hypothyroidism and, if so, by what mechanism. A manuscript summarizing the present status of this project, in preparation for submission for publication, is attached as Appendix B.

1017625

Table V

Relationship of Low Iodine Content to Early Hypothyroidism

Thyroid Iodine at 2-3 Months	Hypothyroid Within 12 Months	Euthyroid at 12 Months or Relapse Within 12 Months	Total
< 2 mg.	14	2	16
≥ 2 mg.	3	13	16

Updated to 16 June 1978:

< 2 mg.	18	4	22
≥ 2 mg.	3	18	21

Inadequate Followup: 9

1017626

E. Technical Progress (cont'd)

3. Instrumentation Projects

a. Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies

SCANNER DESCRIPTION

The PHO/CON-192 Multiplane Imager is a tomographic scanning system developed by Searle Radiographics. It consists of two high performance gamma cameras, each with its own focussed collimator (Fig. 1). The cameras are supported by a moving

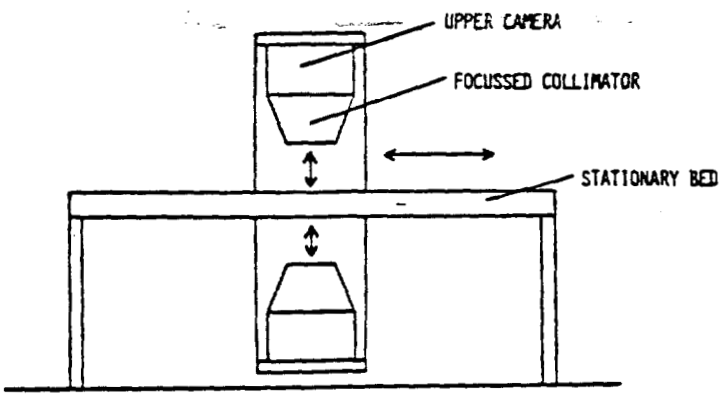


Figure 1.

PHO/CON-192 Multiplane Imager showing upper and lower cameras and the stationary bed.

frame so that one camera is located above and one below a stationary bed. The cameras are moved together in a rectilinear raster by the drive system, maintaining their relative positions throughout the scan. Vertical displacement of each camera can be adjusted individually. Scanning is controlled by the internal electronics of the PHO/CON. Tomographic images are reconstructed by dedicated hardware. Tomographic images of six different planes for each detector are produced on standard x-ray film. The separation between each plane and the distance from the collimator face of the first plane are specified for the upper and lower cameras prior to the start of the scan.

COMPUTER SYSTEM AND RECONSTRUCTION METHODS

The PHO/CON has been interfaced to a PDP-11/34 computer in our laboratory. A digital interface (Fig. 2) containing analog-to-digital convertors, timing and control, multiplexing, and line driving circuits has been developed. This interface encodes scan system moving frame (bed) coordinates, camera coordinates derived from the analog camera voltages, an upper/lower detector flag, and an isotope one/two flag into a 16 bits-per-word data stream which is transmitted to a DMA port in the PDP-11/34. List mode data are collected from the scanner and stored immediately on disk with no processing. Large amounts of data at high speed can be accepted and stored.

1017627

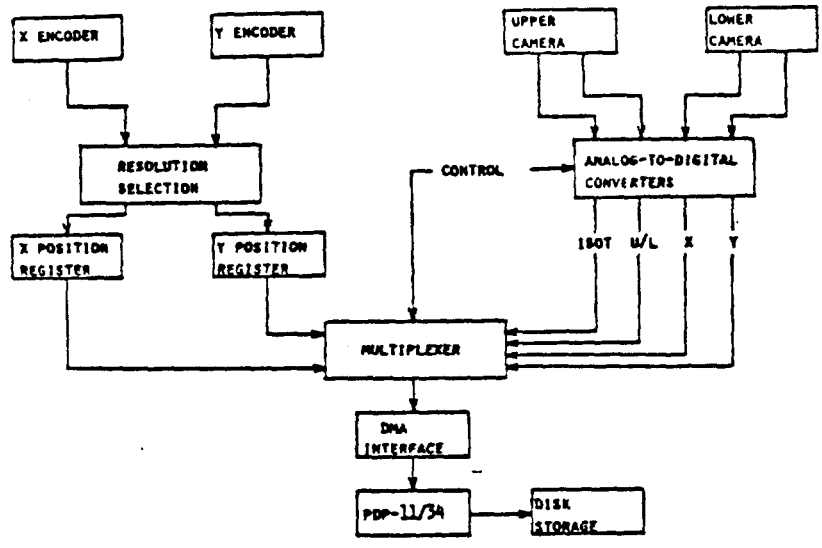


Figure 2.

PHO/CON data encoding and collection hardware block diagram.

A PDP-11/55 computer is used to reconstruct the images because of its larger memory, higher processing speed, and high quality display processor on which the reconstructed images can be viewed.

Reconstruction of individual longitudinal tomographic planes is performed by backprojecting the collected events along the ray paths through the focal point of the camera in which the event was detected. During scanning, events that originate at a particular position on a plane are represented by a specific camera coordinate pair. If a fictitious line is drawn from this coordinate position back through the focal point, the plane from which the event occurred will be intersected at a point (Fig. 3). By summing all of these backprojected intersections on a plane, an estimation of the activity distribution at that plane is obtained. This is an approximation of the true activity distribution because of contributions from activity on other planes which also are summed into the image and contribute a blurring or loss of resolution to the reconstruction.

The list mode data is decoded word by word during reconstruction. The X and Y moving frame coordinates are incorporated into individual data words as the low order 12 bits and are preceded by a flag word of sixteen bits of zeros. Camera data words which follow the Y bed coordinate word contain

1017628

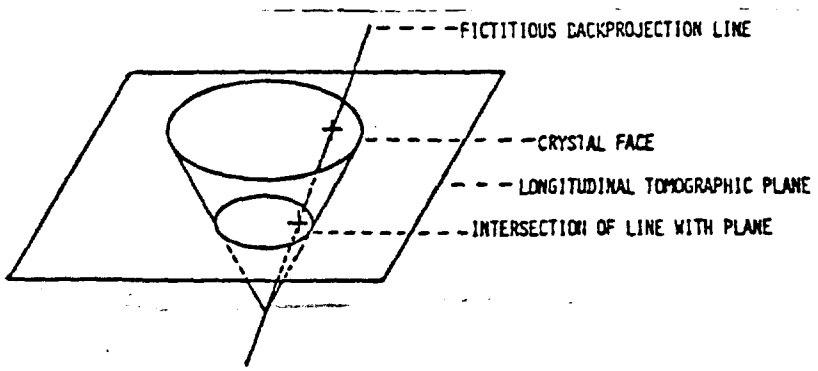


Figure 3.

Backprojection of an event through a longitudinal plane. A fictitious line drawn through a crystal event and through the focal point of the collimator intersects a plane of interest at a point as the crystal is moved in a rectilinear raster.

the seven bit X and seven bit Y coordinates for each camera event. Also, encoded in each camera word are flag bits representing upper or lower detector data and isotope one or two data (Fig.4). Decoding is performed by detecting the flag word as the start of a unit of data. Bit masking extracts the coordinates and flag information from the data words in the proper sequence.

After decoding each data word, the appropriate action is taken to backproject the event. The X and Y bed coordinates are mapped into the final image array. Each camera event at every bed coordinate pair is backprojected on the longitudinal tomoplanes that have been chosen for reconstruction. The current program can build as many as six 128 X 128 byte mode images simultaneously, three each for the upper and lower detectors. Reconstruction times are dependent on the number of counts detected. Typically, reconstruction times for patient studies are about the same as the collection times.

This digital backprojection reconstruction technique yields longitudinal images similar to those which are available from the PHO/CON hardware reconstruction. However, there are several advantages to the computer-generated images. Reconstruction can be done at anytime (or redone, if necessary) since the raw data is stored. This obviates the need for rescanning the patient. Any number of images at any arbitrary plane separation can be reconstructed as needed. The PHO/CON reconstruction yields six images for each detector at a constant separation. Various

1017629

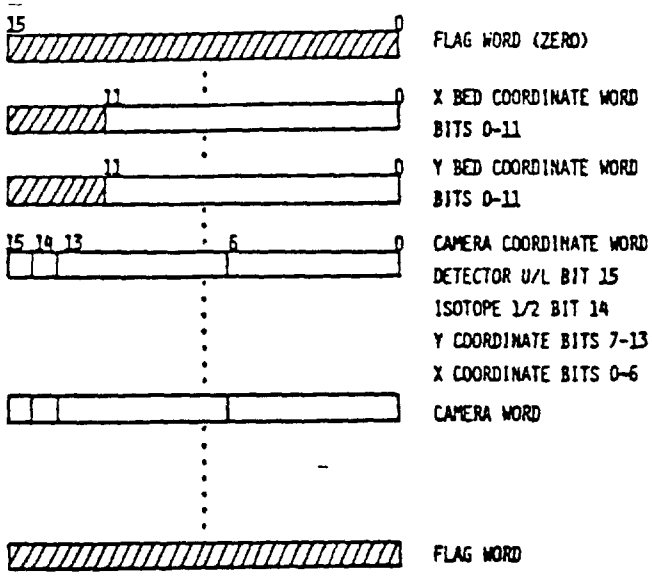


Figure 4.

Digital data stream from the PHO/CON interface. Each change in a bed coordinate results in a new flag word followed by bed coordinate words and camera data at the bed coodinates.

filter and deblurring algorithms can be applied to the digital images to improve the signal-to-noise ratios and enhance the images. This is not a feature of the commercial PHO/CON system.

Backprojection can be used to produce transverse sectional images from the PHO/CON data. Transverse section images are not available from the commercial system. The algorithm used to reconstruct transverse section images is very similar to that used for longitudinal section images, the difference being that the plane of interest of the intersection of a ray path is a transverse plane rather than a longitudinal plane (Fig. 5). The transverse section images are reconstructed as 128 X 128 pixels. The vertical dimension is 34 cm with the geometric focus in the center of the image. The horizontal coordinates of the transverse images are derived from the encoder information for the X axis of the PHO/CON bed, just as are the X-coordinates of the longitudinal scan reconstruction. The vertical coordinates of the transverse images are not derived from the encoder data, but are calculated from the camera data.

Transverse images usually require post-reconstruction processing to produce a final image. Ambiguities can arise in

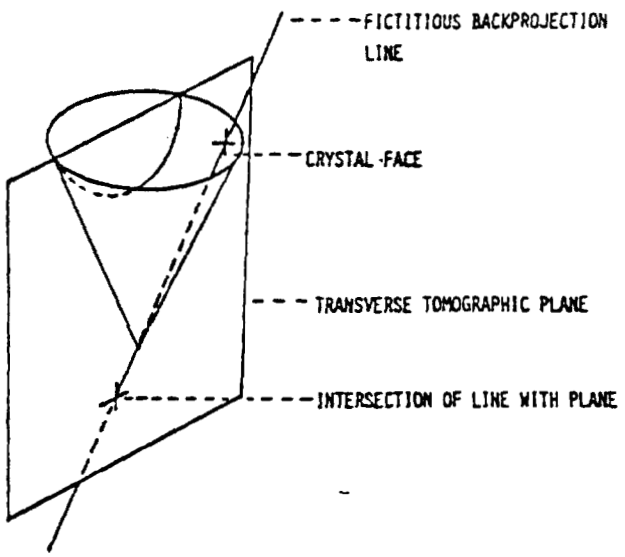


Figure 5.

Backprojection of an event through a transverse plane. A line drawn through a crystal event and through the focus of the collimator intersects a plane of interest at a point.

the calculation of the vertical coordinates because of round-off error. When the camera is positioned squarely over the transverse plane being reconstructed, it is impossible to position some camera events properly in the plane. These events are not used in the reconstruction. Thresholding and smoothing reduces the effects of omitting these data.

RESULTS OF DIGITAL BACKPROJECTION

Numerous phantom scans have been performed with the PHO/CON using Tc-99m. Both the longitudinal and transverse section images have been reconstructed. Patient studies have been done using Tc-99m, Ga-67, and Tl-201.

Figure 6 is a phantom constructed in our laboratory. It has an annular region surrounding a volume region. Within the volume are four separate smaller volumes. For these studies, the annulus and the four volumes were filled with Tc-99m. Figure 7 shows the results of a reconstructed longitudinal scan. Reconstruction was carried out at three levels through the phantom. Figure 7 also shows transverse sections through the phantom. The inner volumes and the vertical portion of the annulus are seen to be separated. This is the expected result because the horizontal resolution is better (about 0.6 cm) than the vertical

1017631

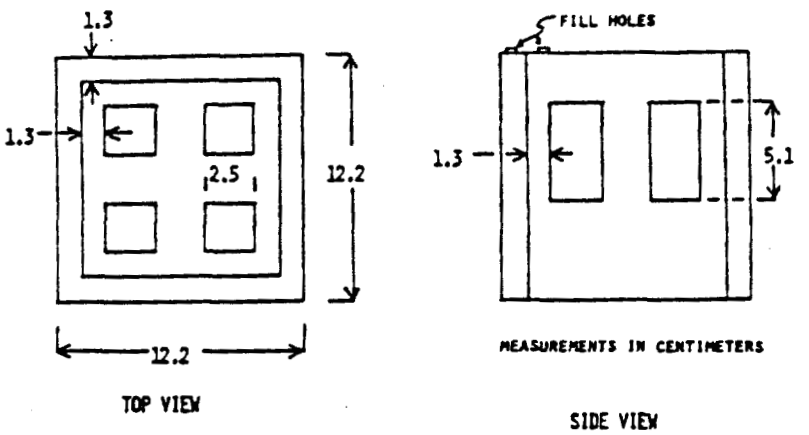


Figure 6.

Plexiglas volume phantom. An annulus surrounding a volume which contains four smaller volumes is seen in the diagram. Each section can be filled separately.

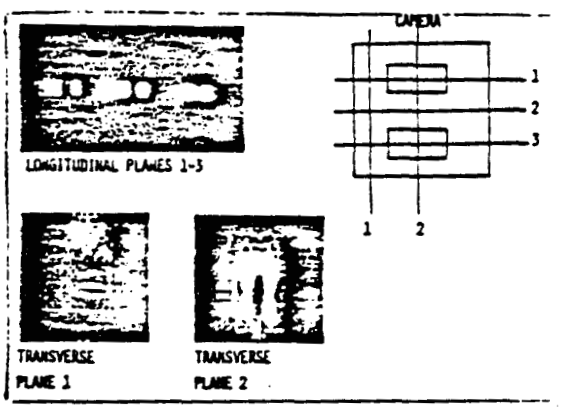


Figure 7.

Tc-99m tomographic scans of the phantom shows three longitudinal planes and two transverse planes.

resolution (estimated at 2.0 cm). The images demonstrate the shape of the phantom.

Figure 8 shows longitudinal tomograms of a 72 hour Gallium-67 patient study. A Tc-99m sulphur colloid study was

1017632

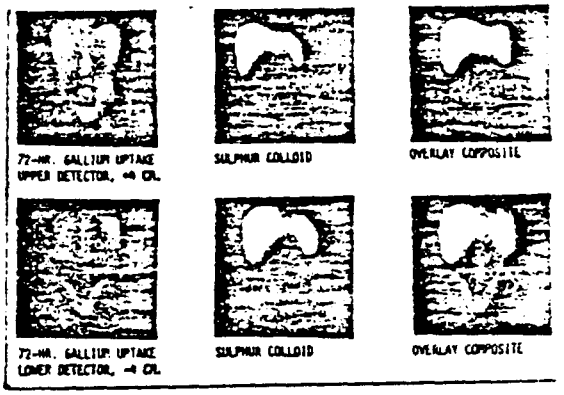


Figure 8.

72-hour Gallium-67 and Tc-99m sulphur colloid scans. Two arbitrary planes of Ga-67 data and corresponding Tc-99m sulphur colloid liver scans are combined by the computer to form an overlay composite. This procedure can be done at any tomographic level.

collected immediately after the gallium scan without moving the patient. The sulphur colloid is seen primarily in the liver. An overlay composite image is generated by the computer. Any number of tomographic overlays at various planes could have been produced from the digital data. Positioning the sulphur colloid liver scan over the gallium whole-body scan was performed easily by the computer and display processor. Other types of processing or enhancement could have been used as needed.

Longitudinal images of the myocardium with Tl-201 from the PHO/CON are seen in Figure 9. The information was collected from the lower detector with the patient lying in the LAO position. A 15 X 15 centimeter scan was performed around the area of the heart. The high resolution collimator was used. The conventional PHO/CON images are characterized by high background content due to uptake of the isotope in other regions of the chest.

Computer reconstruction of the same longitudinal planes are also shown. These digital images are displayed in 64 X 64 pixel format and have been post-reconstruction processed to remove background. The enhancement procedures include band pass filtering, data thresholding, and background subtraction. Figure 10 shows the results of this processing.

Transverse sections through the myocardium are presented in Figure 11. These sections are parallel to the horizontal axis in the longitudinal images. The series of sections moves

1017633

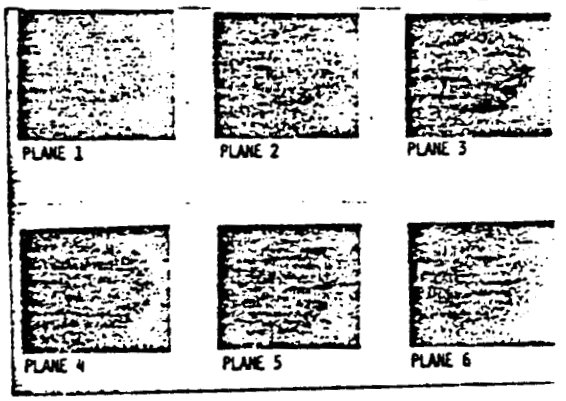


Figure 9.

Tl-201 longitudinal tomograms of the myocardium at 1.5 cm separation. These images are from the standard film output.

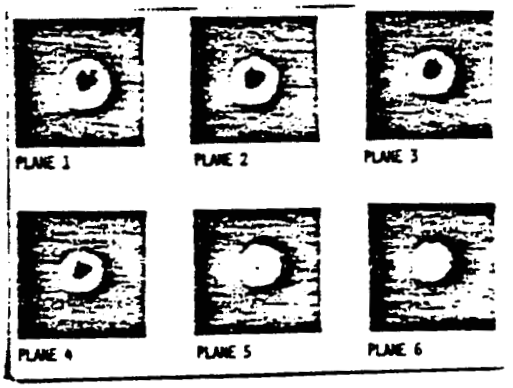


Figure 10.

Tl-201 longitudinal tomograms of the myocardium at one centimeter separation. These are computer processed images.

anterior to posterior through the heart at 0.7 cm intervals and shows the myocardial wall and left ventricular cavity.

DECONVOLUTION DESCRIPTION

Methods of reducing the effects of background noise and off-plane blur information are being investigated. The algorithm of Chang, Macdonald and Perez-Mendez (1) for simultaneous multiplane deconvolution has been applied to

1017634

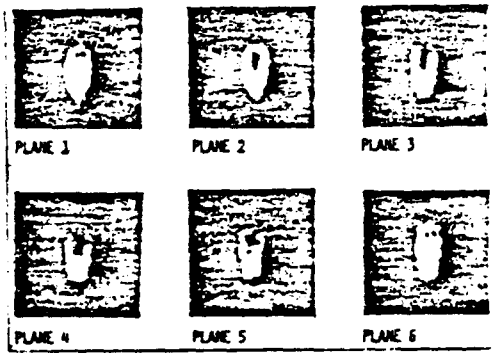


Figure 11.

Tl-201 transverse tomograms of the myocardium at 0.7 centimeter separation. These are sections moving from anterior to posterior.

phantom studies performed with the PHO/CON. Using system theory, one can determine the response of a linear system to any arbitrary input by convolving the input signal with the impulse response of the system. If the impulse response of the imaging system is its point spread function, the convolution of a known distribution with the point spread, assuming linear behavior, will give the output image of the system. Conversely, if the corrupted output image is available as in a clinical scan, in principle it is possible to deconvolve the output image and the point spread function to get an uncorrputed true activity distribution. This technique works perfectly with noise-free ideal images and point spread functions, but not as well with real data. Real images must be low pass filtered to reduce noise contributions. Applying this theory to multiple planes from a tomographic scanner simultaneously yields images with improved signal-to-noise ratios and reduced off-plane contributions. However, problems with noise components can distort the final images.

RESULTS OF DECONVOLUTION

Images of a phantom consisting of the numbers one, two and three separated by 1.5 cm in air are shown in Figure 12. The longitudinal tomographic sections are reconstructed at the plane of each number. Blur artifacts from the other planes are seen in each image. Processing with the algorithm of Chang, et al., yields three images in which the background blur information is reduced in each image (Fig. 12). One problem with the method is the occurrence of mottling which is seen in the processed images. This is due to the noise components of the images becoming larger than the image information at some spatial frequencies. The result is imperfect reconstruction at points in the image.

1017635

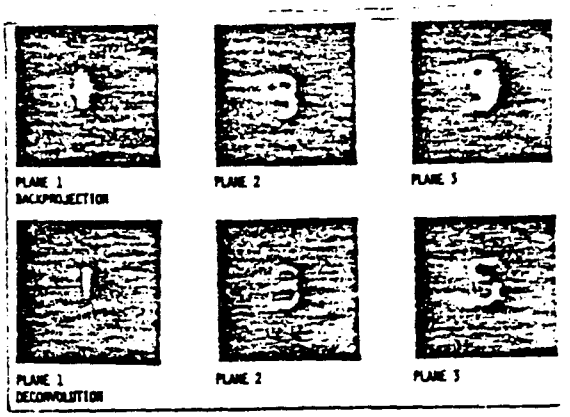


Figure 12.

Multiplane simultaneous deconvolution of PHO/CON images using the algorithm of Chang, et al.

CONCLUSIONS

A Searle PHO/CON-192 multiplane imager has been interfaced to a PDP-11/34 computer. Digital data collected during scans can be backprojected to produce multiple tomographic planes in longitudinal and transverse sections. Digital collection and reconstruction allows image formation and image enhancement that is not available from the commercially available instruments. Further, post-reconstruction processing using the simultaneous multiplane deconvolution algorithm of Chang, et. al, has been applied to phantom studies. Iterative forms of this method are being investigated.

REFERENCES

1. Chang, L.T., Macdonald, B., Perez-Mendez, V.: Axial Tomography and Three Dimensional Image Reconstruction. IEEE Transactions on Nuclear Science NS-23: 568-572, 1976.

1017636

E. Technical Progress (cont'd)

3.b. Microprocessor Controlled Whole-Body scanner for Human Dosimetry Studies

Due to increasing difficulty in maintaining the PDP9 computers which have been used to control and collect data from research scanner instrument in the low-level whole-body counter, we have designed and have contructed a microprocessor controlled interface to operate the low-level whole-body counting facility. This system is based upon an LSI 11 controlled autonomous CAMAC crate connected to a dual floppy disk drive. The LSI 11 contains 32,000 words of solid state memory and the entire system resides in the CAMAC crate. The low-level whole-body counting system is controlled through an output register which generates a command which in turn operates a control register, which controls the mechanical motion of the scanner in the low-level whole-body counting facility. The status of the limit switches and the hand control buttons are returned to the LSI 11 computer through an input register in the CAMAC crate. The incremental encoders attached to the lead screws of the scanner, used to monitor the X and Y position of the scanner, are fed back to the LSI 11 through a encoder follower CAMAC module. The scanner will operate uncer computer control, and data will be collected from both the upper and lower probes through standard nuclear electronics located in a NIM bin in the same electronic rack which holds the CAMAC crate control system. The system is designed to collect up to 4 input channels of data from each detector during its scanning motion. These data are normally stored in memory during the scan, however, for large area scans where large amounts of data are collected these data can be buffer stored on the floppy disks during data acquisition. These data can then be sent after data collection is finished to the departmental PDP1155 or to the central computing facility containing a PDP10 computer. These data are sent through an asynchronous communication port using communications protocols already implemented, and in routine use for communication between

— 01631

these computers. The system has been built and we are currently awaiting delivery of some parts needed for the scanner interface, at which point the system will be installed and the PDP9 removed from service. The module designed for this work could be used to drive a scanning bed, such as is now available in many laboratories. With stationary opposed detectors, such a system would provide a general purpose scanning capability for routine and research studies. Since no U.S. manufacturer currently manufactures a scanner, this may be of general interest to other nuclear medicine research groups.

1017638

STEEL COM INTERFACE PARTS LIST

Integrated Circuits

1-13	SPX74A1		
27-34,37-40	(Spectronics)		
14,15,22	75451B or 75452B	Vcc = 8	Gnd = 4
23,25,26	(See Note 1 on drawing)		
16,17,19			
35,36	74LS14	Vcc = 14	Gnd = 7
18	74LS158	Vcc = 16	Gnd = 8
20	74LS08	Vcc = 14	Gnd = 7
21	74LS02	Vcc = 14	Gnd = 7
24	75468		Gnd = 8

Transient Suppressor

1N5658A (General Semiconductor)

Resistors

2.4K	17 on logic board 8 on line board
1.0K	8 on logic board 4 on line board
150	13 on logic board 8 on line board
390	4 on logic board

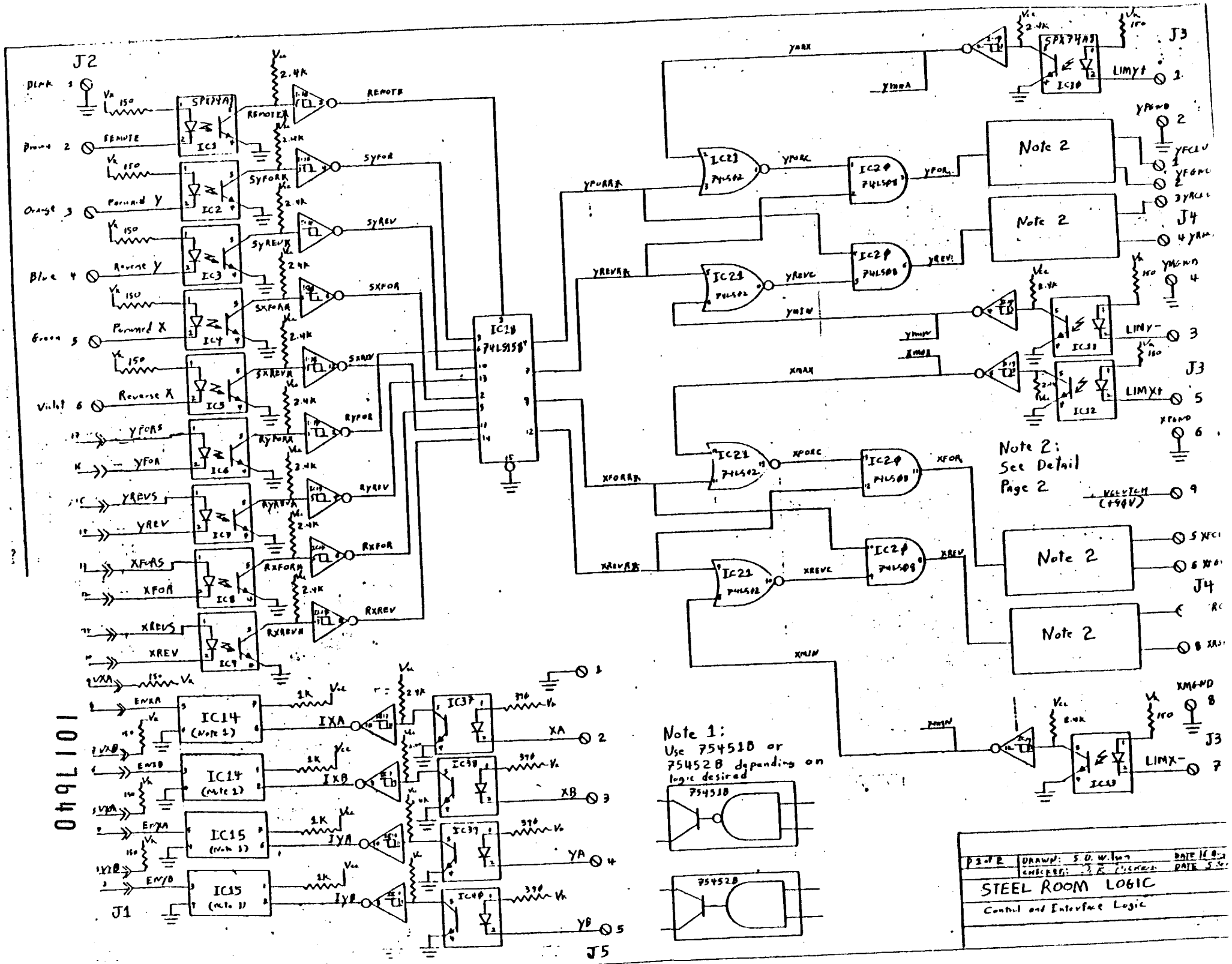
Connectors

J1,J6	DB25
J2	6 terminal
J3	8 terminal
J4	10 terminal
J5	5 terminal
J7	To be specified

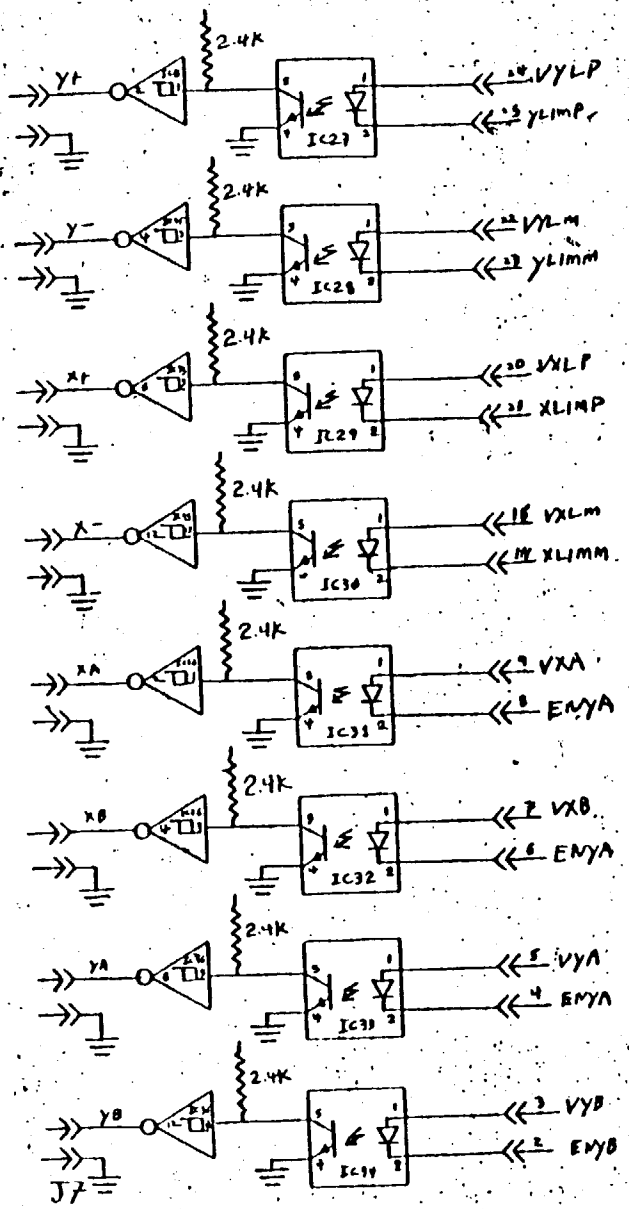
Power Requirements (Maximum):

Vcc (line board) 418ma
Vcc (logic board) 653ma
Vk (logic board) 340ma (5 Volts)
Vcc + Vk 993 ma

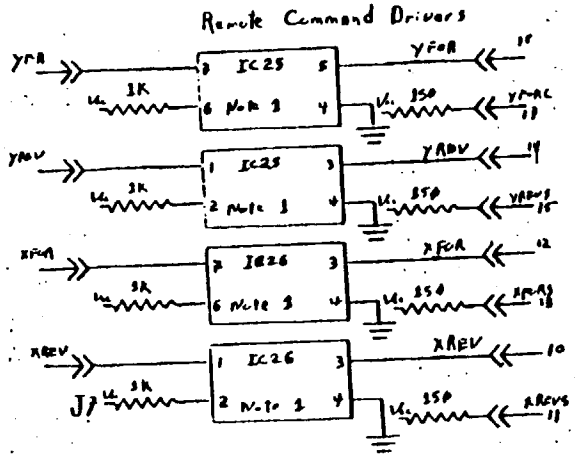
1017639


J2
REMOTE
Forward Y
Reverse Y
Forward X
Reverse X
SYFOR
SYREV
SXFOR
SXREV
RYFOR
RYREV
RXFOR
RXREV
IC28
74LS153
J3
J4
J5
J1
LIMY+
LIMY-
LIMX+
LIMX-
Note 2
Note 2:
See Detail
Page 2
Note 1:
Use 75451B or
75452B depending on
logic desired
75451B
75452B
STEEL ROOM LOGIC
Control and Interface Logic

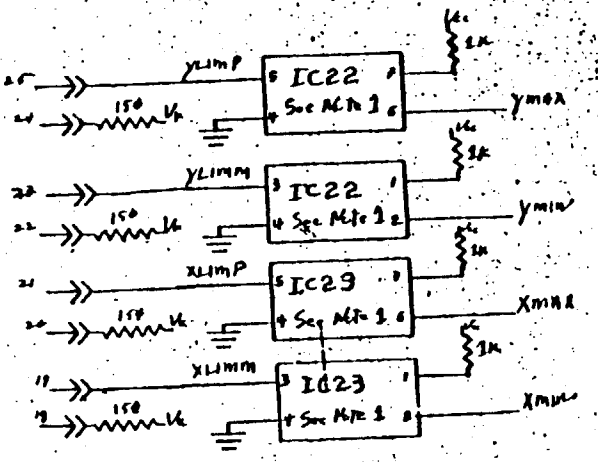
Computer/Line Interface

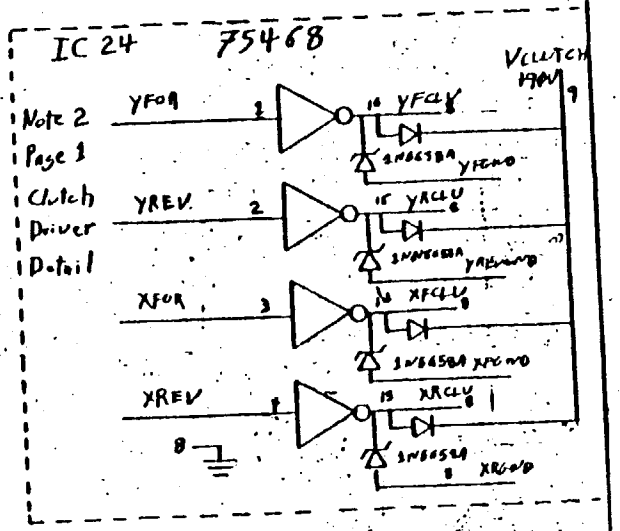


Remote Command Drivers



Limit Switch Drivers





P2-12	Drawn: S.D. Wilson	Date: 4 Sept 79
	Checked: D.R. Pierce	Date: 5 Sept 79

STEEL ROOM LOGIC

Computer/Line Interface, Clutch Drivers, Limit Switch Drivers

1017641

APPENDIX A

April 1979

Iron-59 Dosimetry in Abnormal Human Subjects

RADIATION DOSE ESTIMATES TO HUMANS FROM
52-Fe, 55-Fe, AND 59-Fe
ADMINISTERED IN FORMS CONVERTIBLE TO TRANSFERRIN

RADIOPHARMACEUTICAL

Radioiron (^{52}Fe, ^{55}Fe, or ^{59}Fe) is useful in studies of iron metabolism in various hematological diseases. It is available as a radiopharmaceutical in an acidic solution of ferric chloride, ferrous citrate, or ferrous sulfate. Ferrous and ferric ammonium citrate have also been used. The ionic or chelate form appears to be unimportant except that acidity is necessary to prevent formation of insoluble ferric hydroxide. When mixed with plasma, the iron rapidly becomes bound to transferrin, which has a high association constant for iron, and the original association is lost.

Accelerator-produced ^{55}Fe is available carrier free. Reactor-produced ^{55}Fe and ^{59}Fe are available with specific activities of 2-50 Ci/g, each of these being slightly contaminated with the other isotope. ^{52}Fe is accelerator produced and is not generally available because of its short half-life.

For the present radiation-absorbed dose calculations, 100% radionuclide and radiochemical purity of each radiopharmaceutical is assumed. However, ^{52}Fe decays to radioactive ^{52m}Mn and ^{52}Mn, some of which will be injected with the ^{52}Fe. The ^{52m}Mn and ^{52}Mn produced by decay after injection will also add to the radiation dose. However, because of the low branching ratio the dose from ^{52}Mn is negligible, and it is omitted from the final results. The dosimetry for each of the other nuclides is calculated separately.

101 764 2

NUCLEAR DATA

The nuclear data for radioisotopes of iron and manganese considered in this report are given in Table I.

METHOD

The mean absorbed radiation doses, $\bar{D}$, are calculated by the method described in MIRD Pamphlet No. 1, revised (1), using:

$$\bar{D}_k = \sum_h \tilde{A}_h(0,\infty) \quad S \quad (k \leftarrow h)$$

The required "S" values were abstracted from MIRD Pamphlet No. 11 (2). The $\tilde{A}$ values are derived from the biological data as follows.

BIOLOGICAL DATA

There is an extensive literature on iron kinetics in normal subjects and in various diseases (3-12). In brief, it is known that the distribution of iron in the body and the rates of exchange among the iron pools can be greatly altered in either direction in disease states. Table 2 indicates the normal distribution of iron in the body. Table 3 indicates the patterns of change in several diseases relative to the normal values. However, individuals within each category may show wide variability.

Through the use of compartmental modeling techniques, quantitative external measurements of the peripheral iron storage pools can be combined with the measurements of the circulating iron pools in a self-consistent manner. The ability to measure the turnover of slowly exchanging compartments directly, rather than by inferring

1017643

their kinetics from plasma clearance and red blood cell incorporation of radioiron, provides additional information on the anatomical distribution of these pools within the body and makes possible more reasonable dosimetric calculations.

The data for human tissue radioiron distribution on which the absorbed radiation dose calculations in this report are based were obtained from the literature and from studies by R. Price at Vanderbilt University, Nashville, Tennessee, and by M. Pollycove and H. S. Winchell at the Donner Laboratory of Medical Physics, University of California and the Clinical Laboratories, San Francisco General Hospital. Most of the data have been obtained with ^{59}Fe.

Numerous models have been proposed to describe iron kinetics (3, 6, 8, 9). The model used for the dose estimates in this report (13, 14) is diagrammed in Figure 1. This model has been found to be useful in a majority of the abnormal cases as well as for describing normal kinetics. The criterion for choosing this model over other more complex ferrokinetic models is that it was the simplest model found that was consistent with the measured data for the largest number of studies. It is also particularly useful for dosimetry purposes because the NIH Simulation Analysis and Modeling computer program (SAAM) (15) can directly provide the cumulated activities, $\tilde{A}$ μCi-hr, required for radiation-absorbed dose estimates to the tissue.

With the model shown in Figure 1 we have successfully fitted the individual kinetic data on three normal subjects and 16 abnormal subjects from the Vanderbilt Laboratory, and have validated the fit of the composite data of 15 normal subjects from the Donner Laboratory.

1017644

The presumed diagnoses of the 16 abnormal subjects are indicated in Table 4. In two patients with paroxysmal nocturnal hemoglobinuria (PNH) the model shown in Fig. 1 was inadequate to describe the kidney uptake and urinary excretion of iron. For these studies kidney and urine compartments were added to the model.

A. Normal Kinetics. Following intravenous injection, iron is rapidly bound to transferrin and most of the administered tracer radioiron moves from plasma to bone marrow for hemoglobin synthesis. Some iron is exchanged between plasma and extracellular fluid such as is contained in viscera other than liver. Plasma iron is exchanged with rapidly equilibrating tissue iron pools such as the cellular heme enzyme, and with tissue iron stores.

In normal iron kinetics the decrease in plasma radioiron may be described by a multicomponent exponential curve. The slower components are a result of feedback into the plasma of iron from the extracellular fluid and storage iron. The accumulation of radioactivity in circulating RBCs mirrors the release of radioactivity from the marrow and reaches a plateau within ten days.

The time retention curves of administered radioiron within the liver, spleen, and red marrow were determined from external counting measurements. The fraction of activity in these organs was derived from the literature and experimentally confirmed from external counting measurements combined with the SAAM computer program to determine the most probable value for net content of radioactivity in an organ where the measurement involves a superposition of several compartments.

The radioiron in the liver reaches an equilibrium level of 20-30% of the administered radioiron with 10-15 days, 15-25% of which is due

0017645

to activity in the circulating RBC. The spleen reaches an equilibrium level of 8-12% within 10-15 days with 8-10% of the activity being accounted for by the circulating RBC. A maximum of 70-90% is reached in the red marrow within 24 hours and is released with a mean time of 3-5 days. Upon release from the marrow, the radioiron appears in the RBCs reaching a maximum of 80-90% in 10-15 days. The remaining 4-5% of administered radioiron is assumed to be distributed uniformly throughout the body. Although total body radioactivity measurements (16-18) indicate an iron loss on the order of 0.0001 to 0.001 per day, for the radiation dose estimates in this report it is assumed that there is no loss of radioiron from the body. Any actual loss will, of course, reduce the radiation dose.

Plots of the composite data for 15 normal subjects (data of Pollycove) are shown in Figure 2. By fitting these curves with multiexponential functions, the transfer rate constants shown in Table 5 were derived. However, attempts to obtain the required $\tilde{A}$ values by integration of the multiexponential functions gave inconsistent results, particularly when this method was applied to the data from the abnormal patients. Instead, the computer program SAAM was used to carry out a numerical integration of the time activity curves to arrive at $\tilde{A}$ (μCi · hours) for the liver, spleen, red marrow, and RBC compartments. The integration limits for Fe-59 and Fe-52 were chosen to be approximately ten times the respective physical half-lives (450 days and 4 days, respectively). For Fe-55 a numerical integration was carried out for a period of 450 days after which time the contents of the compartments were assumed to remain unchanged and to experience only physical decay.

0017646

Mn-52 has a relatively short half-life and soon reaches secular equilibrium with ^{52}Fe. Therefore, the value of $\hat{A}$ for ^{52m}Mn was taken to be equal to the $\tilde{A}$ of ^{52}Fe. The available information (19-21) indicates that the ^{52m}Mn decays at or near the site of its production, so its distribution is assumed to be identical with that of ^{52}Fe.

The liver and spleen time-activity curves were estimated by determining the fraction of the slowly equilibrating storage compartments and the circulating blood pool compartments necessary to reproduce the external measurements. Those fractions for normals were found to be:

Liver = 0.67 (fast stores) + 0.15 (slow stores) + 0.26 (RBC)

Spleen = 0.15 (fast stores) + 0.15 (slow stores) + 0.10 (RBC).

The cumulative activity for the liver and spleen includes the fraction of the circulating RBC compartment indicated in the above equations. The fraction of the RBC compartment included in the liver and spleen was determined from a total body scan of ^{51}Cr labeled RBC taken 1 hour after injection of the labeled RBCs. These calculations assume no recirculation of the iron following the death of circulating red blood cells.

B. Abnormal Kinetics. Data from 16 patients listed in Table 4 were analyzed. The ranges of the intercompartmental transfer rate constants are presented in Table 5 as the maximum and minimum transfer rate constant found for each process. These extremes were scattered among the various diseases studied and no combination of maxima and minima would describe any individual patient. Of course, for the absorbed radiation dose calculations a consistent set of rate constants was used for each individual.

101164

Calculations for $\tilde{A}$ in μCi-hr for the marrow, RBC, liver, and spleen were made for each of the abnormal studies. The maxima and minima $\tilde{A}$'s for each source organ in the abnormal group are shown in Table 6. The $\tilde{A}$'s for a composite of 18 normal subjects are also listed in Table 6. In anticipation of the use of these numbers in the dose calculations to follow, the RBC $\tilde{A}$'s are distributed so that the fractions within the liver and spleen are included in the tabulated $\tilde{A}$ values for those organs. The $\tilde{A}$'s tabulated as RBC are then actually the remaining fraction outside of the liver and spleen, and are assumed to have a uniform whole body distribution. The partitioning among the three compartments varies with each patient.

ABSORBED RADIATION DOSE

For the radiation dose calculations, the source organs were assumed to be the liver, spleen, red marrow, and red blood cells, with the red blood cells distributed as described above. The target tissues for which absorbed doses were calculated were the liver, spleen, red marrow, ovaries, testes, and total body. The $\tilde{A}S$ product for each source-target pair and the total average dose for each organ for the normal subjects are listed in Table 7. The maximal and minimal doses for self-irradiation of each target source for the abnormal subjects are listed in Table 8. These were calculated using the "S" values for reference man. To the extent that organ sizes vary in the different disease states, the dose estimates so calculated will be in error. In particular, the spleen size may vary markedly. The data required for more accurate dose estimations were not available.

Table 9 outlines the calculations for the total body dose assuming

1017648

uniform distribution of the administered activity. It is notable that the distribution of activity as determined by the kinetic studies does not greatly affect the total body absorbed radiation dose.

1017649

REFERENCES

1. Berman M: Kinetic Models for Absorbed Dose Calculations, MIRD Pamphlet No. 12. New York, Society of Nuclear Medicine, Jan 1977

2. Snyder WS, Ford MR, Warner GG, et al: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11. New York, Society of Nuclear Medicine, Oct 1975

3. Barosi G, Berzuini C, Cazzola M, et al: An approach by means of mathematical models to the analysis of ferrokinetic data obtained by liquid scintillation counting of ^{59}Fe. J Nucl Biol Med 20:8-22, 1976

4. Bothwell TH, Finch CA: Ferrokinetics. In Iron Metabolism. Boston, Little Brown & Co., 1962

5. Cavill I, Ricketts C: The kinetics of iron metabolism. In Iron in Biochemistry, Jacobs A, Worwood M, eds. New York, Academic Press, 1974

6. Pollycove M: Iron kinetics. In Iron in Clinical Medicine, Wallerstein RO, Mettier, SR, eds. Berkeley, University of California Press, 1958, pp 43-57

7. Pollycove M: Iron kinetics. In Iron Metabolism, Gross F, ed. Berlin, Springer-Verlag, 1964, pp 148-177

8. Pollycove M: Iron metabolism and kinetics. Seminars in Hematology 3:235-298, 1966

9. Pollycove M, Tono M: Studies of the erythron. Seminars in Nuclear Medicine 5:11-61, 1975

10. Finch CA, Deubelbeiss K, Cook JD, et al: Ferrokinetics in man. Medicine 49:17-53, 1970

1017650

11. Saito H, Yamada H: Studies on red cell production and destruction in various hematological disorders in view of ferrokinetics. Acta Haem Jap 36:681-709, 1973

12. Saito H, Yamada H, Hirade M: Determination of effective erythropoieses rate by ferrokinetics in various hematologic disorders (in Japanese). Acta Haem Jap 39:138-144, 1976

13. Price RR, McKee LC, Jr, Krantz SB, et al: Estimation of slow dynamic function parameters in iron kinetics studies using quantitative measurements and compartmental modelling analysis. Proceedings of IAEA Symposium on "Dynamic Studies with Radioisotopes in Medicine," 1974

14. Price RR, Johnston RE, Brill AB, et al: Estimation of radioactive content of body organs by combining direct measurements and distribution models. Proceedings of IAEA Symposium on "Assessment of Radioactive Contamination in Man," 1972

15. Berman M: Compartmental analysis in kinetics. In Computers in Biomedical Research, Stacy RW, Waxman BD, eds. New York, Academic Press, 1965

16. Cook JD, Palmer HE, Pailthorp KG, et al: The measurement of iron absorption by whole body counting. Phys Med Biol 15:467-473, 1970

17. McKee LC, Jr, Price R, Johnston RE, et al: Long term studies of iron metabolism in normal males: Comparison of red blood cell radioactivity with whole body counter data. J Nucl Med 15:156-160, 1974

18. Sargent T, Pollycove M, Carpe L, et al: Dynamics of total body iron: Castrointestinal blood storage and "fixed" components. Clin Res 10:78, 1962

19. Francois PE, Szur L: Use of iron-52 as a radioactive tracer. Nature 182:1665-1667, 1958

20. Van Dyke D, Anger H, Pollycove M: The effect of erythropoietic

I01T651

stimulation on marrow distribution in man, rabbit and rat as shown by ^{59}Fe and ^{52}Fe. Blood 24:356-371, 1964

21. Anger HO, Van Dyke DC: Human bone marrow distribution shown in vivo by iron-52 and the positron scintillation camera. Science 144: 1587-1589, 1964

22. Fairbanks V, Fahey JL, Beutler E: Clinical Disorders of Iron Metabolism. New York, Grune & Stratton, 1971

1017652

FIG. 1. Diagram of model used with SAAM program for radioiron kinetics. The required input data are:

1. Fraction of administered activity in plasma
2. Fraction of activity in circulating red blood cells
3. Fraction of activity in liver from quantitative whole body scan
4. Fraction of activity in spleen from whole body scan
5. Fraction of activity in pelvis from whole body scan
6. Fraction of circulating red blood cell pool in each region of the body (determined from ^{51}Cr labeled red cell whole body scan).

FIG. 2. Curves fitted to composite data for ^{59}Fe in 15 normal subjects.

1017653

TABLE 1. NUCLEAR DATA

Radionuclide	^{52}Fe		^{55}Fe		^{59}Fe		^{52m}Mn		^{52}Mn	
Physical Half-Life	8.27 h		2.7 y		44.6 d		21.1 m		5.59 d	
Mode of Decay	E.C. & β^+ To ^{52m}Mn		E.C.		β^-		E.C., β^+, IT 1.9% to ^{52}Mn		E.C., β^+	
Equilibrium Dose Constant for Non-Penetrating Radiation (g-rad/μCi-h)	0.4375		0.0095		0.2511		2.4105		0.1642	
Principal Photons:	E_i	n_i	E_i	n_i	E_i	n_i	E_i	n_i	E_i	n_i
	0.169	0.993	0.0058	0.2339	0.1922	0.0292	1.434	0.98	0.744	0.90
	0.511	1.16			1.099	0.555	0.511	1.93	0.936	0.95
					1.292	0.441	0.378	0.19	1.434	1.00
									0.511	0.60

E_i = Energy (MeV)
n_i = Mean Number/Transformation

1017654

TABLE 2 . IRON COMPARTMENTS IN NORMAL MAN*

Compartment	Iron Content (mg)	Fraction of Total Body Iron (%)
Hemoglobin	2,500	67
Storage (ferritin, hemosiderin)	1,000	27
Myoglobin	130	3.5
Labile pool	80	2.2
Enzyme	8	0.2
Transport	3	0.08

*These values represent estimates for an "average" man (70 kg; 177 cm (70 inches)). Reference 22, page 47.

1017655

TABLE 3 : COMPARISONS OF IRON KINETICS IN DISEASE STATES WITH NORMAL KINETICS

	POOLS			EXCHANGE RATES	
	Storage Iron	Plasma Iron	Erythrocyte Iron	Plasma-Storage	Plasma-Erythropoietic
Hemochromatosis	30-60 x normal	2 x normal	Normal	Increased	±
Iron Deficiency Anemia	Absent	Decreased	Decreased	±	±
Acute Blood Loss	Decreased	Decreased	Decreased	Storage to Plasma Increased	Increased
Hypoplastic Anemia	Increased	Increased	Decreased	Increased	Decreased
Hemolytic Anemia Myeloid Metaplasia and Chronic Leukemia	Increased	Increased	Decreased	Increased	Increased
Polycythemia Vera (Normal)	Decreased	Decreased	Increased	Increased	Increased
Polycythemia Vera (Hemolytic)	Decreased	Decreased	Increased	Increased	Increased
Pernicious Anemia	Increased	Increased	Decreased	Increased	Increased

FROM REFERENCE 7

1017656

TABLE 4. PATIENT DATA

Code	Age	Sex	Diagnosis
A	62	M	Hemochromatosis
B	32	M	Acute myelogenous leukemia
C	58	M	Myeloid metaplasia
D	55	F	Malignant lymphoma
E	59	F	Intestinal bleeding
F	66	F	Sideroblastic anemia
G	66	M	Refractory anemia, septicemia
H	62	M	Refractory anemia
I	47	M	Pure red cell aplasia in remission
J	23	F	Pure red cell aplasia in remission
K	64	M	Acute myelomonocytic leukemia
L	71	M	Sideroblastic anemia
M	26	F	Pure red cell aplasia in remission
N	57	M	Pure red cell aplasia in remission
O	39	M	Pure red cell aplasia in relapse
P	69	F	Pure red cell aplasia, anemia

1017657

TABLE 5. INTERCOMPARTMENTAL RATE CONSTANTS FOR IRON METABOLISM (FRACTION/HR)

	k_{51}	k_{65}	k_{31}	k_{43}	k_{34}	k_{13}
	Plasma to Marrow	Marrow to RBC	Plasma to Rapid Stores	Rapid Stores to Slow Stores	Slow Stores to Rapid Stores	Rapid Stores to Plasma
Normal	0.333	0.010	0.096	0.022	0.002	0.008
Abnormal maximum	1.25	0.015	0.50	0.571	0.011	0.517
Abnormal minimum	0.010	< 0.001	0.011	0.001	< 0.001	< 0.001

1017658

TABLE 6. CUMULATIVE ACTIVITY
μCi Hr/μCi Administered

	^{52}Fe			^{55}Fe			^{59}Fe		
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
		Maximum	Minimum		Maximum	Minimum		Maximum	Minimum
Liver	1.23	5.70(G)[1]	0.18(D)	8600	23070(O)	4810(A)	372	1034(O)	173(A)
Spleen	0.89	3.82(D)	0.05(B)	3811	15970(H)	910(F)	193	719(H)	36(F)
Red marrow	6.18	9.15(M)	0.45(N)	790	19890(F)	260(H)	93	883(F)	32(H)
RBC[2]	0.45	1.10(A)	0.002(K)	20840	24760(A)	1320(K)	881	856(A)	39(K)
Total	8.75	—[3]	—	34040	—	—	1539	—	—
Average life[4]	11.93	—	—	34150	—	—	1544	—	—

1. Letters in parentheses indicate patient code (Table).
2. Activity in RBCs outside of liver and spleen. For normals the distribution of RBC cumulative activity is liver 0.26, spleen 0.10, other 0.64.
3. Since maximal and minimal for different organs are from different patients, the totals in these columns are meaningless.
4. Average life = half-life/0.69315. This is the maximum possible for the total cumulative activity per μCi.

1017659

TABLE 7. AVERAGE RADIATION ABSORBED DOSE IN NORMAL SUBJECTS FROM RADIOIRON (rads/mCi)

Target Organ	Source Organ				
	Liver	Spleen	Red Marrow	RBC*	Total
			^{52}Fe + ^{52m}Mn		
Liver	2.68	0.03	0.14	0.04	2.89
Spleen	0.03	16.11	0.12	0.04	16.30
Red marrow	0.03	0.02	8.96	0.03	9.05
Ovaries	0.01	0.02	0.48	0.04	0.55
Testes	0.00	0.00	0.05	0.04	0.09
Total body	0.10	0.07	0.47	0.03	0.67
			^{55}Fe		
Liver	60.2	0	0	3.8	64
Spleen	0	267	0	4.0	271
Red marrow	0	0	6.0	3.8	9.8
Ovaries	0	0	0	4.0	4.0
Testes	0	0	0	3.8	3.8
Total body	1.5	0.7	0.1	3.8	6.1
			^{59}Fe		
Liver	127	1.7	0.8	15.9	145
Spleen	3.3	463	0.8	15.0	482
Red marrow	3.1	1.7	18.5	14.1	37
Ovaries	2.7	0.9	2.2	15.0	21
Testes	0.7	0.2	0.3	15.0	16
Total body	6.3	3.3	1.5	13.2	24

*Dose from RBC activity outside of the liver and spleen. Total body "S" values used.

1017660

TABLE 8. AVERAGE RADIATION ABSORBED DOSE IN ABNORMAL SUBJECTS FROM RADIOIRON (rads/mCi)

(self-irradiation dose only)

	^{52}Fe + ^{52m}Mn		^{55}Fe		^{59}Fe	
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Liver	12.4(G)	0.397(D)	161(O)	33.7(A)	351(O)	58.9(A)
Spleen	69.0(D)	0.840(B)	1120(H)	567(F)	1720(H)	86.0(F)
Red marrow	13.3(M)	0.652(N)	151(F)	1.98(H)	176(F)	6.3(H)

Letters in parentheses indicate patient code (Table 4).

1017661

TABLE 9. CALCULATION OF RADIATION ABSORBED DOSE FROM IRON ISOTOPES WITHOUT INVOKING KINETIC DATA

Nuclide	^{52}Fe	^{52m}Mn	$^{52}Fe + {}^{52m}Mn$	^{55}Fe	^{59}Fe
Half-life	8.27 h	21.1 m		2.7 y	44.6 d
$\tilde{\lambda}$ = Average life (hours)	11.9	0.51		34145	1544
S (total body←total body) (rad/μCi h)	1.4×10^{-5}	5.8×10^{-5}		1.8×10^{-7}	1.5×10^{-5}
Total body dose (rad per mCi administered)	0.167	0.690*	0.857	6.146	23.16-

*^{52m}Mn is the daughter product of ^{52}Fe, so the ^{52}Fe $\tilde{\lambda}$ value is used in the dose calculation.

1017662

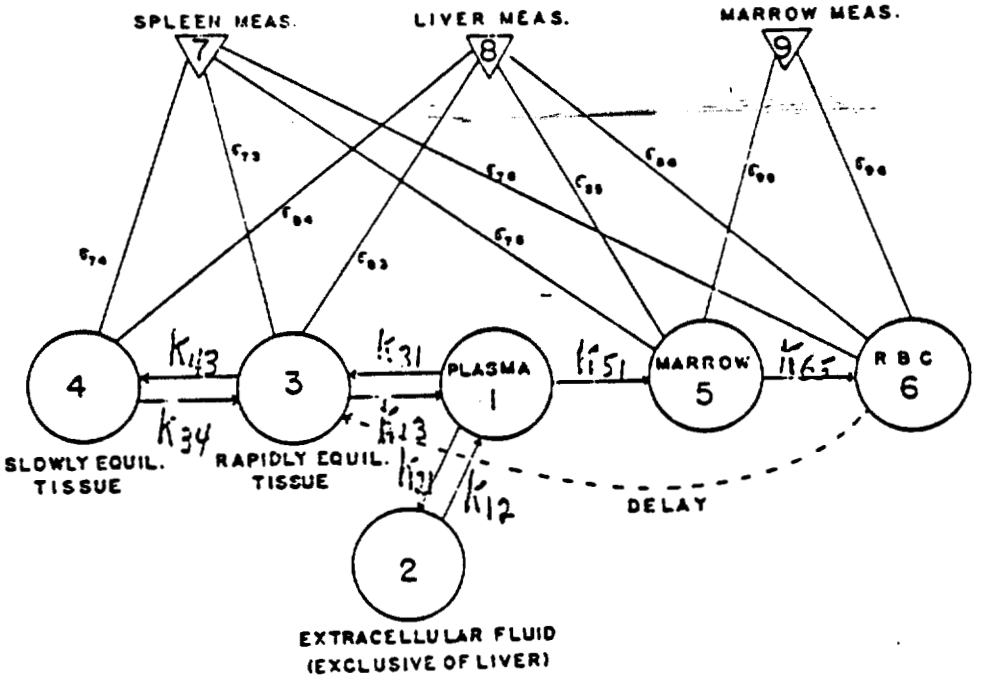


FIGURE 1.

1017663

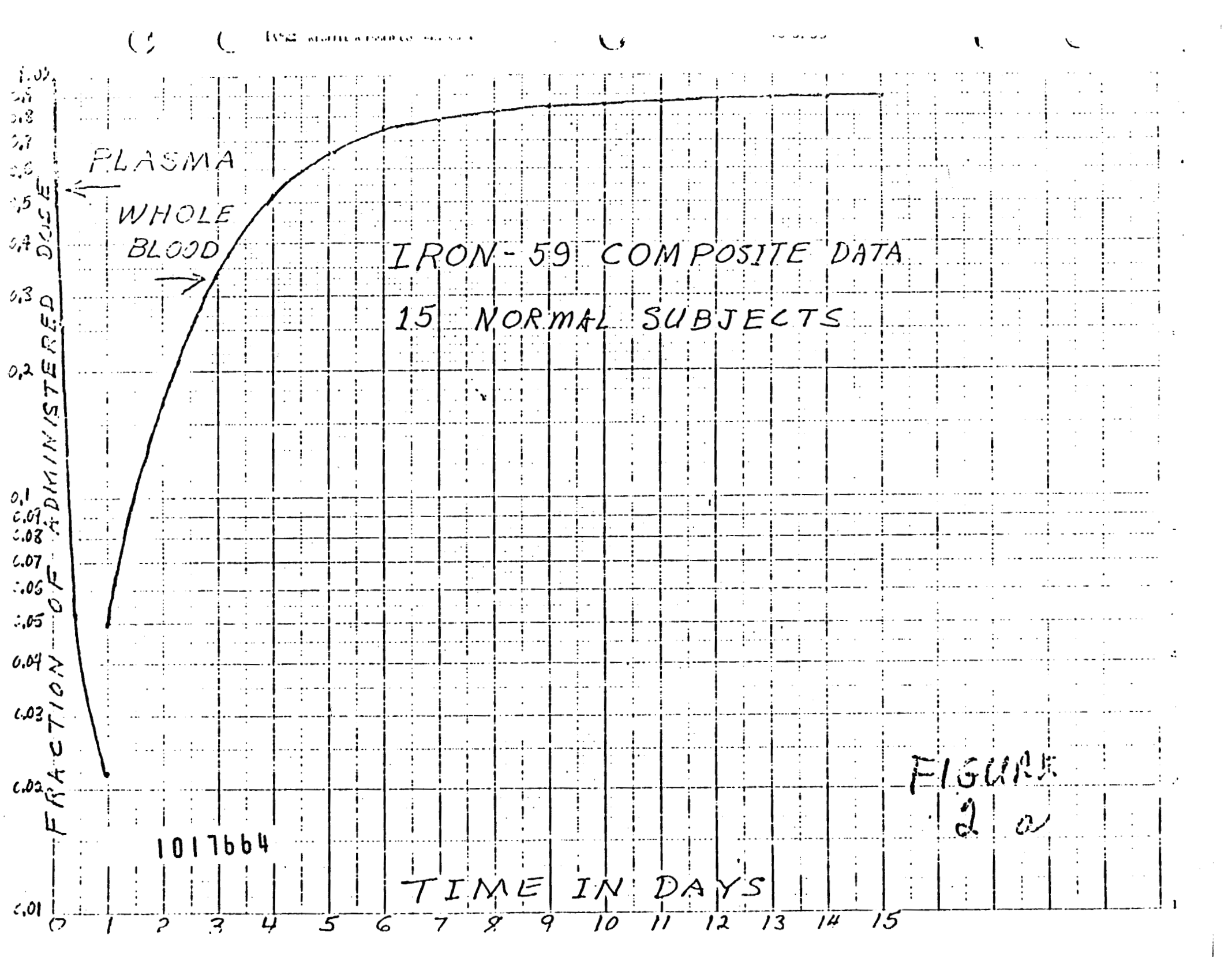

PLASMA
WHOLE BLOOD
IRON-59 COMPOSITE DATA
15 NORMAL SUBJECTS
FRACTION OF ADMINISTERED DOSE
TIME IN DAYS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
1017664

FIGURE 2 a

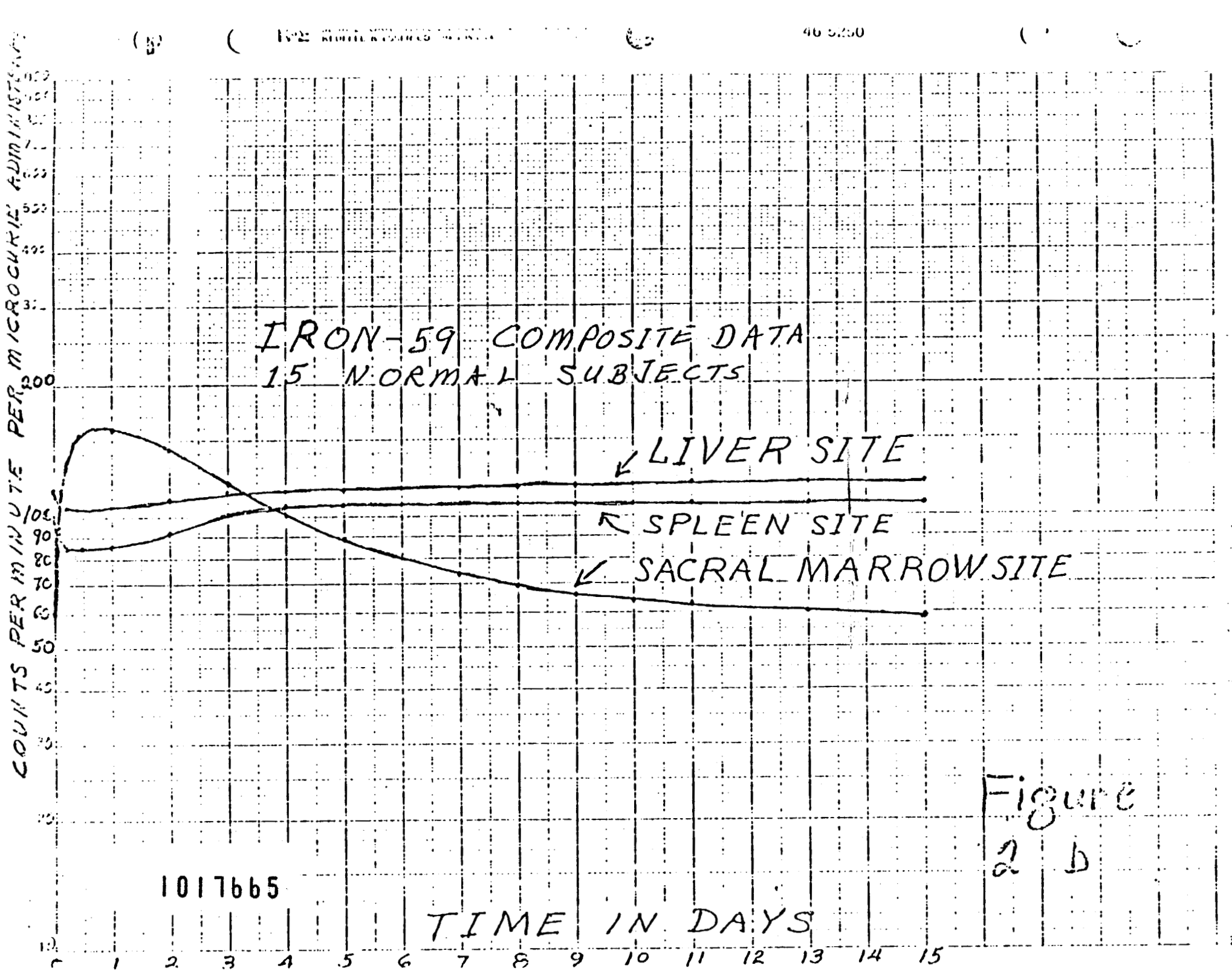


Figure 2 b

1017665

SUPPLEMENTARY INFORMATION

1017666

TABLE . COMPARISON OF ^{59}Fe DOSE ESTIMATES (rad/mCi)

	(1)	(2)	(3)	(4)	(5)
Liver	83	150	100	27	145
Spleen		230	140	57	482
Red marrow	46	140	50	65	37
Ovaries	26	150			21
Testes	22				16
Blood			75-100	77	
Skeleton			13		
Kidneys		90			
Total body	23	30	5-35	23	24

(1) Feller PA, Grossman LW, Sodd VJ, Kereiakes JG: Dosimetry of Fe-52 and Fe-59. To be published (1979)

(2) Hine GJ, Johnston RE: Absorbed dose from radionuclides. J Nucl Med 11:468-469, 1970 (letter)

(3) Garby L, Nosslin B: Radiation Doses from Radioactive Substances in Medical Use. Stockholm, Swedish National Institute of Radiation Protection, 1969 (a compilation)

(4) Cloutier RJ, Edwards CL, Snyder WS: Radiation doses from radionuclides in the blood. In CONF-691212, 1970, pp 325-345

(5) This article

1017667

TABLE III

Absorbed Dose/Microcurie-hr

(rad/μCi-hr)

Fe-59

SOURCE / TARGET	LIVER	SPLEEN	MARROW	TOTAL BODY
LIVER	3.4×10^{-4}	8.9×10^{-6}	8.4×10^{-6}	1.8×10^{-5}
SPLEEN	8.8×10^{-6}	2.4×10^{-3}	8.4×10^{-6}	1.7×10^{-5}
R. MARROW	8.2×10^{-6}	9.0×10^{-6}	2.0×10^{-4}	1.6×10^{-5}
OVARIES	7.2×10^{-6}	4.8×10^{-6}	2.4×10^{-5}	1.7×10^{-5}
TESTES	1.8×10^{-6}	1.0×10^{-6}	2.8×10^{-6}	1.7×10^{-5}
TOTAL BODY	1.7×10^{-5}	1.7×10^{-5}	1.6×10^{-5}	1.5×10^{-5}

Fe-55

SOURCE / TARGET	LIVER	SPLEEN	MARROW	TOTAL BODY
LIVER	7.0×10^{-6}	1.4×10^{-15}	1.7×10^{-10}	1.8×10^{-7}
SPLEEN	1.4×10^{-15}	7.0×10^{-5}	3.1×10^{-10}	1.9×10^{-7}
RED MARROW	1.2×10^{-10}	1.4×10^{-11}	7.6×10^{-6}	1.8×10^{-7}
OVARIES	1.9×10^{-17}	1.9×10^{-19}	1.7×10^{-10}	1.9×10^{-7}
TESTES	4.3×10^{-29}	2.4×10^{-32}	4.9×10^{-12}	1.8×10^{-7}
TOTAL BODY	1.8×10^{-7}	1.8×10^{-7}	1.8×10^{-7}	1.8×10^{-7}

Fe-52

SOURCE / TARGET	LIVER	SPLEEN	MARROW	TOTAL BODY
LIVER	3.8×10^{-4}	6.0×10^{-6}	5.7×10^{-6}	1.6×10^{-5}
SPLEEN	5.6×10^{-6}	3.1×10^{-3}	4.7×10^{-6}	1.6×10^{-5}
RED MARROW	6.6×10^{-6}	7.0×10^{-6}	2.5×10^{-4}	1.6×10^{-5}
OVARIES	1.5×10^{-6}	5.2×10^{-6}	1.9×10^{-5}	1.6×10^{-5}
TESTES	6.0×10^{-7}	4.9×10^{-7}	2.4×10^{-6}	1.6×10^{-5}
TOTAL BODY	1.6×10^{-5}	1.6×10^{-5}	1.5×10^{-5}	1.4×10^{-5}

^{52m}Mn

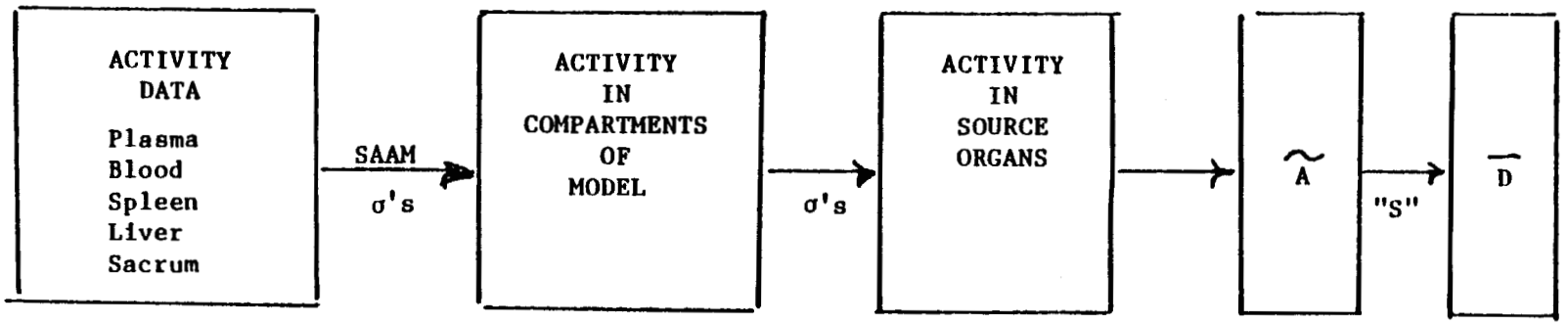
SOURCE / TARGET	LIVER	SPLEEN	RED MARROW	TOTAL BODY
LIVER	1.8×10^{-3}	1.8×10^{-5}	1.7×10^{-5}	6.3×10^{-5}
SPLEEN	1.7×10^{-5}	1.5×10^{-2}	1.5×10^{-5}	6.2×10^{-5}
RED MARROW	1.8×10^{-5}	1.8×10^{-5}	1.2×10^{-3}	6.1×10^{-5}
OVARIES	1.1×10^{-5}	1.4×10^{-5}	5.9×10^{-5}	6.6×10^{-5}
TESTES	2.4×10^{-6}	1.9×10^{-6}	5.1×10^{-6}	6.3×10^{-5}
TOTAL BODY	6.2×10^{-5}	6.2×10^{-5}	6.1×10^{-5}	5.8×10^{-5}

^{52}Mn

SOURCE / TARGET	LIVER	SPLEEN	RED MARROW	TOTAL BODY
LIVER	6.9×10^{-4}	2.6×10^{-5}	2.5×10^{-5}	4.4×10^{-5}
SPLEEN	2.5×10^{-5}	3.9×10^{-3}	2.3×10^{-5}	4.2×10^{-5}
RED MARROW	2.5×10^{-5}	2.7×10^{-5}	2.5×10^{-4}	4.0×10^{-5}
OVARIES	1.8×10^{-5}	1.7×10^{-5}	7.7×10^{-5}	4.3×10^{-5}
TESTES	4.5×10^{-6}	2.8×10^{-6}	8.2×10^{-6}	4.4×10^{-5}
TOTAL BODY	4.3×10^{-5}	4.3×10^{-5}	4.0×10^{-5}	3.7×10^{-5}

1017668

* Snyder, W. S., Ford, M. R., Warner, G. G., and Watson, S. B. "S", absorbed dose per unit cumulated activity for selected radionuclides and organs MIRD pamphlet No. 11, Soc. Nucl. Med., New York, October 1975.

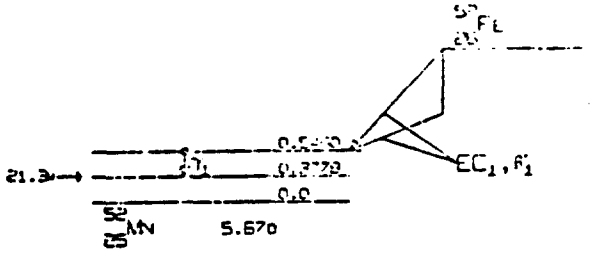


INFORMATION FLOW IN CALCULATION OF $\bar{D}$ FROM KINETIC DATA

1017669

IRON-52

ELECTRON CAPTURE AND BETA-PLUS DECAY



INPUT DATA

26 IRON 52 HALF LIFE = 8.30 HOURS

DECAY MODES- ELECTRON CAPTURE AND BETA PLUS

TRANSITION		MEAN NUMBER/ DISINTE- GRATION	TRANSITION ENERGY (MEV)	OTHER NUCLEAR DATA
ELECT CAPT	1	0.4220	1.8260	ALLOWED
GAMMA	1	1.0000	0.1668	M1, ALPHA(T) = 0.03740
BETA PLUS	1	0.5780	0.0040*	ALLOWED

*ENDPOINT ENERGY

REF.- NUCLEAR DATA B3-5,6-101 (1970).

OUTPUT DATA

26 IRON 52 HALF LIFE = 8.30 HOURS

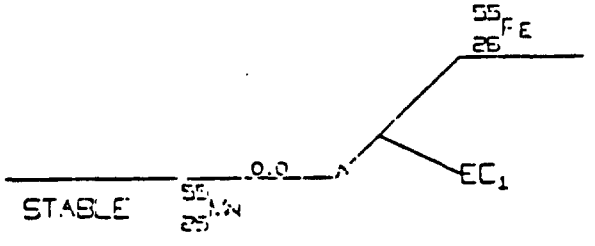
DECAY MODES- ELECTRON CAPTURE AND BETA PLUS

RADIATION		MEAN NUMBER/ DISINTE- GRATION n_i	MEAN ENERGY/ PARTICLE $\bar{E}_i$ (MeV)	EQUILIBRIUM DOSE CONSTANT Δ_i (g-rad/uCi-h)
GAMMA	1	0.9926	0.1680	0.3960
K INT CON ELECT		0.0073	0.1622	0.0025
K ALPHA-1 X-RAY		0.0071	0.0058	0.0008
K ALPHA-2 X-RAY		0.0039	0.0056	0.0004
K BETA-1 X-RAY		0.0011	0.0064	0.0001
KLL AUGER ELECT		0.2226	0.0052	0.0024
KLX AUGER ELECT		0.0527	0.0050	0.0005
LMM AUGER ELECT		0.0373	0.0035	0.0002
MXY AUGER ELECT		1.3e-10	0.0003	0.0001
BETA PLUS	1	0.5780	0.3404	0.4191
ANNIH. RADIATION		1.1560	0.5110	1.2582

DAUGHTER NUCLIDE, MANGANESE 52M IS RADIOACTIVE AND MAY CONTRIBUTE TO THE DOSE. BRANCHING TO 0.3776 MEV, 21.3 MINUTE HALF LIFE, ISOMERIC LEVEL IN MANGANESE-52 IS 1.00 PER DISINTEGRATION OF IRON-52.

IRON-55

ELECTRON CAPTURE DECAY



INPUT DATA

26 IRON 55 HALF LIFE = 2.70 YEARS

DECAY MODE- ELECTRON CAPTURE

TRANSITION		MEAN NUMBER/ DISINTE- GRATION	TRANSITION ENERGY (MEV)	OTHER NUCLEAR DATA
ELECT CAPT	1	1.0000	0.2310	ALLOWED

REF.- NUCLEAR DATA B3, NO. 1-4, JANUARY 1970.

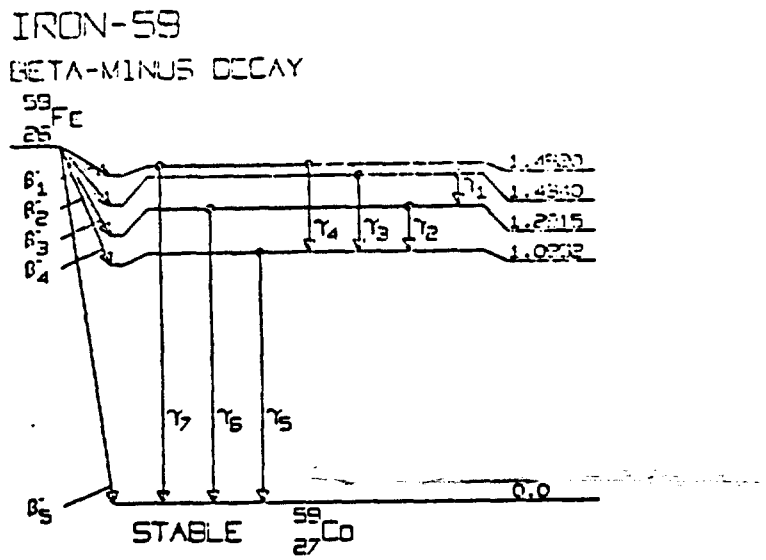
OUTPUT DATA

26 IRON 55 HALF LIFE = 2.70 YEARS

DECAY MODE- ELECTRON CAPTURE

RADIATION		MEAN NUMBER/ DISINTE- GRATION n_i	MEAN ENERGY/ PARTICLE $\bar{E}_i$ (MeV)	EQUILIBRIUM DOSE CONSTANT Δ_i (g-rad/uCi-h)
K ALPHA-1 X-RAY		0.1553	0.0055	0.0018
K ALPHA-2 X-RAY		0.0756	0.0055	0.0008
K BETA-1 X-RAY		0.0257	0.0063	0.0003
KLL AUGER ELECT		0.5155	0.0050	0.0054
KLX AUGER ELECT		0.1220	0.0048	0.0012
LMM AUGER ELECT		1.4907	0.0035	0.0017
MXY AUGER ELECT		3.1174	0.0003	0.0003

0179170



INPUT DATA

26 IRON 59 HALF LIFE = 45.0 DAYS

DECAY MODE- BETA MINUS

TRANSITION		MEAN NUMBER/ DISINTEGRATION	TRANSITION ENERGY (MEV)	OTHER NUCLEAR DATA
BETA MINUS	1	0.0011	0.0910*	ALLOWED
BETA MINUS	2	0.0122	0.1390*	ALLOWED
BETA MINUS	3	0.4609	0.2730*	ALLOWED
BETA MINUS	4	0.5228	0.4670*	ALLOWED
BETA MINUS	5	0.0030	1.5730*	2ND FORBIDDEN
GAMMA	1	0.0098	0.1420	M1, AK(T) = 0.0143 AL(T) = 0.00116
GAMMA	2	0.0295	0.1922	M1, AK(T) = 0.00665 AL(T) = 0.000535
GAMMA	3	0.0024	0.3347	M1, AK(T) = 0.00172 AL(T) = 0.000139
GAMMA	4	0.0002	0.3810	
GAMMA	5	0.5549	1.0990	E2, AK(T) = 0.000154 AL(T) = 0.000313
GAMMA	6	0.4412	1.2920	E2, AK(T) = 0.000107 AL(T) = 0.000009
GAMMA	7	0.0009	1.4810	

*ENDPOINT ENERGY

REF.- LEGRAND, J. ET AL. NUCL. PHYS. A142, 63 (1970).

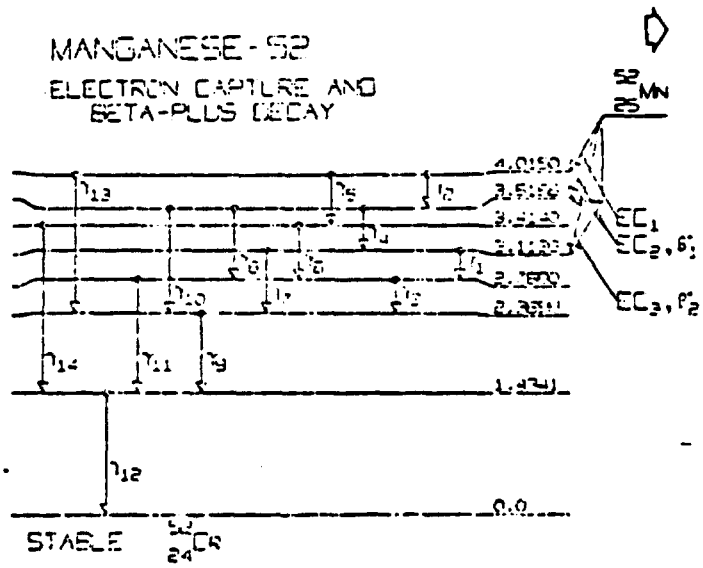
OUTPUT DATA

26 IRON 59 HALF LIFE = 45.0 DAYS

DECAY MODE- BETA MINUS

RADIATION		MEAN NUMBER/ DISINTEGRATION n_i	MEAN ENERGY/ PARTICLE $\bar{E}_i$ (MeV)	EQUILIBRIUM DOSE CONSTANT Δ_i (g-rad/ μCi-h)
BETA MINUS	2	0.0122	0.0381	0.0009
BETA MINUS	3	0.4609	0.0809	0.0793
BETA MINUS	4	0.5228	0.1496	0.1666
BETA MINUS	5	0.0030	0.6396	0.0045
GAMMA	1	0.0096	0.1420	0.0029
GAMMA	2	0.0292	0.1922	0.0119
GAMMA	3	0.0023	0.3347	0.0017
GAMMA	4	0.0002	0.3810	0.0001
GAMMA	5	0.5548	1.0990	1.2997
K INT CON ELECT		0.0000	1.0912	0.0000
GAMMA	6	0.4411	1.2920	1.2148
K INT CON ELECT		0.0000	1.2942	0.0001
GAMMA	7	0.0009	1.4810	0.0028

1017671



INPUT DATA

25 MANGANESE 52 HALF LIFE = 5.67 DAYS

DECAY MODES- ELECTRON CAPTURE AND BETA PLUS

TRANSITION		MEAN NUMBER/ DISINTE-GRATION	TRAN-SITION ENERGY (MEV)	OTHER NUCLEAR DATA
ELECT CAPT	1	0.0059	0.6950	ALLOWED
ELECT CAPT	2	0.6342	1.0940	ALLOWED
ELECT CAPT	3	0.6001	1.5460	ALLOWED
GAMMA	1	0.0097	0.3457	E2, AK= 0.00397
GAMMA	2	0.0006	0.3985	
GAMMA	3	0.0024	0.3985	M1, AK/TI = 0.000806
GAMMA	4	0.0102	0.5028	M1, AK/TI = 0.000481
GAMMA	5	0.0049	0.6006	
GAMMA	6	0.0046	0.6470	M1, AK/TI = 0.000275
GAMMA	7	0.9003	0.7442	E2, AK=0.000324 K/(L+M)= 8.50
GAMMA	8	0.0343	0.8484	M1, AK=0.000185
GAMMA	9	0.9534	0.9356	E2, AK=0.000153 K/(L+M)= 8.90
GAMMA	10	0.0503	1.2470	M1, AK=0.000565
GAMMA	11	0.0663	1.3337	E2, AK=0.000726
GAMMA	12	1.0000	1.4341	E2, AK=0.000567
GAMMA	13	0.0004	1.6450	
GAMMA	14	0.0002	1.9790	
BETA PLUS	1	0.0000	0.0720*	ALLOWED
BETA PLUS	2	0.2997	0.5760*	ALLOWED

*ENDPOINT ENERGY

REF.- NUCLEAR DATA B3, NO. 5-6, APRIL 1970.

OUTPUT DATA

25 MANGANESE 52 HALF LIFE = 5.67 DAYS

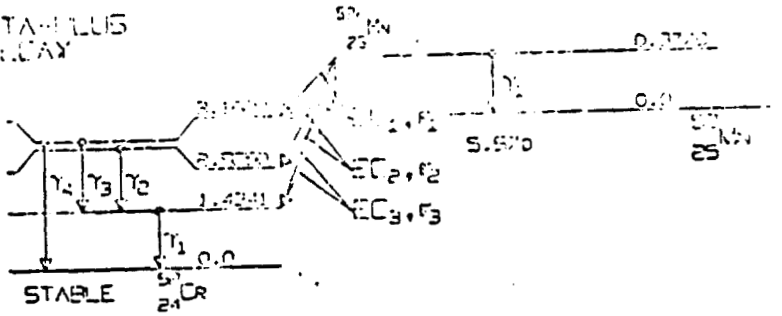
DECAY MODES- ELECTRON CAPTURE AND BETA PLUS

RADIATION		MEAN NUMBER/ DISINTE-GRATION n_i	MEAN ENERGY/ PAR-TICLE $\bar{E}_i$ (MeV)	EQUI-LIBRIUM DOSE CONSTANT Δ_i (g-rad/ μCi-h)
GAMMA	1	0.0097	0.3457	0.0071
GAMMA	2	0.0006	0.3985	0.0005
GAMMA	3	0.0023	0.3985	0.0020
GAMMA	4	0.0101	0.5028	0.0109
GAMMA	5	0.0049	0.6006	0.0041
GAMMA	6	0.0046	0.6470	0.0026
GAMMA	7	0.9003	0.7442	1.4766
K INT CON	ELECT	0.0002	0.7362	0.0004
GAMMA	8	0.0342	0.8484	0.0219
GAMMA	9	0.9532	0.9356	1.0947
K INT CON	ELECT	0.0001	0.9296	0.0002
GAMMA	10	0.0502	1.2470	0.1335
GAMMA	11	0.0662	1.3337	0.1319
GAMMA	12	0.9994	1.4341	1.0930
K INT CON	ELECT	0.0005	1.4282	0.0017
GAMMA	13	0.0004	1.6450	0.0014
GAMMA	14	0.0002	1.9790	0.0011
K ALPHA-1	X-RAY	0.0997	0.0054	0.0011
K ALPHA-2	X-RAY	0.0507	0.0054	0.0005
K BETA-1	X-RAY	0.0149	0.0059	0.0002
KLL AUGER	ELECT	0.3786	0.0046	0.0035
KLX AUGER	ELECT	0.0470	0.0053	0.0005
LMM AUGER	ELECT	1.0575	0.0035	0.0011
MXY AUGER	ELECT	2.2239	0.0030	0.0017
BETA PLUS	2	0.2997	0.2414	0.1941
ANNIH. RADIATION		0.5994	0.5110	0.4574

1017672

MANGANESE-52M

ELECTRON CAPTURE, BETA-PLUS AND ISOMERIC LEVEL DECAY



INPUT DATA

25 MANGANESE 52M HALF LIFE = 21.3 MINUTES

DECAY MODES- ELECTRON CAPTURE, ISOMERIC LEVEL AND BETA PLUS

TRANSITION		MEAN NUMBER/ DISINTEGRATION	TRANSITION ENERGY (MEV)	OTHER NUCLEAR DATA
ELECT CAPT	1	0.0006	1.9330	ALLOWED
ELECT CAPT	2	0.0001	2.2300	ALLOWED
ELECT CAPT	3	0.0139	3.6530	ALLOWED
GAMMA	1	0.9793	1.4341	E2, AR=0.000056
GAMMA	2	0.0007	1.5308	M1, AR(T) = 0.000050
GAMMA	3	0.0020	1.7280	M1, AR(T) = 0.000040
GAMMA	4	0.0002	3.1600	E2, AR(T) = 0.000015
BETA PLUS	1	0.0015	0.4110*	ALLOWED
BETA PLUS	2	0.0005	1.1030*	ALLOWED
BETA PLUS	3	0.9631	2.6310*	ALLOWED
GAMMA	1	0.0198	0.3778	E4, K/(L+M)= 7.20 AR(T) = 0.0570

*ENDPOINT ENERGY

REF.- NUCLEAR DATA B3-5,6-99 (1970).

OUTPUT DATA

25 MANGANESE 52M HALF LIFE = 21.3 MINUTES

DECAY MODES- ELECTRON CAPTURE, ISOMERIC LEVEL AND BETA PLUS

RADIATION		MEAN NUMBER/ DISINTEGRATION n_i	MEAN ENERGY/ PARTICLE $\bar{E}_i$ (MeV)	EQUILIBRIUM DOSE CONSTANT A_i (g-rad/ uCi-h)
GAMMA	1	0.9793	1.4341	2.9931
K INT CON ELECT		0.0000	1.4282	0.0001
GAMMA	2	0.0007	1.5308	0.0025
GAMMA	3	0.0020	1.7280	0.0074
GAMMA	4	0.0002	3.1600	0.0018
BETA PLUS	1	0.0015	0.3857	0.0013
BETA PLUS	2	0.0005	0.4727	0.0006
BETA PLUS	3	0.9631	1.1712	2.4028
ANNIH. RADIATION		1.9306	0.5110	2.1014
GAMMA	1	0.0190	0.3778	0.0153
K INT CON ELECT		0.0007	0.3712	0.0005

DAUGHTER NUCLIDE, MANGANESE 52 IS RADIOACTIVE AND MAY CONTRIBUTE TO THE DOSE.

1017673

SERIAL THYROID IODINE CONTENT IN HYPERTHYROID PATIENTS TREATED WITH RADIOIODINE

G.S. Lee, J.A. Patton, and A.B. Brill

Vanderbilt University Medical Center
Nashville, Tennessee

Methods for measurement of the thyroidal iodine pool have been sought for many years. Most have used radioactive iodine and isotope dilution techniques to estimate thyroid iodine content (1). This technique measures only exchangeable iodide and therefore, may not be accurate, especially in patients with acute disorders of the thyroid in which case steady state assumptions are invalid. Neutron activation has also been used in animals (and a few patients) as a technique for measuring thyroidal iodine content (2). X-ray fluorescence (XRF) techniques have been used for several years as a method for in vivo determiners of thyroid iodine content with significantly lower radiation dose to the gland (3,4,5) then when neutron activation or radioactive iodine is used. Several x-ray fluorescence systems have been developed for imaging the stable iodine distribution within the thyroid. The technique has been shown to yield quantitative results which assist in differentiating between malignant and benign thyroid nodules (6),

X-ray fluorescence scanning involves gamma irradiation of the thyroid by a collimated external source of ($\sim$ 60 Kev from Am-241) and counting (high resolution semiconductor detector) the characteristic x-rays of iodine that result from the presence of iodine within the viewed radiation field. The system is mounted on a rectilinear scanner and produces an intensity-modulated photoplot corresponding to regional iodine content. Since the number of characteristic x-rays detected at a point in the scan is proportional to the amount of iodine present at that point, it is possible to calibrate the data collection process and to quantitate the amount of iodine present in the total gland or selected regions (6). We have also previously reported the utility of quantitative

4L9L10

fluorescence scanning in the differentiation of benign and malignant solitary nodules that are "cold" on radioisotope scans on the basis of the iodine content of the nodule(6).

The present investigation was undertaken to determine the possible utility of thyroid iodine content (TIC) measurements as a diagnostic predictor of I-131 dose and the outcome of radioiodine therapy in patients with hyperthyroidism. Of special interest was the determination of those patients that were at high risk of becoming hypothyroid. To this end, we have studied 60 patients with hyperthyroidism who were studied by fluorescence scanning before I-131 therapy and serially after therapy.

Methods:

Patients included in this study were consecutive patients who were referred to the Nuclear Medicine Division of Vanderbilt University Medical Center for radioiodine therapy after a diagnosis of hyperthyroidism. This diagnosis was confirmed by multiple tests which included radioimmunoassays of thyroxine, tri-iodothyronine and thyrotrophin and occasionally stimulation tests with thyrotrophin-releasing hormone.

Thyroid iodine content (TIC) was measured by quantitative x-ray fluorescence scanning. The amount of I-131 administered was calculated to give a radiation dose of 7,000 rads to the thyroid. The thyroid weight in the calculations was based on estimation of gland size from measurements made with the quantitative x-ray fluorescence and radioisotope scan images as well as by palpation.

The initial TIC measurement was obtained just prior to the radioiodine therapy. Thereafter, measurements were made monthly for the first three months, then every 6-8 weeks for the first year. (Measurements of iodine content were not accurate during the one month post-therapy period because the xenon x-rays associated with I-131 decay could not be resolved from the iodine x-rays, and hence no TIC data are available during that time interval.) At each

0116715

follow-up visit, a clinical assessment of the thyroid state was performed and blood was drawn for radioimmunoassays of thyroxine, tri-iodothyronine and thyrotrophin. Staff endocrinologists supervised the follow-up and medical management of the patients without knowledge of the thyroid iodine content data on individual patients. Follow-up was terminated in those patients who were diagnosed as being hypothyroid, when they were placed on replacement therapy.

Results:

Numbers, Sex, Age:

Sixty hyperthyroid patients were treated with radioiodine over a period of 18 months. Of these, 48 returned for follow-up. Seven relapsed and were re-treated with drugs or radioiodine. Of these 60 cases, 50 were females and 10 were males and their ages ranged from 18 to 77 years with a mean of 45.7 years.

Initial Iodine Content:

The thyroid iodine content in a series of 33 normal euthyroid individuals was found previously to be 10.7 mg with a standard deviation of 4.8 mg (6).

The initial iodine contents before therapy are presented in Table 1 with patients grouped according to their clinical history. The means were significantly elevated, as expected from previous studies, except in those who had lost thyroid tissue mass from previous thyroid surgery or radioiodine therapy. The large values for the standard deviations reflects the wide range of values in each group. There was no significant difference between the mean TIC of the new hyperthyroid patients, i.e. those patients who had never received anti-thyroid drugs (methimazole or propylthiouracil).

Serial Iodine Content:

Serial changes in thyroid iodine content following therapy, have been analyzed based on; a) type of management and b) "clinical" or functional thyroid status at the end of followup. Followup ended (1) when the patients became hypothyroid and replacement therapy was begun, or (2) when the patients

0116176

relapsed and required retreatment, or (3) when they reached 12 months after radioiodine therapy and were clinically and biochemically euthyroid.

The serial iodine content measurements are expressed in two ways: a) as a percentage of the initial iodine content and b) as the actual value of iodine content in milligrams.

The 48 patients who returned for followup had received the following types of management:

A) I-131 therapy only -- 15 cases

B) Antithyroid drugs prior to I-131 therapy -- 3 cases

C) Antithyroid drugs post I-131 therapy -- 10 cases

D) Antithyroid drugs pre- and post - I-131 therapy -- 10 cases, and

E) Thyroid surger or I-131 therapy prior to present I-131 therapy -- 10 cases.

Figure 1 shows the results as considered from the type of management. All cases, irrespective of type of management showed a steep decline of iodine content to a nadir around the third month post-therapy and thereafter, they fluctuated at a low level of less than 5 mg. There was no significant difference between groups in behavior of iodine content except that the group who had had thyroid surgery started at a lower initial thyroid iodine content than the other 4 groups.

For "clinical" or functional state, diagnosis was confirmed by radioimmunoassays of thyroxine, tri-iodothyroinine and thyrotrophin. Permanent hypothyroidism was diagnosed in 17 cases within 12 months post-therapy and these patients were all put on replacement thyroxine by their physicians when that diagnosis was made. The diagnosis was based on the clinical evaluations and the results of the radioimmunoassays. Seven hyperthyroid patients relapsed, and were retreated with antithyroid drugs or another dose of I-131. Eight cases were labelled as euthyroid when, at 12 months after radioiodine therapy they were clinically and biochemically euthyroid.

1017677

Figure 2 shows the results with the patients grouped according to the clinical thyroid state induced by I-131 therapy in the first 12 months. The hypothyroid group had a lower level of iodine content throughout the time period, even at the initial measurement. These cases were examined further with respect to their lowest iodine content between the 2nd and 3rd months post-therapy.

An arbitrary level of 2 mg of iodine was chosen to separate the low TIC group from the remaining patients. Table II shows the TIC's in 43 patients who were followed for 1 year or more. Nine patients were lost to followup and hence were dropped from tabulations. Of the 43 patients, 22 had an iodine content of less than 2 mg while 21 had at least 2 mg of iodine in their glands. Eighty-two percent (18 patients) of those with an iodine content of less than 2 mg developed hypothyroidism within 12 months of radioiodine therapy. Only 14% (3 patients) of those who had greater than 2 mg thyroid iodine became hypothyroid within the first 12 months.

The euthyroid and hypothyroid cases were studied further with respect to their radioiodine uptake at 24 hours and thyroid size, based on size estimates from the fluorescence scan and palpation, since these values were used in the estimations of the amounts of radioiodine to be administered. Table III shows there is no significant difference ($p>.1$) in the 24 hour thyroid radioiodine uptake values; however, the patients who became hypothyroid had significantly lower estimated thyroid gland weight ($p<.025$). Iodine content versus gland weight before therapy is shown in Figure 3. These data show that iodine content varies directly with gland size (correlation coefficient = 0.649).

Figure 4 shows the relationship between TIC and values of thyroxine, triiodothyronine and thyrotrophin as obtained by radioimmunoassay. The range of normal values is included between the vertical and horizontal lines and the individual results are plotted.

0116-018

Low T3, low T4 or high TSH values are associated with low TIC. Normal T3, T4 and TSH levels occur in the presence of low or normal TIC values. On the contrary, with high T3 or T4 levels (subnormal TSH levels are difficult to define) the TIC is unpredictable and can be low, normal or high. This is not surprising since the turnover and reutilization of iodine can be increased many times above the normal rate and may even produce hyperthyrod states in the presence of low TIC.

The best biochemical guide to the underlying functional state of the thyroid in the absence of protein or end-organ abnormalities, is the T4 value. Hence a corollary of the preceding paragraph is that in hyperthyroidism TIC can be normal, high or low; in euthyroidism it is either normal or low while in hypothyroidism it is nearly always low.

1017679

Discussion:

Initial Iodine Content:

Of the 34 hyperthyroid patients who had never received previous anti-thyroid therapy, 65% had a high initial iodine content and 32% were within the normal range of mean ± 1 SD. Similar findings have been reported by other investigators (7). Only 1 case showed a low initial iodine content for unexplained reasons. There was no evidence in this one case of co-existing thyroiditis or interference from drugs.

The 18 cases who received either propylthiouracil or methimazole prior to radioiodine therapy showed an initial thyroid iodine content that was not significantly different from the previously untreated new hyperthyroid group. The duration of drug therapy ranged from 2 weeks to 23 months at the time the TIC was measured initially. Figure 5 shows no correlation between duration of drug therapy and thyroid iodine content. It is known from early studies on rats that organic binding of iodine by the thyroid can be almost completely inhibited by thiouracil-like drugs whereas concentration of inorganic iodide was actually increased (8,9). Another factor could be that at the time of the initial fluorescence scan to measure iodine content, the patients had been off anti-thyroid medication at least 72 hours in order to prepare them for the therapy dose and the thyroid rapidly accumulated iodine during that time interval. Unfortunately, we have no data to test these hypotheses, but the latter seems very unlikely based on the large flow rates that would imply.

In a recent paper by Thrall, et al. (10) it was reported that patients with Grave's disease, who were medically treated for at least five months and were euthyroid, had significantly lower total iodine content than those who remained hyperthyroid. It was suggested that this can be used as a measure of response to medical therapy. This may be true; however, we have no serial

1017680

measurements of medically treated patients and therefore cannot comment on this observation.

Our serial measurements of patients who were medically treated and referred for radioiodine therapy are divided into two groups. In one group, patients were generally referred eight to twelve weeks after medical treatment by their physicians who preferred that they be in a euthyroid state prior to receiving radioiodine therapy. The second group was those who had received more prolonged medical therapy but were never adequately controlled.

Serial Iodine Content:

It is of interest that all cases, irrespective of initial iodine content and type of management prior to and after the radioiodine, showed a rapid acute loss of iodine in 2-3 months following the therapy dose. The thyroid was slow in recovering from this effect as seen by the fact that patients who were euthyroid 12 months post-therapy had a mean iodine content of only 3 mg (S.D. 1.7) at that time. It may be that the loss of iodine occurs even more rapidly than we were able to record, but measurements prior to 4 weeks after therapy dose could not be performed with this system because the x-rays from Xe-131 formed when I-131 decays, could not be separated from stable iodine x-rays.

With respect to the functional status of the thyroid, the means of the iodine content of the hypothyroid group were consistently lower throughout followup than for the hyperthyroid and euthyroid groups. Although the magnitude of the individual differences was not statistically significant, non parametric tests show that the overall effect is significant ($p<.05$).

Examining the course of TIC over the followup period, there appears to be a nadir around the 3rd month post-therapy. If the iodine content at this time is 2 mg or above, there appears only to be about a 14% risk of early hypothyroidism. Whereas if iodine content is below 2 mg, the risk rises to 82%. The measurement of TIC may allow selection of those patients who need a more careful and frequent evaluation during the first 12 months post-therapy.

0017681

In examining further the differences between the hypothyroid and the euthyroid group, the factors which affected the dose given, namely the 24 hour thyroid radioiodine uptake and thyroid gland weight, were studies. The 24 hour uptake mean of 54.2% in the group that was to become hypothyroid, and 61.5% in the euthyroid group were not significantly different. However, gland weight difference was statistically significant ($p<.015$) being 62.7 gm in the group that was to become hypothyroid and 93.8 gm in the euthyroid group. Gland size (as obtained from the fluorescent scan) was determined from the extent of the distribution of iodine. A two standard deviation above background criterion was used to localize the gland border. For glands with greater than 2 mgm iodine, size estimates were felt to be reliable. Only 1 person found to be in the hypothyroid group had an initial low iodine content (3.3 mg); all the others had 6 mg or more and the estimate of their thyroid gland size was felt to be reasonably accurate.

Although clinical experience suggests that there is a higher incidence of hypothyroidism post- I-131 therapy in patients with small glands, it is surprising that size, per se, should affect outcome of therapy since the therapy dose given takes account of gland size. It may be that radiation effect and gland size do not have a simple linear relationship. It may be that the larger glands tend to be nodular and contain tissues of heterogeneous radio-sensitivity. However, clinically no difference was noted in nodularity in our two groups. One in 8 of the euthyroid goiters was recorded as nodular while in the hypothyroid group 2 out of 17 were noted to be nodular. However, it is well known that nodules may not be palpable clinically. Some glands labelled as smooth clinically are found to be cacroscopically nodular at surgery and clinically simple nodules are also not commonly found to be multinodular at surgery.

1017682

Conclusions:

1. Following radioiodine therapy of hyperthyroidism, there is a rapid fall of thyroidal iodine content which stays at low levels for long durations, i.e. even 12 months after I-131 therapy in patients who are clinically euthyroid at that time. This occurs irrespective of initial thyroid iodine content and type of thyroid management the patient receives pre- or post-radioiodine therapy.

2. At the nadir of the iodine content curve, which occurs around the 3rd month post-therapy, the chance of early hypothyroidism (within 12 months) is about 80% if thyroid iodine content is less than 2 mg, but only 14% if thyroid iodine content is 2 mg or more. Patients with TIC of 2 mgm or less should be followed very closely or put on prophylactic replacement therapy with thyroid hormone.

3. The risk of early hypothyroidism is higher if thyroid gland size is 60 gm or less.

4. Though a low iodine content is generally present in hypothyroid states, the converse is not true, as there are many exceptions in patients with hyperthyroid functional states. Thus, on occasion, thyroid function may be hyperactive or normal in the presence of a low thyroid iodine content.

1017683

REFERENCES

1. Riviere, R., Comar, D., Kellershohn, C.: A comparative analysis of the curves of the iodine specific activity determined in man throughout long period studies, in the different compartments of the thyroid metabolic system. Current Topics in Thyroid Research, Academic Press, New York, 1965, 114.

2. Lenihan, J.M.A., Comar, D., Riviere, R., and Kellershohn, C.: Estimating thyroid iodine by activation analysis in vivo. J. Nuc. Med. 9: 110-115 1968.

3. Edholm, P., Jacobson, B.: Quantitative determination of iodine in vivo. Acta. Radiol. 52: 337-346, 1959.

4. Heedman, P., Jacobson, B.: Thyroid iodine determination by x-ray spectrophotometry. J. Clin. Endocrinol. Metab., 24: 246-252, 1964.

5. Hoffer, P.B., Jones, W.B., Crawford, R.B., et al.: Fluorescent thyroid scanning: A new method of imaging the thyroid. Radiology 90: 342-344, 1968.

6. Patton, J.A., Hollifield, J.W., Brill, A.B., et al.: Differentiation between malignant and benign solitary thyroid nodules by fluorescent scanning. J. Nuc. Med. 17: 17-21, 1976.

7. Hoffer, P.B., Bernstein, J. and Gottschalk, A.: Clinical results in fluorescent thyroid scanning. Semiconductor Detectors in the Future of Nuclear Medicine, Society of Nuc. Med., N.Y., 1971, p.233.

8. Taurog, A., Chaikoff, I.L., and Feller, D.D.: The mechanism of iodine concentration by the thyroid gland: its non-organic iodine-binding capacity in the normal and propylthiouracil-treated rat. J. Biol. Chem. 1947, 171, 198.

9. Vanderlaan, J.E., and Vanderlaan, W.P.: The iodine concentrating mechanism of the rat thyroid and its inhibition by thiocyanate. Endocr. 1947, 40, 403.

10. Thrall, J.H. et al.: Quantitative thyroid fluorescent scanning: technique and clinical experience. Am. J. Roentgenol. 130: 517-522, 1978.

1017684

TABLE I

INITIAL IODINE CONTENT

GROUP	NO. CASES	MEAN IODINE CONTENT	STD. DEV.	SIGNIFICANCE
NEW HYPERTHYROIDS	34	24.58 MG.	17.78	<.005
DRUG TREATED HYPERTHYROIDS	18	23.71 MG.	24.89	<.005
PREVIOUS ^{131}I THERAPY	4	16.30 MG.	11.66	<.05
PREVIOUS SURGERY	3	13.10 MG.	14.70	N.S.
PREVIOUS ^{131}I OR SURGERY AND DRUGS AT PRESENT	5	8.46 MG.	4.59	N.S.
EUTHYROID NORMALS	33	10.70 MG.	4.80	---

SIGNIFICANCE IMPLIES P-VALUES AS COMPARED TO EUTHYROID NORMALS.

N.S. = NO SIGNIFICANCE.

1017685

TABLE II

RELATIONSHIP OF LOW IODINE CONTENT TO EARLY HYPOTHYROIDISM

IODINE CONTENT	NO. HYPOTHYROID	NO. EUTHYROID	TOTAL
< 2 MG.	18	4	22
≥ 2 MG.	3	18	21

DATA PRESENTED ARE TICs IN 43 PATIENTS WHO WERE FOLLOWED FOR ONE YEAR OR MORE. NINE PATIENTS WERE LOST TO FOLLOW-UP AND HENCE WERE DROPPED FROM THE TABULATION.

1017686

TABLE III

24 HOUR UPTAKE AND GLAND WEIGHT IN EUTHYROID AND HYPOTHYROID CASES

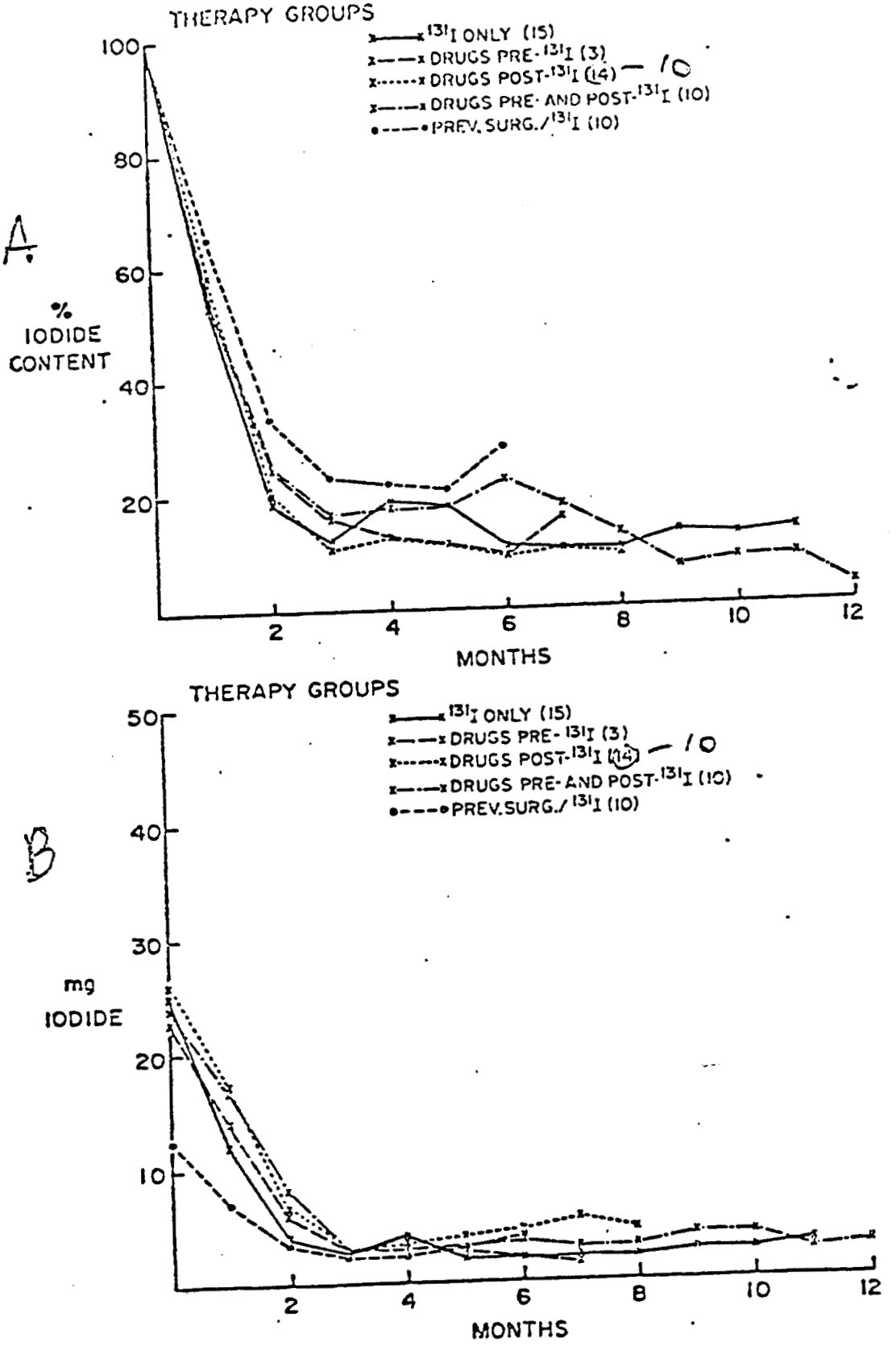
		24 HOUR UPTAKE(%)		GLAND WEIGHT(GRAMS)	
	NO.	MEAN	STD. DEV.	MEAN	STD. DEV.
EUTHYROID	8*	61.5	12.5	93.8	38.7
HYPOTHYROID	17+	54.2	13.8	62.7	28.3

* 1 HAD CLINICALLY NODULAR GLAND

+ 2 HAD CLINICALLY NODULAR GLANDS

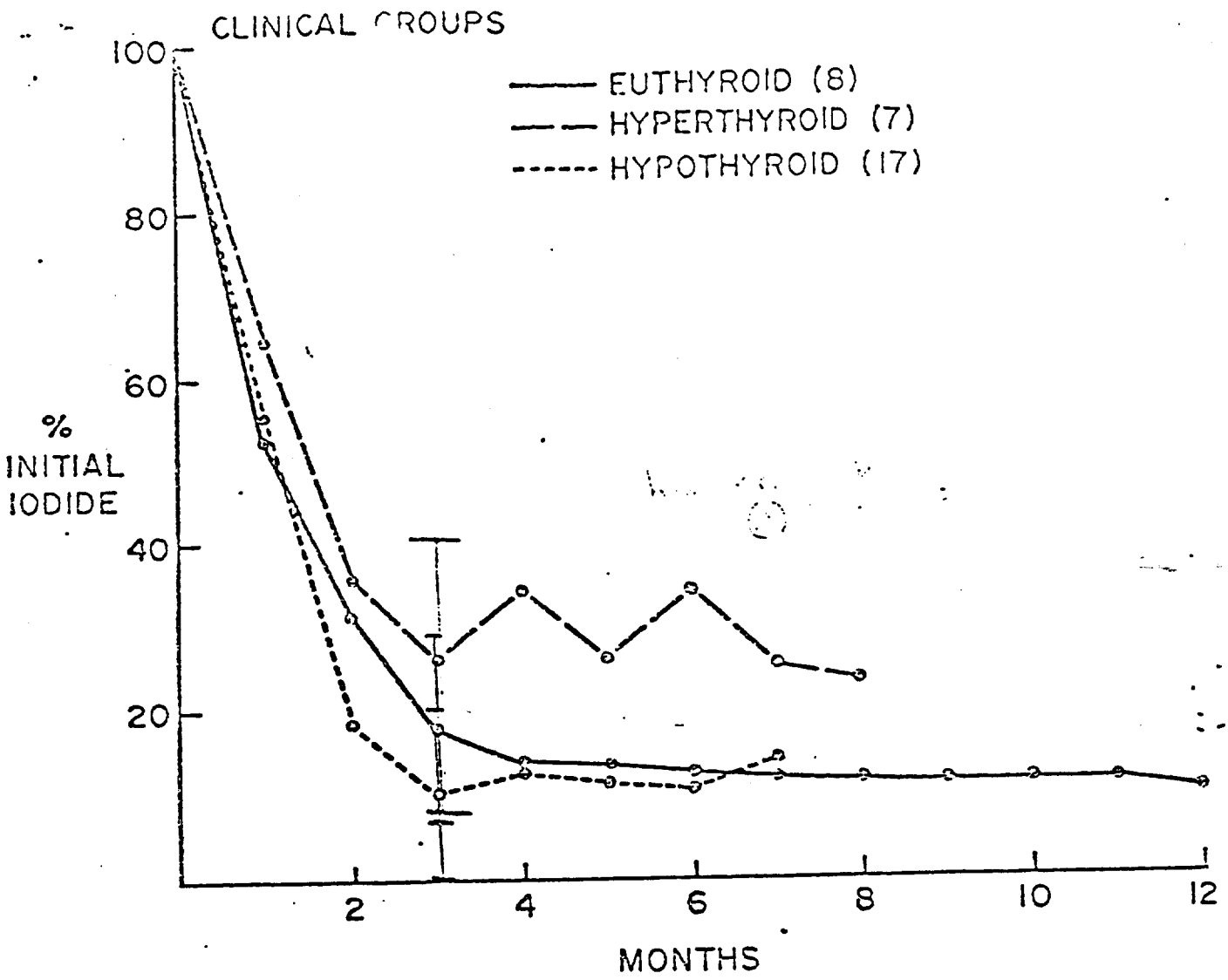
MEANS OF GLAND WEIGHTS ARE SIGNIFICANTLY DIFFERENT ($P < .025$).

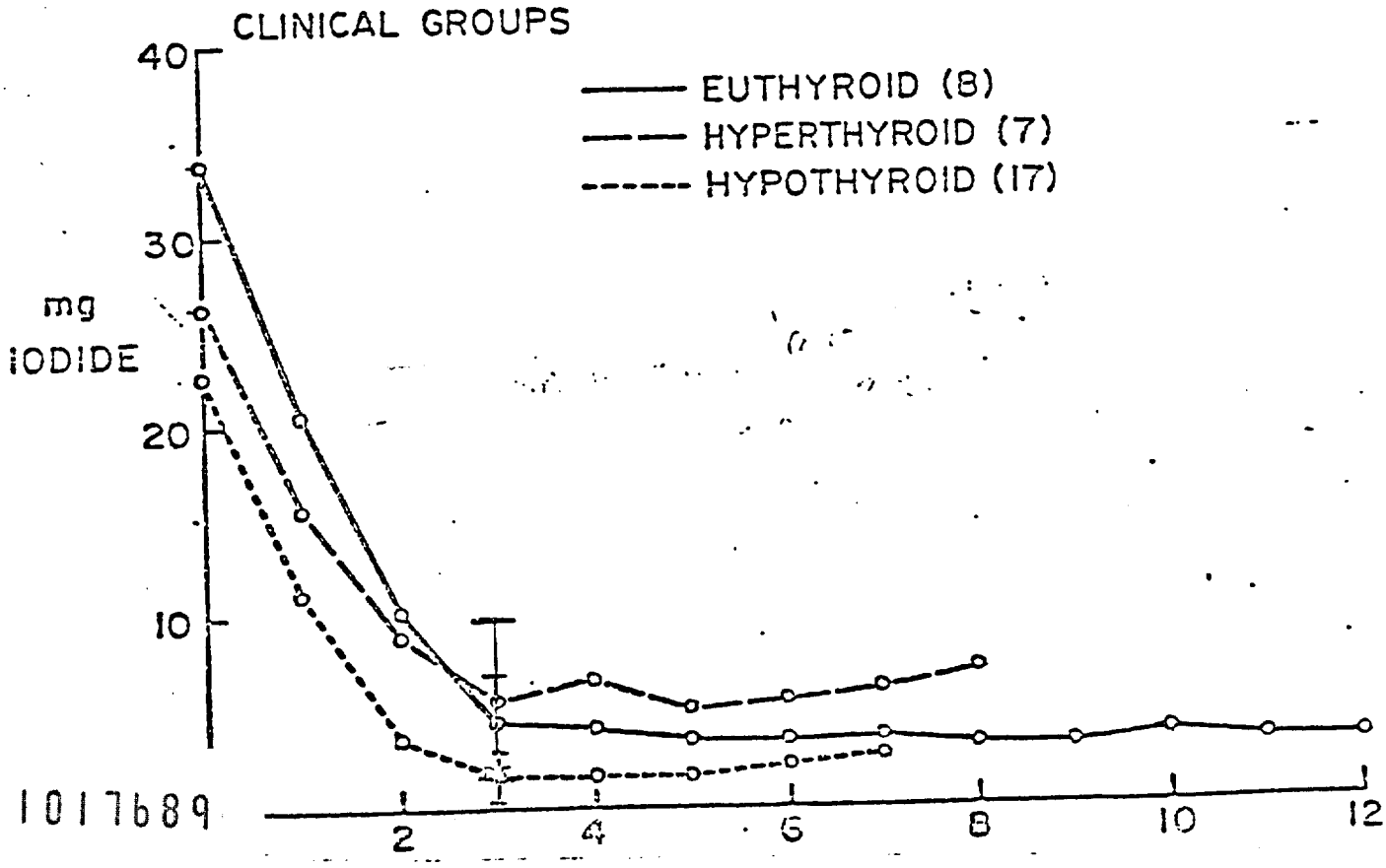
1017687



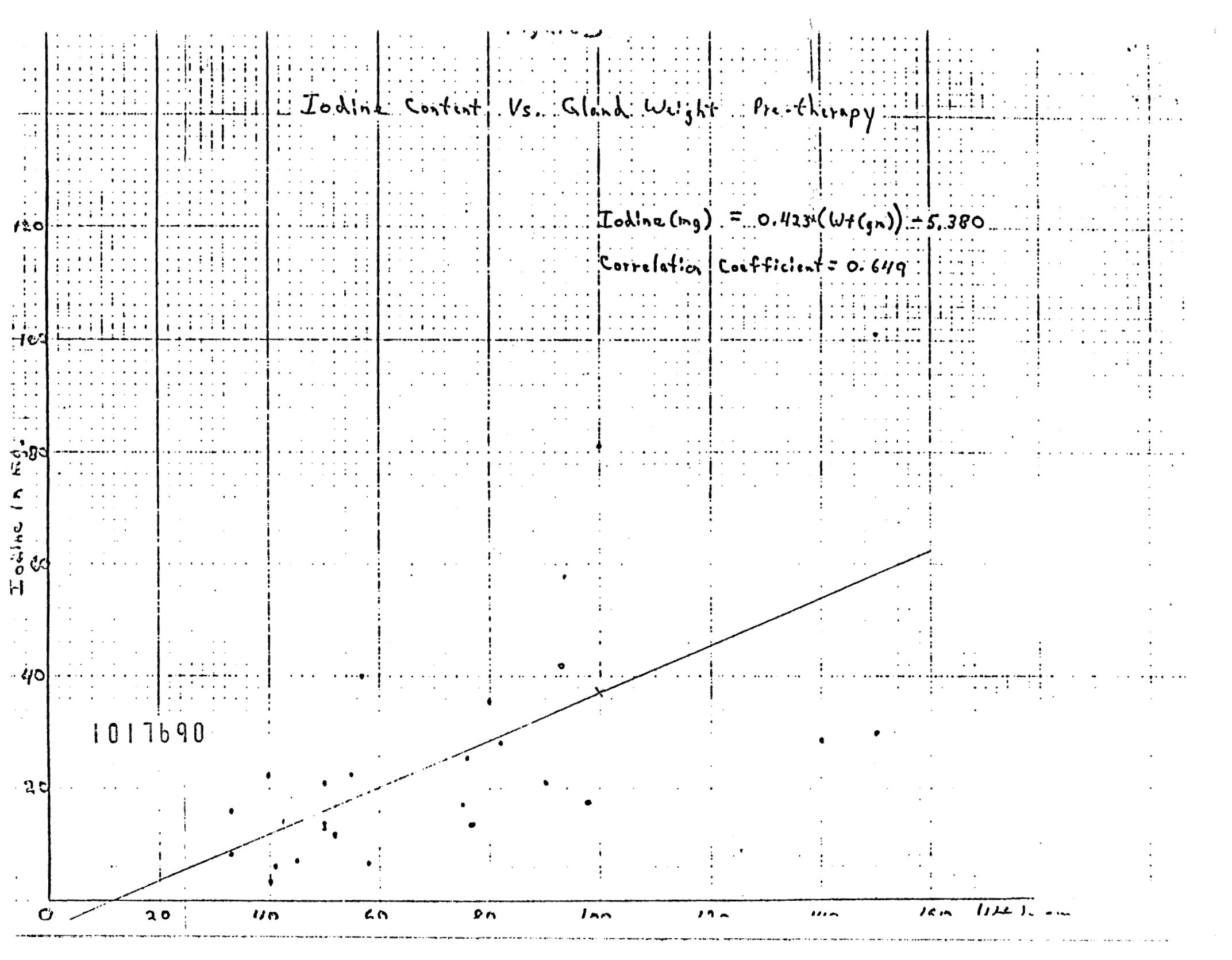
1017688

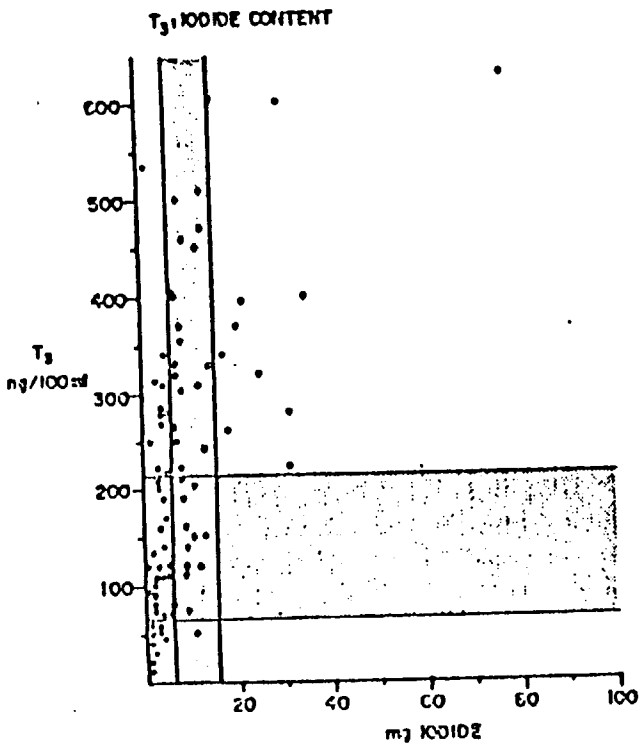
Figure 1

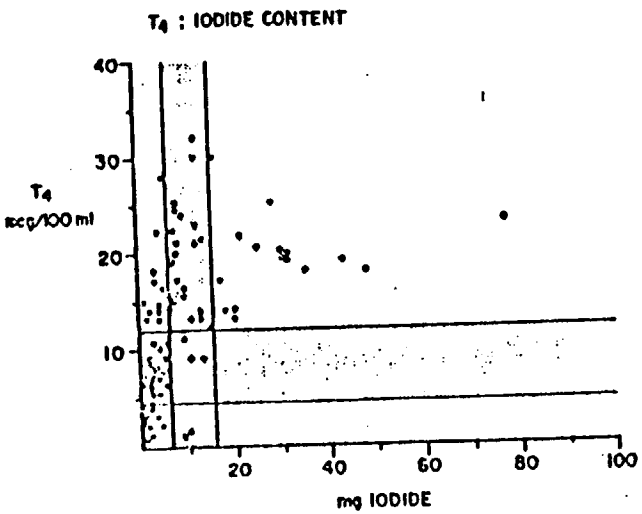

CLINICAL GROUPS
EUTHYROID (8)
HYPERTHYROID (7)
HYPOTHYROID (17)
% INITIAL IODIDE
100
80
60
40
20
2
4
6
8
10
12
MONTHS


CLINICAL GROUPS
EUTHYROID (8)
HYPERTHYROID (7)
HYPOTHYROID (17)
mg IODIDE
40
30
20
10
2
4
6
8
10
12
MONTHS

1017689


Iodine Content Vs. Gland Weight Pre-therapy
Iodine (mg) = 0.423*(Wt(gm)) + 5.380
Correlation Coefficient = 0.649
Iodine (mg)
0
20
40
1017690





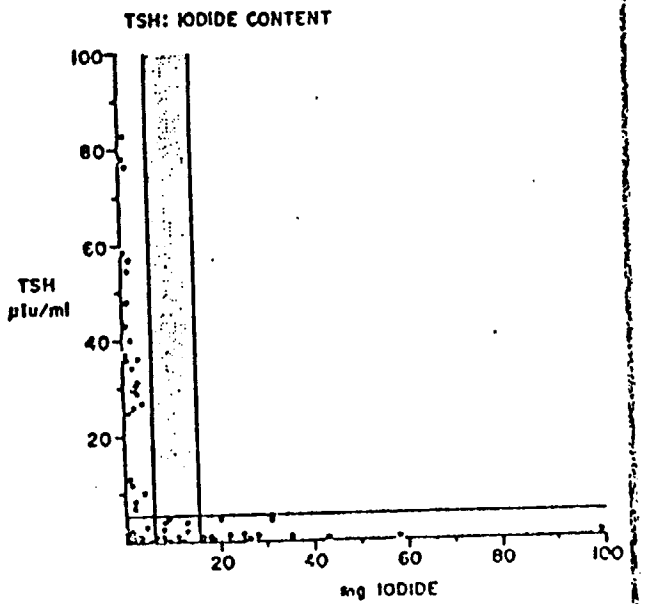


Figure 4

1017691

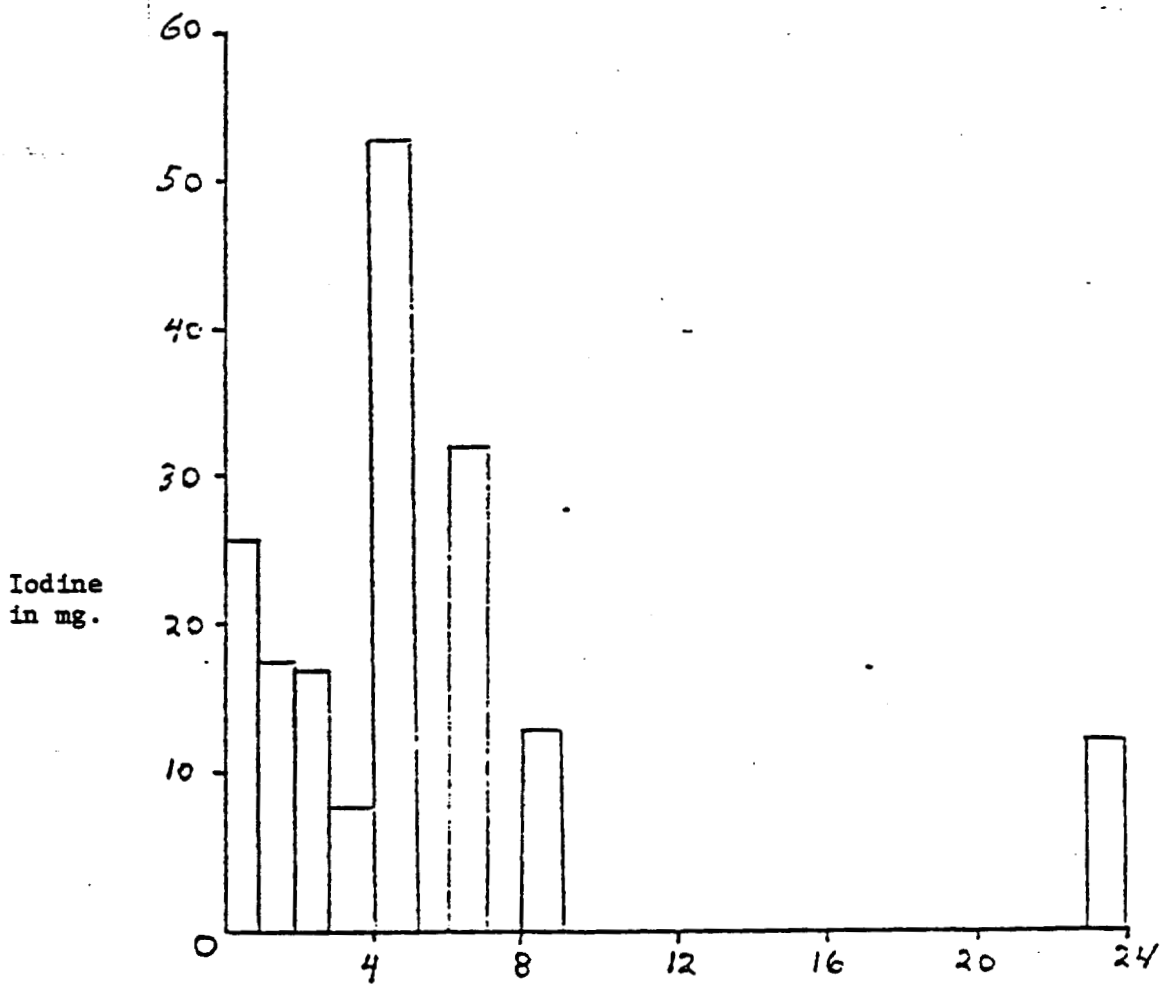


Fig. 5. Iodine content vs. duration of drug therapy prior to I-131 therapy

ERDA

Progress Report

Radioisotope Studies Utilizing a Low Level Whole Body Counter and Clinical Applications of Activation Analysis

July 31, 1978

Prinicpal Investigator

A. B. Brill, M.D., Ph.D.

Vanderbilt University

Medical Center

Nashville, TN 37232

APPROVED FOR RELEASE OR PUBLICATION - O.R. PATENT GROUP BY.... DATE....

1017693

Table of Contents

	Page
V. Scientific Scope	1
A. Specific Dosimetry Projects	1
1. Comparative Dosimetry of Iodocholesterol Compounds	1
2. Iron-59 and In-111 Dosimetry in Abnormal Human Subjects	15
3. Dosimetry of Intraperitoneally Administered P-32 Colloid	25
4. Evaluation of the Standard Man Model for Dosimetry Calculations--Comparison with Laboratory Measurements	30
5. Radiation Sensitivity of the Thyroid During I-131 Therapy	31
6. Nuclear Power Reactor--Environmental Monitoring	37
7. Distribution and Excretion Studies of Two Different Formulations of Commercial Lung Imaging Agents	38
8. Organ Distribution and Excretion of Technetium-99m-Sn-Methylene Diphosphonate	47
B. Supporting Systems Development	56
1. Hardware	56
a. Microprocessor Controlled Quantitative Scanner	56
b. Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies	57
2. Software	60
a. Acquisition/Reconstruction/Display of Tomographic Data	60
b. Sharing Efforts	66
i. Simulation and Modeling	66
ii. Sharing of Computer Programs in Nuclear Medicine	67

1.017694

A. Specific Dosimetry Projects

1. Comparative Dosimetry of Iodocholesterol Adrenal Scanning Agents

The development of I-131-19 iodocholesterol (19IC) as an adrenal scanning agent by Beierwaltes and colleagues at the University of Michigan provided an important tool for diagnosing and localizing adrenal disease. Unfortunately, photon densities are low and significant radiation doses are associated with the procedure.

In 1974, we carried out studies in 24 abnormals (adrenal disease) and 6 normals to measure the time-retention kinetics and associated radiation dose for 19IC. The results of this work were included in an earlier report. Since that time it has become apparent that the material obtained from the Pheonix Laboratories was contaminated with varying amounts of a second iodocholesterol compound, namely the ^{131}I-6-iodo methyl norcholesterol (6NC). These two compounds have now been separated, and Searle is planning to distribute the 19IC, while Phoenix Lab is preparing to distribute 6NC for adrenal visualization studies.

Previously we carried out studies on approximately 25 patients with various adrenal disorders using the Searle 19IC agent with approximately 10 of these patients having repeated studies after being placed on medical therapy. The results of the organ distribution measurements were presented in last year's report (ORO-2401-94) and are included in summary form in Appendix I .

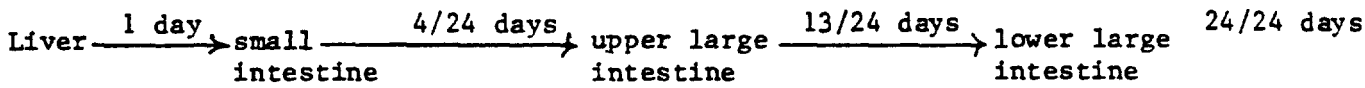
In last year's report we presented preliminary results with a new 6NC compound. We now present the final results of this work and its comparison with the 19IC compound. Each patient receiving the 6NC agent had been studied earlier with the Searle 19IC agent. The improvement of the diagnostic quality of the adrenal images was significant.

The following two sections detail the biological data and develop the comparison of the organ distributions and corresponding dose estimates for the two compounds.

1017695

I. ^{131}I-19-Iodocholesterol

Previous dose estimates have been made using the model of cholesterol kinetics proposed by Bernard and Hayes. The model (shown below) is a catenary compartmental model which assumes instantaneous uptake of the material in the liver with a unidirectional flow in sequence through the small intestine first and then through the large intestine exiting in the feces. The model assumes no reflux, retention or transfer of activity across the intestine wall.



Utilizing the data presented in Appendix I, we have substantiated this model. In Figure 1, we have generated the liver and integrated entire G.I. tract activity curves. The curves were generated assuming the liver and right upper quadrant, mid G.I., and the rectum at all other measurements constituted integrated G.I. activity. The resulting curves showed amazingly good agreement with the model prediction. The liver was found to have an uptake of approximately 72% with a monoexponential release of the activity with a half-life of approximately 1 day. The G.I. activity was observed to have a delayed peak occuring at day 1 with a subsequent monoexponential decay of approximately 1.5 days.

The total body retention curve also corroborates the liver measurement by displaying exponential component with approximately a 2 day half-life and an intercept of approximately 70%. This is interpreted as the fraction of the material that is eliminated via the G.I. tract (72%). The remaining activity (28%) was assumed to be uniformly distributed in total body and eliminated via the urine with a biological half-life of 1.5 days.

The thyroid data was used to estimate an average uptake of $\sim$ 1%. It was assumed to have an effective half-life equal to the physical half-life.

The adrenal activity was taken to be 0.1%. These data were based upon surgical samples and were assumed to come from a normal sized gland of 16g. The effective half-life was also taken to be equal to the physical half-life. Having established the consistency of the model of the 19IC agent, the model was used to determine the following cumulative activities for the liver, small and large intestines as shown in Table 1.

The cumulative activity was then used along with nuclear data in Table 2 to generate the continuation of the penetrating and non-penetrating components of the absorbed dose. The results of these calculations are shown in Table 3.

1017696

19-IC

Figure 1

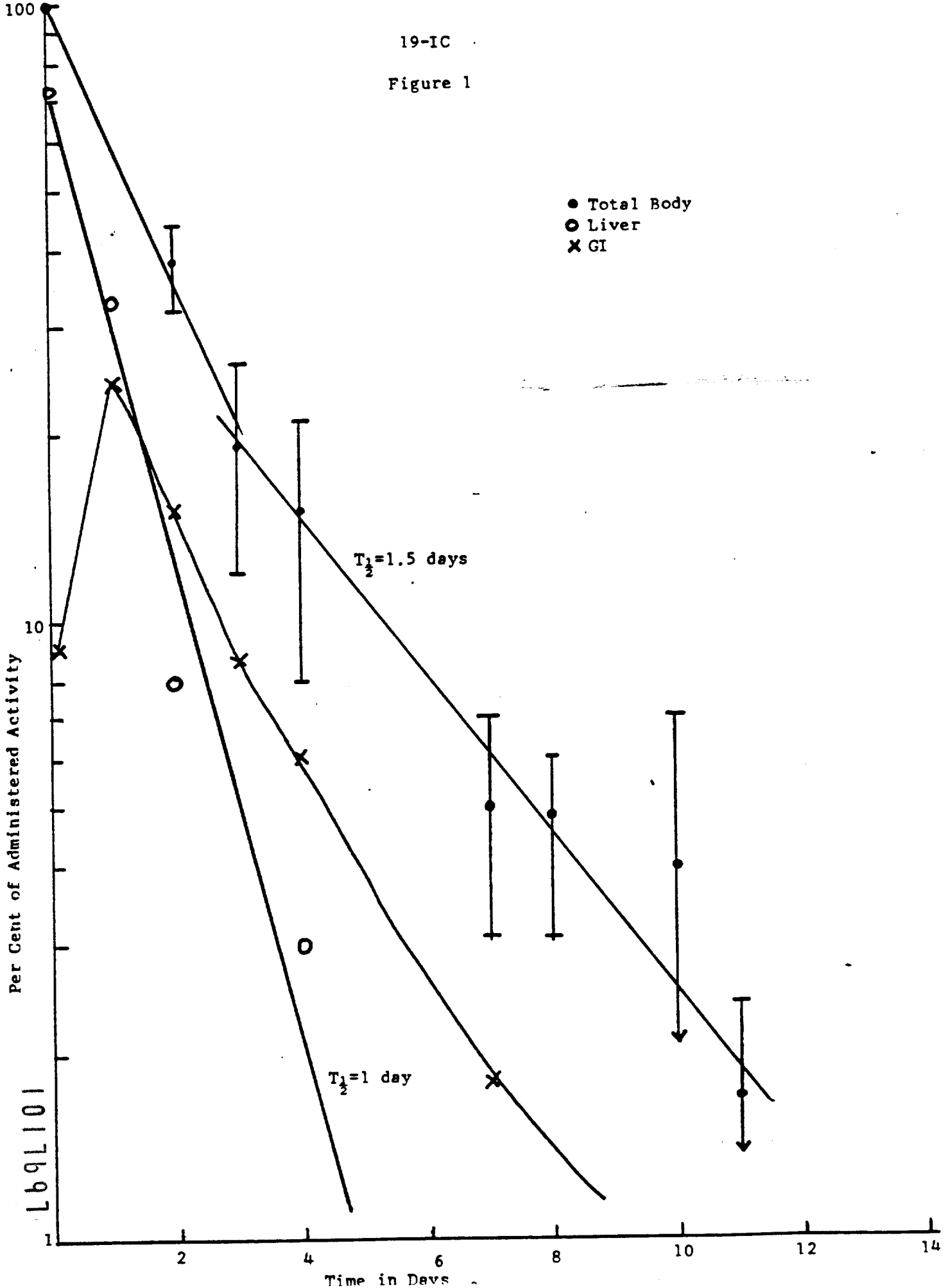


Table 1

Cumulative Activity

^{131}I-19IC

Organ	$\tilde{A}$ ($\frac{\mu Ci \cdot hours}{\mu Ci \text{ administered}}$)
Total Body	12.7
Liver	22.5
Thyroid	2.8
Adrenals	0.28
Small Intestine	3.81
U. Large Intestine	11.02
L. Large Intestine	18.10

1017698

Table 2

Nuclear Data (MIRD) Pamphlet No. 2)

Radionuclide	^{131}I
Physical half-life	8.05 days
Decay Constant	3.59×10^{-3} hours^{-1}
Δ (equilibrium dose constant for non-penetrating radiation)	$.04135 \frac{g \cdot rad}{\mu Ci \cdot hour}$

Principle Photons

	$\bar{E}i$	Δi
Ei, energy	0.0801	0.0030
	0.1772	0.0005
Δi (equilibrium)	0.2843	0.0288
(dose constant)	0.365	0.6477
	0.5 - 0.72	0.1211
	K X-rays	0.0030

1017699

Table 3

Dose Summary ($\overline{D}$ rad/mCi)
(19-IC)

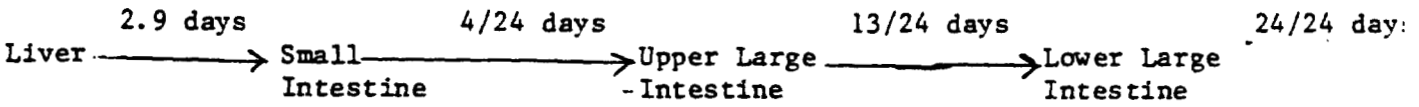
Organ	$\overline{D}p$	$\overline{D}np$	$\overline{D}$ total
Total Body	0.330	0.075	0.405
Liver	1.756	5.06	6.82
S.I. Wall	0.920	0.928	1.848
ULI Wall	1.584	10.90	12.48
LLI Wall	2.800	23.4	26.2
Thyroid	-----	58.2	58.2
Adrenal	-----	7.3	7.3

1017700

II. ^{131}I-6 Iodomethyl Norcholesterol (6NC)

Tables 4 and 5 summarize the biological data for the 6NC compound. Appendix II presents these data in graphical form and also presents a patient by patient comparison of the 19IC and 6NC compounds for those individuals who were studied using both compounds. Initial attempts at dose estimates for the 6NC agent paralleled the approach used for the 19IC agent, namely to use the model of Bernard and Hayes (see the section on 19IC). Further analysis indicated that the 6NC data were inconsistent with the model. Figure 2 is the equivalent data for the 6NC agent as was presented earlier for the 19IC agent in Figure 1. The liver in the compound exhibits a similar behaviour but with a much longer clearance ($\sim$ 3 days). Likewise the G.I. tract exhibits a similar long term transit. These data are also corroborated by the total-body retention (Figure 3).

In an effort to find a compatable model we arrived at the modified Bernard and Hayes model shown below.



If the terminal $T_{\frac{1}{2}}$ of the integrated G.I. compartment shown in Figure 1 for the 19IC compound is used along with the longer liver transfer rate shown above, we arrive at the predicted model curve shown in Figure 2 for the integrated G.I. activity. The predicted curve agreed well with the observed data. The model assumes an instantaneous uptake of the material in the liver equal to 71% of the injected dose.

Using the above model the following organ cummulative activities were derived (Table 6). In a manner similar to the 19-IC calculations, the source organs were assumed to be the total-body, liver, small intestine, upper large intestine, and lower large intestine.

In comparing Table 3 with Table 7 considerable differences can be recognized.

In general the absorbed doses per mCi of administered activity is greater for the 6NC compound relative to the 19-IC. The longer liver retention and the higher practical uptake in the adrenals are the primary reasons for this difference. Since the uptake of the 6NC in the adrenals is much greater than the 19IC, this would obviously lead to higher adrenal doses if the same injected dose is used—this is normally not the case. As a result of this study we have reduced the injected dose of 6NC by a factor of two from the 19-IC.

1017701

Table 4

6-N Cholesterol

Total Body

Study	Day 0	Day 2	Day 4.5	Day 7	Day 9	Day 11	Day 12	Day 13
1	1.000	.9100	.6500	-----	.3000	------	------	------
2	1.000	.8300	.4500	.3500	-----	------	------	.0900
3	1.000	.6100	.3900	.3100	-----	------	------	------
4	1.000	.7949	.3518	.2736	-----	.2550	------	------
5	1.000	.6044	.3208	.1927	-----	.1060	------	------
6	1.000	.6817	.3664	.1900	-----	.1050	------	------
Mean:	1.000	.7385	.4215	.2633	.3000	.1553	------	.0900

Liver

Study	Day 0	Day 2	Day 4.5	Day 7	Day 9	Day 11	Day 12	Day 13
1	.7100	.6188	.2210	-----	.1020	------	------	------
2	.6700	.4482	.2070	.1610	-----	------	------	.0369
3	.6100	.2439	.1365	.1054	-----	------	------	------
4	.8200	.4213	.1442	.0985	-----	.1046	------	------
5	.6800	.3679	.1187	.0828	-----	.0360	------	------
6	.7800	.3136	.1319	.0760	-----	.0400	------	------
Mean:	.7120	.4023	.1599	.1047	.1020	.0620	------	.0369

G.I.

Study	Day 0	Day 2	Day 4.5	Day 7	Day 9	Day 11	Day 12	Day 13
1	.1000	.1820	.3445	-----	.1050	------	------	------
2	.1700	.2164	.0855	.0910	-----	------	------	.0234
3	.0700	.1708	.0819	.1054	-----	------	------	------
4	.1300	.2544	.1372	.1067	-----	.0740	------	------
5	.1800	.1935	.1123	.0675	-----	.0310	------	------
6	.1000	.2318	.1026	.0437	-----	.0230	------	------
Mean:	.1250	.2080	.1440	.0749	.1050	.0427	------	.0234

1017702

6-N Cholesterol

Continued

Thyroid

Study	Day 0	Day 2	Day 4.5	Day 7	Day 9	Day 11	Day 12	Day 13
1	.03	.0182	.026	-----	.057	------	------	------
2	.04	.0332	.0315	.0175	-----	------	------	.0054
3	.03	.0183	.0117	.0062	-----	------	------	------
4	.02	.0318	.0141	.0082	-----	.01	------	------
5	.04	.0242	.016	.0366	-----	.007	------	------
6	.03	.0136	.0293	.0114	-----	.008	------	------
Mean:	.0317	.0232	.0214	.0159	.057	.0083	------	.0054

Other Body Activity

Study	Day 0	Day 2	Day 4.5	Day 7	Day 9	Day 11	Day 12	Day 13
1	.06	.091	.0585	-----	.039	------	------	------
2	.12	.1577	.1350	.0805	-----	------	------	.0243
3	.28	.1769	.1599	.0961	-----	------	------	------
4	.03	.0954	.0563	.0575	-----	.026	------	------
5	.100	.1227	.0706	.0589	-----	.03	------	------
6	.100	.1227	.0989	.0366	-----	.027	------	------
Mean:	.115	.1277	.0965	.0659	.039	.0276	------	.0243

1017703

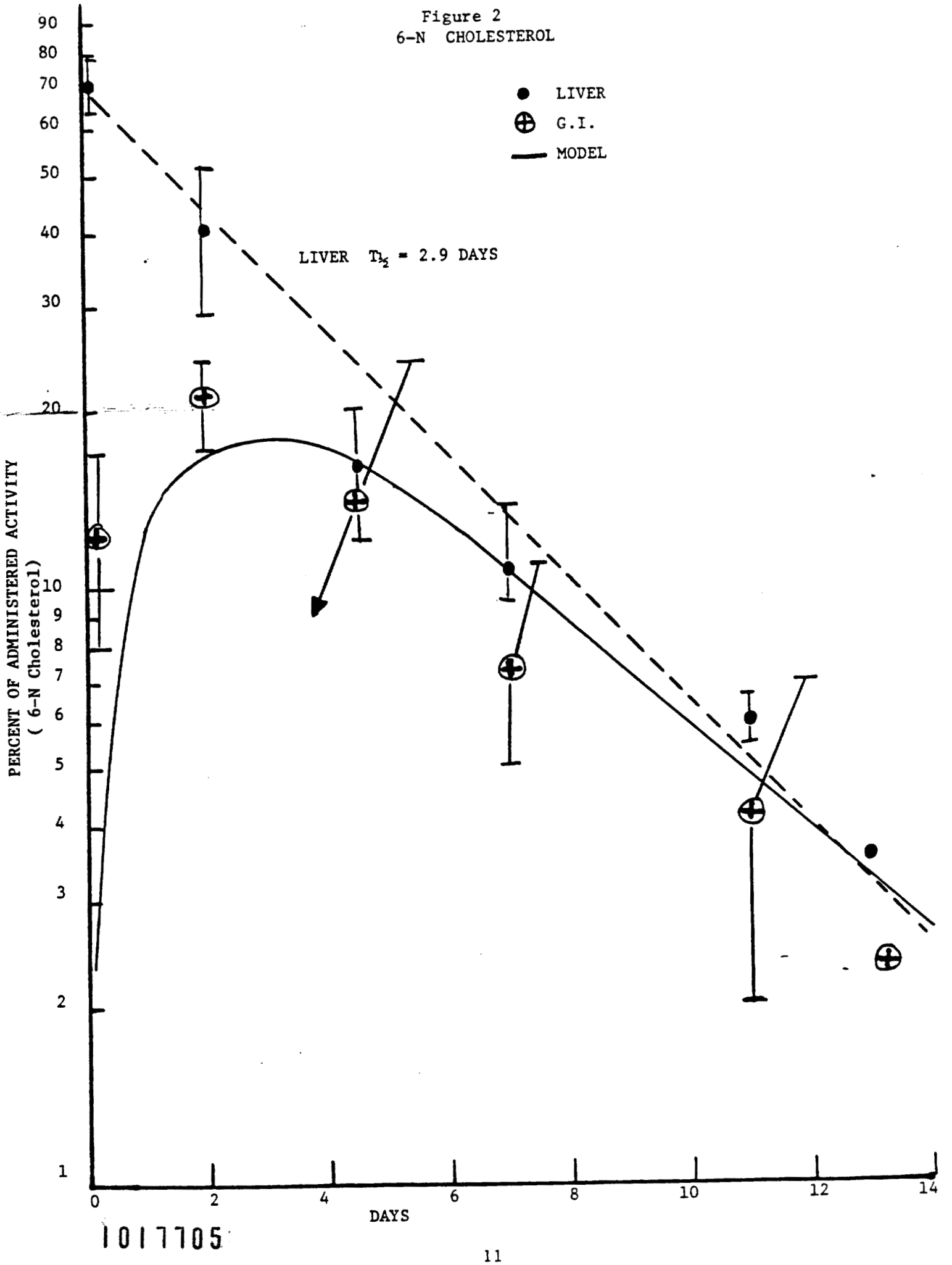
Table 5

Blood Levels

(% of Administered Dose)

Compound	Day 0	Day 2	Day 3	Day 4	Day 7	Day 11
19IC	100	-----	9.3 ± 4.2	-----	1.0 ± 0.5	0.3 ± 0.1
6NC	100	21.2 ± 3.6	-----	8.5 ± 0.7	4.4 ± 0.6	2.0 ± 0.1

1017704

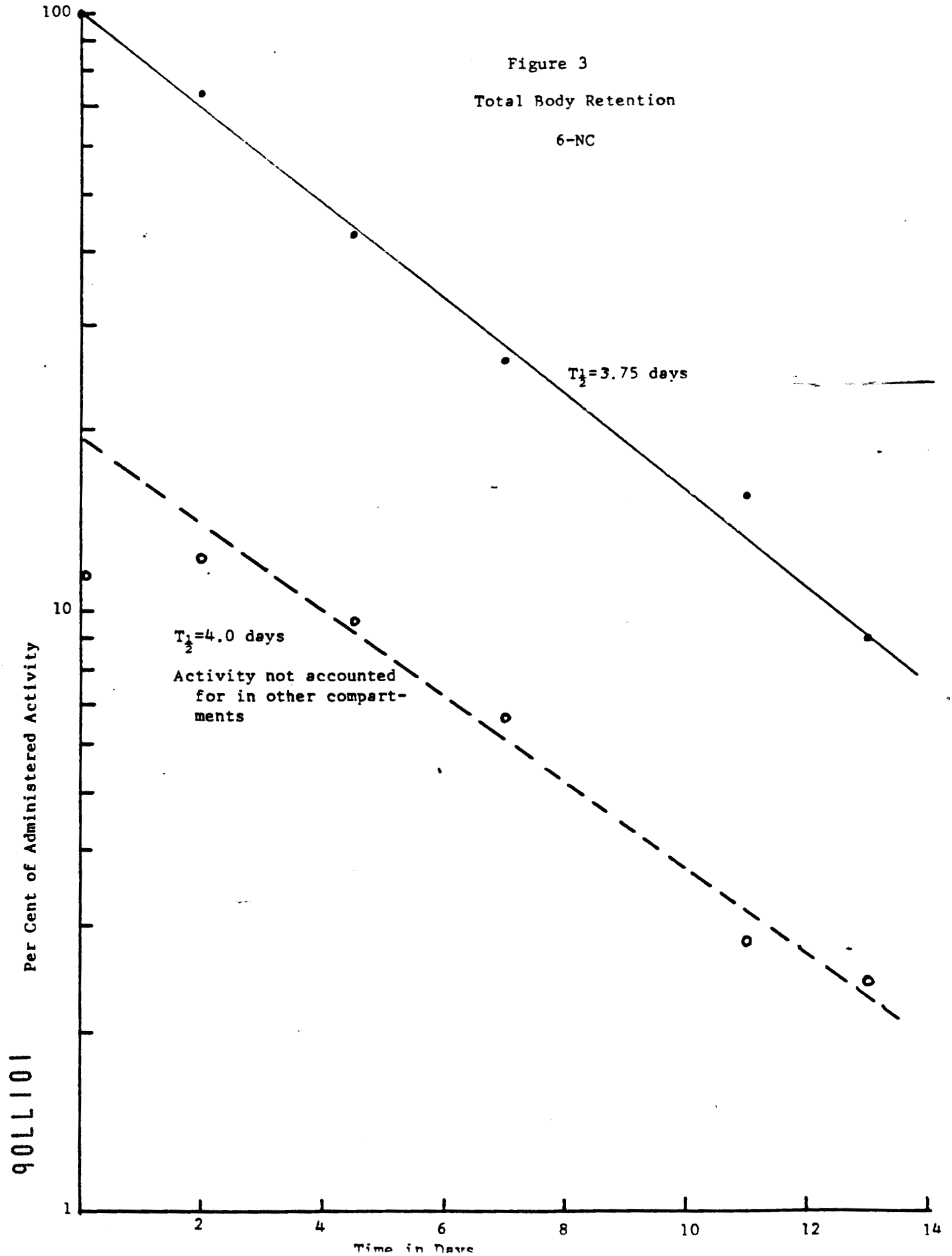

Figure 2
6-N CHOLESTEROL
LIVER
G.I.
MODEL
LIVER $T_{\frac{1}{2}}$ = 2.9 DAYS
PERCENT OF ADMINISTERED ACTIVITY
(6-N Cholesterol)
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
0
2
4
6
8
10
12
14
DAYS

1017705

Figure 3

Total Body Retention

6-NC



901L101

Table 6

Cumulative Activity

^{131}I-6NC

Organ	$\tilde{A}$ ($\frac{\mu Ci \cdot hours}{\mu Ci\ Administered}$)
Total Body	18.5
Liver	52.2
Thyroid	2.8
Adrenals	2.8
Small Intestine	2.95
U. Large Intestine	8.95
L. Large Intestine	14.70

1017707

Table 7

6-NC

Rad/mCi

Organ	Non-penetrating	Penetrating	Total
Total Body	0.109	0.465	0.574
Liver	11.77	3.87	15.64
Small Intestine	0.72	0.93	1.65
Upper Large Intestine	8.85	1.56	10.41
Lower Large Intestine	18.74	2.33	21.07
Thryoid	58.2	0.09	58.29
Adrenals	73.0	0.74	73.74

1017708

2. Iron-59 and In-111 Dosimetry in Abnormal Human Subjects

During the past year we have continued our work to make quantitative measurements of the absolute organ distribution of intravenously administered Fe-59 citrate in abnormal subjects. In cooperation with Dr. Sanford Krantz of the Department of Hematology, we are carrying out detailed studies on a selected group of patients with suspected and proven red-cell aplasia. Our work has allowed us to observe how the kinetics of the radio-iron and the resulting organ distributions may vary greatly from patient to patient depending upon the stage of the disease. The kinetic data we have collected and are using to make dosimetric estimates are also proving useful to Dr. Krantz as an aid in establishing the stage of the disease.

A paper describing the results of our work on a group of patients who were in remission of the disease has been accepted for publication in the American Journal of Hematology. The paper is entitled "Studies on Red Cell Aplasia: Ferro-Kinetics During Remission of the Disease". In this paper we computed the marrow retention curve of the radio-iron in six (6) patients who are in remission of the disease. Dosimetrically, we have determined that the red marrow is the critical organ for patients in full remission while the liver and spleen are the critical organs at other stages of the disease. During remission we have observed great expansions of the active red marrow sites to the knees, ankles, elbows, and the long bones of the arms and legs. We have also observed that the expanded marrow sites may also be accompanied by a prolonged transit time for the radio-iron resulting in an increased radiation dose to the marrow.

The patients in our current study group were classified into three groups with respect to their marrow transit curves. We have observed that the transit curves frequently exhibit two distinct transfer components. We have chosen to describe these two components as (1) erythropoietic (rapid $T\text{-}\frac{1}{2}$ approximately 3 days) and (2) storage ($T\text{-}\frac{1}{2}$ approximately ∞). In normals the second (storage) component is extremely small while in some abnormals the opposite is true. It is the presence and magnitude of the storage components that is the prime contributor to the dose. As shown in Table 1, the three classes have been defined as follows:

A. No significant storage component
B. No significant erythropoietic component
C. Both components present

We have investigated the variation in the radiation dose to the marrow between these three groups. The results of these calculations are shown in Table 2. As seen in the table, the marrow dose may be as much as a factor of 19 higher in those patients with significant marrow storage of the radio-iron. We hope to be able to extend these measurements and calculations to a larger patient population.

The MIRD Committee in the United States has created a task group to gather dosimetric information from the medical uses of Fe-59 citrate. Dr. James Robertson is Chairman of this group and Dr. Price is a member of this group. Vanderbilt's SAAM-25 iron kinetics model has been chosen to be used for the calculation of the cumulative organ activity (A) for the compiled normal and abnormal studies. The results of these measurements and calculations will be published by MIRD.

ORNL-10109

It is known that the marrow spaces in some abnormal states contain a significant amount of the iron storage component. To resolve the functioning marrow components from the storage components using external marrow measurements, we have attempted to use simultaneous scans of In-111 transferrin and Fe-59. The assumption is that the In-transferrin communicates only with the ferritin hemosiderin (storage) pools and not with the hemoglobin (erythropoietic) pool, and thus, we can use the In-111 distribution to measure the storage pools of the marrow sites for Fe-59. The dosimetric implications of the separation are significant since the kinetics of the two components are so different. Fe-59 labelled to hemosiderin but residing in the marrow space would have an essentially infinite biological half life, whereas Fe-59 labelled hemoglobin leaves the marrow in a matter of a few days. The following presents the results of studies in which complete and simultaneous Fe-59 and In-111 kinetic data were obtained.

To date simultaneous Fe-59--In-111 kinetic studies have been carried out only in abnormals. In the studies completed thus far, we have not been able to detect any statistically significant difference in the initial organ distribution of the two radionuclides. For example, in Figure 1 we present a patient with the preliminary diagnosis of sickle cell anemia. Aside from count rate differences the two scans appear virtually identical. For comparison Figure 2 shows a series of scintillation camera images of the In-111 distribution for the same individual. The results presented in Table 3 confirm the impression given by the scan images. Even through the initial distributions are similar, the kinetics of the two radionuclides are greatly different. The total-body retention curves (Figure 3) for the patient shown in Figure 1 indicate that in both iron and indium, the effective half-life is equal to the physical half-life (i.e. very long biological half-life). However if one looks at a marrow site, such as shown in Figure 4, we see that Fe-59 is rapidly cleared while the In-111 remains essentially fixed. Figure 5 shows that the iron is mobalized into the red blood cells while very little indium is incorporated into red cells (< 3%).

Our experience to date with indium has not conformed to our expectations and consequently we have not been able to utilize the indium data in the manner that we had originally proposed. Originally we had expected the indium to produce images qualitatively similar to iron in distribution but quantitatively different. With our current study group, we have not found this to be the case. As we continue to collect more data we hope to better establish the relationship between the kinetics of iron and indium and ultimately to be able to use these data to better define iron storage components which reside in the same physical sites as erythropoietically active components.

1017710

Table 1

Cumulative Activity

$$\tilde{A} \left(\frac{\mu Ci \text{ Days}}{\mu Ci \text{ Administered}}\right)$$

Patient Group	$\tilde{A}$
A Patients with no significant storage component	2.40 - 3.66
B Patients with no significant erythropoietic component	19.4
C Patients with both storage and erythropoietic function	40.0

1017711

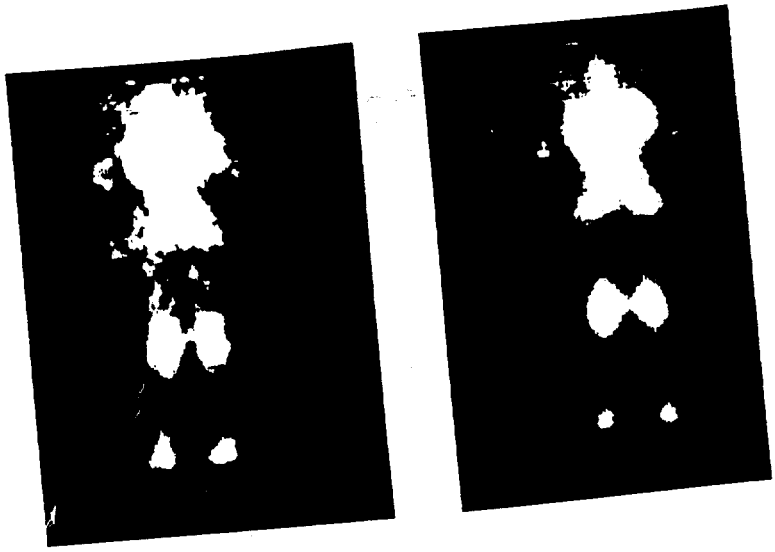
Table 2

Average Radiation Dose to the Red Marrow

($\overline{D}$ rad/μCi Adm.)

Group	$\overline{D}$np (nonpenetrating	$\overline{D}$p (penetrating)	$\overline{D}$ (total)
A	0.008-0.012	0.003-0.005	0.011-0.017
B	0.066	0.027	0.093
C	0.136	0.055	0.191

1017712



Fe-59 In-111

Figure 1: Whole-body scan images (day 5) of Fe-59 (left) and In-111 (right) collected simultaneously.

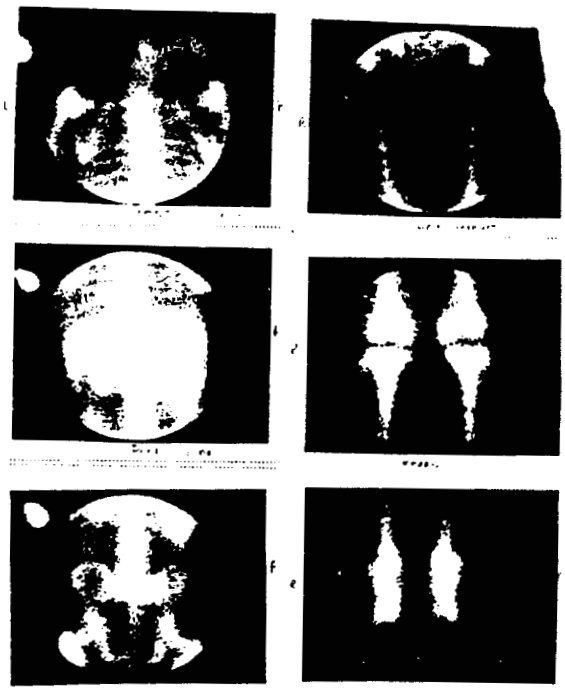


Figure 2: Whole-body survey images from a large-field-of-view camera displaying In-111 distribution in patient shown in Figure 1.

1017714

Figure 3

Total Body Retention

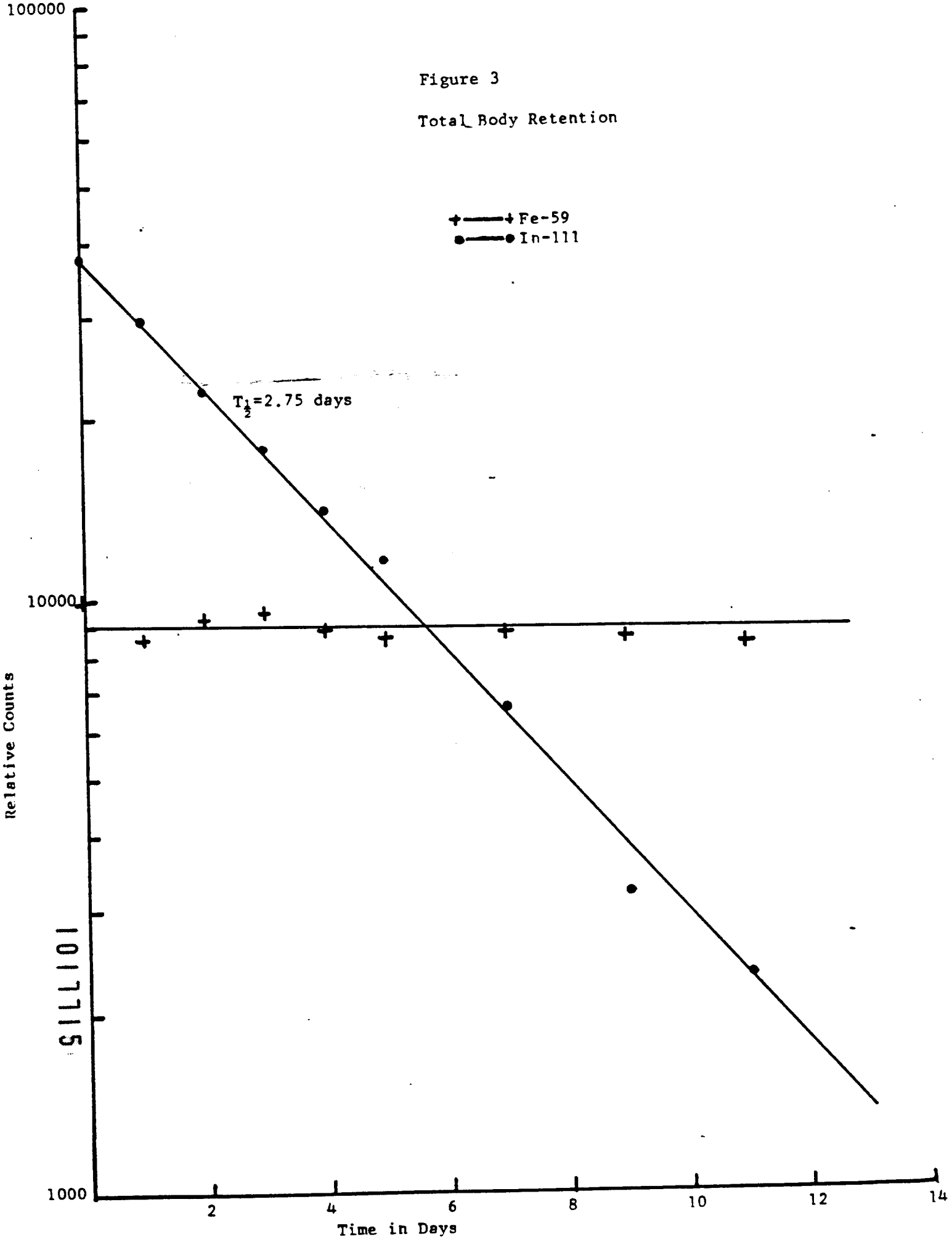


Table 3

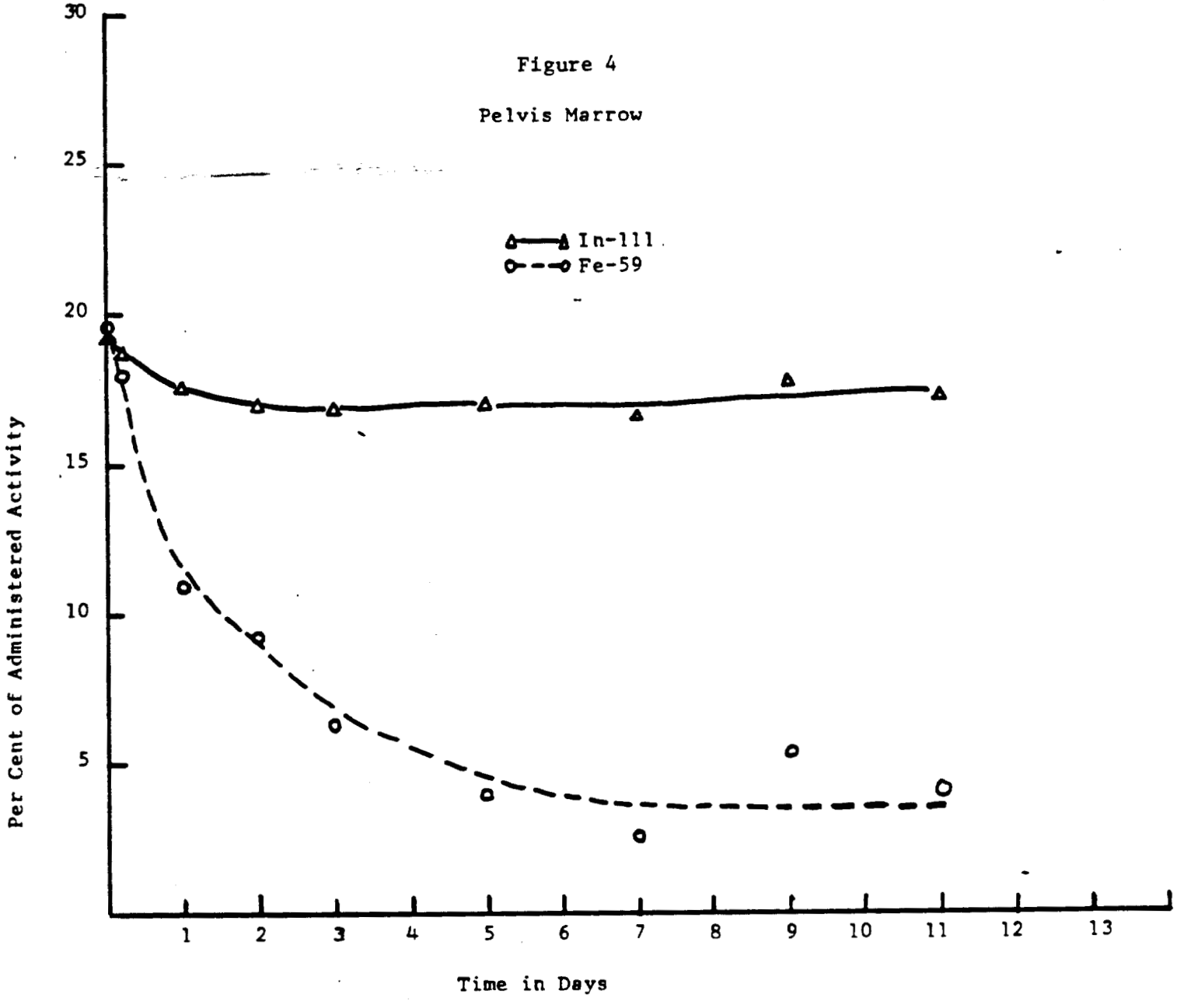
Relative Distribution at 4 Hours

	In-111	Fe-59
Liver	15.0	16.5
Spleen	8.8	10.4
Pelvis	17.9	17.9

1017716

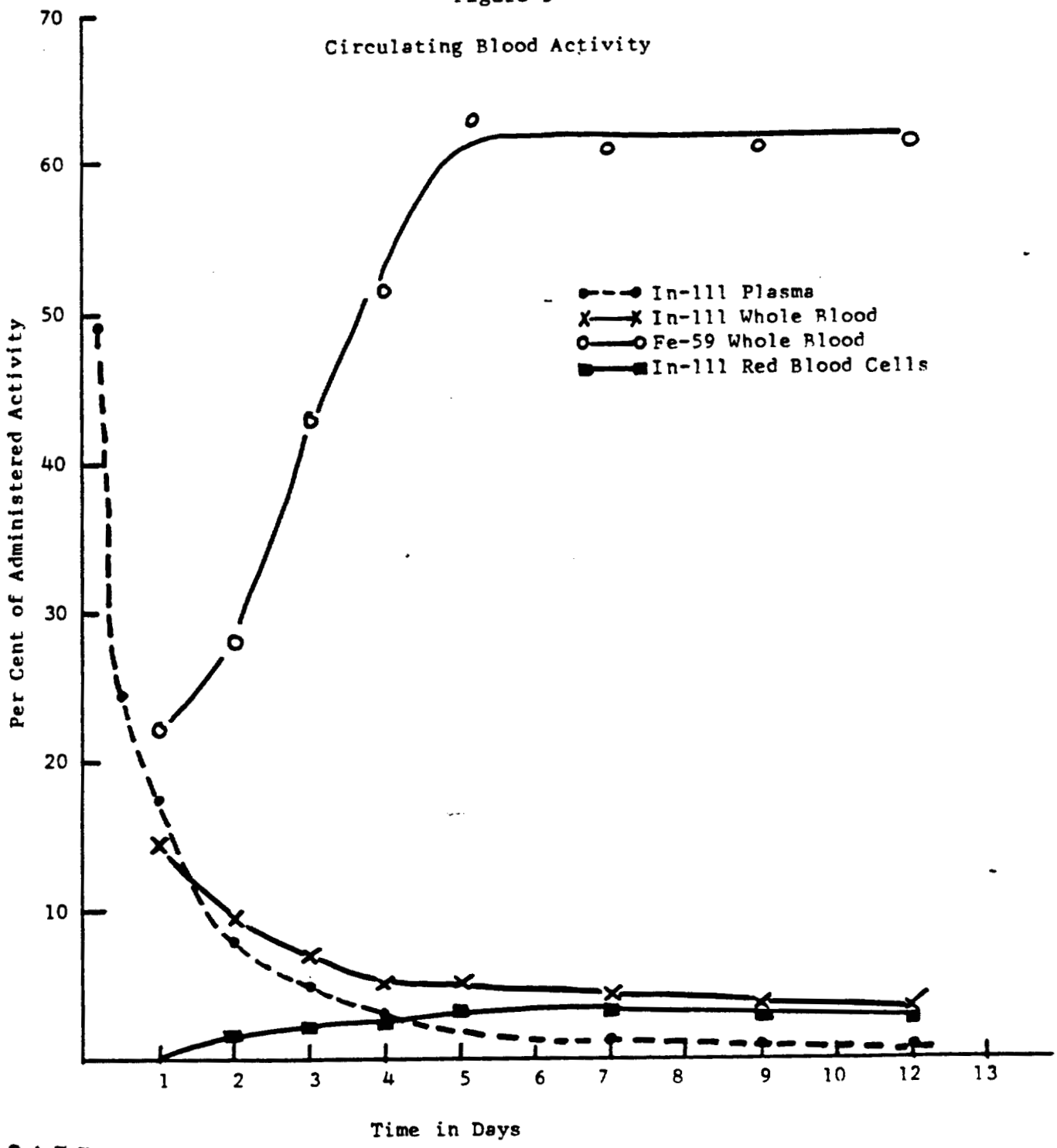
Figure 4

Pelvis Marrow



1017717

Figure 5



1017718

3. Dosimetry of Intraperitoneally Administered P-32 Colloid

We have completed the initial phase of the dosimetry of P-32 colloid used in the therapy of ovarian cancer patients. The purpose of this therapy is to deposit the colloid throughout the abdomen, where it can migrate along the same paths as ovarian metastases and deliver a tumoricidal dose without excessive damage to vital organs. To be effective, the colloid must follow all the migration paths in sufficient, but not excessive amounts. Thus the amount given and the method of administration are exceedingly important.

Our method was to surgically implant LiF dosimeters (TLD's) at selected sites in guinea pigs (diaphragm, parietal peritoneum, para-aortic lymph node area, and lesser sac). Following recovery from surgery, P-32 colloid was given, the animals sacrificed at various intervals, and the TLD's recovered and read out to determine the radiation dose as a function of time. The purposes of this phase were to:

a) identify and correct experimental problems

b) determine approximate dose levels

c) monitor the deposition and movement of colloid

The results are shown graphically in Figures 1-2, where the dose (rads/microcurie given) is plotted versus time for the four sites. With all animals, the volume of colloid solution given was constant (2ml), the injected activity was approximately 100 microcuries (with different activities corrected for), and all injections were made in the mid-to-lower left quadrant of the abdomen.

Experimental Problems

The implantation of TLD's caused two significant problems; surgical complications, and animal reaction to the TLD's themselves. In order to implant the TLD's (a fairly delicate operation), it was necessary to distend the intestines. This procedure had an unknown and presumably variable effect on the abdominal peritoneum configuration and lymphatic drainage system. This could preclude accurate comparisons from one animal to another, which is an essential requirement for this study. Further, in the animals which did tolerate the surgery well, the recovered TLD's were enclosed in a thick membrane which shielded the TLD's from the P-32 beta radiation to some extent. Given the obvious scatter of the results in the figures, we felt these problems must be corrected.

We have decided not to implant the dosimeters. Instead, a small incision is made at the injection site, and a small catheter positioned in the abdomen. Following this minor surgery, the colloid is injected through the catheter, and the catheter removed. After a suitable period of time, the animal is sacrificed, tissue samples removed from the desired sites, and a set of TLD's exposed to the tissue samples. This surgery is expected to be well-tolerated by the animals and assures that the P-32 is injected into the abdominal cavity (not the intestines by accident). The TLD readings will give the activity of

1017719

P-32 on the tissue samples, rather than a direct dose, but many tissue samples can be taken and several TLD's can be placed on a sample to check the uniformity of the P-32 deposition.

The main disadvantage to this method is that a direct dose measurement is not made, requiring a calculated estimate of the dose. Because of the complicated geometry of the in-vivo P-32 distribution, the calculation is subject to unknown errors. However, we now feel that it is best to establish the distribution of P-32 in normal animals before attempting to measure the dose in a surgically altered animal.

Approximate Dose Levels and Colloid Movement

Despite the scatter of the data, one can obtain some idea of the dose levels. The dose in the lesser sac appears to be the largest, reading a level of 33 rads/microcurie in three weeks. Next is the diaphragm at 12 rads/microcurie, also at three weeks. The parietal peritoneum reaches a dose of 10 rads/microcurie within two weeks and appears to stay at that level, while the peri-aortic area dose is only 1-2 rads/microcurie. It must be emphasized that these estimates are for guinea pigs only; the inference for humans is unknown.

As mentioned before, the injection site was in the lower left quadrant of the abdomen. The TLD positions were:

a) lesser sac -- within the lesser sac in the mid-abdomen

b) parietal peritoneum -- along the right anterior body wall

c) peri-aortic area -- to the right of the midline at the peri-aortic lymph nodes in the lower abdomen

d) diaphragm -- along the diaphragm superior to the right lobe of the liver

The curves suggest that the colloid moves to the parietal peritoneum within two days, with some being drained through the peri-aortic area. Little reaches the diaphragm or lesser sac until five to seven days, but thereafter the dose to each increases rapidly. Within two weeks, little colloid remains in the parietal peritoneal area or the peri-aortic area, but irradiation of the lesser sac and diaphragm continues. Data past three weeks are very doubtful because of the membranes that formed around the TLD's.

Colloid Distribution on Membranes

Tissue samples were removed from one animal and several TLD's exposed to each sample to check the uniformity of the P-32 deposition on the tissues. The results for parietal peritoneum, diaphragm, and mesenteric area samples are shown in Table I. A very uneven distribution of colloid is apparent (the animal was sacrificed at 7 days post-administration). If this is truly the case, large variations from one animal to another can be expected, making the dosimetry difficult. A more important implication is that the method of administration is inadequate; which if also true in humans, may compromise the effectiveness of the P-32 therapy.

1017720

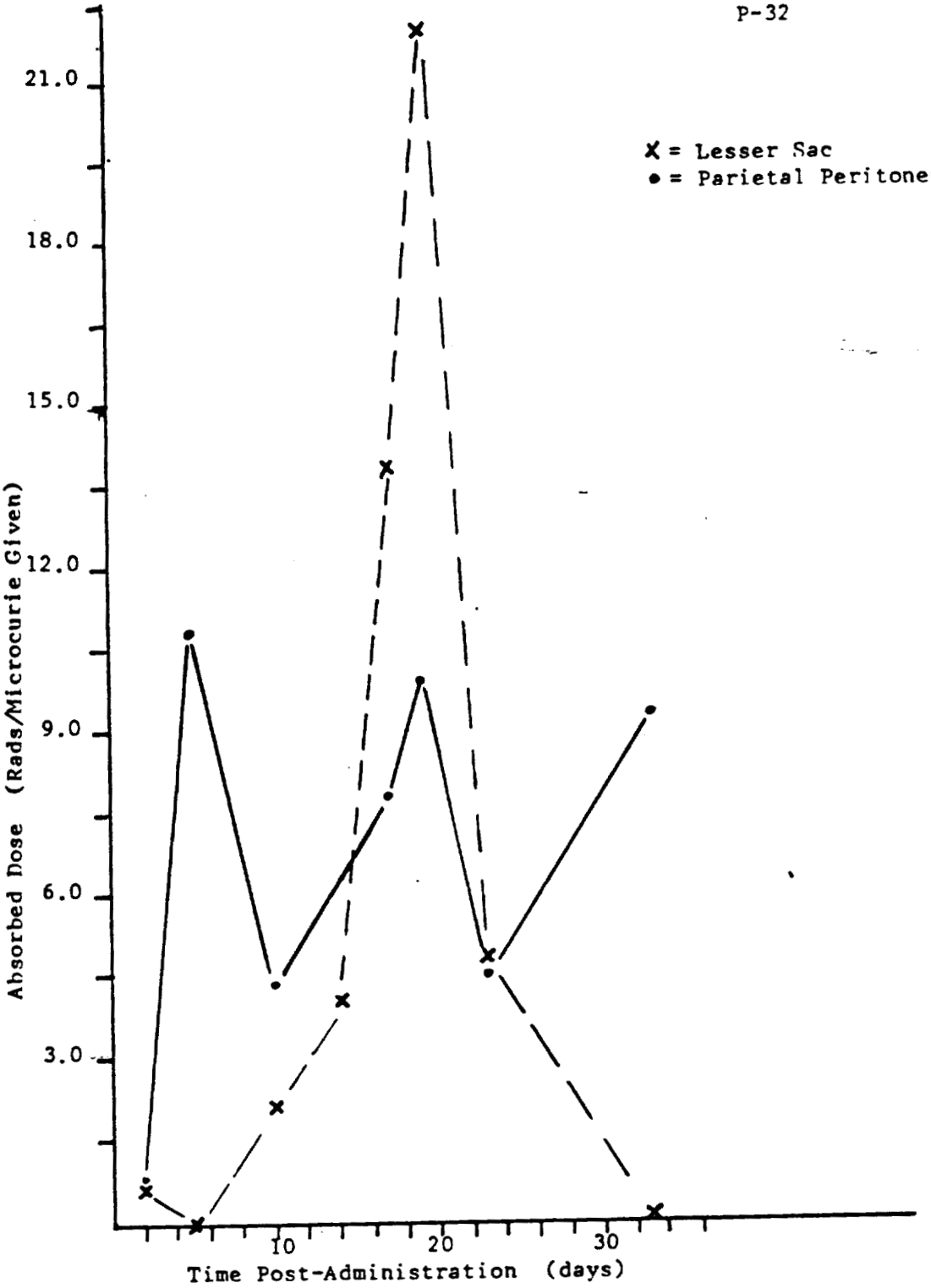


FIGURE 1

1017721

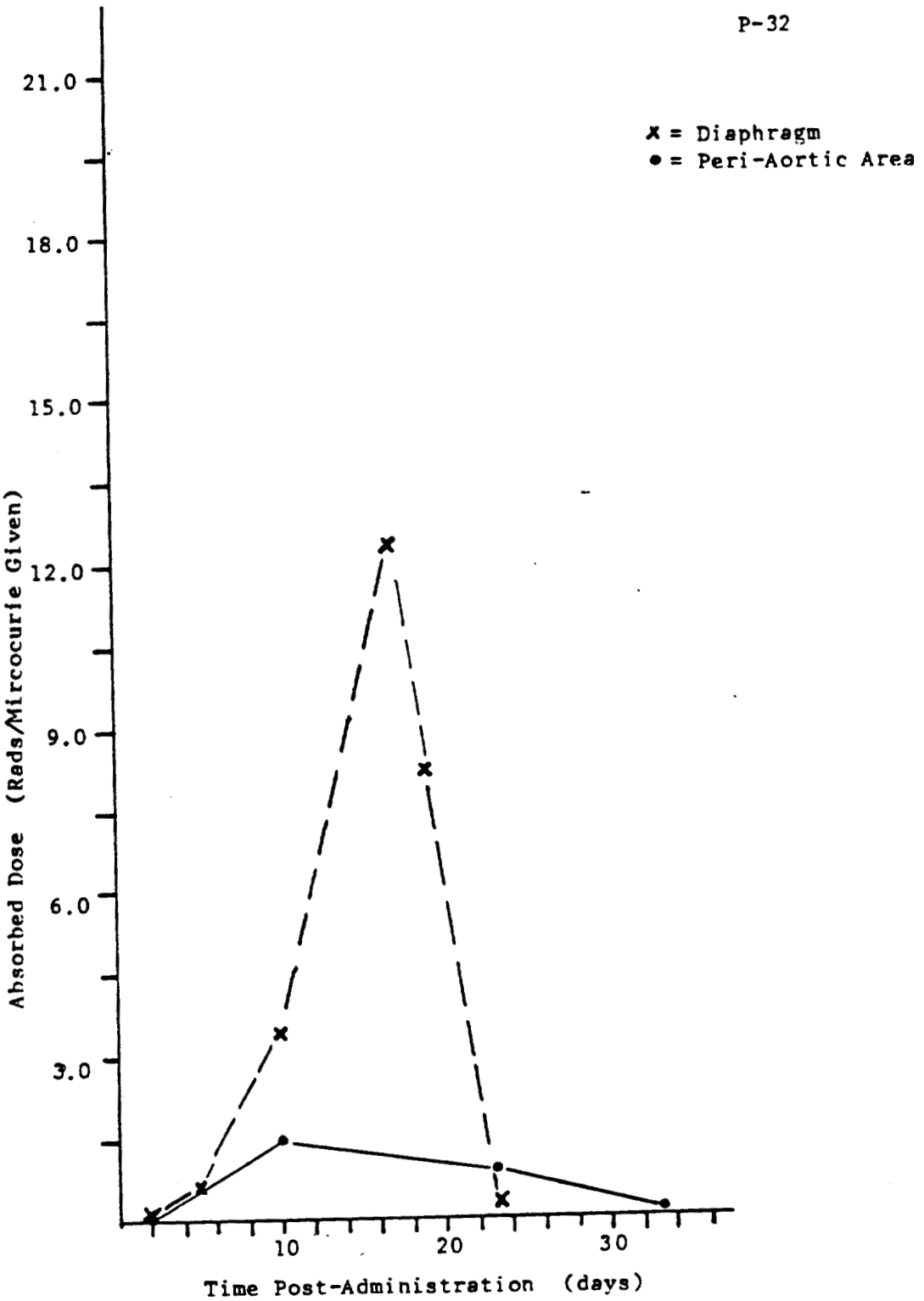


FIGURE 2

1017722

TABLE I

Relative TLD Readings of Tissue Samples (Arbitrary Units)

Perietal Peritoneum	Diaphragm	Mesentery
100	780	455
65	329	208
55	151	1600
59		1645
171		2212
159		2224

1017723

4. Evaluation of the Standard Man Model for Dosimetry Calculations--Comparison with Laboratory Measurements

One of our staff, Dr. Jerry Jones, is a member of NCRP Scientific Committee No. 55, charged to report on the accuracy of internal dosimetry calculations and make recommendations for further research. Although no official recommendations have been made as yet, discussion has been given to the following two projects:

1. Distribute replicas of the MR. ADAM phantom to various laboratories for both internal and external measurements.

2. Support the calculation of external photon energy spectra (due to internal sources), which could then be compared to spectral measurements on humans.

Further meetings of the committee will determine the plan of action.

In regard to the problem of attenuation effects, we have developed programs which will allow us to read the magnetic tape of the Searle whole body CT system. The CT numbers from computed tomography images will be used to investigate the attenuations effects in patients as compared to the standard man model. Assuming a uniform distribution of activity within a body subregion, we can express the effects of self-attenuation in terms of attenuation coefficients and geometry (location and thickness of source as compared to total body thickness). The equations expressing these effects were originally derived to estimate Tc-99m activity in the liver from external scanning measurements. These equations can be used to compare the counts from activity in a patient to those from an equal amount of activity in the standard man model. The advantage of this approach is that one is only simulating the activity in the patient--no injections or emission scans are done. Similarly, there is no need to scan the standard man phantom, because its geometry is defined in MIRD Pamphlet No. 5 and related publications. Thus one is using the human and model geometries to compare their attenuation differences for uniform source distributions.

In our earlier reports we have shown how the use of absorption fractions from the standard man model can lead to erroneous results in patients who differ significantly in size from the standard man. In order to better estimate organ masses we are in the process of developing a system in which sequential transverse section slices through an organ produced by a standard B-mode ultrasound scanner can be used to yield organ volumes. The system utilizes a COLORADO VIDEO CVI-280 video digitizer which has been interfaced to our PDP-11 computer for the purpose of producing digitized ultrasonic images. Once the digitized images have been stored on disk in a Gamma-11 compatable format, the images can then be viewed one at a time and the organ boundaries outlined. The outlined boundary and the plane thickness are used to calculate the fractional volume residing in that plane. The total volume is then estimated by adding all of the planes together. The software systems needed for these calcuations and image manipulations is still in development. However, our preliminary results indicate that reasonably accurate volume estimates for some organs (spleen, kidneys, and liver) can be obtained in this manner. With the availability of organ volume measurements, we will then be able to fold this information into our dosimetry calculations.

1017724

5. Radiation Sensitivity of the Thyroid During I-131 Therapy

Information of iodine uptake, the effective half-time of its retention in the thyroid and thyroid mass are used in calculating the amoung of I-131 to be administered to patients in the treatment of hyperthyroidism. A major variable, however, which we have not yet learned how to assess is radiation sensitivity of the thyroid.

In our work on iodine kinetics, to date, we have evaluated iodine metabolism in large numbers of patients during treatment of thyrotoxicosis and have determined model parameters which are reasonable predictors of absorbed radiation dose to the thyroid, given knowledge of thyroid gland size.

To evaluate thyroid sensitivity, we need to measure a parameter that reflects damage to the thyroid. The rate of loss of iodine from the gland following therapy is due to altered rates of release from the gland and by diminution of uptake. We have measured the iodine content of the gland after therapy by means of x-ray fluorescence scanning in a large number of patients in an attempt to determine if predictions of hypothyroidism can be made from the early changes in iodine content after therapy. We are currently measuring iodine content and other thyroid function parameters in 52 patients who have received radioiodine therapy. The patients have been grouped into the following 5 catagories based upon the course of therapy they received: (1) I-131 only, (2) drugs pre-I-131, (3) drugs post-I-131, (4) drugs pre- and post-I-131, and (5) previous surgery and I-131. These patients were studied at monthly intervals following I-131 therapy and the results of serial quantitative fluorescent scans are shown in Figures 1 and 2. Figure 1 shows the 5 catagories plotted as a function of the percentage of initial iodine content pre-therapy. There appears to be no significant difference in the catagories when plotted in this fashion. All show a steep decline in iodine content between the second and third month post-therapy. Plotting the catagories as a function of the absolute initial iodine content values in milligrams in Figure 2 shows that those patients with previous surgery before therapy had significantly lower initial iodine values than the other four catagories. However, the course following therapy for the five catagories is essentially the same. From these data, we have concluded that the course of treatment before I-131 therapy has very little, if any, effect on the rate of iodine loss following administration of I-131.

We were interested in the effect of drug therapy before radioactive iodine therapy on the iodine content values at the time of iodine administration. Figure 3 shows a histogram plot of the iodine content values at the time of I-131 therapy versus the duration of previous drug therapy. Although the number of patients is small, no appreciable trend can be observed from this plot.

The data in Figures 4 and 5 show plots of the iodine content versus time post-I-131 therapy for 32 of the original 52 patients in which there was adequate follow-up to study the patients for a period of 12 months to a euthyroid status or to the time at which they became biochemically hypothyroid and were placed on replacement drugs or the time that the relapsed and were retreated. From these figures it is noteworthy that those patients who were destined to become hypothyroid had lower iodine content values at the 2-3 month interval than the other two groups. By closely analyzing the currently available data, we have arbitrarily chosen a value of 2mg as the level for making predictions on the outcome of therapy. Applying this seperation criterion to the 43 patients in which adequate follow-up information was available as of

I-01-1725

June 1978 some interesting observations can be made as shown in the lower section of Table 1. Of the 21 patients who had iodine contents of 2mg or greater at the 2-3 month interval, only 3 became hypothyroid within 12 months. The remaining 18 either remined euthyroid or relapsed into hyperthryoidism within 12 months. On the other hand, of the 22 who had iodine contents of less than 2mg at the 2-3 month interval, 18 became hypothyroid within 12 months. From these data it appears that an iodine content of less than 2mg at 2-3 months post therapy with I-131 predisposes the patient to early hypothyroidism. We plan to continue studying therapy patients using the results reported here to determine if we can, in fact, predict early hypothyroidism on the basis of the iodine content values at the 2-3 month interval.

1017726

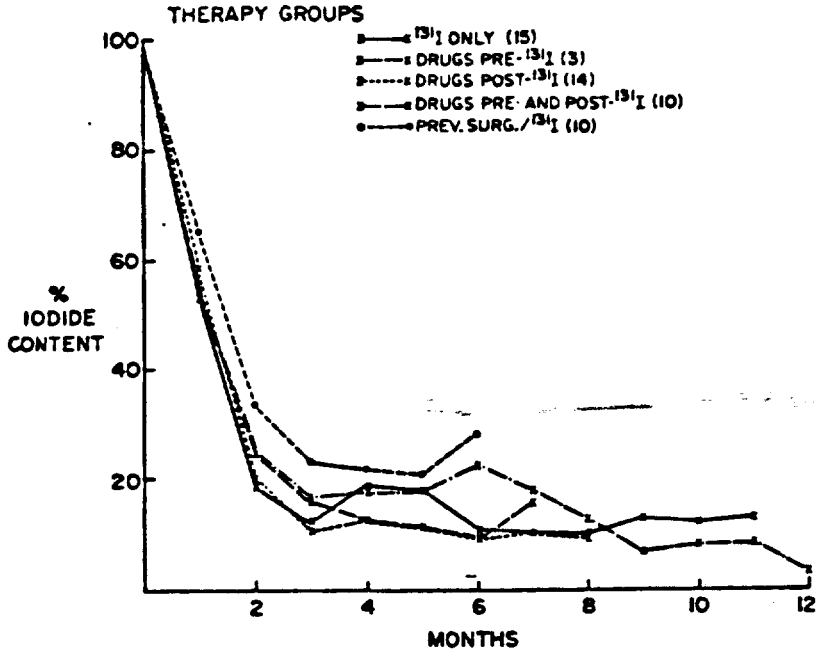


FIGURE 1

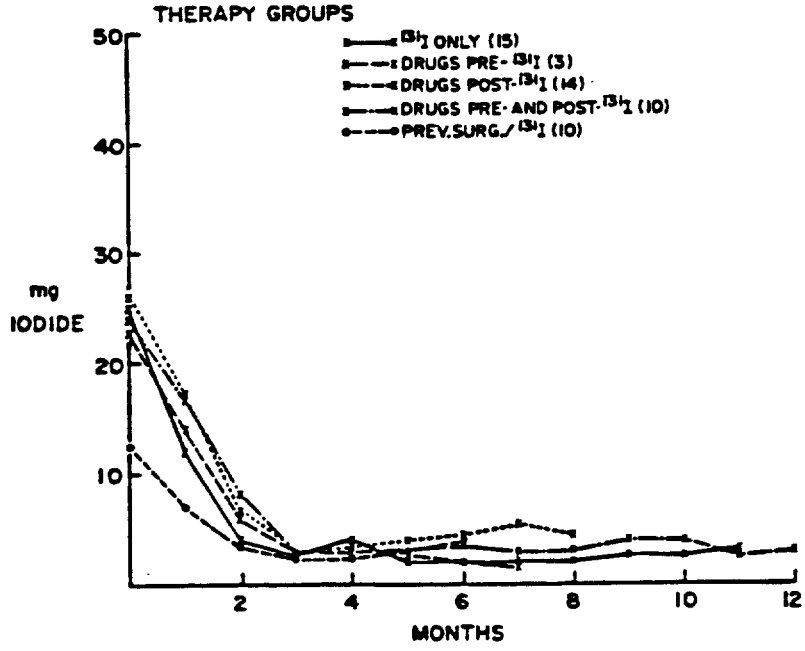


FIGURE 2

1017727

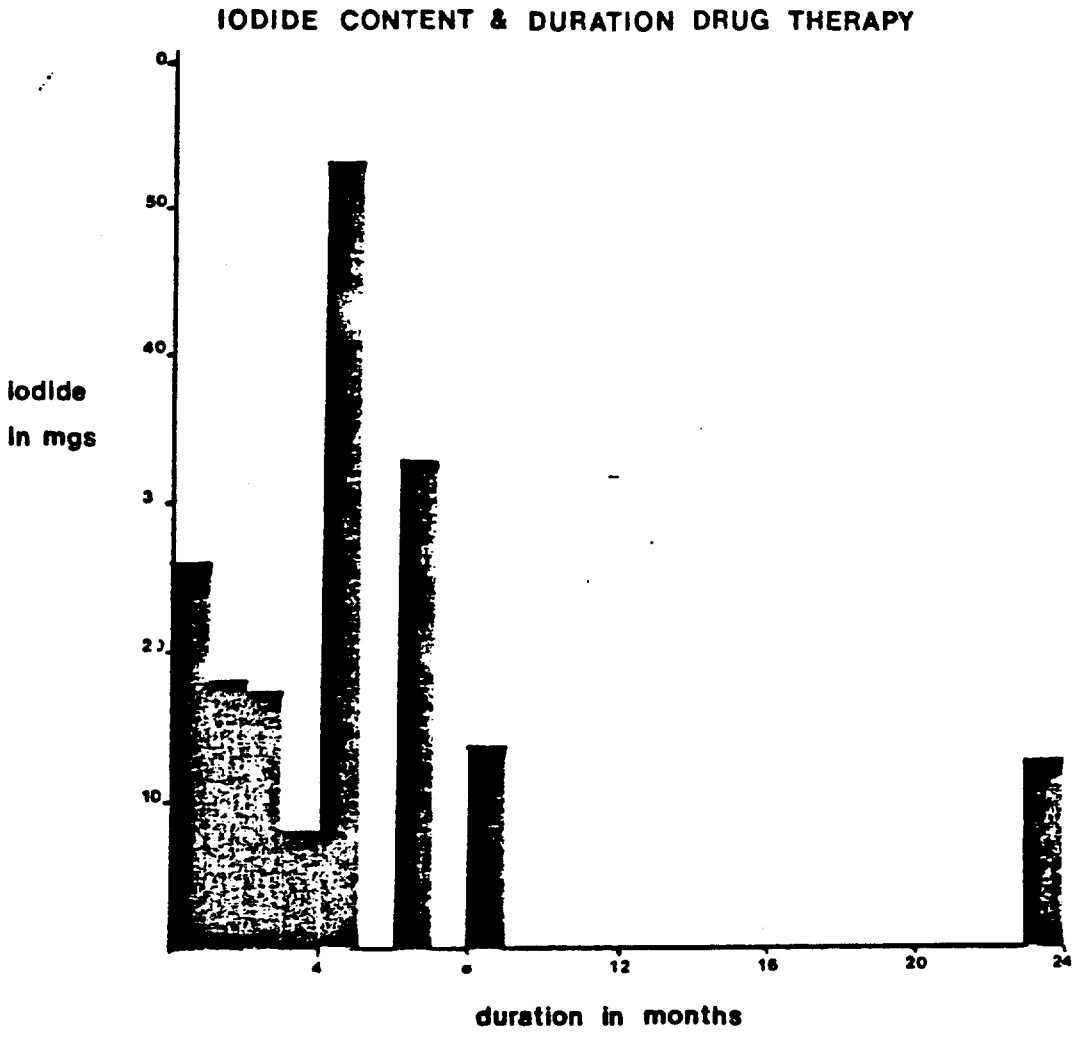


FIGURE 3

1017728

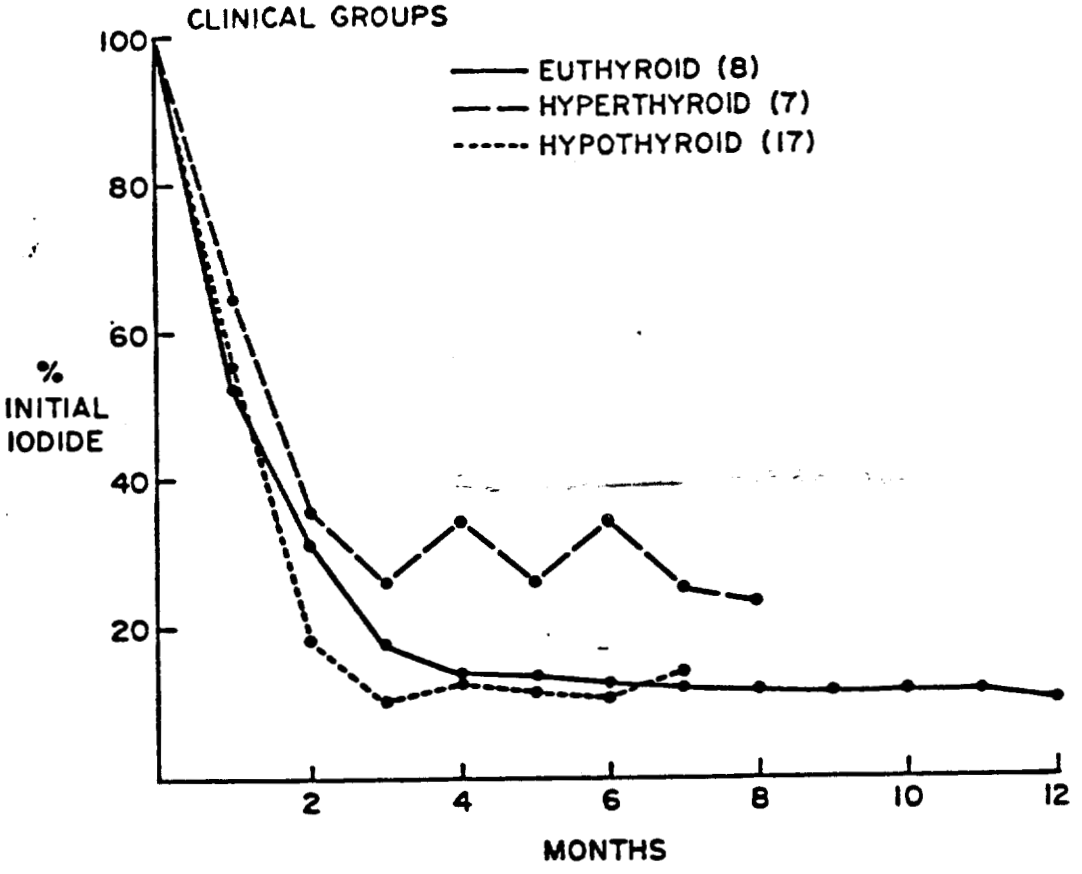
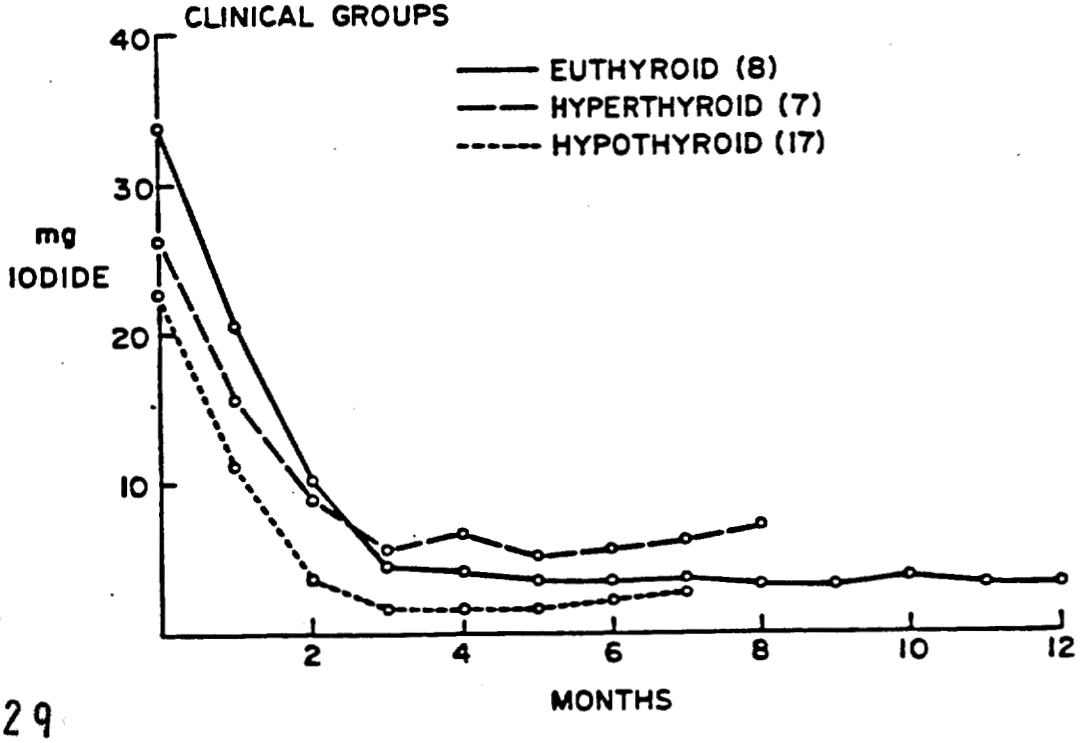


FIGURE 4



1017729

FIGURE 5

TABLE I

RELATIONSHIP OF LOW IODINE CONTENT TO EARLY HYPOTHYROIDISM

Thyroid Iodine at 2-3 Months	Hypothyroid Within 12 Months	Euthyroid at 12 Months or Relapse Within 12 Months	Total
< 2 mg.	14	2	16
≥ 2 mg.	3	13	16
Updated to 16 June 1978:			
< 2 mg.	18	4	22
≥ 2 mg.	3	18	21

Inadequate Followup: 9

1017730

6. Nuclear Power Reactors--Environmental Monitoring

Previous studies conducted in our laboratory have been directed toward the assessment of body burdens of environmental pollutants. In the early 1970's we collected over 1000 placentae from births in Nashville and assayed the content of heavy metals (Pb, Cd, Hg) and carried out neutron activation analysis to determine levels of other trace elements. Comparisons were made between levels found in placenta, blood, and hair samples in normal and abnormal births, in an attempt to identify potential etiological relationships. No gradients suggesting disease correlates were found, and levels were not elevated in this region. No concern has been raised locally with respect to potential hazards from these agents since the data shows no cause for concern.

We have been discussing with TVA representatives the possibility of mounting a similar study in the area of the Hartsville Nuclear Power reactor. We are exploring the feasibility of collecting placental tissues on a sampling basis from persons living at varying distances from the Hartsville plant, and analyzing these tissues for radionuclides that could be expected. Assays should be conducted by a laboratory that is expert on low level counting, and which has the capacity to handle such a volume. We would maintain the basic records, and do the temporal trend and epidemiologic analyses at Vanderbilt which should be considered a neutral observer. Collaboration between epidemiologists, statisticians, OB/GYN specialists, and community agencies should enable such a study to be conducted if sufficient interest suggests it is worth doing. Discussions concerning how our facilities and experience can be used in such studies are still underway.

1017731

7. Distribution and Excretion Studies of Two Different Formulations of Commercial Lung Imaging Agents

Studies were carried out in ten male volunteers with no known pulmonary disease to assess the organ distribution and excretion of two commercial (Tc-99m-Sn-MAA) lung imaging agents. These two agents will be referred to as the new and old formulation.

The study involved a single injection of the lung agents. Five, 5 ml. blood samples were obtained at 30 minutes, 1, 2, 4, and 6 hours post-injection. In addition, urine was collected at 1, 4, and 8 hours post-injection. These samples were used to determine the amount of activity remaining in the blood as well as the amount which has been excreted by the urine. Quantitative whole body images were obtained at 1, 2, 4, 6 and 24 hours. In addition standard scintillation camera images of the lungs, liver/spleen and kidneys were taken and recorded on magnetic disk for quantitative assessment. The percentage of bound Tc-99m and the prepared agent was determined by paper chromatography five minutes after preparation and at four hours after preparation. Whatman # 3 paper and a solvent of 85% methynol was used for the chromatographic procedure. With this system all bound Tc-99m will remain at the origin and the unbound Tc-99m will have a Rf at about .6. The sample spot will not be dry prior to development in the solvent.

Regions of interest were selected in the total body images corresponding to the lungs, kidneys, and bladder. Time activity curves generated for each were used to calculate the cumulative activity for each of the source organs. Table 1 shows the source and target organs chosen for this study and the corresponding S-factor in terms of mRad/μCi-hour.

In each case the total body time activity curves and the time activity curves for the lungs exhibited a mono-exponential form. All of the activity was assumed to be in the lungs initially. The total body activity was assumed to be constant in time and equal to the mean of the six blood activity measurements. The differences in the total body activity and the sum of the lungs, kidneys, bladder and urine was assumed to be in the small intestine.

Table 2-6 were used along with the kidney, bladder and lung activity curves to arrive at the biological parameters found in Table 7. The primary difference between the two agents was in the effective life-time in the lungs. The old formulation was found to breakdown more rapidly than the new formulation: mean $T_{\frac{1}{2}}$ = 2.5 hour as compared to $T_{\frac{1}{2}}$ = 3.9 hour.

Tables 8 and 9 summarize the results. The dosimetry of the two agents are similar except for the lung as could have been predicted from the knowledge of the difference in the lung $T_{\frac{1}{2}}$ of the two agents.

1017732

TABLE I

SOURCE ORGAN	TARGET ORGAN	S-mRad/μCi-Hr
LUNG	Lung	5.2×10^{-2}
	Liver	2.5×10^{-3}
	Kidneys	8.4×10^{-4}
	Spleen	2.3×10^{-3}
	Testes	7.6×10^{-6}
	Total Body	2.0×10^{-3}
TOTAL BODY (BLOOD)	Lung	2.0×10^{-3}
	Liver	2.2×10^{-3}
	Kidneys	2.2×10^{-3}
	Spleen	2.2×10^{-3}
	Testes	1.7×10^{-3}
	Total Body	2.0×10^{-3}
BLADDER	Lung	2.4×10^{-5}
	Liver	1.7×10^{-4}
	Kidneys	2.6×10^{-4}
	Spleen	6.6×10^{-4}
	Testes	4.7×10^{-3}
	Total Body	1.9×10^{-3}
KIDNEYS	Lung	8.5×10^{-4}
	Liver	3.9×10^{-3}
	Kidneys	1.9×10^{-1}
	Spleen	8.6×10^{-3}
	Testes	8.8×10^{-5}
	Total Body	2.2×10^{-3}
G.I. (Small intestine)	Lung	2.2×10^{-4}
	Liver	1.8×10^{-3}
	Kidneys	3.2×10^{-3}
	Spleen	1.5×10^{-3}
	Testes	3.1×10^{-4}
	Total Body	2.4×10^{-3}

1017733

TABLE 2

OLD FORMULATION

TOTAL BODY RETENTION (No correction for physical decay)

(% of Administered)

Subject Number	Time (hours) 0.50	1	2	4	6	24
1	100	92.0	84.0	60.0	45.0	5.3
2	--	83.0	75.0	53.0	37.0	3.1
3	--	84.0	75.0	52.5	40.0	--
4	--	86.0	73.0	54.0	43.0	3.5
5	100	94.0	74.0	48.0	34.0	3.0

1017734

TABLE III

OLD FORMULATION

WHOLE BODY ACTIVITY
(% administered)

Subject Number	Time (hours) 0	0.5	1.0	2.0	4.0	6.0
1	5.6	5.0	4.9	5.0	4.8	4.5
2	6.3	6.1	6.2	5.9	5.8	5.7
3	8.5	7.3	7.1	7.4	7.2	7.2
4	8.7	7.9	7.0	5.8	5.4	5.0
5	8.2	8.2	7.7	7.4	5.9	5.3

1017735

TABLE IV

OLD FORMULATION

CUMULATIVE URINE ACTIVITY AT 8 HOURS

(% of Administered)

Subject Number	% at 8 hours
1	14.9
2	26.2
3	17.6
4	23.0
5	15.5

1017736

TABLE V

NEW FORUMULATION

TOTAL BODY RETENTION

% of Administered
(No physical decay correction)

Subject Number	Time (hours) 0.0	1	2	4	6	24
1	100	83.0	65.0	55.0	44.0	3.7
2	--	79.0	70.0	55.0	44.0	2.7
3	--	93.0	81.0	57.0	46.0	3.6
4	--	81.0	76.0	59.0	42.0	4.4
5	--	86.0	65.0	53.0	40.0	5.1

1017737

TABLE VI

NEW FORMULATION

WHOLE BODY ACTIVITY
(% of administered)

Subject Number	Time (hours) 0	0.5	1.0	2.0	4.0	6.0
1	1.1	10.7	9.9	8.2	7.7	7.7
2	1.8	8.3	7.4	7.4	6.7	6.1
3	1.4	6.7	6.4	6.3	6.1	5.7
4	1.4	4.9	5.0	5.0	5.2	5.0
5	1.7	10.4	8.2	9.2	6.3	4.8

NEW FORMULATION

CUMULATIVE URINE ACTIVITY AT 8 HOURS
(% of Administered)

Subject Number	%
1	27.1
2	18.9
3	15.9
4	10.2
5	15.1

1017738

TABLE VII

BIOLOGICAL PARAMETERS
(OLD FORMULATION)

Subject Number	Lung $T_{\frac{1}{2}}$ (hours)	Total Body $T_{\frac{1}{2}}$ (hours)	Average Blood Activity (%)	Cumulative Kidney Activit (mCi-hours)
1	2.2	5.3	5.0	0.044
2	2.5	4.8	6.0	0.34
3	2.8	4.8	8.0	0.29
4	2.8	5.1	8.0	0.46
5	2.4	5.2	8.0	0.28
Mean	2.5	5.0	7.0	0.28

NEW FORMULATION

1	4.6	5.0	10.0	0.0
2	3.5	5.2	7.5	0.22
3	3.6	5.6	6.0	0.18
4	4.7	5.4	5.0	0.20
5	3.0	4.8	8.0	0.50
Mean	3.9	5.2	7.3	0.22

1017739

TABLE 1

Source Organ		Target Organ	S-Factor Rad/μCi-hour	
	S(1,3)	Bladder Wall	5·1E-7	$y10^4$
	S(1,2)	Bone (Total)	1·2E-5	
	S(1,3)	Kidneys	8·2E-7	
	S(1,4)	Liver	6·6E-7	
Cortical	S(1,5)	Lungs	9·4E-7	
Bone	S(1,6)	Marrow (Red)	4·1E-6	
	S(1,7)	Pancreas	8·5E-7	
	S(1,8)	Spleen	5·8E-7	
	S(1,9)	Testes	6·4E-7	
	S(1,10)	Total Body	2·0E-6	
	S(2,1)	Bladder Wall	2·3E-6	
	S(2,2)	Bone (Total	2·5E-6	
	S(2,3)	Kidneys	2·2E-6	
Total Body	S(2,4)	Liver	2·2E-6	
(Blood)	S(2,5)	Lungs	2·0E-6	
	S(2,6)	Marrow (Red)	2·9E-6	
	S(2,7)	Pancreas	2·4E-6	
	S(2,8)	Spleen	2·2E-6	
	S(2,9)	Testes	1·7E-6	
	S(2,10)	Total Body	2·0E-6	
	S(3,1)	Bladder Wall	1·6E-4	$x10^4$
	S(3,2)	Bone (Total)	9·2E-7	
	S(3,3)	Kidneys	2·6E-7	
	S(3,4)	Liver	1·7E-7	
	S(3,5)	Lungs	2·4E-8	
Bladder	S(3,6)	Marrow (Red)	2·2E-6	
Contents	S(3,7)	Pancreas	2·3E-7	
	S(3,8)	Spleen	6·6E-7	
	S(3,9)	Testes	4·7E-6	
	S(3,10)	Total Body	1·9E-6	

1017740

Table 1
Continued

Source Organ		Target Organ	S-Factor
Kidneys	S(4,1)	Bladder Wall	2·8E-7
	S(4,2)	Bone (Total)	1·4E-6
	S(4,3)	Kidneys	1·9E-4
	S(4,4)	Liver	3·9E-6
	S(4,5)	Lungs	8·5E-7
	S(4,6)	Marrow (Red)	3·8E-6
	S(4,7)	Pancreas	6·6E-6
	S(4,8)	Spleen	8·6E-6
	S(4,9)	Testes	8·8E-6
	S(4,10)	Total Body	2·2E-6

1017741

TABLE 2

Total Body Retention

% Administered

Time (Hours)

Subject	0.5	1	2	4	6	24	32
1	94.3	90.8	40.3	34.4	14.3	1.17	----
2	89.0	84.0	77.0	44.0	24.0	1.78	----
3	91.7	82.7	75.5	26.5	16.7	1.2	0.46
4	91.7	55.2	34.0	30.0	17.6	1.34	0.57
5	91.7	47.4	43.6	24.1	16.1	0.92	0.62

1017742

TABLE 3

Kidney Activity

% Administered

Time (Hours)

Subject	0.5	2	4	6	24
1	0.22	0.34	0.25	0.11	0.013
2	0.33	0.36	0.29	0.24	-----
3	0.16	0.07	0.03	0.06	0.004
4	0.29	0.27	----	0.13	-----
5	0.07	0.05	0.01	----	-----

1017743

TABLE 4

Urine Excretion

% Administered

Time (Hours)

Subject	1	4	8	Total
1	0	45.2	27.3	72.5
2	10.0	22.6	44.9	76.5
3	0	35.9	47.4	83.3
4	10.1	44.6	17.1	71.8
5	13.6	40.4	25.5	79.5

1017744

TABLE 5

Blood Activity

% Administered

Time (Hours)

Subject	0.5	1	2	4	6
1	19.0	10.9	6.0	2.9	1.7
2	10.6	7.8	5.3	3.4	1.9
3	19.3	11.1	4.5	2.8	1.7
4	12.8	6.4	3.9	2.3	1.3
5	13.7	6.8	4.5	2.3	1.4

10177145

TABLE 6

Cumulative Activity

(mCi.hour)

Subject	Blood	Kidneys
1	36.1	2.12
2	32.5	2.08
3	34.6	0.69
4	28.9	2.02
5	30.7	0.17

1017746

TABLE 7

Average Absorbed Dose (mRad/μCi Administered)

Subject No. 1

ABSORBED RADIATION DOSE (MRAD/MCI)		
BLADDER WALL	=	199.21
BONE (TOTAL)	=	41.0276
KIDNEYS	=	7.80442
LIVER	=	3.22893
LUNGS	=	3.82152
MARROW (RED)	=	17.1451
PANCREAS	=	4.04907
SPLEEN	=	1.78798
TESTES	=	8.47224
TOTAL BODY	=	9.5987

Subject No. 2

ABSORBED RADIATION DOSE (MRAD/MCI)		
BLADDER WALL	=	123.521
BONE (TOTAL)	=	56.2511
KIDNEYS	=	8.60171
LIVER	=	3.93352
LUNGS	=	4.9717
MARROW (RED)	=	21.3726
PANCREAS	=	4.9662
SPLEEN	=	1.3907
TESTES	=	7.01055
TOTAL BODY	=	11.2455

Subject No. 3

ABSORBED RADIATION DOSE (MRAD/MCI)		
BLADDER WALL	=	150.052
BONE (TOTAL)	=	46.2389
KIDNEYS	=	5.35365
LIVER	=	3.39311
LUNGS	=	4.20706
MARROW (RED)	=	18.2658
PANCREAS	=	4.24105
SPLEEN	=	1.42841
TESTES	=	7.29181
TOTAL BODY	=	9.87659

Subject No. 4

ABSORBED RADIATION DOSE (MRAD/MCI)		
BLADDER WALL	=	210.177
BONE (TOTAL)	=	42.6226
KIDNEYS	=	7.59104
LIVER	=	3.17259
LUNGS	=	3.81251
MARROW (RED)	=	17.6698
PANCREAS	=	4.0069
SPLEEN	=	1.6666
TESTES	=	8.766
TOTAL BODY	=	9.86932

Subject No. 5

ABSORBED RADIATION DOSE (MRAD/MCI)		
BLADDER WALL	=	233.954
BONE (TOTAL)	=	37.5125
KIDNEYS	=	3.79386
LIVER	=	2.87498
LUNGS	=	3.42326
MARROW (RED)	=	16.1808
PANCREAS	=	3.58847
SPLEEN	=	1.64508
TESTES	=	9.21741
TOTAL BODY	=	9.27073

LhLL101

B.1.a Microprocessor Controlled Quantitative Scanner (CAMAC)

During the past year, we have implemented a rectilinear scanner data acquisition and control system using CAMAC. This system uses the on-line CAMAC crate on the PDP-11/55 to control and acquire data from the High Purity Germanium Array scanner as described in Section B.2.a. We were unable to implement the autonomous CAMAC system as described in Section V.B.1.a of last year's proposal (ORO-2401-94) for two primary reasons. We were unable to obtain the 8K memory module and thus were required to dump data at more frequent intervals throughout the scan. We did implement the DAM port on the PDP-9 as discussed in the proposal but shortly following the implementation, this computer began experiencing intermittant failures at a rate which precluded using it for routine data collection.

We have gained considerable experience in the area of data acquisition from rectilinear scanners but had only limited experience with control of the scanner. By using the on-line CAMAC crate on the PDP-11/55 we were able to implement the collection system in a high level language (FORTRAN). This allowed us to simply attack the algorithms for collection and control of a scanner without being concerned with the new hardware components.

The FORTRAN program we used for collection and control of the scanner portion of the High Purity Germanium Array scanner is included as Appendix and will serve as a guide line for future implementation of assembly language level programs for autonomous CAMAC crates.

1017748

B.1.b Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies

The accuracy of many of our dose estimates have suffered because of an inability to separate overlying structures which contain activity from the activity within the organs of interest. In addition, frequently, our high sensitivity scanner is unable to spatially resolve closely adjacent organs. Both of these problems have been encountered in our recent work with the new I-131 labelled adrenal scanning agents. The adrenals are frequently obscured by activity in the liver, spleen, intentine, and kidneys. With the aid of a high resolution, high sensitivity, tomographic device, the problem would be simplified considerably.

Through arrangements made with the Searle Corporation, we are obtaining a Pho/Con tomographic scanner on loan. This system was to have been installed during the past year but difficulties were encountered. Legal problems developed over the transfer of this system to Vanderbilt on an extended loan basis and a great deal of time was required for the legal and administrative departments of Searle and Vanderbilt to resolve these problems. These difficulties have now been overcome and the system should be arriving in August, 1978. This system consists of two 8 inch diameter by 1 inch thick sodium iodide crystals with focussed collimators operating as scintillation cameras (i.e. they are position sensitive). These detectors are mounted as if they were regular scintillation probes on a whole body rectilinear scanner. We had orginally planned to interface the scanner to our PDP-11 computer using CAMAC and an interface was actually designed. However, Searle has agreed to fabricate the interface for us; therefore, we have designed a special purpose interface for this application.

The computer interface to be constructed is shown in Figure 1. This proposed system will handle the Pho/Con digital output which provides probe position informaton as well as the analog signals from the nuclear detectors. The data to be collected from the scanning mechanism are the following:

1. X & Y positon of the scanner
2. X & Y position of interaction in detector
3. Top or bottom detector
4. Isotope 1 or 2

These data will be collected in the following format in list mode for post-collection reconstruction. The position of the interaction in the detector will be digitized by a Dual ADC as with any scintillation camera and the X and Y coordinates combined into a single word of the format shown below.

Bit # = 0 1 2 - 8 9 - 15

X	X	7 bits Y	7 bits X

Bit 0 = Detector Flag: 0 = Top, 1 = Bottom
Bit 1 = Isotope Flag: 0 = ISOTOPE 1, 1 = ISOTOPE 2

The position of the scanner mechanism will be obtained from encoders mounted on the X and Y axis of the instrument. These will be calibrated to provide a digital resolution equal to the detector digital resolution, i.e. 1.58mm/pt for 8" detector or 2.18mm/pt for 11 inch detector. As the scanner passes from one data cell to the next the bed coordinates will be inserted in the data list as a 3 word element in the following format:

Word 1 = FLAG WORD = ZERO

Word 2 = OSCILLATOR & X COORDINATES

Word 3 = Y COORDINATES

In the word containing the X coordinate of the scanner we will place a 7 bit value representing the output of a precision oscillator. If the scanner speed is stable the detector will remain in each data cell for a constant time period. If it is not stable the time spent in each data cell and therefore the sensitivity will vary from cell to cell. By storing the oscillator counts, we can obtain an accurate monitor of scan speed stability for quantitative scanning studies.

The different data sets will be handled by a 4 to 1 multiplexor. When operating and not transmitting scanner position information, the 4 to 1 multiplexor will be controlled so as to select the output of the buffer registers on the dual ADC's which digitize scintillation data.

If either the X or Y scanner position changes (as indicated by a pulse called DELSCN), the following sequence takes place. The X and Y registers are latched. The two bit counter is cleared to cause the multiplexer to select a zero data word. When the DATA TAKEN pulse is returned, it increments the counter to select the scanner X position and transmits a second DATA RDY pulse. Upon acceptance of this data, the Scanner Y position is transmitted. After this data is accepted, the counter again selects the normal camera input but does not transmit the DATA RDY pulse. Thus the single flag word of all zeros and the 2 scanner position words are transmitted in sequence whenever either axis of the scanner changes. At all other times the single camera data word is transmitted.

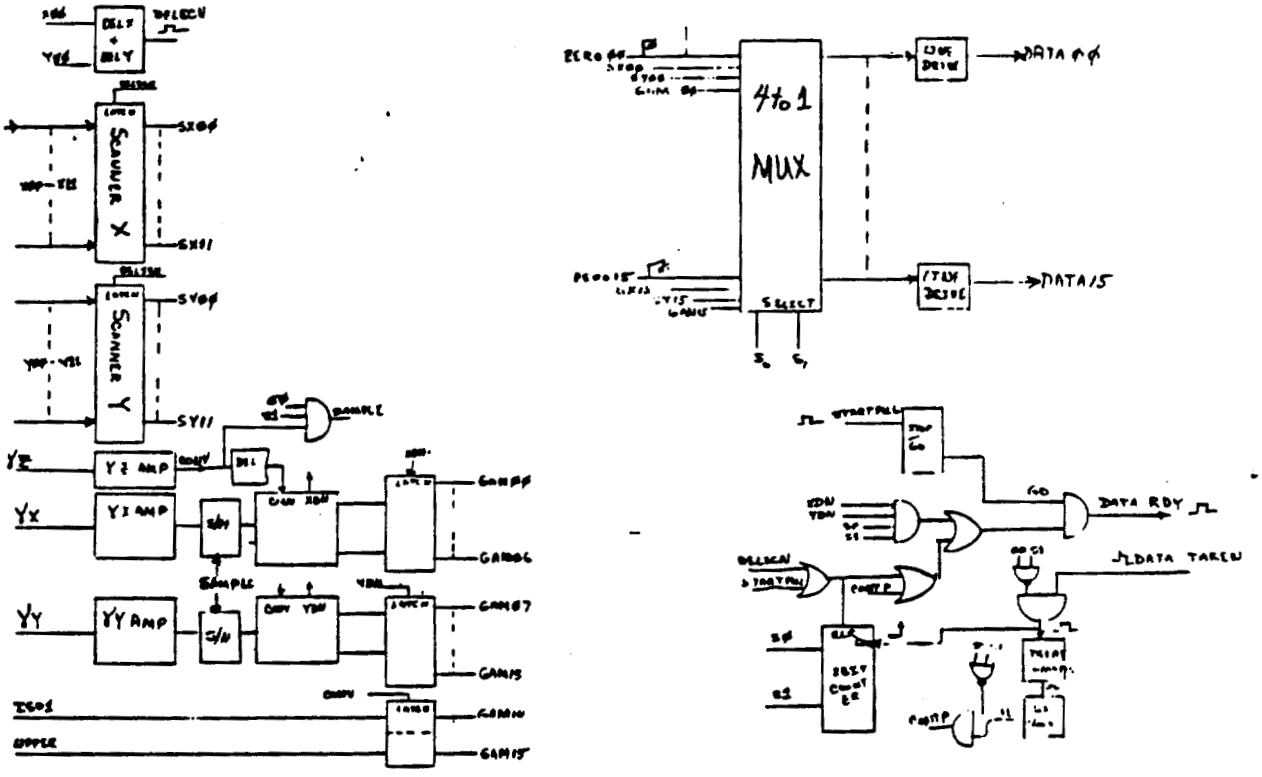
This method of data storage will result in a list of data which will be very amenable to reconstruction of tomographic images. The 3 word block with the leading flag word can be used for other information such as elapsed time for decay correction by use of a different flag word. This is possible since there are a large number of coordinates in 128 X 128 square array into which the circular detector image is digitized that are not used for image data. Any of these coordinates can be used for a flag word.

The data from the interface will enter the PDP-11 computer either through a CAMAC register or a DMA port and will be stored in list mode on disk. Image construction will then be performed after completion of the scan (See section B.2.a).

1017750

Figure 1

Computer Interface for Searle Pho/Con Scanner



1017751

B.2.a. Acquisition/Reconstruction display of Tomographic Data

As discussed in section B.1.b the anticipated arrival time of the Pho/Con tomographic scanner has been delayed and therefore we have no direct experience in the acquisition, reconstruction, and display of tomographic data from this system to report. However, we have been working with a research prototype longitudinal section scanning device similar in concept to the Pho/Con system. This instrument is a nine crystal intrinsic germanium detector system with multiple focussing collimators utilizing a common focal point. The image reconstruction problem for this system is a degenerate case of the Pho/Con reconstruction problem and algorithms developed for this system can be easily applied to the Pho/Con.

For the Pho/Con system data will be acquired in list mode with coordinates stored in relation to two coordinate systems as shown in Figure 1. The position of the center of the camera head will be recorded in relation to the scanner coordinate system and the position of each scintillation on the camera face will be recorded in relation to a camera coordinate system whose origin is at the center of the camera face. Thus an image of a particular plane can be constructed by back projection techniques by simply translating the coordinates of each recorded scintillation within the camera coordinate system and adding them to the proper locations within the scanner coordinate system. The dimension and direction of the translations are determined by the location of the reconstructed plane in relation to the geometric focal plane as shown diagramatically in Figure 1. Thus it will be possible to reconstruct images of the radioisotope distribution in any plane by this technique.

For the germanium system data are collected and stored separately for each of the 9 detectors (equivalent to list mode data collection for the Pho/Con). An image of a particular plane is constructed by translating the data for each detector within the probe coordinate system and adding them to the proper locations within the scanner coordinate system. The geometry and mathematics of performing the translations are the same as shown in Figure 1 for the Pho/Con. The only difference is that instead of having an array of points for each probe position corresponding to the digitized field of view of the scintillation camera at each scanner position we have 9 discrete points for each scanner position. Software packages have been developed at Vanderbilt to construct longitudinal section images by the back-projection technique for the germanium system.

A set of planes constructed by this back-projection technique for a dog with an induced myocardial infarction are shown in Figure 2 to demonstrate the image quality obtainable with this method. The distances shown are in inches from the anterior surface of the dog. The isotope used was Tc-99m pyrophosphate, an agent that accumulates in damaged heart muscle, as well as bone. The knowledge gained in developing this software should greatly simplify the development of image reconstruction software for the new system.

The problem with the back-projection technique is that it is not quantitative (i.e. every detected event goes into the image of each plane). Our goal is to be able to quantitate the amount of activity in each reconstructed plane in order to improve the accuracy of our dose estimates by more accurately determining activity distributions within organs and background activities. We are therefore exploring new reconstruction techniques with the goal of achieving true plane distributions of activity.

1011752

The Pho/Con tomographic scanner (as well as our prototype scanner) produces focal plane tomograms of the activity distribution in the object. Each tomogram reconstructed using the traditional back-projection technique includes not only the image of the true activity distribution in the selected plane but it also contains a superposition of the defocused images of the activity distributions at all other planes. Mathematically it is possible to remove the off-plane smearing thus producing a series of sharply-focused true object activity distributions. We are currently evaluating a pseudo-three-dimensional method proposed by Chang and MacDonald in which the defocused background is eliminated from the sequence of two-dimensional planes through the object using a deconvolution approach.

Using the symbols tj (x,y) to represent the matrix of the back-projected (blurred) tomogram at plane j and $o_i(x',y')$ to be the "true" object activity distribution at plane i, the back-projection process can be expressed mathematically in the following manner:

$$tj(x,y) = \sum_{i}^{n} \int\int_{x'y'} o_i(x',y') h_{ij} (x - x', y - y') \, dx'dy',$$

where h_{ij} $(x - x', y - y')$ is the system response function and gives the response at point (x,y) in plane j to a point source at the point (x',y') in plane i. In this formulation the object is reconstructed in a sequence of n planes. If one takes the Fourier transform of the above equation it becomes:

$$Tj(f_x f_y) = \sum_{i} O_i \, (fxfy) \cdot H_{ij} \, (fxfy)$$

where the capital letters denote the transformed quantity and fx and fy denote the component frequency variables. In Fourier space the above equation represents a set of n simultaneous linear equations with n unknown (O_i's) at each frequency. The formal solution being given by:

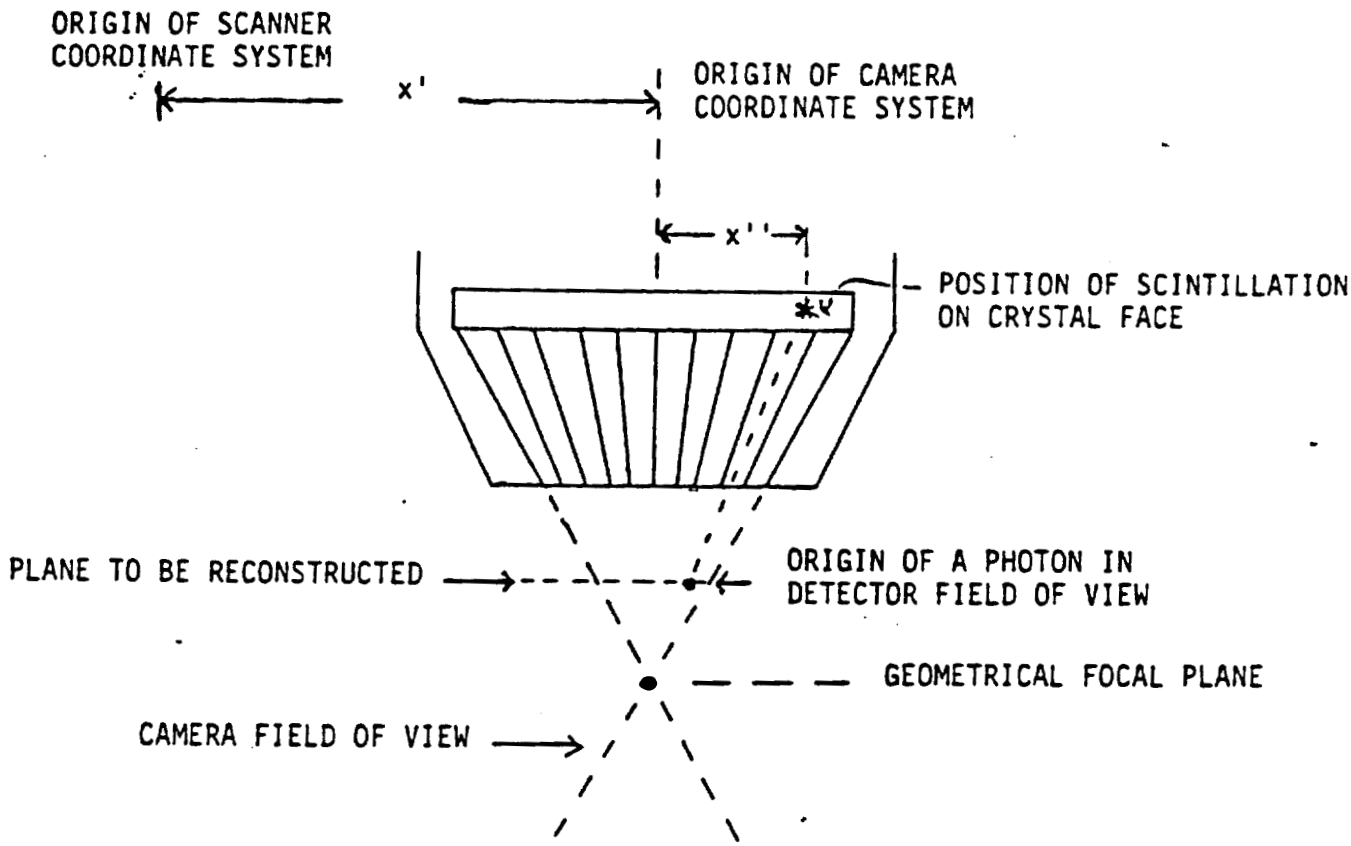
$$Oi \, (fxfy) = \sum_{j} Tj \, (fxfy) \cdot H_{ij}^{-1} \, (fxfy) \, .$$

We have created the H_{ij} matrix by scanning a point source in each of the planes to be reconstructed and then back-projecting it onto each other plane. The back-projected tomograms are then transformed using a Fast Fourier Transform program and then used to construct H(fxfy). Images of the point source response from each of 9 planes used in the reconstruction process are shown in Figure 3. The software system that we have developed to carry out these calculations in Appendix III

1017753

In addition to the Fourier techniques we are currently building into the image reconstruction programs the ability to perform uniformity corrections to correct for variations in sensitivity of the detector system and also attenuation corrections to make allowances for source depth. As soon as this software package is completed we plan to perform quantitative evaluations in phantoms before attempting quantitative tomography in patients.

1017754



$X = x' + kx''$

X = traverse position of recorded event on image of reconstructed plane.

x' = traverse position of center of camera head in relation to scanner coordinate system.

x" = traverse position of scintillation on crystal face in relation to camera coordinate system.

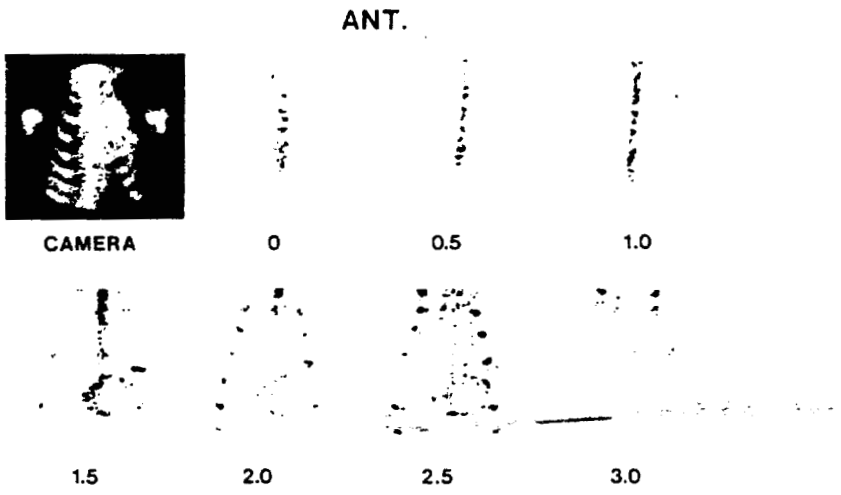
k = constant determined by distance and direction of reconstructed plane from geometrical focal plane.

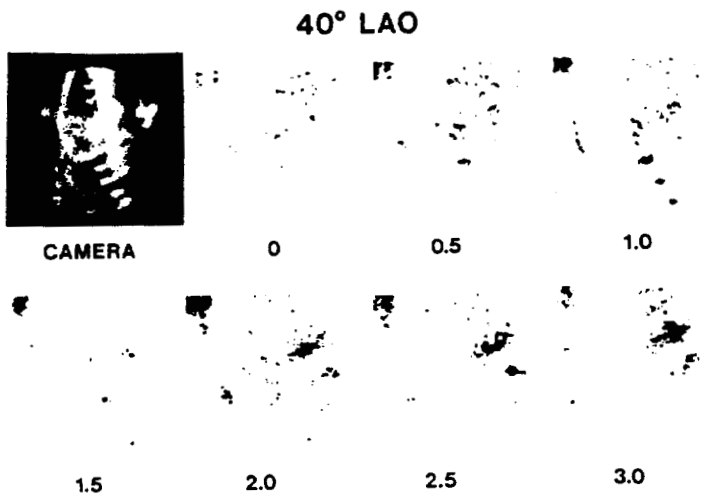
Similarly, the longitudinal position of the recorded event on the image of the reconstructed plane is given by:

$Y = y' + ky''$

FIGURE 1

1017755





e 2 Anterior and 40 degree LAO views of a dog with a surgically
ed infarction imaged with Tc-99m pyrophosphate using the scintillation
a and the high purity germanium array in the tomographic mode. The
ices are in inches from the anterior surface of the dog. Note the
separation of the activity distributions in the tomographic images
are superimposed in the routine frontal plane images from the camera.

1011756

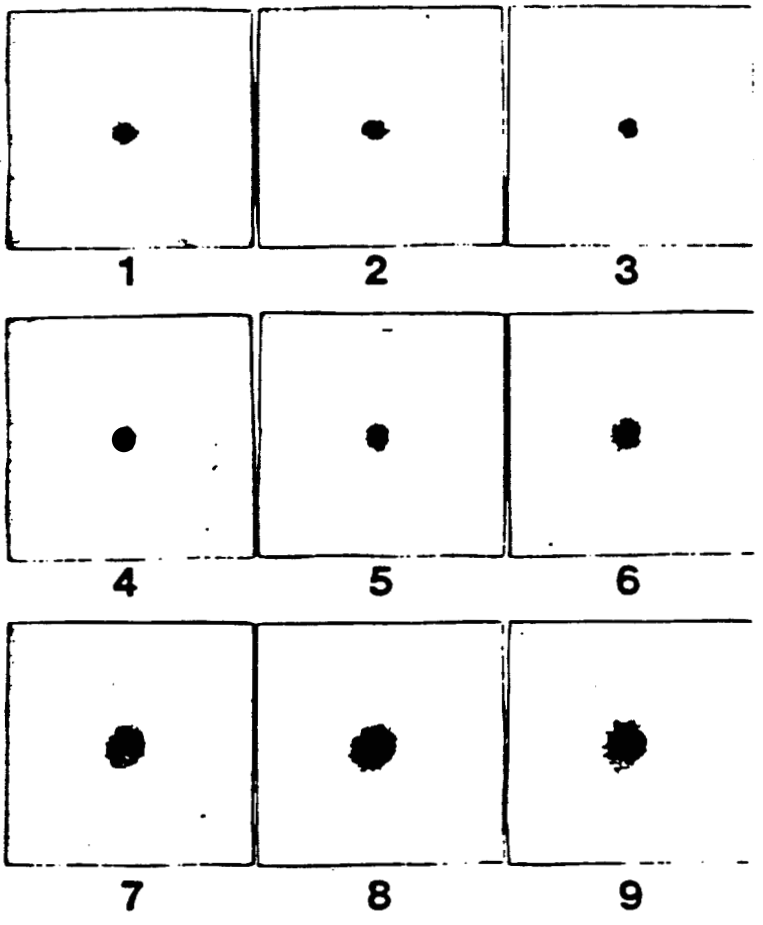


Figure 3 Point source response with Tc-99m (140 keV) for the high purity germanium array at 0.75 inch increments from 1.50 inches above the focal plane to 4.50 inches below the focal plane. Each image is a 64 x 64 array corresponding to a 6 x 6 inch scan field.

1017757

b. Sharing Efforts

i.) Simulation and Modelling

We have continued to develop and test new kinetic models in order to gain a better understanding or the organ and tissue retention of medically administered radioactive materials. Solutions to these models have been sought generally through the compartmental modelling techniques of the NIH (Berman) computer program SAAM. In our recent work SAAM is being used to analyze Fe-59 citrate, I-131 Iodocholesterol, In-111 citrate and I-131 Hippuran data. The advantage of SAAM over other programs is its ease of use and its provision to include data from external measurements. The uniqueness of this work is the use of quantitative external measurements to supplement the routine kinetic data from excretion and blood sample data.

The SAAM program that we are currently using was converted from the NIH-IBM/360 version to run our Xerox Sigma 7 computer. The NIH has now developed an interactive version of SAAM which runs on the PDP-10 computer. During the coming year, we will attempt to acquire this version and implement it on Vanderbilt's PDP-10 system. The ability to interact with the program makes it possible to reduce the solution time considerably and also provides a teaching aid for understanding the behavior of the model.

On April 28 - 31, 1977 we organized and co-sponsored a seminar-workshop for SAAM users. The meeting was attended by approximately 40 people from throughout the country. Dr. Price was elected as the coordinator of the group. During the coming year we propose to orgainize a second SAAM workshop. These workshops will serve as a mechanism for people who are working in the area of kinetic modelling to gather, discuss current topics and share ideas.

1017758

ii) Sharing of Computer Programs in Nuclear Medicine

We continue to work closely with the personnel of the Biomedical Computing Technology Information Center (BCTIC) at Oak Ridge. Dr. Brill is a member of the Advisory Committee and Dr. Erickson co-directed the production of a Nuclear Medicine Computing Directory. The first directory contined documentation on over 80 U.S. and 20 foreign nuclear medicine computer installations. The second edition of the directory is currently in production. This document greatly facilitates the interchange of software and provides software, hardware and clinical contacts at the various institutions.

The SAAM program (IBM-360 version) has now been added to the BCTIC library and is now being distributed. The Sigma-7 version of SAAM has been sent to St. Luke's Childrens Hospital in Memphis, Tennessee and we are currently working with them to help implement it on their own system.

ORIS-11 Evaluation

The Oak Ridge Imaging System (ORIS) has been successfully translated from the original PDP-8 language to the PDP-11 language by Drs. Bell and Dougherty of ORNL. The resulting ORIS-11 version 01 system was designed to operate on a clinical DEC GAMMA-11 nuclear medicine-imaging system. ORIS-11 is not a stand alone system but is used to process raw-data images which have been acquired and stored on disk by the GAMMA-11 system. ORIS-11 version 01 has been implemented on the Vanderbilt clinical GAMMA-11 system and will be evaluated and tested during the coming year. Of particular interest to us are the two-dimensional Fast Fourier Transform (FFT) programs which are available in ORIS. These programs will be used to replace similar FFT programs which are now being used as part of the quantitative tomographic reconstruction programs.

1017759

APPENDIX I

1. Organ distribution data I-131-19-Iodocholesterol

2. Organ distribution data I-131-6-Norcholesterol

1017760

I-131-19-Iodocholesterol

(% of Administered Activity)

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Total Body	1.00	---	.38 ± .06	.19 ± .07	.15 ± .07	---
Liver	.60 ± .05	.33	.08 ± .03	.04 ± .01	.03 ± .01	---
Upper Left Quadrant	.12 ± .03	.12	.06 ± .03	.04	.03 ± .01	---
Mid GI	.03	.05	.04 ± .02	.02 ± .01	.010 ± .006	---
Bladder & Rectum	.06 ± .01	.07	.05 ± .04	.027 ± .002	.02 ± .01	---
Thyroid	.05 ± .04	.03	.02 ± .01	.02 ± .01	.04 ± .02	---
Unaccounted For	.15 ± .06	.08 ± .06	.05 ± .03	.05 ± .03	.02 ± .01	---

	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Total Body	.16	.05 ± .02	.049 ± .009	.065	.04 ± .03	.017 ± .007
Liver	.032	.008 ± .004	.005	.008	.010	.003
Upper Left Quadrant	.02	.006 ± .005	.007 ± .004	.027	.002	.002 ± .001
Mid GI	.01	.004 ± .003	.004	.01	.003 ± .001	.002 ± .003
Bladder & Rectum	.01	.005	.005 ± .002	.001	.003	.002 ± .001
Thyroid	.06	.01 ± .01	.010 ± .017	.0006	.04	.006 ± .005
Unaccounted For	.02	.01 ± .01	.016 ± .008	.02	.010 ± .007	.004 ± .002

1017761

I-131-19-Iodocholesterol

(% of Administered Activity)

Continued

	Day 12	Day 13	Day 14
Total Body	.015 ± .003	---	.008 ± .003
Liver	.003	---	.002
Upper Left Quadrant	.002	---	.001
Mid GI	.002 ± .001	---	.001
Bladder & Rectum	.001	---	.001
Thyroid	.002	---	.002 ± .003
Unaccounted For	.005 ± .002	---	.004

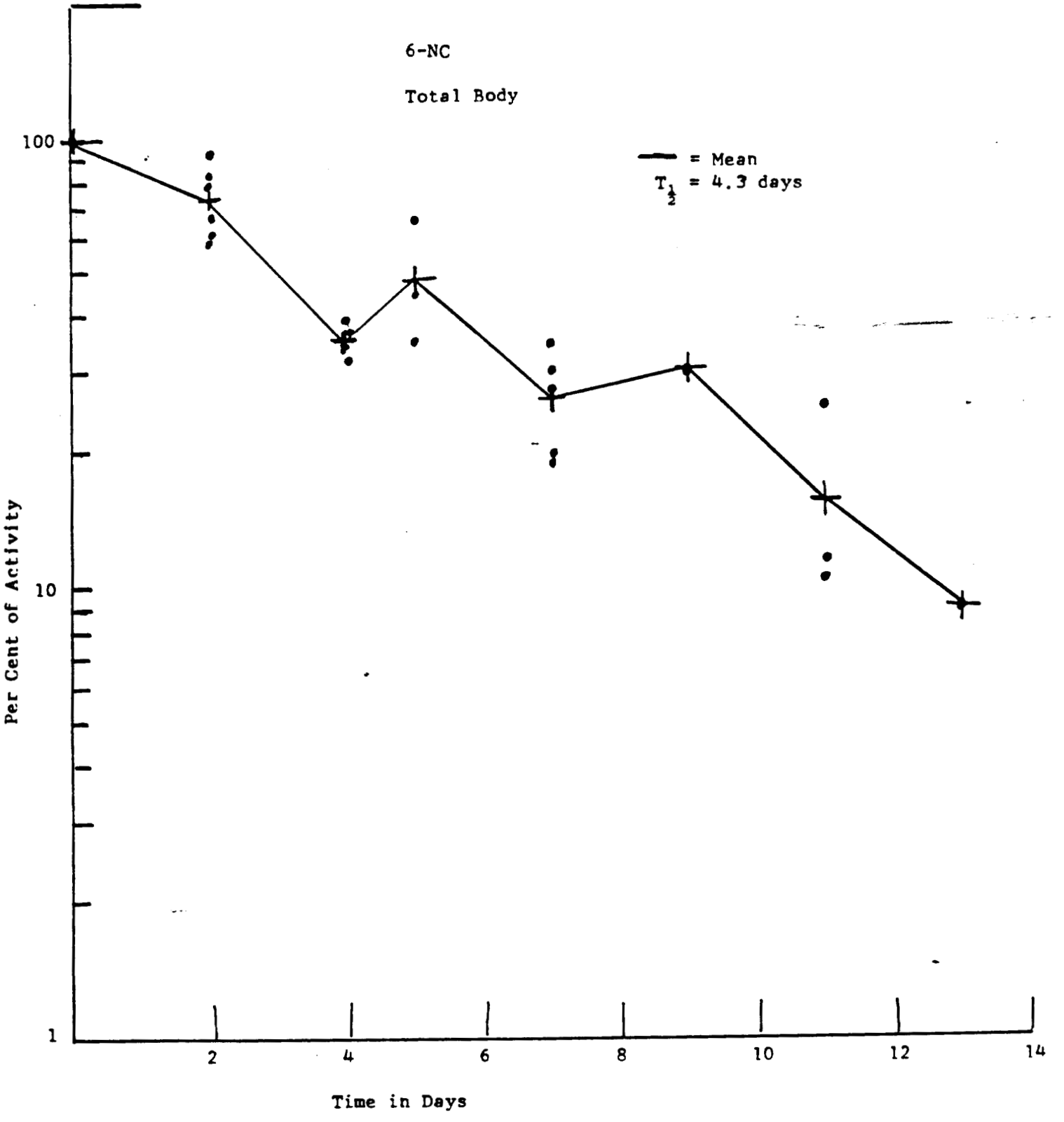
1017762

Blood Levels

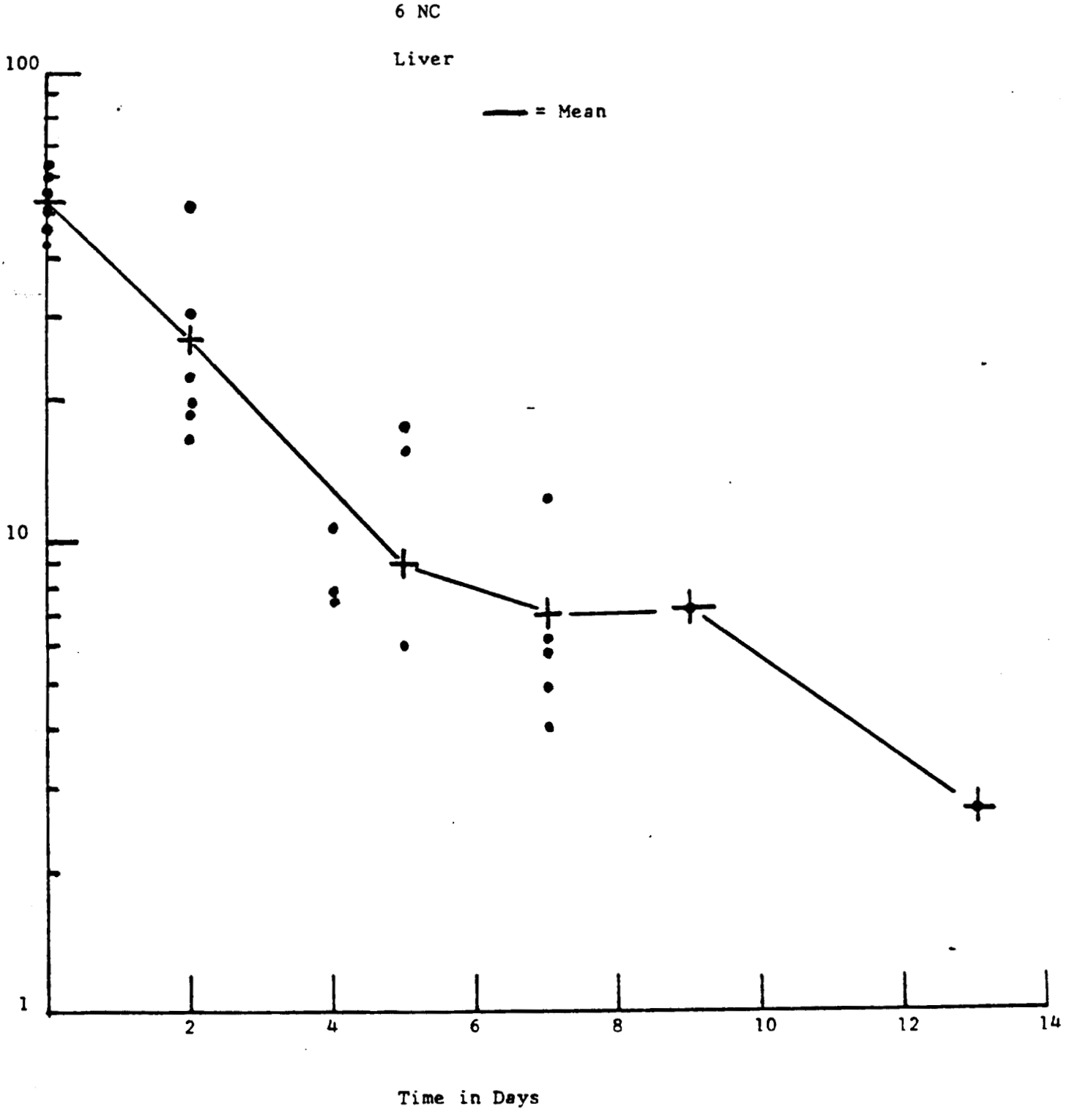
(% of Administered Dose)

Compound	Day 0	Day 2	Day 3	Day 4	Day 7	Day 11
19IC	100	---	9.3 ± 4.2	---	1.0 ± 0.5	0.3 ± 0.1
6NC	100	21.2 ± 3.6	---	8.5 ± 0.7	4.4 ± 0.6	2.0 ± 0.1

1017763


6-NC
Total Body
= Mean
$T_{\frac{1}{2}}$ = 4.3 days
100
10
1
Per Cent of Activity
2
4
6
8
10
12
14
Time in Days

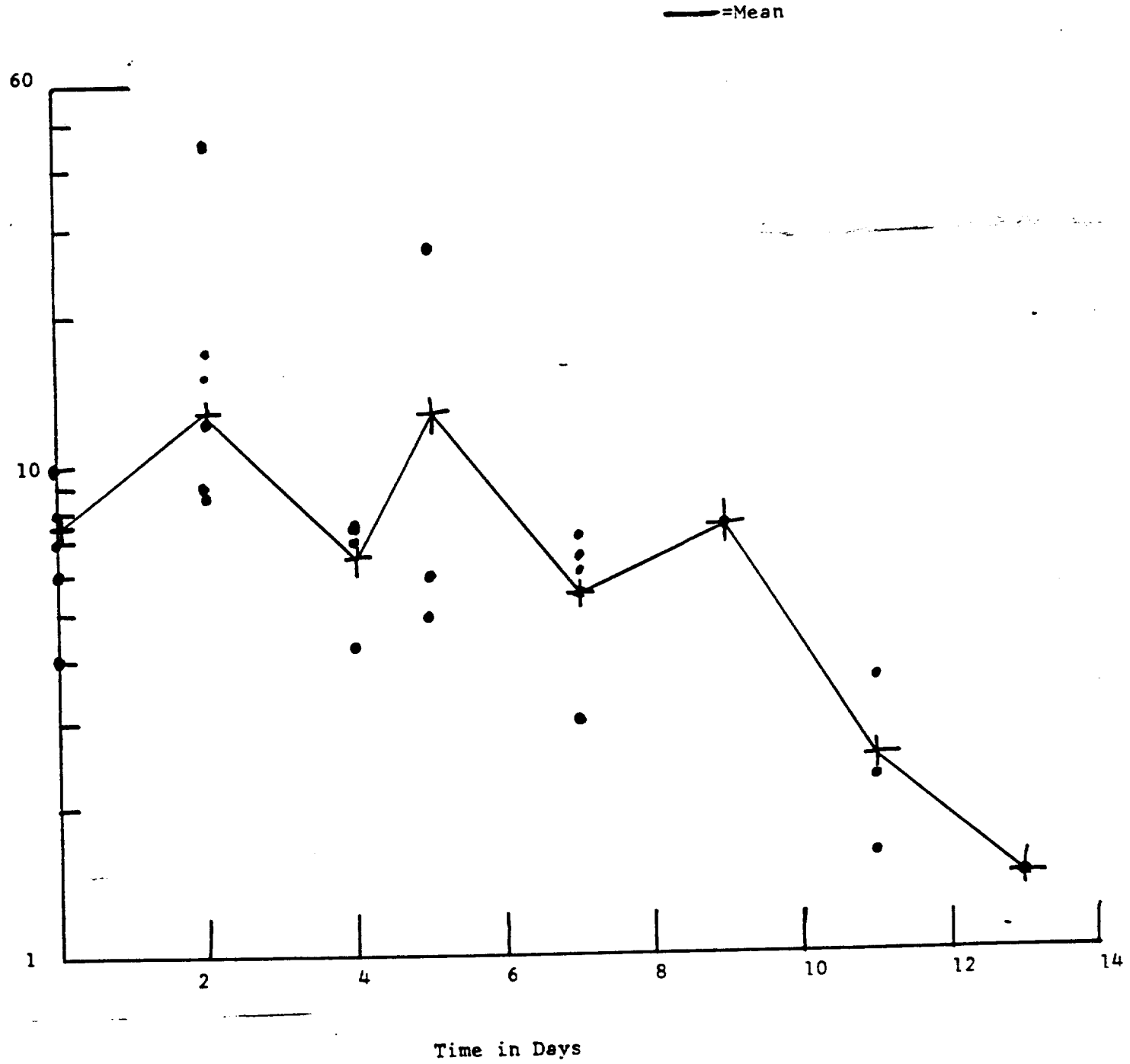
1017764



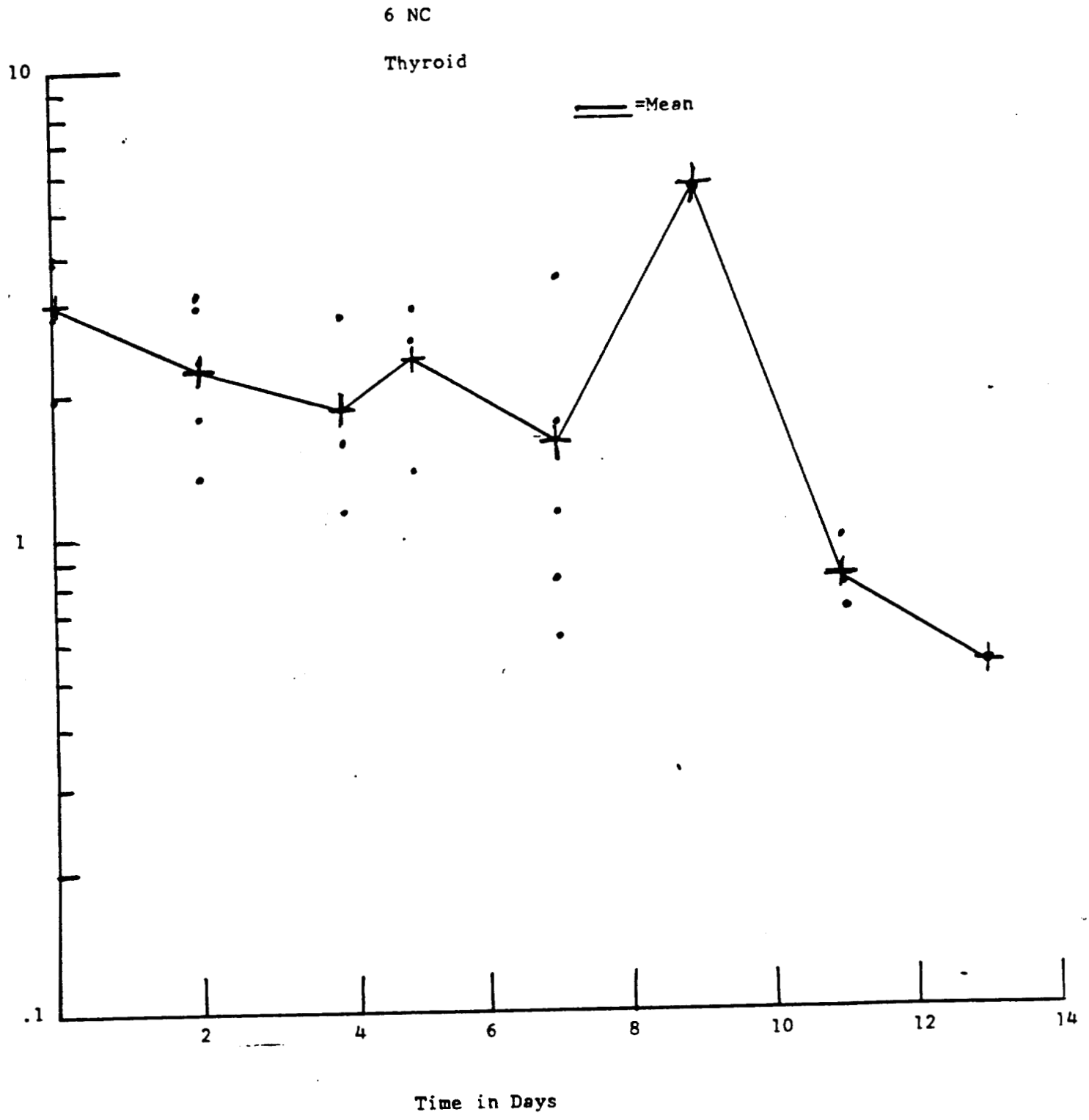
1017765

6 NC

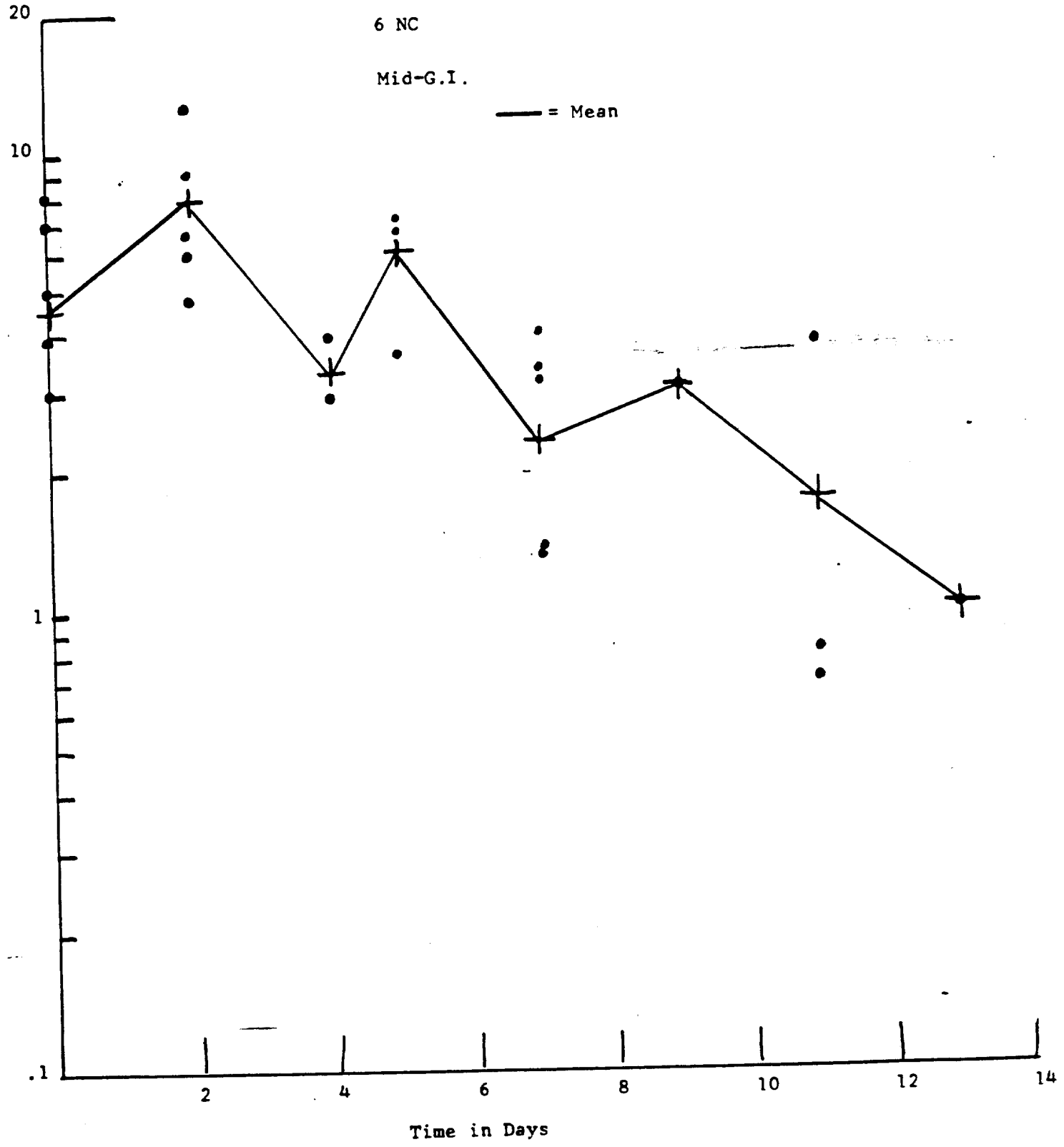
Bladder



1017766



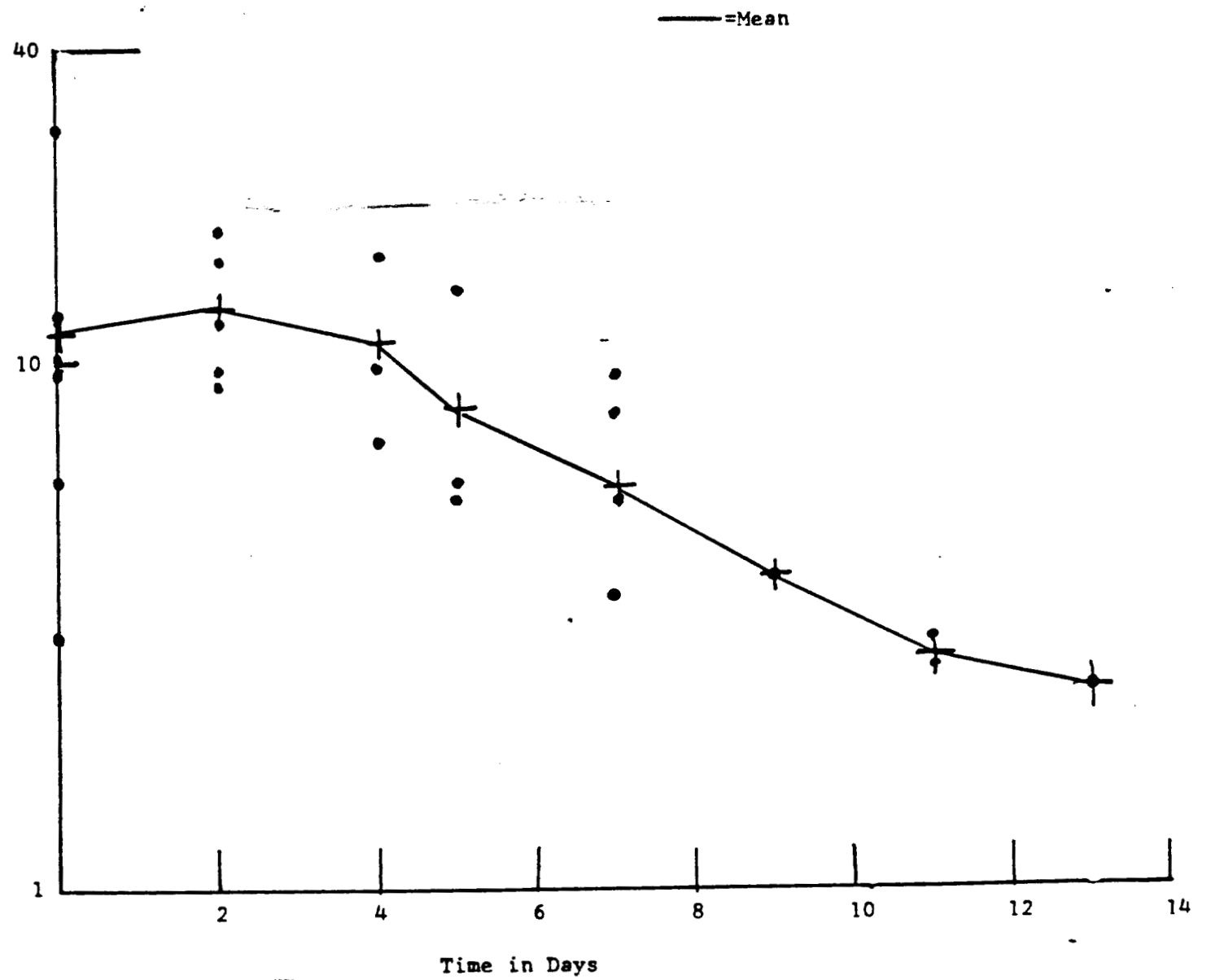
1017767



1017768

6 NC

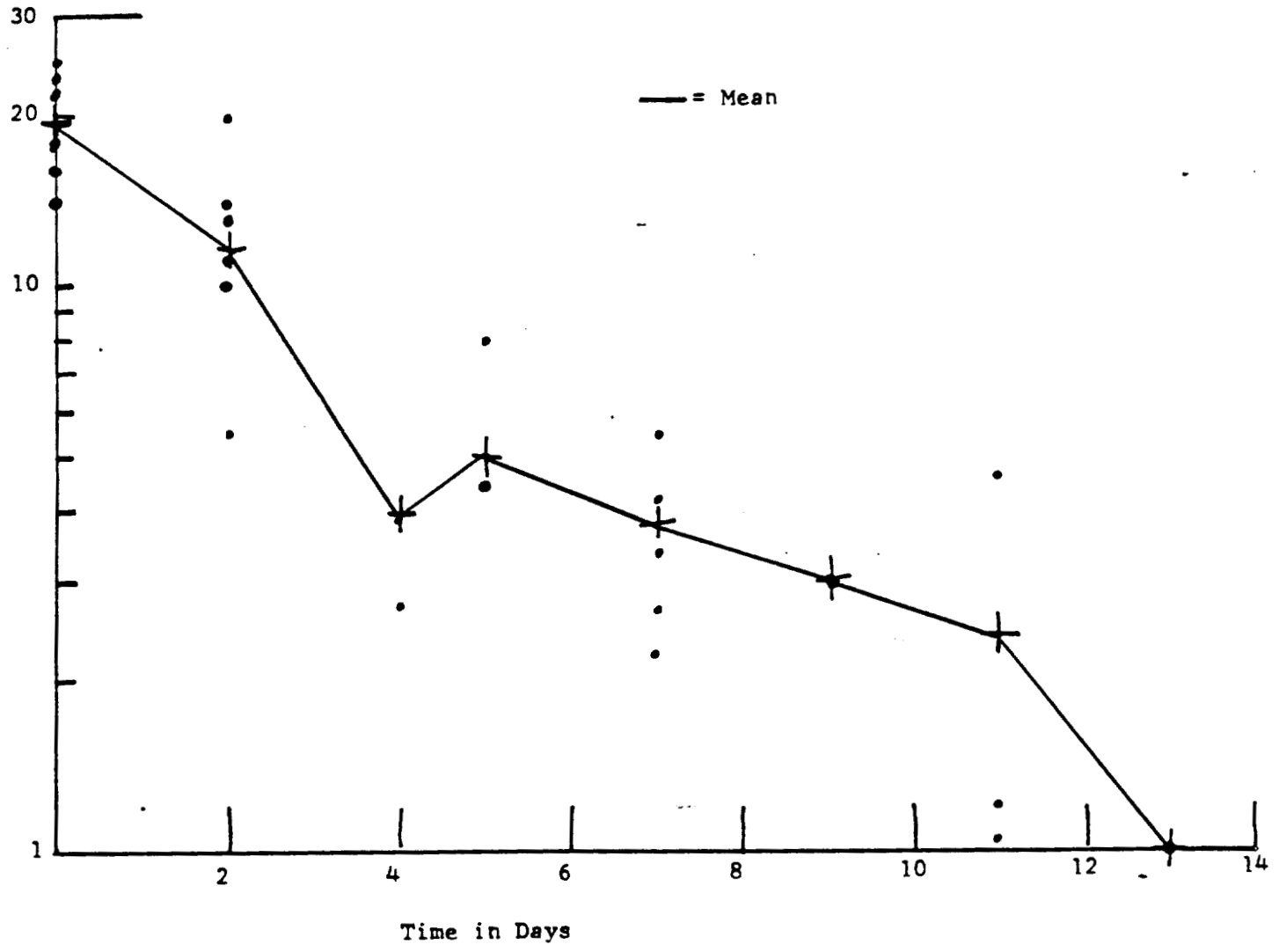
Other Body Activity



1017769

6 NC

Upper Left Quadrant

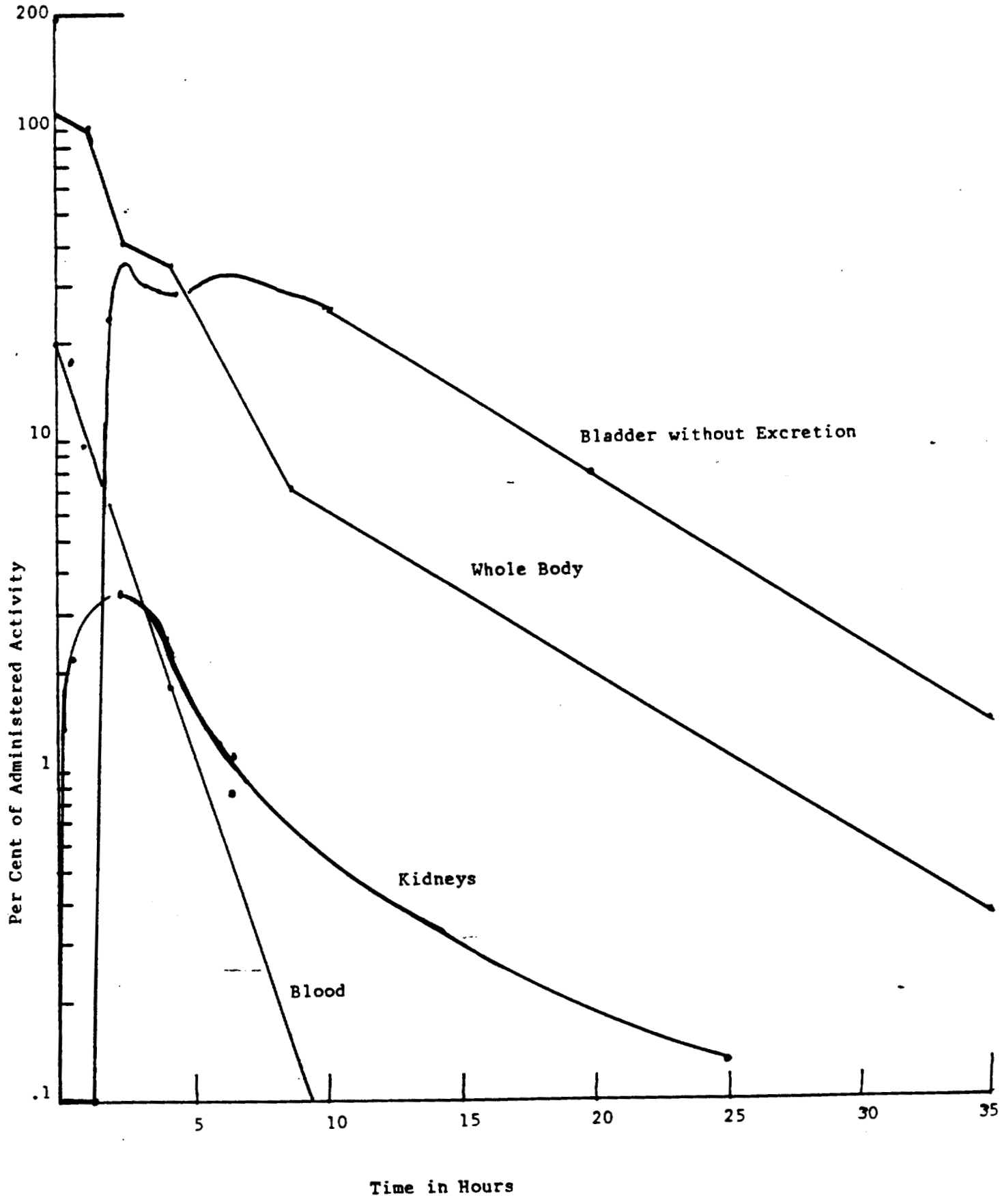


1017770

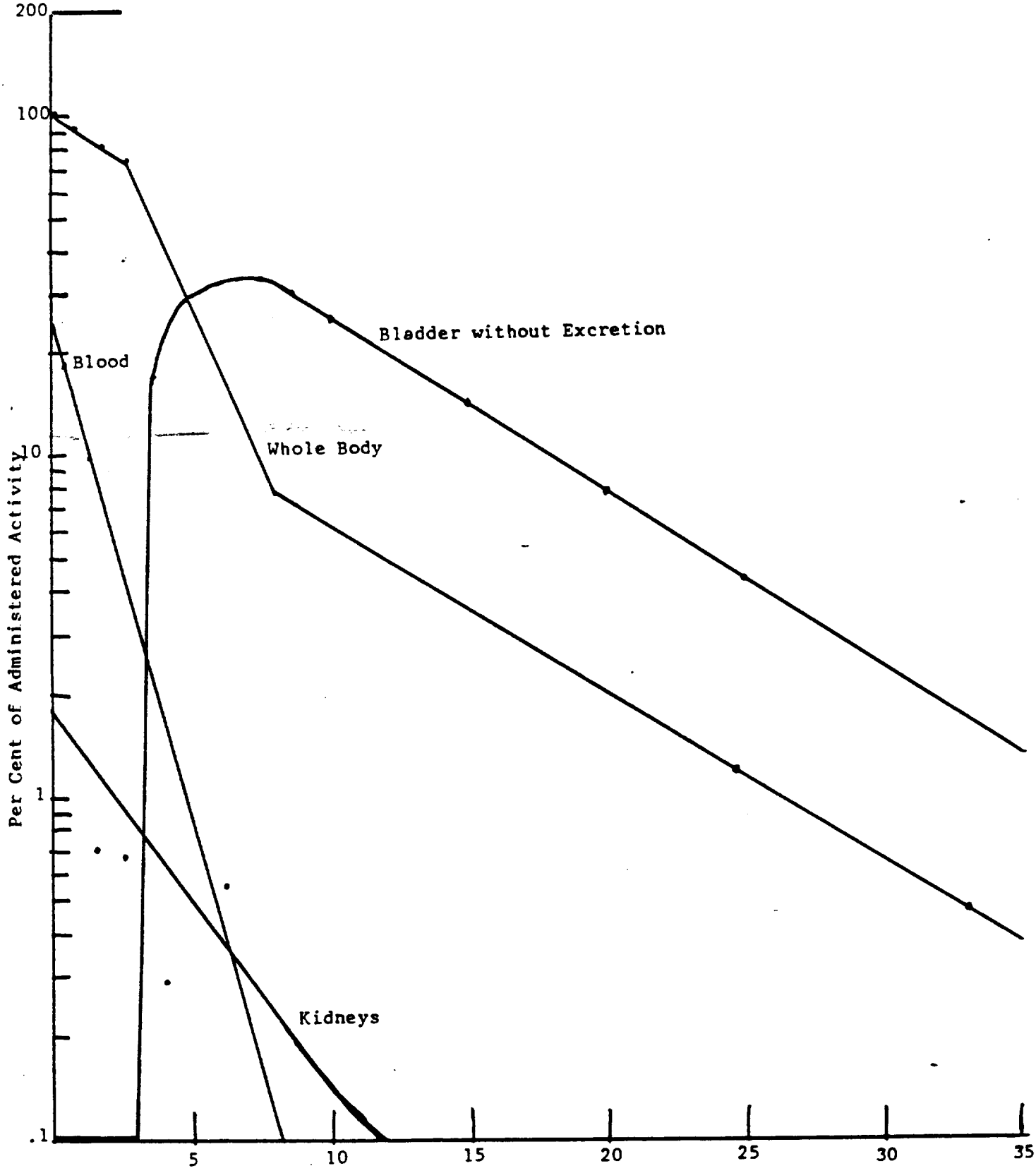
APPENDIX II

Retention curves for Tc-99m-Sn-Methylene Diphosphonate

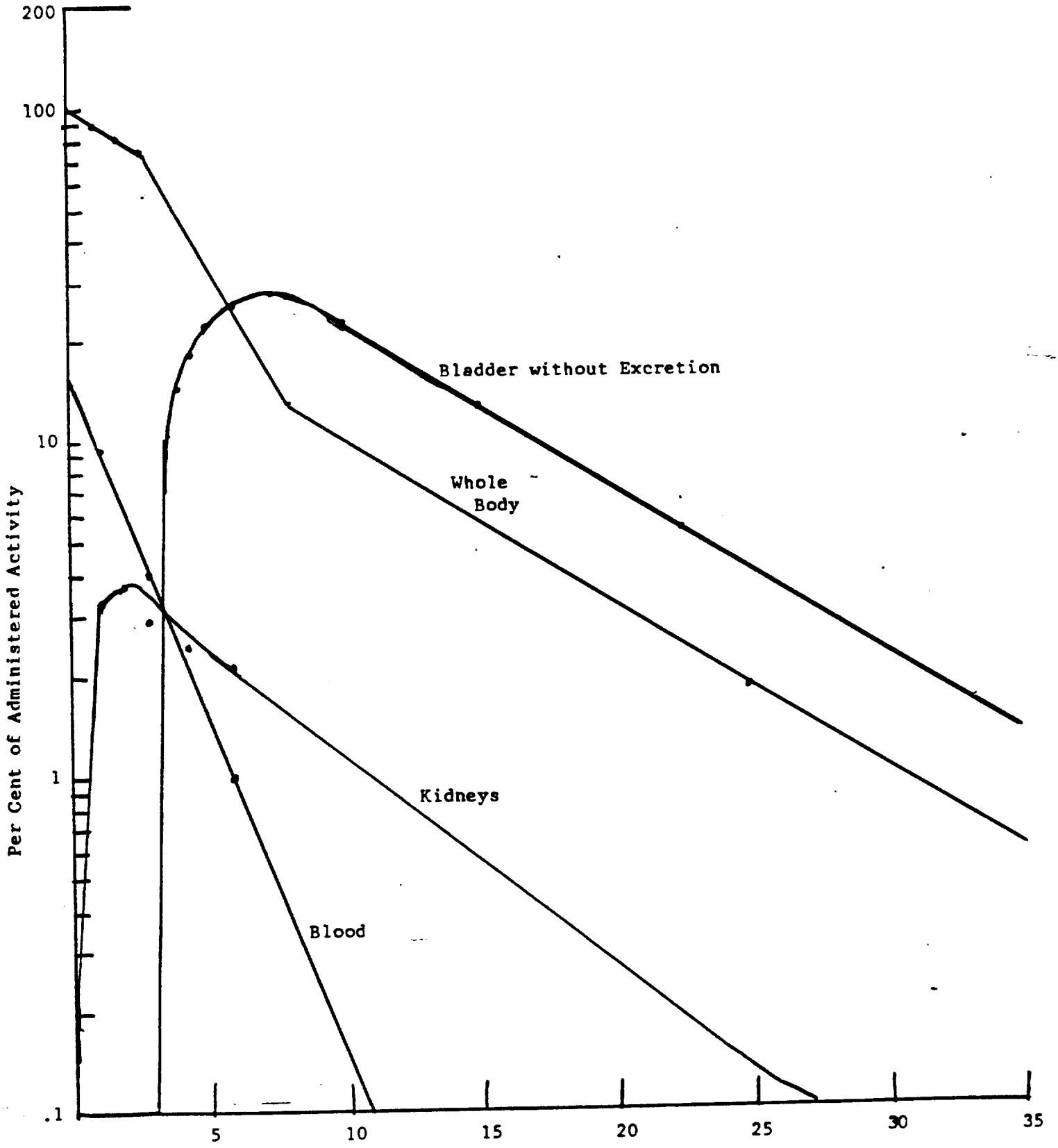
1017771


200
100
10
1
.1
Per Cent of Administered Activity
Bladder without Excretion
Whole Body
Kidneys
Blood
5
10
15
20
25
30
35
Time in Hours

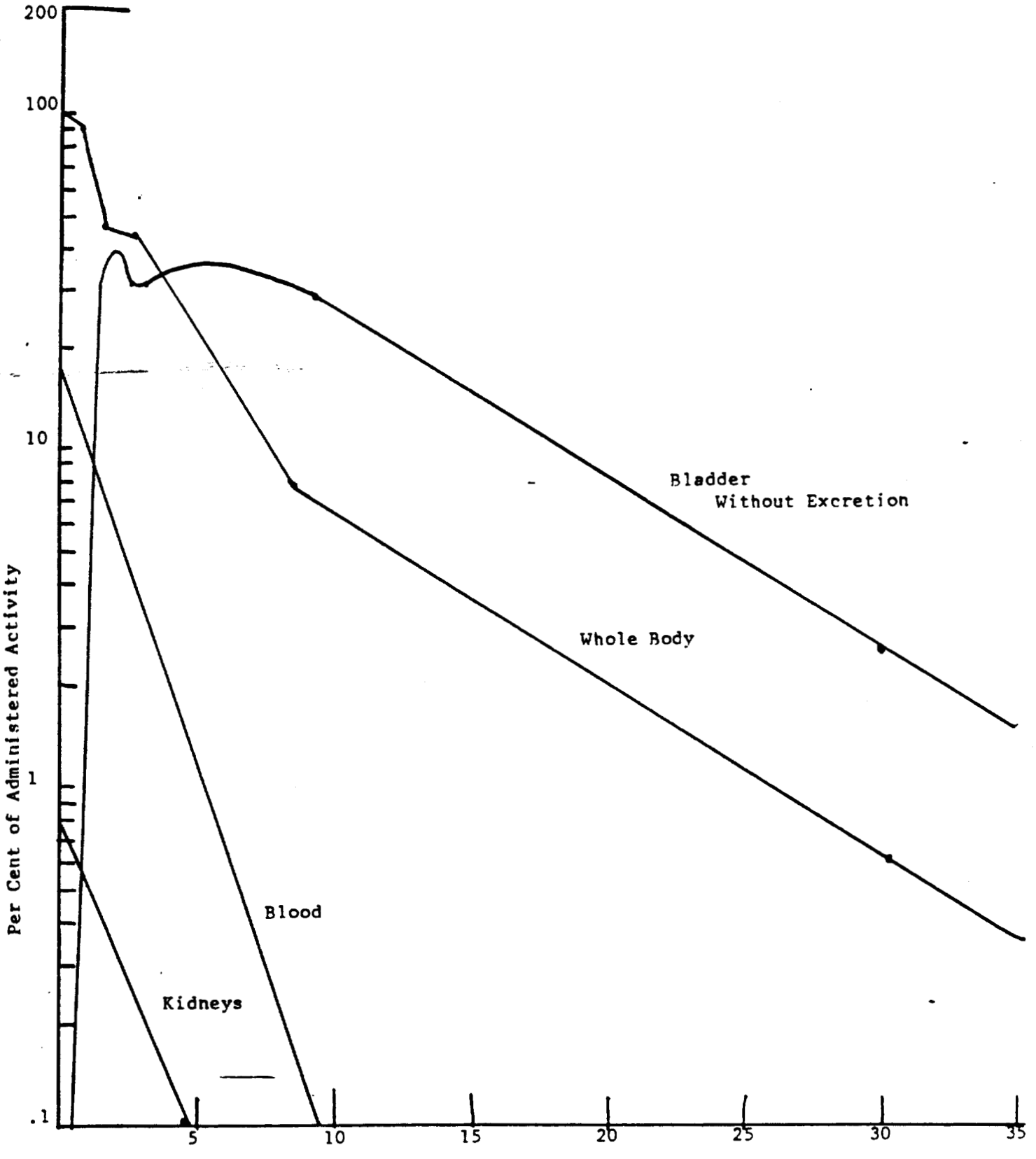
1017772


200
100
10
1
.1
Per Cent of Administered Activity
Blood
Bladder without Excretion
Whole Body
Kidneys
5
10
15
20
25
30
35
Time in Hours

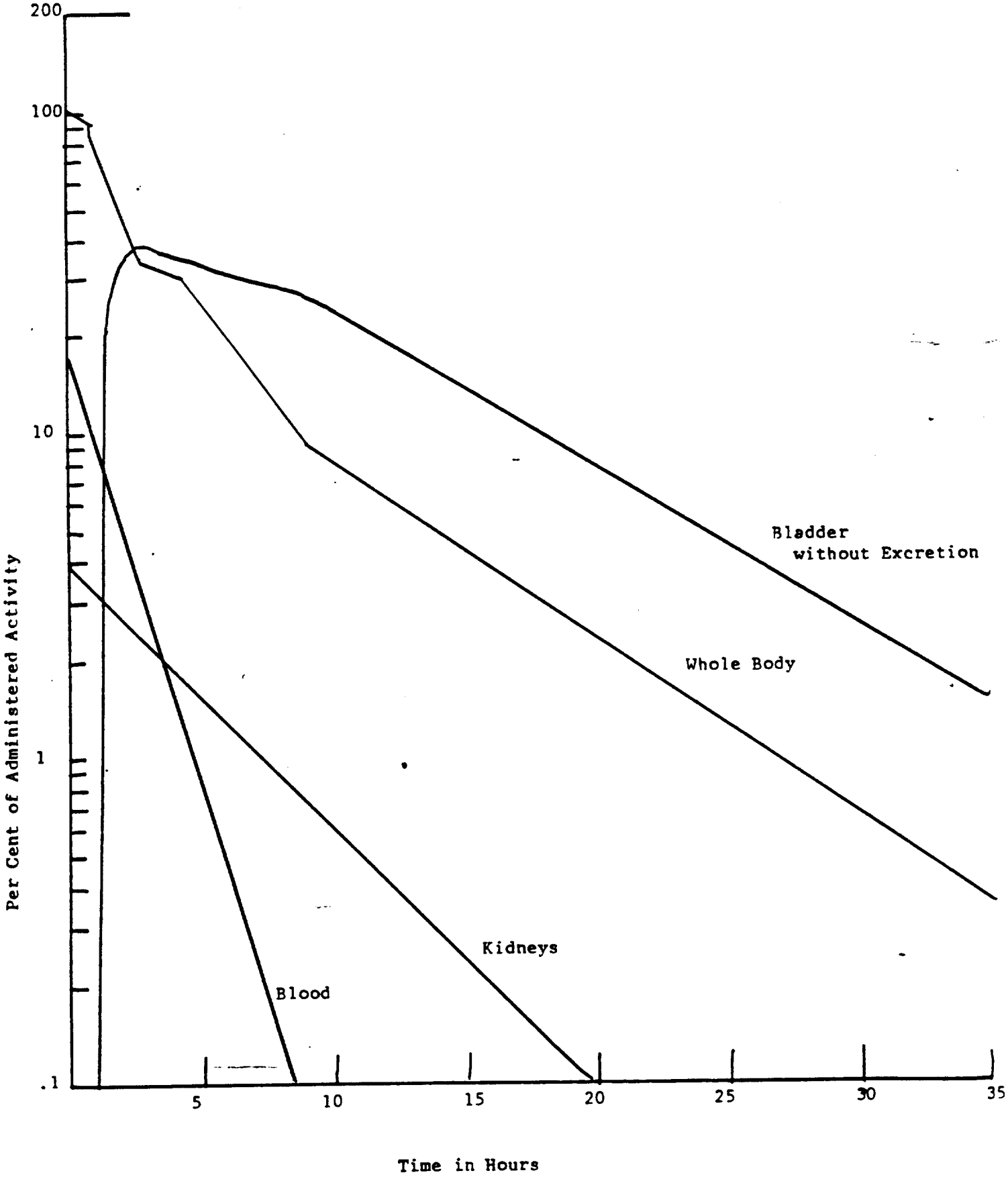
1017773


200
100
10
1
.1
Per Cent of Administered Activity
Bladder without Excretion
Whole Body
Kidneys
Blood
5
10
15
20
25
30
35
Time in Hours

1017774


200
100
10
1
.1
Per Cent of Administered Activity
Bladder
Without Excretion
Whole Body
Blood
Kidneys
5
10
15
20
25
30
35
Time in Hours

1017775


200
100
10
1
.1
Per Cent of Administered Activity
Bladder
without Excretion
Whole Body
Kidneys
Blood
5
10
15
20
25
30
35
Time in Hours

1017776

Appendix III

DECONVOLUTION INFORMATION FLOW

SOFTWARE DESCRIPTION

1. Point source data are obtained for a source at each of nine levels.

2. Tomographic blurred data are obtained for an object in a plane.

3. TRFRM2 converts each image plane and point source plane into its two dimensional Fourier domain representation.

4. Point source information is rearranged by SETUP for processing by HUGE.

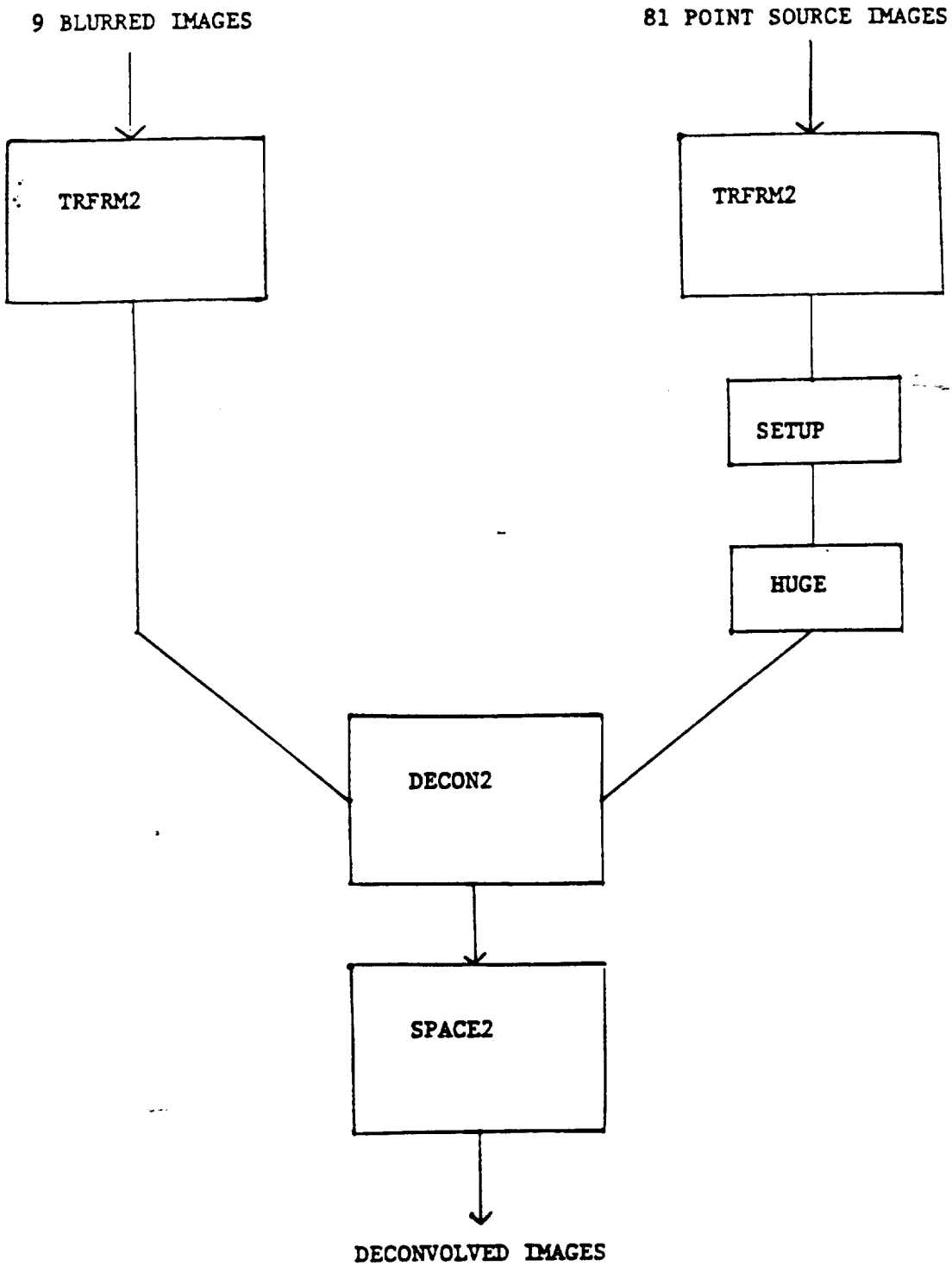
5. HUGE forms a single file containing all point source information which represents the system response and is used for each deconvolution.

6. In DECON2 the Fourier domain image response and the Fourier domain point source responses are used in the solution of the matrix equation $AX = B$, where A is a square matrix representing the point source response at a single spatial frequency, and B is a vector representing the tomographic image response at a single spatial frequency. X is a vector representing the desired deblurred object response at a particular spatial frequency.

7. The solution vectors produced by DECON2 are processed by SPACE2 which performs an inverse Fourier transformation. Nine images are returned representing each deblurred tomographic image.

1017777

DECONVOLUTION INFORMATION FLOW



1017778

TT:=DECONQ.FOR

```
      PROGRAM
C     DECONVOLUTION IN FREQ DOMAIN
C
      DIMENSION RI(9),AI(9),H(18,9)
      DIMENSION B(9,66,4)
      DIMENSION E(9,66)
      DOUBLE PRECISION HSQR(18,18),B(18)
      WRITE(7,20)
   20 FORMAT(1X'INPUT FILE, PT. SRC RESP':6)
      CALL ASSIGN(1,'DK1:'-1,'RDO')
      DEFINE FILE 1(2112,324,U,KR)
      WRITE(7,30)
   30 FORMAT(1X'INPUT FILE,IMAGE RESP ':6)
      CALL ASSIGN(3,'DK1:'-1,'RDO')
      WRITE(7,40)
   40 FORMAT(1X'OUTPUT FILE ':6)
      CALL ASSIGN(2,'DK1:'-1)
      N=18
      KB=0
      DO 1000 JX=1,66,4
      READ(3)B
      DO 2 KNUM=1,4
      NNUM=0
      NUM=0
      DO 1 II=1,33
      NNUM=NNUM+1
      DO 120 I=1,9
   20 RI(I)=B(I,NNUM,KNUM)
      NNUM=NNUM+1
      DO 130 I=1,9
   30 AI(I)=B(I,NNUM,KNUM)

C     REAL AND IMAGINARY PARTS OF B

      K1=9
      DO 3 K=1,9
      K1=K1+1
      B(K)=DBLE(RI(K))
      B(K1)=DBLE(AI(K))

C     FORM REST OF COEF MATRIX M, 18X18

      KB=KB+1
      READ(1'KB)H
      J1=9
      DO 60 J=1,9
      J1=J1+1
      K1=9
      DO 60 I=1,9
      K1=K1+1
      HSQR(J,I)=DBLE(H(I,J))
      HSQR(J1,K1)=DBLE(H(I,J))
      HSQR(J,K1)=DBLE(-H(K1,J))
    3 HSQR(J1,I)=DBLE(H(K1,J))

C     SOLVE LINEAR EQN AX=B BY GAUSSIAN ELIMINATION
C     SOLUTION RETURNED IN B

      CALL GAUSS(HSQR,B,N)

C     WRITE SOLUTION VECTOR

      K1=9
      DO 15 J=1,9
      K1=K1+1
      RI(J)=SNGL(B(J))
      AI(J)=SNGL(B(K1))
   15 CONTINUE
      NUM=NUM+1
      DO 36 I=1,9
      E(I,NUM)=RI(I)
      NUM=NUM+1
      DO 37 I=1,9
      E(I,NUM)=AI(I)
   37 CONTINUE
      WRITE(2)E
   60 CONTINUE
      WRITE(7,202) JX
  202 FORMAT(I3)
    2 CONTINUE
      CALL CLOSE(1)
      CALL CLOSE(2)
      CALL CLOSE(3)
      STOP
      END
```

SUBROUTINE SOLVES LINEAR EQN USING GAUSSIAN ELIMINATION
WITH PARTIAL PIVOTING

```
      SUBROUTINE GAUSS(M1,B,N)
      DOUBLE PRECISION M1(N,N),B(N),X(18)
      DOUBLE PRECISION B(18)
      DIMENSION IPIVOT(18)
      CALL FACTOR(M1,IPIVOT,B,N,IFLAG)

C     CHECK FOR SINGULAR MATRIX AT GIVEN FREQ
C     SET ALL X TO CONSTANT
      IF(IFLAG.EQ.2) GO TO 75
      CALL SUBST(M1,B,X,IPIVOT,N)
      DO 30 I=1,N
      B(I)=X(I)
      GO TO 80
   75 CONTINUE
      DO 90 IS=1,N
      B(IS)=1.0
   90 CONTINUE
      RETURN
      END
```

TT:=SUBST.FOR

```
C     SUBST
C     SUBROUTINE TO PERFORM FORWARD-BACKWARD SUBSTITUTION
C
      SUBROUTINE SUBST(N,B,X,IPIVOT,M)
      DOUBLE PRECISION M(M,M),B(M),X(M),SUM
      DIMENSION IPIVOT(M)
      CALL SETERR (10,255)
      IF(N.GT.1) GO TO 10
      X(1)=B(1)/M(1,1)
      RETURN
   10 IP=IPIVOT(1)
      X(1)=B(IP)
      DO 15 K=2,N
      IP=IPIVOT(K)
      KM1=K-1
      SUM=0.D00
      DO 14 J=1,KM1
   14 SUM=M(IP,J)*X(J)+SUM
   15 X(K)=B(IP)-SUM
   21 X(N)=X(N)/M(IP,N)
   22 K=N
      DO 20 NP1MK=2,N
      KP1=K
      K=K-1
      IP=IPIVOT(K)
      SUM=0.D00
      DO 19 J=KP1,N
   19 SUM=M(IP,J)*X(J)+SUM
   20 X(K)=(X(K)-SUM)/M(IP,K)
   24 RETURN
      END
C     FACTOR
C     SUBROUTINE FORMS UPPER TRIANGULAR MATRIX
C
      SUBROUTINE FACTOR(M,IPIVOT,B,N,IFLAG)
      DOUBLE PRECISION M(N,N),B(N),ROWMAX,AM,COLMAX,AMIKOV,RATIO
      DIMENSION IPIVOT(N)
    8 DO 1200 I=1,N
    8 WRITE(7,1000) I,(M(I,J),J=1,N)
 1000 FORMAT(I3/6E13.6/6E13.6/6E13.6)
 1200 CONTINUE
      IFLAG=1
C
C     INITIALIZE M,IPIVOT,B
C
      DO 10 I=1,N
      IPIVOT(I)=I
      ROWMAX=0.D00

      DO 9 J=1,N
      AM=DABS(M(I,J))
    9 ROWMAX=DMAX1(ROWMAX,AM)
      IF(ROWMAX.EQ.0.)GO TO 999
      B(I)=ROWMAX
   10 CONTINUE
 1150 WRITE(7,1100) (B(I),I=1,18)
 1100 FORMAT(1X,3(6E13.6/))
    8 DO 1300 I=1,N
    8 WRITE(7,1000) I,(M(I,J),J=1,N)
 1300 CONTINUE
C
C     GAUSS ELIM W/ SCALED PARTIAL PIVOTING
C
      NM1=N-1
      IF(NM1.EQ.0.) RETURN
      DO 20 K=1,NM1
      JK=K
      KP1=K+1
      IP=IPIVOT(K)
      COLMAX=DABS(M(IP,K))/B(IP)
      DO 11 I=KP1,N
      IP=IPIVOT(I)
      AMIKOV=DABS(M(IP,K))/B(IP)
      IF(AMIKOV.LE.COLMAX) GO TO 11
      COLMAX=AMIKOV
      JK=I
   11 CONTINUE
      IF(COLMAX.EQ.0.D00) GO TO 999
C
      IPK=IPIVOT(JK)
      IPIVOT(JK)=IPIVOT(K)
      IPIVOT(K)=IPK
      DO 20 I=KP1,N
      IP=IPIVOT(I)
      M(IP,K)=M(IP,K)/M(IPK,K)
      RATIO=-M(IP,K)
      DO 20 J=KP1,N
   20 M(IP,J)=RATIO*M(IPK,J)+M(IP,J)
      IF(M(IP,N).EQ.0.D00) GO TO 999
      RETURN
  999 IFLAG=2
    8 WRITE(7,360)
  350 FORMAT(' END FACTOR')
  360 FORMAT(' END FACTOR, SMALL NO.')
      RETURN
      END
    8
```

1017779

```
C
C       TRFRM2 TRANSFORMS 64X64 IMAGE FROM SPACE DOMAIN
C       TO FREQUENCY DOMAIN AND STORES ON DISK.
C       THIS PROGRAM MUST BE USED WITH DECOM2
C       DAVE PEARSE  22-JUNE-78.
C
        COMMON DATA(4224),IC(64),DC(64)
        DIMENSION H(2), DI(9,64,4)
        DATA N(1),N(2)/64,64/
2       NDIM=2
        WRITE(7,5)
5       FORMAT(1X 'WRITE FILE! ',$)
        CALL ASSIGN(2,'DK1:',-1)
        CALL ASSIGN (3,'DK1:XYZ.DAT',0,'SCR')
        DO 100 IARY=1,9
        WRITE(7,7)IARY
7       FORMAT(1X 'READ FILE 0',I1,'  ',$)
        CALL ASSIGN(1,'DK1:',-1,'RDO')
        DO 10 I=4097,4224
10      DATA(I)=0.0
        K=1
        DO 20 J=1,64
        READ(1)IC
        DO 15 I=1,64
        DATA(K)=IC(I)
15      K=K+1
20      CONTINUE
        CALL FOUR2(N,NDIM,-1,0)
        CALL CLOSE(1)
        WRITE(3)DATA
        WRITE(7,79)IARY
79      FORMAT(1X 'ARRAY 0',I1,' FINISHED.')
100     CONTINUE
        ENDFILE 3
        DO 120 J=1,64,4
        REWIND 3
        NUM=(J-1)864
        DO 110 I=1,9
        NN=NUM
        READ(3)DATA
        DO 110 M=1,4
        DO 110 K=1,64
        NN=NN+1
110     DI(I,K,M)=DATA(NN)
120     WRITE(2)DI
        CALL CLOSE(2)
        CALL CLOSE (3)
        STOP
        END
```

```
TT:\X\!-SETUP.FOR
C       SETUP
C       FROM REFORMATS H DATA FROM TRFRM2
C
        DIMENSION C(9,64,4),H(18)
1       WRITE(7,20)
20      FORMAT(' WRITE FILE',$)
        CALL ASSIGN(1,'DK1!',-1)
        WRITE(7,30)
30      FORMAT(' READ FILE',$)
        CALL ASSIGN(2,'DK1!',-1,'RDO')
        DO 120 I=1,16
        READ(2)C
        DO 120 IMAX=1,4
        K1=0
        DO 120 J1=1,33
        K=0
        DO 100 J3=1,2
        K1=K1+1
        DO 100 J2=1,9
        K=K+1
100     H(K)=C(J2,K1,IMAX)
        WRITE(1)H
120     CONTINUE
        CALL CLOSE(1)
        CALL CLOSE(2)
        GO TO 1
        STOP
        END
$
```

```
TT!=SPACE2.FOR
C       SPACE2
C       CONVERTS FROM FREQ. TO SPACE
C       THIS PROGRAM CAN ONLY BE USED
C       WITH DECOM2
        DIMENSION NX(2),E(9,64)
        COMMON DATA(4224),IC(64),DC(64),NN(4096)
        DATA NX(1),NX(2)/64,64/
        WRITE(7,2)
2       FORMAT(1X' ENTER INPUT FILE ',$)
        CALL ASSIGN(1,'DK1!',-1,'RDO')
C       DO LOOP OVER 9 IMAGES
100     DO 1 M=1,9
        WRITE(7,5)M
5       FORMAT(1X,'WRITE FILE 0',I1,' ?',$)
        CALL ASSIGN (2,'DK1!',-1)
        NC=0
        DO 3 L=1,64
        READ(1)E
        DO 3 M=1,64
        NC=NC+1
        DATA(NC)=E(L,M)
3       CONTINUE
        NDIM=2
        CALL FOUR2(NX,NDIM,+1,-1)
$       AN=-1.
$       ANN=1.
$       DATA(1)=DATA(2)
$       DO 10 J=1,4096
$       AN=AMAX1(AN,DATA(J))
$       ANN=AMIN1(ANN,DATA(J))
310     CONTINUE
$       R=AN-ANN
$       IF(R.NE.0.0) GO TO 30
$       DO 20 I=1,64
$       DO 15 J=1,64
315     IC(J)=0
320     WRITE(2)IC
$       GO TO 50
330     CONTINUE
        NN=0
        DO 40 J=1,4096
        NN=NN+1
C       IC(NN)=(DATA(J)/100.)
$       IC(NN)=((DATA(J)-ANN)/R)*100
        IF(NN.NE.64) GO TO 40
        NN=0
        WRITE(2)IC
40      CONTINUE
30      CONTINUE
        CALL CLOSE(2)
        REWIND 1
1       CONTINUE
        STOP
        END
$
```

```
TT!=MUGE.FOR
C       MUGE
C       PROG TO REARRANGE 9 FILES FROM SETUP INTO A SERIES
C       OF FILES ORGANIZED 18X9X2112 READY FOR DECOM2
C
        DIMENSION H(18),HPULSE(18,9)
        WRITE(7,10)
10      FORMAT(' ENTER OUTPUT FILENAME ',$)
        CALL ASSIGN(1,'DK1!',-1)
        DEFINE FILE 1(2112,324,U,KR)
        I1=0
        DO 50 I=1,19
        I1=I1+1
        WRITE(7,20)I1
20      FORMAT(' ENTER READ FILE FOR LEVEL',I2,1X,$)
        CALL ASSIGN(I,'DK1!',-1,'RDO')
50      CONTINUE
C
C       10 FILES OPEN! 9 READ, 1 WRITE
C       BEGIN READ/ REARRANGE/ WRITE! FILES BY FREQ 18X9X2112
C
        KK=0
        DO 150 KB=1,2112
        K=0
        DO 140 I=11,19
        K=K+1
        READ(I) H
        DO 120 J1=1,18
120     HPULSE(J1,K)=H(J1)
140     CONTINUE
        WRITE(1'KB)HPULSE
$       WRITE(6,141)HPULSE
8141    FORMAT(1X,9E12.5)
        KK=KK+1
        IF(KK.NE.20) GO TO 150
        NUM=KB/10
        WRITE(7,143)NUM
143     FORMAT(1X,I5)
        KK=0
150     CONTINUE
        DO 200 I=11,19
        CALL CLOSE(I)
200     CONTINUE
        CALL CLOSE(1)
        STOP
        END
$
```

1017780

C. APPENDIX III: Publications

No.		Erda Report No.
1.	Price, R.R., Touya, J.J., Branch, R., Goddard, J., and Brill, A.B.: Validation of Renal Transit-Time Calculations Using Compartmental Models and Direct Measurements, A Review of Information Processing in Medical Imaging, Proceedings of the Fifth International Conference, Brill, A.B., and Price, R.R. (Eds), Vanderbilt University, Nashville, TN 1978, p. 536-554.	109
2.	Efron, U., Kedem, Dan, Kedem, Drora, Smith, C.W., Erickson, J., Price, R.R., Nelson, J.H., and Brill A.B.: New Methods for Pulsatile Blood Flow Measurement Using Cine-Densitometry, A Review of Information Processing in Medical Imaging, Proceedings of the Fifth International Conference, Brill, A.B., and Price, R.R. (Eds), Vanderbilt University, Nashville, TN 1978, p. 66-84.	110
3.	Brill, A.B., and Price, R.R., (Eds): A Review of Information Processing in Medical Imaging. Proceedings of the Fifth International Conference held at Vanderbilt University, Nashville, TN, 1978	111
4.	Brill, A.B., and Erickson, J.J.: Display Systems in Nuclear Medicine, Seminars in Nuclear Medicine, Vol. VIII, No. 2 (April), 1978, pp. 155-161.	112
5.	Kedem, Dan, Kedem, Drora, Smith, C.W., Dean, R.H., and Brill, A.B.: Velocity Distribution and Blood Flow Measurements Using Videodensitometric Methods, Investigative Radiology, Vol. 13, No. 1, pp. 46-56.	113
6.	Price, R.R., Erickson, J.J., Patton, J.A., Jones, J.P., Lagen, J.E., and Rollo, F.D.: Pratical Clinical Applications of the Computer in Nuclear Medicine, 25th Annual Meeting of the Society of Nuclear Medicine, Anaheim, California, June 26-27, 1978.	114
7.	Larson, K.H.: Measurement of Regional and Total Body Bone Mineral Content in Vivo Using Transmission Scanning and Neutron Activation Analysis. Ph.D. Thesis. Vanderbilt University, Unpublished, 1978.	115
8.	Brill, A.B., Lindstrom, D.P., Nelson, J.H., Rhea, T.C., Kedem, Dan, Kedem, Drora, Price, R.R., Erickson, J.J., Graham, T.P., Smith, C.W.: A Versatile Digital Densitometry System for Cardiovascular Studies, Roentgen-Video Techniques, D.H. Heintzen and J.H. Bursch, (Eds), George Thieme Publishers (1978), pp.12-14	116

1017781

APPROVED FOR RELEASE OR PUBLICATION - O.R. PATENT GROUP
BY ... DATE ...

9. Price, R.R., Branch, R., Ramage, A.A., Touya, J.J., and Brill, A.B.: Deconvolution Analysis of Transplant Renograms, Medical Imaging, Vol. 2, No. 2, pp. 46-47, 1978. 117

10. Brill, A.B., Rao, Gopala U.V., Novak, G., Price, R.R., James, A.E., Trussel, H.J., Janney, D.H., and Askins, B.S.: Dose Reduction in Mammography—Preliminary Studies Utilizing Computer Enhancement and Autoradiographic Image Intensification, in press. 118

11. Brill, A.B., Erickson, J., Goddard, J., Patton, J.A., Price, R.R., Rollo, F.D., and Touya, J.J.: Computer Applications in Nuclear Medicine, in press. 119

12. Lee, G.S., Patton, J.A., and Brill, A.B.: Serial Thyroid Iodide Content in Hyperthyroid Patients Treated with Radioiodine, The Journal of Nuclear Medicine, Vol. 19, No. 6, p. 742, 1978. 120

1017782

VALIDATION OF RENAL TRANSIT-TIME CALCULATIONS USING COMPARTMENTAL MODELS AND DIRECT MEASUREMENTS

Ronald R. Price, J.J. Touya, R. Branch,
J. Goddard and A.B. Brill
Vanderbilt University Medical Center
Nashville, Tennessee U.S.A.

ABSTRACT

This work presents an investigation into the accuracy and limitations of the deconvolution techniques used in our laboratory for estimating renal transit-time distributions. These investigations have utilized both analytical (compartmental modelling) methods and direct measurements in experimental animals. Compartmental modelling was used to study the effects of random noise, data smoothing and filtering, blood background, variations in data sampling intervals, non-linear systems and multiple transfer paths. Direct measurements have been used to establish the precision of the techniques through repeated measurements in dogs. The accuracy of the techniques have been tested over a wide range of renal function through the use of direct renal artery injections in dogs.

Serial studies extending over a period of 50 days in a patient with a newly transplanted kidney are presented. The sequential transit-time distributions are compared with the sequential renograms.

Supported in part by ERDA Contract EY-76-S-05-2401

1017783

VALIDATION OF RENAL TRANSIT-TIME CALCULATIONS USING COMPARTMENTAL MODELS AND DIRECT MEASUREMENTS

Ronald R. Price, J.J. Touya, R. Branch,
J. Goddard and A.B. Brill
Vanderbilt University Medical Center
Nashville, Tennessee U.S.A.

Introduction

Current interest in the clinical utility of the renal transit-time distribution of I-131 labelled Orthoiodohippurate (OIH) has prompted us to explore a number of mathematical deconvolution techniques and to investigate the inherent uncertainties associated with each. Our interest in the technique was generated in part by an earlier work of Drs. Brown and Britton (1). Their work indicated that the renal transit-time distribution of I-131-OIH contained information regarding regional renal blood flow. This information is particularly relevant to our ongoing study of renal vascular hypertension.

Although the literature contains a number of reports on the clinical applications of the deconvolution techniques (2-4), few studies designed to validate or test the limitations of the techniques have been presented. In this work we present our investigations into the accuracy and limitations of the deconvolution technique as used in our laboratory. To this end, our work has included the use of both analytical techniques (compartmental modelling) and direct measurements in prepared animal models.

Mathematical deconvolution of the renogram curve requires that the kidney be regarded as a linear system and that all of the system parameters remain constant in time. If these assumptions are satisfied then the output of the kidney will be a convolution of the input function (the measured blood level of the ^{131}I-OIH) and the transfer function of the kidney. It is the purpose of the deconvolution calculation to determine the transfer function (transit-time distribution). The solution to the deconvolution equation for the transfer function can be carried out using a number of well known techniques if the input and output curves are known. An equivalent calculation can be carried out using the composite renogram in place of the output curve. The resulting transfer function will be related to the integral of the transit-time distribution and will be referred to later as the retention function. We have used two deconvolution techniques: 1) Fourier Tranform and 2) a discrete point-by-point calculation. Both can be carried out easily and rapidly on a small clinical computer.

Compartmental Model

A schematic of the basic compartmental model used in these studies is shown in Figure 1. Even though this model has been used successfully by others (5) to describe renal function in a variety disease states, the physiological accuracy of the model is not of central importance to our work. The necessary

0117184

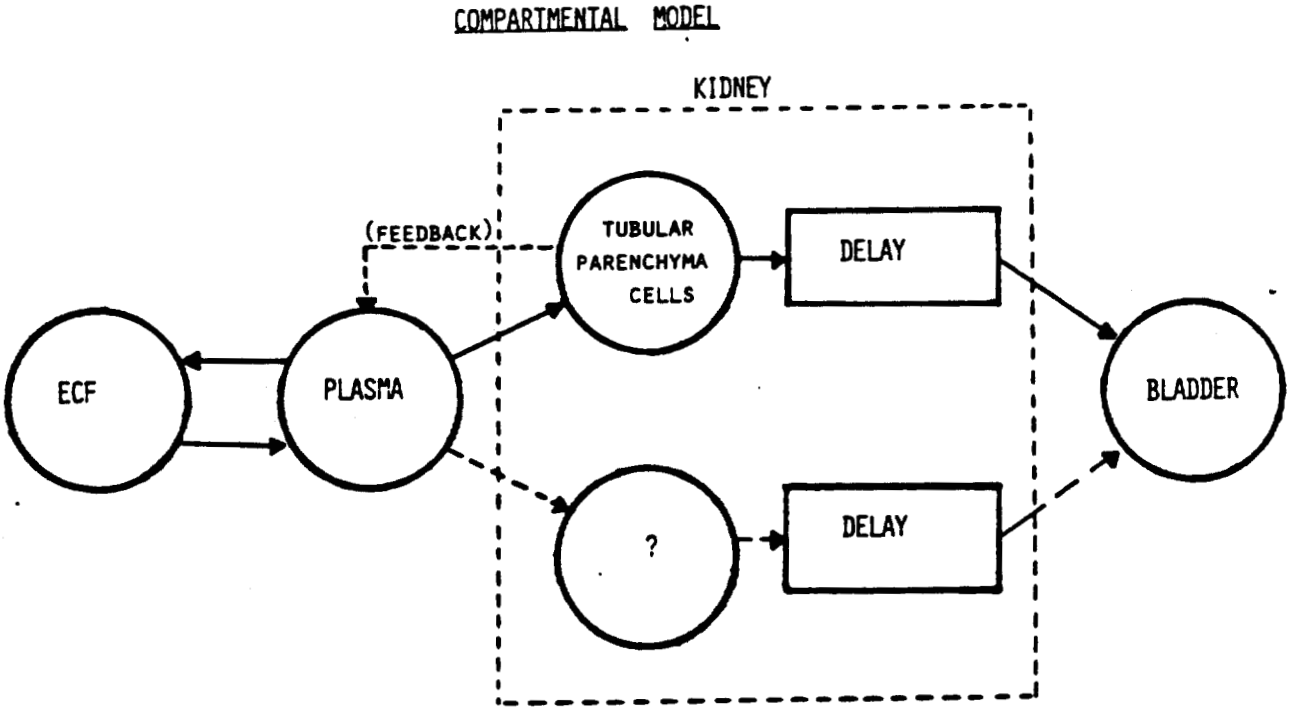


Figure 1. Schematic of the compartmental model used to simulate I-131-OIH kinetics

1017785

requirements of the model for our purposes are: (1) that it employ algorithms which are independent of the deconvolution calculations and (2) it have sufficient complexity and flexibility to yield a variety of realistic states of renal function.

We have found the model to be a flexible tool and have found it useful for investigating a variety of questions relating to the deconvolution calculations. These have included a study of the effects of:

1) random noise levels in the data

2) various data smoothing and filtering algorithms

3) blood background interference

4) variations in the data sampling intervals

5) non-linear systems (feedback), and

6) multiple paralled transfer paths.

The model includes plasma, extra-cellular fluid, "kidney" and bladder or urine compartments. The "kidney" is assumed to be composed of a single mixing compartment (labelled as "tubular cells" in the figure) plus a delaying component. To investigate the effects of multiple transfer paths within the kidney, we simply include additional equivalent pathways in parallel with the first (see figure). The simulated external measurement of the kidney in every case was taken as a linear combination of all the compartments and delays (dashed box). The intercompartmental rate constants were chosen to yield the transfer functions shown in Figure 2. The single pathway simulation presented in this work used a transfer function with a mean transit-time of 1.5 minutes. The curves presented to demonstrate two pathway systems used both of the transfer functions shown in Figure 2.

Of all the factors affecting the deconvolution calculations, we found for the I-131-OIH data that the errors introduced by random noise were the most significant. Simulated noise free kidney and blood activity curves are shown in Figure 3, along with the same curves after random noise has been added. The Poisson noise level depends upon the contents in each data interval ($\pm\sqrt{n}$). The maximum counts in the kidney curve in Figure 3 was 1,000 in a 10 second interval corresponding to an error of approximately 3% at the peak. In our institution using a scintillation camera, this count rate is obtained only with patients who have good renal function. From these curves the input and output curves were then generated. The input curve was taken to be proportional to the blood level and the output curve was determined by the technique of Britton and Brown where a kidney removal component is determined from the extrapolated kidney uptake. It is the derivative of the difference between the removal component and the measured renogram that yields the output curve.

Figure 4 shows the results of the output curve calculation and the corresponding transit-time distribution for the curves shown in Figure 3. The solid curve is the transit time curve corresponding to the expected distribution as determined from the noise free system. Even this relatively small amount of noise completely obscured even the major characteristics of the distribution. In an effort to resolve this problem, we have investigated a number of data filtering techniques. The results of applying one such filter is shown. This filter was applied only to the raw renogram data and not the blood curve and was designed to attenuate fluctuations in the data which had periods less than about one minute. The optimum filter must be chosen to suppress noise while still maintaining adequate time resolution. All of the data presented in this paper have been processed by this filter.

0 1 7 8 6

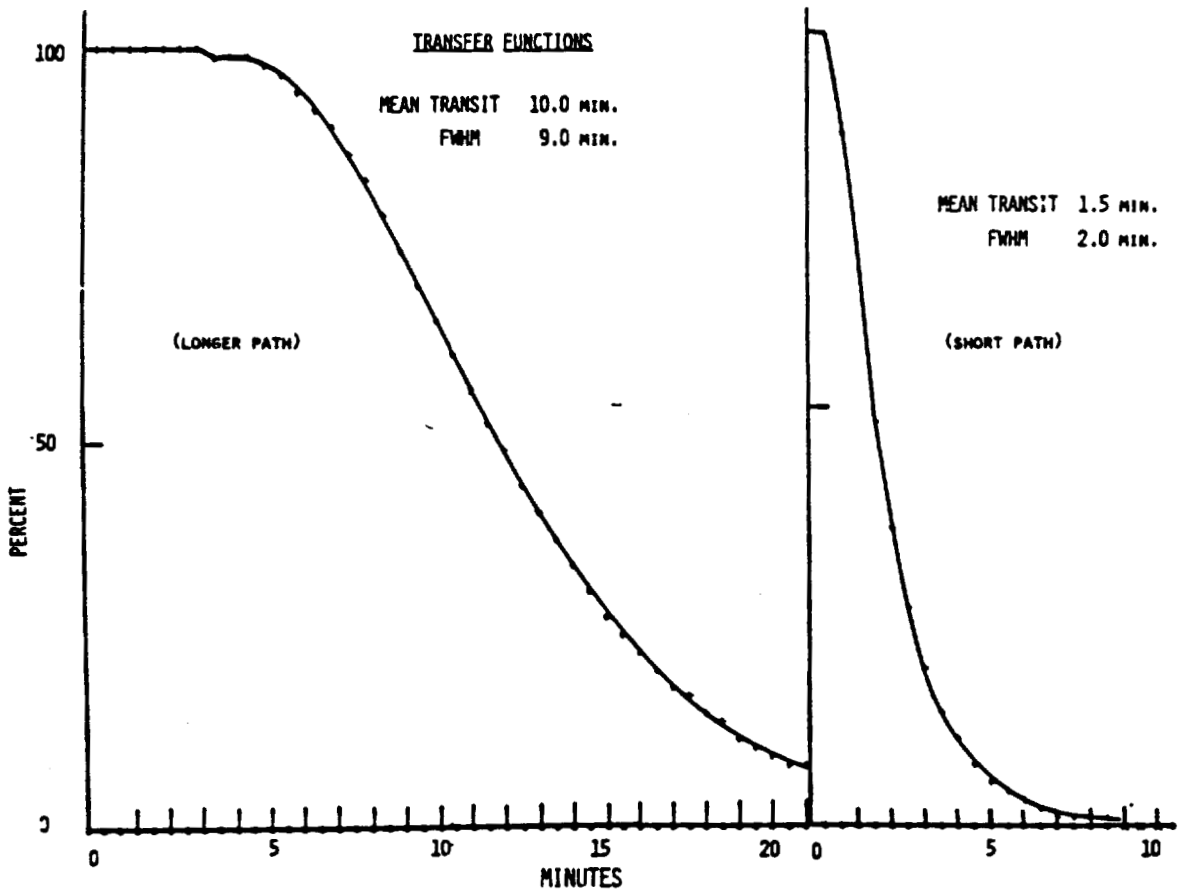


Figure 2. Renal transfer functions of I-131-OIH used to simulate renograms with single and multiple parallel pathways.

1017787

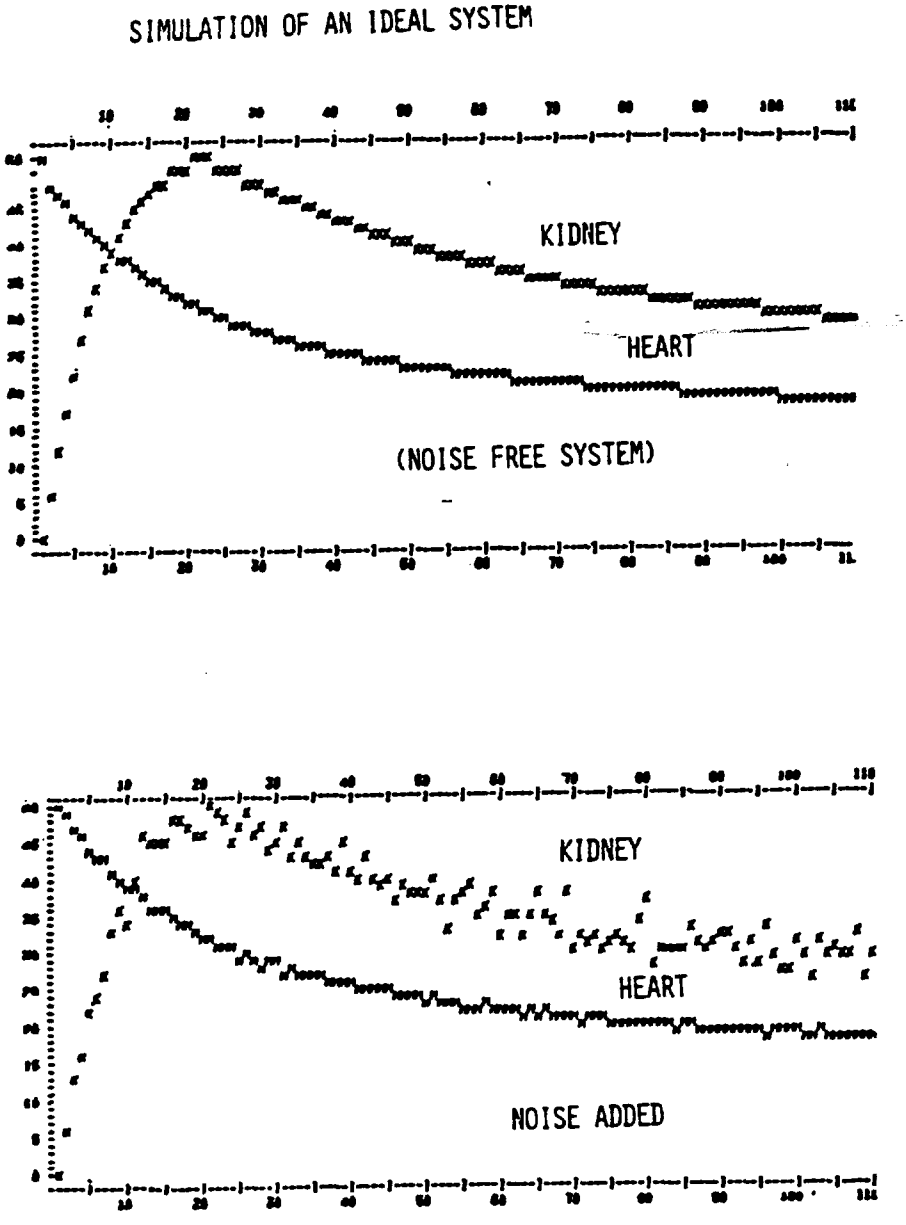


Figure 3. Simulated renogram and blood activity curve using a compartmental model. (above) Noise free simulation, (below) same curves after the addition of random noise. Maximum count in each curve is 1000.

1017788

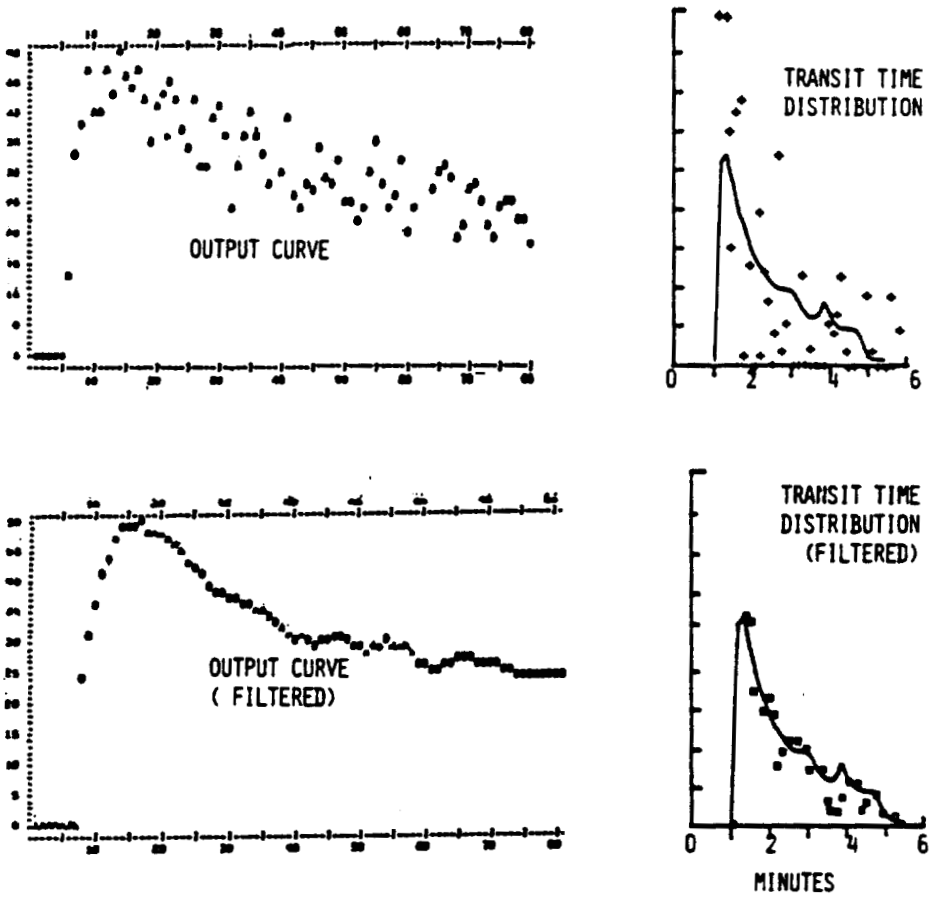


Figure 4. Renal output curves derived from renogram shown in Figure 3, (right) corresponding transit-time distribution. Solid line is the transit-time distribution for the noise free system. (Below) Same curves after processing with a low pass filter.

1017789

was to look for a bimodal behavior in the transit-time spectrum. Britton and Brown have observed this structure in normal kidneys and have suggested that this curve structure reflects contributions from two distinct nephron populations. They also suggested that the relative areas under the two transit-time populations yield information on regional renal function. In order to assure ourselves that our bounding and filtering routines did not distort or filter out a bimodal structure in the transit time spectrum, we again utilized model simulated data.

In Figure 5 are shown simulated kidney and blood curves in which two distinct and parallel renal transfer functions are operating. The transfer functions illustrated in Figure 2 were used for these curves. Since the renogram is a convolution of the transfer function with the blood curve, the renogram can contain no frequencies higher than the narrowest transfer function. The criterion which the filter must satisfy, therefore, is whether or not the shortest transfer function will be preserved. Also included in Figure 5 are two different noise level simulations. The count rates were chosen to simulate typical data rates that might be observed in a Tc-99m DTPA renogram (5000,2500) and a typical I-131-OIH renogram (1000,500). The heart maximum was chosen to be twice the peak kidney count to approximate what is generally obtained with our measurement systems.

The same filter described earlier was used to process the curves in Figure 5. The results of the deconvolution calculations are shown in Figure 6. The solid line corresponds to the point-by-point calculation and the F's correspond to the Fourier transform calculation. The noise-free calculation (within round-off errors) was found to be identical to the expected analytical expressions formed from the sum of the two transfer functions. In comparison to the noise free curve, the higher count rate data (5000,2500) was found to have a 25% improvement in the Chi-square value over the lower count rate curve (1000,500). Especially in the point-by-point calculation the data processing introduced an uncertainty in the minimum transit-time. However, in every case the peak position and widths of the two components remained relatively stable. In the lower count rate data, additional (artifactual) components were beginning to appear, indicating a stronger filter may be warranted. Our decision was to stay with these filter parameters rather than introduce further distortions in the minimum transit-time.

The effects of varing levels of blood background is illustrated in Figure 7. The only effect on the retention function (shown by the "R" curves), was the spike artifact produced in the first element. This results when the blood background is high, since the kidney curve then tends to follow the blood curve exactly. By discarding the first element of the retention curve one may retrieve the correct retention function. When looking at the differential curve (transit-time distribution) we see that this will introduce an uncertainty in the minimum transit-time. The magnitude of the uncertainty depends upon the derivative interval.

The deconvolution-calculation assumes no reflex of the tracer from the kidney back into the circulating blood pool. In the normal, reflux is known to be minimal; however, for some radiopharmaceuticals and in some disease states reflux or the reappearance of the unbound nuclide may become sizeable. Compartmental model simulations were also used to study the distortion imposed upon the deconvolved renal transfer function as a function of the magnitude of refluxed or reappearing tracer.

Referring back to the model schematic (Fig. 1) reflux is easily introduced into the model by including a flow path from the kidney back to the plasma. Fairly large values for the feedback (25-50 percent of the forward flow) manifested themselves by very subtle changes in the renogram. As might be expected,

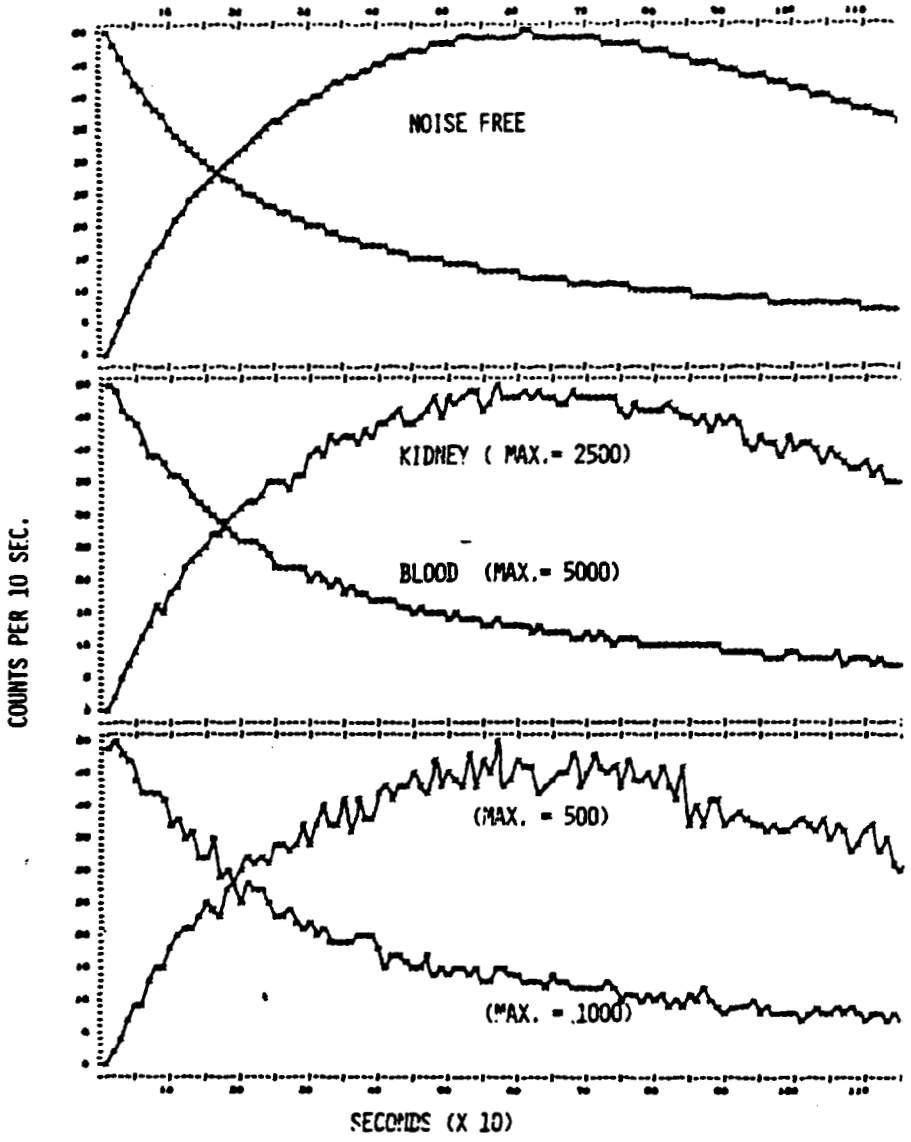


Figure 5. Simulated kidney and blood curves in which two transfer functions are operating. (Top) noise free, (middle) random noise added-kidney maximum count = 2500, blood maximum = 5000, (bottom) random noise added-kidney = 500, blood = 1000.

1017791

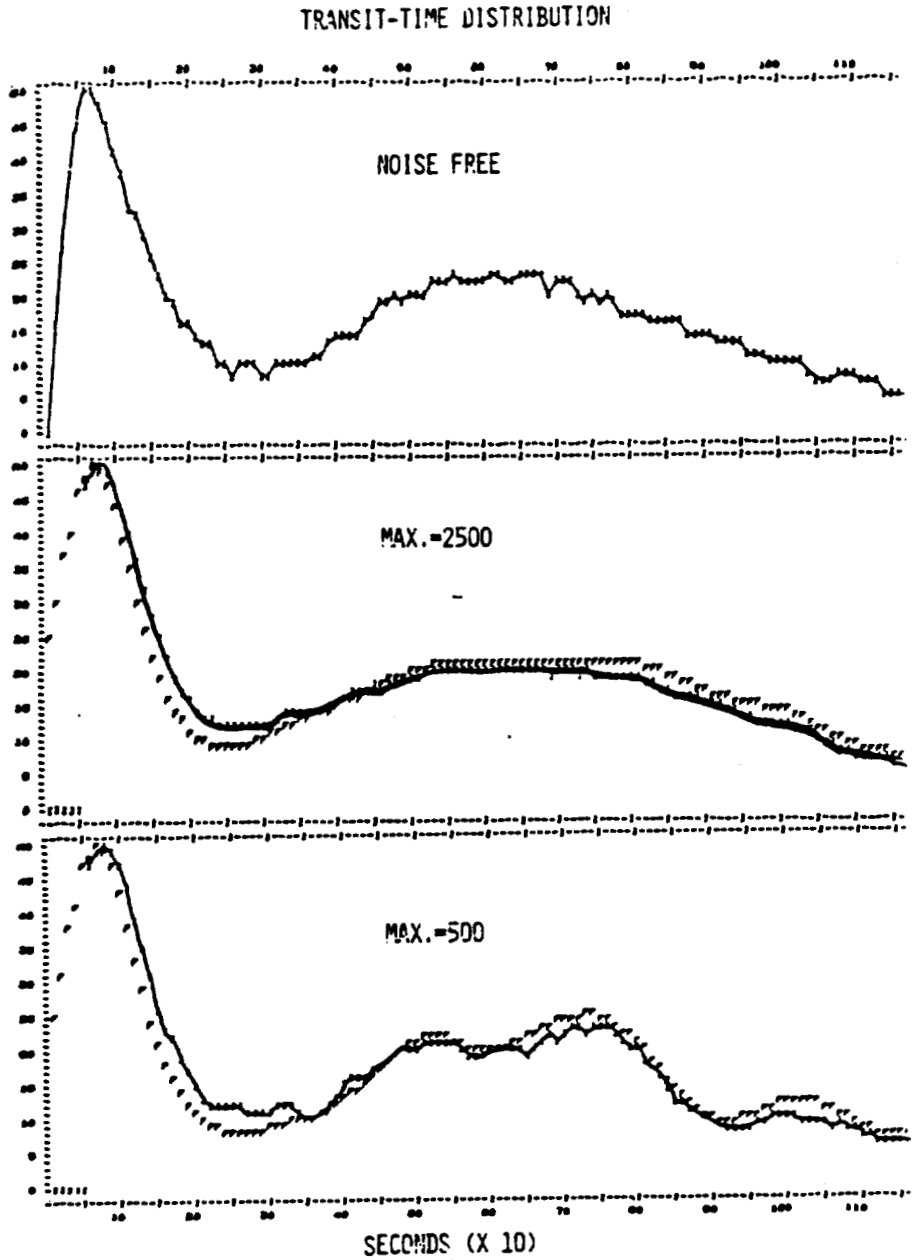


Figure 6. Deconvolved transit-time distributions corresponding to Figure 5. Solid line corresponds to the point-by-point discrete calculations and the F's correspond to the Fourier transform calculation.

1017792

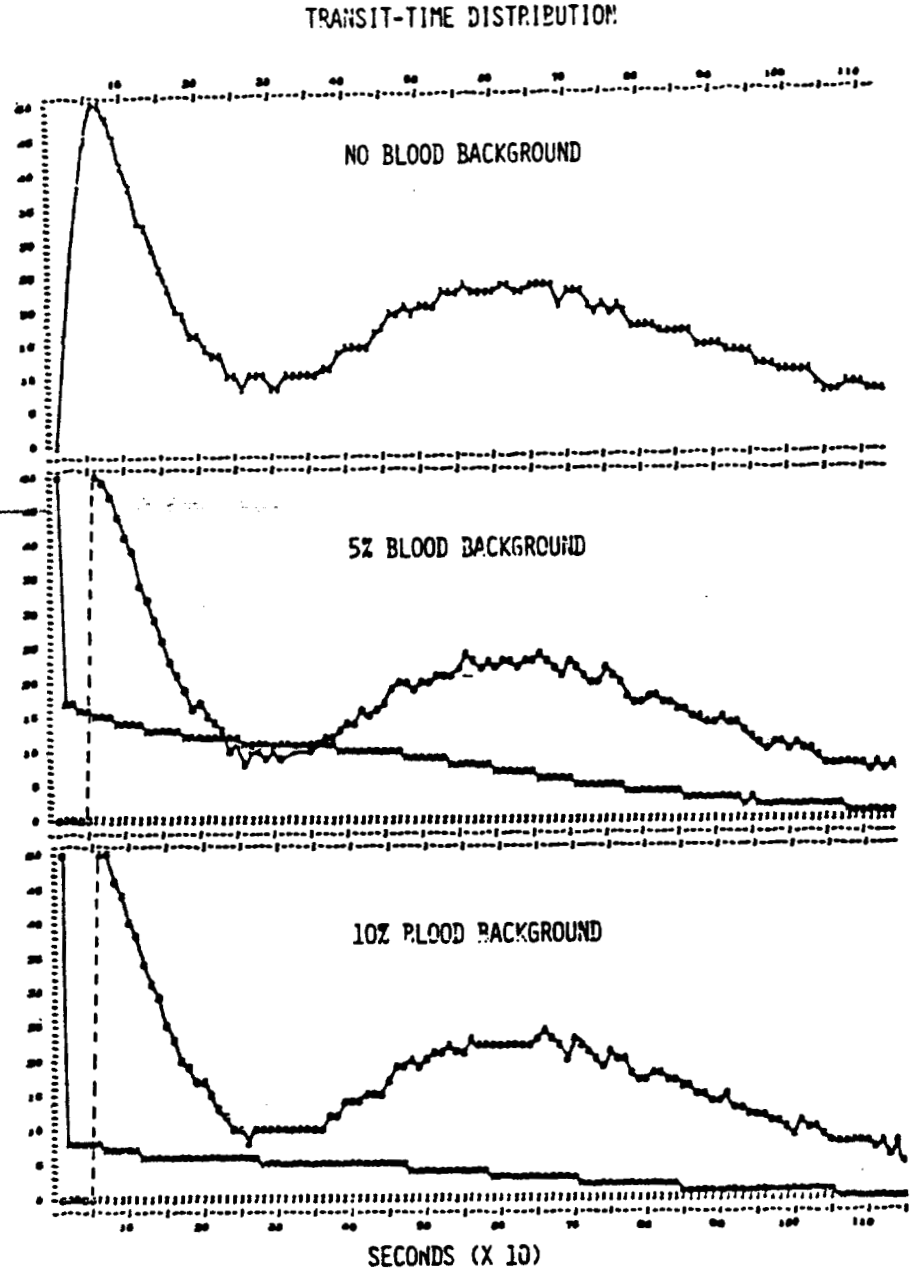


Figure 7. Deconvolved transit-time distributions (G's) as a function blood background. (Top) No blood background, (middle) blood background equal to 5% of the blood pool activity and (bottom) background equal to 10%. R's refer to retention functions.

1017793

the deconvolution calculation showed the new systems have increasingly rapid transit-times as the magnitude of the feedback component increased. In Figure 8 are shown the retention functions corresponding to normal flow patterns compared with a system in which the feedback component was equal to 50% of the forward flow. The mean transit-time decreased from 90 seconds to 45 seconds in this case.

Direct Measurements

Having established the adequacy of the deconvolution calculations in simulated data we extended our work to controlled measurements in prepared dog models. Our first measurements were designed to test the precision of the techniques by making three sets of sequential measurements on the same dog maintained in the same functional state. Figure 9 shows the results of one of these studies. We concluded that the results were in good agreement.

The second phase of the validation was to test the accuracy of the technique by comparison with direct renal artery injections. Figure 10 shows two renograms taken from a dog in two distinctly different functional states. The decreased function state was created by the injection of drugs. The calculated transit-time distributions for each case are shown to the right. Note the difference in normalization and also the relative excretion percentages for the two cases. At the same time that these renograms (resulting from a peripheral IV injection) were made we measured the transfer function directly by making a bolus injection of I-131-OIH directly into the renal artery. Figure 11 shows the results of the direct measurement of the retention function as compared with the retention function derived from the deconvolution of the I.V. renogram. In both cases we see reasonably good agreement. In the case of the control study we see an approximately 90% extraction efficiency for OIH. This results in about 10% of the OIH passing through the kidney during the first pass and then becoming diluted over the blood pool. Thus 10% of the bolus looks very similiar to an I.V. injection. If one subtracts this component we get a result that almost exactly duplicates the deconvolution curve and is shown by the x's in the figure.

To check the program's calculation of the output curve a catheter was placed into the dog's ureter and urine samples were taken every 30 seconds. Within the counting errors of the urine samples, the urine activity curve compared favorably with the derived output curve.

From the results of the dog studies, in particular the intraarterial injection which has very good counting statistics, we have not seen any evidence of a bimodal character in these curves. If the effect is there it is very likely that the counting statistics available from an intravenous injection will not be adequate to resolve the second component. Rather the kidney seems to behave very similiar to a classical one-compartment system plus a delay.

Analysis of Transplant Renogram

After the validation phase we extended our work to study the transplanted kidney. Figures 12 and 13 show eight selected studies from a series of approximately 15 serial studies of a patient who had received a transplanted kidney. This particular patient was chosen because of the extreme variations in renal function ranging from excellent to poor function, including a rejection phase followed by a complete recovery to good function again. The retention function and the renogram plus bladder curve are presented for comparison. One day post operatively the patient had a BUN of 49 and a creatine clearance of 2.6. This continued to improve until day 12 (BUN = 26, creatine = 1.0) at which time he was discharged. Approximately one week later the patient returned running a temperature, urine volume had dropped to one-fourth (BUN = 200 and creatine =

0117h

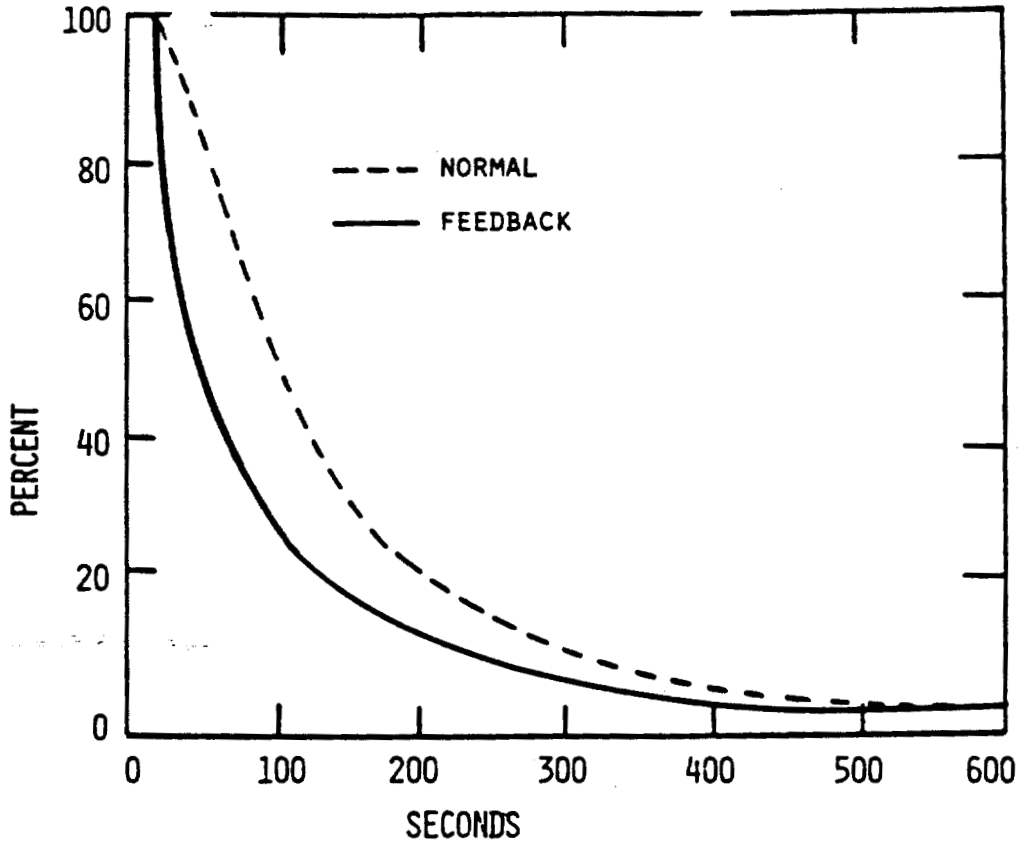


Figure 8. Retention function corresponding to a normal flow pattern compared to retention function of a system in which a feedback component equal to 50% of the forward flow was operating.

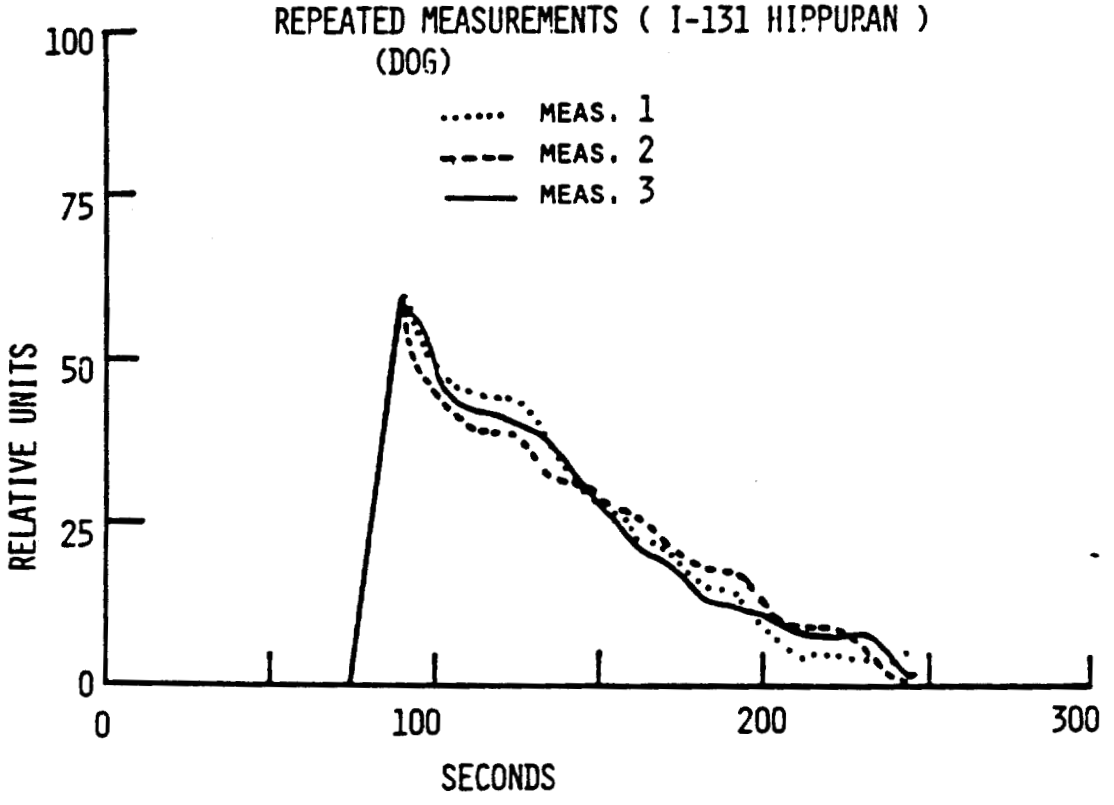


Figure 9. Tests of the precision of the deconvolved techniques. Transit-time distributions from sequential studies on the same dog maintained in the same functional state.

1017795

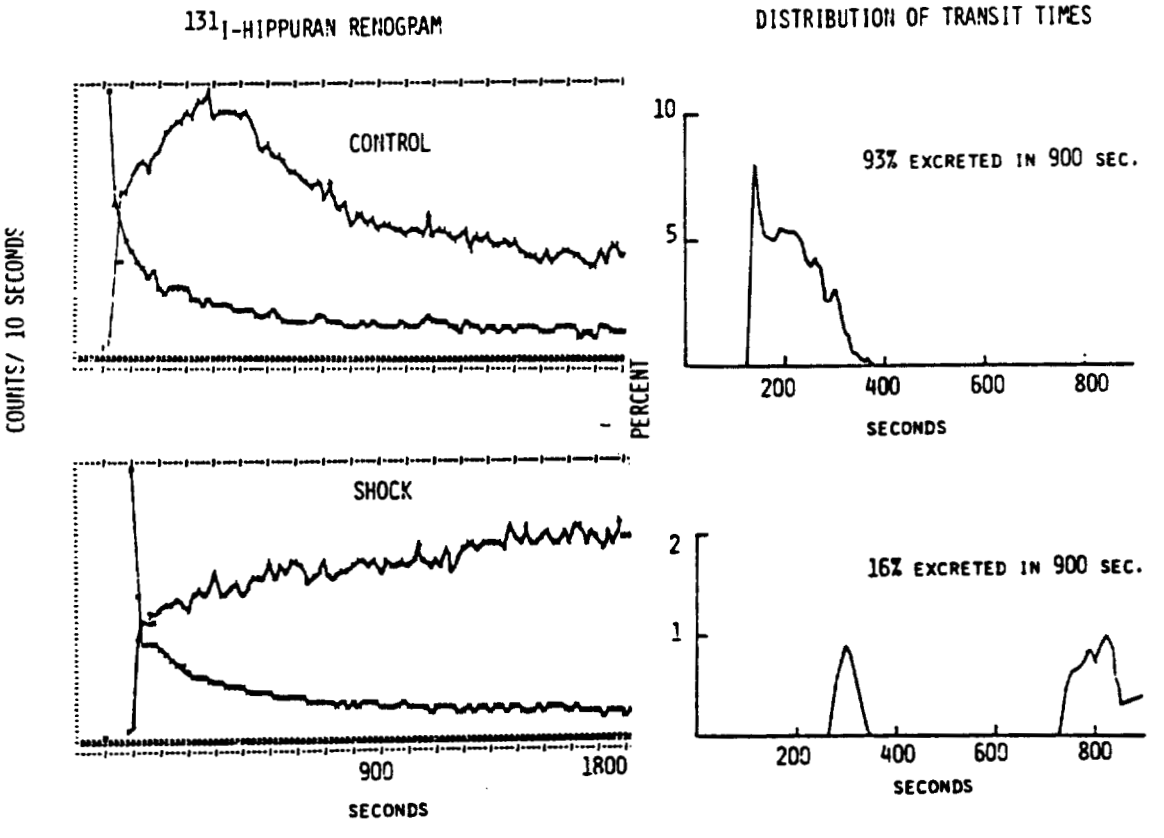


Figure 10. Renograms from a prepared dog in two different functional states. (Right) Corresponding deconvolved transit-time distributions.

1017796

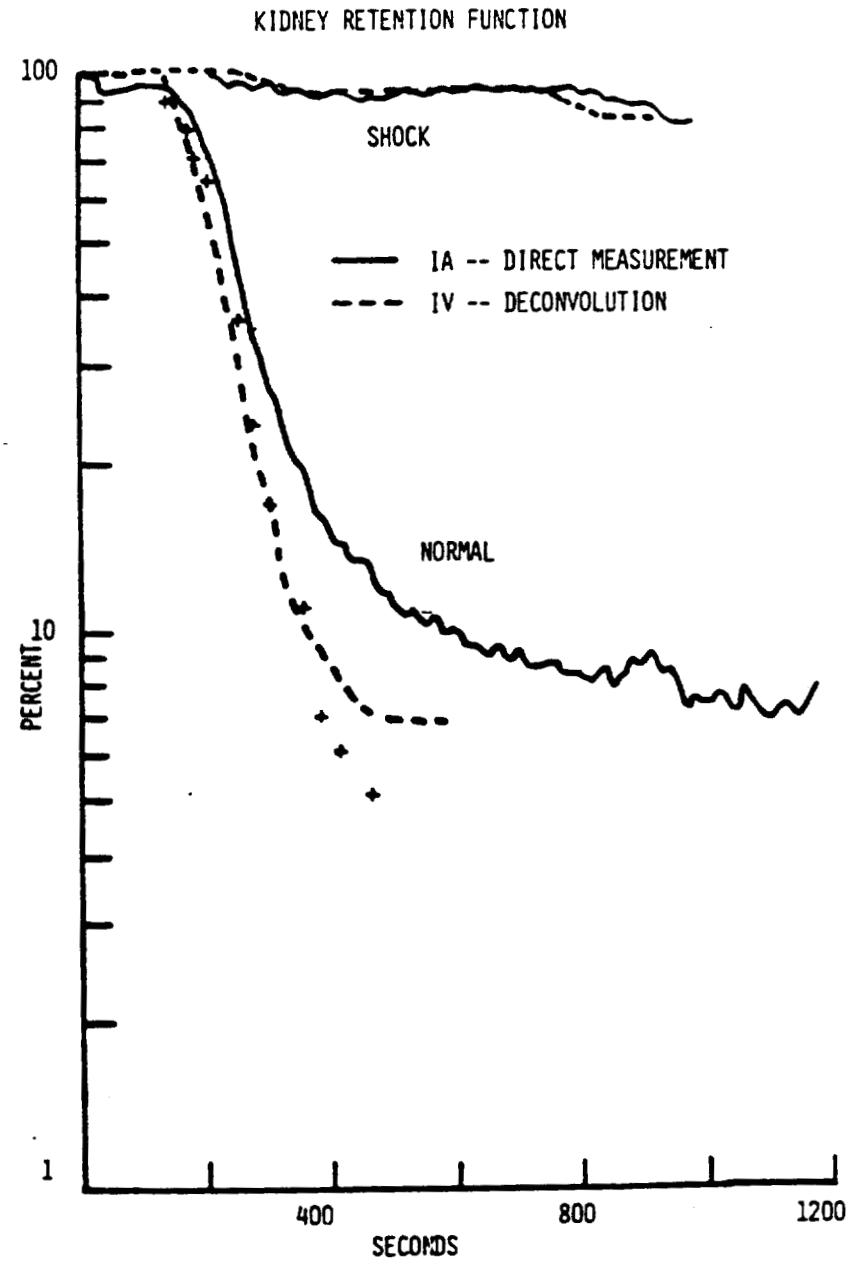


Figure 11. Direct measurements of renal retention function by means of intraarterial injection of I-131-OIH compared with deconvolved retention function from intravenous injection. T's correspond to deconvolved retention function corrected for extraction efficiency.

1017797

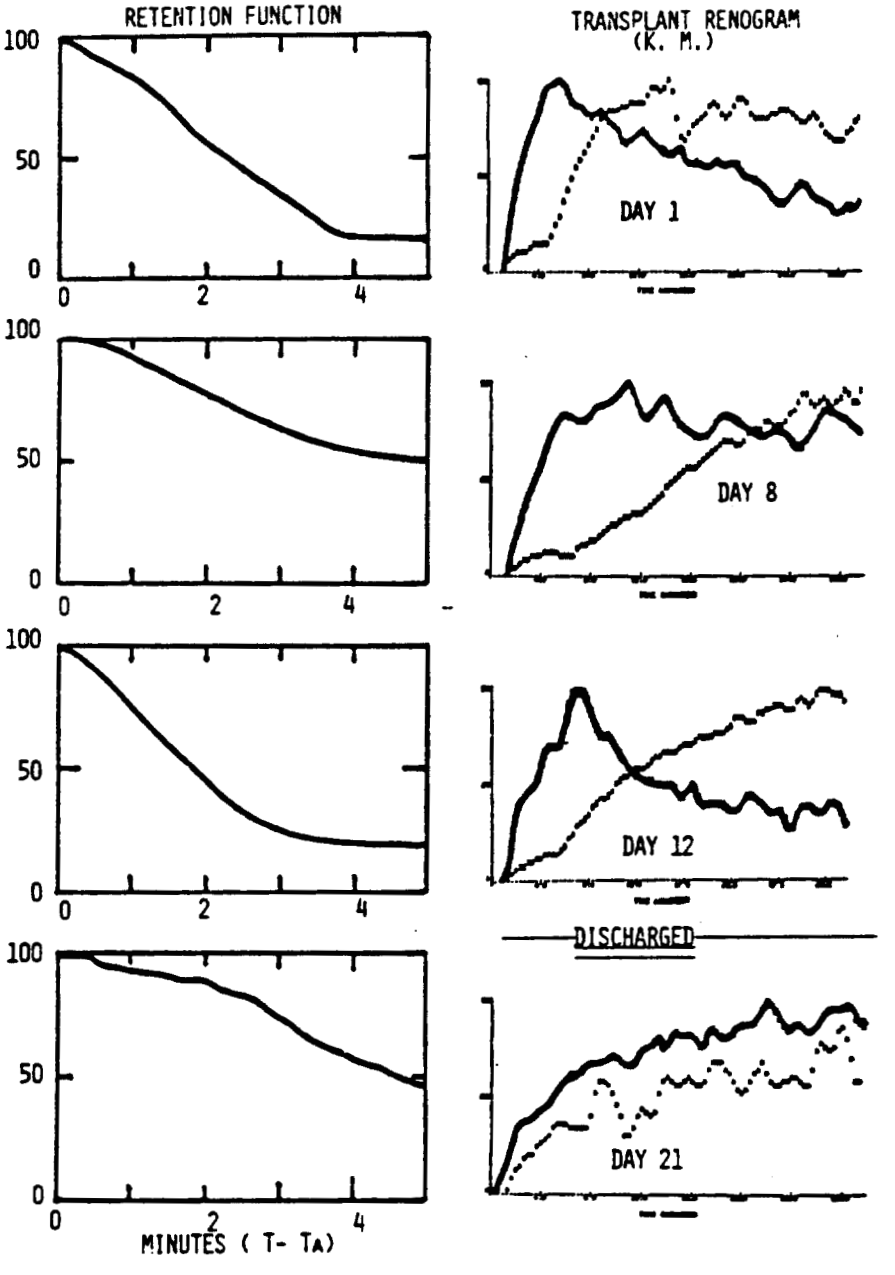


Figure 12. Sequential studies on a patient with a transplanted kidney. (Left) Deconvolved retention function days 1 through 21 after transplantation, (right) corresponding renogram.

1017798

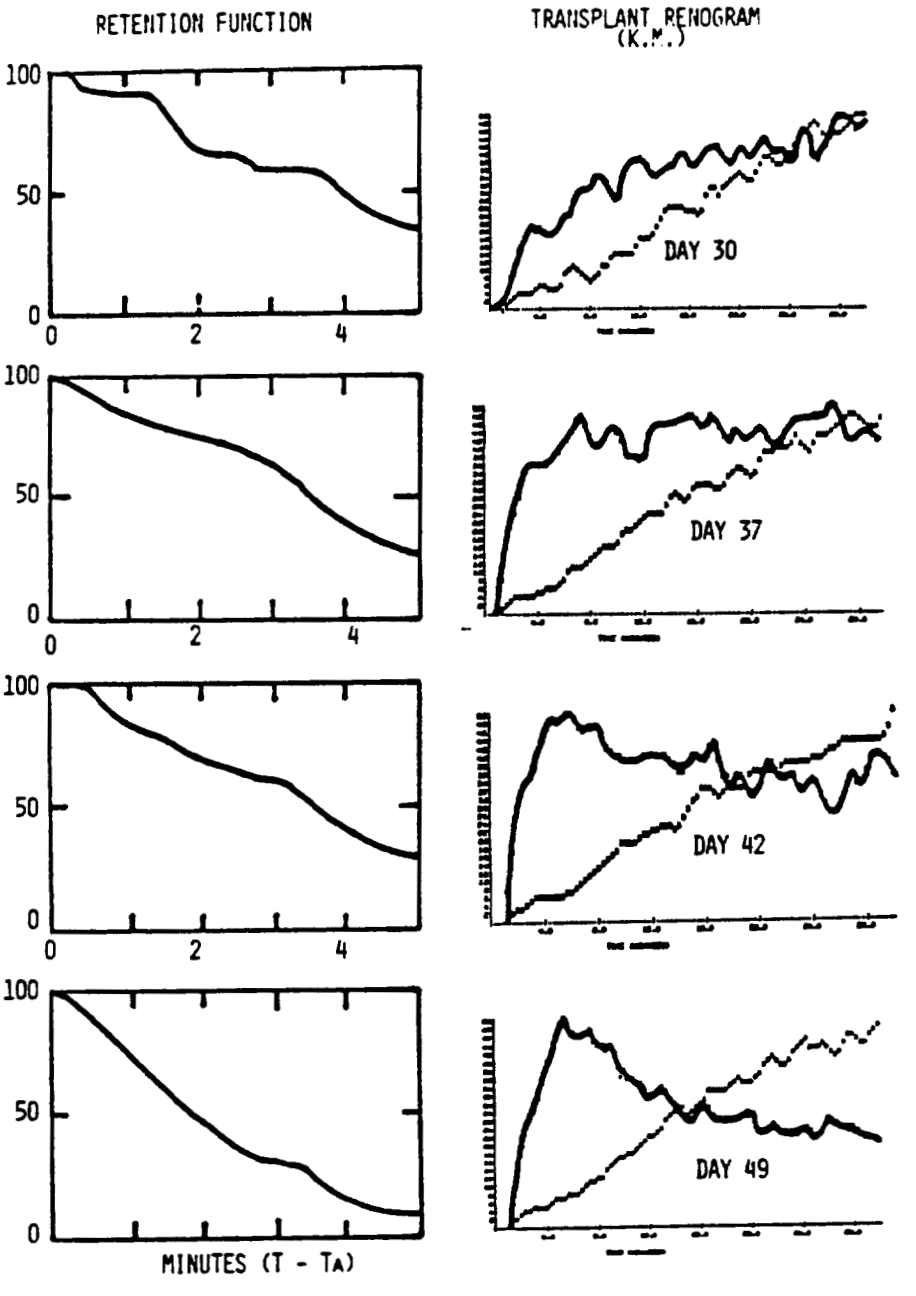


Figure 13. Continuation of Figure 12, days 30 to 49.

1017799

10%. At this time an intensive course of both steroid and radiation therapy was begun. He began to respond to therapy, regaining good function and by day 49 was released from the hospital (BUN = 40, creatine = 1.9).

In general, as is the case in this example, the retention function curve is easy to interpret and is quite sensitive to changes in renal function. The retention function takes out differential rates of uptake from the kidney curves and enables one to view the rate of release of the compound from the kidney after trapping. However, the clinical utility of this technique relative to that of the routine renogram remains to be tested.

Summary and Conclusions

We have investigated two deconvolution techniques for estimating renal transit-time distributions. These were the Fast Fourier Transform technique and a point-by-point discrete deconvolution. In most situations both techniques yielded good results. However, we routinely used the point-by-point technique because of its increased speed of calculation, its insensitivity to "end effects" in the data and its relative insensitivity to high frequency components in the data.

Both deconvolution techniques were found to be extremely sensitive to the level of random noise in the data. Unprocessed data at count levels normally obtained in an I-131-OIH renogram gave uninterpretable results. Some form of data processing to reduce the effects of random noise was found to be essential. We arrived at a low frequency pass filter which attenuated frequencies with periods shorter than one minute. This filter was found to introduce an uncertainty in the determination of minimum transit-times less than one minute. This was not found to be a limitation in any of our animal or patient studies.

The presence of a blood background component in the renogram was found to also introduce an uncertainty in the minimum transit-time.

The deconvolution technique was unable to detect the presence of non-linearity in the system. Systems with reflux were interpreted as having an accelerated transit-time.

Direct measurements in experimental animals displayed the precision and accuracy of the deconvolution technique to be good over a wide range of renal function. We have seen no evidence for a bimodal structure in any of our transit-time curves. This observation includes in particular the intraarterial injections in dogs where the counting statistics were exceptionally good. All of our observations lead us to the conclusion that the normal kidney behaves very similiar to a classical mixing compartment plus a delay.

The relative clinical utility of the deconvolution technique with respect to the traditional renogram is not clear at this time.

REFERENCES

1. Britton, K.E., and Brown, N.J.G.: "The Clinical Use of C.A.B.B.S. Renography," Br. J. Radiology, 41, page 570, 1968.

2. Kenny, R.W., Ackery, D.M., Fleming, J.S., Goddard, B.A., and Grant, R.W.: "Deconvolution Analysis of the Scintillation Renogram," Br. J. Radiology, 48, page 481, 1975.

3. Britton, K.E., and Brown, M.J.: Clinical Renography, Lloyd-Luke, London, 1971.

4. Meldolesi, U., Roncari, G., Fidenga, M.A., et al.: "First Attempts of Clinical Application of a Method for the Quantitative Interpretation of Renogram with Radiohippuran." J. Nucl. Biol. Med. 13: p. 94, 1969.

5. Lindmo, T., Skretting, A. and Nakken, K.F.: "An Examination of Different Mathematical Models of Renal Function as Measured by ^{131}I-Hippuran Renography." Medical Physics, Vol. 1., No. 4., p. 193, 1974.

DISCUSSION:

Britton commented that in the transit time distributions presented he did not see the bimodality often observed. Britton stated that he felt that the shape of the distribution that he had re

Britton commented that in the transit time distributions presented he did not see the bimodality that he had often observed. Britton stated that he felt that the shape of the distribution was related to differences in cortical and juxtamedullary function.

Price noted that he had not seen multiple components in the transit time distribution in dogs. He noted further that they considered the possibility that these features were being filtered out, but stated that he was convinced that this was not the case. He stated that it appears their data can be described with a simple one compartment model with a delay.

Britton, in answering the questions arising about the validity of a technique, stated that he felt it imperative to evaluate and understand the factors influencing the distribution of transit times in the normal kidney. Otherwise, it should be very difficult to estimate the effects of noise and physiologic variation on the results in abnormal patients. He noted that several pieces of clinical and experimental evidence which seem to indicate that the distributions of transit time spectra do have clinical correlates. Britton described an early set of studies where sodium and potassium intake in a population of hypertensive patients was conducted. They studied the proportion of Hippuran traveling through the kidney with transit times under the first mode of a bimodal distribution. The proportion under the first mode in the state of low salt intake was over twice that in the state of high salt intake. The salt intake therefore does alter the distribution of transit times and is just as important to consider as the control of water intake. In another study, they measured plasma renin levels in patients with cirrhosis on a low salt diet. The renal function in these patients was normal; they all demonstrated creatinine clearances above 90 ml/min. The results showed that when the first or cortical component of the transit time distribution was large, the renin levels were normal. There was a significant negative correlation between the area under the first peak and the level of renin activity. Thus, he concludes that they have found that it is very important to control the various physiologic factors which can affect the transit time distributions before statements can be made about the effects of pathological influences.

Brill suggested that to resolve the apparent discrepancy between the shapes of the time distributions, it would be useful to determine if details of the distributions are being observed by mathematical manipulations. He suggested a comparison of the results computed from the same group of patient studies would be very helpful.

1017801

NEW METHODS FOR PULSATILE BLOOD FLOW MEASUREMENT USING CINE-DENSITOMETRY[+]

U. Efron*, Dan Kedem**, Drora Kedem**, C.W. Smith,
J. Erickson, R.R. Price, J.H. Nelson, and A.B. Brill
Vanderbilt University Medical Center
Nashville, Tennessee U.S.A.

ABSTRACT

Experimental measurements of pulsatile blood flow were carried out using standard cine-angiography techniques with subsequent digitization and computer processing of the cine film. New approaches to measurement of blood flow were examined. The commonly used center of gravity method for the bolus transit time determination is shown to be subject to serious error when backflow is present. An analytic method for the determination of instantaneous blood velocity has been developed and tested experimentally using controlled constant and pulsatile flow systems. The results show good agreement with the known flow values. The method was applied to cine recorded data of arterial blood flow in dogs. The results are in good agreement with the known shape of the velocity distribution curve in the normal aorta.

[+]This research was supported in part by SCOR grant HL-14192.

*On leave from Soreq Nuclear Research Center, Yavne, Israel.
**Soreq Nuclear Research Center, Yavne, Israel.

1017802

INTRODUCTION

Previous cine and video densitometry methods of measuring blood flow have shown quite scattered results for pulsatile systems whereas the correlations in constant-flow systems were usually quite good. (1-4)

The method employed consisted of cine and/or video tape recording of the x-ray image of the rapidly injected intraarterial radiopaque contrast dye. The subsequent analysis of the recording was aimed at obtaining the transit time of the bolus between two sites or "windows" along the blood vessel. This was done by observing the frame to frame progress of a well-defined point in the bolus density curve such as the leading edge or the peak point. A commonly employed method uses the time center of gravity (C.O.G.), of the density curve obtained at the two sites. The transit time is then taken as the time difference between these two centers of gravity time.

This report presents an analysis of both the currently used (C.O.G.) method and a newly developed instantaneous velocity method for the determination of blood flow.

Blood flow simulation experiments were carried out under both stationary and pulsatile flow conditions. Animal studies are also reported. The mathematical basis for both data processing methods is presented (i.e. the "conventional" C.O.G. method and the newly developed "Instantaneous velocity" method). The experimental data are analyzed using both methods, and the results compared.

Good correlation with the known flow values is found using both methods under stationary flow condition. In pulsatile flow conditions, poor correlation is found for the C.O.G. method whereas the instantaneous velocity method produces results with good correlations. It is verified that the new method correctly determines the direction of flow in cases where a visually observed backflow is present. The velocity distribution data obtained by applying the instantaneous velocity to dogs' aortic flow data compares well with the expected aortic blood flow distribution in normal dogs.

Finally, a comparison of the two methods for the determination of the average flow is carried out. In particular, an analysis of the limitation in applying the C.O.G. method to pulsatile flow condition is presented.

METHODS

Experimental Setup

The experiments were conducted in the Cardiac Catheterization Laboratory. at Vanderbilt University Hospital. The experimental setup is shown in Figure 1.

The x-ray tube operated at 50kv was pulsed synchronously with the cine camera at 60 c.p.s. with pulse durations of 2-5 msec. One (1) ml. of contrast dye -- "Renografin - 76" -- was injected using a programmable injector, at an injection speed of 59cc/sec. Experiments included both simulated blood flow studies and studies in the descending aorta in dogs.

1017803

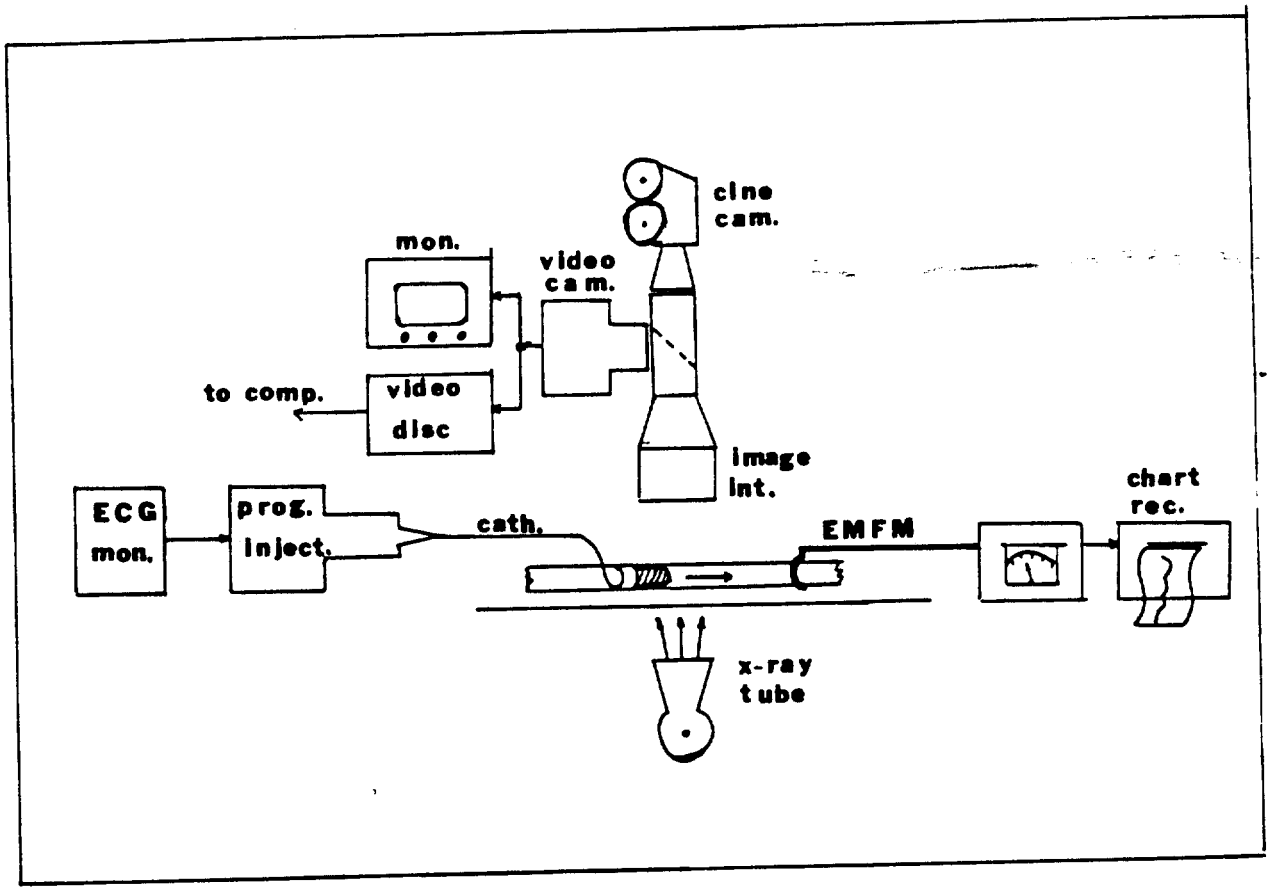


Figure 1. The experimental set up.

1017804

The experimental calibration studies used constant (gravitational) flow and pulsatile flow systems. In the constant flow simulation study, saline flowing under the influence of gravity controlled by a valve at the outlet of the container was used. The pump used in the pulsatile flow was a Travelol rotary pump with a cycle time of approximately 810 msec. Injections at several flow rates were made at the beginning and end of a pump rotation cycle. For flow corresponding to average velocities of 20 cm/s or less, backflow was visually observed. The flow in both continuous and pulsatile simulation experiments was measured using time sampled flow into a graduated cylinder. The tubing used was p.v.c. type with an inside diameter = 4.76 mm.

Dog studies were performed on anesthesized animals. A pigtail type catheter inserted into the abdominal aorta above the ostium of the right renal artery. Several injections were made throughout the cardiac cycle using the E.C.G. triggering capability of a programmable injector. The 35 mm cine film type was CFS Kodak. It was developed in an Oscar Fisher G-12 Developer.

Data Processing System

The cine film was mounted on a film transport device and trans-illuminated by diffused light. The image was digitized using a vidicon camera (Cohu 810) coupled to a video compressor (Colorado Video 270). The vidicon resolution was about 800 lines. The digitizer frequency was 10 MHz. Digitized data were transferred to a PDP-9 computer (Digital Equipment Corporation) using special routines to digitize selected regions of interests (usually lines across the vessel) and to store the total logarithmic intensity at the selected sites. The digitization of one frame (10 sites of ~ 100 point each), required about 10 sec. The number of frames digitized were 30-60 for a typical study.

The methods used for blood-flow determination

The method of the center of gravity (C.O.G.)

This method is based on the determination of transit time of the bolus between two sampling sites located along the vessel. The transit time is determined by calculating the time difference between the centers of gravity of the density curves at both sites.

The mathematical expression for the transit time obtained by using the C.O.G. method is given by:

$$\Delta t = t_B - t_A = \frac{1}{S_B}\int C_B(t).t.dt - \frac{1}{S_A}\int C_A(t).t.dt \ldots (1) \quad ,$$

where the "B" site is located downstream with respect to "A". $C_A(t)$, $C_B(t)$ are instantaneous densities of contrast dye observed respectively at sites "A" and "B".

S_A and S_B are the total (integral) amount of dye at "A" and "B" respectively.

Usually 6-10 equally spaced sites were digitized -- the program then proceeded to calculate the C.O.G. of the density curves at the sites analyzed using the data from the sequence of frames.

1017805

The density curves at multiple sites along the vessel possess spatial and temporal information related to the bolus density function B(x,t). In order to make use of this information, we developed the technique which is called the instantaneous velocity method.

As the bolus is carried downstream, its profile is gradually changed due to intermixing with blood. However, for closely adjacent sites (i.e. several millimeters apart in an average blood velocity of 20-30 cm/s), one would expect the bolus shape to appear almost identical at both sites. The general mathematical expression for a physical phenomenon B(x,t) moving at a constant speed V_0 in the +x direction, without changing its shape is:

$$B(x,t) \equiv B(x-V_0 t) \quad . \qquad (2)$$

(This expression states that a density observed at point 0 at time 0 will be observed at point x and time t where $x = V_0 t$.)

In the pulsatile case, the velocity is a time-dependent quantity, and hence the above expression must be replaced by:

$$B(x,t) \equiv B(x-I(t)) \quad , \qquad (3)$$

where

$$I(t) = \int^{t} V(t)dt \quad . \qquad (4)$$

The form (2.3) of the bolus function B(x,t) leads to the following relation between the spatial and temporal derivates of B(x,t):

$$\frac{\partial B}{\partial x} = - \frac{\partial B}{\partial I(t)} \quad . \qquad (5)$$

However, since I(t) is a time integral of V(t) one may write:

$$\delta I = V(t).\delta t \quad . \qquad (6)$$

Inserting (2.6) in (2.5) leads to

$$\frac{\partial B}{\partial x} = \frac{-1}{V(t)} \frac{\partial B}{\partial t} \quad . \qquad (7)$$

Finally, rearranging egn. (2.7) one obtains the desired expression for instantaneous velocity:

$$V(t) = - \frac{\partial B/\partial t}{\partial B/\partial x} \quad . \qquad (8)$$

A simple implementation of this result for injected bolus experiments is to use the time density curve obtained at two sites "A" and "B" several mm apart. In this case one may write approximately:

1017806

$$V_{AB}(t_i) = - \frac{B_B(t_i) - B_B(t_{i-1})}{B_A(t_i) + B_B(t_{i-1}) - B_A(t_{i-1})} \quad (9)$$

where $B_A(t_i)$, $B_B(t_i)$ are the density value at sites A and B respectively in frame (time) t_i.

The instantaneous velocity subroutine used density data stored for the selected sites. The sites were grouped into equally separated pairs and the digitized density differences between sites and frames were computed according to eq. (9). Usually 4-5 pair were taken and the instantaneous velocity respresents an averaged value of those pairs.

RESULTS

C.O.G. Method

Results of the stationary flow study are shown in Figure 2. A good correlation is observed (correlation coefficient is .960). However, the results are quite scattered with a mean deviation of 24% over the whole range of velocities covered (9-80 cm/s). The method was checked by using different site-separations (4mm-3cm) and no significant changes were observed.

The pulsatile flow results are shown in the second column of Table 1. The following points should be noted:

(i) The pump cycle lasted about 49 frames whereas at average velocities of 36 and 31 cm/s the bolus lasted for a shorter period. The averaging over cycle was, therefore, incomplete.

(ii) It is observed that no substantial change is obtained by using wider site-separations.

(iii) The reduction in flow was accomplished by narrowing the inlet tube to the pump so that at velocities below 31 cm/s an increasing backflow component was visually observed as flow was further reduced. It is possible that backflow persisted also in the study where V = 36 cm/s.

As may be seen, there is no significant correlation between the known and calculated results using the C.O.G. method in this case.

"Instantaneous Velocity" Method

A typical result of a study under constant flow conditions performed at four (4) sites separated 4mm apart is shown in Table 2. As may be seen, the results at different sites in each frame are consistent. It is observed that the largest velocities were observed in the first few frames, followed by a general decrease with time.

Figure 3 shows the correlation obtained between the average instantaneous velocity computed from the cine-densitometric data and the experimentally determined average velocity in the constant (gravitational) velocity case. The correlation coefficient is 0.99 in this case. The mean deviation from the unity slope line is 8%. The error bars refer to mean deviations of the instantaneous velocity (non-averaged) in each study. The average deviation of those is 35%.

In Figure 4, a sequence of cine frames from a pulsatile flow study is shown; the bolus is seen to appear and progress in the direction (downstream) then a reversal of the direction of motion is observed. Table 3 shows the resultant instantaneous velocity at these sites, its average and standard deviation. It is observed that the positive values for the forward flow change into negative during backflow as expected.

Figure 5 shows the correlation between computed instantaneous velocities averaged over a cycle (810 msec) and the experimentally determined average velocity (measured over 70 cycles) in the pulsatile study. It is observed that the correlation is good (r=0.91). The standard deviation is 10%. At high flow rates, corresponding to 20cm/s, the persistence of the bolus at the sites studied was too short, thus the averaging was performed over about 80-90% only of the pump's cycle. At measured flow rates corresponding to 10,16, 20 cm/s, backflow was observed visually. Table 1 summarizes the results of the instantaneous velocity along with those of the C.O.G. method.

Figure 6 shows the results of similar flow measurements in a dog's descending aorta along with a typical density curve at one of the sites studied. The general features of forward flow, the peak value of forward flow,backward flow region and the one cardiac cycle separation between the peaks are in agreement with the experimentally determined velocity distributions. For comparison, an example of velocity distribution in the dog's femoral artery is shown in Figure 7. Similar results for two other dogs studied are shown in Figures 8 and 9.

DISCUSSION

Limitation of the C.O.G. method under pulsatile flow conditions

As evidenced by the experimental results, the traditional C.O.G. method cannot be used in high velocity pulsatile flow cases. In the following, the general limitation of the C.O.G. method when applied to pulsatile flow are discussed.

The first limitation of the application of the C.O.G. method to pulsatile flow condition is related to the time averaging period. The persistence of the bolus at the sites studied depends on such factors as the injection time, the phase at the cardiac cycle in which the injection is made and the magnitude of flow. The bolus length at the sites cannot therefore be "tailored" so that it will cover an exact integer number of cardiac cycle(s). However, in order to obtain the true mean flow under pulsatile condition, one must have an exact average over complete cardiac cycle(s). Neglect of this point may have been another cause for the widely scattered results obtained in the past.

The second limitation of the method is related to cases where a large backflow (BF)component is present. In this case, one must reanalyze the concept of transit time, as the dye material moves back and forth between sites "A" and "B" (where "B" is located downstream with respect to "A".) As was pointed out above, the only meaningful discussion of average flow and of the corresponding transit time will be to analyze complete cardiac cycle(s). The following discussion deals therefore with transit time definition where one complete cycle is analyzed.

Consider first a single dye particle travelling back and forth under backflow. It is clear that in this case the definition of average transit time between "A" and "B" should read: The time between the particle first arriving at "A", and its lastly leaving "B". When a continuous distribution of dye "particles" is present, one may define two distribution times: The time distribution of the particles' first appearance at "A" and the time distribution

80L101

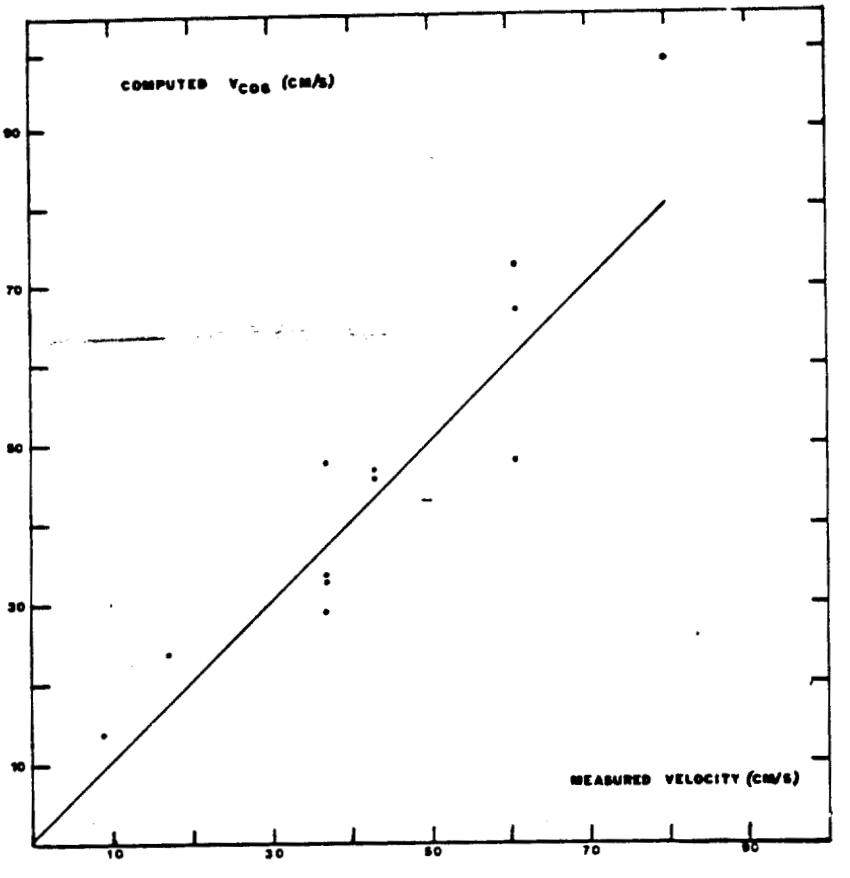


Figure 2. The correlation between computed and measured flow velocities using the C.O.G. method in a study at constant gravitational flow.

TABLE 1

PULSATILE FLOW

VELOCITIES OBTAINED BY THE C.O.G. AND

INSTANTANEOUS VELOCITY METHODS

Measured velocity cm/s	$\bar{V}$ C.O.G. cm/s	$\bar{V}$ Instantaneous cm/s
36	40;47;55	39*
31	67;31	28*
20	31;47	18;17*
16	65;61	17;17
11	53	10;11

* Averaged over .8-.9 of a cycle

1017810

TABLE 2

GRAVITATIONAL FLOW-INSTANTANEOUS VELOCITY DETERMINATION

V MEASURED = 43 cm/sec

DISTANCE BETWEEN SITES: 0.4 cm.

FRM	INSVEL1	INSVEL2	INSVEL3	INSVEL4	AVEL	STAN.DEV.
1	73.8	69.3	72.1	*124.1	84.8	22.7
2	67.6	54.4	67.2	83.7	68.2	15.5
3	50.3	39.4	31.9	*-3.7	29.4	20.2
4	10.7	10.9	23.2	28.5	18.3	7.7
5	70.0	39.6	50.7	30.8	47.8	14.7
6	47.0	55.9	*106.2	33.4	60.6	27.6
7	22.8	36.5	50.4	24.8	33.6	11.0
8	35.1	32.1	38.7	28.1	33.5	3.9
9	27.3	24.5	19.7	19.5	22.7	3.3
10	6.2	17.2	14.9	9.2	11.6	4.6
11	28.0	37.3	27.5	21.2	28.5	5.7
12	18.6	31.2	20.9	19.3	22.5	5.1
13	25.6	30.1	23.2	22.0	25.3	3.1
14	26.2	26.6	25.0	20.7	24.6	2.4

AVERAGE = 37 cm/sec

* High deviations

1017811

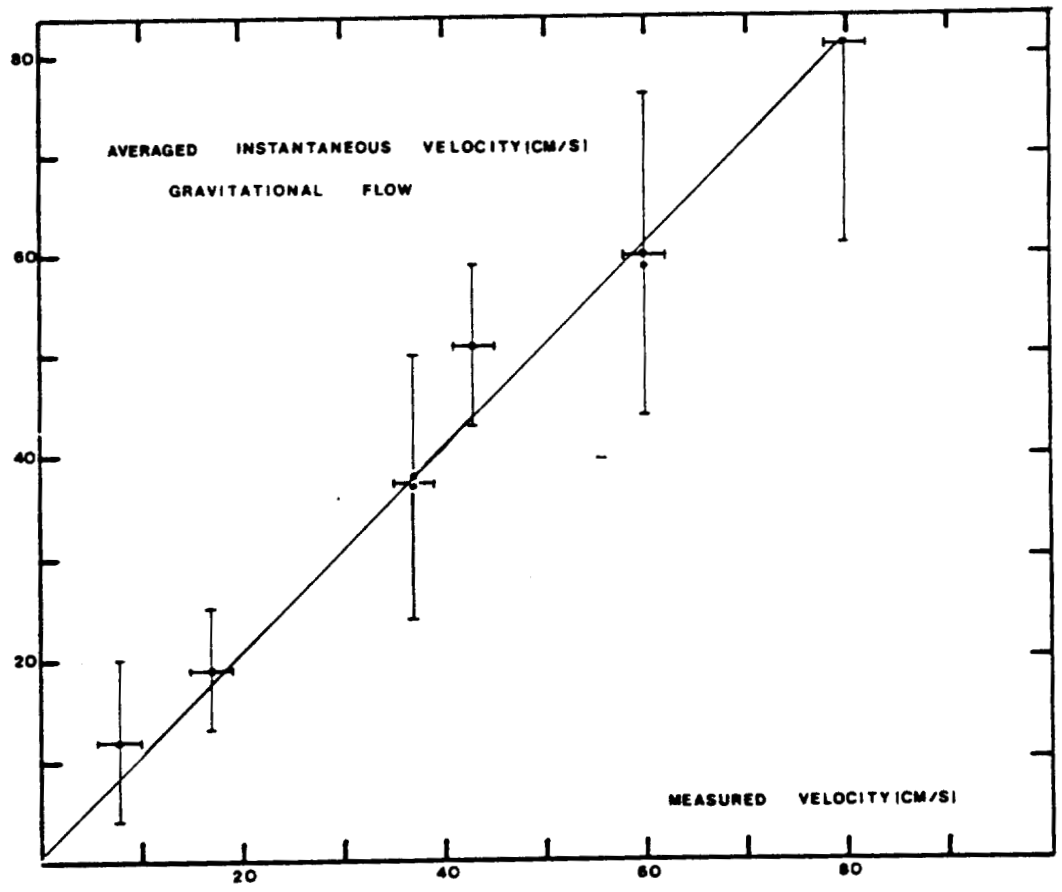


Figure 3. Results of the average velocity obtained using the instantaneous velocity method vs. measured flow velocity in the constant flow study.

1017812

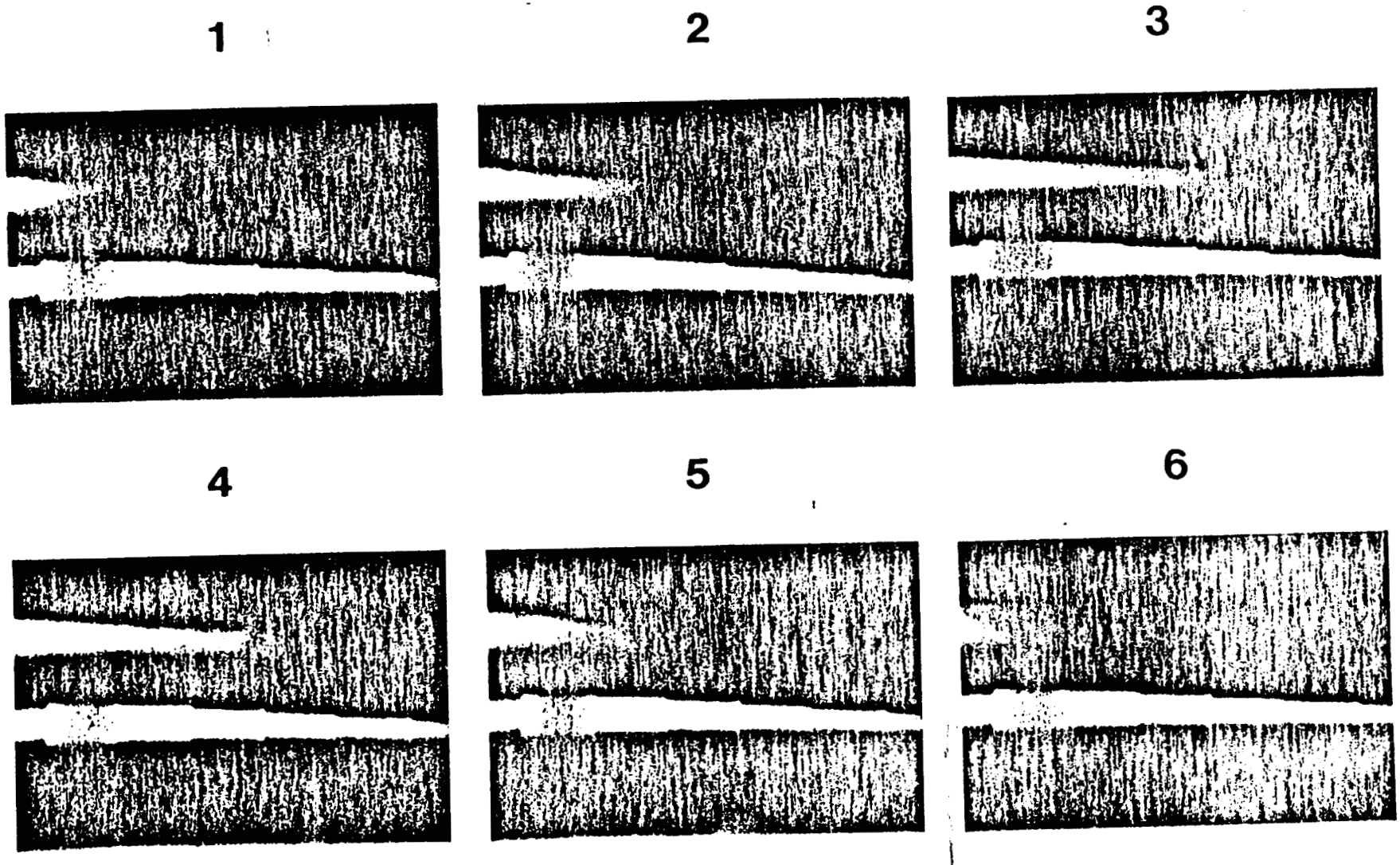


Figure 4. A sequence of 6 cine frames showing a case of backflow. The bolus enters and then reverses its direction clearing the region of vessel analyzed.

1017813

TABLE 3

INSTANTANEOUS VELOCITY RESULTS

FOR THE CASE OF BACKFLOW

(cm/s)

FRAME	V(1)	V(2)	V(3)	V(4)	V(5)	AVERAGE	STAN. DEV.
1	39.7	40.9	38.8	36.0	36.5	38.0	1.9
2	51.6	49.7	45.6	39.5	39.5	45.2	5.0
3	31.0	32.4	35.2	38.8	31.1	33.7	2.9
4	14.9	20.6	11.7	8.1	15.2	14.1	4.1
5	4.6	-10.1	-4.3	3.5	2.7	-0.7	5.7
6	-14.4	-8.9	-10.5	-14.2	-16.7	-12.9	2.9
7	-30.9	-31.3	-26.0	-19.9	-20.3	-25.7	4.9
8	-39.8	-39.5	-35.6	-31.8	-32.0	-35.8	3.5
9	-41.2	-43.6	-51.9	-61.6	-69.3	-53.5	10.7
10	-34.5	-36.2	-32.6	-35.5	-43.7	-36.5	3.8

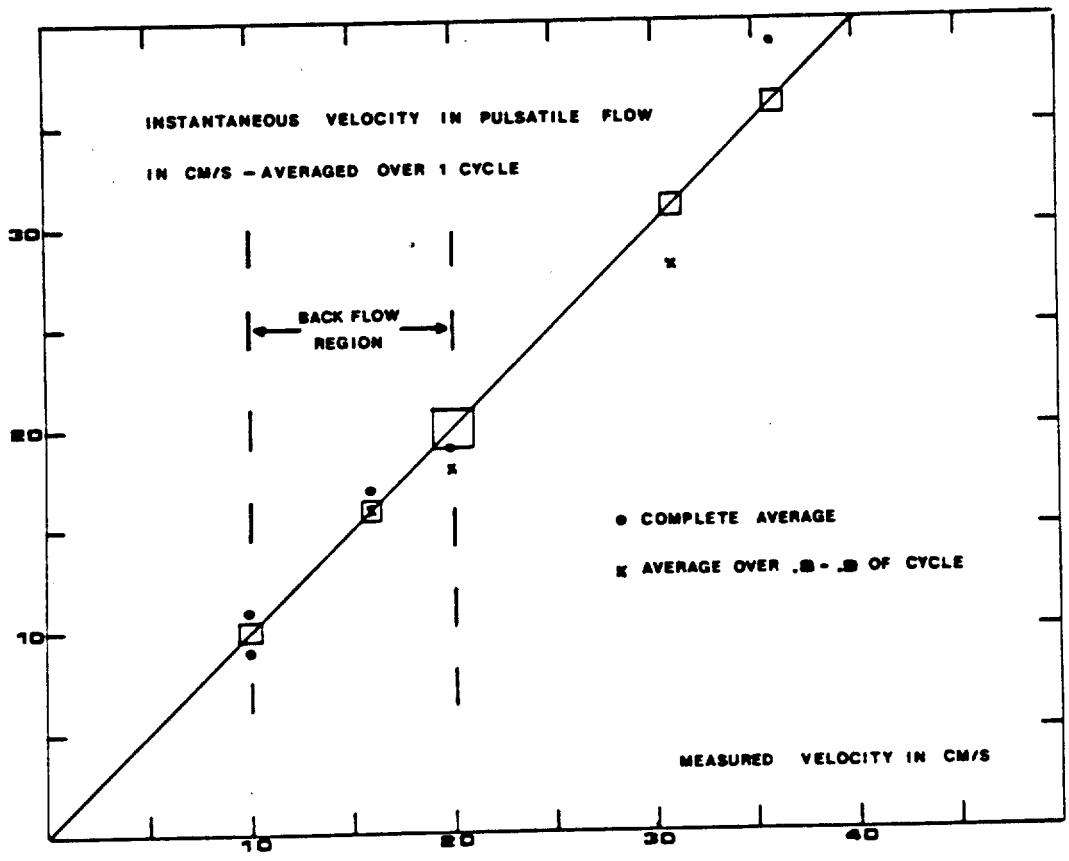


Figure 5. Results of instantaneous velocity averaged over one pump-cycle in a pulsatile flow study. Squares indicate the regions of uncertainty due to experimental errors.

1017814

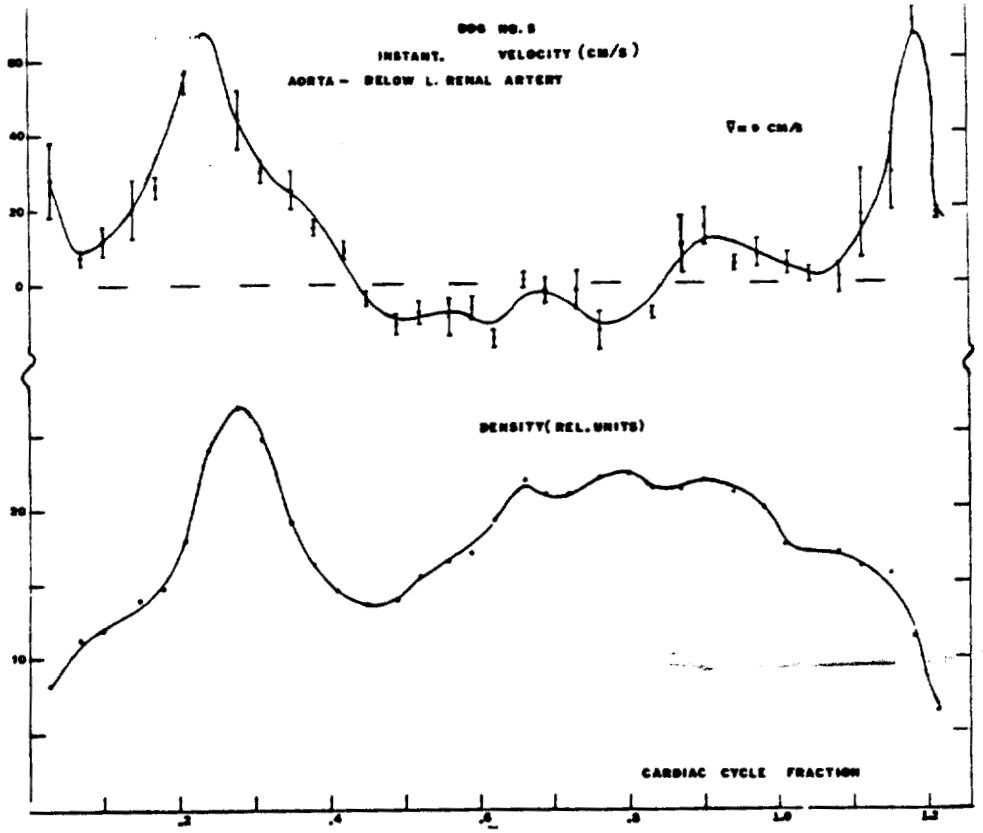


Figure 6. The application of the instantaneous velocity method to dog's arterial blood flow data taken below left renal artery. Top: Instantaneous velocity distribution. Bottom: Typical density curve at one of the sites analyzed.

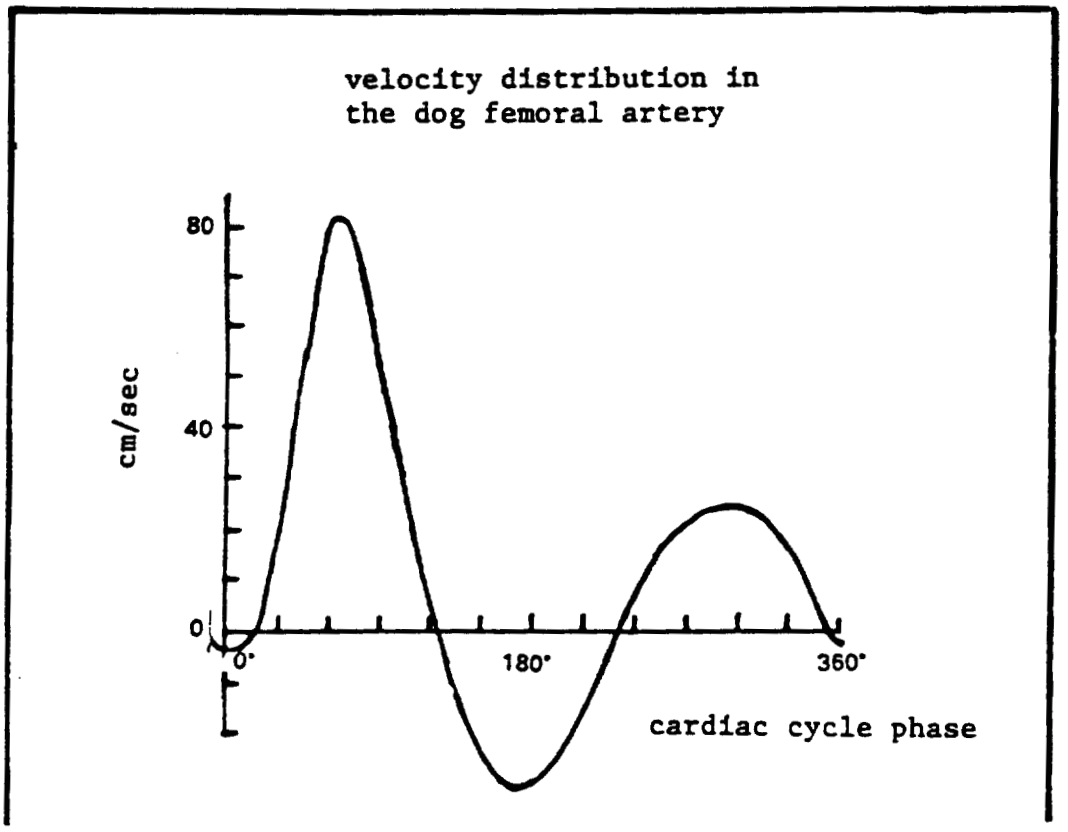


Figure 7. Velocity distribution in the dog's femoral artery-using high speed optical cineatography (5).

1017815

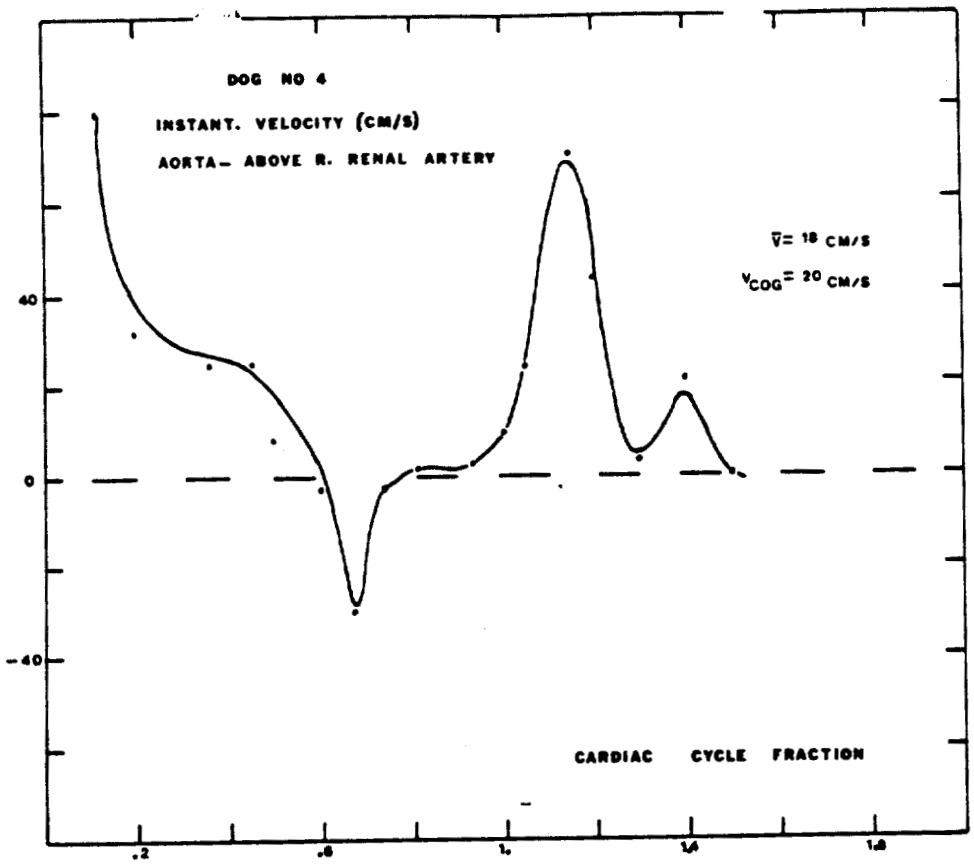


Figure 8. The instantaneous velocity distribution determined from cine data of dog's aortic blood flow.

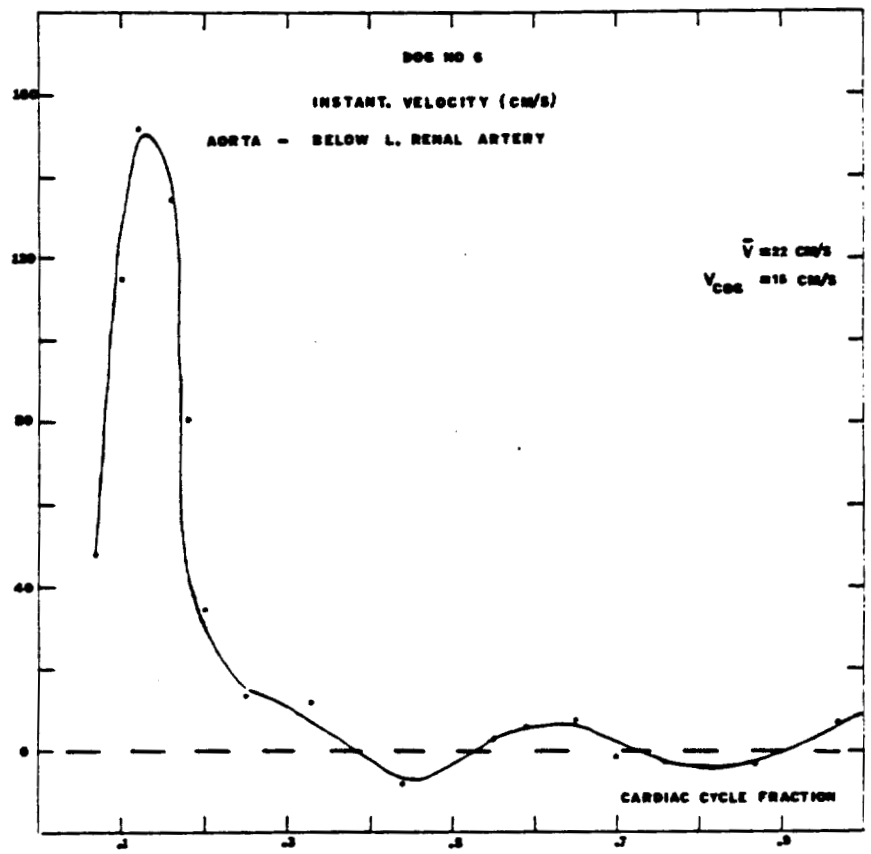


Figure 9. The instantaneous velocity distribution determined from cine data of dog's aortic blood flow.

1017816

difference between the averages (or centers of gravity) of those two time distributions. However, these time distribution curves do not coincide with the density curves obtained by measuring the density vs. time of the dye in each site. This is so since while measuring density at the sites, each crossing and recrossing of the dye material at the sites will appear as peaks in the density curves, whereas by the definition of the time distributions stated above, only one passage through each of the "A" or "B" sites will be recorded in this case--namely, the first crossing of the "A" site and the last crossing of the "B" site.

It should be noted that some error is also expected when calculating the transit-time using the cross correlation (6) method. This is so, since this method correlates the shapes of the density curves at the two sites to obtain the mean time difference between them. The occurance of several peaks at site "A" and the corresponding appearance of several peaks in the reverse (time) order at "B" due to the bolus recrossing of the sites under backflow, will introduce an error in the cross correlation and consequently in the transit time obtained.

One could overcome the first (time) limitation discussed above. In the case of an arbitrary bolus length, by computing the C.O.G. of those portions of the density curves corresponding to complete cardiac cycles. However, much of the information related to the transit time is contained in the time difference of the leading and trailing edges of the density curves. Thus, when using only a portion of the curve either the leading or trailing edge information would be lost.

A way to overcome the second difficulty is to use the C.O.G. method restricted to either the FF or BF regions (7). One may use multiple short bolus injections in various phases of the cardiac cycle to scan the whole FF or BF region. This method requires, however, that one be able to distinguish between the backward and forward flow regions. Difficulties are also encountered in the intermediate region in which the flow changes its direction.

The "Instantaneous Velocity" Method

The results obtained with the instantaneous velocity method are reasonable for steady and pulsatile flow measurements in simulators and in real studies. The results are dispersed, due to noisy data, and hence signal averaging is required. Standard deviations obtained at the constant flow experiments are about 20-30% for the instantaneous (non-average) values. Higher deviations are observed in the pulsatile flow studies. There are several causes for these fluctuations:

(i) As previously stated, we have taken the simplest way to implement the instantaneous velocity relations (8) by computation based on (9). This simple form is not suitable for use in cases of either high velocities or highly non-uniform bolus profile along the vessel. In both cases, the temporal and spatial derivative will show large variation. To overcome this difficulty one must use a program which will select the appropriate site and temporal separation based on initial velocity information obtained e.g. by using the present method of instantaneous velocity. This will then be repeated iteratively to minimize deviations.

(ii) Due to noise present in the digitizing system, spatial and temporal gradients below a certain level will have to be rejected. In addition, a smoothing of the density curves must be applied. This may involve either partial integration over several frames or the use of low pass Fourier Filtering.

(iii) As indicated previously, there is a general tendency for instantaneous velocity values to decrease with time in the constant velocity studies. This is explained as follows: Since the velocity profile across the vessel is close to parabolic, the bolus will first appear at the central (high velocity) portion of the sites. This central region will gradually be depleted and the bolus's "tail" will be confined mainly to the lateral (low velocity portion of the vessel). This phenomenon is shown in Figure 10 where the density profile across the vessel at a certain site is shown. A high central density is observed at the first few frames (1-6) a "normal" shape at frames (8-10) and a center depleted density at the end frames (16-24). To overcome this difficulty one must use the density profile across the vessel and the experimentally determined parabolic velocity profile constants. These may be determined in one measurement as they are not expected to be velocity dependent.

It should be noted that whereas this phenomenon does affect the instantaneous velocity values, it tends to be averaged out when average velocity over cycle(s) is computed.

An additional advantage of this "differential" method over the C.O.G. "Integral" method is its relative insensitivity to non-linearities present in the imaging or recording systems. This is so, since in analyzing density curves using the C.O.G. method, one must use the whole dynamic range of the images. Densitometric results will therefore be affected by the non-linearities present in either the imaging system (image intensifier) or recording media (film). When using the instantaneous velocity method, one deals with differences of images which is equivalent to using a small dynamic range of the image.

CONCLUSIONS

An instantaneous velocity method for the determination of both instantaneous and average blood flow has been developed for cine-or video-densitometric angiographic data. The method has been validated under stationary and pulsatile flow condition. The velocity distribution obtained by applying this method to experimental animal studies are in agreement with the expected results.

The main advantages of this method are:

1. Instantaneous flow information is provided.

2. It permits the determination of average flow under highly pulsatile conditions.

3. Insensitivity to non-linearities in the imaging or recording systems.

4. The use of comparatively small (~1cc) amounts of contrast dye.

The drawbacks in this method are:

1. Highly fluctuating results and the consequent need for a smoothing procedure.

2. Some correction must be applied to instantaneous velocity data if velocity distribution is needed.

The limitations of the C.O.G. method under pulsatile flow conditions have been discussed. This method is applicable under two main restrictions:

1. An average over complete cycle(s) must be made.

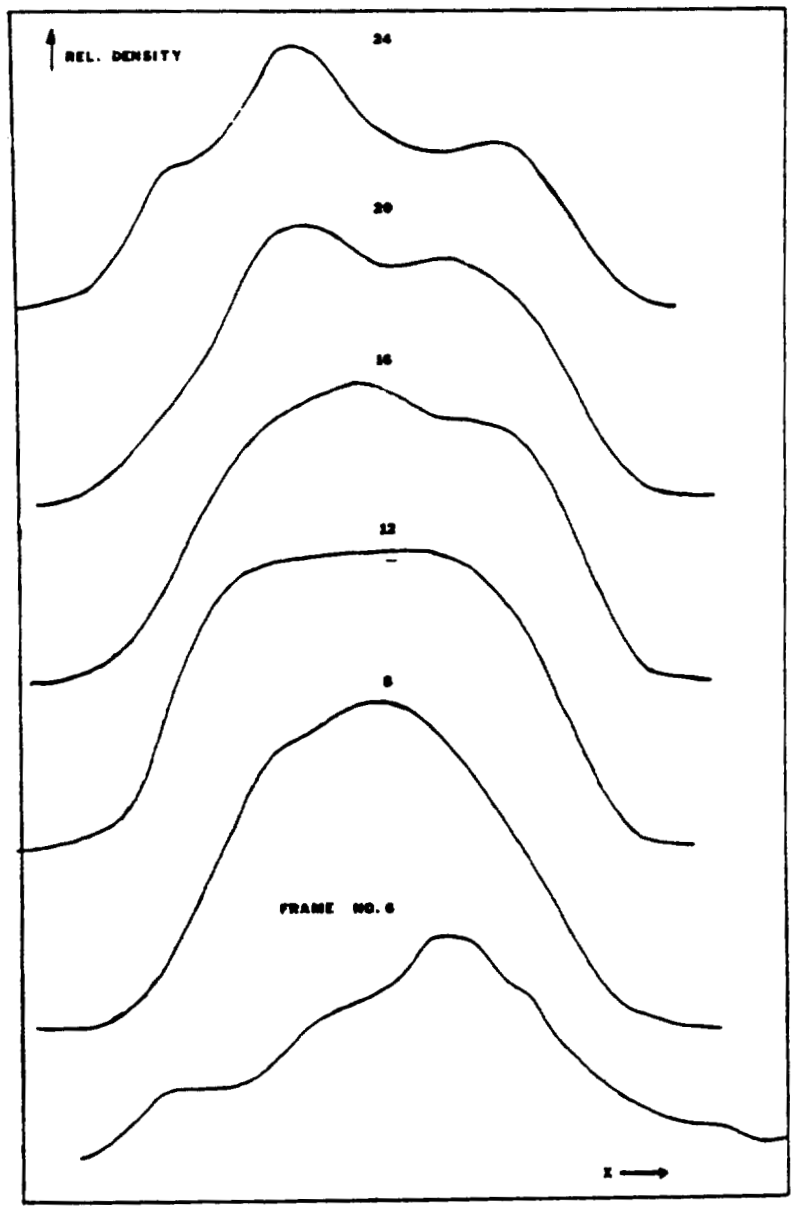


Figure 10. Density profile across the vessel taken at the same site during the various phases of the bolus progress. Frame #6- appearance of the bolus at the site, frame #24-low density "tail" of bolus is shown.

1017819

2. Low component of backflow, i.e. the time integral of the negative flow region must be small compared to the whole integrated flow.

Acknowledgement

The authors gratefully acknowledge the assistance of Mr. G. Novak and Mr. J. Norris in conducting the flow experiments.

REFERENCES

1. Rutischauser, W., et al.: Am. J. Roentgenol. Rad. Therapy and Nuc. Med. 109, 12, (1970).

2. Rutischauser, W., et al.: Circulation 36, 961, (1967).

3. Itzchak, Y., et al.: Invest. Rad. 10, 1 (1975).

4. Smith, H.C., et al.: "Simultaneous Indicator dilution--curves at selected sites in the coronary artery saphenous vein grafts by Roentgen Video-densitometry," Roentgen, Cine and Videodensitometry. Ed. P.H. Heintzen Stuttgart, Thieme, 1971, pp. 152-157.

5. McDonald, D.A., et al.: Blood flow in arteries, Ed. Williams and Wilkins Co. 1974, p. 130.

6. Rosen, L., et al.: Radiology 103, 305 (1973).
Silverman, N.R., et al.: Invest. Radiol. 12, 319 (1977).

7. Kedem, D., et al.: "Velocity distribution and blood flow measurements using video densitometric methods," Invest. Radiology - to be published.

DISCUSSION:

In reply to a question from K. Britton, Effron stated that in calculating flow, blood vessel cross sections were assumed to be circular. B. Oppenheim asked why corrections for the flow profile across a vessel are required in determining transit time: do not flow measurement determinations of transit time inherently average over the various simultaneous velocities? Effron explained that corrections for backward flow components were required in order to separate forward flow from net flow.

1017820

PRACTICAL CLINICAL APPLICATIONS

OF THE COMPUTER IN NUCLEAR MEDICINE

R.R. Price, J.J. Erickson, J.A. Patton, J.P. Jones,
J.E. Lagan and F.D. Rollo

Division of Nuclear Medicine
Vanderbilt University Medical Center
Nashville, Tennessee 37232

1017821

PRACTICAL CLINICAL APPLICATIONS

OF THE COMPUTER IN NUCLEAR MEDICINE

I. SYSTEM COMPONENTS AND COMPUTER TERMINOLOGY

   a. The Central Processing Unit (CPU) or Basic Computer

   b. Storage Media

   c. Gamma Camera Interface and Physiological Monitors

   d. Image Display

   e. Hard Copy Output

   f. User Console

II. CARDIOVASCULAR

   a. First pass cardiac function studies

   b. ECG gated acquisition at equilibrium

III. RENAL FUNCTION

IV. RELATIVE BLOOD FLOW

   a. Cerebral

   b. Renal

V. OTHER APPLICATIONS

   a. Imaging

   b. Non-imaging

1017822

INTRODUCTION

The impact of the computer on the practice of nuclear medicine has been felt primarily in the area of rapid dynamic studies. At this point in time it is difficult to find a clinic which routinely performs computer processing of static images.

The general purpose digital computer is a sophisticated and flexible instrument. The number of applications for which one can use the computer to augment data acquisition, analysis or display is essentially unlimited. In this light, the purpose of this exhibit is not to describe all possible applications of the computer in nuclear medicine but rahter to illustrate those applications which have generally been accepted as "practical" in the routine clinical environment.

Specifically, we have chosen examples of computer augmented cardiac, and renal functions studies as well as examples of relative organ blood flow studies. In addition, a short description of basic-computer components and terminology along with few examples of non-imaging applications are presented.

1017823

I. SYSTEM COMPONENTS AND COMPUTER TERMINOLOGY

a. The Central Processing Unit (CPU) or Basic Computer:
Contains the memory, maintains control over the various peripherals and performs all the arithmetic operations required for data analysis.

Common Descriptors:

Memory size: The number of words of memory that can be used to hold programs while they are executed and data that is being analyzed. Commonly available are 16,000 and 32,000 word memories.

Word size: Specifies the number of binary digits (BIT) in each memory location. Determines the largest number that can be stored in any given memory word. Eight bits (often referred to as BYTE) can hold 256 while 16 can hold 65,534.

Languages: The most common user languages for scientific programming are FORTAN and BASIC.

Operating System: The master program which oversees the operation of the entire computer system. Will determine how many users can use the system at one time.

b. Storage Media:
Used for permanent storage of both programs and clinical data. Modern systems have primarily two forms magnetic disc and magnetic tape. The discs are either large hard disc (removable or fixed) or small flexible ("floppy") discs. Magnetic tape is a special tape and is written several tracks at a time. The most common form is 9 track tape which can write one 8 bit byte at time on the tape.

Common Descriptors:

Capacity: The number of data words which can be stored on the medium. Large fixed discs usually hold 1.25 to 80 million words. Removable hard disc cartridges hold 1.25 to 5 million words. Floppy discs can hold 150,000 to one million words. All of these values depend on the size of the computer word and the format of the data storage.

Transfer Rate: Specifies the rate in words per second at which data can be transferred to the medium. If the storage medium is to be used during data collection it is important that this rate is high. Typical values range from 16,000 words per second for magnetic tape to one million words/second for large fixed discs.

1017824

c. Gamma camera interface and physiological monitor:
Converts the analog position signals from the gamma camera into digital numbers which can be used by the computer to build images. The physiological monitor can be used to synchronize the data acquisition from the camera to physiological phenomonon such as heart beat.

Common descriptors:

Conversion time: Specifies the time it takes for the analog to digital converter in the interface to convert the analog position signals to the digital number. It should be small (1-10 micro seconds) so as not to cause data to be lost while it is converting.

Conversion resolution: Specifies the maximum number of bits in the digital word that is produced by the analog to digital converter. Normally specified in terms of image resolution achieved by the system, i.e. 64 X 64 (6 bits), 128 X 128 (7 bits) or 256 X 256 (8 bits). This determines how much of the original spatial resolution of the gamma camera is retained in the digitized image.

Collection modes: Not strictly a parameter of only the gamma camera interface but also depends on the programming of the computer. The various modes that are currently available are:

a. Frame Mode: The image is built up in memory during collection by incrementing the memory location specified by the analog to digital converter.

b. List Mode: The numbers from the analog to digital converter are saved in a list as they come from the interface, along with a clock register for use in rebuilding the images at a later time.

c. Dual Isotope: May be either frame or list mode collection but the digital numbers coming from the interface also have a flag attached to them to indicate that they represent counts from either isotope A or isotope B.

d. Gated Acquisition: May be list or frame mode acquisition but the data from the interface is synchronized with the physiological signal and allocated to images representing preselected portions of the physiological cycle.

d. Image Display:
The part of the system displays the images which have been collected and/or processed by the computer system. May have its own memory and color generation system. May also be part of the user interaction system in that it may display a cursor which the user positions to indicate regions of interest for further processing or flow curve generation.

Common Descriptors:

Image array size: Describes the number of elements used to generate the image displayed. If a small number, e.g. 64 X 64 are used the picture may appear grainy while a large number, e.g., 256 X 256 may produce a pleasing display but cannot increase the spatial resolution of the image over that at which the data were collected.

Number of gray levels: Describes the number of discrete intensities that are produced ty the image. A small number such as 8 levels produces a contoured image which may result in an unsatisfactory image for clinical analysis while a large number such as 64 or 128 produce a satisfactory image but may be expensive. In the case of a color display the count levels are converted to colors of various hues and intensities. In most cases the user has control over the selection of the color spectrum used for the display.

Region of interest selection: There are three methods for selection of region of interest. These are: the light pen which is pointed at the area of interest on the display. The timing of the light sensed by the pen tells the computer in what area the user is interested. The joy stick or track ball is a device containing potentiometers that are monitored by the computer and converted to positions in the image as the user changes the position of the control handle. The least satisfactory is the keyboard in which the user moves the cursor that is displayed on the image by repeatedly striking specified keys on the console keyboard.

e. Hard Copy Output:
Used to provide the user with a means of producing a printed form of the clinical results which can be placed in the patient's chart or records for permanent storage:

Common types:

Line printer: A high speed printing device which normally prints text. Can be used for printing reports and simple curves. Not a good device for grey scale images.

Thermal matrix printers: A high resolution device which can produce grey scale images as well as text for reports. Usually requires special paper and software to operate.

Matrix Transparency: Similar to the multi-format devices used to generate time dependent images from the gamma camera but accept the video signal from the image display systems. Good for grey scale images and reproduce what ever is generated on the image display system.

f. User Consoles:
These are used by the users to enter textual data and commands for the operation of the system. They are often used in conjunction with the image displays for display of the text being entered.

1017827

II. Cardiovascular

A. First pass cardiac function studies

PRINCIPLE

One of the uses of the computer in nuclear medicine is the first-transit analysis of cardiac function. The quantitative analysis of the flow of a radioactive blood tracer through the central circulation can provide information on ejection fractions, intra cardiac shunts, pulmonary transit times and wall motion abnoralities.

TYPICAL DATA ACQUISITION PARAMETERS

Mode:	Dynamic frame or list mode
Frame Rate:	10-20/second
Image Matrix Size:	32 X 32 or 64 X 64
Study Duration:	60-90 seconds

Time-activity curves can be generated from regions of interest selected over cardiac chambers and lung. Left-ventricular curves are used to determine left ventricular ejection fractions. Computer generated cine playback images are frequently found.

The computer can also be used to create a series of images from the first-transit data which represent the various phases of the ventricle over the cardiac cycle. This is accomplished by averaging data over a number of cycles during the left ventricular phase of the bolus flow. The data averaging is synchronized with the cardiac cycle either by a recorded ECG gate signal or by a visual identification of the end-systolic (ES) or end-diastolic (ED) states from the valleys and peaks, respectively in the time-activity curves. The images of the representative cycle can be used to assess ejection fraction or regional wall motion.

Advantages	Disadvantages
Low extra cardiac background	One view per injection
Short study time	Limited counting statistics
Simultaneous evaluation of shunt flow and transit times	Study repetition limited by effective life time or radiopharmaceutical
	Incomplete tracer mixing
	Positioning difficulties
	Limited wall motion information

B. ECG Gated Acquisition at Equilibrium

PRINCIPLE

When imaging the left ventricular blood pool at equilibrium, images taken at a frame rate adequate to resolve the cardiac motion are severely count rate limited. The technique of gated synchronized acquisition (GSA) is used to overcome this count rate limitation by averaging data that has been collected over many cardiac cycles.

1017828

An electrocardiographic gating device and disposable self-adhering electrocardographic (ECG) electrodes are required. ECG electrodes should be placed on the patient's chest, preferably over boney prominences. One should ensure that all electrodes are making good contact and that the ECG tracing is free of 60 cycle and motion artifacts. The electrocardiographic QRS complex should be larger than the Pand T waves, and the operators should verify that a single valid, QRS-gated pulse is being received for each complex.

PATIENT POSITION

Proper position should be determined individually for each pateint by a physician. Frequently used postions are as follows: a) Left Anterior Oblique (40^0-60^0): Camera head is positioned to the patient's left at an angle of 40^0-60^0 from the horizontal plane. The optimal angle allows the best view of the interventricular system and widest separation of the right and left ventricular (RV and RL) blood pool activity. Angling the detector 15-20^0 toward the feet allows optimal separation of the left atruim (LA) from the LV region of interest. The RV and LV should be positioned as nearly as possible in the center of the camera crystal since "zoom"-mode acquisition is most frequently used. In zoom-mode only the central region of the detector field-of-view will be recorded by the computer. Background activity around the heart should be included in the image. b) Right Anterior Oblique (30^0): Camera head is positioned to the patient's right at an angle of 30^0 from the horizontal plane. LAO protocol should be followed otherwise.

DATA ACQUISITION AND ANALYSIS

The data may be collected as either an in-core gated study, or gated list mode. Because of its minimal storage requirements and the lack of restrictions on the total number of collected counts, the in-core collection should be used whenever possible. In those studies where a highly irregular heart rate is encountered the gated list mode acquisition may be the best choice.

In order to achieve the high temporal resolution needed for the ejection fraction calculation, the LAO study is usually collected in a 32 X 32 image matrix at 24-48 frames per cycle. To evaluate wall motion a higher resolution is desirable. The RAO view is best suited for anterior and inferior wall motion evaluation and is most frequently collected in a 64 X 64 image matrix.

The background (B) corrected time-activity curve is generated for a region of interest selected over the left ventricle. The region-of-interest may be defined either manually or automatically. The count rates obtained during the end-daistolic (ED) frame (curve peak activity) and during the end-systolic (ES) frame (curve minimum activity) is used to calculate the ejection fraction (EF).

$$EF = \frac{(ED - B_{ed}) - (ES - B_{es})}{(ED - B_{ed})}$$

The background activity is subtracted from each frame and is frequently determined from the ES frame as the region between the ES and ED boundaries, the average counts per data cell in the background region is multiplies by the total number of cells in the ventricular region-of-interest to cbtain an estimate of the ventricular background. The background determined in this manner is then subtracted from the total counts within the ventricular region-of-interest.

OUTPUT

In addition to making the EF calculation, the computer is used to generate hard copy reports of the ventricular time-activity (volume) curves.

The computer display is used in the evaluation of wall motion abnormalities. The computer is used to display the images from the representative cycle in a cine format.

Wall motion abnormalities are evaluated from the computer generated cine display of the images making up the representative cycle. In order to enhance the preception of the motion abnormalities, frequently only the ventricular boundaries are displayed.

Advantages	Disadvantages
Good counting statistics	Long study time
Multiple views from a single injection	High extracardiac background
Multiple studies from a single injection	Limited information on shunts and transit times
Well mixed tracer	
Good wall-motion information	

1017830

III. RENAL FUNCTION

PRINCIPLE

When an appropriate radiopharmaceutical is injected intravenously, its clearance from the plasma and excretion by the kidney into the bladder can be monitored by means of a scintillation camera interfaced to a computer system. The most popular of these are orthoiodohippurate labeled with either I-131 or I-123 and DTPA labeled with Tc-99m. Histograms of the activity concentration within the kidney as a function of time can be used to characterize renal function.

PATIENT POSITION

The patient with a transplanted kidney is positioned in the supine position on an imaging table. The camera is positioned anterior to the patient with the kidney/bladder region approximately at the center of the camera crystal. Patients with two kidneys are imaged from the posterior projection with the camera placed under the table.

DATA ACQUISITION AND ANALYSIS

The data are generally collected as a frame mode dynamic study using a 64 X 64 image matrix. The frame rate should be from 10-20 second per frame with a total study time of 20-30 minutes. These acquisition parameters will result in a dynamic study consisting of from 60-180 frames in length.

Background corrected time-activity histograms are generated for each kidney region of interest, the bladder (when visible) and the heart (when visible). Parameters chosen to characterize the patterns presented by the curves are then extracted by the computer. Some of these parameters are: the time-to-peak activity for each kidney, the time for each kidney to washout to 75% of its peak value, the time of appearance of the bladder activity and the ratio of the bladder to kidney count rate at some specific time (usually 20 minutes).

The kidney region-of-interests are usually selected using a light pen or joystick and are usually chosen to avoid the renal pelvis. The background region-of-interest is usually chosen either just above and just below the kidney or occasionally the average of both of these regions.

Frequently the activity histograms are smoothed before presentation and before curve parameters are calculated. For patients who have had a series of studies residual activity must also be subtracted. Residual activity will not be properly accounted for using the background correction alone.

OUTPUT

The analysis program should provide a hard copy report of kidney and bladder count rate curves. Derived parameters are also printed along with the curves.

1017831

IV. a. CEREBRAL BLOOD FLOW

PRINCIPLE

The blood supply to the cerebral hemispheres can be evaluated by visualizing the floow of a radioactive blood tracer which has been injected as a rapid high activity bolus. A computer/scintillation camera system has proven to be a useful system for this procedure because of its ability to acquire and store rapid image data and its flexibility in retrieving and processing the stored data. Time-activity curves from symmetric regions of the brain are generated and compared for symmetry. Computer generated images presented in a cine format have also been found to be useful.

PATIENT POSITION

Proper position should be determined individually for each patient by the Nuclear Medicine physician. The most commonly used views are anterior, posterior, and vertex. For the vertex view it is necessary to place a lead cape over the patient's shoulder in order to avoid interference from activity outside the head and neck.

DATA ACQUISITION

Mode: Dynamic

Frame Rate: 4 frames/second

Image Matrix Size: 64 X 64

Duration: 60 seconds

OUTPUT

Time-activity curves generated from symmetric regions in each hemisphere output in report format.

Cine-formatted playback of dynamic images.

1017832

IV. b. RELATIVE RENAL BLOOD FLOW

PRINCIPLE

Relative blood flow to the kidneys is evaluated using bolus techniques similar to those described above for cerebral blood flow. After the bolus injection of a blood tracer region-of-interest curves are generated for the kidneys, aorta and iliac arteries (if visible). The heights with respect to that of the aorta are indicators of the relative blood flow to the kidneys.

DATA ACQUISITION

Mode:	Dynamic
Frame Rate:	4-10 frames/second
Image Matrix size:	64 X 64
Duration:	30-60 seconds

OUTPUT

Report formatted time activity curves with extracted curve parameters.

1017833

V. OTHER APPLICATONS

a. IMAGING

Sophisticated algorithms for processing static images have not as yet been shown to be practical for routine use. A number of simple computer processing algorithms, on the other hand, are used routinely. These include flat-field flood correction, image subtraction, background erase, and image smoothing.

b. NON-IMAGING

1. In Vitro data processing
2. Quality control of laboratory instrumentation.
3. Laboratory and radiation safety record keeping.
4. Radiopharmaceutical inventory control and dosimetry calculations.
5. Computer-assisted instruction.
6. Storage and retrieval of patient studies.
7. Modeling of tracer kinetics.
8. Emission computed tomography.

1017834

ORO-2401-116

A Versatile Digital Densitometry System for Cardiovascular Studies

A.B. Brill, D.P. Lindstrom, J.H. Nelson, T.C. Rhea, Dan Kedem, Drora Kedem, R.R. Price, J.J. Ericson, T.P. Graham, C.W. Smith, Nashville, Tenn., USA

In the last few years several laboratories have developed various types of systems to do quantitative densitometry on video- and cineangiocardiograms (1-4). Most of these systems have been basically analog in nature with only the integrated density signal from a rectangular „window" being digitized for numerical evaluation. There are cases, however, in which one might need greater versatility. Windows of arbitrary size and shape are sometimes desired (3); occasionally many such windows are needed within a single image. Special effects are often called for such as shading of arbitrary areas in a video field. In addition, there is often a need to implement automatic border recognition procedures. All of these problems can readily be reduced to FORTRAN programming details with an appropriate digital densitometry system.

System

The purpose of the system described here is first to preprocess, store, and digitize videoradiographic images, and second, to make calculations on them, and to store and display the results in video form. In the Cardiac Catheterization Laboratory a two-camera videocombiner circuit (Fig. 1) creates a split screen image containing A-P and lateral video images. A video-ECG circuit graphically overlays the patient's ECG onto the videoangiographic image in real time for convenient registration when replaying from a recorder. A Hamamatsu Model C701 Video Data Coder then multiplexes digitized sampled values from up to eight analogue transducers on the left border of the video image for exact time correspondence for later replaying into a computer from a video recording.

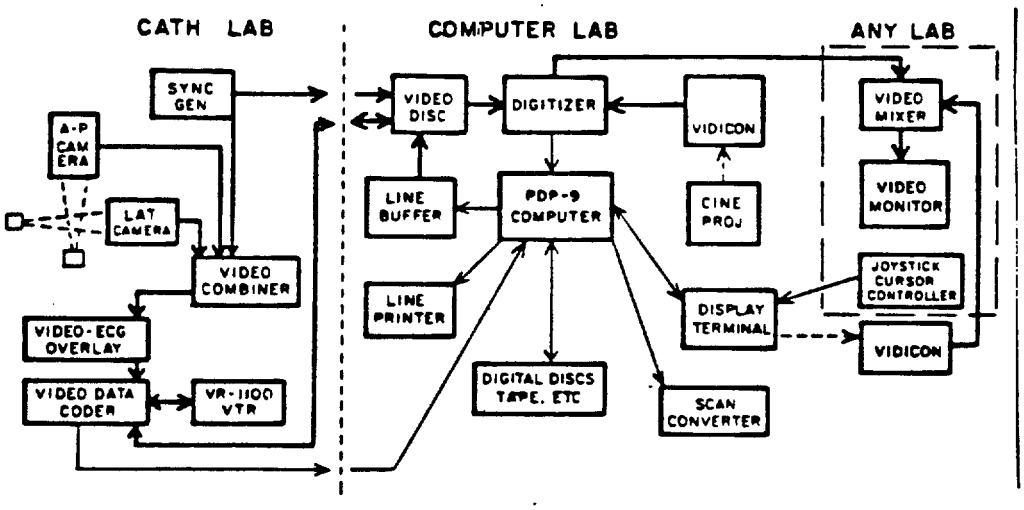


Fig. 1 Digital densitometry system. Dark arrows are video lines; light arrows are data lines. The items labeled „Any Lab" can be located in the catheterization laboratory, animal experimentation laboratory, or elsewhere to allow interactive processing of radiographs recorded on video disk or cine film

1017835

The video data analysis system consists of a 32K PDP-9 computer, a video disk recorder, and several interfaces which link the disk, the computer, and display device. The video disk recorder (Data Disc 310) provides storage for up to 600 video frames during processing and also provides the necessary timing pulses for digitizing video and converting digital data into video form. In addition to the timing tracks from which video sync is derived, a 5 MHz clock track is recorded on the disk to synchronize AD and DA conversions. All of the primary control functions of the disk have been multiplexed to a touch-tone decoder system so that with touch-tone encoding keyboards the disk can be controlled from various remote locations. The frame number is displayed in a corner of the video image to aid in positioning the read heads at the disired track.

An interface has been built which allows digitizing a selected protion of a video image which has been recorded on the video disk. Digitizing is done in a vertical scan, so that 6-bit words are read by the computer at the video line rates, – 15,750 Hz. At the conclusion of a field, the digitization is resumed at the next vertical column which is $(5\ MHz)^{-1} = 200\ nS$ to the right of the previous column. The interface assembles three 6-bit pixels (picture elements) into an 18-bit computer word before the transfer to the I/0 bus occurs. The rectangle defining the region to be digitized is set manually via thumbwheel switches and is overlaid on the monitor image. This region may be all or any part of a video frame. Other functions of the interface include reading the values of the cursors and the track number and stepping the video disk heads.

Conversion of digital data to video format is done in two ways. A video scan converter is interfaced to the computer using 10-bit DACs for the x, y, and z axes in a random address mode. Also, a video line buffer (VLB) interface has been constructed. The VLB contains a 512 x 10 bit bipolar memory (Intel IN50) with a 100 nS cycle time. This memory can be loaded in a random fashion by the computer and then read out at video rates at a selected video line and field. The burst of data is routed through a high speed DAC to the video disk, where the data are recorded a line at a time. Presently the 5 MHz track on the disk supplies the clock signals, yielding about 250 pixels per line, although the system is designed for clock signals, yielding about 250 pixels per line, although the system is designed for clock rates to 10 MHz. About 8.5 sec is required to write an entire video frame of 512 lines.

When the video disk is replayed for digitization and/or calculation, a method is needed to allow an operator to designate a specific point or area of the video picture for special treatment by the computer. We accomplish this by using a specially designed joystick cursor controller connected to a Tektronix 4013 display terminal. The terminal, operating under control of the computer program, can display alphanumeric characters and graphics and can send to the computer the coordinates of the cursors positioned by the joystick. A video camera continuously views the terminal screen, and a mixer allows one to overlay the characters, graphics and cursors onto the disk output. A monitor displaying this mixed signal is then used by an operator to trace around a particular object in the picture with the cursors for the computer while the computer draws a line on the screen behind the cursors as they are moved. The computer then recognized the area outlined in this manner as corresponding to specific elements in the array of the digitized video picture in core, and can do calculations on selected elements under program control. Any number of such areas can be outlined. One can also control the program by selecting options with corsors displayed on the screen in menu fashion. A mechanical arm allows the camera to be moved away from the front of the display terminal for use of the keyboard and to swing back easily when needed.

Accompanying papers by Dan Kedem et. al. (5, 6) describe the use of this digital densitometry system for measurements of blood flow and net forward ejection fraction.

References

1 Sturm, R.E., E.H. Wood: Roentgen image-intensifier, television, recording system for dynamic measurements of roentgen density for circulatory studies. Heintzen. Roentgen-, Cine- and Videodensitometry 23 (1971)

2 Higgins, C.B., D.R. Helland, L. Rosen, N.R. Silverman: Velocity of left ventricular wall motion determined by fluoroscopic video-densitometry. Investigative Radiology, vol. II. Jan.-Feb. 24, 1976

1017836

3 Heintzen, P., J. Pilarczyk: Videodensitometry with contoured and controlled windows. Roentgen-, Cine- and Videodensitometry 23, 1971

4 Schuette, W., L.E. Grauer, W.C. Whitehouse, S.B. Itscoitz, D.R. Redwood: Measurement of ejection fraction in man by videodensitometry. Catheterization and Cardiovascular Diagnosis 1:223-232, 1975

5 Kedem, Dan, Drora Kedem, C.W. Smith, and A.B. Brill: Blood flow and velocity distribution measurements by means of digital densitometry. (This volume)

6 Kedem, Dan, Drora Kedem, T.C. Rhea, Jr., J.H. Nelson, T.P. Graham, Jr., and A.B. Brill: Left ventricular volume and ejection parameter-analysis by digital densitometry. (This volume)

1017837

Nuclear Medicine

men of the bowel. A stopcock was used to initiate or stop bleeding. This technique was quite satisfactory for a high bleeding rate. For a slower bleeding rate, a Pitressin infusion pump was used. The lowest rate achieved was .17 ml/min. An even slower bleeding rate of .05 ml/min was produced by using a Harvard pump. For this project, 10-15 mCi of technetium sulfur colloid was used predominantly.

With the high bleeding rate, the site of bleeding was seen even during the rapid-sequence flow study. However, when the study was carried further, the bleeding loop became more clearly outlined. Several minutes later, the bleeding site was distinctly evident. At a bleeding site with a rate of 2 ml/min, the left flank also appears quite active because of continued hemorrhage after splenectomy.

For the upper-GI bleeding, agents cleared by the kidneys were used initially. In spite of fast clearance of ^{131}I hippuran from circulation, the images obtained were of poor quality, mainly because of the limited number of counts reaching the detector. The authors recently attempted to demonstrate the upper-GI bleeding site by subtracting the image of the liver and spleen from the image of combined liver-spleen and the bleeding site.

Finally, in 2 dogs, several mucosal bleeding sites were created using a biopsy instrument. These sites were considered to represent more venous than arterial bleeding. In summary, the project presents an atraumatic and sensitive technique for external detection of acute GI bleeding.

• • • •

Bone Imaging: Unusual Aspects

Robert J. Cowan, Division of Nuclear Medicine, Bowman Gray School of Medicine, Winston-Salem, N.C. Presented at the General Radiology Updated Seminar sponsored by Bowman Gray School of Medicine, Winston-Salem, N.C., March 1977.

While most abnormalities on radionuclide bone images present as areas of increased activity, it is less often recognized that areas of decreased activity may also indicate bone pathology. Photopenic areas may result from a number of processes, including: (1) multiple myeloma and other purely osteolytic tumors; (2) acute osteomyelitis reflecting ischemia of the osseous microcirculation; (3) early stages of bone infarction; (4) Legg-Perthes disease (femoral epiphysis); (5) resection of bone (craniotomy, joint replacement, etc.) and nonviable bone grafts; (6) attenuation from breast prostheses, pacemakers, metallic jewelry, or barium, where these overlie normal bone; and (7) portions of bone included in radiotherapy fields.

A 2nd phenomenon is the occurrence of "nonskeletal" uptake of the radiopharmaceutical itself. Focal uptake of phosphates may occur in cases of cerebral and myocardial infarction, myocardiopathies, calcific pericarditis, cardiac trauma, neoplastic invasion, ventricular aneurysms, lung metastases from osteogenic sarcoma, meningiomas, and occasionally other primary pulmonary neoplasms. Most cerebral neoplasms, on the other hand, tend to concentrate technetium pertechnetate to a greater degree than the phosphates. Unilateral or asymmetrical breast activity usually reflects pathology such as carcinoma. Diffuse hemithoracic uptake can occur with large pleural effusion (usually malignant) or miliary pulmonary metastases, while bilateral lung uptake associated with activity in organs such as the stomach or kidneys may reflect hypercalcemia with metastatic calcification.

Urinary excretion of phosphate complexes permits detection of renal abnormalities such as cysts, tumors, and hematomas, which are photopenic; whereas obstructive uropathy produces impressive activity in the collecting system and ureters. Diffuse activity in the skeletal system ("super-scans") has been described in metastatic carcinoma (typically prostate), diffuse lymphoma, systemic mastocytosis, Paget's disease, and hyperparathyroidism. Other nonskeletal activity would include liver pathology, such as metastatic adenocarcinoma of the colon, and soft-tissue abnormalities, such as dermatomyositis, rhabdomyolysis, myositis ossificans, or soft-tissue tumors.

• • • •

ORO - 2001 - 117

Deconvolution Analysis of Transplant Renograms

R.R. Price, R. Branch, A.A. Ramage, J.J. Touya, and A.B. Brill, Vanderbilt University Medical Center, Nashville, Tenn. Presented at the Society of Nuclear Medicine Symposium on Computer-Assisted Data Processing in Nuclear Medicine, Atlanta, Ga., January 1977.

The purpose of this work was to investigate the utility of parameters extracted from the renal transit-time distribution of ^{131}I-labeled hippuran. In particular, the utility of these parameters for assessing renal function in the renal transplant patient was explored. The transit-time distribution — or, alternatively, the transfer function — was obtained by a mathematical deconvolution of the measured renogram. The data needed for these calculations are the hippuran renograms as obtained either from stationary probes or from sequential scintillation-camera images of the kidney, and the corresponding blood-activity levels as measured by a probe placed over the heart.

Mathematical deconvolution of the renogram curve requires that the kidney be regarded as a linear system and that all of the system parameters remain constant in time. If these assumptions are satisfied, then the output of the kidney will be a convolution of the input function (the measured blood level of the hippuran) and the transfer function of the kidney. It is the purpose of the deconvolution calculation to determine the nature of this transfer function (transit-time distribution). If the input and output curves are known, the solution to this equation can be carried out using a number of well-known techniques. An equivalent calculation can be carried out using the composite renogram in place of the output curve. The resulting transfer function will be related to the integral of the transit-time distribution. Two deconvolution techniques were used: (1) the Fourier transform; and (2) discrete lag products. Both can be carried out easily and rapidly on a small clinical computer.

The results of the technique have been shown to be reproducible as determined by repeated animal studies. The technique was also shown to accurately reproduce direct measurements of

0 0 3 8 1 0 1

the kidney retention function in animals by using data obtained from intravenous injections of ^{131}I-labeled hippuran.

• • • •

Thallium-201 Imaging and Gated Cardiac Blood-Pool Scans in Patients with Ischemic and Idiopathic Congestive Cardiomyopathy: A Clinical and Pathologic Study

Bernadine H. Bulkley, Grover M. Hutchins, Ian Bailey, H. William Strauss, and Bertram Pitt, the Johns Hopkins Medical Institutions, Baltimore, Md. Presented at the 26th Annual Meeting of the American College of Cardiology, Las Vegas, Nev., March 1977.

^{201}Tl myocardial perfusion imaging and ^{99m}Tc human-serum-albumin gated cardiac blood-pool scanning allow a noninvasive evaluation of left-ventricular myocardial perfusion and function. ^{201}Tl myocardial perfusion imaging has proved useful in evaluation of coronary artery disease. Its uptake reflects not only coronary perfusion but also myocardial viability as an agent that is actively taken up and concentrated by the myocardial cell. Areas of myocardium devoid of viable muscle for any reason appear as cold spots on the thallium image. ^{99m}Tc human-serum-albumin gated cardiac blood-pool scanning provides a noninvasive evaluation of ventricular function. Left-ventricular ejection fraction determined by this technique has correlated well with standard left-ventricular contrast angiography. The combined use of these techniques has been useful in the detection and localization of myocardial infarction. They also have been found to be useful in the evaluation of primary hypertrophic and secondary cardiomyopathies. The purpose of the study was to determine whether these noninvasive techniques could be used to distinguish ischemic from primary idiopathic congestive cardiomyopathy.

Thirty-five patients were evaluated, including 13 with ischemic congestive cardiomyopathy, 8 with idiopathic congestive cardiomyopathy, and 14 normal control subjects. Ischemic cardiomyopathy was defined as severe left-ventricular dysfunction due to myocardial damage resulting from occlusive coronary-artery disease. Idiopathic congestive cardiomyopathy was defined as severe or intractable idiopathic left-ventricular failure. Both pathologies were further defined based on angiography, arteriography, and postmortem examination whenever possible.

The results of the evaluation of radioactive tracer studies showed all of the normal images were correctly identified as being normal. All of the 13 patients with angiographically and/or autopsy-proven ischemic cardiomyopathy and 7 of 8 patients with angiographically and/or autopsy-proven idiopathic congestive cardiomyopathy were correctly identified.

• • • •

Removal of Bolus Shape from Flow Studies via Fourier Deconvolution

Thomas R. Nelson, Martin W. Herman, L. Stephen Graham, and Ismael Mena, UCLA-Harbor General Hospital, Torrance, Calif. Presented at the Society of Nuclear Medicine Symposium on Computer-Assisted Data Processing in Medicine, Atlanta, Ga., January 1977.

A technique based on the process of Fourier deconvolution allows elimination of the influence of bolus shape from time-activity curves obtained in nuclear medicine flow studies of heart, lung, brain, etc., thereby generating a transfer function for the organ in question. Basic theory behind the Fourier transform is discussed, with emphasis on its practical implementation and on application of Fourier deconvolution techniques to the minicomputer systems in use today in most nuclear medicine departments.

Deconvolution of flow studies requires time-activity curves for the region of interest (output curve) and for a region prior to the region of interest (input curve). Also, the system must be linear — *i.e.*, involving one input, one output, and continuous flow. A Fourier transform of each curve is made using the fast Fourier transform, and the transform of the output curve is divided by the transform of the input curve. The inverse Fourier transform of the quotient is made, and this curve is the output curve corrected for the shape of the bolus or transfer function.

Difficulties presented by aliasing, zero-crossing divisions, numerical precision, and curve characteristics and requirements are discussed. Practical solutions are presented concerning the use of high-frequency filters, long dt framing, slope analysis, and the use of windowing functions. The transfer function obtained through this method represents the distribution of transit times for the organ and is independent of bolus shape.

Instrumentation

Quantitative Aspects of CT Images

Mokhtar Gado, John Eichling, and Michael Currie, Washington University School of Medicine, St. Louis, Mo. Presented at the Postgraduate Course on Computed Tomography, sponsored by the University of California School of Medicine, San Francisco, Calif., February 1977.

The CT image is a pictorial display of calculated values of relative radiodensity that are known as CT numbers or attenu-

0017839

CPO-2451-15

Dose Reduction in Mammography -- Preliminary Studies Utilizing Computer Enhancement and Autoradiographic Image Intensification

A. B. Brill, M.D., Ph.D.
Gopala U. V. Rao, Sc.D.
Gary Novak, L.A.T.
Ron Price, Ph.D.
A. Everette James, M.D.
*H. Joel Trussell, Ph.D.**
*Don H. Janney, Ph.D.**
and
*Barbara S. Askins, M.S.***

Department of Radiological Sciences
School of Medicine
Vanderbilt University
Nashville, Tennessee 37232

* *Los Alamos Scientific Laboratory, Los Alamos, N.M., 87545*
Work performed under the auspices of the U.S. Energy Research and Development Administration, Contract No. 7405-ENG-36.

** *NASA Marshall Space Flight Center, Alabama 35812*

1017840

Abstract

Information can be recovered from underexposed photographic images by computer image enhancement (CE) and by autoradiographic (AR) image intensification. In order to assess whether AR enhancement might be useful in an important medical area, we have conducted a pilot study. Six accidentally underexposed x-ray mammograms were analyzed by these two techniques to determine whether usable images could be obtained without the need for repeat exposure. Initial results with both of these techniques are promising and suggest that it may be possible to retrieve useful diagnostic information from underexposed images, where the radiation exposure is as low as 10 to 20 percent of usual patient doses.

Key Indexing Words: Mammography; Breast cancer; Image enhancement, computer; Autoradiography.

1017841

Introduction

Two technologic approaches are feasible to enhance the utility of mammography. The first requires the development of new kinds of radiation recording procedures which provide higher quality information at lower exposure. A second approach is to develop means of extracting more information from available radiographic film techniques, but with lower patient exposures. This feasibility study was directed toward the second approach.

Methods

Computer enhancement and autoradiographic image intensification procedures were carried out on several underexposed films in the following way. The underexposed films were sent first to Los Alamos Scientific Laboratory (LASL), where they were scanned with a microdensitometer and computer enhanced; images of the underprocessed (digitized) and enhanced data were recorded on 35 mm transparency film. The original films were then sent to NASA's Marshall Space Flight Center (MSFC) where the autoradiographic image intensification process was carried out. The resulting image was photographed at Vanderbilt University (VU). The enhanced images and the properly exposed reference image were projected and studied at different times by three radiologists skilled in mammographic interpretation.

Computer Image Enhancement Method:

The basic principles involved in computer image enhancement are described in numerous journals and books (1,2,5,6,8,9), and only the fundamental concepts are outlined here. Figure 1 shows the general hardware system that was utilized. A microdensitometer was used for digitizing the information on the x-ray images and converting it to a string of numerical values which represent film densities. The scanning aperture was 50 μ x 50

1017842

μ in size, and the spacing between measured data points was 100 microns. A 10.23 x 10.23 cm field was chosen on each film, resulting in a two-dimensional array of 1024 x 1024 points. The resulting numbers were transferred to a digital computer and processed. The time required for a microdensitometer scan of a single film was about an hour. Processing time in the computer (CDC 7600) for the enhancement was about 4.5 minutes.

In the mammographic enhancements discussed here, the frequency filter used can be represented by the following analytical expression: $H(f) = 2.0\ (1 - e^{-2.0\ f})$ where f is the spatial frequency in cycles/mm and H (f) is the filter function by which each frequency component is multiplied. This filter suppresses the low frequencies while permitting the high frequencies to pass through, thus producing an effect similar to xeroradiography. Filters with a different analytic form or with other numerical constants could be used to enhance features of different classes.

In addition to frequency filtering, other contrast varying techniques can be used during enhancement with the computer. In the work reported here, the frequency filtering was followed by a nonlinear density stretching routine known as histogram equalization, which is based on the concept of reassigning film densities so that each density value occurs with equal probability. This procedure maximizes the information theoretic entropy measure: $\Sigma\ p_i \log p_i$, where p_i is the probability that the i^{th} density value will occur. The visual result is to increase the contrast of the image by spreading the histogram.

Computer enhanced images were displayed using a 35 mm microfilm. If routine clinical examination of computer enhanced mammograms were proposed, multiple filtered images could be viewed on-line with the diagnostician able to select the desired enhancement from several established options.

Autoradiographic Intensification Method:

The autoradiographic intensification technique involves the conversion of the silver sulfide in the image to radioactive silver sulfide (Ag_2S^{35}) and then making an autoradiograph from the activated film. The image on the autoradiograph, enhanced in density and contrast, reveals details which are invisible or only faintly visible on the original (3,4,7).

1017843

In practice, the mammograms are first rinsed in dilute photographic fixer, then in methanol-water solution, and finally in distilled water. They are then immersed in an aqueous solution of thiourea-S^{35}, under constant agitation, for approximately 30 minutes. The activating solution of thiourea-S^{35} has an activity of 0.5 mCi. Either ammonium hydroxide or sodium hydroxide is added to bring the pH to a value between 10.0 to 12.0 range. After rinsing and drying, the activated negatives are held in intimate contact with an industrial x-ray film (Type AA) for 2 to 3 hours. The autoradiographs are then developed in the usual manner in an automatic processor.

Results

Figures 2 and 3 illustrate the results obtained with two patients. The patient in Figure 2 has a proven cancer (by surgical biopsy) that was not easily seen on the optimally exposed original film nor on the AR-enhanced film or on the CE image. However, the CE image revealed the lesion more clearly than the original or the AR-enhanced films. In the patient studies shown in Figure 3, the optimally exposed mammogram was interpreted as showing no evidence of malignancy although the patient was found to have an infiltrating scirrhous mammary carcinoma at operation. A prominent ductal pattern was better seen on the CE study, although the lobular pattern noted by one radiologist was not seen on the CE image but was noted on the AR as well as on the properly exposed film.

In another study (not illustrated), exposed in the 20 to 25 percent range, a lesion which could be seen in the original film could not be perceived in the computer-processed display. The autographically enhanced image showed the lesion clearly.

Discussion

The computer enhancement technique utilized a single mathematical filter which from previous experience was known to produce a xeroradiographic edge enhancement effect. In those regions of the image where exposures ranged above 20 to 25 percent of the proper exposure, image enhancement highlighted structural details in the tissue patterns that could be seen less clearly in the original film. In regions of the films exposed at less than 20 prcent of proper output, the changes in signal densities are very small and hence the signal to noise ratio is very small. In these cases, the computer image enhancement filters used did not provide useful image enhancement.

If any structure is visible on the film, it is possible for CE to make its image stand out more clearly and-with improved resolution by CE. Sometimes the microdensitometer detects minute film-density differences which are not perceivable to the eye. In those instances, CE creates a useful image where none apparently existed before. It is noted that for optimum performance, different classes of filters are needed for different classes of objects. It seems likely that if two or three filters were used on the same image in order to bring out different structures in the scene, then the diagnostic information in reasonably exposed images would be highlighted effectively.

The autoradiographic method reveals details in the most severely underexposed images that cannot be seen in the original or computer-processed scenes. The utility of this means of image intensification seems to extend below the range of exposures that can be used with the computer enhancement techniques. With this enhancement method the degree of contrast increase is controlled by the autoradiographic exposure time. it is possible, and sometimes desirable, to make more than one autoradiograph using different exposure times to bring out areas of different densities in the original. The diagnosis also may be based on information read from both the underexposed film and from the autoradiograph; for example, the nipple region may be overexposed on the autoradiograph but of readable density on the original film which was otherwise underexposed.

1017845

The use of the AR method could permit a tenfold reduction in radiation exposures, whereas the computer method permits approximately five-fold reduction. It is possible that the two methods could be combined to decrease the dose requirement further, but this possibility has not yet been assessed.

The results of these feasibility studies suggest that it may be possible to recover additional diagnostic information from present procedures or permit lower patient dose while maintaining equivalent diagnostic information. The quantitative magnitudes of expected improvements are uncertain. They are based on very few studies and used non-optimized procedures. Our conclusion is that both methods appear to be worthy of further evaluation. The immediate practical implications for routine patient care would require further technologic developments which may be encouraged by our observations, and these results may suggest alternative methods that may be even more useful.

Summary

1. Image enhancement techniques (CE and AR) provide improved contrast and often produce more pleasing images.
2. Both of the image enhancement methods utilized bring out details in underexposed film that are not easily perceived in the originals.
3. The AR method recovered more detail from objects with low spatial frequencies than the computer method.
4. The AR method requires several hours for film processing and at present is mechanically cumbersome.
5. The computer method presently requires expensive equipment for its proper conduct. By using multiple filters, a broader class of objects could be highlighted.
6. Radiation exposure could be reduced tenfold using AR intensification and possibly greater than tenfold using CE of AR-enhanced images.
7. Further work on both approaches is justified to determine the diagnostic utility of these methods.

1017846

References

1. Andrews, H.C. and Hunt, B.R.: Digital Image Restoration, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1977.

2. Andrews, H.C., Tescher, A.G. and Kruger, R.P.: Image processing by digital computer. IEE Spectrum 9: 20-32, July 1972.

3. Askins, B.S., Brill, A.B., Rao, G.U.V. and Novak, G.: Autoradiographic enhancement of mammograms: Investigation of a possible dose reduction technique. Accepted for Publication (Preprint available on request).

4. Askins, B.S.: Ap. Opt. 15 (11): 2860, 1976.

5. Hunt, B.R.: Digital image processing. Proc. IEEE 63: 693-708, April 1975.

6. Janney, D.H., Hunt, B.R. and Zeigler, R.K.: Concepts of radiographic image enhancement. Material Evaluation 30: 195ff, September 1972.

7. Rao, G. and Askins, B.S.: Potential reduction of x-ray exposure through autoradiographic intensification of underexposed radiographs. Medical Imaging 2: 43, 1977.

8. Rosenfeld, A. and Kak, A.C.: Digital Picture Processing, Academic Press, New York, N.Y., 1976.

9. Trussell, H.J., Janney, D.H. and Hunt, B.R.: Digital enhancement of biomedical radiographs. Proc. of the San Diego Biomedical Symposium, February 5 - 7, 1975, pp. 197-185.

1017847

Acknowledgements

The authors express grateful thanks to Dr. Craig Coulam, Dr. Floyd Osterman, and Dr. Carlos Muhletaler for interpreting the images and to Mr. John Bobbitt and Mr. David Speich for the photographic work.

10178 48

Figure Captions

Figure 1. *Block diagram showing the components of the computer enhancement process.*

Figure 2. (A) *Optimally exposed mammogram of a patient with suspected carcinoma. Notice that the skin thickening is minimal.*

(B) *Autoradiographically enhanced image of an underexposed (with only 20 percent of the dose) mammogram of the same patient. This image is again comparable to the optimally exposed film.*

(C) *Computer enhanced image of the same underexposed film showing skin thickening, veins and ductal patterns much better than in the optimally exposed film (A) or the autoradiographically exposed film (B).*

Figure 3. (A) *Optimally exposed mammogram of a patient with proven carcinoma (by surgical biopsy). The diagnosis was missed in interpreting this film.*

(B) *Autoradiographically enhanced image of an underexposed film of the same patient (with only 20 percent of the dose) showing prominent ducts and a lobular pattern which is comparable to that seen in the optimally exposed film.*

(C) *Computer enhanced image of the same underexposed film, showing the ductal pattern better than in (A). The lobular pattern, however, is seen to be not as pronounced.*

1017849

OPO-2401-119

COMPUTER APPLICATIONS IN NUCLEAR MEDICINE

A. B. Brill, M.D., Ph.D.
J. Erickson, Ph.D.
J. Goddard, Ph.D.
J.A. Patton, Ph.D.
R.R. Price, Ph.D.
F.D. Rollo, M.D., Ph.D.
and
J.J. Touya, M.D.

Department of Radiology & Radiological Sciences
Division of Nuclear Medicine
Vanderbilt University Hospital
Nashville, Tennessee 37232

1017850

This review of clinical applications of computers in Nuclear Medicine includes examples of administrative, in vitro and in vivo studies. The basics of computing systems, and algorithms for specific applications are described in many general texts and scientific articles utilizing these techniques and these topics are not discussed. In this chapter, we survey those areas in which computers are being used effectively in Nuclear Medicine. Selected applications were chosen to illustrate some of the major areas of current interest. No attempt has been made to be comprehensive in this review, and the references cited are intended to lead the reader to the pertinent literature.

A wide range of computing applications in Nuclear Medicine are described in the first six citations. These documents (1-6), the proceedings of the first six symposia on the sharing of computer programs and technology in Nuclear Medicine, contain examples from the different areas in which computers are being applied in Nuclear Medicine. In some cases, program listings are included in the papers, and in other cases, programs have been placed on file in an Information Center, located at the Oak Ridge National Laboratory (BCTIC), from which they can be obtained (158).

The IAEA sponsored meetings on Medical Radioisotpe Scintigraphy (7-11) contain many papers in which computer applications are discussed. The proceedings of several International Conferences on Information Processing in Scintigraphy (12-13), contain detailed articles on timely topics. Published proceedings of several meetings held during the early 1970's (16-18) provide extensive discussions of technical problems relating to hardware difficulties which occupied much attention at that time.

1017851

I. ADMINISTRATIVE APPLICATIONS:

A. Information Storage and Retrieval

The rapid expansion of Nuclear Medicine as a diagnostic tool has created a need for new automated methods to gather, store, retrieve, and disseminate information generated within the Nuclear Medicine Laboratory. A prime example of this need is the generation and distribution of the patient study report. The traditional nuclear medicine report is generated by dictation. The dictated report is taken to a secretarial pool where the report is typed and checked for typographical errors. Each report is then returned to the physician for his final review and correction. Reporting errors in this environment are numerous. The typical interval between the time when the referring physician requests a Nuclear Medicine study and the time at which he has the final reports, and can prescribe treatment based upon this information, is 24 hours. The primary goal of a computer-augmented reporting system is to minimize the time between the clinical study and the reporting of the results to the referring physician. The reduction of this time will ultimately result in improved health care delivery and should help to reduce the average hospital stay for the patient. Although time is a primary goal, report accuracy and reliability must also be maximized.

To date most of the effort in developing automated reporting systems has been in the area of diagnostic radiology reporting (27-31,38). Extensions to Nuclear Medicine are now being made (36,37,39). Basically, two approaches have been taken toward computer automated reporting systems. These use free text or structured vocabularies. The free text systems such as have been implemented at the University of Nebraska (28) have the advantage of allowing the physician to continue to use the traditional reporting procedures including a dictating machine and an unlimited vocabulary. In

1017852

addition, these systems generally provide accurate and reliable reports with access to a great deal of information relevant to administrative and research needs. Their disadvantage is that they usually require a large scale computer to carry out the time consuming word-by-word searches for the required matching and editing operations. Consequently, the processing time for a report with these systems is frequently 24 hours or more.

A number of structured vocabulary systems have been developed and implemented throughout the medical community (27,31,36-39). An advantage of these systems is that they generally can be accommodated by a medium-sized laboratory computer. These systems can be either "on line" or "off line" operations. On line systems are characterized by a dialogue between the physician and computer in which "canned" phrases are selected and formed into a report. The technique for picking the phrases depend upon the particular system. The "MARS" system at the University of Missouri (31) utilizes a CRT terminal with a keyboard whereby the physician selects items from a menu of options displayed on the CRT screen. Using the MARS system, their reporting times decreased from an average of 24 hours to an average of about 4 hours. Other systems have used a variety of techniques and instruments to effect the physician/computer dialogue. For example, the Johns Hopkins Hospital system (27) utilizes the computer to control the projection of images of a number of "menus" upon a computer sensitive grid. The physician can then select phrases by simply touching the appropriate grid point (phrase) with a probe.

The most successful off-line systems have been those which utilize a computer compatible input medium, such as mark-sense cards, to capture the information. In this manner the physician is able to record computer readable information directly, thus eliminating errors in transcription. A system utilizing mark sense cards for nuclear medicine applications has been implemented at the University of Minnesota (23). A more general system which utilizes the mark sense format is now being offered commercially for both nuclear medicine and

1017853

general radiographic applications. The commercial system has been described by Mani (38).

The primary disadvantages encountered with the structured vocabulary systems are the physician's reluctance to use specialized computer terminals and their reluctance to conform to a fixed vocabulary.

The areas of reporting and scheduling have received the most attention, however, a few computer systems have been designed to support essentially all aspects of departmental information processing. Systems such as are in use at the Massachusetts General Hospital (32), Washington University (24) and the University of Missouri (31) carry out the billing and accounting operations, generate departmental statistics, carry out film library control, as well as reporting and scheduling services. The systems described above, utilize dedicated medium scale computers. Other departments have chosen to develop their recordkeeping and fiscal management systems using large general purpose time-shared computers (42,44).

The nuclear medicine laboratory has its own unique recordkeeping problem relating to the ordering and accounting for radioactive pharmaceuticals. This is more complicated than the usual inventory problem due to the added factor of radioactive decay of the labelled pharmaceuticals. Dedicated laboratory computers as well as time-shared computers have been used effectively to maintain records of radiopharmaceutical inventory, dose preparation, and isotope disposition. The radiation safety and quality control records are required by law and represent a considerable investment in time without the aid of a computer. Systems for carrying out these functions have been developed and are in current use at several institutions (25,33-35,40).

An interesting area of computer applications in medicine (although not yet widely used) is computer aided instruction (CAI). Several U.S. medical schools are now offering their students the choice of CAI or conventional instruction for some of the preclinical

1017854

courses. The results of board examinations have shown little difference in the performance of students relating to which instructional mode they utilized. (Ohio State University, 1974). Special Nuclear Medicine CAI training programs have been developed at the University of Colorado (41).

The calculation of radiation absorbed doses from internally administrered radiopharmaceuticals is time consuming, tedious, and complex for many radionuclides (especially those with complex decay schemes). Computer programs have been developed by Berman (43) at the NIH and by Feller (26) at the Cincinnati General Hospital. These programs use tabulated values of the absorbed fractions for photons of different energies for different source-target geometries along with tabulated equilibrium dose constants to calculate radiation absorbed doses for most routinely used radionuclides.

1017855

II. IN VITRO APPLICATIONS:

A. Quality Control

1. Counting Systems

As the number of recommended and mandatory quality control procedures for nuclear medicine counting systems increases so it becomes more necessary for a computer based facility to permit rapid and reliable analysis of the quality control data (45-48).

Typically, the parameters of laboratory counting systems which need to be checked frequently are sensitivity and linearity (for dose calibrators). The computer may be used as a convenient way of recording these measurements, of plotting up-to-date control charts, and of performing statistical analyses on the data to determine significant variations in the parameters.

1017856

2. RIA:

Rodbard has stressed the need for a stringent quality assurance program in the RIA laboratory in order to permit evaluation of the stability and reproducibility of the assay system (54). In practice, each assay should include two or three control samples which cover the range of patient values. After each assay is performed the "within-assay" mean and standard deviation values should be computed and compared with previous values. The current assay is deemed to be satisfactory (regarding control levels) if there is no statistically significant difference between the values of the current and previous control samples. If the two estimates are comparable then they may be combined into an updated current value (47-54).

The types of calculations indicated above may be readily performed immediately before computer processing of the standard and patient values. The results of the statistical computations may be displayed conveniently in digital and graphic form to permit accurate and rapid evaluation of the data. A digital mini computer implementation of this facility has been described by Tobin, et al. (1964).

1017857

B. Results Calculation

1. RIA:

To facilitate automatic computation of radioimmunoassay data, many groups have developed computer techniques for obtaining the best fit of the standard points with subsequent calculation of the unknown sample concentrations and their errors (55-63, 68). Many mathematical procedures have been used for curve fitting including the use of polynomials (57,58) and spline functions (62). It appears, however, that the most widely applicable technique at present is a curve linearizing routine using of the logit-log method (54). One equation which is used to linearize the data is,

$$\text{logit}(B/Bo) = a + \cdot \log_e (c) \ldots\ldots\ldots (1)$$

where B/Bo is the ratio of counts bound for arbitrary ligand concentration relative to that of zero concentration (with both counts corrected for non-specific binding), a and b are constants and c is the concentration of unlabelled ligand. Rodbard (50,54) and Rodbard and Hunt (63) have made a detailed study of the logit-log method and stress the importance of a non-uniformly weighted regression analysis to overcome the problem of non-uniformity of variance of the data.

In most applications, the radioimmunoassay data are conveniently introduced into the computer via punched paper tape. An immediate printout is often useful for manual verification of the data and correction for missing or mishandled tubes. If the assay samples are run in duplicate, the duplicate averages and differences may next be computed and an error flag set if any difference is greater than some predetermined level (typically 10%). The standard curve parameters plus their errors may be computed by a fit of standard sample values to an appropriate mathematical function and a printout obtained of the

1017858

standard curve and the curve parameters. The unknown sample concentrations plus errors may then be calculated and the results printed in tabular form.

1017859

2. Sample Counting:

The uses of computers in sample counting may be split into two types of applications. That is, firstly, to perform relatively simple calculations on large numbers of samples. An example is the processing of liquid scintillation counting data in order to rapidly calculate disintegrations per minute and to make quench corrections (65,66), and secondly to perform relatively more complex calculations of small numbers of samples. An example is the calculation of the GFR following an intravenous injection of several millicuries of ^{99m}Tc - DTPA. Count rates from patient plasma samples, the standard and the background may be entered manually into the computer and then printed for manual verification. The count rates for plasma samples (at 2, 3, and 4 hours) are then fitted to an exponential function which permits calculation of the GFR according to the "height/area" formula. The experimental value for GFR may then be compared to a predicted value (computed from the patient's height and weight) to indicate statistically significant deviations from normality.

1017860

3. Report Generation/Retrieval:

The number of samples processed each day in even a small in vitro laboratory engaged in RIA work may be quite large (of the order of several hundred or more) so that manual generation and retrieval of the reports of results may be very laborious and time consuming. Computer generation and retrieval of reports is therefore an attractive alternative which is easily realized. Several systems implemented on time-shared computers and stand alone mini-computers have been described (68-71). In many instances the raw data pertaining to the radioimmunoassay are entered into the computer via a paper tape reader. Generation of reports following the computation of results usually involves, therefore, a small additional amount of programming.

1017861

III. IN VIVO STUDIES

A. Non Imaging:

The applications of computers to in vivo studies in nuclear medicine are many and varied. Very early in the development of nuclear medicine techniques it was observed that the computer had obvious advantages in handling the large amount of data generated from patients studied with radioisotopes. One of the first applications was in the non-imaging area (i.e. whole body counting and probe data collection). In whole body counting by means of gamma ray spectroscopy one collects energy spectra from the body by means of stationary or moving detectors. The computer can be used to collect the data, separate the spectra associated with given photopeaks (spectral stripping), integrate photopeak areas, evaluate errors, reduce noise effects by smoothing techniques, correct for detector efficiencies that vary with energy, and organize the data into a suitable output format (72, 171).

The use of the computer in studies where the radioisotope content in various areas of the body are monitored by stationary probes permits the rapid collection and storage of data in order to measure changes in the radioisotope distributions accurately and quantitatively. The data can then be smoothed, if necessary, to eliminate noise effects, normalized or scaled, and displayed in formats suitable for interpretation (73). Parameters can then be extracted from the data and reported as indicators of organ function in various disease states. An obvious application of these techniques is in the mapping of blood flow. Monitoring of blood flow through the head yields measurements of regional cerebral blood flow. Simultaneous measurements of the passage of a bolus of activity through the head, lungs, and right and left heart yields measurements

1017862

of right-to-left and left-to-right shunts as well as cardiac output and ejection fractions (73).

Techniques have also been developed for measuring bone mineral content in the extremities by means of a single detector and an opposed source of activity. By measuring the attenuation of the beam of activity as it passes across an extremity the bone mineral content can be calculated. Single photon techniques require the use of a water bag to compensate for soft tissue effects; however, dual photon techniques have been developed which eliminate this necessity (74).

X-ray fluorescence is a relatively new technique for in vivo measurement of non-radioactive materials. An external source of radiation (either x-ray tube or radioisotope) is used to irradiate an area which is simultaneously monitored by a high resolution semiconductor detector to measure the characteristic x-rays emitted from the area. By collimating the source and detector and intersecting their fields of view at 90°, a small sensitive volume may be defined. By then introducing high atomic number stable isotopes (such as iodine) into the body, the passage of these isotopes through the sensitive volume can be monitored by the computer (75). This technique has been used with iodine compounds to measure regional cerebral blood flow and blood volume (76), cardiac output (77), and hepatic iodine concentration (78). X-ray fluorescence has also been used in body composition studies to quantitative the amount of particular elements present within the sensitive volume of measurement. For example, the lead content of children's teeth (79) and the copper content of the eye in patients with Wilson's disease (80) have been studied.

B. Scanners:

The computer has been used by investigators in many applications involving imaging devices (i.e. systems that produce pictures of in vivo distributions of radioisotopes). In the area of rectilinear

1017863

scanning, the computer has been used to maintain quality control by insuring the accuracy and reproducibility of studies of test objects obtained with this instrument (81,167). As a data collection device, the computer is useful as a back-up medium for the scanner photoplotters. If the routine images obtained are not aceptable, images may then be obtained from the computer which eliminate the need for repeating the study. This advantage is significant especially in total body imaging studies requiring 1 - 2 hours of scan time (82). In addition to providing images of the raw data, the computer makes it possible to improve the quality of the images by the use of programs developed for background subtraction, data bounding, smoothing, resolution recovery filtering, contrast enhancement, and contour generation. By simultaneously monitoring the output of a stable oscillator during the data collection process it is also possible to correct for speed instabilities of the scanner (83). If the scanner were under control of the computer, it would be possible to correct for organ motion, such as movement of the thyroid during swallowing, or motion of the liver due to respiration (84). These corrections would permit the maintainence of high quality images.

Introducing the computer into the data collection process, also, makes it possible to perform studies that are impossible with a stand-alone rectilinear scanner system. Greater sensitivity and therefore reductions in scan time can be obtained by utilizing multiple windows in imaging isotopes with more than one photopeak, such as Ga-67. Also, it has been shown by Beck (85) that other portions of the spectrum, besdies the photopeak, contain useful information on the source distribution and multiple window recording may prove useful. Multiple window inputs such as are available when modular systems are used for computer interfacing, i.e. NIM (159) or CAMC (160), also make it possible to collect data from multiple isotopes simultaneously. This has proved useful in a number of clinical situations (86,96).

1017864

Computerized scanning techniques have been used for both regional and total body quantitative measurements of radioactivity. These procedures involve scanner systems that are (1) passively followed by a computer, or (2) controlled by a computer (86). Such systems are calibrated using geometrical phantoms simulating body shapes and organs and containing known amounts of radioactive material. Uniform response throughout the body thickness is obtained by using collimators with long depths of response and mathematical techniques such as the geometric mean of the data from dual-opposed detectors. A scan is performed immediately after administration of the radioisotope to serve as a measure of the administered dose (i.e. 100% value). It is then possible to scan the regions of interest at later times and determine the radioisotope content as a fraction of the administred dose. Using these techniques in vivo quantitations with accuracies on the order of 5 to 10% have been obtained (87,88).

It is also possible within limits to quantitate the amount of stable elements present in certain organs by means of x-ray fluorescence scanning. This is done by mounting an irradiation source and a semiconductor detector on a rectilinear scanner such that their fields of view intersect. As the system scans in a rectilinear faster, the area of interest is irradiated point-by-point and the characteristic x-rays of the element under study are counted and recorded in the computer. The technique is quantitative (i.e. the greater the concentration at a point, the greater the count rate measured at that point) and thus an array of numbers is collected in the computer corresponding to the distribution of the element. The procedure is calibrated by scanning known sample contents in a geometry similar to that of the organ to be studied. This technique has been applied successfully to the determination of the iodine content of the thyroid gland with uncertainties of the order of $\pm$ 10% (89).

Computerized quantitative rectilinear scanning techniques are particularly suited for kinetic studies in which the radioisotope

1017865

distributions are changing slowly with time. These techniques are used to determine the fraction of the administered dose present at multiple times after administration in the organs of interest. These data can then be used with compartmental analysis techniques to describe normal and abnormal physiological processes using mathematical models (90).

Another area where these techniques have application is in the determination of radiation dose to specific organs for administered radiopharmaceuticals. The biological half-life of the radiopharmaceutical can be measured, expressed as the fraction of the administered dose which is present in an organ as a function of time, and the radiation dose to that organ (and other organs) can then be calculated (91).

These techniques are not only applicable to measuring the activity within an organ, but also the projected dimensions of the organ. This is possible because the size of each data cell is known and the measurements are standardized. The isotope distribution within the organ is used to define the organ outline, and linear dimensions can then be obtained from this distribution. Geometrical shapes can be assumed for the organs, and volumes can then be calculated. For example, the thyroid can be approximated by two prolate ellipsoids (92). It is also possible to use multiple views at different orientations to get more measurements on irregular organs, such as the liver, and from these measurements volume determinations can be made using Simpson's Rule.

Computerized rectilinear scanning techniques have been used in conjunction with a transmission source for measuring effective body thickness and determinating body volume. This is done by scanning in rectilinear fashion with a narrow well-collimated beam of radiation passing through the patient to an opposed detector which maps the transmitted intensity. By knowing the unattenuated intensity of the beam and the effective attenuation coefficient of the body for the source energy used, it is then possible to determine a map of

1017866

effective thicknesses of the body which then can be used to determine body volume (74). As an extension of this technique one can use multiphoton beams to resolve additional components of the effective thickness (161). Systems have been developed at the University of Wisconsin using a two photon beam to measure changes in tissue fluid content in burn patients and in patients following surgery (162). Similar systems have been used to measure lung tissue hydration (164). Others have used the two photon techniques to measure regional and total body fat-to-lean ratios (88).

Regional blood volumes can also be determined using a rectilinear scanner. Quantitative whole-body scans of Cr-51 labelled red blood cells can be used to determine the fractional steady state blood pool in the major organs of the body (172).

As described above, bone mineral content measurements can be performed by using a well collimated detector and an opposed source, also with adequate collimation, to define a narrow beam of radiation. The mating of a rectilinear whole-body scanner with a two-photon transmission source (usually Gd-153) allows one to make quantitative images of regional and total-body bone mineral content. Total body scans taking from 15-20 minutes deliver a radiation absorbed dose of less than 10 mrads with a precision error of 1 - 2%. Individual vertebral bodies can be well resolved and quantified with a precision error of less than 5% (74,93).

Computerized data collection systems are especially useful in scanning systems involving multiple detectors. In order to increase sensitivity while maintaining uniform resolution with depth, rectilinear scanning systems have been constructed consisting of multiple, small detectors arrayed in various configurations. The computer makes it possible to correct for nonuniformities in sensitivity between detectors and to reconstruct the images. This is accomplished by measuring the response of each detector to a uniform source and performing corrections of the data from each detector as counts are collected and then storing the data in a final image array

1017867

corresponding to the position of that event (9,94). The task of the computer becomes even more significant in systems using multi-angular arrays of detectors for transverse section tomography. In this application, data are collected from detectors positioned at multiple angles about the body. The data are maintained separately from each detector and are used to reconstruct cross-sectional images of activity. The computer is a necessity in these areas because of the need to use either Fourier or iterative mathematical techniques in the reconstruction process (95,97,98).

1017868

C. Scintillation Camera:

The digital computer can be applied to the problem of day to day quality control (167) of the scintillation camera, as well as the more complex problems of correction for inherent deficiencies in its operation (100,101,102).

1. Quality Control:

Several variables are of interest in the daily quality control of a scintillation camera. Among these are the energy spectrum of the detector system, the positional linearity and the sensitivity uniformity. The computer is capable of monitoring each of these variables from information provided in the form of an image of an array of point sources of known geometric onfiguration. By imaging a lead sheet containing an array of holes one can provide this image and perform measurements on the day to day positional and intensity variations in the image points. This can then be stored for subsequent use in correctional procedures or simply displayed to the user for comparison with preset limits beyond which corrective maintenance is required.

2. Distortion Correction:

The Anger type scintillation camera suffers from three problems which can compromise its utility in various clinical applications. These are the non-uniformity of image field, spatial non-linearity and processing dead time. Of these, uniformity has perhaps received the most attention from computer users. In this case, a camera illuminated with a uniform radioactive source will display an image in which prominant areas of increased and decreased count rate are visible. The classical method of correcting for this non-uniformity to use a high count image (7 1,000,000 counts) to produce an array of normalization factors which in turn can be used to correct clinical

1017869

images for regional variations in image intensity. Most early scintillation cameras had a severe problem with field uniformity and often required corrections for non-uniformity of the order of ± 15% - well within the range of discernment by the human eye. However, more recent cameras are capable of achieving uniformities on the order of ± 5%. This variation is not usually detectable by eye, but could influence quantitative studies. It has been pointed out by Padikal et al (100) that a simple renormalization is not always an adequate correction because of the multiplicity of factors which combine to produce an image and should be approached with caution.

If a regular array of points or grid lines are imaged by a scintillation camera the image will be somewhat distorted. Near the edges of the image, the lines will be seen to depart from their expected position and either a pin cushion or barrel distortion will be observed. It is possible to correct for this by computer redistribution of counts in the image (101) in the following manner. A matrix of points is imaged with the system. The image data are then examined to determine the position of the centroids of the imaged points in the array. A two dimensional correctional shift matrix is then generated which would move the imaged points to their true position as determined by the actual point source locations. This same shifting matrix can then be applied to any image which one desires to correct (173).

The third area in which the scintillation camera encounters difficulty is one which can significantly alter clinical results of dynamic studies. This is the dead time of the system. Because the camera/computer system is a serial system, i.e., counts are processed one after the other, there is a definite time period while a count is being processed during which other counts are ignored. This dead time can alter significantly the shape of flow curves generated during high count rate bolus studies. The actual effect of the dead time is to flatten the curves artificially and distort the apparent maxima. Several methods for mathematical correction of this problem have been

1017870

proposed (102,102a). These include placing a source of known activity in the field of view during the data acquisition and based on the changes in the observed counts for this source, correct the count rate of the rest of the image (174). This method, while easily implemented suffers from the fact that for the reference source count to be statistically significant the standard must contribute a sizable portion of the dead time losses. A second method is that of introducing a fixed pulse rate into the detector system at a positional coordinate outside the field (175). This is accurate at a lower standard count rate because there are no random statistics involved, but requires electronic modification of the detector system which one may not be willing or able to perform. A third method is to count the events in the sum peak above the energy of interest (176). This can be implemented with a separate analyzer system monitoring the energy spectrum of the camera and has been found to be accurate at count rates up to 200K counts per second. The problem of dead time correction will become more severe as higher activity boluses are used, but the correction for losses is a relatively straightforward calculation provided one knows the shape of the observed vs. true count rate curve for the geometrical configuration of the study.

3. Static Studies:

The application of computers to the processing of static images is an area where the computational power of the computer allows one to produce images or meaningful results which would otherwise be impossible to obtain. A typical example of this is the dual isotope pancreas imaging. In this process Se^{75} seleno methionine is injected and imaged with the image being stored in the computer. Following this and without moving the patient TC^{99m} sulfur colloid is injected and imaged. Because the Se^{75} is taken up by both the liver and the pancreas it is difficult frequently to determine where one organ ends and the other begins. By using the Tc^{99m} image and

1017871

normalizing to an area in the liver it is possible to subtract counts from the liver area of the Se^{75} image and be left with what is effectively only pancreas (163). Also possible is the comparison of two pharmaceuticals which are concentrated by different mechanisms, e.g., colloidal trapping in liver phagocytes vs. physiological concentration of a drug (103, 165). Using the computer one can perform accurate overlays with quantitative estimates of the relative uptakes in questionable areas.

In at least one study it appears that the ability to process data from two cameras would be a desirable capability. This is the Xe^{133} ventilation study. The low energy of the Xe^{133} gamma ray causes a very strong depth dependence when it is used for imaging. With a computer and two scintillation cameras-- one anterior and one posterior to the patient, two simultaneous images of the Xe distribution can be stored. These images can then be used to calculate a less depth dependent image of the Xe distribution.

In several areas of organ imaging, ordinary physiological motion during imaging causes severe degradation of the results. In this case, it is possible to monitor the function by routine methods, i.e. ECG or respiratory monitor, and use this information to construct images of the organ at any one of several points in the cycle.

This method has been used in liver imaging to reduce the effects of respiration which tend to blur the image and distort the organ detail. The imaging of the heart has benefited to a much greater extent from the use of the ECG to generate images of the ventricles at various stages of the cardiac cycle (105,106,107). It is possible to synchronize (gate) the camera with a physiological monitor and produce an analog image of the desired portion of the cycle. However, in doing this one loses data from the other portions of the cycle. Furthermore if the patient is not "normal" the variations in a monitored signal such as an ECG make it extremely difficult to apriori select and maintain an accurate temporal gate. By storing all

1017872

the image data and the physiological data, post-processing can produce optimized images in which aberrant cycles are ignored or emphasized.

Displays:

The problem of display of computer image information has been greatly simplified in recent years by the appearance of high speed, inexpensive solid state memory arrays. Until recently it has been difficult and expensive to construct displays which would adequately reproduce the spatial and intensity resolution which the computer processed images require. With present technology it is feasible to produce a flicker-free image in a 512 x 512 matrix with up to 64 intensity levels (108). Color is gaining in popularity, especially in displays where the color intensity as well as hue can be varied continuously. Because of the wide range of activity within single images it is necessary for the display system to allow interaction by the user.

The processing of static images by digital computer early on received enthusiastic support from research groups in the early years, but has not been widely applied clinically, This results from three problems, the relatively coarse resolution of the imaging devices, the coarse digital resolution of the digital arrays, and lastly the paucity of computational systems capable of performing significant processing with an acceptable turn around time in the routine clinical environment. As both analog and digtal technology have advanced in recent years all three of these diadvantages have been overcome. At the present time, there are several image processing algorithms which are used to improve image quality as an aid to visual diagnosis by the clinicians (109,110). Perhaps the simplest is smoothing and data bounding which is applied to noisy images to remove some of the "snow" in the image and allow the eye to see the organ detail without being distracted by the random counting statistics. Fast Fourier transforms can be applied to perform both a noise removal and edge enhancement based on an a priori knowledge of the imaging system. Increased

1017873

digital image resolution allows the use of much more sophisticated and precise processing such as image refocussing for the removal of scatter effects. As the scintillation camera approaches its theoretical intrinsic resolution the application of computer processing of the images may allow image quality to be even further enhanced.

The IAEA sponsored a multi-national coordinated research program to evaluate the role of image processing in scintigraphy using a liver-like test object. The conclusions from that study show that unprocessed digital images are inferior to processed digital images, which are inferior, generally, to properly exposed analog images directly from the scintillation camera. With display processing, enhanced information was extracted from the digitized images, although in only one laboratory was there a slight benefit of the digital over the analog processing. More benefit was gained by increasing counts than by computer processing. The importance of matching the algorithm to the display device was indicated clearly by the pattern of results obtained in different laboratories using similar algorithms with different displays and vice versa.

Dynamic Studies:

One of the most significant areas of computer application to scintillation camera datails in the area of dynamic studies. This is because of the large amount of data involved in even a slow, low frame count study. The first consideration in the application to dynamic studies is the problem of sampling frequency, both in the spatial and temporal domain (111). Because, in general, a dynamic function study is performed to allow quantitative analysis of the flow characteristics, it is not necessary to collect data in a form which will produce visually pleasing images. It may well be possible to collect data in 32 x 32 digital arrays, or even less, since areas of the image will be summed together to produce the temporal data points. If this is the case, the 32 x 32 collection has reduced the required

1017874

data storage to one fourth that was required for the same data in 64 x 64 or one sixteenth that for 128 x 128.

In dynamic studies the digital resolution used should be that required to define the regions of interest in the organs adequately, and no finer, as this simply increases the storage overhead with no resultant benefit. It is possible a priori to designate a large region of the image in which one is interested and store only those data points which lie in this area. This can produce a significant savings in storage space.

The second problem of temporal resolution can be approached in a similar manner. One does not need to save many images a second to quantitate flow studies with time constants on the order of many seconds. Two techniques are commonly used for data storage. These are frame or histogram node and list node. In frame mode, sequential images are saved. While the temporal relationship between counts in a given image is lost, the temporal relationship between frames is maintained and can be used to determine flow constants of functions with time constants greater than twice the framing time. If the rates are not known or if they are too high to be determined by frame mode data collection, one may use list mode. In list mode, the images are not constructed before storage. Only a list of coordinates of detected events along with a high speed clock ($\leq$ 100cps) is saved. This list then can be used to reconstruct images at any desired frame rate after data collection is complete. For high count rate or extended studies this mode of collection requires large amounts of storage media and often long reconstruction times, but does provide the finest temporal resolution available.

As mentioned above in the discussion of static image studies, it is often desirable to collect physiological data simultaneously with the scintillation camera data (112). This is of importance primarily in list mode studies and may consist of simply a QRS discriminator pulse or the entire digitized ECG signal. In this application the sampled physiological signal is inserted into the list of data in the same manner as the clock, and, is used to control the image

1017875

reconstruction in a similar manner. This technique has proven very useful in cardiac examinations in which information is collected over hundreds of cardiac cycles and then used to reconstruct images representing 16 to 32 temporal segments of the cycle. These sequential images are then replayed in movie fashion to illustrate the beating heart's motion for the diagnostician (105,106,107).

A method of data presentation which is becoming widely accepted is that of functional images. Often several variables are of interest in a flow study. For example in the cerebral blood flow study, the spatial distributions of maximum count values, the times of maximum count and washout slopes are of interest. To display this in a form meaningful to the clinician grey scale displays of these variables are generated. In the case of time to maximum display, the data frames are scanned and each image point is examined to determine the frame in which each point reaches its maximum. The frame time is then inserted in a display image in the corresponding point. This process produces an image in which points reaching a maximum at a later time will be represented by brighter points while the earlier maxima are less bright. The technique is the same for other functions and produces an image which is easily interpretable by the viewer.

Because of the multiplicity of information contained in dynamic studies, it is necessary to use another method to display as much of it as possible in a few images. A method for superimposing temporal information on top of the spatial distributions is the use of color for the temporal dimension. If the study time is divided into several time periods and each interval displayed in a separate color the color of the image is indicative of the time during which the counts were detected. In fact, if a region of the image contains counts from one or more temporal periods of the collection, the color of the image will be the sum of two individual colors and thus indicate that isotope was actually present during the two or more periods (113).

Because of the universality of video techniques and the availability of low cost, high quality video monitors, this media

1017876

offers very desirable properties for displays. This can be used in several ways. The data can be transferred from the computer to a solid state memory, or a scan converter electrical storage tube from which it can be displayed in standard video format. This is most useful for static images. Alternatively, it can be transferred from the computer to a video disc or video tape for storage, distribution and display. This method allows one to store sequential images and replay them in movie format so that the changing distributions can be more readily appreciated.

Photography:

The computer allows the user to produce high quality CRT displays of scintillation camera images but this display cannot be directly photographed if one wishes to produce a high quality photographic image. This is because the response of film, especially color film, to the CRT is quite different from the response of the eye. For this reason the exposure range of the film must be matched to the intensity range of the image using the computer to perform this match is a desirable function of the system. In fact, with appropriate calibration, it is possible to maintain information about several films and use the correspondence table for the particular film being used. This has been shown to produce superior photographs over the simple photography of the unadjusted image (115) and can in fact be used to emphasize count ranges of particular interest.

1017877

D. Clinical Examples:

Computers are being used for many different clinical studies. The most common clinical studies utilizing computers are reviewed in the following sections:

1. Brain:

The applications of computers in neuronuclear medicine can be divided into the following sections: measurement of cerebral blood flow, radionuclide brain angiography (RBA), static radionuclide brain scanning (SRBS), and transaxial emission computer tomography (ECT).

The applications of inert radioactive gases as tracers for measuring the brain blood flow, resulted in a significant improvement in the accuracy of the available procedures. Through the application of radionuclide techniques it became possible, for the first time, to make under physiological conditions external measurements of the blood flow in individual regions of the brain.

The basic technique, which was first proposed by Lassen and Ingvar (195,196) in the early 1960's, is today still regarded as the standard method for measuring regional cerebral blood flow in physiological research studies. In principle, the standard method (197) involves labelling the cerebral tissues by means of a rapid intra-carotid arterial injection of ^{133}Xe in saline. The subsequent clearance of the tracer from a number of regions of the brain may then be followed simultaneously by means of an array of collimated scintillation detectors or a gamma-camera connected on-line to a digital mini-computer.

The regional cerebral blood flow can be estimated from the clearance curve in a number of ways. One method of analysis involves fitting the curve by the sum of two exponential components. it is usual to relate the faster component to the washout of tracer from the grey matter compartment and the slower component to the washout from the white matter compartment. That is,

1017878

$$CBF = \frac{100 \cdot \lambda \cdot 0.693}{T\ 1/2}\ ml/min/100\ gm$$

where λ is the blood brain partition coefficient and T 1/2 is the half time of tracer washout.

The "initial height over area" formula may be used without the need for bi-exponential analysis of the curve, that is,

$$CBF = \frac{\lambda \cdot H}{A.}\ ml/min/100\ gm$$

where λ is the average brain blood partition coefficient, A is the total area under the curve, and H is the peak height of the curve.

The acquisition of raw data from each detector (some authors use as many as 64 detectors) or from a gamma camera and subsequent data processing requires the use of a digital computer. Acquisition is done on line, whereas processing may be done with an off-line digital computer. Computer-generated results of brain flow data are clearly presented by functional images of brain blood flow (198).

Other radionuclide procedures for measuring regional and total hemispheric blood flow, based on the intravenous injection of non-diffusible tracer ^{133}Xe, also require the use of a computer for the storage and data analysis operations.

Radionuclide brain angiography consists of the sequential imaging of a bolus of non-diffusible radiopharmaceutical as it passes through the vessels of the neck and head following antecubital venous injection. According to sapirstein's tracer fractionation principle (199) the distribution of the activity to different brain regions is proportional to the amount of blood flow in each of these regions.

The use of an on-line computer for data acquisition, storage, display and processing of information is very convenient. The analysis of a radionuclide brain angiogram consists of the comparison of the activity-time curve of each brain region with the activity time curve of its symmetrical region in the other brain hemisphere. For this analysis the following should be considered: 1) the time from the injection to the peak of the curve, 2) the maximum height of the

0178101

curve and 3) the width of the curve. By means of these three parameters differences in the regional blood flow can be defined in the vascular resistances and in the length of the vessels supplying the two symmetrical areas (200). Programs for the automatic generation of areas of interest, for creating the regional activity/time curves and for their comparative analysis have been designed and evaluated (201). The time from the injection of the bolus to the peak of the activity/time curve can be determined for each pixel of the frame containing the brain view, and displayed in a new frame. Images obtained in this way have been called functional or parametric images (202,203). Functional images of the time to the peak height of the curve and of the width of the activity/time curve are useful in defining the characteristics of the regional blood circulation in the brain. They provide valuable information about the physiology and physio-pathology of the brain blood circulation and the intrinsic and extrinsic mechanisms of its control. However, it should be kept in mind that it has not yet been demonstrated that information other than that obtained in the reading of the unprocessed sequential images is clinically useful for the diagnosis and management of patients (204).

The storage of information in any analog or digital recording system is not essential, but it can avoid the repetition of approximately 10% of otherwise useless studies resulting from inadequate set-up of the CRT light intensity, failure of the photographic camera, or poor film processing.

At the end of the 60's multiple programs were developed to improve the image resolution and the diagnostic efficacy of the static radionuclide brain scan. The objectives of these programs were to correct the uneven spatial response of the gamma cameras, to correct for the dead time of the cameras, to filter the image to correct the artifacts produced by patient movement, to provide displays with different levels of background cut-off and contrast enhancement. Some of these programs were applied in routine clinical practice. However, rapid improvements in instrumentation made most of the programs obsolete and unnecessary. Today programmable computers have little use in static brain scintigraphy.

0017880

The three dimensional representation of the distribution of a radiopharmaceutical in the brain can be obtained by emmission computer tomography (ECT). Data obtained from linear scans at discrete angles around the head are processed using one of a number of algorithms to solve for the unknown cross-sectional activity in the plane of interest. The mathematical approach to the three-dimensional problem is initially reduced to a series of two dimensional problems assuming that the cross-section has no thickness. The two dimensional problem is then partitioned into a series of one dimensional problems which are individually solved assuming that the data from each point of the linear scan represents a linear equation.

Two categories of algorithms are used for the imaging reconstruction; algebraic techniques generally use iterative schemes and, Fourier techniques which use Fourier transforms or convolution techniques. These algorithms ae common to both transmission and emission computerized tomography.

The main limitation in ECT is the large radiation dose required to produce good resolution images. ECT systems based on single photon counting or annihilation coincidence detection have been designed and experimentally tested. It is true that ECT has not advanced to the same degree as TCT (205,206,207). However, it should be recognized that it offers the unique advantage of a physiological three dimensional approach which will open new ways of studying and managing neurological patients (208).

1017881

2. Thyroid:

Thyroid uptake of ^{131}I was the first Nuclear Medicine test to be utilized widely. The relatively high thyroid dose from ^{131}I (roughly 1 rad/μCi administered to a typical normal subject), has led to the increased use of in vitro tests for thyroid function assessment based on hormone levels. With increasing attention to dose reduction, more laboratories are using Tc-99m pertechnetate for evaluation of thyroid trapping. The large uptake of pertechnetate in the salivary glands, and high blood background at 20 min., with the measurements are usually made, makes it necessary to use a computer-coupled imaging device for these determinations. In this way, regional uptake, stimulation and suppression tests can be performed (120,121).

The measurement of thyroid uptake with pertechnetate requires the measurement of neck uptake followed by subtraction of appropriately selected background regions. In view of the high uptake of technetium inf the salivary glands, those structures, and swallowed activity in the esophagus have to be excluded from the thyroid and background fields. The use of digital storage and display systems permits the quantitation of the thyroid uptake with good precision and good correlation with iodine uptake. In the system used at Vanderbilt University (Ref. 4, p. 129-139), the dose to be administered is measured, followed by the patient measurement 20 minutes following injection. A region of interest (ROI) is chosen which includes the thyroid. Background is derived from counts in a 3 pixels deep annulus just inside the ROI. Uptake is calculated from the background corrected counts.

The size of the thyroid gland can be estimated from the projected dimensions of the gland with reasonable accuracy (92). A measure of thyroid gland size is needed for planning the therapy of thyrotoxicosis using ^{131}I. The absorbed dose to the thyroid from a given ingested amount of ^{131}I varies inversely with gland size. Since estimates of thyroid gland size vary widely between observers, a standardized means of establishing thyroid size is needed. This is especially true for small glands where palpation may be especially

1017882

difficult. The estimation of the size of the thyroid functioning nodule or gland can be established on the basis of single views, given an assumed geometrical shape. The results of such correlations using isotope scans have been reviewed by Spencer (92). The measurement of uptake over ROI's, i.e. over normal areas and from nodules, permits the evaluation of T3 suppression and TSH stimulation tests at an anatomical level, which assists in the differential diagnosis of hyper and hypo functioning nodules (121).

Reference values for the dimensions and weight of the thyroid gland during pre and post natal life are tabulated in ICRP publications (177).

Improved diagnosis of thyroid diseases are obtained by processing of thyroid scans, especially in glands with poor uptake (122). Automated techniques for classifying thyroid disorders by computer analysis of images have been developed. (93). Although they are not clinically useful at the moment, pattern recognition techniques, including texture analysis, are promising tools which are receiving increasing attention.

A number of workers have utilized computer techniques to assist in the diagnosis of thyroid disease. In general, the methods have been highly successful in classifying patients into proper thyroid function status category, but less successful in classifying the thyroid disorder, per se (178). A new judgement space technique (179) has been applied reasonably successfully to thyroid disease classification, and is currently being tested with a larger data base (180).

3. Lung:

Radionuclides have furnished important fundamental knowledge of pulmonary pathophysiology. The most important early studies were performed with short-lived positron-emitting isotopes of ^{11}C, and ^{15}O, and used multiple opposed NaI detectors (181).

The development of the Anger Scintillation Camera made it possible to obtain clinically useful information on pulmonary ventilation (using radioactive noble gases), and blood flow (using

10-1883

radiolabelled particulates). Loken pioneered in the application of computers to analysis of ^{133}Xe rates of inflow, and outflow using single and opposed camera measurement systems (125). Careful studies of blood flow patterns in relation to gravitational fields were carried out at the Mayo Clinic (126). A comprehensive review of clinical applications of these techniques was published in 1973 (127), and describes methods that are in wide use.

An important role for computer analysis of pulmonary function using radiotracers awaits the availability of improved tracers. The evaluation of pulmonary ventilation patterns with ^{133}Xe and ^{81m}Kr offers significant advantages over ^{133}Xe and should make it possible to obtain clinically useful numerical information on pulmonary ventilation. The evaluation of pulmonary ventilation can be made from analysis of the rate of appearance of radiogas in small lung segments following a single breath (182). With such technique radiation dose to the subject is reduced relative to the usual equilibrium method, and analogous information is obtained.

The equilibrium method provides an opportunity to obtain physiological information on regional ventilation, i.e. tidal volumes, maximum inspiratory and expiratory reserves, FEV_1, etc., i.e. information which ordinarily requires invasive complex procedures (as from regional bronchospirometry). In most Nuclear Medicine laboratories, routine ventilation studies involve rebreathing the labelled gas to equilibrium (5-15 minutes) followed by measurement of rates of clearance, after the source of gas is disconnected from the patient.

When the rate of ventilation is related to fractional perfusion, estimates of ventilation/perfusion ratios can be obtained (183). The presence of intact ventilation in poorly perfused regions is a strong indicator of pulmonary embolism. The display of such data by two colors, one which shows the well ventilated segments, the other which shows the well perfused segments, provides a vivid display of these spatially varying distributions by differential color mixing. Such displays can be obtained with color film viewing the ventilation distribution image through one color filter, followed by a super-

1017884

imposed image of perfusion through a second color filter. The proper selection of photographic intensities is a time and film consuming process. Computer generation of dual isotope color TV displays is a simple rapid process and now that suitable commercial displays are available, that is the preferred method.

The generation of ventilation images has been approached in two general ways. In the first, one estimates parameters for each image element. A number of mathematical techniques have been used to extract flow related information. The most common extracted parameters from equilibrium data include slopes of the early washout phase, height over area, and centers of moments (124). The second general technique used produces synchronized signal averaged cinematic displays. Techniques analogous to those used successfully in gated ventricular wall motion studies have been applied to ventilation studies recently by Wagner and his colleagues, and the preliminary results appear promising (184).

A more comprehensive analysis of regional pulmonary function based upon information extracted from images, coupled with knowledge of blood pH and gas partial pressures, has been published by Line (166). This is an excellent example of how computers may be used to integrate and utilize multiple signals from diverse sources when a valid model of the physiological system is established.

4. Heart:

Over the past several years, nuclear cardiology has received considerable attention by a number of investigators. Clinical applications of this area include the evaluation of patients having suspected atrial and/or ventricular shunts, the assessment of ejection fractions as well as wall motion, measurement of regional myocardial perfusion and the assessment of the patient for acute myocardial infarction. In each of these areas, the application of the computer has provided important information which could not easily be obtained from the images alone. Several applications of the computer to the area of nuclear cardiology will be briefly reviewed.

1017885

a. Intracardiac Shunt Function Studies

The conventional method of demonstrating the presence of intracardiac shunts in children and adults using cardiac catheterization is contrast angiography. This method is generally considered time consuming, expensive and not without risk. The advent of the computer assisted nuclear cardiology technique for diagnosing intracardiac shunts has therefore been considered to be an important adjunctant to the presurgical workup of the patient. In general, the technique requires but a single injection, essentially no risk to the patient and detailed evaluation of the study can be performed without the patient present. The method is considered to be a reliable, non-invasive screening procedure for diagnosis of intracardiac shunts of hemodynamic and surgical significance.

A dual isotope method has been described for diagnosis of intracardiac shunts (185). In this method, a time activity curve is generated on the first pass of Xe133 (saline) through the heart. The curve has a single peak from the right side of the heart only, since the Xenon is cleared by the lungs through the pulmonary circulation. A subsequent injection of technetium-99m produces sequential single peak curves over the right heart and the left heart. The appearance of label on the left side of the heart following the Xenon-133 injection is indicative of a right to left shunt. On the other hand, appearance of technetium-99m label on the right side of the heart at the time of appearance of label within the left heart suggests a left to right shunt. By appropriately selecting regions of interest in the atria or ventricles, one can assess both atrial septal defects as well as ventricular septal defects.

A more sophisticated computer analysis of intracardiac shunts has also been described (128). This method incorporates a pulsatile heart model for radiocardiogram simulation and analysis. The model consists of a series of compartments pulsating alternately. From each compartment a certain fraction of indicator is injected into the next compartment and added to the indicator retained there. Each cardiac chamber is represented by one compartment, while pulmonary and systemic circulation are represented by a series of paired number of

01-1880

compartments. For shunt simulation a certain fraction can be ejected backward or forward along the series. As was the case in the dual isotope method for diagnosing intracardiac shunts, the abnormal appearance of recirculation peaks is used to diagnose hemodynamically significant shunts.

The computer assisted evaluation of intracardiac shunts is now considered to be a well established procedure in most nuclear medicine laboratories.

b. Cardiac Output:

The application of the computer to nuclear cardiology has greatly facilitated the calculation of cardiac output. The method is based on basic indicator dilution theory and utilizes the following equation:

$$CO = \left[C_{eq} \Big/ \int_0^\infty C\ (t)\ dt \right] BV$$

Where C_{eq} is the count rate at equilibrium, and the denominator is the area under the first pass curve generated downstream from the ejection after mixing has occurred. BV is the blood volume obtained at the time of the study. In practice, the gamma variate function is applied to the time activity curve obtained from the injection of the radionuclide into the superior vena cava. The fitting of these curves to gamma functions has particular advantage when cardiac output is low or chamber volume is high, making exponential extrapolation of the descending portion of the time activity curve difficult and inaccurate. Cardiac output measured by this method have shown excellent agreement with measurements made by contrast angiography (130,131).

c. Ejection Fraction:

A number of nuclear cardiology techniques have been described for measuring ejection fractions (132, 133, 135). Most methods involve the injection of a radioactive agent such as technetium-99m human serum albumin or cold pyrophosphate followed by the injection of technetium-99m. In the latter technique, the sequence of injection

1017887

leads to the labelling of red blood cells. In the conventional method, end-diastolic and end-systolic digital cardiac images are gated from the electrocardiogram. Since the number of counts contained in a selected region of interest is directly proportional to blood volume, area of interest capabilities can be used to obtain the number of counts in the left ventricle at end systole as well as end-diastole. Appropriately correcting for background, ejection fraction can be computed directly from the diastole and systole counts.

Single pass techniques have also been described which allow calculation of the ejection fraction following the collection of counts of activity on the first pass through the left ventricle. The method requires collecting data at frame rates of 25 per second or greater. Left ventricular volume curves collected at these rapid frame rates are used to determine end-systole as well as end-diastole counts within the left ventricle. The application of the conventional ejection fraction equation is again used. The first pass method has the advantage of allowing determination of the ejection fraction during a data acquisition phase of 20 to 30 second as opposed to the 30 to 40 minutes required in gated studies.

d. Wall Motion:

There currently is a great deal of interest in evaluating the wall motion of patients being considered for cardiac bypass procedures. The simplicity with which wall motion can be assessed using nuclear cardiology techniques has caused this method to become widely accepted as a screening procedure to determine those patients which have enough compromise in wall motion that they should be considered for bypass procedures. Wall motion may be assessed either using first pass rapid sequence imaging, or the more conventional gated wall motion technique.

In the first pass method, activity times curves are generated from data acquired at a frame ratio of 25 per second, following the injection of Tc99m labelled agents into the superior vena cava. Composite, end-systole and end-diastole images are obtained using

10 17888

region of interest capabilities of the computer. The end-diastole and end-systole images of the left ventricle are superimposed to identify areas of abnormal wall motion. Although the method is rapid, data are collected in only one view and the number of counts in the image is generally limited because of the brief data collection interval.

The second approach involves determination of end-systolic and end-diastolic images at the time the injected tracer has reached equilibrium within the vasculature. The scintillation camera is gated to record images only during selected portions of the cardiac cycle to a total of 200,000 counts from several hundred cardiac cycles.

This method produces a high quality image with all counts obtained only during the desired portion of the cardiac cycle. This method has the advantage of allowing images to be recorded in several projections, and is not statistically limited to cadiac wall motion.

In both methods, the correlation with contrast ventriculography techniques has been excellent.

e. Myocardial Blood Flow:

1. Diffusible Tracers

There has been a great deal of interest in measuring myocardial blood flod in patients suspected of having ischemic heart disease. The interest stems from the desire to extend knowledge about the pathophysiological aspects of ischemic heart disease as well as from the desire to improve the functional diagnostic capability of the individual patient. The earliest method used the diffusible indicator, Xenon-133. The method involves the injection of Xenon-133 (in saline) and measuring the activity over the myocardium as a function of time. Collection of scintillation camera images in the computer allows one to establish Xenon-133 washout curves for various portions of the myocardium. The technique has been found to be a sensitive method for detecting ischemic areas within the myocardium. The principal disadvantage of the method relates to the fact that

1017889

the Xenon can freely diffuse into epicardial fat causing hold-up in the clearance of label not related to ischemic heart disease. In addition, the 80 keV photons associated with Xenon are not readily imaged from the posterior myocardium.

Microspheres labelled with a variety of radionuclides can be used to measure myocardial blood flow. The technique involves the injection of a known quantity of radioactive microspheres each having diameters of approximately ten to twenty microns into the left side of the heart. The microspheres mix with and are quantitatively distributed in the same manner as the arterial blood if the diameter of the microspheres is such that the tracers are physically trapped by the microvasculature. By injecting radioactive labelled particles directly into selective coronary arteries, the distribution of particles within the myocardium supplied by that vessel can be used to assess regional blood flow.

Images collected on the computer following the injection of labelled microspheres into selective coronary arteries can be used to assess regional myocardial blood flow. The injection of microspheres having different labels under different conditions can be used to assess changes in myocardial blood flow. For example, microspheres labelled with technetium-99m may be injected into a coronary artery at the time of maximum stress to assess myocardial perfusion with the vessels maximally dilated. This can be followed by the injection of microspheres labelled with Indium-113m with the patient at rest. The distribution of particles under this condition when compared with the distribution of technetium-99m at the time of maximum stress can be used to assess the relative blood flow to the myocardium at rest versus exercise. This information can be used to accurately assess the presence of ischemic heart disease.

1017890

While the microsphere technique provides much valuable information on regional myocardial blood flow, it is clearly not a non-invasive technique and has well-defined risks associated with its application. For this reason, it is not widely used.

f. Myocardial Infarction:

For the most part, the assessment of acute myocardial infarction using technetium-99m pyrophosphate imaging can be accomplished with the scintillation camera alone. In certain cases, however, activity within the skeletal structure can be confused with abnormal accumulation within the myocardium. In such cases, the computer can be used to effectively subtract rib activity from the myocadium to more accurately define the presence of activity within the myocardium (140,141).

In general, the application of the computer to myocardial imaging has significantly increased the variety of studies which can be effectively performed in nuclear cardiology. Computer applications have also increased the scope of studies which can be performed, and they have significantly decreased the length of time required to perform studies as well as increase the diagnostic accuracy in the interpretation of nuclear cardiology images.

5. Liver:

a. Blood Flow:

Liver blood flow can be measured externally by measuring the extraction of dyes by the polygonal cells or by the extraction of particulate matter which is phagocytized by the recticuloendothelial cells of the liver. This latter method is preferred primarily because the efficiency of removal is nearly 100%.

External counting of the gamma radiation of colloidal gold-198 was first described by Vetter in 1954 (186). Other phagocytized materials such as tchnetium-99m labelled sulfur colloid and radio-

— 0178 —

nuclide labelled albumin and microspheres have subsequently been shown to be useful in estimating blood flow into the liver. The method involves collecting a sequence of images from the liver, onto a disk of a computer system, following the injection of the colloid material into the circulation. The computer analysis involves fitting a series of exponential functions to the collected data. The resulting colloid blood disappearance curve is resolved into two components. The fast component has been shown to be due solely to hepatic removal while the slow component is due to extrahepatic removal.

The curve components are used in conventional equations to calculate liver blood flow. When the information is collected using a scintillation camera, it is possible to select regions of interest within the liver to determine regional liver blood flow. The technique has been found to be especially useful in evaluating the degree of liver involvement in cirrhosis. Alterations in distribution such as the characteristic central accumulation secondary to increase shunting in cirrhotics have provided a valuable index of disease severity (142).

b. Hepatocyte Clearance/Excretion:

Computer assisted techniques for blood background subtraction in hepatic studies with I-131 and I-123 Bromosulphthalein (BSP) have been described (144). The technique involves performing dynamic studies of the liver using a scintillation camera placed over the region of interest, with a second scintillation detector placed over the head to record a blood clearance curve. Two compartmental analysis gives the liver BSP uptake curve and the BSP outflow curve. The method also requires injection of Indium-113m Chloride before I-131 BSP to determine the normalization factor required for the BSP blood clearance curve to correct the BSP liver curve for BSP remaining in the blood pool in the liver and its environment. In normal subjects a discrete unimodal spectrum of BSP transit times to the liver is found. This implies the presence of interactive self-regulatory systems for the liver subunits. In the abnormal liver, different transit time patterns, especially delayed transits, occur which may

1017892

enable identification of various hepatocellular disorders in their early stages.

C. Image Analysis:

Conventional liver imaging utilizes Technetium-99m sulfur colloid as the imaging agent. An abnormal liver image is characterized by the presence of focal abnormalities. Oftentimes it is difficult to distinguish between areas of non-uniformity versus focal abnormalities. The collection of images within the computer allows data processing to be performed on the liver image without destroying the original data collected. For example, data smoothing, contrast enhancement, background subtract can all be applied to a select image. The degree of data processing can be continued until an acceptable image is obtained. The data processing can be stopped at any point, and alternate degrees of data processing can be employed starting each time with the raw data. This technique can oftentimes lead to an increased degree of certainty when making a diagnosis.

Other techniques of data processing in liver imaging have been describes (145). For example, a dual tracer technique can be used to differentiate tumor from non-tumor within the liver. Basically, tumor liver tissue are labelled simultaenously by various tracers and, in addition, liver parenchyma is labelled with radiocolloid. By means of a subtraction technique, normal parts of the liver can be suppressed in the image while parts of the liver with a relative prevalence of the first tracer are presented. For example, a Technetium sulfur colloid image of the liver containing a hepatoma would show an absence of labels within the tumor mass. Gallium-67 imaging on the other hand not only labels the normal liver parenchyma but also labels the tumor mass. The subtraction technique often demonstrates that the focal area of decreased labelling on sulfur colloid does in fact fill in with Gallium, therefore identifying the tumor mass. This technique can be especially useful when trying to identify small lesions.

1017893

6. Kidney:

Nephro-nuclear medicine started with the use of ^{131}I-hippurate renography as a non-invasive procedure to screen renovascular hypertension. Today, 22 years after Taplin's (187) first publication, radionuclide techniques to assess renal blood flow (RBF), glomerular filtration rate (GFR), effective renal plasma flow (ERPF), split renal function, renal morphology, evolution of kidney transplants, and the angiotensin renin system activity have gained general acceptance, being routinely used by large- and medium-sized hospitals. The use of scintillation cameras on line with digital computers allows the study of renal physiology and pathophysiology without invasion of the urinary tract. It should be further recognized that this modern approach to renal physiology may replace the more difficult clinical and laboratory procedures, such as differential renal function studies. The more invasive procedures previously used to obtain comparable information are associated with greater morbidity, and the information often is not physiological.

Nephro-nuclear medicine procedures are based on teh same physiological principles as those employing non-radioactive markers. Thus, teh concept of renal clearance of a substance established by van Slyke and the mathematical principles outlined by Sapirstein (188) provide the basis for radionuclide nephro-urology procedures.

$^{99m}TcDTPA$ and ^{125}I-Iothalamate are the radiopharmaceuticals most commonly used to measure glomerular filtration rate. Both of them meet the following specifications:

(1) They are filtered at the glomerulus and they neither combine with nor become absorbed by plasma proteins.
(2) They are not synthesized or destroyed by the tubules.
(3) They are physiologically inert.
(4) They are not reabsorbed or secreted by the tubules.

1017894

^{131}I-Hippuran and ^{123}I-Hippuran, being more than 90% extracted from the renal plasma during one pass through the kidneys, are the radioactive tracers used to measure the effective renal plasma flow.

After a single dose of a radioactive GFR or ERPF agent is injected into the blood stream, the disappearance of the compound from the plasma is related to both its distribution throughout the body water spaces and its excretion by the kidney. An analysis of the disappearance curve in its entirety can theoretically define the number and size of the individual compartments of distribution, provided that the mixing in the first volume of distribution is sufficiently rapid and the renal clearance negligible in the first several minutes after injection. The clearance from each compartment to the next can be individualized as a component of the plasma disappearance curve. The slope of the last component of the curve becomes the renal component after equilibration in all body compartments, assuming that the kidneys are the ultimate exit from the plasma compartment.

Accurate analysis of an entire plasma curve obviously requires a large number of blood samples, or continuous external monitoring of the blood activity and calibration of the recorded curve by the activity per unit of volume in a blood sample obtained at a known point of the curve. As demonstrated by Donath (189), the analysis of the plasma curve by either a two-compartment or one-compartment system has the accuracy required for clinical purposes and consumes less computer time than an analysis by more complex compartmental models. In the GFR and ERPF assays, the computer is used for doing the following calculations and corrections:

(1) Background substraction and correction for radioactive decay
(2) Correction for the contribution of the high energy radionuclide in the counting window of the lower energy nuclide when GFR and ERPF are simultaneously measured
(3) Estimation fo the two components of the curve by the best-fitting line through the points obtained by substracting the

10178995

terminal slope from the plasma curve.

(4) Calculation of the size of the second compartment using the zero intercept of the curve components, the size of the injected dose and the calibration factor provided by the radioactivity of the blood sample.

(5) Estimation of the renal blood clearance from the slope of the second component and its estimated volume.

(6) Estimation of the GFR and/or ERPF corrected for 1.73 m^2 of body area using the patient weight, height, and the DuBois formula.

(7) To print out the results in a standard format.

To measure the functional value of each kidney, several procedures have been proposed and discussed by C. Raynaud (191). Most of these procedures require the use of an on-line computer for the acquisition of information, data processing, and display of results.

In our institution we offer a renal profile test, which consists of an estimation of the distribution of the renal blood flow in each kidney, the measurement of the total GFR, ERPF, and tubular function performed by each kidney. The instrumentation used for this test consists of a scintillation camera provided with three window spectrometers, an external scintillation probe, and an on-line computer. First the patient is injected with ^{99m}Tc DMSA and one hour later an index is obtained of the distribution of the tubular function in both kidneys, calculating the geometric average of the counts detected in each kidney on the anterior and posterior abdominal views. After that, ^{99m}Tc DTPA and ^{131}I-Hippuran are injected using a bolus technique. Four frames per second are acquired for the first 60 seconds and 3 frames per minute for the following 30 minutes. The background of the ^{99m}Tc DMSA and the contribution of the ^{131}I-Hippuran in the window of ^{99m}Technetium is subtracted from the ^{99m}Tc DTPA frames. The radionuclide renal angiogram is obtained, creating a sequence of 1.5 second frames of the first passage of the ^{99m}Tc DTPA bolus throughout the kidneys. Areas of interest are drawn over the projection of the aorta and both kidneys

1017896

to generate activity curves of the passage of the bolus through these structures. The time between the peak activity sensed from the aorta and each kidney is measured as an estimation of the blood flow to each kidney. These areas of interest are also used to generate the time-activity curve of hippuran and DTPA in each kidney. Indices to evaluate the transit time of the radiopharmaceuticals throughout the kidney parenchyma, calices, and pelvis and ureter are computed and printed at the bottom of each curve (Fig. 1). Fifteen sequential images, each of two minutes duration produced by the addition of the raw data are used for further evaluation of the kidneys and urinary tract.

Britton (192,193) has proposed that the limitation of the traditional renogram to differentiate between renal artery stenosis and partial ureteral obstruction could be overcome through the use of the renal transit-time spectrum. The renal transit-time spectrum for a given radiopharmaceutical is determined by means of a mathematical deconvolution of the renal input and output functions. The input function to each kidney is generally taken as the blood activity level, as measured with an external probe positioned over the heart, head, or other blood pool. The renal output function is calculated from the traditional renogram by first deriving an uptake component which is then in turn subtracted from the renogram to yield an output component. The uptake component is estimated from the initial upslope of the renogram during the time period when no excretion has taken place. Blood background is generally subtracted from the renogram in this technique and becomes most important when renal function is poor.

A direct measurement of the transit-time spectrum may be obtained by measuring the renal activity following the injection of a short bolus directly into the renal artery. This technique has been used by Price, et al (194) in dogs to validate the deconvolution of renograms resulting from I.V. injections.

The deconvolution technique has not, as yet, become a routine procedure in our institution. However, we are gaining further experience with the technique in our research laboratory where it continues to show promise in the new diagnostic parameters it provides.

L01T89T

Another important application of computers in nephro-nuclear medicine is in the follow-up of transplanted kidneys. In our institution, the function of the transplanted kidney is tested every 48 hours until the patient is discharged from the hospital. The nephrologists involved in the management of these patients found that the renal activity curve of ^{131}xDI-hippuran provides good information for the early diagnosis of renal function deterioration and to evaluate the efficacy of therapy used for acute tubular necrosis and/or rejection. The computer is used for data acquisition and processing of the information. The renal activity curves of each patient are stored in an individual file and when a new study is performed the curves of the previous studies are displayed for comparison. Figure 2 shows the print-out of the results of one study, which is included in the patient's hospital chart.

Conclusion

The list of currently popular computer applications is rapidly growing. The utility of the different methods are in the process of being tested. It seems clear that computers are here to stay and that their utility is limited by the availability of well documented validated progress, and adequate display systems. Both of these deficiencies are being remedied. Systems costs are coming down and hence it seems likely that many more laboratories will become involved with computers in the future. Skilled computer programmers and operators are needed in research oriented departments, and part-time services of such persons is needed even for routine service work.

1017898

REFERENCES

1. Proceedings of the First Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Oak Ridge, Tennessee, April 2-3, 1971, U.S. Technical Information Center AEC CONF-710425.

2. Proceedings of the Second Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Oak Ridge, Tennessee, April 21-22, 1972, U.S. Technical Information Center, AEC CONF-720430.

3. Proceedings of the Third Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Miami, Florida, June 15-16, 1973, U.S. Technical Information Center, AEC CONF-730627.

4. Proceedings of the Fourth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Oak Ridge, Tennessee, May 8-10, 1974, U.S. Technical Information Center, AEC CONF-740531.

5. Proceedings of the Fifth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Salt Lake City, Utah, January 15-16, 1975, U.S. Technical Information Center, ERDA CONF-750124.

6. Proceedings of the Sixth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine. Atlanta, Georgia, January 25-26, 1976, Barbara Y. Howard (ed), Society of Nuclear Medicine Publication, New York.

7. Medical Radioisotope Scintigraphy. (Proceedings of a symposium. Salzburg, 1968) IAEA, Vienna (1969).

8. Medical Radioisotope Scintigraphy (Proceedings of a symposium. Monte Carlo, 1972) IAEA, Vienna (1973).

9. Medical Radioisotope Scintigraphy (Proceedings of a symposium. Los Angeles, 1976) IAEA, Vienna (1977).

10. Dynamic Studies with Radioisotopes in Medicine. (Proceedings of a symposium. Rotterdam, 1970) IAEA, Vienna (1971).

11. Dynamic Studies with Radioisotopes in Medicine. (Proceedings of a symposium. Knoxville, 1974) IAEA, Vienna (1975).

12. Information Processings in Scintigraphy (proceedings Third International Conference on Data Handling and Image Processing in Scintigraphy. Cambridge, 1973.) U.S. Technical Information Center. ERDA CONF-730687.

1017899

13. Information Processing in Scintigraphy (Proceedings of IVth International Conference, Orsay, 1975). C. Raynaud and A. Todd-Pokropek (eds). French AEC, Saclay, 1976.

14. Instrumentation in Nuclear Medicine, Vol. I., G. J. Hine (ed), New York, Academic Press, 1967.

15. Instrumentation in Nuclear Medicine, Vol. 2., G.J. Hine & J.A. Sorenson (ed), Academic Press, New York, 1974.

16. Symposium on Computers and Scanning, J.U. Hidalgo (ed), New York, Society of Nuclear Medicine, 1967.

17. Computer Processings of Dynamic Images from an Anger Scintillation Camera. K. B. Larson and Jerome R. Cox (eds), New York, Society of Nuclear Medicine, 1971.

18. Quantitative Organ Visualization in Nuclear Medicine. P. Kenny and E. Smith (eds), University of Miami Press, 1971.

19. Radionuclides in Nephrology (Proc. of Int. Symp.) M. Donald Blaufox and Jean Louis Fenck-Brentano (eds). New York, Grune and Stratton Inc., 1972.

20. Timmermans, L.M., and Merchie, G.A. Radioisotopes in the Diagnosis of Diseases of the Kidneys and the Urinary Tract, I.C.S. 178. Excerpta Medica Foundation, 1969.

21. Radionuclides in Nephrology (Proceedings IIIrd International Symposium, Berlin, 1974) Winkel, Blaufox and Funck-Brentano (eds) Stuttgart, George Thieme Publishers, 1975.

22. Progress in Nuclear Medicine: Evaluation of Renal Function and Disease with Radionuclides, M.Donald Blaufox (ed). New York, S. Karger, 1972.

23. Reinke, D.B.: Data Storage and Retrieval System for a Nuclear Medicine Department. J. Nuc. Med., 16: No. 4, 275, 1975.

24. Jost, R.G.: Building a Patient-Information System for Radiology, The Modular Approach. Applied Radiology 6: 99, 1977.

25. Weber, D.A.: Computer Programming Applications in Nuclear Medicine. In Ref. 3, P. 77-89.

26. Dellwe, P.A.: (CAMIRD) Computer Assisted Internal Radiation Dosimetry. Bureau of Rad. Health Publication. Cincinnati General Hospital.

1017900

27. Wheeler, P.S., Gitlin, J.N., Simborg, D.W.: The Johns Hopkins Computer Reporting System for Diagnostic Radiology. Chapter in Proceedings of the Third Conference on Computer Applications in Radiology. University of Missouri-Columbia Medical Center, Columbia, Mo., September 12-15, 1972.

28. Wilson, W.J., Perry, J.T. and Smith, J.P.: A computer-Mediated Radiology Information System. Chapter in Proceedings of the Third Conference on Computer Applications in Radiology. University of Missouri-Columbia Medical Center, Columbia, Mo., September 12-15, 1972.

29. Simon, M., Leeming, B.W., Bleich, H.L.: Computerized Radiology Reporting Using Coded Language. Radiology 113: 343-349, 1974.

30. Brolin, I.: Radiologic Reporting. Acta Radiol., Supplement 2 323, 1973.

31. Lehr, J.L., Lodwick, G.S., Nicholson, B.F. et al: Experience with MARS (Missouri Automated Radiology System), Radiology. 106: 289-294, 1973.

32. Lazarus, C.B., Poitras, J.W., Mitchell, W.P. et al: Automation of Scheduling and File-Room Functions of a Diagnostic Radiology Department. U. S. DHEW Publication No. (FDA) 75-8020, 1975.

33. Glass, H.I.: The Role of Computers in the Nuclear Medicine Laboratory. Seminars in Nuclear Medicine 3: 303, 1973.

34. Brown, D.W.: General Purpose Computers for Processing of Image Data. In Ref. 18, p. 431.

35. Brown, D.W.: Computer Systems for Nuclear Medicine. In Ref. 15, p. 161.

36. Anger, R.T.: Preliminary Report on a Nuclear Medicine Patient Data Reporting System Utilizing an on-site Mini Computer. In Ref. 4, p.6.

37. Price, R.R.: Computer-Aided Nuclear Medicine Report Generations at Vanderbilt. In Ref. 4, p. 18.

38. Mani, R.L.: A Computer Assisted Radiographic Reporting System Utilizing Mark Sense Format. Proceedings of Third Conference of Computer Applications in Radiology. U. of Mo., Sept. 12-15, 1972.

39. Hoops, R.C., Alexander, G.W., Saenger, E.L.: A Fixed Format Lexicon for Nuclear Medicine Reports. DHEW (FDA) 74-8009, 1973.

1017901

40. Brown, D.W.: An On-Line Computer System for the Nuclear Medicine Laboratory. J. Nuc. Med. 11: 253, 1970.

41. Brown, D.W. and Groome, D.S.: Computer Assisted Instruction in Nuclear Medicine. JAMA 206: 1, 059, 1968.

42. Baruch, J.J.: Hospital Automation Via Computer Time-Sharing in Computers in Biomedical Research, Vol. II, Ralph W. Stacey and Bruce Waxman (eds), New York, Academic Press (1965).

43. Berman, M., Shaw, J. and Del Priore, J.: Practical Aspects of Internal Dose Calculations and Computer Program. NIH Publications, Laboratory of Theoretical Biology, National Institute of Health, Bethesda, Md.

44. Kelso, J.: Vanderbilt Nuclear Medicine Database Manager Operating Manual. Vanderbilt University Internal Report, Nashville, Tennessee, 1977.

45. Calibration of Germanium Detectors for Measurement of Gamma-Ray Emission Rates of Radionuclides. N.B.S. Draft Standard N717.

46. Ionization Chamber Assay of Radionuclides. N.B.S. Draft Standard N713.

47. Covell, D.F.: Quality Control for the Gamma-Ray Scintillation Spectrometer. In Applications of Computers to Nuclear and Radiochemistry. O'Kelly, G.D. (ed), Oak Ridge National Lab., 1962.

48. Crouch, D.F. and Health, R.L.: Evaluation and Calibration of Pulse Height Analyzer Systems for Computer Data Processing. In Applications of Computers to Nuclear and Radiochemistry. O'Kelly, G.D. (ed). Oak Ridge National Lab., 1962.

49. Hidalgo, J.U. et al: Precision of Radioimmunoassay with Emphasis on Curve Fitting Procedures. Seminars Nucl. Med. 5, No. 2: 153-156, 1975.

50. Rodbard, D.: Statistical Aspects of Radioimmunoassays. -In Principles of Competitive Protein-Binding Assays. Odell, W.D. and Daughaday, W.H. (eds), Philadelphia, J.B. Lippincott, 1971.

51. Feldman, H. and Rodbard, D.: Mathematical Theory of Radioimmunoassay. In Principles of Competitive Protein-Binding Assays. Odell, W.D. and Daughaday, W.H. (eds), Philadelphia, J.B. Lippincott, 1971.

1017902

52. Boyd, C.M. et al: Quality Control and Normal Ranges. In Practical Radioimmunoassay. Moss, A.J., Jr. et al (eds), Mosby, St. Louis, 1976.

53. Reward, R.J. and Trainer, T.D.: Data Handling and Quality

64. Erickson, J.J. et al: In Vitro Test Programming at Vanderbilt. Proc. Vth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Salt Lake City, 1975.

65. Catalogue of Computer Programs, Packard Instrument Co., Inc., 2200 Warrenville Road, Illinois 60515.
Program Numbers: 08701, 11662, 05661, 12665, (Liquid 06661, 01672, 08661, 06572, Scintillation 09663, 09672, 09665, 07661, Counting)
11661, 07801

09661, 10661 (NaI Scintillation Counting)

66. Spratt, J.L.: Computer Programs for Calculation of Liquid Scintillation Counting Data. Int. J. Appl. Radiat. 16: 439-441, 1965.

67. Quittner, P.: Gamma Ray Spectoscopy, Adams Hilger Ltd., London, 1972.

68. Brown, D. W. et al: Computer Systems for Nuclear Medicine. In Instrumentation on Nuclear Medicine, Hine, G.H. and Sorenson, J.A. (eds), Academic Press, New York, 1974.

69. Seigel, J.H. and Strom, B.L.: An Automated Consultation System to Aid the Physician in the Care of the Desperately Sick Patient. In Computers in Biomedical Research, Vol. 4, Stacy, R.W. & Waxman, B.D. (eds), Academic Press, New York, 1974.

70. Lieberman, D.E. et al: High Speed Indexing of Patient Report Data Using the Nuclear Medicine Computer. Proc. IVth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, 1974.

71. Anger, R.T., Jr. et al: Preliminary Report on a Nuclear Medicine Patient Data Reporting System Utilizing an On-Site Minicomputer. Proc. IVth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, 1974.

72. Meneely, G.R. et al: The Use of Computers in Whole-Body-Counter Data Processing. In Whole-Body Counting, Proceedings of the IAEA Symposium in Vienna, Austria, 1961, p. 379-390.

73. MacIntyre, W.J.: In Vivo Tracer Studies by External X-Ray Counting. In ref. 14, p. 351-380.

74. Sorenson, J.A. & Cameron, J.R.: Transmission Scanning Techniques. In ref. 15, p. 350-385

4061-10

75. Tinney, J.F.: In Vivo X-ray Fluorescence Analysis - Concepts and Equipment. In Semiconductor Detectors in the Future of Nuclear Medicine, New York, Society of Nuclear Medicine, 1971, pp. 214-229.

76. Ter-Pogossian, M.M. et al: In Vivo Measurement of Regional Cerebral Blood Flow and Blood Volume by Means of Stimulated X-ray Fluorescence. In Semiconductor Detectors in the Future of Nuclear Medicine, New York, Society of Nuclear Medicine, 1971, pp. 240-257.

77. Kaufman, K. et al: A New Method of Measuring Cardiac Output Using Fluorescent Excitation. In Semiconductor Detectors in Medicine, Oak Ridge, Tenn., USAEC CONF-730321, 1973, pp. 353-364.

78. Koehler, R.E. et al: In Vivo Measurement of Hepatic Iodine Concentration Using Fluorescent Excitation Analysis, Investigative Radiology, 11: 134-137, 1976.

79. Bloch, P. et al: Measurement of Lead Content of Children's Teeth in Situ by X-ray Fluorescence, Phys. Med. Biol. 20:56-63, Jan. 1977.

80. Loewinger, E. et al: In Vivo X-ray Fluorescence Measurements as a Diagnostic Tool, Phys. Med. Biol. 20: 142, Jan. 1977.

81. Hayes, M.: Techniques of Evaluation of Nuclear Medicine Instrumentation, Critical Reviews in Clinical Radiology and Nuclear Medicine. 6: 31-55, 1975.

82. Erickson, J.J. et al: Applications of a CAMAC Data Acquisition System to Problems in Nuclear Medicine, USAEC CONF 730267, Oak Ridge, Tenn., 1973, pp. 173-182.

83. Brill, A.B. et al: Computer Programs Used in a Nuclear Medicine Clinic and Research Laboratory. In ref. 1, pp. 123-145.

84. Brill, A.B. et al: Evaluation of Ge(Li) Detectors for Radioisotope Scanning and Activation Analysis Studies. In Semiconductor Detectors in the Future of Nuclear Medicine, New York, Society of Nuclear Medicine, 1971, pp. 114-130.

85. Beck, R.N. et al: A Theory of Optimum Utilization of all Detected Radiation. In Semiconductor Detectors in Medicine, USAEC CONF-731321, 1973, pp. 87-106.

86. Brill, A.B. et al: CAMAC Applications in Nuclear Medicine at Vanderbilt: Present Status and Future Plans. Proceedings of IEEE Nuclear Science Symposium, 1973.

1017905

87. Watts, J.: Methods for Quantitative Assay of Radioactivity in Man: Total Body and Regional Distributions. Ph.D. Dissertation, Vanderbilt University, 1971.

88. Sorenson, J.: Quantitative Measurement of Radioactivity in Vivo by Whole Body Counting. In ref. 15, pp. 312-349.

89. Patton, J.A. et al: Differentiation Between Malignant and Benign Solitary Thyroid Nodules by Fluorescent Scanning. Journal of Nuclear Medicine 17: 17-21, Jan. 1976.

90. Berman, M.: The Application of Multicompartmental Analysis to Problems of Clinical Medicine. Ann. Int. Med. 68: 423, 1968.

91. Jones, J.: In Vivo Evaluation of Standard Man Model Dose Calculations Using Tc-99m Sulfur Colloid. Ph.D. Dissertation, Vanderbilt University, 1976.

92. Spencer, R. P. and Waldman, R.: Size and Positional Relationships Between Thyroid Lobes in the Adult as Determined by Scintillation Scanning. Journal of Nuclear Medicine 6: 53-58, 1965.

93. Price, R.R. et al: Bone Mineral Content of the Lumbar Spine Using a Rectilinear Scanner. Physics in Medicine and Biology 22: 122, Jan. 1977.

94. Paton, J.A. et al: A Mosaic Intrinsic Germanium Radioisotope Scanning Device with Longitudinal Section Scanning Capability. In ref. 9.

95. Anger, H.O.: Tomography and Other Depth-Discrimination Techniques. In ref. 15, pp. 62-101.

96. Bell, P.R. et al: A Scanning System with Two Data Channels. Data Reduction and Display. In ref. 2, pp. 109-123.

97. Brooks, R.A. and Di Chiro, G.: Principles of Computer Assisted Tomography (CAT) in Radiographic and Radioisotopic Imaging. Phys. Med. Biol. 21, 689-737, 1976.

98. Kuhl, D.E., Edwards, R.Q., Ricci, A.B. et al: The Mark IV System for Radionuclide Computed Tomography of the Brain. Radiology 121: 405-413, 1976.

99. Rollo, F.D., Farmer, R.E., Shames, D.M.: Computer Assisted Technique for Evaluating Performance of Scintillation Cameras. In ref. 4, pp. 181-193.

1017906

100. Padikal, T.N., Ashare, A.B., Kereiakes, J.G.: Field Uniformity Correction Benefits or Pitfalls? Journal of Nuclear Medicine. 171: 653-656, 1976.

101. Spector, S.S., Brookman, V.A., Klystra, C. et al: Analysis and Corrections of Spatial Distortions Produced by the Gamma Camera. J. Nucl. Med. 13: 307-312, 1972.

102. Sorenson, J.A.: Methods of Correcting Anger Camera Dead Time Losses. J. Nucl. Med. 17: 137-141, 1976.

103. Hamamoto, K., Torizuka, K., Mukai, T. et al: Usefulness of Computer Scintigraphy for Detecting Liver Tumor with Ga-67 Citrate and the Scintillation Camera. J. Nucl. Med. 13: 667-672, 1972.

104. Williams, L.E., Ponto, R.A., Goldberg, J.T. et al: A Dual Camera-Dual Isotope Data Acquisition System for Nuclear Medicine Studies. In ref. 3, pp. 123-132.

105. Berman, D.S., Salel, A.F., DeNardo, G.L. et al: Clinical Assessment of Left Ventricular Regional Contraction Patterns and Ejection Fraction by High Resolution Gated Scintigraphy. J. Nucl. Med. 16: 865-874, 1975.

106. Bacharach, S.C., Green, M.V., Borer, J.S. et al: A Real-Time System for Multi-Image Gated Cardiac Studies. J. Nucl. Med. 18: 79-84, 1977.

107. Green, M.V., Ostrow, H.G., Douglas, M.A. et al: Clinical Assessment of Scintigraphic Angiography. J. Nucl. Med. 16: 95-98, 1975.

108. Todd-Pokropek, A.E., and Pizer, S.M.: Displays in Scintigraphy. In ref. 9.

109. Sebern, M.J., Horgan, J.D., Meade, R.C.: Minicomputer Enhancement of Scintillation Camera Images Using Fast Fourier Transform TEchniques. J. Nucl. Med. 17: 647-657, 1976.

110. Goris, M.L., Daspit, S.G., McLaughlin, P. et al: Interpolative Background Subtraction. J. Nucl. Med. 17: 744-747, 1976.

111. Brill, A.B., Erickson, J.J.: Factors Affecting the Collection and Analysis of Radiotracer Images. Seminars in Nuclear Medicine III. 285-3000, 1973.

112. Nickles, R.J., Holden, J.E., Kiuru, A.J. et al: Inclusion of Physiological Data into Computerized Nuclear Medicine Dynamic Studies. J. Nucl. Med. 17: 297-300, 1976.

1017907

113. Toyama, H., Iio, M., Lisaka, J. et al: Color Functional Images of the Ceerebral Blood Flow. J. Nucl. Med. 17: 953-958, 1976.

114. Brill, A.B., Richardson, P., Erickson, J.J. et al: The Use of Video Systems for Acquisitions and Display of Static and Dynamic Function Images. In ref. 2, pp. 359-368.

115. Carlson, J.C.: Grayscale Distortion of Computer Displays in Brain Imaging. In ref. 3, pp. 233-238.

116. Ronai, P.M. et al: Computer Analysis of Regional Cerebral Perfusion, A Critical Analysis. In ref. 11, Vol. 2, pp. 51-71.

117. McLaughlin, W.T., Price, D.D., Butler, T., and Scheibe, P.O.: An Update of the Computer Analysis Cephaloangioscintigraphy Data. In ref. 5, pp. 138-154.

118. Holman, B.L., Concepts and Clinical Utility of Cerebral Blood Flow. Seminars in Nucl. Med. 6: 233-252, 1976.

119. Lassen, N.A.: Intra-Arterial Methods for Measurement of Cerebral Blood Flow in Man. Chap. 18, C.N.,S. Investigation with Radionuclides, Ed. by Gilson, J.A. and Smoak,W.M.,Jr., C. Thomas, 1971.

120. Hurley, P.J. et al: A Computerized System for Rapid Evaluation of Thyroid Function. J. Clin, Endoc. & Metab. 34: 54, 1972.

121. Atkins, H.L. et al: Measurement of Thyroid Uptake of Technetium 99m Measured by the Gamma Camera and Computer. Amer. J. Roentgenol. 118: 831, 1973.

122. Moller, T., et al: Computer Evaluation of Thyroid Scans in Clinical Routine, In ref. 8, Vol. 2, pp. 519-528.

123. Sprawls, P.: Digital Computer Interpretation of Radioisotope Distribution Patterns. J. Nucl. Med. 10: 681, 1969.

124. Alpert, N.M., Correia, J.A., McKusick, K.A. et al: A Simple Functional Image of Lung Ventilation-Mean Transit Time, In ref. 5, pp. 161-171.

125. Loken, M.K. et al: Techniques of Nuclear Medicine for Evaluation of Lung Function. CRC Crit. Rev. Clin. Radiol. Nucl. Med. 5: 337, 1974.

126. Greenleaf, J.F. et al: Computer Acquisition, Analysis, and Display of Scintiscanner Data for Determination of Spatial Distribution of Blood Flow, In ref. 1, pp. 61-83.

1017908

127. Secker-Walker, R.H. and Evens, R.G.: The Clinical Application of Computers in Ventilation-Perfusion Studies. In Progress in Nuclear Medicine, Vol. 3, pp. 166-193, Karger, Basel & Univ. Park Press, Baltimore, 1973.

128. Ivancevic, D. et al: Computer Analysis of Radiocardiograms of Patients with Intra-Cardiac Shunts, In ref. 11, Vol. 2, pp. 229-250.

129. Kirch, D. et al: Quantification of Cardiac Valvular Regurgitation. In ref. 11, Vol. 2, pp. 271-283.

130. Zierler, K.L.: The Cardiovascular System in Compartment, Pools & Spaces. USAEC Symp. Series #11: 265-281, 1967.

131. Pierson, R.N. et al: Radiocardiography in Clinical Cardiology. Seminars in Nucl. Med. 7: 85-100, 1977.

132. Luig, H. et al: Non-Invasive Determination of Volume-Equivalent Curves of the Left Ventricle. In ref. 11, Vol. 2, pp. 207-217.

133. Steele, P.P. et al: Evaluation of Central Circulatory Dynamics with the Scintillation Probe. In ref. 11, Vol. 2, pp. 219-227.

134. Harris, L.D. et al: A Technique for the Detection of Asynergistic Motion in the Left Ventricle. Computers and Biomedical Research 7: 380-394, 1974.

135. Agress, H. et al: Functional Imaging Methodology: Recent Clinical and Research Applications. In ref. 13, pp. 189-208.

136. Bassingthwaite, J.B. et al: Flow and Diffusion in the Myocardium Modelling of the Convection-Diffusion Interrelationships Governing the Use of Solute Washout for Estimating Blood Flow. In ref. 3, pp. 1-10.

137. Klocke, F.J., and Wittenberg, S.M.: Methodological Considerations in Inert Gas Measurements of Coronary Blood Flow. In Myocardial Blood Flow in Man. pp. 121-135, Maseri (ed) Minerva Medica, 1972.

138. Kirk, G.A. et al: Particulate Myocardial Perfusion Scintigraphy: Its Clinical Usefullness in the Evaluation of Coronary Artery Disease. Seminars in Nucl. Med. 7: 67-84, 1977.

139. Hamilton, G.W. et al: Myocardial Perfusion Imaging with Tc-99m or in 113m Macroaggregated Albumin. Am. Heart J. 89: 708, 1975.

1017909

140. Botvinick, E.H. et al: Noninvasive Quantitation of Myocardial Infarction with TEchnetium 99m Pyrophosphate. Circ. 52: 909-915, 1975.

141. Parkey, R.W. et al: Myocardial Imaging with TEchnetium 99m Phosphates. Seminars in Nucl. Med. 7: 15-28, 1977.

142. Christie, J.H. and Chaudhuri, T.K.: Measurements of Hepatic Blood Flow. Seminars in Nucl. Med. 2: 97-107, 1972.

143. Rosenthal, L.: The Application of Radioiodinated Rose Bengal and Colloidal Radiogold in the Detection of Hepatobiliary Disease, W.H. Green, Inc., St. Louis, Mo., 1969.

144. Britton, K.E. et al: Computer-Assisted Blood Background Subtraction (CABBS) Hepatography with 131 I- and 123 I-Bromosulphthalein (BSP), IAEA, In ref. 11, Vol. 1, pp. 157-171.

145. Snaider, J., et al: Data Processing in Liver Scintigraphy. In ref. 8, Vol. 2, pp. 97-108.

146. Amman, W.W. and Vaknine, R.: Structure Analysis - A New Method for Evaluating Scintigrams. In ref. 13, pp. 66-79.

147. DiPaola, R. et al: Factor Analysis and Scintigraphy. In ref. 13, pp. 91-123.

148. Hollenberg, N.K. et al: Assessment of Intrarenal Perfusion with Radioxenon: A Critical Review of Analytical Factors and their Implication in Man. Seminars in Nucl. Med. 6: 193-216, 1976.

149. Peters, P.E. et al: Measurement of Renal Blood Flow by Means of Radioactive Water Labelled with O^{15}. In ref. 19, pp. 27-36.

150. Bianchi, C.: Measurement of the GFR. In ref. 22, Chap. 3.

151. Atkins, H.L. et al: The Technetium - DTPA Renal Study. In ref. 8, Vol. II, pp. 251-262.

152. Ponto, R.A. et al: Dual Isotope Renal Clearance Studies Using a Scintillation Camera. In ref. 21, pp. 302-309.

153. Brown, N.J.G., and Britton, K.E.: The Theory of Renography and Analysis of Results. In ref. 19, pp. 315-324.

154. Blaufox, M.D. and Wedeen, R.P.: The Normal Renogram. In ref. 22, Chap. 7.

1017910

155. Conway, J.J.: Direct and Indirect Radionuclide Cystography. Seminars in Nucl. Med. 4: 197-211, 1974.

156. Hilson, A.J.W. et al: Quantitative Assessment of Renal Transplant Perfusion in the Post Operative Period. Proc. of the 7th SNM Computer Council Mtg. 1977 (In Press).

157. Price, R.R. et al: Deconvolution Analysis of Transplant Renograms. Proc. of the 7th SNM, Computer Council Mtg., 1977 (In Press).

158. Biomedical Computing Technology Information Center, ORNL, P.O. Box X, Oak Ridge, Tennessee 37830.

159. Standard Nuclear Instrumentation Modules - Adopted by AEC NIM Comm. July 1974. TID-20893 (Ref. 4), Prepared by L. Costrell, NBS. U.S. A.E.C., Washington, D.C. 20545.

160. CAMAC Tutorial Issue, IEEE Transactions on Nuclear Science. NS-20, No. 2, p. 3-71, April 1973.

161. Digest of the Fourth International Conference on Medical Physics. Physics in Canada 32, July 1976. R.R. Price, et al. Bone Mineral Content of the Lumbar Spine using a Rectilinear Scanner, p. 95.

162. Mazess, R.B., Witt, R.M., Peppler, W.W., et al: Progress in Photon Absorptiometric Determination of Bone Mineral and Body Composition. Proc. ERDA X - and Gamma-Ray Symp. Ann Arbor (Conf. 760539) P. 111, (1976).

163. Gose, E.E. et al: Object Detection in Multiple Images. Proceedings of 2nd Int. Cong. on Pattern REcognition, pp. 531-537, 1974.

164. Kaufman, L., Gamsu, G., Savoca, C., et al: Measurement of Absolute Lung Density by Compton-Scatter Densitometry IEEE Trans. Nucl. Sci. NS-23: 599, 1976.

165. Arnold, J.S.: Dynamic Studies of the Hepatobiliary System. Proc. of the 7th SNM Computer Council Mtg., 1977 (In Press).

166. Line, B.R. et al: An Algorithm for the Prediction of Regional Gas Partial Pressures and Blood Content from Scintigraphic and Physiologic Data Using an Alveolar Gas Exchange Model. Proc. of the 7th SNM Computer Council Mtg., 1977 (In Press).

167. Paras, P.: Quality Assurance in Nuclear Medicine. In ref. 9 (In Press).

1017911

168. Tobin, M. et al: Computer Processing of Nuclear Medicine in Vitro Studies Incorporating Quality Control. Proc. of the 7th SNM Computer Council Mtg., 1977 (In Press).

169. Vossepoel, A.M. and Pauwels, E.K.J.: Integration of a Nuclear Medicine Computer System into a Hospital Information System. Proc. of the 7th SNM Computer Council Mtg., 1977 (In Press).

170. Goddard, J. et al: Atraumatic Cerebral Blood Flow Estimation in Man. In Clinical Blood Flow Estimation. Chap. 26, J. Woodcock (ed), Putman Medical Publishing Co., Ltd., London, 1976.

171. Cohn, S.H., and Palmer, H.E.: Recent advances in whole-body counting: A review. J. Nucl. Med. and Biol. 1, 155-165, 1974.

172. Price, R.R. et al: Estimation of Radioactive Content of Body Organs Combining Direct Measurements and Distribution Models. In Assessment of Radioactive Contamination in Man. Proceedings of IAEA Symposium. Stockholm, 1971, p. 45-59, IAEA, Vienna.

173. Price, R.R., et al: Analysis of Cardiac Function and Regional Myocardial Blood Flow Using Radioisotopic and Radiographic Images. Proc. IVth Int. Conf. on Information Processing in Scintigraphy. Orsay (1975), pp. 136-163.

174. Freedman, G. et al: A correction method for high-count-rate quantitative radionuclide angiography. Radiology 104: 713-715, 1972.

175. Adams, R. et al: Dead Time Correction in Quantitative Nuclear Cardiology, Section 8.7 in Ref. 161.

176. Sorenson, J.A.: Methods of correcting anger camera dead time losses. J. Nucl. Med. 17: 137-141, 1976.

177. Report of the Task Group on Reference Man. ICRP No. 23, Pergamon Press, Oxford, England, 1975, p. 196-200.

178. Nordyke, R.A. and Kulikowski, C.W. A comparison of methods for the automated diagnosis of thyroid dysfunction. Comput. Biomed. Res. 4: 374-389, 1971.

179. Jeffrey, H.J. and Ossario, P.G.: A New Technique for Implementing Human Knowledge and Abilities on the Computer. Tech. Rep. 76-4. SIS Dept., Vanderbilt University, Nashville, Tennessee.

180. J. D. Johannes: Automatic Thyroid Diagnosis via Simulation of Physician Judgement Doctoral Dissertation, Vanderbilt University, Department of Systems and Information Sciences, August 1977.

1017912

181. West, J.B.: Ventilation/Blood Flow and Gas Exchange. F. A. Davis Co., Philadelphia, 1965.

182. Alpert, N.M. et al: Initial assessment of a simple functional image of ventilation. J. Nucl. Med. 17: 88-92, 1976.

183. Loken, M.K. et al: Radioisotope Studies Evaluating Lung Function in Clinical Uses of Radionuclides: Critical Comparison with other techniques. Oak Ridge Technical Info. Center, p. 506-521, 1971.

184. Wagner, H.N., Jr. et al: Computer-assisted cinematic displays in nuclear medicine. J. Nucl. Med. 18: 615, 1977.

185. Bosnakovic, B. et al: Dual isotope method for diagnosis of intracardiac shunts. J. Nucl. Med. 14: 514-521, 1973.

186. Vetter, H. et al: The disappearance rate of colloidal radial gold from the circulation and its application to the estimation of liver blood flow in normal and cirrhotic subjects. J. Clin. Invest. 33: 1594, 1954.

187. Taplin, G.V., Meredith, O.M., and Kade, H.: The Radioisotope Renogram. USAEC Report, UCLA-388, June 1955.

188. Sapirstein, L.A., Vidt, D.G., Mandel, M.J. and Hanusek, G.: Volumes of distribution and clearances of intravenously injected creatinine in the dog. Am. J. Physiol. 181: 330, 1955.

189. Donath, A.: The simultaneous determination in children of glomerular filtration rate and effective renal plasma flow by the single injection clearance tecnique. Acta Pediatr. Scand. 6: 512, 1974.

190. Grünfeld, J.P., Sabto, J., Bankir, L. and Funk-Brentano, J.L. Methods for measurement of renal blood flow in man. Sem. Nucl. Med. 4: 39, 1974.

191. Raynaud, C.: A technique for the quantitative measurement of the function of each kidney. Sem. Nucl. Med. 4: 51, 1974.

192. Britton, K.E. and Brown, N.J.G.: Clinical Renography. Lloyd-Lake, London, 1971.

193. Britton, K.E. and Brown, N.J.G.: The clinical use of C.A.B.B.S. Renography. Br. J. Radiology 41: 570, 1968.

194. Price, R.R., Branch, R., Romage, A., Touya, J.J. and Brill, A.B.: Deconvolution analysis of transplant renograms. Proceedings of the Society of Nuclear Medicine Computer Council Meeting, Atlanta, Georgia, January 1977 (in press).

1017913

195. Lassen, N.A. and Ingvar, D.H.: The blood flow of the cerebral cortex determined by radioactive ^{85}krypton. Experentia 17: 42, 1961.

196. Ingvar, D.H. and Lassen, N.,A.: Quantitative determination of regional cerebral blood flow in man. Lancet 2: 806, 1961.

197. Hoedt-Rasmussen, K.: "Regional Cerebral Blood Flow. The Intra-Arterial Method." Munksgaard, Copenhagen, 1967.

198. Wyper, D.J., Rowan, J.D.: "Regional Cerebral Blood Flow Maps in Clinical Blood Flow Measurements." Edited by John Woodcock, Sector Publ. Limited, London, 1976.

199. Sapirstein, L.A.: Regional blood flow by fractional distribution of indicators. Am. J. Physiol. 193: 161, 1958.

200. Touya, J.J., and Goddard, J., Radionuclide Brain Angiography in "Medicina Nuclear" Ed. by H. Gotta (in press).

201. Ronai, P.N., O'Reilly, R.J., and Collins, P.J.: Computer Analysis of Regional Cerebral Perfusion--A Critical Clinical Analysis. IAEA Symposium on Dynamic Studies with Radioisotopes in Medicine, Knoxville, Tennessee, IAEA/SM-185/9, July 15-19, 1974, Vol. II, p. 51.

202. Wiener, S.M., Borkat, F.R. and Floyd, M.: Functional imaging: A method of analysis and display using regional rate constants. J. Nucl. Med. 15: 65, 1974.

203. Natarajan, T.K., Natarajan and Wagner, J.H.N.: Functional Images of the Lungs "Dynamic Studies with Radioisotopes in Medicine." Proc. Symp. of IAEA, Knoxville, Vol. II, 357, 1974.

204. Budinger, T.F., DeLand, F.H., Duggan, H.E., Bouz, J.J., Hoop, B., McLaughlin, W.T. and Weber, P.M.: Dynamic Time-Dependent Analysis and Static Three-Dimensional Imaging Procedures for Computer Assisted CNS Studies. In "Noninvasive Brain Imaging: Computed Tomography and Radionuclides." Edited by DeBlanc, Jr., H.J. and Sorenson, J.A., p. 45. Published by the Society of Nuclear Medicine, New York, 1975.

205. Kuhl, D.E., Edwards, R.R.: Image separation radioisotope scanning. Radiology 80: 653, 1963.

206. Derenzo, S.E., Zaklad, H., Budinger, T.F.: Analytical study of high resolution positron ring detector system for transaxial reconstruction tomography. J. Nucl. Med. 16: 1166, 1975.

1017914

207. Cho, Z.H., Cohen, M.D., Singh, M., Ericksson, L., Chan, J., and MacDonald: Performance and Evaluation of the Circular Ring Transverse Axial Positron Camera (CRTAPC)* Proc. Symp. of IAEA, Los Angeles, Vol. I, p. 269, 1977.

208. Phelps, M.E., Hoffman, E.J., and Kuhl, D.E.: Physiologic Tomography (PT). A New Approach to In-vivo Measure of metabolism and Physiological Function. "Medical Radionuclide Imaging" Proc. Symp. of IAEA, Los Angeles, Vol. I, 233, 1977.

1017915

ORO-2401-120

THE JOURNAL OF NUCLEAR MEDICINE

June 1978, Volume 19, Number 6
Page 742

SERIAL THYROID IODIDE CONTENT IN HYPERTHYROID PATIENTS TREATED WITH RADIOIODINE. C.S. Lee, J.A. Patton, A.B. Brill.
Vanderbilt University Medical Center. Nashville, TN.

Sixty consecutive hyperthyroid patients referred to the Nuclear Medicine Division for radioiodine therapy were studied using quantitative x-ray fluorescent scanning techniques to measure the thyroidal iodide pool. Forty-eight patients returned for serial follow-up studies after the radioiodine dose. Follow-ups were correlated with estimations of T3, T4, and TSH radioimmunoassays.

Initial iodide content before radioiodine therapy was generally normal or high in untreated cases and in those who had previously received drug therapy. Iodide content was low in those who had undergone previous surgery or radioiodine therapy.

Follow-up studies show a sharp decline of iodide content in the first 3 months post-therapy irrespective of type of management before or after radioiodine. Thereafter, the values tended to fluctuate at a low to low-normal level. In patients who ultimately became hypothyroid, a low iodide value preceeded the rise in TSH and the drop in T4.

It was shown that when thyroid iodide content is 2 mg. or less between 2-3 months after radioiodine therapy, there is close to 90% chance of developing hypothyroidism in the next 4-5 months. The low iodide value generally preceeded biochemical changes of hypothyroidism by an average of 2 months. Also, contrary to expectation, the mean initial iodide content was found to be no different in the untreated group compared to the drug-treated group.

Supported in part by ERDA Contract EY-76-S-05-2401

1017916

19

PART 2 of 4

REPOSITORY Oak Ridge Ops. Office

COLLECTION Reading Room

BOX No. RHA Shipment 9162 Box 6-7

FOLDER New York Times FOIA Requests 88-91

OFFICE OF CHIEF COUNSEL
FILE
No papers will be removed herefrom
without special authority

— 88-91 —

1017917

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

JUN 2 0 1972

Vanderbilt University
ATTN: Miss Carolyn Gregory
Research Coordinator
Nashville, Tennessee 37203

REASSIGNMENT OF CONTRACT FOR ADMINISTRATION

Gentlemen:

Effective June 15, 1972, the following listed AEC contracts with your organization have been reassigned from the Laboratory and University Division to the Research Contracts, Procedures and Reports Branch, Contract Division, for administration:

Contract No. AT-(40-1)-4021
Contract No. AT-(40-1)-4025
Contract No. AT-(40-1)-4065

All future correspondence and other documents pertaining to the above contract(s) should be addressed as follows:

A. H. Frost, Jr., Chief
Research Contracts, Procedures and Reports Branch
Contract Division
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

Requests for funding changes, renewal of contracts, and term extension must be in writing and be endorsed by the appropriate administrative official(s) before submission to the AEC for approval. All Financial reports should also be endorsed by the appropriate administrative official of your organization.

Please advise appropriate personnel within your organization, accordingly.

Sincerely,

Ralph Elson, Director
Contract Division
Oak Ridge Operations

COPY

ACR:AHF

CC: Office of Chief Counsel
Finance Division

0017918

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 20

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 29th day of December, 1972, effective the 1st day of August, 1972, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the U. S. ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 19 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954, as amended, and Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date September 30, 1973, is changed to July 31, 1973.

2. In ARTICLE III - CONSIDERATION, the amount $187,958 is increased to $242,125.

3. Appendix "A", attached hereto, shall constitute the Contract Appendix "A" applicable to the period indicated thereon.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: U. S. ATOMIC ENERGY COMMISSION

BY: David E. Miller

TITLE: David E. Miller, Deputy Director
Contract Division, OSR

VANDERBILT UNIVERSITY

BY:

TITLE: Assoc. Vice Chancellor for Medical Affairs for Operations and Fiscal Planning

1017919

APPENDIX "A"

VANDERBILT UNIVERSITY
CONTRACT NO. AT-(40-1)-2401

For the contract period August 1, 1972 through July 31, 1973.

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue development of analytical techniques and instrumentation for the quantitation of isotope metabolism, primarily in the clinical situation. Studies will be made using radioactive and stable isotopes as tracers, the role of high-resolution measurement systems such as germanium and silicon detectors for patient diagnosis and sosimetry, use of computer-controlled scanning systems including quantitative regional kinetic analyses for Iron-59 and Calcium-47, with improvement of scanning.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 25% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages (Includes Fringe Benefits): $ 42,425

(2) Equipment to be Purchased or Fabricated by the Contractor: $ 4,600

a Equipment Estimated to Cost Less than $1,000:

Electronic Components (Maintenance and Repairs)

b Equipment Estimated to Cost in Excess of $1,000:

Electronic Components (Interface Development)

(3) Travel: $ 1,200

Domestic ---------- $ 1,200
Foreign ---------- $ 0

1017920

(4) Other Direct Costs: $ 9,602

(5) Indirect Costs (Based on a predetermined rate of 44% of Salaries and Wages and Fringe Benefits): $ 18,667

(b) Items, if any, Significant to the Performance of this Contract, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

(1) Items to be Contributed by the Contractor:

Part-time salaries, related overhead, and employee benefits for five Research Associates, (Johnston, Baglan, D. Patton, Price, and J. Patton) - approximately 26% of time. (One of the Research Associate's (Price) salary is supported by the V. A.)

(2) Items to be Contributed by the Government:

None

(c) Time or Effort of Principal Investigator Contributed by Contractor, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

All costs including salary, fringe benefits, and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $76,494; the Commission will pay 85% of the acutal costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and Article B-XXIX. The estimated AEC Support Cost for the contract period stated in this Appendix "A" is $65,000.

The estimated AEC Support Cost if funded as follows:

(a) Estimated unexpended balance from the prior periods $ 0

(b) New funds for the current period: $ 65,000

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article B-XI.

1017921

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERISTY
Modification No. 19

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 27th day of September, 1972, effective the 1st day of August, 1972, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the U. S. ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 18 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; and (b) the restatement of the contract in its entirety, with the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954, as amended, and Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices) is hereby further amended to read in its entirety, effective as of the date of this modification, as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall, to the best of its ability, furnish personnel, facilities, equipment, materials, supplies, and services, except such as are furnished by the Government, necessary for the performance of the research provided for in Appendix "A", and shall perform the research and report thereon pursuant to the provisions of this contract. It is understood that Appendix "A", a guide to the performance of this contract, may be deviated from by the Contractor subject to the specific requirements of this contract.

(b) This work shall be conducted under the direction of Dr. A. B. Brill or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

1017922

ARTICLE II - THE PERIOD OF PERFORMANCE

The period of performance under this contract shall commence on February 1, 1970, and expire on September 30, 1973. Performance may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder, the Commission shall furnish the equipment, supplies, materials, and services, if any, listed in Article A-II(b)(2) and pay the Contractor the sum of $187,958, hereinafter called the "Support Ceiling," which sum shall be subject to adjustment as hereinafter provided.

(b) Payments to the Contractor shall equal the "Cumulative Support Cost" of performance of this contract, as the term "Cumulative Support Cost" is defined in Article B-XXIX[1/]; Provided, however, And notwithstanding any other provision of this contract, that the Government's monetary liability under this contract shall not exceed the Support Ceiling specified in (a) above. The Commission shall not pay more than the Support Ceiling or an amount equal to the Cumulative Support Cost,

1/ The term "Cumulative Support Cost" refers to the cost of items under A-II(a) of Appendix "A", for the initial contract period plus any extension periods, that may be properly chargeable to the AEC. If proportionate cost-sharing is involved, the Support Cost is the AEC's share of such costs, and it does not include the cost of items excluded from Article A-II(a), such as items to be contributed solely by the Contractor or property to be furnished by the Government. Charges to the AEC will be reported after the conclusion of each contract period set forth in Appendix "A" (generally an annual period); in addition to the limitations on charges to the AEC provided for by this Article III, charges to the AEC for a specified contract period may not exceed 110 percent of the estimated Support Cost for that contract period except as approved by the AEC (see Article B-XXX). The estimated Support Cost for each pertinent period of contract performance will be set forth in Article A-III. If Article A-III of Appendix "A" provides that the cost of the items listed under Article A-II(a) is to be proportionately shared by the parties, the charges to the AEC shall be determined by applying the AEC's sharing percentage set forth in Article A-III to the cost for items under Article A-II(a) incurred during the specified contract period; such charges to the AEC shall also be subject to the 110 percent limitation mentioned above as well as to the provisions of this Article III.

1017923

whichever is less. The Contractor shall be obligated to perform under this contract throughout the agreed-upon period of performance, and to bear all costs which the Commission has not agreed to pay; Provided, however, That the Contractor shall have the right to cease to perform the research provided for in this contract, upon written notice to the Commission to that effect, at any time when or after the Cumulative Support Cost equals or exceeds the Support Ceiling.

(c) The Support Ceiling specified in (a) above may be increased unilaterally by the Commission by written notice to the Contractor and may be increased or decreased by written agreement of the parties (whether or not by formal modification to this contract). In the event the stated period of contract performance is extended, the Support Ceiling will be revised to reflect any increased Commission support for the extended period or periods.

(d) Upon termination, or expiration of the total period of performance, the Contractor shall promptly refund to the Commission (or make such disposition as the Commission may in writing direct) any sums paid by the Commission to the Contractor under this contract, through direct payment or under letter of credit, in excess of the Cumulative Support Cost incurred in performance under the contract.

ARTICLE IV - GOVERNMENT PROPERTY

The following items of property procured or fabricated by the Contractor are hereby listed as "Government Property":

(1) Card Reader
(2) 717 Printer
(3) Printer Control
(4) Card Reader Control.

ARTICLE V - APPENDICES

Appendix "A", Appendix "B"--General Provisions, and Appendix "C"--Statement of Costs, are hereby attached to and made a part of this contract.

ARTICLE VI - CIVIL RIGHTS ACT OF 1964

The Contractor agrees to comply with the Atomic Energy Commission's Regulation (Part 4 of Title 10, Chapter 1, Code of Federal Regulations), as amended, effectuating the provisions of Title VI of the Civil Rights Act of 1964.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: U. S. ATOMIC ENERGY COMMISSION

BY: David E. Miller

TITLE: David E. Miller, Deputy Director
Contract Division, ORO

VANDERBILT UNIVERSITY

BY: Paul Gazzerro Jr.

TITLE: Assistant Director of Medical Affairs for Operations and Fiscal Planning

I, G. G. Hamilton, certify that I am the Treasurer of the Contractor named under this contract; that Paul Gazzerro, Jr. who signed this contract on behalf of said Contractor was then Assistant Director of Medical Affairs for Operations & Fiscal Planning of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

(Attester) (Title) (Signatory) (Title)

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt University

Contract No.: AT-(40-1)-2401

APPENDIX "A"

VANDERBILT UNIVERSITY

CONTRACT NO. AT-(40-1)-2401

For the Contract Period August 1, 1972 through September 30, 1973.

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct a study of radioisotope distributing and radiation absorbed dose from medical radionuclides.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 25% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1)	Salaries and Wages and Employee Benefits:	$ 5,132
(2)	Equipment to be Purchased or Fabricated by the Contractor:	$ 0
	a Equipment Estimated to Cost Less than $1,000:	
	None	
	b Equipment Estimated to Cost in Excess of $1,000:	
	None	
(3)	Travel:	$ 250
	Domestic ---------- $250	
	Foreign ---------- None	
(4)	Other Direct Costs:	$ 3,193
(5)	Indirect Costs: (Based on a predetermined rate of 44% of Salaries and Wages and Employee Benefits)	$ 2,258

(b) Items, if any, Significant to the Performance of this Contract, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

1017926

(1) Items to be Contributed by the Contractor:

All costs of the Principal Investigator including salary, employee benefits and related overhead.

(2) Items to be Contributed by the Government:

None

(c) Time or Effort of Principal Investigator Contributed by Contractor, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

None under this paragraph

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $10,833; the Commission will pay 100% of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and Article B-XXIX. The estimated AEC Support Cost for the contract period stated in this Appendix "A" is $10,833.

The estimated AEC Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior periods	$ 0
(b) New funds for the current period	$10,833

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article B-XI.

1017927

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"--GENERAL PROVISIONS

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the U. S. Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer, except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS, AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, and consistent with the requirements of OMB Circular No. A-21, revised, as constituted with the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a contractor contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit the Commission to determine the extent of the contribution. If professional staff members are included under Article A-II(b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of Section J.7.b. of OMB Circular No. A-21, revised.

(d) The Commission shall at all reasonable times be afforded access to the premises and to those books and records and to related

1017928

correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, in accordance with the retention requirements referenced in Article B-XVIII, Examination of Records by Comptroller General, of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish six (6) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder, or subsequent thereto, the Contractor, its employees, or its subcontractors, may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery; such invention or discovery shall be promptly reported to the Commission for patent review and possible filing of a patent application, and such information shall thereafter be withheld from public disclosure for a period of four (4) months unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence of Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party

1017929

accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable

1017930

material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of Sections (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders, other than purchase orders for standard commercial items, provisions making this

1017931

article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

(e) With respect to any U. S. Patent Application filed by the Contractor on any contract invention or discovery made or conceived in the course of the contract, the Contractor will incorporate in the first paragraph of the U. S. Patent Application the following statement:

> "The invention described herein was made in the course of, or under, a contract (if desired, may substitute contract with identifying number) with the U. S. Atomic Energy Commission."

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this Section (a) and Section (b) of this Article B-IX, title to all material, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto: And, provided, There is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to Sections (b), (c), (d), (e), and (f) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

1017932

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by the Commission, the Contractor shall use Government property only for the purposes of this contract: Provided, however, That the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use: (1) Does not interfere with its work under this contract, (2) is not prohibited by provisions of the other Federal agreements, and (3) is promptly reported by the Contractor to the Commission under this contract.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

1017933

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination, the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the Notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under Section (c) shall be governed by the contract cost principles and procedures in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3) in effect on the date of this contract, except that if the Contractor is not an educational institution any costs claimed, agreed to, or determined pursuant to Sections

1017934

(c) or (e) hereof shall be in accordance with Subpart 1-15.2 of the Federal Procurement Regulations (41 CFR 1-15.2) in effect on the date of this contract.

(e) Subject to the provisions of Section (c) above, and subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the

1017935

Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of 45 percent of the new funds as set forth in Article A-III(b) of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional 45 percent of the new funds as set forth in Article A-III(b) of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the new funds set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC support cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report required by Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the AEC support cost and evidencing the Contractor's performance under the contract and compliance by the Contractor with the patent provisions of this contract.

1017936

(b) The payments made pursuant to Section (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Fiscal Requirements Manual, Part VI, Section 1020, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the new funds as set forth in Article A-III(b) of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Fiscal Requirements Manual, Part VI, Section 1020, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a payment voucher on letter of credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the new funds as set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC support cost for the pertinent period and evidencing the Contractor's performance under the contract.

(2) The Commission reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to

1017937

subsection (c)(1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following article is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor (41 CFR, ch. 60).)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity article.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity article, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto,

1017938

and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity article of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of Sections (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT--OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder:

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess

1017939

of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of Section (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of Section (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by Section (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of Section (b).

(d) Subcontracts. The Contractor shall insert Sections (a) through (d) of this article in all subcontracts and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for

1017940

the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in Section (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract, if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XVIII - EXAMINATION OF RECORDS BY COMPTROLLER GENERAL

(a) This article is applicable if the amount of this contract exceeds $2,500 and was entered into by means of negotiation, including small business restricted advertising, but is not applicable if this contract was entered into by means of formal advertising.

(b) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three (3) years after final payment under

1017941

this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(c) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three (3) years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (1) purchase orders not exceeding $2,500 and (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(d) The periods of access and examination described in (b) and (c) above, for records which relate to (1) appeals under the "Disputes" article of this contract, (2) litigation or the settlement of claims arising out of the performance of this contract, or (3) costs and expenses of this contract as to which exception has been taken by the Comptroller General or any of his duly authorized representatives, shall continue until such appeals, litigation, claims, or exceptions have been disposed of.

(e) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestice source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B),

1017942

components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Research Contracts, Procedures, and Reports Branch, Contract Division, Oak Ridge Operations Office, U. S. Atomic Energy Commission, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term.

1017943

Technical reports, preprints, and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three (3) months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of Equipment Purchased or Fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $200 purchased or fabricated by the Contractor when title to such equipment is vested in the Contractor pursuant to the Grant Act (Public Law 85-934)--omit any items appearing in Article IV--and submit a report thereof within three (3) months after the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $1,000, they will be listed individually. Where individual items cost $200 to $1,000, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "six motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established with the certified statement required by Article B-XXIX of this contract.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer for each separate trip regardless of whether funds for such travel are contained in an approved budget. Foreign travel is defined as any travel outside of Canada and the United States and its territories and possessions.

1017944

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Services Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

(The following article is applicable if this contract exceeds $5,000.)

(a) It is the policy of the Government to award contracts to labor surplus area concerns that (1) have been certified by the Secretary of Labor (hereafter referred to as certified-eligible concerns with first or second preferences) regarding the employment of a proportionate number of disadvantaged individuals and have agreed to perform substantially (i) in or near sections of concentrated unemployment or underemployment or in persistent or substantial labor surplus areas or (ii) in other areas of the United States, respectively, or (2) are noncertified concerns which have agreed to perform substantially in persistent or substantial labor surplus areas, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy.

(b) In complying with Section (a) of this article and with Section (b) of the article of this contract entitled "Utilization of Small Business Concerns" the Contractor in placing its subcontracts shall observe the following order of preference: (1) Certified-eligible concerns with a first preference which are also small business concerns; (2) other certified-eligible concerns with a first preference; (3) certified-eligible concerns with a second preference which are also small business concerns; (4) other certified-eligible concerns with a second preference; (5) persistent or substantial labor surplus area concerns which are also small business concerns; (6) other persistent or substantial labor surplus area concerns; and (7) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

1017945

ARTICLE B-XXVI - UTILIZATION OF MINORITY BUSINESS ENTERPRISES

(a) It is the policy of the Government that minority business enterprises shall have the maximum practicable opportunity to participate in the performance of Government contracts.

(b) The Contractor agrees to use its best efforts to carry out this policy in the award of its subcontracts to the fullest extent consistent with the efficient performance of this contract. As used in this contract, the term "minority business enterprise" means a business, at least 50 percent of which is owned by minority group members or, in case of publicly owned businesses, at least 51 percent of the stock of which is owned by minority group members. For the purposes of this definition, minority group members are Negroes, Spanish-speaking American persons, American-Orientals, American-Indians, American-Eskimos, and American-Aleuts. Contractors may rely on written representations by subcontractors regarding their status as minority business enterprises in lieu of an independent investigation.

ARTICLE B-XXVII - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

ARTICLE B-XXVIII - LISTING OF EMPLOYMENT OPENINGS

(This article is applicable pursuant to 41 CFR 50-250 if this contract is for $10,000 or more and will generate 400 or more man-days of employment.)

(a) The Contractor agrees that all employment openings of the Contractor which exist at the time of the execution of this contract and those which occur during the performance of this contract, including

1017946

those not generated by this contract and including those occurring at an establishment of the Contractor other than the one wherein the contract is being performed but excluding those of independently operated corporate affiliates, shall, to the maximum extent feasible, be offered for listing at an appropriate local office of the state employment service system wherein the opening occurs and to provide such periodic reports to such local office regarding employment openings and hires as may be required.

(b) Listing of employment openings with the employment service system pursuant to this article shall be made at least concurrently with the use of any other recruitment source or effort and shall involve only the normal obligations which attach to the placing of a bona fide job order but does not require the hiring of any job applicant by the employment service system.

(c) The periodic reports required by Section (a) of this article shall be filed at least quarterly with the appropriate local office or, where the Contractor has more than one establishment in a state, with the central office of that state employment service. Such reports shall indicate for each establishment the number of individuals who were hired during the reporting period and the number of hires who were veterans who served in the Armed Forces on or after August 5, 1964, and who received other than a dishonorable discharge. The Contractor shall maintain copies of the reports submitted until the expiration of one year after final payment under the contract, during which time they shall be made available, upon request, for examination by any authorized representatives of the Contracting Officer or of the Secretary of Labor.

(d) Whenever the Contractor becomes contractually bound to the listing provisions of this article, it shall advise the employment service system in each state wherein it has establishments of the name and location of each such establishment in the state. As long as the Contractor is contractually bound to these provisions and has so advised the state employment service system, there is no need to advise the state system of subsequent contracts. The Contractor may advise the state systems when it is no longer bound by this contract article.

(e) This article does not apply (1) to the listing of employment openings which occur outside the 50 States, the District of Columbia, the Commonwealth of Puerto Rico, Guam, and the Virgin Islands, and (2) to contracts with state and local governments.

(f) This article does not apply to openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement. This exclusion does not apply to a particular opening once an employer decides

1017947

to consider applicants outside its own organization or employer-union arrangement for that opening.

(g) As used in this article:

(1) "All employment openings" includes, but is not limited to, openings which occur in the following job categories: Production and nonproduction; plant and office; laborers and mechanics; supervisory and nonsupervisory; technical; and executive, administrative, and professional openings which are compensated on a salary basis of less than $18,000 per year. This term includes full-time employment, temporary employment of more than 3 days' duration, and part-time employment.

(2) "Appropriate office of the state employment service system" means the local office of the Federal-State national system of public employment offices with assigned responsibility for serving the area of the establishment where the employment opening is to be filled, including the District of Columbia, the Commonwealth of Puerto Rico, Guam, and the Virgin Islands.

(3) "Openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement" means employment openings for which no consideration will be given to persons outside the Contractor's organization (including any affiliates, subsidiaries, and parent companies) or outside of a special hiring arrangement which is part of the customary and traditional employment relationship which exists between the Contractor and representatives of its employees and includes any openings which the Contractor proposes to fill from regularly established "recall" or "rehire" lists or from union hiring halls.

(4) "Man-day of employment" means any day during which an employee performs more than one hour of work.

(h) The Contractor agrees to place this article (excluding this Section (h)) in any subcontract directly under this contract.

1017948

ARTICLE B-XXIX - DETERMINATION OF SUPPORT COSTS

(a) The term "support cost" as used in this contract means the Commission's share[1/] of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to the AEC in accordance with (b) below. The term "cumulative support cost" as used in this contract means the total of the support cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three (3) months after the end of each contract period set forth in Appendix "A", and within three (3) months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of OMB Circular No. A-21, revised, as constituted on the effective commencement date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The certified statement should be in agreement with the institution's financial records and shall reflect only expenditures actually made during the period covered, including transfers from inventory. It shall not include commitments, as a part of such expenditures, for goods

1/ In those cases in which there is no proportionate sharing of costs, the Commission's "share" will be 100 percent. With respect to any period in which proportionate cost sharing is applicable pursuant to Article A-III, it is understood that the support cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110 percent of the estimated support cost set forth in Article A-III for that contract period except as otherwise approved by the AEC.

1017949

or services on order, but not received or those received but not paid for unless the Contractor is operating under an established and consistently applied system of accrual accounting. If this is the case, the certified statement shall be footnoted. A combination of accrual and cash accounting for cost accumulation and reporting purposes shall not be used. The renewal proposal budget should be footnoted to show the estimated amount of outstanding commitments for property at the end of the current contract period. The certified statement contains a space in which should be inserted the actual amount of outstanding commitments for property at the end of the period covered by the statement. This commitment amount is for information only and is not a part of the expenditure calculation. The Contractor understands that the Commission expects to rely on this certified statement for determining the support cost for the pertinent contract period. With respect to any period in which proportionate cost sharing is applicable, the support cost for the pertinent period will be determined by applying the percentage figure included in Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to the AEC shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Article B-II(c) to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(1).

ARTICLE B-XXX - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain the Commission's approval for:

(1) A change of the principal investigator, co-investigator, or other key people as might be named in this contract or continuation of the research work for any one period in excess of three (3) months without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining Commission approval; however, a representative of the institution shall consult with the appropriate AEC Headquarters program representative if the principal investigator plans to, or becomes aware that he will devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work and what modification to the contract, if any, may be appropriate.

(2) No change in the phenomenon or phenomena under study; i.e., broad category of the research under the contract shall be

1017950

made without the specific written approval of the AEC; ordinarily, such changes, if approved by the AEC, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in the contract: Provided, It gives the AEC prompt notification of such changes; and the Contractor may continue to follow the new objectives while the Commission determines whether it wishes to continue the program under the changed approach. Significant changes in methods or procedures employed in performing the research should be reported in the first technical progress report issued subsequent to the changes.

(3) Acquisition of:

(i) An item of equipment not itemized in Appendix "A", the cost of which is $1,000 or more. Approval is not required if the equipment is merely a different model of an item listed in Appendix "A"; or

(ii) An item or items of equipment the cost of which will cause the total equipment dollar level shown in Article A-II(a) of the contract to be in excess of 125 percent thereof (if plant and capital equipment funds are provided for the acquisition of equipment with title to be vested in the Government, the total cost of such shall not exceed the amount provided for such equipment unless prior AEC approval has been obtained).

(4) Purchase of any general-purpose equipment, such as office furniture, air conditioning, etc., not specifically provided for in Appendix "A".

(5) Incurring costs for items set forth in Article A-II(a), during the pertinent contract period stated in Appendix "A", in excess of 110 percent of the total estimated cost specified in Article A-III. Charges to the Commission for any such costs incurred with the approval of the Commission shall also be subject to the limitations of Article III.

(6) Any proposed foreign travel (see Article B-XXII).

(7) Expenditures for domestic travel in excess of $500, or 125 percent of the amount shown in Article A-II(a) for such travel, whichever is greater.

(8) Acquisition of excess personal property.

1017951

APPENDIX "C"

U. S. ATOMIC ENERGY COMMISSION

STATEMENT OF COSTS

1. Name and address of Contractor: _____

_____.

2. Contract Number: _____.

3. Beginning and ending date of pertinent contract period: _____

_____.

4. Costs incurred during the pertinent contract period. [List only those costs which are to be reimbursed by the AEC or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.]

Cost categories[1/]	Amount
a. Salaries and wages----------	$_____
b. Equipment---------- [List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from AEC.]	_____
c. Travel [show amounts for both foreign and domestic. If none, state none.]	$_____
Domestic----------	_____
Foreign----------	_____
d. Other direct costs----------	_____
e. Total direct expenditures----------	_____
f. Indirect charges---------- [Indicate percent and expenditures to which percent is applied.]	$_____

5. Total costs for items under Article A-II(a) for pertinent contract period---------- _____

1/ The listing of categories should be consistent with the itemization in Appendix "A".

1017952

6. Support cost for the pertinent contract period set forth in Appendix "A", as defined in Article B-XXIX of the contract, chargeable to AEC for the pertinent contract period (percent of total costs using percent shown in Article A-III of Appendix "A" for pertinent period of contract)---------- $_____

7. Cumulative support cost (support cost under this statement plus support cost for previous periods of the contract)---------- $_____

8. Accumulated support ceiling in Article III of the contract---------- $_____

9. The difference between lines 7 and 8---------- $_____

10. Provide information regarding contributions by the Contractor of items listed in Article A-II(b) of Appendix "A" during pertinent contract period. State the extent of the Contractor's actual contribution, the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II(b), e.g., time, dollar, etc.---------- $_____

11. Actual outstanding commitments for property at the end of the period covered by this statement---------- $_____

I hereby certify that this report is true and correct to the best of my knowledge and belief and that the costs listed herein were incurred in connection with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein.

_____
(Name and title of authorized representative)

_____ _____
(Signature) (Date)

1017953

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1017954

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc Countries or other countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

1017955

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

(2) The transmittals to countries listed in Section 2, above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but

1017956

which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosures of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1017957

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 18

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 21st day of September, 1971, effective the 1st day of August, 1971, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 17 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date July 31, 1971, is changed to July 31, 1972.

2. In ARTICLE III - CONSIDERATION, the amount $112,125 is increased to $177,125.

3. Appendix "A", attached hereto, shall constitute the Contract Appendix "A" applicable to the period indicated thereon.

4. In ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS, the Appendix "B" attached hereto is made applicable to the contract effective as of the effective date of this modification.

1017958

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Richard B. Martin

TITLE: Acting [illegible] Division

VANDERBILT UNIVERSITY

BY: George Kaludis

TITLE: Vice Chancellor for Operations and Fiscal Planning

I, G. G. Halliburton, certify that I am the Treasurer of the Contractor named under this contract; that George Kaludis who signed this contract on behalf of said Contractor was then V. Ch. for Oper.&Fisc.Planning of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt University

Contract No.: AT-(40-1)-2401

G. G. Halliburton

G.G.Halliburton
Treasurer

APPENDIX "A"

For the Contract Period August 1, 1971 through July 31, 1972.

ARTICLE A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue studies utilizing a low level body counter and clinical applications of activation analysis. Calibration of a whole body scanner will be completed for high-energy radionuclides, organ distribution and turnover will be determined for these in the normal and diseased subject. Definition and monitoring of cesium-137 levels in a stable population will be continued, and special research will be directed to ^{59}Fe metabolism in hematological disease, ^{47}Ca turnover in Paget's disease in relation to calcitonin, and studies will be carried out on ^{67}Ga for tumor localization.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 25% of his time or effort to the project.

ARTICLE A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages: $35,418

5 Research Associates
Research Assistant
Technician
Secretary

(2) Employee Benefits: 2,181

(3) Materials, Services, and Supplies: 14,793

Computer supplies and time, electronic components, maintenance contracts, radioisotopes, stable isotopes, chemicals, equipment rental, and patient participation.

(4) Equipment to be Purchased or Fabricated by the Contractor: 6,600

a Equipment Estimated to Cost Less than $1,000:

None

b Equipment Estimated to Cost in Excess of $1,000:

Computer memory addition

(5) Travel: 1,500

(6) Publications: 700

(7) Indirect Costs (Fixed at 39% of Salaries and Wages and employee benefits): $14,664

(b) Items, if any, Significant to the Performance of this Contract, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

(1) Items to be Contributed by the Contractor:

a All costs of the Principal Investigator including employee benefits and related overhead.

b Salaries, employee benefits, and related overhead for two Research Associates (Baglan and D. Patton).

c It is recognized that the support of the following personnel will be contributed from other sources:

Co-Investigator (R. E. Johnston) - Veterans Administration
Research Associate (R. Price) - Veterans Administration
Research Assistant (J. A. Patton) - Hertz Foundation

(2) Items to be Contributed by the Government:

None

(c) Time or Effort of Principal Investigator(s) Contributed by Contractor, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

None under this paragraph

ARTICLE A-III The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $75,856; the Commission will pay 86% of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and Article B-XXVII. The estimated AEC Support Cost for the contract period stated in this Appendix "A" is $65,000.

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the U. S. Atomic Energy Commission or any duly authorized representative thereof, including the contracting officer, except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS, AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, and consistent with the requirements of BoB Circular No. A-21 as constituted on the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a contractor contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit the Commission to determine the extent of the contribution. If professional staff members are included under Article A-II(b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of section J.7.b. of BoB Circular No. A-21.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish six (6) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withehld from public disclosure if it discloses an invention or discovery which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence of Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material

1017963

becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kinds.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the

1017964

right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders, other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters

1017965

Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

(e) With respect to any U. S. Patent Application filed by the Contractor on any contract invention or discovery made or conceived in the course of the contract, the Contractor will incorporate in the first paragraph of the U. S. Patent Application the following statement:

> "The invention described herein was made in the course of, or under, a contract (if desired, may substitute contract with identifying number) with the U. S. Atomic Energy Commission."

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto: And, provided, There is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), (e), and (f) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of

1017966

Government property. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by the Commission, the Contractor shall use Government property only for the purposes of this contract: Provided, however, That the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use (1) does not interfere with its work under this contract, (2) is not prohibited by provisions of the other Federal agreements, and (3) is promptly reported by the Contractor to the Commission under this contract.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therfor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

1017967

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by AECPR 9-15.50 (41 CFR 9-15.50).

1017968

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any oustanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to

1017969

the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of 45 percent of the estimated AEC Support Cost as set forth in Article A-III of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional 45 percent of the estimated AEC Support Cost as set forth in Article A-III of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the currently estimated AEC Support Cost for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC Support Cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report required by Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the AEC Support Cost and evidencing the Contractor's performance under the contract.

1017970

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Department Circular No. 1075, as revised April 10, 1969, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the estimated AEC Support Cost as set forth in Article A-II of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Department Circular No. 1075, as revised April 10, 1969, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a Payment Voucher on Letter of Credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the currently estimated AEC Support Cost for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC Support Cost for the pertinent period and evidencing the Contractor's performance under the contract.

(2) The Commission reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of

1017971

consideration provided for in Article III or is taken pursuant to subparagraph (c)(1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor (41 CFR, ch. 60).)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity clause.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the

1017972

rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity clause of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interest of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT--OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder:

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any

1017973

laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy the Contractor mails or otherwise furnishes

1017974

to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Comptroller general of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

1017975

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (1) purchase orders not exceeding $2,500 and (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

1017976

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Laboratory and University Division, U. S. Atomic Energy Commission, Oak Ridge Operations Office, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports, preprints, and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications

1017977

issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of Equipment Purchased or Fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated by the Contractor when title to such equipment is vested in the Contractor pursuant to the Grant Act (Public Law 85-934)--omit any items appearing in Article V--and submit a report thereof within three months after the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $1,000, they will be listed individually. Where individual items cost $100 to $1,000, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "six motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates. This report may be submitted in conjunction with the certified statement required by Article B-XXVII of this contract.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Services Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

(The following clause is applicable if this contract exceeds $5,000.)

(a) It is the policy of the Government to award contracts to labor surplus area concerns that (1) have been certified by the Secretary of Labor (hereafter referred to as certified-eligible concerns with first or second preferences) regarding the employment of a proportionate number of disadvantaged individuals and have agreed to perform substantially (i) in or near sections of concentrated unemployment or underemployment or in persistent or substantial labor surplus areas or (ii) in

1017978

other areas of the United States, respectively, or (2) are noncertified concerns which have agreed to perform substantially in persistent or substantial labor surplus areas, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy.

(b) In complying with paragraph (a) of this article and with paragraph (b) of the article of this contract entitled "Utilization of Small Business Concerns" the Contractor in placing its subcontracts shall observe the following order of preference: (1) Certified-eligible concerns with a first preference which are also small business concerns; (2) other certified-eligible concerns with a first preference; (3) certified-eligible concerns with a second preference which are also small business concerns; (4) other certified-eligible concerns with a second preference; (5) persistent or substantial labor surplus area concerns which are also small business concerns; (6) other persistent or substantial labor surplus area concerns; and (7) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

1017979

ARTICLE B-XXVII - DETERMINATION OF SUPPORT COSTS

(a) The term "Support Cost" as used in this contract means the Commission's share1/ of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to the AEC in accordance with (b) below. The term "Cumulative Support Cost" as used in this contract means the total of the Support Cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three months after the end of each contract period set forth in Appendix "A", and within three months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor and also signed by the principal investigator, showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of the Bureau of the Budget Circular A-21, as constituted on the effective commencement date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The Contractor understands that the Commission expects to rely on this certified statement for determining the Support Cost for the pertinent contract period. With respect to any period in which

---

1/ In those cases in which there is no proportionate sharing of costs, the Commission's "share" will be 100 percent. With respect to any period in which proportionate cost-sharing is applicable pursuant to Article A-III, it is understood that the Support Cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110 percent of the estimated Support Cost set forth in Article A-III for that contract period except as otherwise approved by the AEC.

1017980

proportionate cost-sharing is applicable, the Support Cost for the pertinent period will be determined by applying the percentage figure included in Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to the AEC shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Article B-II(c) to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(1).

ARTICLE B-XXVIII - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain the Commission's approval for:

(1) Acquisition of:

(i) An item of equipment, not itemized in Appendix "A", involving an acquisition cost in excess of $1,000 or 2 percent of the total estimated cost specified in A-III of Appendix "A", whichever is greater, unless such equipment is merely a different model of an item listed in Appendix "A". (When plant and equipment funds are provided for the acquisition of Government property, the Headquarters Program Divisions may require, in specific cases, that such funds be used only for acquiring the equipment designated in Article V, unless prior AEC approval has been obtained.)

(ii) Any equipment not itemized in Appendix "A", the acquisition cost of which will cause the equipment dollar level shown in Article A-II(a) of Appendix "A" to be increased by $500 or more. (If plant and equipment funds are provided for the acquisition of equipment, with title to be vested in the Government, the total cost of such equipment acquisitions shall not exceed the amount budgeted for such equipment unless prior AEC approval has been obtained.)

(2) Purchase of any general-purpose equipment, such as office furniture or air conditioning, not specifically provided for in Appendix "A", except that purchased without cost to the Commission.

(3) Incurring costs during the pertinent contract period set forth in Appendix "A", for items set forth in Article A-II(a), in excess of 110 percent of the estimated cost specified in Article A-III for the pertinent contract period; charges to the Commission for any such costs incurred with the approval of the Commission shall also be subject to the limitations of Article III.

1017981

(4) A change of the principal investigator, or continuation of the research work without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining Commission approval; however, the principal investigator shall consult with the appropriate AEC Headquarters program representative if he plans to, or becomes aware that he will, devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work.

(b) No change in the phenomenon or phenomena under study; i.e., broad category of the research under this contract, shall be made without the specific written approval of the Commission; ordinarily, such changes, if approved by the Commission, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in this contract, provided it gives the Commission prompt notification of such changes; and the Contractor may continue to follow the new objectives while the Commission determines whether it wishes to continue the program under the changed approach.

1017982

7-1-69

APPENDIX "C"

U. S. ATOMIC ENERGY COMMISSION

STATEMENT OF COSTS

1. Name and address of Contractor: _____

_____

2. Contract Number: _____

3. Beginning and ending date of pertinent contract period: _____

_____

4. Costs incurred during the pertinent contract period. [List only those costs which are to be reimbursed by the AEC or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.]

Cost categories[1/]	Amount
a. Salaries and wages	$_____
[List personnel included in Article A-II(a) of Appendix "A" in same detail as shown in the Contractor's payroll distribution or time and attendance records.]	
b. Supplies and materials	_____
[Show in same detail as in Appendix "A".]	
c. Equipment	_____
[List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from AEC.]	
d. Publications	_____
e. Travel	_____

1/ The listing of categories should be consistent with the itemization in Appendix "A".

1017983

Cost categories	Amount
f. Other _____	_____
[List separately each type of cost included in this category.]	
g. Total Direct Expenditures _____	$_____
h. Indirect Charges _____	_____
[Indicate percent and expenditures to which percent is applied.]	
5. Total Costs for items under Article A-II(a) for pertinent contract period _____	_____
6. Support Cost for the pertinent contract period set forth in Appendix "A", as defined in Article B-XXVII of the contract, chargeable to AEC for the pertinent contract period (percent of Total Costs using percent shown in Article A-III of Appendix "A" for pertinent period of contract). _____	_____
7. Cumulative Support Cost (Support Cost under this statement plus Support Cost for previous periods of the contract). _____	_____
8. Accumulated Support Ceiling in Article III of the contract. _____	_____
9. Provide information regarding contributions by the Contractor of items listed in Article A-II(b) of Appendix "A" during pertinent contract period. State the extent of the Contractor's actual contribution; the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II(b); e.g., time, dollar, etc. _____	
_____	_____

I hereby certify that this report is true and correct to the best of my knowledge and belief and that the costs listed herein were incurred in connection with the performance of the research provided for under

10179 84

this contract and in accordance with the terms and conditions set forth therein.

_____

(Name and title of principal investigator)

_____ _____

(Signature) (Date)

_____

(Name and title of business officer)

_____ _____

(Signature) (Date)

1017985

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1017986

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc Countries or other countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

1017987

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

(2) The transmittals to countries listed in Section 2, above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are <u>not</u> available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

1017988

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosures of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1017989

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 17

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 19th day of October, 1970, effective the 1st day of August, 1970, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 16 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date July 31, 1970, is changed to July 31, 1971.

2. In ARTICLE III - CONSIDERATION, the amount $37,375 is increased to $112,125.

3. Appendix "A", attached hereto, shall constitute the Contract Appendix "A" applicable to the period indicated thereon.

4. In Appendix "B", Section (a) of ARTICLE B-III - PUBLICATION OF RESULTS, Section (c)(1) of ARTICLE B-XI - PAYMENTS, and Section (a) of ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS are revised to read as shown on the attached pages nos. B-2, B-10, and B-16 dated August 19, 1970.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

Herman M. Roth

TITLE: Director
Laboratory and University Division

VANDERBILT UNIVERSITY

BY: James S. Worley

James S. Worley

TITLE: Associate Provost

I, Robert A. McGaw, certify that I am the Secretary of the corporation named as the Contractor herein; that James S. Worley who signed this contract on behalf of the Contractor was then Associate Provost of said corporation; that said contract was duly signed for and on behalf of said corporation by authority of its governing body and is within the scope of its corporate powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said corporation.

(Corporate Seal) Robert A. McGaw

Contractor: VANDERBILT UNIVERSITY

Contract No.: AT-(40-1)-2401, Mod. 17

1017991

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period August 1, 1970 through July 31, 1971.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue radioisotope medical studies with the whole body counter and clinical applications of activation analysis to include theoretical and applied studies on adult and fetal radiation dose exposures from radionuclides. Extension will be made of the RADOS Library on radiation dosimetry, and biological and physical data will be added for nuclides in common use. The program will include data analysis on Iodine-131-labeled human serum albumin, Xenon-133 will be used in blood flow and pulmonary function studies, Iron-59 in haematological disorders. Studies on fetal exposures will be conducted with radioisotopes, and an evaluation will be made of the adequacy of different means for the diminution of fetal dose from Iodine-131 due to planned or accidental exposures. Stable tracer studies with Chromium-50-labeled red blood cells will be made related to intracranial hemorrhage and hyaline membrane disease in the newborn. Iron absorption and transport studies will be continued.

Dr. A. B. Brill, Principal Investigator, expects to devote approximately 25% of his time or effort to the contract work.

A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages: $46,051.00

Principal Investigator
5 Research Associates
Radioisotope Operations Technician
Secretary

(2) Employee Benefits: 2,961.00

(3) Materials, Services, and Supplies: 14,136.00

Computer supplies and time, electronic components, maintenance contracts, equipment rental, radioisotopes, stable isotopes, and chemicals.

(4) Equipment: 4,000.00

a Equipment Estimated to Cost Less than $1,000:

None

b Equipment Estimated to Cost in Excess of $1,000:

Co-axial Ge(li) detector

1017992

(5) Publications: $ 350.00

(6) Travel: 1,500.00

(7) Indirect Costs (Fixed at 37.5% of Salaries and Wages plus Fringe Benefits): 18,380.00

(b) Items, if any, Significant to the Performance of this Contract but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

(1) Items to be Contributed by the Contractor:

Part-time salaries, related overhead, and employee benefits for:

4 Research Associates and a Research Assistant as indicated in the contractor's proposal dated October 31, 1969 - Approximately 30% of time (One of the Research Associates is devoting 5% of his time to the project whose salary is supported by the PHS and the Research Assistant who is devoting approximately 50% of his time is a Hertz Foundation Fellow).

(2) Items to be Contributed by the Government:

None

(c) Time or Effort of Principal Investigator(s) Contributed by the Contractor, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

None under this paragraph

A-III The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $87,378.00; the Commission will pay 86% of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and Article B-XXVII. The estimated AEC Support Cost for the contract period stated in this Appendix "A" is $74,750.00.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish six (6) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence of Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material

1017994

required by Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the AEC Support Cost and evidencing the Contractor's performance under the contract.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Department Circular No. 1075, as revised April 10, 1969, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the estimated AEC Support Cost as set forth in Article A-III of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Department Circular No. 1075, as revised April 10, 1969, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a Payment Voucher on Letter of Credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the currently estimated AEC Support Cost for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC Support Cost for the pertinent period and evidencing the Contractor's performance under the contract.

1017995

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Laboratory and University Division, U. S. Atomic Energy Commission, Oak Ridge Operations Office, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports, preprints and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and

1017996

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 16

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 1st day of May, 1970, effective the 1st day of February, 1970, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 15 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; and (b) the restatement of the contract in its entirety, with the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby further amended to read in its entirety, effective as of the effective date of this modification, as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall, to the best of its ability, furnish personnel, facilities, equipment, materials, supplies, and services, except such as are furnished by the Government, necessary for the performance of the research provided for in Appendix "A" hereto, and shall perform the research and report thereon pursuant to the provisions of this contract. It is understood that Appendix "A", a guide to the performance of this contract, may be deviated from by the Contractor subject to the specific requirements of this contract.

(b) This work shall be conducted under the direction of Dr. A. B. Brill or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

1017997

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period of performance under this contract shall commence on February 1, 1970, and expire on July 31, 1970. Performance may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder, the Commission shall furnish the equipment, supplies, materials, and services, if any, listed in Article A-II(b)(2) and pay the Contractor the sum of $37,375.00, hereinafter called the "Support Ceiling," which sum shall be subject to adjustment as hereinafter provided. The Commission shall also transfer to the Contractor title to the following items of equipment: (1) Eight Crystals NAI (Tl), 1-1/2" x 1/2 and (2) Eight Photomultiplier Tubes.

(b) Payments to the Contractor shall equal the "Cumulative Support Cost" of performance of this contract, as the term "Cumulative Support Cost" is defined in Article B-XXVII[1/]; Provided, however, and notwithstanding any other provision of this contract, that the Government's monetary liability under this contract shall not exceed the Support Ceiling specified in (a) above. The Commission shall not pay more than the Support Ceiling or an amount equal to the Cumulative Support Cost, whichever is less. The Contractor shall be obligated to perform under this contract throughout the agreed-upon period of performance, and to bear all costs which the Commission has not agreed to pay; Provided, however, that the Contractor shall have the right to cease to perform the research provided for in this contract, upon written notice to the Commission to that effect, at any time when or after the Cumulative Support Cost equals or exceeds the Support Ceiling.

(c) The Support Ceiling specified in (a) above may be revised as the parties may mutually agree in writing. In the event the stated period of contract performance is extended, the Support Ceiling will be revised to reflect any increased Commission support for the extended period or periods.

(d) Upon termination, or expiration of the total period of performance, the Contractor shall promptly refund to the Commission any sums paid by the Commission to the Contractor under this contract,

---

1/ See NOTE on page 4.

through direct payment or under letter of credit, in excess of the Cumulative Support Cost incurred in performance under the contract.

ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS

Appendix "B", attached hereto and made a part hereof, sets forth additional general provisions of this contract.

ARTICLE V - GOVERNMENT PROPERTY

The following items of property procured or fabricated by the Contractor are hereby listed as "Government Property":

(1) Card Reader
(2) 717 Printer
(3) Printer Control
(4) Card Reader Control.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth
Herman M. Roth

TITLE: Director
Laboratory and University Division

VANDERBILT UNIVERSITY

BY: William W. Force
William W. Force

TITLE: Vice Chancellor for Business Affairs

I, Robert A. McGaw, certify that I am the Secretary of the corporation named as the Contractor herein; that William W. Force who signed this contract on behalf of the Contractor was then Vice Chan. for Bus. Affairs of said corporation; that said contract was duly signed for and on behalf of said corporation by authority of its governing body and is within the scope of its corporate powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said corporation.

(Corporate Seal) Robert A McLeod

Contractor: VANDERBILT UNIVERSITY

Contract No.: AT-(40-1)-2401, Mod. No. 16

NOTE: The term "Cumulative Support Cost" refers to the cost of items under A-II(a) of Appendix "A", for the initial contract period plus any extension periods, that may be properly chargeable to the AEC. If proportionate cost-sharing is involved, the Support Cost is the AEC's share of such costs, and it does not include the cost of items excluded from Article A-II(a), such as items to be contributed solely by the Contractor or property to be furnished by the Government. Charges to the AEC will be reported after the conclusion of each contract period set forth in Appendix "A" (generally an annual period); in addition to the limitations on charges to the AEC provided for by this Article III, charges to the AEC for a specified contract period may not exceed 110 percent of the estimated Support Cost for that contract period except as approved by the AEC (see Article B-XXVIII). The estimated Support Cost for each pertinent period of contract performance will be set forth in Article A-III. If Article A-III of Appendix "A" provides that the cost of the items listed under Article A-II(a) is to be proportionately shared by the parties, the charges to the AEC shall be determined by applying the AEC's sharing percentage set forth in Article A-III to the cost for items under Article A-II(a) incurred during the specified contract period; such charges to the AEC shall also be subject to the 110 percent limitation mentioned above as well as to the provisions of this Article III.

1018000

APPENDIX "A"

For the Contract Period February 1, 1970 through July 31, 1970.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue radioisotope medical studies with the whole body counter and clinical applications of activation analysis to include theoretical and applied studies on adult and fetal radiation dose exposures from radionuclides. Extension will be made of the RADOS Library on radiation dosimetry, and biological and physical data will be added for nuclides in common use. The program will include data analysis on Iodine-131-labeled human serum albumin, Xenon-133 will be used in blood flow and pulmonary function studies, Iron-59 in haematological disorders. Studies on fetal exposures will be conducted with radioisotopes, and an evaluation will be made of the adequacy of different means for the diminution of fetal dose from Iodine-131 due to planned or accidental exposures. Stable tracer studies with Chromium-50-labeled red blood cells will be made related to intracranial hemorrhage and hyaline membrane disease in the newborn. Iron absorption and transport studies will be continued.

The Principal Investigator expects to devote approximately 25% of his time or effort to the contract work.

A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1)	Salaries and Wages:	$18,584.00
	Dr. A. B. Brill, Principal Investigator 5 Research Associates 3 Research Assistants Radioisotope Operations Technician 2 Secretaries	
(2)	Employee Benefits:	1,368.00
(3)	Materials, Services, and Supplies:	11,391.00
	Computer supplies and time, electronic components, maintenance contracts, equipment rental, radioisotopes, stable isotopes, and chemicals.	
(4)	Equipment:	4,000.00
	Co-axial Ge(li) detector	
(5)	Publications:	100.00

(6) Travel: $ 750.00

(7) Indirect Costs (Fixed at 37.5% of Salaries and Wages plus Fringe Benefits): 7,482.00

(b) Items, if any, Significant to the Performance of this Contract but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

(1) Items to be Contributed by the Contractor:

Part-time salaries, related overhead, and employee benefits for:

3 Research Associates - Approximately 25% of time (One of the Research Associates is devoting 50% of his time to the project whose salary is supported by the Veterans Administration)

(2) Items to be Contributed by the Government:

None

(c) Time or Effort of Principal Investigator(s) Contributed by the Contractor, but Excluded from Computation of Support Cost and from Consideration in Proportioning Costs:

None under this paragraph

A-III The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $43,675.00; the Commission will pay 86% of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and Article B-XXVII. The estimated AEC support cost for the contract period stated in this Appendix "A" is $37,375.

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer, except for the purpose of deciding an appeal under the article entitled, "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, and consistent with the requirements of BOB Circular No. A-21 as constituted on the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a contract contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit the Commission to determine the extent of the contribution. If professional staff members are included under Article A-II (b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of Section J.7.b. of BOD Circular No. A-21.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion

1018003

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954 or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. Seven (7) copies of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish seven (7) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence of Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material

1018004

becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of

1018005

performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the

1018006

Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

(e) With respect to any U. S. Patent Application filed by the Contractor on any contract invention or discovery made or conceived in the course of the contract, the Contractor will incorporate in the first paragraph of the U. S. Patent Application the following statement:

> "The invention described herein was made in the course of, or under, a contract (if desired, may substitute contract with identifying number) with the U. S. Atomic Energy Commission."

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto and, provided there is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government Property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), (e), and (f) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

1018007

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by the Commission, the Contractor shall use Government property only for the purposes of this contract; provided, however, that the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use (1) does not interfere with its work under this contract, (2) is not prohibited by provisions of the other Federal agreements, and (3) is promptly reported by the Contractor to the Commission under this contract.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activites under other Federal research agreements as are

1018008

appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, determine on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

1018009

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by AECPR 9-15.50 (41 CFR 9-15.50).

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

1018010

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any dispute as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payment to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of forty-five percent of the estimated AEC Support Cost as set forth in Article A-III of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional forty-five percent of the estimated AEC Support Cost as set forth in Article A-III of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the currently estimated AEC Support Cost for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC Support Cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report

1018011

required by Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the AEC Support Cost and evidencing the Contractor's performance under the contract.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Department Circular No. 1075, Revised, of February 13, 1967, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the estimated AEC Support Cost as set forth in Article A-III of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Department Circular No. 1075, Revised, of February 13, 1967, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XVI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a Payment Voucher on Letter of Credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the currently estimated AEC Support Cost for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the AEC Support Cost for the pertinent period and evidencing the Contractor's performance under the contract.

1018012

(2) The Commission reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (c)(1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor (41 CFR, ch. 60).)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity clause.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

1018013

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity clause of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder:

1018014

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish

1018015

a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a coporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

1018016

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (i) purchase orders not exceeding $2,500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U.S. Code 10 a-d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

1018017

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish seven (7) copies of the following reports and renewal proposals, if any, addressed to the Laboratory and University Division, U. S. Atomic Energy Commission, Oak Ridge Operations Office, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and

10180 18

shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of Equipment Purchased or Fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated by the Contractor when title to such equipment is vested in the Contractor pursuant to the Grant Act (Public Law 85-934)--omit any items appearing in Article V--and submit a report thereof within three months after the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $1,000, they will be listed individually. Where individual items cost $100 to $1,000, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "six motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates. This report may be submitted in conjunction with the certified statement required by Article B-XXVII of this contract.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Services Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

1018019

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in or near concentrated unemployment or underemployment sections of States or in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy. In complying with the foregoing and with paragraph (b) of the clause of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (a) Certified-eligible concerns which are also small business concerns; (b) other certified-eligible concerns; (c) persistent labor surplus area concerns which are also small business concerns; (d) other persistent labor surplus area concerns; (e) substantial labor surplus area concerns which are also small business concerns; (f) other substantial labor surplus area concerns; and (g) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018020

ARTICLE B-XXVII - DETERMINATION OF SUPPORT COSTS

(a) The term "Support Cost" as used in this contract means the Commission's share[1/] of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to the AEC in accordance with (b) below. The term "Cumulative Support Cost" as used in this contract means the total of the Support Cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three months after the end of each contract period set forth in Appendix "A", and within three months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor and also signed by the principal investigator, showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of the Bureau of the Budget Circular A-21, as constituted on the effective commencment date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The Contractor understands that the Commission expects to rely on this certified statement for determining the Support Cost for the pertinent contract period. With respect to any period in which proportionate cost-sharing is applicable, the Support Cost for the pertinent period will be determined by applying the percentage figure included in

---

1/ In those cases in which there is no proportionate sharing of costs, the Commission's "share" will be 100%. With respect to any period in which proportionate cost-sharing is applicable pursuant to Article A-III, it is understood that the Support Cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110% of the estimated Support Cost set forth in Article A-III for that contract period except as otherwise approved by the AEC.

1018021

Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to the AEC shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Article B-II(c) to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(1).

ARTICLE B-XXVIII - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain the Commission's approval for:

(1) Acquisition of:

(i) An item of equipment, not itemized in Appendix "A", involving an acquisition cost in excess of $1,000 or 2 percent of the total estimated cost specified in A-III of Appendix "A", whichever is greater, unless such equipment is merely a different model of an item listed in Appendix "A". [When plant and equipment funds are provided for the acquisition of Government property, the Headquarters Program Divisions may require, in specific cases, that such funds be used only for acquiring the equipment designated in Article V, unless prior AEC approval has been obtained.]

(ii) Any equipment not itemized in Appendix "A", the acquisition cost of which will cause the equipment dollar level shown in Article A-II(a) of Appendix "A" to be increased by $500 or more. (If plant and equipment funds are provided for the acquisition of equipment, with title to be vested in the Government, the total cost of such equipment acquisitions shall not exceed the amount budgeted for such equipment unless prior AEC approval has been obtained.)

(2) Purchase of any general-purpose equipment, such as office furniture or air conditioning, not specifically provided for in Appendix "A", except that purchased without cost to the Commission.

(3) Incurring costs during the pertinent contract period set forth in Appendix "A", for items set forth in Article A-II(a), in excess of 110% of the estimated cost specified in Article A-III for the pertinent contract period; charges to the Commission for any such costs incurred with the approval of the Commission shall also be subject to the limitations of Article III.

1018022

(4) A change of the principal investigator, or continuation of the research work without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining Commission approval; however, the principal investigator shall consult with the appropriate AEC Headquarters program representative if he plans to, or becomes aware that he will, devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work.

(b) No change in the phenomenon or phenomena under study; i.e., broad category of the research under this contract, shall be made without the specific written approval of the Commission; ordinarily, such changes, if approved by the Commission, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in this contract, provided it gives the Commission prompt notification of such changes; and the Contractor may continue to follow the new objectives while the Commission determines whether it wishes to continue the program under the changed approach.

1018023

APPENDIX "C"

U. S. ATOMIC ENERGY COMMISSION

STATEMENT OF COSTS

1. Name and address of Contractor: _____

_____

2. Contract number: _____

3. Beginning and ending date of pertinent contract period: _____

4. Costs incurred during the pertinent contract period. (List only those costs which are to be reimbursed by the AEC or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.)

Cost categories[1/]	Amount
a. Salaries and wages	
(List personnel included in Article A-II(a) of Appendix "A" in same detail as shown in the Contractor's payroll distribution or time and attendance records)	
b. Supplies and materials	
(Show in same detail as in Appendix "A".)	
c. Equipment	
(List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from AEC.)	
d. Publications	
e. Travel	

1/ The listing of categories should be consistent with the itemization in Appendix "A"

1018024

Cost Categories	Amount
f. Other _____	_____
(List separately each type of cost included in this category.)	
g. Total Direct Expenditures _____	_____
h. Indirect Charges _____	_____
(Indicate percent and expenditures to which percent is applied.)	

5. Total Costs for items under Article A-II(a) for pertinent contract period. _____

6. Support Cost for the pertinent contract period set forth in Appendix "A", as defined in Article B-XXVII of the contract, chargeable to AEC for the pertinent contract period (percent of Total Costs using percent shown in Article A-III of Appendix "A" for pertinent period of contract). _____

7. Cumulative Support Cost (Support Cost under this statement plus Support Cost for previous periods of the contract). _____

8. Accumulated Support Ceiling in Article III of the contract. _____

9. Provide information regarding contributions by the Contractor of items listed in Article A-II(b) of Appendix "A" during pertinent contract period. State the extent of the Contractor's actual contribution; the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II(b); e.g., time, dollar, etc. _____

I hereby certify that this report is true and correct to the best of my knowledge and belief and that the costs listed herein were incurred in

1018025

connection with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein.

_____

Name and title of principal investigator

_____ _____

Signature Date

_____

Name and title of business officer

_____ _____

Signature Date

1018026

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018027

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc or other countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

1018028

(2) The transmittals to countries listed in Section 2., above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosures of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018029

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 15

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 11th day of June, 1969, effective the 1st day of February, 1969, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 14 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; and (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby further amended as follows:

1. The date "January 31, 1969," as such appears in ARTICLE II - THE PERIOD FOR PERFORMANCE, is deleted and the date "January 31, 1970," is substituted therefor.

2. In ARTICLE III - CONSIDERATION, the following restatement of Paragraph (a) and establishment of a percentage of support for use in Paragraphs (b), (c), and (d) apply to the period February 1, 1969, through January 31, 1970:

> "(a) In full consideration of the Contractor's performance for the period commencing February 1, 1969, and expiring on January 31, 1970, the Commission shall pay to the Contractor the sum of $74,750.00, hereinafter called the 'Support Ceiling,' which sum shall be subject to adjustment as hereinafter provided."

1018030

The percentage for use in Paragraphs (b), (c), and (d) is 84%.

3. Appendix "A" attached hereto shall constitute the Contract Appendix "A" applicable to the period indicated thereon.

4. In ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS, the Appendix "B" attached hereto is made applicable to the contract effective as of the effective date of this modification.

5. The following items of property on loan to the Contractor are hereby listed as Government Property:

(a) Card Reader

(b) 717 Printer

(c) Printer Control

(d) Card Reader Control

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth

TITLE: Herman M. Roth
~~Director~~
Laboratory and University Division

VANDERBILT UNIVERSITY

BY: W. William Force

William W. Force

TITLE: Vice Chancellor for Business Affai

I, Robert A. McGaw, certify that I am the Secretary of the corporation named as the Contractor herein; that William W. Force who signed this contract on behalf of the Contractor was then Vice Chancellor for Business Affairs of said corporation; that said contract was duly signed for and on behalf of said corporation by authority of its governing body and is within the scope of its corporate powers.

1018031

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said corporation.

(Corporate Seal) Robert A McKay

Contractor: VANDERBILT UNIVERSITY

Contract No.: AT-(40-1)-2401, Mod. 15

1018032

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1969, through January 31, 1970.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue research with radioisotopes and utilization of the whole body counter with clinical applications of activation analysis to include improvement in equipment, integration of a computer into the systems, development for a scanner and scanning techniques and analysis techniques for evaluation of kinetic data. Determinations of the radiation absorbed dose subsequent to the use of selected radionuclides with emphasis on fetal organs and the central nervous system will be done. In addition the use of stable isotopes with subsequent in vitro neutron activation will be explored. Radiotracer studies in patients having significant gastrointestinal surgery and in familial periodic paralysis will also be made.

The Principal Investigator expects to devote approximately 25% of his time or effort to the work.

A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1)	Salaries and Wages:	$53,358.00
	Dr. A. B. Brill - Principal Investigator (25% of time) 10 Research Associates* (Approximately 55% of time) 3 Technical and clerical Personnel (As needed) * It is recognized that salaries of three Research Associates are provided from other sources.	
(2)	Employee Benefits:	3,022.00
(3)	Steel Room Modifications:	1,500.00
(4)	Supplies, Materials, and Services:	8,279.00
	Electronic components, chemicals, maintenance contracts, isotopes, computer and reactor time, and equipment rental.	
(5)	Publications:	850.00
(6)	Travel:	1,400.00
(7)	Indirect Costs (37.5% of Salaries and Wages, and Fringe Benefits):	21,143.00

1018033

(b) Items Significant to the Performance of This Contract, But Excluded From Computation of Total Cost and From Consideration in Proportioning Costs:

None

(c) Time or Effort of Principal Investigator To Be Contributed by Contractor:

None under this paragraph

A-III The total estimated project cost of A-II (a) above for the contract period stated above is $89,552.00.

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer, except for the purpose of deciding an appeal under the article entitled, "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, and consistent with the requirements of BOB Circular No. A-21 as constituted on the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a contractor contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit the Commission to determine the extent of the contribution. If professional staff members are included under Article A-II(b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of Section J.7.b. of BOB Circular No. A-21.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

1018035

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954 or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. Seven (7) copies of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish seven (7) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence of Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material

1018036

becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of

1018037

performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the

1018038

Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

(e) With respect to any U. S. Patent Application filed by the Contractor on any contract invention or discovery made or conceived in the course of the contract, the Contractor will incorporate in the first paragraph of the U. S. Patent Application the following statement:

> "The invention described herein was made in the course of, or under, a contract (if desired, may substitute contract with identifying number) with the U. S. Atomic Energy Commission."

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto and, provided there is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government Property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), (e), and (f) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

1018039

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by the Commission, the Contractor shall use Government property only for the purposes of this contract; provided, however, that the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use (1) does not interfere with its work under this contract, (2) is not prohibited by provisions of the other Federal agreements, and (3) is promptly reported by the Contractor to the Commission under this contract.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are

1018040

appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, determine on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

1018041

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by AECPR 9-15.50 (41 CFR 9-15.50).

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

1018042

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any dispute as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration prescribed in paragraph (a) of Article III of this contract as follows:

(1) Forty-five percent following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional forty-five percent upon receipt of a written request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the AEC support ceiling or AEC's share of currently estimated total project costs for the expiring period, whichever is less; a concluding payment for the pertinent period, if appropriate, will be made following submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final

1018043

report required by Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) All payments under this contract, except the first payment provided in (a) above, will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

(d) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Department Circular No. 1075, Revised, of February 13, 1967, under which payments to the Contractor with respect to the amount of consideration provided for in paragraph (a) of Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the amount of consideration provided for in said paragraph (a) of Article III will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Department Circular No. 1075, Revised, of February 13, 1967, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a Payment Voucher on Letter of Credit, in accordance with the procedure described above. If, following an annual report, the contract is extended for an additional period of performance, said concluding payment will similarly be paid for the expired period, and ten (10) percent will be retained with respect to the added period of performance.

1018044

(2) The Commission reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (d) (1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor (41 CFR, ch. 60).)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity clause.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

1018045

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity clause of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder:

1018046

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish

1018047

a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a coporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

1018048

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (i) purchase orders not exceeding $2,500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U.S. Code 10 a-d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purpose of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

1018049

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish seven (7) copies of the following reports and renewal proposals, if any, addressed to the Laboratory and University Division, U. S. Atomic Energy Commission, Oak Ridge Operations Office, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and

1018050

shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of Equipment Purchased or Fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated by the Contractor when title to such equipment is vested in the Contractor pursuant to the Grant Act (Public Law 85-934)--omit any items appearing in Article V--and submit a report thereof within three months after the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $1,000, they will be listed individually. Where individual items cost $100 to $1,000, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or six motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates. This report may be submitted in conjunction with the certified statement required by Article B-XXVII of this contract.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Services Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy. In complying with the foregoing and with paragraph (b) of the article of this contract entitled, "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (1) persistent labor surplus area concerns which are also small business concerns; (2) other persistent labor surplus area concerns; (3) substantial labor surplus area concerns which are also small business concerns; (4) other substantial labor surplus area concerns; and (5) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018052

ARTICLE B-XXVII - DETERMINATION OF TOTAL COSTS

(a) The term "total cost" as used in this contract means the sum of costs incurred by the Contractor for items included under Article A-II (a) of Appendix "A", which are in furtherance of the work hereunder, and may include the following: expenditures of cash, exclusive of cash payments relating to items included in the total cost of a prior period; the cost of material and supplies transferred from stores inventory; unpaid delivered orders for services, supplies, and equipment; unpaid undelivered orders (commitments) for items of equipment; unpaid delivered orders (commitments) for materials and supplies purchased in normal and reasonable quantities; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of this contract. Except as the parties may otherwise specifically agree in writing, total cost will apply separately to each annual (or lesser) period of performance. Total cost for a contract period shall be determined consistent with the principles of the Bureau of the Budget Circular A-21, as constituted on the effective commencement date of said period.

(b) Within three months after the end of each contract period and within three months after the expiration or termination of the contract, the Contractor shall furnish its certified statement, executed by an official of the Contractor and also signed by the principal investigator, showing the Contractor's total cost and evidencing its performance under the contract. The statement shall be in the form set forth in Appendix "C". The Contractor understands that the Commission expects to rely on this certified statement. The Contractor is expected to maintain auditable records as contemplated by Paragraph (c) of Article B-II to substantiate the total costs incurred under this contract.

ARTICLE B-XXVIII - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain the Commission's approval for:

(1) Acquisition of:

(i) An item of equipment, not itemized in Appendix "A", involving an acquisition cost in excess of $1,000 or 2 percent of the total estimated project cost specified in A-III of Appendix "A", whichever is greater, unless such equipment is merely a different model of an item itemized in Appendix "A". (When plant and equipment funds are provided for the acquisition of Government property, the Headquarters Program

1018053

Divisions may require, in specific cases, that such funds be used only for acquiring the equipment designated in Article V, unless prior AEC approval has been obtained.)

(ii) Any equipment not itemized in Appendix "A", the acquisition cost of which will cause the equipment dollar level shown in Appendix "A" to be increased by $500 or more. (If plant and equipment funds are provided for the acquisition of equipment, with title to be vested in the Government, the total cost of such equipment acquisitions shall not exceed the amount budgeted for such equipment unless prior AEC approval has been obtained.)

(2) Purchase of any general-purpose equipment, such as office furniture or air conditioning, not specifically provided for in Appendix "A".

(3) Reserved.

(4) A change of the principal investigator, or continuation of the research work without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining Commission approval; however, the principal investigator shall consult with the appropriate AEC Headquarters program representative if he plans to, or becomes aware that he will, devote substantially less effort to the work than anticipated in Article A-1. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work.

(b) No change in the phenomenon or phenomena under study; i.e., broad category of the research under this contract, shall be made without the specific written approval of the Commission; ordinarily, such changes, if approved by the Commission, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in this contract, provided it gives the Commission prompt notification of such changes; and the Contractor may continue to follow the new objectives while the Commission determines whether it wishes to continue the program under the changed approach.

1018054

5-22-68

APPENDIX "C"[1/]

U. S. ATOMIC ENERGY COMMISSION

Statement of Annual Costs

1. Name and address of Contractor: _____

2. Contract Number: _____

3. Beginning and ending date of pertinent contract period: _____

4. Support ceiling for the pertinent contract period: _____

5. Costs incurred during the pertinent contract period. (List only those costs which are to be reimbursed by the AEC or proportionately shared by the parties in accordance with Article A-II (a).):

Cost Categories	Amount
a. Salaries and Wages (List principal investigator and other personnel in same detail as shown in Article A-II (a) of Appendix "A".)	$_____
b. Supplies and Materials (Show in same detail as in Appendix "A".)	$_____
c. Equipment (List cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from AEC.)	$_____
d. Publications	$_____
e. Travel	$_____
f. Other (List separately each type of cost included in this category.)	$_____
Total Direct Expenditures	$_____

1/ Appendix "C" is a sample statement. The actual statement furnished by the Contractor should be consistent with the itemization in Appendix "A".

1018055

Cost Categories	Amount
g. Indirect Charges (Indicate percent and expenditures to which percent is applied.)	$_____
h. Orders delivered but not paid for (Break down, by types of cost, items delivered or services provided that were not paid for at the close of the contract period.)	$_____
i. Unpaid undelivered orders for equipment, supplies, and materials (Break down, by types of costs, items ordered but not delivered at the close of the contract period.)	$_____
j. Items of equipment specifically authorized by AEC for purchase in prior contract period and for inclusion in the total costs for this contract period	$_____
Total Costs	$_____
Total Costs as defined in Article B-XXVII of the contract chargeable to AEC (% of total using % shown in contract)	$_____

6. Information regarding prior period costs (identify amounts of undelivered orders in prior periods where the cost claimed was not incurred and any other differences in costs incurred from those claimed) $_____

7. Provide information regarding contributions by the Contractor of items listed in Article A-II (b) of Appendix "A". State the extent of the Contractor's actual contribution; the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II (b); e.g., time, dollars, etc.

I hereby certify that this report is true and correct to the best of my knowledge and belief and that the costs and commitments listed herein were incurred, except as provided in j. above, during the period indicated, in connection

with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein.

Name and title of Principal Investigator

Signature Date

Name and title of business officer

Signature Date

1018057

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018058

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc Countries or other countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

1018059

(2) The transmittals to countries listed in Section 2., above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosures of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018060

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 14

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 14th day of June, 1968, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 13 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research and to provide for certain other changes; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended, and Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that said contract, as amended, is hereby further amended in the following particulars, but in no others:

1. In Paragraph (a) of ARTICLE III - CONSIDERATION, the dollar amount "$62,000.00" is deleted and the dollar amount of "$92,000.00" is substituted therefor.

2. The provisions of Appendix "A" to the contract are deleted and the provisions of the revised Appendix "A", attached hereto and made a part hereof, are substituted therefor.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

Herman M. Roth

TITLE: Director
Laboratory and University Division

VANDERBILT UNIVERSITY

BY: William W. Force

William W. Force, Vice Chancellor
Vanderbilt University

TITLE: Nashville, Tennessee

1018061

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"
(REVISED)

For the Contract Period February 1, 1968 through January 31, 1969.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct research divided into two programs; viz., (I) using the whole-body counter for efficiency evaluation, calculation of the absorbed dose in patients under diagnostic nuclear medicine procedures, development of techniques with evaluation of effectiveness in acquisition, analysis, and display of data collected from diagnostic radioisotope procedures in man, whole-body composition studies in the obese following by-pass surgery and on patients with non-surgically-induced potassium loss, with studies of the effects of magnesium on potassium repletion, and also (II) studies of activation analysis on iron absorption during pregnancy, transport of iron from mother to fetus using Fe-59, plus studies of red blood cell mass utilizing stable tracers.

A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages: $44,223.00

Dr. A. B. Brill, Principal Investigator (10% of time)
6 Research Associates* (Approx. 40% of time)
5 Research Assistants** (Approx. 30% of time)
2 Technical Personnel (Electronics and Operations) (80% of time)

*It is recognized that a portion of the salary of one of the Research Associates is provided from other sources.

**Salaries of four of the Research Assistants are provided from other sources.

(2) Employee Benefits: 2,705.00

(3) Supplies, Materials and Services: 22,238.00

Equipment rental, chemicals, glassware, radioisotopes, electronic components, computer time, publications, shipping, reproduction, irradiation time, stable isotopes, radioisotopes, and subject material for kinetic studies.

1018062

(4) Equipment: $ 6,984.00

Biased amplifier and stretcher, linear amplifier with power supply, preamplifier, Ge(Li) detector, cryostat, dewar, iron cell for atomic absorption spectrophotometer, and a calculator.

(5) Travel: 2,325.00

(6) Indirect Costs (39% of Salaries and Fringe Benefits): 18,302.00

(b) Items Significant to the Performance of This Contract But Excluded From Computation of Total Cost and From Consideration in Proportioning Costs:

None

A-III The total estimated project cost of A-II (a) above for the contract period stated above is $96,777.00.

1018063

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 13

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 3rd day of April, 1968, effective the 1st day of February, 1968, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 12 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by the Atomic Energy Act of 1954, as amended, and Section 302(c)(15) of the Federal Property and Administrative Services Act of 1949, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby revised to read as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall furnish the personnel, facilities, equipment, materials, and supplies as indicated in Appendix "A", endeavor to procure or fabricate the items specified in A-II of Appendix "A", and therewith perform to the best of its ability the research provided for in Appendix "A" and report thereon pursuant to the provisions of this contract. It is understood that Appendix "A", a guide to the performance of this contract, may be deviated from by the Contractor subject to the specific requirements of this contract.

(b) This work shall be conducted under the direction of Dr. A. B. Brill or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period of performance under this contract shall commence on February 1, 1968, and expire on January 31, 1969. Performance may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1968, and expiring on January 31, 1969, the Commission shall pay the Contractor the sum of $62,000.00, hereinafter called the "Support Ceiling," which sum shall be subject to adjustment as hereinafter provided. The Commission shall also loan to the Contractor the following items of equipment:

Card Reader
717 Printer
Printer Control
Card Reader Control.

(b) Payments to the Contractor shall equal 96% of the total cost of performance of this contract, as the term "total cost" is defined in Article B-XXVII; provided, however, and notwithstanding any other provision of this contract, that the Government's monetary liability under this contract shall not exceed the Support Ceiling specified in (a) above. The Commission shall not pay more than the Support Ceiling or 96% of the total cost, whichever is less. The Contractor shall be obligated to perform under this contract throughout the pertinent annual period of performance, and to bear all costs which the Commission has not agreed to pay; provided, however, that the Contractor shall have the right to cease to perform the research provided for in this contract, upon written notice to the Commission to that effect, at any time when or after the Support Ceiling on the Commission's liability for any pertinent annual period of performance is reached.

(c) At any time during an annual period of performance subsequent to the initial annual period of performance,* the Commission, in its sole discretion, may increase the Support Ceiling for the pertinent annual

*For the purpose of this contract provision, the period covered by this Modification No. 13 shall be considered to be subsequent to the "initial annual period of performance."

period of performance by written notice to that effect to the Contractor; provided, however, that the Commission may not unilaterally increase the Support Ceiling to an amount greater than 96% of the total estimated project cost specified in the pertinent Appendix "A", for said period. No such increase in the Support Ceiling shall be deemed to increase or affect the percentage of total cost which the Commission has agreed to pay for the pertinent period.

(d) Except as provided in (e) below, at the end of each contract period, the Contractor will refund to the Commission, or make such disposition as the Commission may, in writing, otherwise direct, any sums advanced by the Commission to the Contractor under this contract through direct payment or under letter of credit in excess of 96% of the total cost of performance, as the term "total cost" is defined in Article B-XXVII.

(e) If the total amount the Commission is required to pay during an annual period of performance is less than the Support Ceiling established for said period, the difference between said total and the Support Ceiling will be added by the Commission to the Support Ceiling established for the next succeeding contract period, if any; provided that such addition does not raise the level of the Support Ceiling for the succeeding period above that percentage of the total estimated project cost which the Commission has agreed to pay during said period.

(f) After receipt of an annual certified statement pursuant to Article B-XXVII, which establishes the difference referred to in (e) above, and upon subsequent determination of any amounts the Commission wants to add pursuant to (c) above, the Commission will send a letter notification to the Contractor stating the increased Support Ceiling for the pertinent period. For the purpose only of formalizing the increased Support Ceiling, said letter shall be considered a contractual document. In the same letter the Commission will endeavor to state, for convenient reference, the total amount which the Commission has obligated under the contract from the beginning of the first annual period to date, as adjusted in accordance with this article, but said statement shall have no evidentiary or contractual effect.

ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS

Appendix "B", attached hereto and made a part hereof, sets forth additional general provisions of this contract.

ARTICLE V - GOVERNMENT PROPERTY

The following items of property on loan to the Contractor are hereby listed as "Government Property":

1. Card Reader
2. 717 Printer
3. Printer Control
4. Card Reader Control.

ARTICLE VI - CIVIL RIGHTS ACT OF 1964

The Contractor agrees to comply with the Atomic Energy Commission's Regulations (Part 4 of Title 10, Chapter 1, Code of Federal Regulations), as amended, effectuating the provisions of Title VI of the Civil Rights Act of 1964.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: _____

TITLE: _____

VANDERBILT UNIVERSITY

BY: _____
William W. Force

TITLE: Vice Chancellor for Business Affairs

I, Robert A. McGaw, certify that I am the Secretary of the corporation named as the Contractor herein; that William W. Force who signed this contract on behalf of the Contractor was then Vice Chancellor for Business Affairs of said corporation; that said contract was duly signed for and on behalf of said corporation by authority of its governing body and is within the scope of its corporate powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said corporation.

(Corporate Seal) _____

Contractor: VANDERBILT UNIVERSITY

Contract No.: AT-(40-1)-2401, Mod. 13

1018067

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1968 through January 31, 1969.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue with research involving radioisotopes and the low-level whole-body counter to include (1) evaluation of effectiveness and versatility of the new configuration whole body counter; (2) evaluation of absorbed radiation dose in patients under diagnostic nuclear medicine procedures, with special reference to short-lived radionuclides and daughter nuclides; (3) development of new techniques with evaluation of their effectiveness in acquisition, analysis and display of data collected in course of diagnostic radioisotope procedures in man; and (4) continue body composition studies involving the obese patients on whom intestinal by-pass surgery is performed and patients with non-surgically-induced potassium-losing syndromes. Effects of magnesium on potassium repletion will also be assessed.

A-II WAYS AND MEANS OF PERFORMANCE

(a) Items Included in Total Estimated Cost:

(1) Salaries and Wages: $33,414.00

Dr. A. B. Brill, Principal Investigator (10% of time)

5 Research Associates* (Approx. 35% of time)

5 Research Assistants** (Approx. 30% of time)

2 Technical Personnel (Electronics and Operations) (80% of time)

*It is recognized that a portion of the salary of one of the Research Associates is provided from other sources.

**Salaries of four of the Research Assistants are provided from other sources.

(2) Employee Benefits: 1,809.00

(3) Supplies, Materials and Services: 13,138.00

Equipment rental, chemicals, glassware, radioisotopes, electronic components, computer time, publications, and reproduction.

(4) Equipment: 1,600.00

1018068

(5) Travel: 1,500.00

(6) Indirect Costs (39% of Salaries and Fringe Benefits): 13,737.00

(b) Items Significant to the Performance of This Contract But Excluded From Computation of Total Cost and From Consideration in Proportioning Costs:

None

A-III The total estimated project cost of A-II (a) above for the contract period stated above is $65,198.00.

1018069

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer, except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, covering its costs and expenditures for items included under Article A-II (a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a contractor contribution is excluded from Article A-II (a), and listed in Article A-II (b), the Contractor shall maintain records adequate to permit the AEC to determine whether the commitment has been fulfilled to the extent necessary; if the principal investigator or other professional research staff are listed under Article A-II (b), the Contractor shall maintain time or effort records in support of the costs of such personnel to the same extent as if such personnel were included under Article A-II (a).

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

1018070

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954 or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by the Commission. Seven (7) copies of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish seven (7) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may from time to time desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

If so indicated in the article entitled "Alterations" of this contract, the following sentence shall be deemed to govern in lieu of the last sentence in Article B-III:

> "In order that public disclosure of such information will not adversely affect the patent interest of the Commission, patent approval for release shall be secured from the Commission prior to any such publication."

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material

1018071

becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of

1018072

performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders other than purchase orders for standard commercial items, provisions

1018073

making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

(e) With respect to any U. S. Patent Application filed by the Contractor on any contract invention or discovery made or conceived in the course of the contract, the Contractor will incorporate in the first paragraph of the U. S. Patent Application the following statement:

> "The invention described herein was made in the course of, or under, a contract (if desired, may substitute contract with identifying number) with the U. S. Atomic Energy Commission."

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto and, provided there is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), (e), and (f) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

1018074

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by the Commission, the Contractor shall use Government property only for the purposes of this contract; provided, however, that the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use (1) does not interfere with its work under this contract, (2) is not prohibited by provisions of the other Federal agreements, and (3) is promptly reported by the Contractor to the Commission under this contract.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from wilful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by

1018075

reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, determine on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

1018076

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by AECPR 9-15.50 (41 CFR 9-15.50).

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the Commission's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

1018077

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration prescribed in paragraph (a) of Article III of this contract as follows:

(1) Forty-five percent following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional forty-five percent upon receipt of a written request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) A concluding payment for the pertinent period, if necessary, following submission by the Contractor of the annual Progress Report or final report, provided for in Article B-XXI, in form and content satisfactory to the Commission and submission of a certified statement showing the total cost for the contract period and evidencing the Contractor's performance under the contract.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

1018078

(c) All payments under this contract, except the first payment provided in (a) above, will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

(d) The Commission, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) The Commission shall issue a letter of credit as provided for by Treasury Department Circular No. 1075, Revised, of February 13, 1967, under which payment to the Contractor with respect to the amount of consideration provided for in paragraph (a) of Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the amount of consideration provided for in said paragraph (a) of Article III will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (Standard Form 218), in accordance with procedures based upon Treasury Department Circular No. 1075, Revised, of February 13, 1967, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in Article B-XXI, in form and content satisfactory to the Commission, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission, the Commission shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a Payment Voucher on Letter of Credit, in accordance with the procedure described above. If, following an annual report, the contract is extended for an additional period of performance, said concluding payment will similarly be paid for the expired period, and ten (10) percent will be retained with respect to the added period of performance.

(2) The Commission reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (d) (1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

1018079

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules and regulations of the Secretary of Labor (41 CFR, Ch. 60). Exemptions include contracts and subcontracts (i) not exceeding $10,000, (ii) not exceeding $100,000 for standard commercial supplies or raw materials, and (iii) under which work is performed outside the United States and no recruitment of workers within the United States is involved.)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee

pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the nondiscrimination clauses of this contract or with any of such rules, regulations, or orders, this contract may be canceled, terminated or suspended in whole or in part and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder:

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve

1018081

the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such work-week, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard work-week of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2 (a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish

1018082

a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

1018083

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (i) purchase orders not exceeding $2,500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10 a-d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a) (iii) (B), components of foreign origin of the same type or kind as the products referred to in (b) (ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

1018084

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish seven (7) copies of the following reports and renewal proposals, if any, addressed to the Laboratory and University Division, U. S. Atomic Energy Commission, Oak Ridge Operations Office, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

1018085

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of Equipment Purchased or Fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated (omit any items appearing in Article V) and submit a report thereof immediately following the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $1,000, they will be listed individually. Where individual items cost $100 to $1,000, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "6 motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Services Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy. In complying with the foregoing and with

1018086

paragraph (b) of the article of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (1) persistent labor surplus area concerns which are also small business concerns; (2) other persistent labor surplus area concerns; (3) substantial labor surplus area concerns which are also small business concerns; (4) other substantial labor surplus area concerns; and (5) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

ARTICLE B-XXVII - DETERMINATION OF TOTAL COSTS

(a) The term "total cost" as used in this contract means the sum of costs incurred by the Contractor for items included under Article A-II (a) of Appendix "A", which are in furtherance of the work hereunder, and may include the following: expenditures of cash, exclusive of cash payments relating to items included in the total cost of a prior period; the cost of material and supplies transferred from stores inventory; unpaid delivered orders for services, supplies, and equipment; unpaid undelivered orders (commitments) for items of equipment; unpaid delivered orders (commitments) for materials and supplies purchased in normal and reasonable quantities; and the amount due the Contractor for indirect costs in

1018087

accordance with the rate and factor or factors shown in Appendix "A" of this contract. Except as the parties may otherwise specifically agree in writing, total cost will apply separately to each annual (or lesser) period of performance. Total cost for a contract period shall be determined consistent with the principles of the Bureau of the Budget Circular A-21, as constituted on the effective commencement date of said period.

(b) Within three months after the end of each contract period and within three months after the expiration or termination of the contract, the Contractor shall furnish its certified statement, executed by an official of the Contractor and also signed by the principal investigator, showing the Contractor's total cost and evidencing its performance under the contract. The statement shall be in the form set forth in Appendix "C". The Contractor understands that the Commission expects to rely on this certified statement. The Contractor is expected to maintain auditable records as contemplated by Paragraph (c) of Article B-II to substantiate the total costs incurred under this contract.

ARTICLE B-XXVIII - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain the Commission's approval for:

(1) Acquisition of:

(i) An item of equipment, not itemized in Appendix "A", involving an acquisition cost in excess of $1,000 or 2 percent of the total estimated project cost specified in A-III of Appendix "A", whichever is greater, unless such equipment is merely a different model of an item itemized in Appendix "A". (When plant and equipment funds are provided for the acquisition of Government property, the Headquarters Program Divisions may require, in specific cases, that such funds be used only for acquiring the equipment designated in Article V, unless prior AEC approval has been obtained.)

(ii) Any equipment not itemized in Appendix "A", the acquisition cost of which will cause the equipment dollar level shown in Appendix "A" to be increased by $500 or more. (If plant and equipment funds are provided for the acquisition of equipment, with title to be vested in the Government, the total cost of such equipment acquisitions shall not exceed the amount budgeted for such equipment unless prior AEC approval has been obtained.)

(2) Purchase of any general-purpose equipment, such as office furniture or air conditioning, not specifically provided for in Appendix "A".

1018088

(3) Transfer of:

(i) Funds from the equipment category to the travel category.

(ii) Funds for support of junior investigator category to the equipment category.

(When plant and equipment funds are provided for the acquisition of Government property, such funds shall not be transferred to other budget categories, and, conversely, funds from other budget categories shall not be used to acquire such equipment.)

(4) Change of the principal investigator or reduction of 15 percent or more in the amount of time and effort the principal investigator will devote to the work.

(b) No change in the phenomenon or phenomena under study; i.e., broad category of the research under this contract, shall be made without the specific written approval of the Commission; ordinarily, such changes, if approved by the Commission, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in this contract, provided it gives the Commission prompt notification of such changes; and the Contractor may continue to follow the new objectives while the Commission determines whether it wishes to continue the program under the changed approach.

1018089

APPENDIX "C"[1/]

U. S. ATOMIC ENERGY COMMISSION

Statement of Annual Costs

1. Name and address of Contractor: _____

2. Contract number: _____

3. Beginning and ending date of pertinent contract period: _____

4. Support ceiling for the pertinent contract period: _____

5. Costs incurred during the pertinent contract period:

Cost Categories	Amount
a. Salaries and Wages (List principal investigator and other personnel in same detail as shown in Appendix "A" to the contract and indicate the related cost for each; and, in addition, indicate the approximate percentage of time or effort devoted to contract work by principal investigator.)	$_____
b. Supplies and Materials (Show in same detail as in Appendix "A")	$_____
c. Equipment (List cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from AEC.)	$_____
d. Publications	$_____
e. Travel	$_____
f. Other (List separately each type of cost included in this category)	$_____
Total Direct expenditures	$_____

1/ Appendix "C" is a sample statement. The actual statement furnished by the Contractor should be consistent with the itemization in Appendix "A".

1018090

Cost Categories	Amount
g. Indirect Charges (Indicate percent and expenditures to which percent is applied.)	$_____
h. Orders delivered but not paid for (Break down, by types of cost, items delivered or services provided that were not paid for at the close of the contract period.)	$_____
i. Unpaid undelivered orders for equipment, supplies, and materials (Break down, by types of costs, items ordered but not delivered at the close of the contract period.)	$_____
j. Items of equipment specifically authorized by AEC for purchase in prior contract period and for inclusion in the total costs for this contract period	$_____
Total Costs	$_____
Total Costs as defined in Article B-XXVII of the contract chargeable to AEC (% of total using % shown in contract)	$_____
6. Information regarding prior period costs (Identify amounts of undelivered orders in prior periods where the cost claimed was not incurred and any other differences in costs incurred from those claimed.)	$_____
7. Information regarding contributions by the Contractor and not included in proportionate sharing of costs. State the extent of the Contractor's actual contribution of items listed under Article A-II (b) of Appendix "A"; the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II (b); e.g., time, dollars, etc. A contractor contribution of a principal investigator or other professional research staff shall be reported in terms of time or effort and costs for each such investigator.	$_____

I hereby certify that this report is true and correct to the best of my knowledge and belief and that the costs and commitments listed herein were incurred, except as provided in j. above, during the period indicated,

1018091

in connection with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein.

Name and title of principal investigator

Signature Date

Name and title of business officer

Signature Date

1018092

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to Countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "Countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

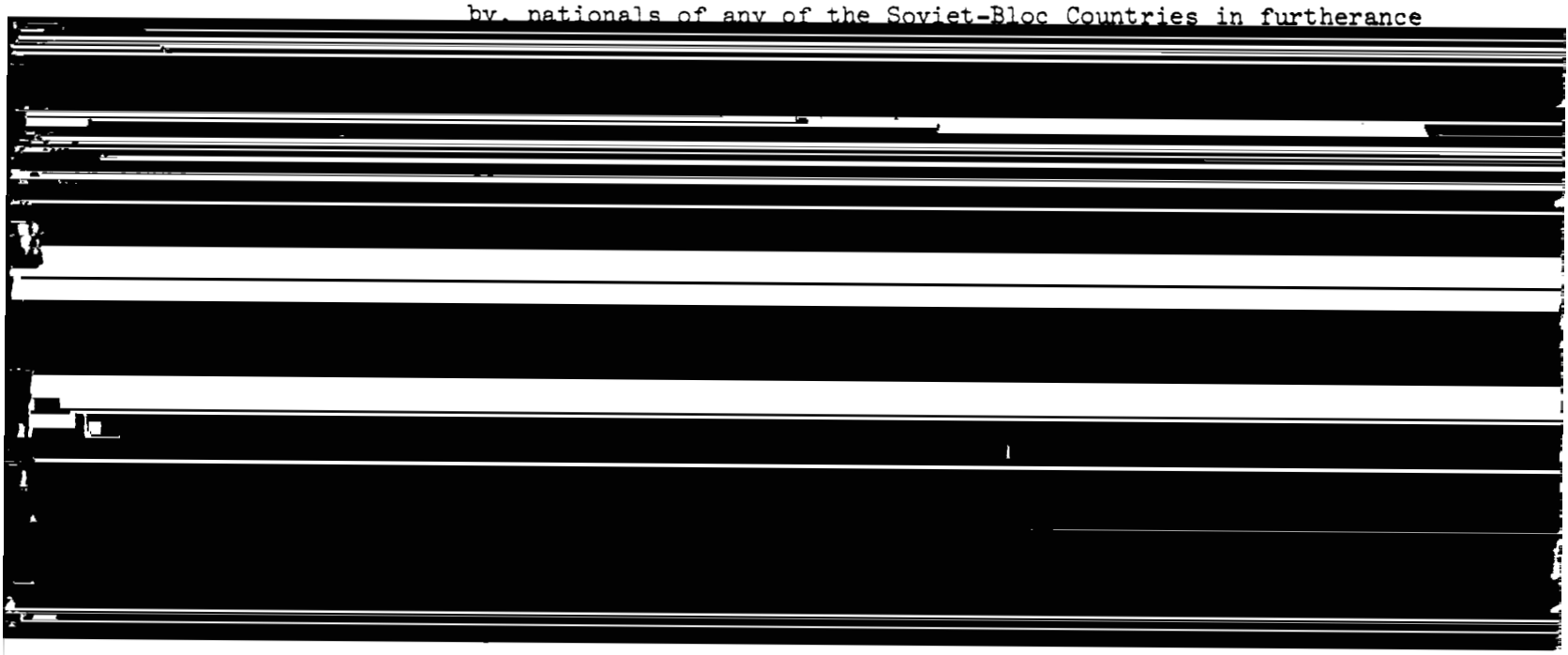
China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018093

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance



c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc or other Countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and

(2) The transmittals to Countries listed in Section 2., above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosures of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018095

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 12

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 6th day of April, 1967, effective as of the 1st day of February, 1967, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 11 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by and negotiated under the Federal Property and Administrative Services Act of 1949, as amended, and the Atomic Energy Act of 1954, as amended;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby revised to read as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall furnish personnel, facilities, equipment, materials, and supplies substantially to the extent set forth in Appendix "A", attached hereto and made a part hereof, endeavor to procure or fabricate the items specified in A-III of said Appendix "A", and therewith perform to the best of its ability the research provided for in Appendix "A" and report thereon pursuant to the provisions of this contract. Substantial deviations from the foregoing shall be discussed with and subject to the written approval of the Commission.

(b) This work shall be conducted under the direction of Dr. Robert M. Heyssel or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

1018096

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period for performance under this contract shall expire on January 31, 1968; provided, however, that this period may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1967, and expiring on January 31, 1968, the Commission shall pay the Contractor the sum of $54,000.00.

ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS

Appendix "B", attached hereto and made a part hereof, sets forth additional general provisions of this contract.

ARTICLE V - GOVERNMENT PROPERTY

(a) The following items of property to be procured or fabricated by the Contractor are hereby listed as "Government property": None.

ARTICLE VI - CIVIL RIGHTS ACT OF 1964

The Contractor agrees to comply with the Atomic Energy Commission's Regulations (Part 4 of Title 10, Chapter 1, Code of Federal Regulations), as amended, effectuating the provisions of Title VI of the Civil Rights Act of 1964.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth
HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: William W. Force

TITLE: Vice-Chancellor for Business Affairs

1018097

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1967 through January 31, 1968.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on the dosimetry, quantitation, and metabolism of medically important radionuclides and other trace elements utilizing a low-level whole body counter. This work will include such approaches as study of (1) applications of the whole body counter utilizing appropriate radioisotopes or isotopically labeled compounds, (2) iron and vitamin B-12 metabolism. (3) the relationship of potassium to hypertension, (4) body composition, (5) possible revision and improvement of the counter geometry, (6) absolute calibration of radiopharmaceuticals, (7) concentration of radioisotopes in the human body, (8) system stability directed at enhancing the counter's efficiency, and (9) dosimetry in various organs and/or tissues under various clinical conditions.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

	Approx. % of time
Dr. R. M. Heyssel, Principal Investigator	10%
5 Research Associates	45%
8 Research Assistants	50%
2 Technicians (Electronic & Radiochemistry)	60%
2 Secretaries	75%

It is recognized that certain support from other sources will be provided for partial payment of salaries of some of the above personnel.

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

Adequate facilities and equipment are available to conduct the proposed radioisotope studies utilizing a low-level whole body counter.

A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE

None

1018098

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its activities under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, covering its costs and expenditures for the research work under this contract.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act

1018099

of 1954 or other classified information shall be disclosed to unauthorized persons. Such publication shall indicate that the research was supported by the Commission. Seven (7) copies of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish seven (7) copies of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may, from time to time, desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery, which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

1018100

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

1018101

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for precuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission the Contractor will insert in all subcontracts and purchase orders, other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), and (e) of this Article B-IX.

1018102

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property, and unless otherwise authorized in writing by the Commission, shall use Government property only for the purposes of this contract. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from wilful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

1018103

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this clause, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the contracting agency's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by the cost principles set forth in Subpart 9-15.50 of the Atomic Energy Commission Procurement Regulations (41 CFR 9-15.50).

1018104

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the contracting agency's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this clause, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this clause, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the

1018105

Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" clause of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration for each period as provided for in Article III of this contract as follows:

45% - following execution of this contract (and following the effectuation of each extended period).

45% - upon subsequent receipt of written request from the Contractor when the Contractor determines the amount requested is then required in connection with work under the contract.

10% - following submission by the Contractor of the annual progress report or final report provided for in Article B-XXI, in form and content satisfactory to the Commission, within a reasonable period of time following the expiration of an annual contract period.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary or otherwise indicative of the amount or proportion of the work actually performed by the Contractor, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) All payments under this contract, except the first payment provided in (a) above, will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

(d) With respect to any portion of the first ninety percent of the amount of consideration provided for in Article III of this contract not

1018106

previously paid to the Contractor by the Commission under paragraph (a) above, it is understood and agreed that the Commission shall have the right, exercisable at any time during the term of this contract, to issue a Letter of Credit as provided for by Treasury Department Circular No. 1075 of May 28, 1964, under which payments of the balance of the first ninety percent of the amount of said consideration will be made. The Contractor agrees that such payments will be under the Letter of Credit, and will be subject to the submission by the Contractor of Payment Vouchers on Letter of Credit (Standard Form 218), in accord with procedures based upon Treasury Department Circular No. 1075 of May 28, 1964, and instructions issued by the Commission which are agreed to by the parties. The final ten percent of the consideration provided for in Article III of this contract will be paid to the Contractor by the Commission in accordance with paragraphs (a) - (c) above. The Commission reserves the right to cancel or modify, increase or decrease the amount covered by the Letter of Credit, if such action is required because of a change in the amount of consideration provided for in Article III of this contract. The issuance and use of a Letter of Credit and receipt of funds pursuant thereto shall not prejudice or otherwise affect adversely any of the Government's rights under this contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules and regulations of the Secretary of Labor (41 CFR, Ch. 60). Exemptions include contracts and subcontracts (i) not exceeding $10,000, (ii) not exceeding $100,000 for standard commercial supplies or raw materials, and (iii) under which work is performed outside the United States and no recruitment of workers within the United States is involved.)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to the following: employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this nondiscrimination clause.

1018107

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under Section 202 of Executive Order No. 11246 of September 24, 1965, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the non-discrimination clauses of this contract or with any of such rules, regulations, or orders, this contract may be cancelled, terminated or suspended in whole or in part and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder.

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

1018109

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this clause in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established

1018110

commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Commission and the Comptroller General of the United States or any of their duly authorized representatives shall have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract until the expiration of three years after final payment under this contract unless the Commission authorizes their prior disposition.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract unless the Commission authorizes their prior disposition. The term "subcontract" as used in this clause excludes (i) purchase orders not exceeding $2500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10 a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(i) "Components" means those articles, materials, and supplies, which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States

and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a) (iii) (B), components of foreign origin of the same type or kind as the products referred to in (b) (ii) or (iii) of this clause shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish seven (7) copies of the following reports and renewal proposals, if any, addressed to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

(a) Technical Progress Report. The technical progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also explain any significant differences between

1018112

the actual level of effort and that contemplated in the contract (see Article I). Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable course and level of effort of the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in level of effort or scientific results between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

(d) Report of equipment purchased or fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated (omit any items appearing in Article V) and submit a report thereof immediately following the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $500, they will be listed individually. Where individual items cost $100 to $500, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "6 motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Service Administration in obtaining controlled materials and other

1018113

products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy. In complying with the foregoing and with paragraph (b) of the clause of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (a) persistent labor surplus area concerns which are also small business concerns; (b) other persistent labor surplus area concerns; (c) substantial labor surplus area concerns which are also small business concerns; (d) other substantial labor surplus area concerns; and (e) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D", attached hereto and made a part of this contract, relating to the countries listed herein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018114

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to Countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "Countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018115

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc or other Countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

(2) The transmittals to Countries listed in Section 2., above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints, preprints, page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosure of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018117

Contract No. AT-(40-1)-2401
Modification No. 11

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 6th day of April, 1966, effective as of the 1st day of February, 1966, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and modifications thereto numbered 1 through 10 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby revised to read as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall furnish personnel, facilities, equipment, materials, and supplies substantially to the extent set forth in Appendix "A", attached hereto and made a part hereof, endeavor to procure or fabricate the items specified in A-III of said Appendix "A", and therewith perform to the best of its ability the research provided for in Appendix "A" and report thereon pursuant to the provisions of this contract. Substantial deviations from the foregoing shall be discussed with and subject to the written approval of the Commission.

(b) This work shall be conducted under the direction of Dr. Robert M. Heyssel and Dr. E. D. Denman or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

1018118

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period for performance under this contract shall expire on January 31, 1967; provided, however, that this period may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1966, and expiring on January 31, 1967, the Commission shall pay the Contractor the sum of $52,000.00.

ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS

Appendix "B", attached hereto and made a part hereof, sets forth additional general provisions of this contract.

ARTICLE V - GOVERNMENT PROPERTY

(a) The following items of property to be procured or fabricated by the Contractor are hereby listed as "Government property": None.

ARTICLE VI - CIVIL RIGHTS ACT OF 1964

The Contractor agrees to comply with AEC's Regulations (Part 4 of Title 10, Chapter 1, C.F.R.), as amended, effectuating the provisions of Title VI of the Civil Rights Act of 1964.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R. R. Purdy

Dr. R. R. Purdy

TITLE: Vice-Chancellor

1018119

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1966 through January 31, 1967.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on the applications of the whole body counter utilizing appropriate radioisotopes or isotopically labeled compounds. Included in this work will be such areas as (1) study of iron and Vitamin B-12 metabolism, (2) study of the relationship of potassium to hypertension, (3) study of the composition of the body, (4) efforts directed at revision and improvements of the counter geometry, (5) absolute calibration of radiopharmaceuticals, (6) counting of humans with high body concentrations of radioisotopes, (7) further efforts as system stabilization to enhance the counter's efficiency in counting very low levels of radioactivity, and (8) dosimetry studies in various organs and/or tissues under various clinical conditions.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

	Approx. % of time
Dr. R. M. Heyssel, Co-Principal Investigator	25%
Dr. E. D. Denman, Co-Principal Investigator	30%
Principal Scientist	50%
6 Research Associates	30%
10 Research Assistants	20%
Steel Room Operations Officer	75%
2 Secretaries	75%
Radiochemistry Technician	10%

It is recognized that certain support from other sources will be provided for partial payment of salaries of some of the above personnel.

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

Adequate facilities and equipment are available to conduct the proposed research on utilization of a low level whole body counting facility in the measurement of electrolyte composition and metabolism in man.

A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE

None

1018120

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its activities under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, covering its costs and expenditures for the research work under this contract.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act

1018121

of 1954 or other classified information shall be disclosed to unauthorized persons. Such publication shall indicate that the research was supported by the Commission. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish a copy of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors may, from time to time, desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery, which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

1018122

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

1018123

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall promptly furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights in and to any invention or discovery and any patent application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for precuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission the Contractor will insert in all subcontracts and purchase orders, other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), and (e) of this Article B-IX.

1018124

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed el where in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property, and unless otherwise authorized in writing by the Commission, shall use Government property only for the purposes of this contract. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from wilful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

(e) With the written approval of the Commission, the Contractor may sell, transfer or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

1018125

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this clause, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the contracting agency's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by the cost principles set forth in Subpart 9-15.50 of the Atomic Energy Commission Procurement Regulations (41 CFR 9-15.50).

1018126

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the contracting agency's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this clause, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this clause, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the

1018127

Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" clause of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration for each period as provided for in Article A-III of this contract as follows:

45% - following execution of this contract (and following the effectuation of each extended period).

45% - upon subsequent receipt of written request from the Contractor when the Contractor determines the amount requested is then required in connection with work under the contract.

10% - following submission by the Contractor of the annual progress report or final report provided for in Article B-XXI, in form and content satisfactory to the Commission, within a reasonable period of time following the expiration of an annual contract period.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary or otherwise indicative of the amount or proportion of the work actually performed by the Contractor, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) All payments under this contract, except the first payment provided in (a) above, will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

(d) With respect to any portion of the first ninety percent of the amount of consideration provided for in Article III of this contract not

1018128

previously paid to the Contractor by the Commission under paragraph (a) above, it is understood and agreed that the Commission shall have the right, exercisable at any time during the term of this contract, to issue a Letter of Credit as provided for by Treasury Department Circular No. 1075 of May 28, 1964, under which payments of the balance of the first ninety percent of the amount of said consideration will be made. The Contractor agrees that such payments will be under the Letter of Credit, and will be subject to the submission by the Contractor of Payment Vouchers on Letter of Credit (Standard Form 218), in accord with procedures based upon Treasury Department Circular No. 1075 of May 28, 1964, and instructions issued by the Commission which are agreed to by the parties. The final ten percent of the consideration provided for in Article III of this contract will be paid to the Contractor by the Commission in accordance with paragraphs (a) - (c) above. The Commission reserves the right to cancel or modify, increase or decrease the amount covered by the Letter of Credit, if such action is required because of a change in the amount of consideration provided for in Article III of this contract. The issuance and use of a Letter of Credit and receipt of funds pursuant thereto shall not prejudice or otherwise affect adversely any of the Government's rights under this contract.

ARTICLE B-XII - EQUAL OPPORTUNITY

(The following clause is applicable unless this contract is exempt under the rules and regulations of the Secretary of Labor (41 CFR, Ch. 60). Exemptions include contracts and subcontracts (i) not exceeding $10,000, (ii) not exceeding $100,000 for standard commercial supplies or raw materials, and (iii) under which work is performed outside the United States and no recruitment of workers within the United States is involved.)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to the following: employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this nondiscrimination clause.

1018129

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under Section 202 of Executive Order No. 11246 of September 24, 1965, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by the Commission and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the non-discrimination clauses of this contract or with any of such rules, regulations, or orders, this contract may be cancelled, terminated or suspended in whole or in part and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - CONTRACT WORK HOURS STANDARDS ACT - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours Standards Act (40 U.S.C. 327-330), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder.

(a) Overtime requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers or mechanics shall require or permit any laborer or mechanic in any workweek in which he is employed on such work to work in excess of eight hours in any calendar day or in excess of forty hours in such workweek on work subject to the provisions of the Contract Work Hours Standards Act unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; liability for unpaid wages; liquidated damages. In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of eight hours or in excess of the standard workweek of forty hours without payment of the overtime wages required by paragraph (a).

(c) Withholding for unpaid wages and liquidated damages. The Contracting Officer may withhold from the Government Prime Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of paragraph (b).

1018131

(d) Subcontracts. The Contractor shall insert paragraphs (a) through (d) of this clause in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established

1018132

commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Commission and the Comptroller General of the United States or any of their duly authorized representatives shall have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract until the expiration of three years after final payment under this contract unless the Commission authorizes their prior disposition.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract unless the Commission authorizes their prior disposition. The term "subcontract" as used in this clause excludes (i) purchase orders not exceeding $2500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10 a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(i) "Components" means those articles, materials, and supplies, which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States

1018133

and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a) (iii) (B), components of foreign origin of the same type or kind as the products referred to in (b) (ii) or (iii) of this clause shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee 37830

(a) Progress report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also explain any significant differences between the

1018134

actual level of effort and that contemplated in the contract (see Article I). Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable course and level of effort of the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in level of effort or scientific results between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal proposals. A renewal proposal, if any, shall accompany the progress report.

(d) Report of equipment purchased or fabricated. The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100 purchased or fabricated (omit any items appearing in Article V) and submit a report thereof immediately following the expiration of the contract year specified in Article II. Where the cost of individual pieces of equipment exceeds $500, they will be listed individually. Where individual items cost $100 to $500, they will also be individually listed to the extent practical or grouped in general categories, such as "electronic equipment" or "6 motors," with the total dollar amount of such category. The cost of purchased items shall be determined by the actual invoice cost of such items, but the cost of fabricated items may be established by engineering estimates.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Service Administration in obtaining controlled materials and other

1018135

products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

ARTICLE B-XXIV - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy. In complying with the foregoing and with paragraph (b) of the clause of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (a) persistent labor surplus area concerns which are also small business concerns; (b) other persistent labor surplus area concerns; (c) substantial labor surplus area concerns which are also small business concerns; (d) other substantial labor surplus area concerns; and (e) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXV - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXVI - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D", attached hereto and made a part of this contract, relating to the countries listed herein. From time to time, by written notice to the Contractor, the Commission shall have the right to change the listing of countries in Appendix "D" upon a determination by the Commission that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to the Commission if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by the Commission pursuant to the preceding sentence. If the Contractor elects to terminate performance the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018136

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to Countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "Countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018137

a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc or other Countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

1018138

(2) The transmittals to Countries listed in Section 2., above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to Countries listed in Group B of Section 2., above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints, preprints, page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosure of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018139

Contract No. AT-(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 10

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 11th day of January, 1966, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 9 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and to provide for certain other changes; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954 and Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that said contract, as amended, is hereby further amended in the following particulars, but in no others:

1. In Paragraph (a) of ARTICLE III - CONSIDERATION, the dollar amount "50,000.00" is deleted and the dollar amount "$54,800.00" is substituted therefor.

2. A-III of Appendix "A" is revised to read as follows:

"A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE

		Estimated Cost
1.	Card Punch Coupler	$ 2,035.00
2.	Closed Loop Television System	963.00
3.	Multichannel Radiation Analyzer	10,434.00
4.	Photomultiplier Tube (installed)	800.00
5.	Moving Crystal Assembly	4,000.00"

3. Paragraph (b) of ARTICLE V - GOVERNMENT PROPERTY is revised to read as follows:

"(b) The following items of property heretofore procured or fabricated by the Contractor or heretofore furnished the Contractor are also hereby listed as 'Government property': None."

4. The following article is added to the provisions of Appendix "B":

"ARTICLE B-XXVII - CIVIL RIGHTS ACT OF 1964

"The Contractor agrees to comply with AEC's Regulations (Part 4 of Title 10, Chapter 1, C.F.R.), as amended, effectuating the provisions of Title VI of the Civil Rights Act of 1964."

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth
HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R R Purdy
Dr. R. R. Purdy

TITLE: Vice Chancellor

Contract No. AT-(40-1)-2401
Modification No. 9

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 24th day of February, 1965, effective as of the 1st day of February, 1965, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 8 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research and to provide for certain other changes; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that said contract, as amended, is hereby further amended in the following particulars, but in no others:

1. The date "January 31, 1965", as such appears in ARTICLE II - THE PERIOD FOR PERFORMANCE, is deleted and the date "January 31, 1966", is substituted therefor.

2. Paragraph (a) of ARTICLE III - CONSIDERATION is revised to read as follows:

> "(a) In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1965, and expiring on January 31, 1966, the Commission shall pay the Contractor the sum of $50,000.00."

3. The provisions of Appendix "A" to the contract are deleted and the provisions of the revised Appendix "A", attached hereto and made a part hereof, are substituted therefor.

4. ARTICLE B-XXVII - CIVIL RIGHTS ACT OF 1964 is deleted in its entirety.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth
HERMAN M. ROTH
DIRECTOR
~~RESEARCH AND DEVELOPMENT DIVISION~~
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R R Purdy
Dr. R. R. Purdy

TITLE: Vice-Chancellor

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1965 through January 31, 1966.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on medical applications of radioisotopes utilizing a low level whole body counter. This research will include such approaches as (1) continuation of the study on body electrolytes, particularly sodium and potassium and the requirements and turnover of minerals and vitamins, (2) continuation of the population survey to determine the body burden of radioactivity and additional accumulation of radioactivity in the body that may come from inhalation or ingestion of radioactive materials, (3) absorption studies of iron and vitamin B-12 in patients with malabsorption syndromes, (4) ferrokinetic studies in patients with iron deficiency, hemolytic, and aplastic anemia, (5) Radium-226 studies designed to identify and clinically investigate persons with high Ra-226 body burdens, (6) study of calcium metabolism in patients with various disorders of bone metabolism, and (7) study of the degree and times at which various parameters of thyroid function are altered during the course of radioiodine therapy of thyroid disease.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

	Approx. % of time
Dr. R. M. Heyssel, Co-Principal Investigator*	50%
Dr. R. T. Lagemann, Co-Principal Investigator	10%
5 Research Associates	58%
Radiochemist*	25%
7 Research Assistants*	26%
2 Technicians	37%
2 Secretaries	62%
Secretary*	25%

* Support to be provided from other sources.

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

Adequate facilities and equipment are available to conduct the proposed research on utilization of a low level whole body counting facility in the measurement of electrolyte composition and metabolism in man.

A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE

None

1018144

Contract No. AT-(40-1)-2401
Modification No. 8

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 13th day of October, 1964, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 7 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research and to provide for certain other changes; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that said contract, as amended, is hereby further amended in the following particulars, but in no others:

1. In Paragraph (a) of ARTICLE III - CONSIDERATION, the dollar amount "$44,106.00" is deleted and the dollar amount "$54,540.00" is substituted therefor.

2. A-III of Appendix "A" is revised to read as follows:

"A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE	Estimated Cost
1. Card Punch Coupler	$ 2,035.00
2. Closed Loop Television System	963.00
3. Multichannel Radiation Analyzer	10,434.00"

3. The following ARTICLE B-XXVII is added to Appendix "B":

"ARTICLE B-XXVII - CIVIL RIGHTS ACT OF 1964

"It is agreed that when implementing rules, regulations or orders are issued and made effective pursuant to Sec. 602 of Title VI of the Civil Rights Act of 1964, the Contractor shall, to the extent a grant or program or activity under the contract is covered by such rules, regulations or orders, promptly notify the Commission in writing that

it will comply therewith or, alternatively, that it elects not to accept them as conditions of the contract or grant, as the case may be. Should the choice be the latter, the Commission may terminate the contract pursuant to the provisions of this contract respecting the right to terminate for the convenience of the Government or may terminate the grant; in the latter regard, the Commission may require that the Contractor revest in the Government title to any items of equipment, in the Contractor's possession or custody, vested in the Contractor by grant from the Commission between July 9, 1964, and the date of termination."

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R. R. Furgy

Dr. R. R. Furgy

TITLE: Vice-Chancellor

1018146

Contract No. AT-(40-1)-2401
Modification No. 7

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 6th day of March, 1964, effective as of the 1st day of February, 1964, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and modifications thereto numbered 1 through 6 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract further to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby revised to read as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

(a) The Contractor shall furnish personnel, facilities, equipment, materials, and supplies substantially to the extent set forth in Appendix "A", attached hereto and made a part hereof, endeavor to procure or fabricate the items specified in A-III of said Appendix "A", and therewith perform to the best of its ability the research provided for in Appendix "A" and report thereon pursuant to the provisions of this contract. Substantial deviations from the foregoing shall be discussed with and subject to the written approval of the Commission.

1018147

(b) This work shall be conducted under the direction of Dr. R. M. Heyssel and Dr. R. T. Lagemann or such other member of the Contractor's staff as may be mutually satisfactory to the parties.

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period for performance under this contract shall expire on January 31, 1965; provided, however, that this period may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

(a) In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1964, and expiring on January 31, 1965, the Commission shall pay the Contractor the sum of $44,106.00.

ARTICLE IV - ADDITIONAL CONTRACT PROVISIONS

Appendix "B", attached hereto and made a part hereof, sets forth additional general contract provisions of this contract.

ARTICLE V - GOVERNMENT PROPERTY

(a) The following items of property to be procured or fabricated by the Contractor are hereby listed as "Government property": None.

(b) The following items of property heretofore procured or fabricated by the Contractor or heretofore furnished the Contractor are also hereby listed as "Government property":

Low Level Whole Body Counting Device consisting of:

1. Steel Room
2. Probe and Crane, Sensing Device (crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyzer)
3. Humidity and Temperature Control
4. Crystal Assembly
5. Preamplifiers
6. Shields
7. High-voltage Dividing Networks.

1018148

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION

(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R. R. Purdy

Dr. R. R. Purdy

TITLE: Vice-Chancellor

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1964 through January 31, 1965.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on the use of radioactive tracers in human patients utilizing a low level total body counter. This research will include such areas as (1) study of body electrolytes and the requirements and turnover of minerals and vitamins, (2) study of the "usual" body burdens of radioactivity in the body that may come about as a result of inhalation or ingestion of radioactive material, and (3) study of albumen turnover, iron metabolism, Vitamin B_{12} absorption and turnover and metabolism of sodium in infants.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

	Approx. % of time
Dr. R. M. Heyssel - Co-Principal Investigator*	50%
Dr. R. T. Lagemann - Co-Principal Investigator	Advisory Capacity
Senior Scientist	44%
2 Research Associates	27%
Consultant	As Needed
7 Research Assistants	21%
Operations Officer, Steel Room	100%
2 Radioisotopes Technicians	50%
2 Secretarial Clerks	50%
Clerk	58%
Radiochemist*	25%
Post Doctorate Trainee*	50%

*Support to be provided from other sources.

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

Adequate facilities are available to conduct research on utilization of a low level whole body counting facility in the measurement of electrolyte composition and metabolism in man. These include an adequately equipped (1) low level counting facility with whole body counter, multi-channel analyzer room, and electronics shop, (2) computer center, (3) clinical research center, (4) clinical radioisotope laboratory and (5) animal house.

A-III ITEMS OF EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR COSTING $500 OR MORE

	Estimated Cost
1. Card Punch Coupler	$2,035.00
2. Closed Loop Television System	963.00

APPENDIX "B"

ARTICLE B-I - DEFINITIONS

(a) The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS AND ACCOUNTS

(a) The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its activities under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XXI. The Contractor shall also make such other reports to the Commission, with respect to its activities under this contract, as the Commission may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, covering its costs and expenditures for the research work under this contract.

(d) The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

(a) Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the

1018151

Atomic Energy Act of 1954 or other classified information shall be disclosed to unauthorized persons. Such publication shall indicate that the research was supported by the Commission. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission. The Contractor shall also inform the Commission when the article is published and furnish a copy of the article as finally published.

(b) It is recognized that during the course of the work hereunder or subsequent thereto, the Contractor, its employees, or its subcontractors, may from time to time, desire to publish, within the limit of security requirements, information regarding technical or scientific developments arising in the course of the contract. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention or discovery, which shall be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and the Commission's regulations or requirements.

1018152

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves a Commission license the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-VI - FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VII - WRITTEN MATERIAL

(a) The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent, that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

(b) The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

1018153

(c) The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

ARTICLE B-VIII - PATENTS

(a) Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

(b) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(c) Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs (a) and (b) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

(d) Except as otherwise authorized in writing by the Commission the Contractor will insert in all subcontracts and purchase orders other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or purchase order. Except as otherwise authorized in writing by the Commission, the Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use, or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

ARTICLE B-IX - PROPERTY ITEMS

(a) Except as otherwise provided in this paragraph (a) and paragraph (b) of this Article B-IX, title to all materials, supplies,

1018154

and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs (b), (c), (d), and (e) of this Article B-IX.

(b) Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property, and unless otherwise authorized in writing by the Commission, shall use Government property only for the purposes of this contract. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located.

(d) The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from wilful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

1018155

(e) With the written approval of the Commission, the Contractor may sell, transfer or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

ARTICLE B-X - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the notice. With respect to such canceled commitments the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this clause, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of

1018156

Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by the Contracting agency's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under paragraph (c) shall be governed by the cost principles set forth in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3), as in effect on the date of this contract, except that if the Contractor is not an educational institution the determination shall be governed by the cost principles set forth in Subpart 9-15.50 of the Atomic Energy Commission Procurement Regulations (41 CFR 9-15.50).

(e) Subject to the provisions of paragraph (c) above, and subject to any review required by the contracting agency's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this clause, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this clause, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate

1018157

of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" clause of this contract.

ARTICLE B-XI - PAYMENTS

(a) The Commission shall make payments to the Contractor with respect to the amount of consideration for each period as provided for in Article A-III of this contract as follows:

45% - following execution of this contract (and following the effectuation of each extended period).

45% - upon subsequent receipt of written request from the Contractor when the Contractor determines the amount requested is then required in connection with work under the contract.

1018158

10% - following submission by the Contractor of the annual progress report or final report provided for in Article B-XXI, in form and content satisfactory to the Commission, within a reasonable period of time following the expiration of an annual contract period.

(b) The payments made pursuant to paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-X hereof, these payments shall not be construed as evidentiary or otherwise indicative of the amount or proportion of the work actually performed by the Contractor, and any excess payment in the light of Article B-X shall be promptly returned to the Commission.

(c) All payments under this contract, except the first payment provided in (a) above, will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

ARTICLE B-XII - NONDISCRIMINATION IN EMPLOYMENT

(The following clause is applicable unless this contract is exempt under the rules and regulations of the President's Committee on Equal Employment Opportunity issued pursuant to Executive Order No. 10925 of March 6, 1961 (26 F.R. 1977).)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to, the following: employment, upgrading, demotion or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this nondiscrimination clause.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

1018159

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the agency Contracting Officer, advising the said labor union or workers' representative of the Contractor's commitments under this clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 10925 of March 6, 1961, as amended, and of the rules, regulations, and relevant orders of the President's Committee on Equal Employment Opportunity created thereby.

(e) The Contractor will furnish all information and reports required by Executive Order No. 10925 of March 6, 1961, as amended, and by the rules, regulations, and orders of the said Committee, or pursuant thereto, and will permit access to its books, records, and accounts by the contracting agency and the Committee for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the nondiscrimination clauses of this contract or with any of the said rules, regulations, or orders, this contract may be cancelled, terminated, or suspended in whole or in part and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 10925 of March 6, 1961, as amended, and such other sanctions may be imposed and remedies invoked as provided in the said Executive Order or by rule, regulation, or order of the President's Committee on Equal Employment Opportunity, or as otherwise provided by law.

(g) The Contractor will include the provisions of paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the President's Committee on Equal Employment Opportunity issued pursuant to section 303 of Executive Order No. 10925 of March 6, 1961, as amended, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the contracting agency may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, that in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the contracting agency, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

1018160

ARTICLE B-XIII - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

ARTICLE B-XIV - WORK HOURS ACT OF 1962 - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Work Hours Act of 1962 (Public Law 87-581, 76 Stat. 357-360) and is not covered by the Walsh-Healey Public Contracts Act (41 U.S.C. 35-45), is subject to the following provisions and to all other provisions and exceptions of said Work Hours Act of 1962. If this contract is with a state or political subdivision thereof this Article shall not apply to work performed by employees of the Contractor.

(a) No contractor or subcontractor contracting for any part of the contract work shall require or permit any laborer or mechanic to be employed on such work in excess of eight hours in any calendar day or in excess of forty hours in any workweek unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

(b) In the event of any violation of the provisions of paragraph (a), the Contractor and any subcontractor responsible for such violation shall be liable to any affected employee for his unpaid wages. In addition, such contractor or subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed, with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph (a), in the sum of $10 for each calendar day on which such employee was required or permitted to work in excess of eight hours or in excess of forty hours in a workweek without payment of the required overtime wages.

(c) The Contracting Officer may withhold, or cause to be withheld, from any moneys payable on account of work performed by the Contractor or subcontractor, the full amount of wages required by this contract and such sums as may administratively be determined to be necessary to satisfy any liabilities of such contractor or subcontractor for liquidated damages as provided in paragraph (b).

(d) The Contractor agrees to insert the foregoing paragraphs (a), (b), and (c), and this paragraph (d) in all subcontracts.

1018161

ARTICLE B-XV - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XVI - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVII - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

1018162

ARTICLE B-XVIII - EXAMINATION OF RECORDS

(a) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(b) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this clause excludes (i) purchase orders not exceeding $2,500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(c) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XIX - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(i) "Components" means those articles, materials, and supplies, which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the costs of all its components. For the purposes of this (a) (iii) (B), components of foreign origin of the same type or kind as the products referred to in (b) (ii) or (iii) of this clause shall be treated as components mined, produced, or manufactured in the United States.

1018163

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XX - ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

ARTICLE B-XXI - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee (37831)

(a) Progress Report

The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also explain any significant differences between the actual level of effort and that contemplated in the contract (see Article I). Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the

1018164

report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable course and level of effort of the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in level of effort or scientific results between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report

Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals

A renewal proposal, if any, shall accompany the progress report.

(d) Report of Equipment Purchased or Fabricated

The Contractor shall itemize equipment having a useful life expectancy in excess of one year and an acquisition cost in excess of $100.00, purchased or fabricated (omit any items appearing in Article V) and submit a report thereof immediately following the expiration of the contract year specified in Article II. This report shall show the actual invoice cost of each item purchased and an engineering estimate of the cost of each item fabricated.

ARTICLE B-XXII - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXIII - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Service Administration in obtaining controlled materials and other products and materials needed to fill this order. This contract carries rating: DO-E-2 certified for national defense under DMS Regulation 1.

1018165

elects to terminate performance the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018166

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other Commission programs to Countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "Countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang; Tibet; the former Kwantung Leased Territory, the present Fort Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa).
Communist-controlled area of Viet Nam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)
North Korea
Outer Mongolia

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of the Commission on an individual case basis:

1018167

a. Employees of the Contractor engaging in employment by, activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by the Commission.

b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by Commission funds or are organized and directed by persons receiving financial support for such activities from the Commission and acting in the name of the Commission or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold a Commission security clearance will be subject to the prior approval of the Commission on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held a Commission security clearance of the Commission's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify the Commission of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is of cost type rather than a fixed-price type, shall inform the Commission, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc or other Countries shall be subject to the following policy and procedure:

a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to Countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission;

1018168

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer; and

(2) The transmittals to Countries listed in Section 2, above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to Countries listed in Group B of Section 2, above, are made in the name of the Contractor or the individual scientist and not in the name of the Commission.

c. Requests for information not falling within the scope of the above stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) Requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) Official correspondence from any government other than the United States, its territories and possessions.

As used in this Section 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints, preprints, page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within Commission programs, and available either from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

1018169

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints, preprints, page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originating within Commission programs but which are not available from the Division of Technical Information Extension, Oak Ridge, Tennessee, AEC depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosure of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosure of any information that would adversely affect the patent interest of the Commission in violation of the provisions of this contract.

1018170

Contract No. AT-(40-1)-2401
Modification No. 6

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 13th day of March, 1963, effective as of the 1st day of February, 1963, by and between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), as represented by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter referred to as the "Commission"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 5 providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to further amend the contract to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by law, including the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices), as amended, is hereby revised to read as follows:

ARTICLE I - THE RESEARCH TO BE PERFORMED

1. The Contractor shall furnish personnel facilities, equipment, materials, and supplies substantially to the extent set forth in Appendix "A" attached hereto and made a part hereof, endeavor to procure the items that may be listed under III of said Appendix "A", and therewith perform to the best of its ability the research provided for in Appendix "A" and report thereon pursuant to the provisions of this contract.

2. This work shall be conducted under the direction of Dr. R. M. Heyssel and Dr. R. T. Lagemann or such other members of the Contractor's staff as may be mutually satisfactory to the parties.

1018171

ARTICLE II - THE PERIOD FOR PERFORMANCE

The period for performance under this contract shall expire on January 31, 1964; provided, however, that this period may be extended for additional periods by the mutual written agreement of the parties.

ARTICLE III - CONSIDERATION

In full consideration of the Contractor's performance hereunder for the period commencing on February 1, 1963, and expiring on January 31, 1964, the Commission shall pay the Contractor the sum of $44,000.00.

ARTICLE IV - THE REMAINING CONTRACT PROVISIONS

Appendices "A" and "B" set forth the other provisions of this contract.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth

HERMAN ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: [signature]

TITLE: R. R. PURDY
VICE CHANCELLOR

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

APPENDIX "A"

For the Contract Period February 1, 1963 through January 31, 1964.

A-I RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct research on radioisotope tracer studies utilizing a low level whole body counting facility. Work is to be carried out in the following areas: (1) medical research by introduction of gamma emitting radioisotopes into suitable subjects including ambulatory patients from the Divisions of Endocrinology, Gastroenterology, and Hematology which allow admission of patients to the Clinical Research Center for study of disease states utilizing whole body counting methods, and (2) the measurement of levels of gamma emitting radioisotopes such as Cesium-137, and Iodine-131, in human subjects as a result of fallout from nuclear weapons tests.

A-II APPROXIMATE LEVEL OF RESEARCH EFFORT

(a) Contractor Personnel:

		Approx. % of time
Dr. R. M. Heyssel - Co-Principal Investigator		50%
Dr. R. T. Lagemann - Co-Principal Investigator	Academic	10%
	2 mos. summer	75%
Project Officer		75%
7 Research Associates		23%
Research Assistant		50%
Operations Officer, Steel Room		100%
4 Technicians		79%
Laboratory Helper		50%
2 Secretarial-Clerical		90%

(b) Premises, Facilities, and Materials to be Furnished by the Contractor:

The University's Clinical Research Center is available to conduct research on radioisotope tracer studies utilizing a low level whole body counting facility. It is adequately equipped with items necessary in carrying out the research work such as a whole body counting facility, tilting chair, card punch coupler, closed-loop television system, printer, key punch, and a calculator.

1018173

A-III EQUIPMENT TO BE PURCHASED OR FABRICATED BY CONTRACTOR

		Estimated Cost
1.	Tilting Chair	$ 488.00
2.	Card Punch Coupler	2,035.00
3.	Closed Loop Television System	963.00
4.	Printer	200.00
	TOTAL	$3,686.00

A-IV EQUIPMENT TITLE TO WHICH IS TO REMAIN WITH GOVERNMENT

Equipment previously acquired under the contract -

Low Level Whole Body Counting Device consisting of:

1. Steel Room
2. Probe and Crane, Sensing Device (crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyzer.)
3. Humidity and Temperature Control
4. Crystal assembly
5. Preamplifiers
6. Shields
7. High-voltage Dividing Networks

A-V SUBSTANTIAL DEVIATIONS

Substantial deviations from the foregoing shall be discussed with and subject to the written approval of the Commission.

APPENDIX "B"

October 12, 1962

ARTICLE B-I DEFINITIONS

1. The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for the purpose of deciding an appeal under the article entitled "Disputes".

2. The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

ARTICLE B-II INSPECTION, REPORTS, RECORDS AND ACCOUNTS, AND RESULTS

1. The Commission shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its activities under this contract.

2. The Contractor shall make progress and other reports in such manner and at such times as specified in Article B-XX. The Contractor shall also make such other reports to the Commission with respect to its activities under this contract, as the Commission may reasonably require from time to time. A copy of each article submitted by the Contractor for publication shall be promptly sent to the Commission and the Contractor shall furnish the Commission with a reprint when the article is published.

3. The Contractor agrees to keep records and books of account, in accordance with generally accepted accounting principles and practices, covering its costs and expenditures for the research work under this contract.

4. The Commission shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, for a period of three (3) years after completion of this contract.

5. Research results obtained under this contract shall be made available to all through normal and accepted channels except that no

1018175

"restricted data" as defined in the Atomic Energy Act of 1954, or other classified information, shall be disclosed to unauthorized persons. In order that public disclosure of such information will not adversely affect the patent interest of the Commission, such information shall be withheld from public disclosure if it discloses an invention, which should be promptly reported to the Commission, and in such case, it shall be withheld for a period of four (4) months after submission of the information to the Commission for patent review and possible patent application, unless the Commission approves earlier release. Any publication shall indicate that the research was supported by the Commission.

ARTICLE B-III DISCLOSURE OF INFORMATION

1. It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

2. Except as the Commission may authorize in accordance with the Atomic Energy Act of 1954, as amended, the Contractor shall not permit any individual to have access to Restricted Data until the designated investigating agency shall have made an investigation and report to the Commission on the character, associations, and loyalty of such individual and the Commission shall have determined that permitting such person to have access to Restricted Data will not endanger the common defense and security. As used in this paragraph the term "designated investigating agency" means the United States Civil Service Commission or the Federal Bureau of Investigation, or both, as determined pursuant to the provisions of the Atomic Energy Act of 1954, as amended.

3. The term "Restricted Data" as used in this Article means all data concerning the design, manufacture or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

1018176

ARTICLE B-IV RESPONSIBILITY FOR THE WORK

1. The Contractor is solely responsible for the conduct of the work.

2. Attention is directed to the fact that, among other legal requirements that may be applicable to the conduct of the work, the Contractor will be obliged to satisfy all of the Commission's regulatory requirements (including those pertaining to the obtainment of Commission licenses) that may be pertinent.

ARTICLE B-V FELLOWSHIPS

The Contractor agrees that, unless the Commission shall give its prior written approval, the Contractor shall not use any of the funds provided by the Commission under this contract to pay the stipend of any appointment for which commensurate services are not rendered under this contract or to pay any part of the stipend of a fellowship of any kind.

ARTICLE B-VI WRITTEN MATERIAL

1. The Contractor hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others to do so, all copyrightable material produced or composed or delivered to the Government or its designees under this contract, including work not first produced or composed by the Contractor in the course of performance under this contract but incorporated in the material produced or composed or delivered under this contract (but only to the extent, that the Contractor now has, or prior to final settlement of the contract may have, the right to grant such license to such previously produced or composed work without becoming liable to pay compensation to others solely because of such grant).

2. The Contractor agrees that, except as the Commission may otherwise specifically authorize in writing, the Contractor will not include in any report or other material delivered under this contract, or in any published material relating to the work under this contract, any copyrighted material owned by others which such owners have not consented to have so included.

3. Anything in this Article or otherwise in this contract notwithstanding, the Commission shall have the right to inspect, use, and have used by others, and to publish and have published at its convenience, any written material first produced or composed under this contract. The Commission will not publish in advance of the Contractor's publication without prior consultation with the Contractor.

1018177

ARTICLE B-VII PATENTS

1. Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

2. No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

3. Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purpose of paragraphs 1 and 2 of this Article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

4. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts and purchase orders, other than purchase orders for standard commercial items, provisions making this article applicable to the subcontract or the purchase order. The Contractor will insert in purchase orders for standard commercial items a provision indemnifying the Government against liability for the use of any invention or discovery and for the infringement of any Letters Patent arising by reason of the purchase, use or disposal by or for the account of the Government of items manufactured or supplied under the purchase order.

ARTICLE B-VIII PROPERTY ITEMS

1. Except as otherwise provided in this paragraph 1 and paragraph 2 of this Article B-VIII, title to all materials, supplies and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to paragraphs 2, 3, 4 and 5 of this Article B-VIII.

1018178

2. Subject to the mutual agreement of the Commission and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property, are hereinafter referred to as "Government property". Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lost its identity as personalty by reason of affixation to any realty.

3. To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain at all times and in a manner satisfactory to the Commission records showing the use and disposition of Government property, and unless otherwise authorized in writing by the Commission, shall use Government property only for the purposes of this contract. Such records shall be subject to Commission inspection at all reasonable times and the Commission shall at all reasonable times have access to the premises wherein any items of Government property are located.

4. The Contractor shall promptly notify the Commission of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from wilful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission; if the Contractor is not liable therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of the Commission.

5. With the written approval of the Commission, the Contractor may sell, transfer or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may be mutually agreed upon in writing by the Contractor and the Commission. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of Commission payments to be made under this contract, as the Commission may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to the Commission upon request (suitably packed and shipped at the Government's expense).

1018179

ARTICLE B-IX TERMINATION BY GOVERNMENT

1. The period for performance under this contract may be terminated by the Commission by written notice, either because of the breach by the Contractor of the provisions of this contract or for the convenience of the Government. In the event of such termination, the Contractor shall promptly furnish to the Commission such of the results of the work performed under this contract (and not theretofore furnished) as the Commission may request.

2. Upon a termination for convenience hereunder the parties shall agree in writing upon such amount to be paid the Contractor, in lieu of the monetary consideration specified in this contract with respect to the pertinent period, as they mutually consider to be fair and reasonable under the circumstances. If the parties fail so to agree in writing within a reasonable time, the amount shall be determined under the "Disputes" provisions of this contract. The amount otherwise due the Contractor under this contract shall be subject to such claims (if any) as the Government may have against the Contractor by reason of this contract. In the event of a termination for breach, the parties may, to the extent they mutually agree, stipulate, in writing, any monetary aspects of the stiuation.

3. In the event of a termination hereunder, the Contractor shall promptly comply with any Commission request for a refund of any partial payments in excess of such sums as are determined to be due to the Contractor under paragraph 2. above, theretofore made or for the delivery to Commission-designated recipients of any of the items of Government property acquired by the Contractor with the funds supplied by the Commission under this contract and which are then in the Contractor's possession or custody; said property shall be suitably packed and shipped at the Government's expense.

ARTICLE B-X PAYMENTS

1. The Commission shall make payments to the Contractor with respect to the amount specified in Article III of the contract, as follows:

45% - following execution of this contract, upon receipt of written request therefor from the Contractor.

45% - upon subsequent receipt of written request from the Contractor when the Contractor determines the amount requested is then required in connection with work under the contract.

1018180

10% - following submission by the Contractor of the annual progress report or final report provided for in Article B-XX, in form and content satisfactory to the Commission, within a reasonable period of time following the expiration of an annual contract period.

2. The payments made pursuant to paragraph 1 above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to Article B-IX hereof, these payments shall not be construed as evidentiary or otherwise indicative of the amount or proportion of the work actually performed by the Contractor, and any excess payment in the light of Article B-IX shall be promptly returned to the Commission.

3. All payments under this contract will be subject to the submission by the Contractor to the Commission of such invoices or vouchers as are satisfactory to the Commission.

ARTICLE B-XI NONDISCRIMINATION IN EMPLOYMENT

(The following clause is applicable unless this contract is exempt under the rules and regulations of the President's Committee on Equal Employment Opportunity issued pursuant to Executive Order No. 10925 of March 6, 1961 (26 F.R. 1977).)

In connection with the performance of work under this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to, the following: employment, upgrading, demotion or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Nondiscrimination clause.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which he has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the agency Contracting Officer, advising the said labor union or workers' representative of the

1018181

Contractor's commitments under this Nondiscrimination clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 10925 of March 6, 1961, and of the rules, regulations, and relevant orders of the President's Committee on Equal Employment Opportunity created thereby.

(e) The Contractor will furnish all information and reports required by Executive Order No. 10925 of March 6, 1961, and by the rules, regulations, and orders of the said Committee, or pursuant thereto, and will permit access to his books, records, and accounts by the contracting agency and the Committee for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Nondiscrimination clause of this contract or with any of the said rules, regulations, or orders, this contract may be cancelled in whole or in part and the Contractor may be declared ineligible for further government contracts in accordance with procedures authorized in Executive Order No. 10925 of March 6, 1961, and such other sanctions may be imposed and remedies invoked as provided in the said Executive Order or by rule, regulation, or order of the President's Committee on Equal Employment Opportunity, or as otherwise provided by law.

(g) The Contractor will include the provisions of the foregoing paragraphs (a) through (f) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the President's Committee on Equal Employment Opportunity issued pursuant to Section 303 of Executive Order No. 10925 of March 6, 1961, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the contracting agency may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the contracting agency, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

ARTICLE B-XII CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

1018182

ARTICLE B-XIII WORK HOURS ACT OF 1962 - OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Work Hours Act of 1962 (Public Law 87-581, 76 Stat. 357-360) and is not covered by the Walsh-Healey Public Contracts Act (41 U.S.C. 35-45), is subject to the following provisions and to all other provisions and exceptions of said Work Hours Act of 1962.

1. No contractor or subcontractor contracting for any part of the contract work shall require or permit any laborer or mechanic to be employed on such work in excess of eight hours in any calendar day or in excess of forty hours in any workweek unless such laborer or mechanic receives compensation at a rate not less than one and one-half times his basic rate of pay for all hours worked in excess of eight hours in any calendar day or in excess of forty hours in such workweek, whichever is the greater number of overtime hours.

2. In the event of any violation of the provisions of paragraph 1., the contractor and any subcontractor responsible for such violation shall be liable to any affected employee for his unpaid wages. In addition, such contractor or subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed, with respect to each individual laborer or mechanic employed in violation of the provisions of paragraph 1., in the sum of $10 for each calendar day on which such employee was required or permitted to work in excess of eight hours or in excess of forty hours in a workweek without payment of the required overtime wages.

3. The Contracting Officer may withhold, or cause to be withheld, from any moneys payable on account of work performed by the contractor or subcontractor, the full amount of wages required by this contract and such sums as may administratively be determined to be necessary to satisfy any liabilities of such contractor or subcontractor for liquidated damages as provided in paragraph 2.

4. The Contractor agrees to insert the foregoing provisions 1., 2., and 3., and this provision 4. in all subcontracts.

ARTICLE B-XIV DISPUTES

1. Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or his duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of

1018183

competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

2. This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph 1 above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XV OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XVI COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XVII EXAMINATION OF RECORDS

1. The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

2. The Contractor further agrees to include in all his subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this clause excluded (i) purchase orders not exceeding $2,500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

1018184

3. Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XVIII BUY AMERICAN ACT

1. In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(a) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(b) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(c) A "domestic source end product" means (i) an unmanufactured end product which has been mined or produced in the United States and (ii) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the costs of all its components. For the purposes of this 1(c) (ii), components of foreign origin of the same type or kind as the products referred to in (2) (b) or (c) of this clause shall be treated as components mined, produced, or manufactured in the United States.

2. The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(a) Which are for use outside the United States;

(b) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(c) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(d) As to which the Commission determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XIX ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Commission. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Commission.

1018185

ARTICLE B-XX REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee

(a) PROGRESS REPORT.

The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also explain any significant differences between the actual level of effort and that contemplated in the contract (see Appendix "A"). Technical reports and articles prepared for publication shall be listed with bibliographic references. Reprints or preprints of all such material shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable course and level of effort of the remainder of the current contract term. Except as the Commission may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in level of effort or scientific results between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) FINAL REPORT

Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the enitre period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) RENEWAL PROPOSALS

A renewal proposal, if any, shall accompany the progress report.

(d) REPORT OF EQUIPMENT PURCHASED OR FABRICATED

The Contractor shall itemize equipment purchased or fabricated, referred to in A-III of Appendix "A" (omit any items also appearing in A-IV of Appendix "A"), and submit a report thereof immediately following the expiration of the contract year specified in Appendix "A". This report shall show the actual invoice cost of each item purchased and an engineering estimate of the cost of each item fabricated.

1018186

ARTICLE B-XXI FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer.

ARTICLE B-XXII PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

1. This contract carries rating: DO-E-2, Certified for national defense use under DMS Reg. 1.

2. The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Business and Defense Service Administration in obtaining controlled materials and other products and materials needed to fill this order.

ARTICLE B-XXIII UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use his best efforts to place his subcontracts in accordance with this policy. In complying with the foregoing and with paragraph 2 of the article of this contract entitled "Utilization of Small Business Concerns", the Contractor in placing his subcontracts shall observe the following order of preference: (a) persistent labor surplus area concerns which are also small business concerns; (b) other persistent labor surplus area concerns; (c) substantial labor surplus area concerns which are also small business concerns; (d) other substantial labor surplus area concerns; and (e) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXIV UTILIZATION OF SMALL BUSINESS CONCERNS

1. It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

2. The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXV SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with all regulations or requirements of the Commission relating to Soviet-Bloc countries as identified by the AEC regulations or requirements.

1018187

Contract No. AT-(40-1)-2401
Modification No. 5

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 22nd day of January, 1963, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 4 (hereinafter called the "contract") providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract to provide for the performance of additional research and to provide for certain other changes; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that said contract is hereby amended in the following particulars, but in no others:

1. Subsection 1.e. of Article III is revised to read as follows:

"e. In consideration for the performance of the additional work described in Title V (as revised) of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Thirty-one Thousand, Six Hundred Ninety-two Dollars ($31,692.00), the Government will pay to the Contractor Forty-five Thousand Dollars ($45,000.00)."

2. Subsections 2.a. and 2.b. of Article III are revised to read as follows:

"a. On or before the date of commencement of the work on the project described in Appendix "A", the Government shall pay to the Contractor upon submission by the Contractor of a proper voucher, 45 per cent of the agreed consideration; provided, however, that this payment shall be reduced by the amount or amounts as may have heretofore been paid to the Contractor pursuant to Subsection 2.a. of Article III of the contract for the Contractor's anticipated performance of the research described in the original Title V of Appendix "A".

1018188

"b. On or before the expiration of six months from the date of commencement of the project, the Government shall pay to the Contractor, upon submission by the Contractor of a proper voucher 45 per cent of the agreed consideration; provided, however, that this payment shall be reduced by the amount or amounts as may have heretofore been paid to the Contractor pursuant to Subsection 2.b. of Article III of the contract for the Contractor's anticipated and/or partial performance of the research described in the original Title V of Appendix "A"."

3. Title V (as revised), attached hereto and made a part hereof, is added to Appendix "A".

4. The provisions of Appendix "B" dated April 1, 1962, which appendix is attached hereto and made a part hereof, are hereby made a part of the contract in lieu of the provisions of Appendix "B" to the contract, dated October 1, 1961.

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M. Roth
HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION

(Contracting Officer)

WITNESSES:

Nashville 7, Tennessee
1902 Dickerson Rd.
(Address)

1410 Leaf Avenue
Murfreesboro, Tennessee
(Address)

VANDERBILT UNIVERSITY

BY: Rob Roy Purdy
Dr. Rob Roy Purdy

TITLE: Vice-Chancellor

ACCEPTANCE BY SENIOR INVESTIGATOR

I have read the foregoing Supplemental Agreement and the Appendices attached hereto and made a part hereof and agree to be bound by the provisions of this document.

Senior Investigator

1018189

APPENDIX "A"

TITLE V
(REVISED)

This revised TITLE V describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will continue to conduct research on the electrolyte composition and metabolism in man through measurement of gamma emitting isotopes within the human body which are (a) naturally occurring, (b) of atmospheric origin, (c) due to accidental exposure, and (d) administered for therapeutic or research purposes. Research will be conducted in the areas of gamma ray spectrometer calibration and electronic data processing and utilization of the Low Level Whole Body Gamma Ray Spectrometer. Parameters being established in relation to the research include age, sex, race, height, weight, etc. Cooperative investigation with the Division of Endocrinology and Nutrition, Vanderbilt University, on sodium and potassium in hypertensive patients, and potassium studies in patients with heart failure are contemplated.

2. BUDGET

a. Outline of Cost Estimates

(1)	Salaries and Wages:		$47,190.00
	Dr. R. M. Heyssel (30% of time)	$ 4,140.00	
	Dr. R. T. Lagemann (10% of time)	1,500.00	
	Research Associates	13,020.00	
	Consultants	3,900.00	
	Research Assistants and Technicians	21,630.00	
	Secretarial Assistance	3,000.00	
(2)	Blue Cross, FICA, and Insurance:		1,927.00
(3)	Supplies and Services:		5,737.00
(4)	Equipment:		5,000.00

1018190

(5)	Travel:	1,500.00
(6)	Overhead (25% of Direct Costs):	15,338.00
	TOTAL	$76,692.00*

*It is recognized that the project may receive additional financial assistance from other sources as described in the Contractor's proposal to the Commission.

b. Items of property to be procured or manufactured by the Contractor, or to be furnished by the Government, title to which will vest or remain in the Government (see Article V): The following property procured or manufactured by the Contractor or furnished by the Government under earlier TITLES as well as additions and/or modifications thereto under this current TITLE:

Low Level Whole Body Counting Device consisting of:

1. Steel Room
2. Probe and Crane, Sensing Device (Crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyser)
3. Humidity and Temperature Control
4. Crystal Assembly
5. Preamplifiers
6. Shields
7. High-Voltage Dividing Networks

APPENDIX "B"

GENERAL PROVISIONS
April 1, 1962

(FOR DIRECT AEC RESEARCH CONTRACTS)

1. Patents

a. Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

b. No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

c. Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs a. and b. of this clause from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

d. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts provisions making this clause applicable to the subcontractor and its employees.

e. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all purchase orders and supply subcontracts, for the procurement of any materials, tools, machinery, equipment or supplies described in subsection 2.b. of Appendix "A" of this contract, provisions securing for itself and for the Government indemnification against liability for patent infringement with respect to the manufacture, use and sale of such materials, tools, machinery, equipment or supplies.

1018192

2. Publications

It is intended that the Contractor shall have full freedom of publication of the results of the research under this contract and the Contractor is urged to disseminate the results of the work through customary scientific publication channels, except that "Restricted Data" as defined in the Atomic Energy Act of 1954 shall be governed by the provisions of Clause 3. of this Appendix "B" entitled "Disclosure of Information".

However, in order to insure that the public disclosure of such results will not adversely affect the patent interests of the Government provided in Clause 1. of this Appendix "B" entitled "Patents", approval for such release shall be secured from the Commission prior to any such publication.

All publications shall include a reference that the results were developed under a Commission sponsored project.

3. Disclosure of Information

a. It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of the Commission, and shall promptly inform the Commission in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the contractor shall have the right to terminate performance of the work under this contract. In such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

b. Except as the Commission may authorize in accordance with the Atomic Energy Act of 1954, as amended, the Contractor shall not permit any individual to have access to Restricted Data until the designated investigating agency shall have made an investigation and report to the Commission on the character, associations, and loyalty of such individual and the Commission shall have determined that permitting such person to have access to Restricted Data will not endanger the common defense and security. As used

in this paragraph the term "designated investigating agency" means the United States Civil Service Commission or the Federal Bureau of Investigation, or both, as determined pursuant to the provisions of the Atomic Energy Act of 1954, as amended.

c. The term "Restricted Data" as used in this Article means all data concerning the design, manufacture or utilization of atomic weapons, the production of special nuclear material, or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954, as amended.

4. Soviet-Bloc Controls

In connection with the contract activities, the contractor agrees to comply with all regulations or requirements of the Commission relating to Soviet-bloc countries as identified by the AEC regulations or requirements.

5. Copyright

a. The Contractor (i) agrees that the Commission shall determine the disposition of the title to and the rights under any copyright secured by the Contractor or its employees on copyrightable material first produced or composed and delivered to the Government under this contract and (ii) hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others so to do, all copyrighted or copyrightable work not first produced or composed by the Contractor in the performance of this contract but which is incorporated in the material furnished under the contract, provided that such license shall be only to the extent the Contractor now has, or prior to the completion or final settlement of the contract may acquire, the right to grant such license without becoming liable to pay compensation to others solely because of such grant.

b. The Contractor agrees that it will not include any copyrighted material in any written or copyrightable material furnished or delivered under this contract, without a license as provided for in paragraph a. of this clause, or without the consent of the copyright owner unless specific written approval of the Commission to the inclusion of such copyrighted material is secured.

c. The Contractor agrees to report in writing to the Commission, promptly and in reasonable detail, any notice or claim of copyright infringement received by the Contractor with respect to any material delivered under this contract.

6. Disputes

a. Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless, within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

b. This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph a. of this clause; Provided, that nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

7. Safety, Health and Fire Protection

The Contractor shall take all reasonable precautions in the performance of the work under this contract to protect the health and safety of employees and members of the public and to minimize danger from all hazards to life and property, and shall comply with all health, safety, and fire protection regulations and requirements (including reporting requirements) of the Commission. In the event that the Contractor fails to comply with said regulations or requirements of the Commission, the Contracting Officer may, without prejudice to any other legal or contractual rights of the Commission,

issue an order stopping all or any part of the work; thereafter a start order for resumption of work may be issued at the discretion of the Contracting Officer. The Contractor shall make no claim for an extension of time or for compensation or damages by reason of or in connection with such work stoppage.

8. Officials Not to Benefit

No member of or delegate to Congress or resident commissioner shall be admitted to any share or part of this contract or to any benefit that may arise therefrom but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

9. Covenant Against Contingent Fees

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

10. Convict Labor

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

11. Termination

a. The Commission may at any time upon 120 days' written notice terminate this contract in whole or in part.

b. In the event of termination pursuant to paragraph a. of this clause, the Contractor shall submit a statement of costs incurred in performance of the work under the contract prior to such termination, and the Government shall pay to the Contractor that portion of the costs incurred which bears the same relationship to the total as the agreed Government support for the full term bears to the total of cost estimates for the full term, less the amount of all payments

theretofore made. If the total payments theretofore made to the Contractor exceed the amount to which it is entitled hereunder, the Contractor shall promptly remit the amount of any such excess to the Government.

12. Eight-Hour Law

a. This contract, to the extent that it is of a character specified in the Eight-Hour Law of 1912, as amended (40 U. S. Code 324-326), and is not covered by the Walsh-Healey Public Contracts Act (41 U. S. Code 35-45), is subject to the following provisions and exceptions of said Eight-Hour Law of 1912, as amended, and to all other provisions and exceptions of said Law:

No laborer or mechanic doing any part of the work contemplated by this contract, in the employ of the Contractor or any subcontractor contracting for any part of said work contemplated, shall be required or permitted to work more than eight hours in any one calendar day upon such work, except upon the condition that compensation is paid to such laborer or mechanic in accordance with the provisions of this clause. The wages of every laborer and mechanic employed by the Contractor or any subcontractor engaged in the performance of this contract shall be computed on a basic day rate of eight hours per day; and work in excess of eight hours per day is permitted only upon the condition that every such laborer and mechanic shall be compensated for all hours worked in excess of eight hours per day at not less than one and one-half times the basic rate of pay. For each violation of the requirements of this clause a penalty of five dollars shall be imposed for each laborer or mechanic for every calendar day in which such employee is required or permitted to labor more than eight hours upon said work without receiving compensation computed in accordance with this clause, and all penalties thus imposed shall be withheld for the use and benefit of the Government.

b. If this contract is with a state or political subdivision thereof:

(1) Paragraph a. of this clause shall not apply to the work performed by employees of the Contractor.

(2) The Contractor agrees to insert paragraph a. of this clause in all subcontracts hereunder with private persons or firms.

13. Nondiscrimination in Employment

(The following clause is applicable unless this contract is exempt under the rules and regulations of the President's Committee on Equal Employment Opportunity issued pursuant to Executive Order No. 10925 of March 6, 1961 (26 F.R. 1977).)

In connection with the performance of work under this contract, the Contractor agrees as follows:

a. The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to, the following: employment, upgrading, demotion or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Commission setting forth the provisions of this Nondiscrimination clause.

b. The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

c. The Contractor will send to each labor union or representative of workers with which he has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Commission, advising the said labor union or workers' representative of the Contractor's commitments under this Nondiscrimination clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

d. The Contractor will comply with all provisions of Executive Order No. 10925 of March 6, 1961, and of the rules, regulations, and relevant orders of the President's Committee on Equal Employment Opportunity created thereby.

e. The Contractor will furnish all information and reports required by Executive Order No. 10925 of March 6, 1961, and by the rules, regulations, and orders of the said Committee, or pursuant thereto, and will permit access to his books, records, and accounts by the Commission and the Committee for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

f. In the event of the Contractor's noncompliance with the Nondiscrimination clause of this contract or with any of the said rules, regulations, or orders, this contract may be cancelled in whole or in part and the Contractor may be declared ineligible for further government contracts in accordance with procedures authorized in Executive Order No. 10925 of March 6, 1961, and such other sanctions may be imposed and remedies invoked as provided in the said Executive order or by rule, regulation, or order of the President's Committee on Equal Employment Opportunity, or as otherwise provided by law.

g. The Contractor will include the provisions of the foregoing paragraphs a. through f. in every subcontract or purchase order unless exempted by rules, regulations, or orders of the President's Committee on Equal Employment Opportunity issued pursuant to section 303 of Executive Order No. 10925 of March 6, 1961, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

14. Definitions

As used in this contract:

a. The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successor or any duly authorized representative of such person.

b. The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for deciding an appeal under the clause entitled "Disputes".

c. Except as otherwise provided in this contract, the term "subcontract" shall include purchase orders under this contract.

15. Fellowships

It is understood by the Contractor that none of the funds supplied by the Commission under this contract shall be used in any way to pay the stipend of any appointment for which commensurate services are not rendered under this contract; nor shall any of the funds be used to confer a fellowship, or to pay any part of the stipend of a fellowship, of any kind.

16. Foreign Travel

It is agreed that none of the funds supplied by the Commission under this contract shall be used to pay the expenses of foreign travel, except where such foreign travel is made with the prior approval of the Commission. "Foreign travel" as used herein means travel outside the continental United States, excepting, however, travel to Canada.

17. Buy American Act

a. In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(1) "Components" means those articles, materials, and supplies, which are directly incorporated in the end products;

(2) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(3) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 per cent of the costs of all its components. For the purposes of this a.(3)(B), components of foreign origin of the same type or kind as the products referred to in b.(2) or (3) of this clause shall be treated as components mined, produced, or manufactured in the United States.

b. The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

1018200

(1) Which are for use outside the United States;

(2) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(3) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(4) As to which the Commission determines the cost to the Government to be unreasonable.

18. Utilization of Concerns in Labor Surplus Areas

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus where this can be done consistent with the efficient performance of the contract, at prices no higher than are obtainable elsewhere. The Contractor agrees to use his best efforts to place his subcontracts in accordance with this policy. In complying with the foregoing and with paragraph b. of the clause of this contract entitled "Utilization of Small Business Concerns", the Contractor in placing his subcontracts shall observe the following order of preference: (1) persistent labor surplus area concerns which are also small business concerns; (2) other persistent labor surplus area concerns; (3) substantial labor surplus area concerns which are also small business concerns; (4) other substantial labor surplus area concerns; and (5) small business concerns which are not labor surplus area concerns.

19. Utilization of Small Business Concerns

a. It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

b. The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

Contract No. AT-(40-1)-2401
Modification No. 4

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 5th day of April, 1962, effective as of the 1st day of February 1962, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the parties hereto have heretofore entered into Contract No. AT-(40-1)-2401 and Modifications thereto numbered 1 through 3 (hereinafter called the "contract") providing for the Contractor's performance of certain research; and

WHEREAS, the parties desire to amend the contract to provide for: (a) the continuance of this research and/or the performance of additional research; (b) the revisions and/or additions of certain provisions thereof in accordance with current applicable rules and regulations of the Commission; and (c) as a result thereof, restate the provisions of this contract as of the effective date of this Supplemental Agreement; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties do mutually agree that the contract (including its Appendices) is hereby revised to read as follows:

ARTICLE I - SCOPE

1. The work shall consist of research concerning utilization of low level whole body counting facility in the measurement of electrolyte composition and metabolism in man. The plan of approach to the problem and the agreed upon program and budget for the project are described in Appendix "A", which is hereby made a part of this contract. The Contractor shall be guided by, but not bound to conform to the details of, the budget described in Appendix "A".

2. The Contractor shall furnish all services, facilities, equipment, supplies and materials (except such services, equipment, supplies and materials as the Government has agreed to furnish herein) required for the performance of the research program described in section 1, above.

1018202

3. The work will be carried out by the Contractor under the direction of Dr. Robert T. Lagemann and Dr. Robert M. Heyssel as Senior Investigators. Any change in Senior Investigators shall be made only with the written concurrence of the Commission, but without the necessity of a formal modification of the contract.

4. The Contractor shall commence the work as soon as feasible, prosecute it with due diligence and submit the reports required in Appendix "C", attached hereto and made a part hereof, as early as practicable but not later than the dates specified in Appendix "C".

ARTICLE II - SCHEDULE

5. The period during which the work under the contract may be conducted shall end on January 31, 1963.

ARTICLE III

1. Consideration

e. In consideration of the performance of the research activities described in TITLE V of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Thirty Thousand, Four Hundred Forty-two Dollars ($30,442.00), the Government shall pay to the Contractor Forty Thousand Dollars ($40,000.00).

2. Payment

a. On or before the date of commencement of work on the project described in Appendix "A", the Government shall pay to the Contractor, upon submission by the Contractor of a proper voucher, 45 per cent of the agreed consideration.

b. On or before the expiration of six months from the date of commencement of the project, the Government shall pay to the Contractor, upon submission by the Contractor of a proper voucher, 45 per cent of the agreed consideration.

c. Upon receipt and acceptance of a satisfactory progress report in cases where the contract is to be renewed, or the final report if

1018203

the contract is not to be renewed, the Government shall pay to the Contractor, upon submission by the Contractor of a proper voucher, the remaining 10 per cent of the agreed consideration. An extension of the contract work without additional funds shall not be considered a renewal of the contract and in such cases the retained 10 per cent of the agreed consideration will be paid upon submission and acceptance of a satisfactory final report.

d. In the event the contract is renewed, payments to the Contractor of any additional amount to be paid by the Government shall be made for the extended work in accordance with the schedule outlined in subsections a, b, and c, above.

3. Contract Renewal

When renewal of the contract is desired, the Contractor shall submit a renewal proposal, a progress report and a 200-word summary in such manner and at such times as specified in Appendix "C". The Contractor and the Commission shall then negotiate as to the amounts each will contribute for the additional research activities to be conducted, taking into consideration the actual costs incurred for the current work in comparison with the cost estimates in the contract, and, upon agreement, shall execute a formal modification of the contract.

ARTICLE IV - REPORTS, RECORDS AND INSPECTION

1. The Commission shall have the right to inspect in such manner and at such times as it deems appropriate all activities of the Contractor arising in the course of the work under this contract.

2. The Commission shall at all times be afforded access to the premises and to all technical records, correspondence, instructions, drawings and memoranda of record value of the Contractor pertaining to said work.

3. The Contractor shall submit a complete scientific report and such other reports as may be required in Appendix "C" in such manner and at such times as specified in Appendix "C" and shall submit such other reports as required by this contract in such manner and at such times as requested by the Commission.

4. Examination of Records

a. The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly

1018204

pertinent books, documents, papers and records of the Contractor involving transactions related to this contract.

b. The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this clause excludes (i) purchase orders not exceeding $2500 and (ii) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

c. Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE V - PROPERTY

1. In consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies acquired from any source, including the Government, or manufactured by the Contractor under this contract, shall vest in the Contractor, except that title to items of property described in subsection 2.b. of Appendix "A" shall vest or remain in the Government. Additional items may be added to such subsection 2.b. in writing without the necessity for a formal modification of the contract.

2. a. Title to Property. All property listed in subsection 2.b. of Appendix "A", title to which shall vest or remain in the Government, is hereinafter referred to as "Government Property". Title to any property acquired by the Contractor for the Government as provided in this contract shall pass directly from the vendor thereof to the Government. Title to Government Property shall not be affected by the incorporation of the property into or the attachment of it to any property not owned by the Government, nor shall such Government Property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

b. Identification. To the extent directed by the Contracting Officer, the Contractor shall identify Government Property coming into the Contractor's possession or custody by marking or segregation in such a way, satisfactory to the Contracting Officer, as shall indicate its ownership by the Government.

1018205

c. Disposition. The Contractor shall make such disposition of Government Property which has come into the possession or custody of the Contractor under this contract as the Contracting Officer shall direct. When authorized in writing by the Contracting Officer during the progress of the work or upon completion or termination of this contract, the Contractor may, upon such terms and conditions as the Contracting Officer may approve, sell or exchange such property, or acquire such property at a price agreed upon by the Contracting Officer and the Contractor as the fair value thereof. The amount received by the Contractor as the result of any disposition, or the amount of the agreed fair value of any such property acquired by the Contractor, shall be applied in reduction of the consideration provided by the Government under this contract, or shall be otherwise credited to the account of the Government, as the Contracting Officer may direct. Upon completion of the work or the termination of this contract, or at such earlier time as may be requested by the Contracting Officer, the Contractor shall render an accounting, as prescribed by the Contracting Officer, of all Government Property which has come into the possession or custody of the Contractor under this contract.

d. Protection of Government Property - Classified Materials. The Contractor shall take all reasonable precautions, as directed by the Contracting Officer, or in the absence of such directions in accordance with sound industrial practice, to safeguard and protect Government Property in the Contractor's possession or custody. Special measures shall be taken by the Contractor in the protection of and accounting for any classified or special materials involved in the performance of this contract, in accordance with the regulations and requirements of the Commission.

e. Risk of Loss of Government Property. The Contractor shall not be liable for loss or destruction of or damage to Government Property in the Contractor's possession unless such loss, destruction or damage results from wilful misconduct or lack of good faith on the part of the Contractor's corporate officers or the Senior Investigator under this contract, or unless such loss, destruction or damage results from a failure on the part of the Contractor's corporate officers or the Senior Investigator under this contract to take all reasonable steps to comply with any appropriate written directives of the Contracting Officer to safeguard such property under subsection 2.d. hereof.

f. Steps to be Taken In Event of Loss. Upon the happening of any loss or destruction of or damage to Government Property in the possession or custody of the Contractor, the Contractor shall immediately inform the Contracting Officer of the occasion and extent thereof, shall take all reasonable steps to protect the property remaining, and shall repair or replace the lost, destroyed, or damaged property if and as directed by the Contracting Officer, but shall take no action prejudicial to the right of the Government to recover therefor and shall furnish to the Government on request all reasonable assistance in obtaining recovery.

g. Government Property for Government Use Only. Except as otherwise authorized by the Contracting Officer, Government Property shall be used only for the performance of this contract.

ARTICLE VI - PROCUREMENT OF MATERIAL AND SERVICES FROM COMMISSION FACILITIES; COMPLIANCE WITH COMMISSION REGULATIONS

The Contractor shall comply with all licensing and other requirements of the Commission with respect to possession and use of by-product material, source material, and special nuclear material (as these terms are defined in the Atomic Energy Act of 1954), and may purchase or acquire such materials, irradiation services, other radioactive material, cyclotron time, etc., from the Commission or Commission facilities in accordance with applicable procedures.

ARTICLE VII - GENERAL PROVISIONS

The provisions of Appendix "B", dated October 1, 1961, attached hereto, are hereby made a part of this contract.

ARTICLE VIII - ALTERATIONS

The following alterations to this contract were made by mutual agreement of the parties prior to its execution: None.

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Richard B. Martin

RESEARCH

(Contracting Officer)

WITNESSES:

Nashville 5, Tenn.
(Address)

Nashville 5, Tenn.
(Address)

VANDERBILT UNIVERSITY

BY: John H. Stambaugh

TITLE: Vice-Chancellor

ACCEPTANCE BY SENIOR INVESTIGATORS

We have read the foregoing Supplemental Agreement and the Appendices attached hereto and made a part hereof and agree to be bound by the provisions of this document.

Senior Investigator

Senior Investigator

APPENDIX "A"

TITLE V

This TITLE V describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will continue to conduct research on the electrolyte composition and metabolism in man through measurement of gamma emitting isotopes within the human body which are (a) naturally occurring, (b) of atmospheric origin, (c) due to accidental exposure, and (d) administered for therapeutic or research purposes. Research will be conducted in the areas of gamma ray spectrometer calibration and electronic data processing and utilization of the Low Level Whole Body Gamma Ray Spectrometer. Parameters being established in relation to the research include age, sex, race, height, weight, etc. Cooperative investigation with the Division of Endocrinology and Nutrition, Vanderbilt University, on sodium and potassium in hypertensive patients, and potassium studies in patients with heart failure are contemplated.

2. BUDGET

a. Outline of Cost Estimates:

(1)	Salaries and Wages:		$47,190.00
	Dr. R. M. Heyssel (30% of time)	$ 4,140.00	
	Dr. R. T. Lagemann (10% of time)	1,500.00	
	Research Associates	13,020.00	
	Consultants	3,900.00	
	Research Assistants and Technicians	21,630.00	
	Secretarial Assistance	3,000.00	
(2)	Blue Cross, FICA, and Insurance:		1,927.00
(3)	Supplies and Services:		5,737.00

(4)	Travel:	1,500.00
(5)	Overhead (25% of Direct Costs):	14,088.00
	TOTAL	$70,442.00*

*It is recognized that the project may receive additional financial assistance from other sources as described in the Contractor's proposal to the Commission.

b. Items of property to be procured or manufactured by the Contractor, or to be furnished by the Government, title to which will vest or remain in the Government (see Article V): None, except that it is recognized that title to the following property procured or manufactured by the Contractor or furnished by the Government under earlier TITLES remains in the Government:

Low Level Whole Body Counting Device consisting of:

1. Steel Room

2. Probe and Crane, Sensing Device (Crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyser)

3. Humidity and Temperature Control

APPENDIX "B"

GENERAL PROVISIONS
October 1, 1961

(FOR DIRECT AEC RESEARCH CONTRACTS)

1. Patents

a. Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of or under this contract, the Contractor shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

b. No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

c. Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs a. and b. of this clause from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

d. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts provisions making this clause applicable to the subcontractor and its employees.

e. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all purchase orders and supply subcontracts, for the procurement of any materials, tools, machinery, equipment or supplies described in subsection 2.b. of Appendix "A" of this contract, provisions securing for itself and for the Government indemnification against liability for patent infringement with respect to the manufacture, use and sale of such materials, tools, machinery, equipment or supplies.

1018211

2. Publications

It is intended that the Contractor shall have full freedom of publication of the results of the research under this contract and the Contractor is urged to disseminate the results of the work through customary scientific publication channels, except that "Restricted Data" as defined in the Atomic Energy Act of 1954 shall be governed by the provisions of Clause 3. of this Appendix "B" entitled "Security".

However, in order to insure that the public disclosure of such results will not adversely affect the patent interests of the Government provided in Clause 1. of this Appendix "B" entitled "Patents", approval for such release shall be secured from the Commission prior to any such publication.

All publications shall include a reference that the results were developed under a Commission sponsored project.

3. Security

a. It is understood that the work under this contract will not involve restricted data or other classified matter and that the Contractor will perform such work as unclassified work. However, if in the course of such work any discoveries are made or any data used or developed that constitute restricted data or other classified matter, the Contractor shall promptly inform the Commission and will be bound by the following:

(1) Contractor's Duty to Safeguard Restricted Data and Other Classified Information. In the performance of the work under this contract the Contractor shall, in accordance with the Commission's security regulations and requirements, be responsible for safeguarding restricted data and other classified matter and protecting against sabotage, espionage, loss and theft, the classified documents, materials, equipment, processes, etc., as well as such other material of high intrinsic or strategic value as may be in the Contractor's possession in connection with performance of work under this contract. Except as otherwise expressly provided in the specifications the Contractor shall upon completion or termination of this contract transmit to the Commission any classified matter in the possession of the Contractor or any person under the Contractor's control in connection with performance of this contract.

(2) Regulations. The Contractor agrees to conform to all security regulations and requirements of the Commission.

(3) Definition of Restricted Data. The term "Restricted Data", as used in this clause, means all data concerning (1) design, manufacture, or utilization of atomic weapons; (2) the production of special nuclear material; or (3) the use of special nuclear material in the production of energy, but shall not include data declassifed or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954.

(4) Security Clearance of Personnel. Except as the Commission may authorize, in accordance with the Atomic Energy Act of 1954, the Contractor shall not permit any individual to have access to Restricted Data until the designated investigating agency shall have made an investigation and report to the Commission on the character, associations, and loyalty of such individual and the Commission shall have determined that permitting such person to have access to Restricted Data will not endanger the common defense and security. As used in this paragraph, the term "designated investigating agency" means the United States Civil Service Commission or the Federal Bureau of Investigation, or both, as determined pursuant to the provisions of the Atomic Energy Act of 1954. Access to classified information other than Restricted Data shall not be granted unless the recipient possesses appropriate security clearance.

(5) Criminal Liability. It is understood that disclosure of information relating to the work or services ordered hereunder to any person not entitled to receive it, or failure to safeguard any Restricted Data or any top secret, secret, or confidential matter that may come to the Contractor or any person under the Contractor's control in connection with work under this contract, may subject the Contractor, its agents, employees, and subcontractors to criminal liability under the laws of the United States. (See the Atomic Energy Act of 1954, 68 Stat. 919), (See also Executive Order 10104 of February 1, 1950, 15 F. R. 597).

(6) Subcontracts and Purchase Orders. Except as otherwise authorized in writing by the Contracting Officer, the Contractor shall insert provisions similar to the foregoing in all subcontracts and purchase orders under this contract.

b. The continuation by the Contractor of work found to involve restricted data will be subject to mutual agreement of the Commission and the Contractor and shall be covered by a modification of this agreement.

4. Disputes

a. Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless, within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

b. This "Disputes" clause does not preclude consideration of law questions in connection with decisions provided for in paragraph a. of this clause; Provided, that nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

5. Safety, Health and Fire Protection

The Contractor shall take all reasonable precautions in the performance of the work under this contract to protect the health and safety of employees and members of the public and to minimize danger from all hazards to life and property, and shall comply with all health, safety, and fire protection regulations and requirements (including reporting requirements) of the Commission. In the event that the Contractor fails to comply with said regulations or requirements of the Commission, the Contracting Officer may, without prejudice to any other legal or contractual rights of the Commission,

issue an order stopping all or any part of the work; thereafter a start order for resumption of work may be issued at the discretion of the Contracting Officer. The Contractor shall make no claim for an extension of time or for compensation or damages by reason of or in connection with such work stoppage.

6. Officials Not to Benefit

No member of or delegate to Congress or resident commissioner shall be admitted to any share or part of this contract or to any benefit that may arise therefrom but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

7. Covenant Against Contingent Fees

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

8. Convict Labor

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment at hard labor.

9. Termination

a. The Commission may at any time upon 120 days' written notice terminate this contract in whole or in part.

b. In the event of termination pursuant to paragraph a. of this clause, the Contractor shall submit a statement of costs incurred in performance of the work under the contract prior to such termination, and the Government shall pay to the Contractor that portion of the costs incurred which bears the same relationship to the total as the agreed Government support for the full term bears to the total of cost estimates for the full term, less the amount of all payments

theretofore made. If the total payments theretofore made to the Contractor exceed the amount to which it is entitled hereunder, the Contractor shall promptly remit the amount of any such excess to the Government.

10. Eight-Hour Law

a. This contract, to the extent that it is of a character specified in the Eight-Hour Law of 1912, as amended (40 U. S. Code 324-326), and is not covered by the Walsh-Healey Public Contracts Act (41 U. S. Code 35-45), is subject to the following provisions and exceptions of said Eight-Hour Law of 1912, as amended, and to all other provisions and exceptions of said Law:

No laborer or mechanic doing any part of the work contemplated by this contract, in the employ of the Contractor or any subcontractor contracting for any part of said work contemplated, shall be required or permitted to work more than eight hours in any one calendar day upon such work, except upon the condition that compensation is paid to such laborer or mechanic in accordance with the provisions of this clause. The wages of every laborer and mechanic employed by the Contractor or any subcontractor engaged in the performance of this contract shall be computed on a basic day rate of eight hours per day; and work in excess of eight hours per day is permitted only upon the condition that every such laborer and mechanic shall be compensated for all hours worked in excess of eight hours per day at not less than one and one-half times the basic rate of pay. For each violation of the requirements of this clause a penalty of five dollars shall be imposed for each laborer or mechanic for every calendar day in which such employee is required or permitted to labor more than eight hours upon said work without receiving compensation computed in accordance with this clause, and all penalties thus imposed shall be withheld for the use and benefit of the Government.

b. If this contract is with a state or political subdivision thereof:

(1) Paragraph a. of this clause shall not apply to the work performed by employees of the Contractor.

(2) The Contractor agrees to insert paragraph a. of this clause in all subcontracts hereunder with private persons or firms.

11. Nondiscrimination in Employment

In connection with the performance of work under this contract, the Contractor agrees as follows:

a. The Contractor will not discriminate against any employee or applicant for employment because of race, creed, color, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin. Such action shall include, but not be limited to, the following: employment, upgrading, demotion or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Commission setting forth the provisions of this Nondiscrimination clause.

b. The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, creed, color, or national origin.

c. The Contractor will send to each labor union or representative of workers with which he has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Commission, advising the said labor union or workers' representative of the Contractor's commitments under this Nondiscrimination clause, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

d. The Contractor will comply with all provisions of Executive Order No. 10925 of March 6, 1961, and of the rules, regulations, and relevant orders of the President's Committee on Equal Employment Opportunity created thereby.

e. The Contractor will furnish all information and reports required by Executive Order No. 10925 of March 6, 1961, and by the rules, regulations, and orders of the said Committee, or pursuant thereto, and will permit access to his books, records, and accounts by the Commission and the Committee for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

f. In the event of the Contractor's noncompliance with the Nondiscrimination clause of this contract or with any of the said rules, regulations, or orders, this contract may be cancelled in whole or in part and the Contractor may be declared ineligible for further government contracts in accordance with procedures authorized in Executive Order No. 10925 of March 6, 1961, and such other sanctions may be imposed and remedies invoked as provided in the said Executive order or by rule, regulation, or order of the President's Committee on Equal Employment Opportunity, or as otherwise provided by law.

g. The Contractor will include the provisions of the foregoing paragraphs a. through f. in every subcontract or purchase order unless exempted by rules, regulations, or orders of the President's Committee on Equal Employment Opportunity issued pursuant to section 303 of Executive Order No. 10925 of March 6, 1961, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Commission may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by the Commission, the Contractor may request the United States to enter into such litigation to protect the interests of the United States.

12. Definitions

As used in this contract:

a. The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successor or any duly authorized representative of such person.

b. The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for deciding an appeal under the clause entitled "Disputes".

c. Except as otherwise provided in this contract, the term "subcontract" shall include purchase orders under this contract.

13. Fellowships

It is understood by the Contractor that none of the funds supplied by the Commission under this contract shall be used in any way to pay the stipend of any appointment for which commensurate services are not rendered under this contract; nor shall any of the funds be used to confer a fellowship, or to pay any part of the stipend of a fellowship, of any kind.

14. Foreign Travel

It is agreed that none of the funds supplied by the Commission under this contract shall be used to pay the expenses of foreign travel, except where such foreign travel is made with the prior approval of the Commission. "Foreign travel" as used herein means travel outside the continental United States, excepting, however, travel to Canada.

15. Buy American Act

a. In acquiring end products, the Buy American Act (41 U.S. Code 10a-d) provides that the Government give preference to domestic source end products. For the purpose of this clause:

(1) "Components" means those articles, materials, and supplies, which are directly incorporated in the end products;

(2) "End products" means those articles, materials, and supplies, which are to be acquired under this contract for public use; and

(3) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the costs of all its components. For the purposes of this a.(3)(B), components of foreign origin of the same type or kind as the products referred to in b.(2) or (3) of this clause shall be treated as components mined, produced, or manufactured in the United States.

b. The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(1) Which are for use outside the United States;

(2) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(3) As to which the Commission determines the domestic preference to be inconsistent with the public interest; or

(4) As to which the Commission determines the cost to the Government to be unreasonable.

16. Utilization of Concerns in Labor Surplus Areas

It is the policy of the Government to place contracts with concerns which will perform such contracts substantially in areas of persistent or substantial labor surplus where this can be done consistent with the efficient performance of the contract, at prices no higher than are obtainable elsewhere. The Contractor agrees to use his best efforts to place his subcontracts in accordance with this policy. In complying with the foregoing and with paragraph b. of the clause of this contract entitled "Utilization of Small Business Concerns", the Contractor in placing his subcontracts shall observe the following order of preference: (1) persistent labor surplus area concerns which are also small business concerns; (2) other persistent labor surplus area concerns; (3) substantial labor surplus area concerns which are also small business concerns; (4) other substantial labor surplus area concerns; and (5) small business concerns which are not labor surplus area concerns.

17. Utilization of Small Business Concerns

a. It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

b. The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

18. Copyright

a. The Contractor (i) agrees that the Commission shall determine the disposition of the title to and the rights under any copyright secured by the Contractor or its employees on copyrightable material first produced or composed and delivered to the Government under this contract and (ii) hereby grants to the Government a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use and dispose of, and to authorize others so to do, all copyrighted or copyrightable work not first produced or composed by the Contractor in the performance of this contract but which is incorporated in the material furnished under the contract, provided that such license shall be only to the extent the Contractor now has, or prior to the completion or final settlement of the contract may acquire, the right to grant such license without becoming liable to pay compensation to others solely because of such grant.

b. The Contractor agrees that it will not include any copyrighted material in any written or copyrightable material furnished or delivered under this contract, without a license as provided for in paragraph a. of this clause, or without the consent of the copyright owner unless specific written approval of the Commission to the inclusion of such copyrighted material is secured.

c. The Contractor agrees to report in writing to the Commission, promptly and in reasonable detail, any notice or claim of copyright infringement received by the Contractor with respect to any material delivered under this contract.

1018221

APPENDIX "C"

REPORTS AND PROPOSALS
August 1, 1961

(FOR DIRECT AEC RESEARCH CONTRACTS OTHER THAN OID)

1. If the Contractor contemplates renewal of this contract, the Contractor shall submit the number of copies of the following as indicated:

a. Renewal Proposal	Six (6)
b. Progress Report	Six (6)
c. 200-Word Summary of Purpose and Scope of Proposed Research	Three (3)

The above may be submitted at any time after the expiration of six (6) months of the current contract period, but in no event shall the above be submitted later than ninety (90) days prior to the date of expiration of the current contract period.

2. If the Contractor does not contemplate a renewal of this contract, or if the Contractor's renewal proposal is not accepted by the Commission, the Contractor shall submit six (6) copies of a Complete Scientific Report on the date of expiration of this contract.

3. Brief reports or manuscripts may be submitted as desired by the Senior Investigator.

4. All reports shall be addressed and delivered, postage prepaid, to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee

5. The Complete Scientific Report shall include a complete technical summary of the results of the research performed under the contract from the date of its inception through the date of its expiration. Results of the investigations and developments should be described in sufficient detail to allow other interested groups to fully utilize the information.

1018222

6. The 200-Word Summary shall be set forth on a form entitled "Notice of Research Project". This form will be furnished by the Commission.

7. The Progress Report shall briefly describe the scope of investigations undertaken and the significant results obtained. It should also explain any significant differences between the actual level of activity (expressed in the various categories of man months, facilities procured, travel performed, etc.) and that contemplated in the contract. Technical reports and articles prepared for publication should be listed with bibliographic references. Reprints or preprints of all such material should be appended and material contained therein need not be duplicated in the report.

8. Renewal proposals shall contain the type of information outlined below unless the information is already contained in earlier proposals or in the accompanying progress report. Any contemplated change in program or scope for the additional work should be clearly explained and the cost estimated should be based upon past experience.

   a. Title of the project.

   b. The institution and department in which the work will be done.

   c. Scientific background including literature relevant to the proposal, the significance, and the motivation. If the proposal is for continuation of work already in progress the extent of present support should be stated identifying amounts received from other Federal agencies.

   d. Scientific scope of the proposed research, its objectives, its relation to present knowledge and to comparable work in progress elsewhere, and a plan of accomplishments for the work.

   e. Scientific Personnel. Give the name, highest academic degree, position in the institution, scientific experience, publications and accomplishments of the Senior Investigator (the individual who will actively direct the research program) and of each regular staff scientist who it is proposed will engage in the work. Indicate the approximate fraction of the time of each to be devoted to the project. Scientific personnel to be newly employed for the project should be so designated, and professional records given if possible.

f. Other Personnel. The number of persons of each sub-professional grade and the fraction of the time of each to be devoted to the project should be listed. Graduate student employees should be identified as such if their thesis is to be related to the project.

g. Other Financial Assistance. If assistance for this or other activities involving the same personnel or facilities is to be proposed to or received from other Federal or non-university sources the extent of that assistance should be clearly stated, and the interplay of the arrangements should be fully explained.

h. Materials, Equipment and Facilities. List those already available for the work and justify the need for major items to be procured.

i. Travel and Other Items. Explain the purpose of the proposed travel, and of any other major items in the budget. Travel rates and the use of contract funds for attendance at regular scientific meetings should conform with the policy of the institution in the use of its own funds for these purposes.

j. Budget. This should list in detail all items of cost necessary to carry the project. It should include: a list of the individual salaries attributable to the project, supplies and services, equipment (defined as things individually costing more than $500 which will retain their utility for more than a year), travel, communication and publication, and the indirect costs allocable to the project. The basis for computing the indirect costs should be briefly explained. The budget should not include the stipend of fellows. All salaries chargeable to the project should be in accord with the established policies of the institution, or, if not, an explanation should be submitted.

k. Amount Requested. A statement of the part of the total amount listed in the budget which the institution is prepared to bear, and the amount requested from the AEC, and a statement of any other sponsors of the project with the amounts contributed by each. The proposal should be signed by the Senior Investigator and endorsed by a responsible administrative officer of the institution.

l. Statement of Current Expenditures. A current statement of its expenditures for the project, and an estimate of expenses to be incurred.

1018224

m. Residual Funds. Any difference in the scope of the work from that contemplated in the contract, as brought out in the report, may be reflected in the amount requested. If no new funds are required, the contract may be renewed without funds. A proposal for such renewal should state the scope of the work proposed for use of residual funds.

1018225

Contract No. AT-(40-1)-2401
Vanderbilt University
Modification No. 3

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this [illegible] day of [illegible], 1961, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-2401, dated June 3, 1958, providing for the establishment and operation of a low level whole body counting facility; and

WHEREAS, the Contract has been amended heretofore by Modifications Nos. 1 and 2; and

WHEREAS, the Commission desires to provide for additional research as more particularly described in TITLE IV of Appendix "A", to obtain reports thereon, and to effect certain other changes as are hereinafter more particularly described; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties hereto do mutually agree that this Contract is hereby modified in the following particulars, but in no others:

1. The following new section "4." is added to Article II:

"4. The period during which the work under this Contract may be conducted is hereby extended to January 31, 1962."

2. The following new subsection "1.d." is added in Article III:

"d. In consideration of the performance of the additional work described in TITLE IV of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Thirty-seven Thousand, Six Hundred Ninety-five Dollars ($37,695.00), the Government will pay to the Contractor Forty Thousand Dollars ($40,000.00)."

1018226

3. Subsection 2.a. of Article III is revised to read as follows:

"a. On or before the date of commencement of the work on the project described in Appendix "A", the Government shall pay to the Contractor upon submission by the Contractor of a proper voucher, 45 per cent of the agreed consideration."

4. The following sentence is added to subparagraph 3.a. (4) of Appendix "B":

"Access to classified information other than Restricted Data shall not be granted unless the recipient possesses appropriate security clearance."

5. Paragraph 16. of Appendix "B" is revised to read as follows:

"16. Use of Concerns in Labor Surplus Areas

It is the policy of the Government to place supply contracts with suppliers who will perform such contracts substantially in areas of current labor surplus where this can be done at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy to the extent consistent with the efficient performance of this contract. In complying with the foregoing, the Contractor, in placing its subcontracts, shall observe the following order of preference:

a. small business concerns located in labor surplus areas;

b. other concerns located in labor surplus areas;

c. small business concerns not located in labor surplus areas; and

d. any other concerns."

6. The following new paragraph "17." is added to Appendix "B":

"17. Use of Small Business Concerns

a. It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services be procured from small business concerns.

b. The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract."

1018227

7. Article V is deleted in its entirety, and the following new Article V is substituted therefor:

"ARTICLE V - PROPERTY

"1. In consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies acquired from any source, including the Government, or manufactured by the Contractor under this contract, shall vest in the Contractor, except that title to items of property described in section 2.b. of Appendix "A" shall vest or remain in the Government. Additional items may be added to such section 2.b. in writing without the necessity for a formal modification of the contract.

"2. (a) Title to Property. All property listed in section 2.b. of Appendix "A", title to which shall vest or remain in the Government, is hereinafter referred to as Government property. Title to any property acquired by the Contractor for the Government as provided in this contract shall pass directly from the vendor thereof to the Government. Title to Government property shall not be affected by the incorporation of the property into or the attachment of it to any property not owned by the Government, nor shall such Government property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(b) Identification. To the extent directed by the Contracting Officer, the Contractor shall identify Government property coming into the Contractor's possession or custody by marking or segregation in such a way, satisfactory to the Contracting Officer, as shall indicate its ownership by the Government.

(c) Disposition. The Contractor shall make such disposition of Government property which has come into the possession or custody of the Contractor under this contract as the Contracting Officer shall direct. When authorized in writing by the Contracting Officer during the progress of the work or upon completion or termination of this contract, the Contractor may, upon such terms and conditions as the Contracting Officer may approve, sell or exchange such property, or acquire such property at a price agreed upon by the Contracting Officer and the Contractor as the fair value thereof. The amount received by the Contractor as the result of any disposition, or the amount of the agreed fair value of any such property acquired by the Contractor, shall be applied in reduction of the consideration provided by the Government under this contract, or shall be otherwise credited to the account of

the Government, as the Contracting Officer may direct. Upon completion of the work or the termination of this contract, or at such earlier time as may be requested by the Contracting Officer, the Contractor shall render an accounting, as prescribed by the Contracting Officer, of all Government property which has come into the possession or custody of the Contractor under this contract.

(d) Protection of Government Property - Classified Materials. The Contractor shall take all reasonable precautions, as directed by the Contracting Officer, or in the absence of such directions in accordance with sound industrial practice, to safeguard and protect Government property in the Contractor's possession or custody. Special measures shall be taken by the Contractor in the protection of and accounting for any classified or special materials involved in the performance of this contract, in accordance with the regulations and requirements of the Commission.

(e) Risk of Loss of Government Property. The Contractor shall not be liable for loss or destruction of or damage to Government property in the Contractor's possession unless such loss, destruction or damage results from wilful misconduct or lack of good faith on the part of the Contractor's corporate officers or the Senior Investigator under this contract, or unless such loss, destruction or damage results from a failure on the part of the Contractor's corporate officers or the Senior Investigator under this contract to take all reasonable steps to comply with any appropriate written directives of the Contracting Officer to safeguard such property under paragraph (d) hereof.

(f) Steps to be Taken in Event of Loss. Upon the happening of any loss or destruction of or damage to Government property in the possession or custody of the Contractor, the Contractor shall immediately inform the Contracting Officer of the occasion and extent thereof, shall take all reasonable steps to protect the property remaining, and shall repair or replace the lost, destroyed, or damaged property if and as directed by the Contracting Officer, but shall take no action prejudical to the right of the Government to recover therefor and shall furnish to the Government on request all reasonable assistance in obtaining recovery.

(g) Government Property for Government Use Only. Except as otherwise authorized by the Contracting Officer, Government property shall be used only for the performance of this contract."

8. The TITLE IV attached hereto and made a part hereof is added to Appendix "A".

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth

(Contracting Officer)

WITNESSES:

Frances Sutton

Nashville, Tennessee
(Address)

Linda Howard

Nashville, Tennessee
(Address)

VANDERBILT UNIVERSITY

BY: John W. Patterson

TITLE: Vice Chancellor for Medical Affairs

ACCEPTANCE BY SENIOR INVESTIGATORS

We have read the foregoing Supplemental Agreement and the TITLE IV attached hereto and made a part hereof and agree to be bound by the provisions of this document.

Senior Investigator

Robert T. Lagemann

Senior Investigator

APPENDIX "A"

TITLE IV

This TITLE IV describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will continue to use the Low Level Whole Body Counting Device and the Whole Body Counting Facility to measure gamma emitting radioisotopes within the human body which are (a) naturally occurring, (b) of atmospheric origin, (c) due to accidental exposure to fallout or industrial or laboratory exposure, and (d) administered for diagnostic or research purposes. The work of standardization of the measurement of the radioisotopes in the human body by means of the Whole Body Counter will be continued. In addition the Whole Body Counting Facility will continue to be used in the measurement of electrolyte composition and metabolism in man in conjunction with the metabolism ward program at the Vanderbilt University Hospital including (1) patients under endocrine therapy, (2) patients with hypertension, and (3) seriously ill surgical patients. Other planned projects include such areas as human internal radioisotope dosimetry, instrumentation, prophylaxis and therapy.

2. BUDGET

a. Outline of Cost Estimates:

(1) Salaries and Wages:		$49,556.00
Dr. G. R. Meneely (20% of time)	$ 3,900.00	
Dr. R. T. Lagemann (15% of time)	2,325.00	
Research Associates	10,500.00	
Consultants	3,600.00	
Research Assistants and Technicians	20,360.00	
Administrative, Secretarial and Clerical Assistance	6,965.00	
FICA and Insurance	1,906.00	

1018231

(2)	Supplies:	8,100.00
(3)	Travel:	4,500.00
(4)	Overhead (25% of direct costs):	15,539.00
	TOTAL	$77,695.00*

*It is recognized that the project may receive additional financial assistance from other sources as described in the Contractor's proposal.

b. Items of property to be procured or manufactured by the Contractor, or to be furnished by the Government, title to which will vest or remain in the Government (see Article V): None, except that it is recognized that title to the following property procured or manufactured by the Contractor or furnished by the Government under earlier TITLES remains in the Government:

Low Level Whole Body Counting Device consisting of:

1. Steel Room
2. Probe and Crane, Sensing Device (Crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyser)
3. Humidity and Temperature Control

Contract No. AT-(40-1)-2401
Vanderbilt University
Modification No. 2

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 29th day of June, 1960, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-2401, dated June 3, 1958, providing for the establishment and operation of a low level whole body counting facility; and

WHEREAS, the contract has been amended heretofore by Modification No. 1; and

WHEREAS, the Commission desires to provide for additional research as more particularly described in TITLE III of Appendix "A", to obtain reports thereon, and to effect certain other changes as are hereinafter more particularly described; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties hereto do mutually agree that said contract is hereby modified in the following particulars, but in no others:

1. The first sentence of section 2. of Article I is revised to read as follows:

> "The work shall consist of research by the Contractor involving the utilization of a low level whole body counting facility in the measurement of electrolyte composition and metabolism in man."

2. The following new section "3." is added to Article II:

> "3. The period during which the work under this contract may be conducted is hereby extended to January 31, 1961."

1018233

3. The following new subsection "1. c." is added in Article III:

"c. In consideration of the performance of the additional work described in TITLE III of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Forty-eight Thousand, Three Hundred Twenty Dollars ($48,320.00), the Government will pay to the Contractor Thirty-eight Thousand, Two Hundred Fifty-five Dollars ($38,255.00) ($38,155.00 in new funds and $100.00 agreed to be the balance remaining unexpended from previous work under this contract)."

4. In subsection 2. d. of Article III, delete the word "term" and substitute therefor the word "work".

5. Subsections a. and b. of section 4., Examination of Records, of Article IV are revised to read as follows:

"a. The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers and records of the Contractor involving transactions related to this contract.

"b. The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term 'subcontract' as used in this clause excludes (1) purchase orders not exceeding $2500; (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public; and (3) subcontracts or purchase orders for general inventory items not specifically identifiable with the work under this contract."

10I8234

6. Article V is deleted in its entirety, and the following new Article V is substituted therefor:

"ARTICLE V - PROPERTY

"In consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies acquired from any source, including the Government, or manufactured by the Contractor under this contract, shall vest in the Contractor, except that title to items of property described in section 2. b. of Appendix "A" shall vest or remain in the Government. Additional items may be added to such section 2. b. in writing without the necessity for a formal modification of the contract."

7. In Appendix "B", paragraph 4. is revised to read as follows:

"4. Disputes

"a. Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless, within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to the Commission. The decision of the Commission or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

1018235

"b. This 'Disputes' clause does not preclude consideration of law questions in connection with decisions provided for in paragraph a., above; Provided, that nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law."

8. In Appendix "B", the second sentence of paragraph 7., Covenant Against Contingent Fees, is revised to read as follows:

"For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee."

9. In Appendix "B", subparagraph 11 b. is revised to read as follows:

"b. The Contractor further agrees to insert the foregoing provision in all subcontracts hereunder, except subcontracts for standard commercial supplies or raw materials."

10. The following new paragraph "16." is added in Appendix "B":

"16. Placing Orders and Subcontracts with Firms Located in Areas of Substantial Labor Surplus

It is the policy of the Government to place supply contracts with suppliers who will perform such contracts substantially in areas of current labor surplus where this can be done at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts and purchase orders in accordance with this policy to the extent consistent with the efficient performance of this contract."

11. The TITLE III attached hereto, and made a part hereof, is added to Appendix "A".

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: _____

J. A. Johnston
Acting Director, Contract Division, CROO
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: _____

TITLE: Vice Chancellor

WITNESSES:

_____

_____
(Address)

_____

_____
(Address)

ACCEPTANCE BY SENIOR INVESTIGATORS

We have read the foregoing Supplemental Agreement and the TITLE III of Appendix "A" attached hereto and made a part hereof and agree to be bound by the provisions of this document.

_____
Senior Investigator

_____
Senior Investigator

1018237

APPENDIX "A"

TITLE III

This TITLE III describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will continue with completion and calibration and use of a whole-body low-background counting facility to include studies on measurement of gamma-emitting radioisotopes in the body which are (a) naturally occurring, (b) of atmospheric origin, (c) fallout origin, (d) from industrial or laboratory exposure, or (e) administered for diagnostic or research purposes. Potassium studies, utilizing phantoms and subjects, will be carried out. Sodium standardization and cesium standardization will be conducted. Studies of human geometry, body sodium and potassium, membrane transfer of electrolytes, and spectrum analysis, with appropriate associated studies, will continue.

2. BUDGET

a. Outline of Cost Estimates:

(1)	Salaries and Wages:		$49,200.00
	Dr. George R. Meneely (30% of time)	$ 5,400.00	
	Dr. Robert T. Lagemann (10% of time)	1,200.00	
	Research Associates	13,100.00	
	Consultants	3,600.00	
	Research Assistants and Technicians	19,600.00	
	Administrative Assistant	3,300.00	
	Secretarial Assistance	3,000.00	
(2)	FICA and Insurance:		2,460.00
(3)	Supplies and Materials:		7,600.00
(4)	Computer Time:		6,000.00
(5)	Travel:		4,000.00
(6)	Overhead (25% of direct costs):		17,315.00
		Total	$86,575.00

1018238

b. Items of property to be procured or manufactured by the Contractor, or to be furnished by the Government, title to which will vest or remain in the Government (see Article V). None, except that it is recognized that title to the following property procured or manufactured by the Contractor or furnished by the Government under earlier TITLES remains in the Government:

Low Level Whole Body Counting Device consisting of:

1. Steel Room

2. Probe and Crane, Sensing Device (Crystal, shield, photomultiplier tubes, and associated 256 channel pulse analyser)

3. Humidity and Temperature Control

Contract No. AT-(40-1)-2401
Vanderbilt University
Modification No. 1

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into this 25th day of March, 1959, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), represented herein by the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission"), and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

WITNESSETH THAT:

WHEREAS, the Government and the Contractor entered into Contract No. AT-(40-1)-2401, dated June 3, 1958, providing for the establishment and operation of a low level whole body counting facility; and

WHEREAS, the Commission desires to provide for additional research as more particularly described in TITLE II of Appendix "A", to obtain reports thereon, and to effect certain other changes as are hereinafter more particularly described; and

WHEREAS, this Supplemental Agreement is authorized by and executed under the Atomic Energy Act of 1954;

NOW, THEREFORE, the parties hereto do mutually agree that said Contract is hereby modified in the following particulars, but in no others:

1. The following new section "2." is added to Article II:

"2. The period during which the work under this Contract may be conducted is hereby extended to January 31, 1960."

2. The following new subsection "1. b." is added in Article III:

"b. In consideration of the performance of the additional work described in TITLE II of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Forty-five Thousand, Nine Hundred Fifty Dollars ($45,950.00), the Government will pay to the Contractor Twenty-nine Thousand, Eight Hundred Forty-nine Dollars ($29,849.00), ($29,000.00 in new funds and $849.00 agreed to be the balance remaining unexpended from previous work under this Contract). The item of $849.00 for Electronic Components under 2. a. (2) of TITLE II was previously expended and is not included in the contribution of the parties."

3. Subsection 2. a. of Article III is revised to read as follows:

1018240

"a. On or before the date of commencement of the work on the project described in Appendix "A", the Government shall pay to the Contractor upon submission by the Contractor of a proper voucher, 45 per cent of the agreed consideration; provided, however, that this payment shall be reduced by the amount of the balance agreed to be remaining unexpended from previous work under this contract."

4. In subsections 2. b. and 2. c. of Article III, delete the words "properly certified voucher" and substitute therefor in each instance the words "proper voucher".

5. The TITLE II attached hereto and made a part hereof is added in Appendix "A".

IN WITNESS WHEREOF, the parties hereto have executed this Supplemental Agreement the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth

[illegible] AND DEVELOPMENT DIVISION

(Contracting Officer)

WITNESSES:

Sheryl B. Caldwell

Nashville Tennessee
(Address)

R. J. Estes

Nashville, Tennessee
(Address)

VANDERBILT UNIVERSITY

BY: [signature]

TITLE: Vice Chancellor

ACCEPTANCE BY SENIOR INVESTIGATORS

We have read the foregoing Supplemental Agreement and the Appendix "A" attached hereto and made a part hereof and agree to be bound by the provisions of this document.

[signature]
Senior Investigator

Robert T. Legemann
Senior Investigator

APPENDIX "A"

TITLE II

This TITLE II describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will continue construction and testing of a whole body low level counting facility for biomedical research purposes and for use in clinical studies, to include measurement of gamma-emitting radioisotopes present within the body which are (1) naturally-occurring, (2) of atmospheric origin, (3) are due to accidental exposure to fallout or industrial or laboratory exposure, and (4) those administered for diagnostic or research purposes. Additional work will include applications to studies on human internal radioisotope dosimetry instrumentation, prophylaxis and therapy.

2. BUDGET

a. Outline of Cost Estimates:

(1)	Salaries and Wages:		$50,055.00
	Dr. G. R. Meneely (30% of time)	$ 6,000.00	
	Dr. R. T. Lagemann (15% of time)	2,700.00	
	Research Associates	21,370.00	
	Research Assistants and Technicians	13,350.00	
	Administrative and Secretarial Assistants	4,380.00	
	FICA and Insurance	2,255.00	
(2)	Equipment:		8,849.00
	Lead for 8" Collimator	$ 3,500.00	
	Humidity and Temperature Contol	3,500.00	
	Office and Laboratory Equipment	1,000.00	
	Electronic Components	849.00	
(3)	Supplies:		5,300.00
(4)	Travel:		3,600.00
(5)	Overhead (15% of Operating Expenses):		8,844.00
		Total	$76,648.00

1018242

b. Items of property to be procured or manufactured by the Contractor, title to which will vest in the Government (see Article V):

1. 8" Collimator
2. Humidity and Temperature Control
3. Electronic Components

1018243

UNITED STATES
ATOMIC ENERGY COMMISSION

LUMP SUM
RESEARCH CONTRACT

Contract No. AT-(40-1)-2401

THIS CONTRACT, entered into this 3rd day of June, 1958, effective as of February 1, 1958, by and between the UNITED STATES OF AMERICA (hereinafter called the "Government"), acting through the UNITED STATES ATOMIC ENERGY COMMISSION (hereinafter called the "Commission") and VANDERBILT UNIVERSITY (hereinafter called the "Contractor");

ARTICLE I - PURPOSE AND SCOPE

1. The Commission, in furtherance of its policy of assisting and fostering private research, desires to support the Contractor's fundamental research in the field of atomic energy.

2. The work shall consist of research by the Contractor involving the establishment and operation of a low level whole body counting facility. The plan of approach to the problem and the agreed upon program and budget for the project are described in Appendix "A", which is hereby made a part of this contract. The Contractor shall be guided by, but not bound to conform to the details of, the budget described in Appendix "A".

3. The Contractor shall furnish all services, facilities, equipment, supplies and materials (except such services, equipment, supplies and materials as the Government has agreed to furnish herein) required for the performance of the research program described in Section 2. above.

4. The work will be carried out by the Contractor under the direction of Dr. George R. Meneely and Dr. Robert T. Lagemann as Senior Investigators.

5. The Contractor shall commence the work as soon as feasible, prosecute it with due diligence and submit the reports required hereunder as early as practicable, and not later than the dates specified in Appendix "C".

ARTICLE II - SCHEDULE

1. The period during which the work under this contract may be conducted shall end on January 31, 1959.

ARTICLE III

1. Consideration

a. In consideration of the performance of the research activities described in TITLE I of Appendix "A", and the Contractor's agreement to support that work in the estimated amount of Forty-seven Thousand, Nine Hundred Twenty-one Dollars ($47,921.00), the Government will pay to the Contractor Sixty-six Thousand, Eight Hundred Sixty-five Dollars ($66,865.00).

1018244

2. Payment

a. On or before the date of commencement of work on the project described in Appendix "A", the Government shall pay to the Contractor upon submission by the Contractor of a properly certified voucher, 45 per cent of the agreed consideration.

b. On or before the expiration of six months from the date of commencement of the project, the Government shall pay to the Contractor, upon submission by the Contractor of a properly certified voucher, 45 per cent of the agreed consideration.

c. Upon receipt and acceptance of a satisfactory progress report, in cases where the contract is to be renewed, or the final report if the contract is not to be renewed, the Government shall pay to the Contractor, upon submission by the Contractor of a properly certified voucher, the remaining 10 per cent of the agreed consideration. An extension of the contract work without additional funds shall not be considered a renewal of the contract and in such cases the retained 10 per cent of the agreed consideration will be paid upon submission and acceptance of a satisfactory final report.

d. In the event the contract is renewed, payments to the Contractor of any additional amount to be paid by the Government shall be made for the extended term in accordance with the schedule outlined in Paragraphs a., b., and c., above.

3. Program and Budget for Subsequent Periods

When renewal of the contract is desired, the Contractor shall submit to the Commission's Oak Ridge Operations Office a renewal proposal as outlined in Appendix "C" attached hereto. The Contractor and the Commission shall then negotiate as to the amounts each will contribute for the additional research activities to be conducted, taking into consideration the actual costs incurred for the current work in comparison with the cost estimates in the contract, and, upon agreement, shall execute a formal modification of the contract.

ARTICLE IV - REPORTS, RECORDS AND INSPECTION

1. The Commission shall have the right to inspect in such manner and at such times as it deems appropriate all activities of the Contractor arising in the course of the work under this contract.

2. The Commission shall at all times be afforded access to the premises and to all technical records, correspondence, instructions, drawings and memoranda of record value of the Contractor pertaining to said work.

3. The Contractor shall make progress and other reports in such manner and at such times as specified in Appendix "C" which is attached and hereby made a part of this contract.

4. Examination of Records

a. The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall have access to and the right to examine any directly pertinent books, documents, papers and records of the Contractor involving transactions related to this contract until the expiration of three years after final payment under this contract.

b. The Contractor further agrees to include in all his subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor involving transactions related to the subcontract until the expiration of three years after final payment under this contract. The term "subcontract" as used herein means any purchase order or agreement to perform all or any part of the

work or to make or furnish any materials required for the performance of this contract, but does not include (1) purchase orders not exceeding $1,000, (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public, or (3) subcontracts or purchase orders for general inventory items not specifically identifiable with the work under this contract.

c. Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE V - PROPERTY

1. In consideration of the Contractor's contribution to the research project described in Appendix "A" of this contract, title to all materials, tools, machinery, equipment and supplies, acquired from any source including the Government, or manufactured by the Contractor under this contract shall vest in the Contractor, except that title to items of property described in Section 2. b. of Appendix "A" shall vest in the Government.

2. Property described in Section 2. b. of Appendix "A" is hereinafter referred to as "Government Property".

3. Title to Government Property shall not be affected by the incorporation of the property into or the attachment of it to any property not owned by the Government, nor shall such Government Property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

4. The Contractor shall identify Government Property coming into the Contractor's possession or custody by conspicuously marking it "PROPERTY OF U. S. GOVERNMENT, AEC" or in such other way, satisfactory to the Contracting Officer as shall indicate its ownership by the Government.

5. The Contractor shall take all reasonable precautions, as directed by the Contracting Officer, or in the absence of such directions, in accordance with sound industrial practice, to safeguard and protect Government Property in the Contractor's possession or custody.

6. The Contractor shall not be liable for loss or destruction of or damage to Government Property in the Contractor's possession unless such loss, destruction or damage results from wilful misconduct or lack of good faith on the part of a corporate officer of the Contractor or a Senior Investigator under this contract.

7. Upon the happening of any loss or destruction of or damage to Government Property in the possession or custody of the Contractor, the Contractor shall immediately inform the Contracting Officer of the occasion and extent thereof, shall take all reasonable steps to protect the property remaining, and shall repair or replace the lost, destroyed or damaged property at Government expense,

1018247

if and as directed by the Contracting Officer, but shall take no action prejudicial to the right of the Government to recover therefor and shall furnish to the Government on request all reasonable assistance in obtaining recovery.

8. The Contractor shall furnish to the Commission a receiving report on all items of Government Property.

9. Government Property shall be used only for the performance of this contract.

10. The Contractor shall make such disposition of Government Property which has come into the possession or custody of the Contractor under this contract as the Contracting Officer shall direct. When authorized in writing by the Contracting Officer, the Contractor may, upon such terms and conditions as the Contracting Officer may approve, acquire such property at a price agreed upon by the parties.

ARTICLE VI - PROCUREMENT OF MATERIAL AND SERVICES FROM COMMISSION FACILITIES: COMPLIANCE WITH COMMISSION REGULATIONS

The Contractor shall comply with all licensing and other requirements of the Commission with respect to possession and use of by-product material, source material, and special nuclear material (as these terms are defined in the Atomic Energy Act of 1954), and may purchase or acquire such materials, irradiation services, other radioactive material, cyclotron time, etc. from the Commission or Commission facilities in accordance with applicable procedures.

ARTICLE VII - PURCHASE OF RADIOISOTOPES UNDER AN AEC DISCOUNT CERTIFICATE

If any radioisotopes are budgeted in the outline of cost estimates at the full amount of the price as established by the Commission, but are purchased at less than such established prices under an AEC Discount Certificate issued to the Contractor (See: Title 10 C.F.R., Part 37), then any difference between the established price and the price so paid shall be paid by the Contractor to the Government or otherwise credited to the Government's account as the Contracting Officer may direct or approve. The requirement for a report to be submitted to the Commission indicating the purchases under the discount program is outlined in Appendix "C".

ARTICLE VIII - GENERAL PROVISIONS

The provisions of Appendix "B", attached hereto, are hereby made a part of this contract.

ARTICLE IX - ALTERATIONS

The following alterations to this contract were made by mutual agreement of the parties prior to its execution: None.

IN WITNESS WHEREOF, the parties hereto have executed this contract the day and year first above written.

UNITED STATES OF AMERICA

BY: UNITED STATES ATOMIC ENERGY COMMISSION

BY: Herman M Roth

HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION

(Contracting Officer)

WITNESSES:

(Address)

(Address)

VANDERBILT UNIVERSITY

BY:

TITLE: Vice Chancellor

ACCEPTANCE BY SENIOR INVESTIGATORS

We have read the foregoing contract and the Appendices attached hereto and made a part hereof and agree to be bound by the provisions of this document.

Senior Investigator

Senior Investigator

1018249

Contract N AT-(4C)-2401
Vanderbilt niversity

APPENDIX "A"

TITLE I

This TITLE I describes the research program and cost estimates agreed upon between the Commission and the Contractor.

1. PROGRAM

a. Scope and Plan of Approach:

The Contractor will construct and operate a whole body counting facility. This facility will be used to obtain an energy spectrum of gamma rays from sources of very low intensity by virtue of a highly sensitive gamma ray detector operating in a very low background area. Specifically its uses are to measure gamma emitting isotopes within the human body which (a) are naturally occurring, (b) are due to general atmospheric origin, (c) entered the body accidentally due to exposure to fallout, nuclear reactor accident, industrial or laboratory exposure and (d) or administered for diagnostic or research purposes. The Contractor shall conduct such additional experiments involving radiation exposure as are mutually agreed upon by the parties. It is recognized that the Contractor may charge the usual charges for patient care prior to and after use of the Low Level Whole Body Counting Device.

2. BUDGET

a. Outline of Cost Estimates:

(1)	Salaries and Wages		$ 27,233.00
	Dr. George R. Meneely (30% of time)	$5,000.00	
	Dr. Robert T. Lagemann (10% of time for 4 mos. and 15% of time for 2 mos.)	1,700.00	
	Research Associate	7,000.00	
	Research Assistants and Technicians	8,000.00	
	Administrative and Secretarial Assistants	5,000.00	
	FICA and Insurance	533.00	
(2)	Supplies:		3,600.00
(3)	Equipment:		9,508.00
(4)	Low Level Whole Body Counting Device:		43,900.00
	Steel Room	26,500.00	
	Probe and Crane, Sensing Device (Crystal, shield, photomultiplier tubes, and associated pulse analyser)	17,400.00	
(5)	*Building:		25,000.00
(6)	Travel:		800.00
(7)	Overhead:(15% of Operating Expenses):		4,745.00
		TOTAL	$114,786.00**

1018250

*No part of the Government's contribution to the contract work will be applied to the cost of the building.

**It is recognized that the research project may receive additional financial support from other sources.

b. Items of property to be procured or manufactured by the Contractor, title to which will vest in the Government (see Article V): Low Level Whole Body Counting Device described in subsection 2. a. (4) of this TITLE I.

APPENDIX "B"

GENERAL PROVISIONS

(FOR DIRECT AEC RESEARCH CONTRACTS)

1. Patents

a. Whenever any invention or discovery is made or conceived by the Contractor or its employees in the course of, in connection with, or under the terms of this contract, the Contractor shall furnish the Commission with complete information thereon; and the Commission shall have the sole power to determine whether or not and where a patent application shall be filed, and to determine the disposition of the title to and rights under any application or patent that may result. The judgment of the Commission on these matters shall be accepted as final; and the Contractor, for itself and for its employees, agrees that the inventor or inventors will execute all documents and do all things necessary or proper to carry out the judgment of the Commission.

b. No claim for pecuniary award or compensation under the provisions of the Atomic Energy Acts of 1946 and 1954 shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of, in connection with, or under the terms of this contract.

c. Except as otherwise authorized in writing by the Commission, the Contractor will obtain patent agreements to effectuate the purposes of paragraphs a. and b. of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

d. Except as otherwise authorized in writing by the Commission, the Contractor will insert in all subcontracts provisions making this article applicable to the subcontractor and its employees.

2. Publications

It is intended that the Contractor shall have full freedom of publication of the results of the research under this contract and the Contractor is urged to disseminate the results of the work through customary scientific publication channels, except that "restricted data" as defined in the Atomic Energy Act of 1954 shall be governed by the provisions of Paragraph 3. of this Appendix "B".

However, in order to insure that the public disclosure of such results will not adversely affect the patent interests of the Government provided in Paragraph 1. of this Appendix "B" entitled "Patents" approval for such release shall be secured from the Commission prior to any such publication.

All publications shall include a reference that the results were developed under a Commission sponsored project.

1018252

3. Security

a. It is understood that the work under this contract will not involve restricted data or other classified matter and that the Contractor will perform such work as unclassified work. However, if in the course of such work any discoveries are made or any data used or developed that constitute restricted data or other classified matter, the Contractor shall promptly inform the Commission and will be bound by the following:

(1) Contractor's Duty to Safeguard Restricted Data and Other Classified Information. In the performance of the work under this contract the Contractor shall, in accordance with the Commission's security regulations and requirements, be responsible for safeguarding restricted data and other classified matter and protecting against sabotage, espionage, loss and theft, the classified documents, materials, equipment, processes, etc., as well as such other material of high intrinsic or strategic value as may be in the Contractor's possession in connection with performance of work under this contract. Except as otherwise expressly provided in the specifications the Contractor shall upon completion or termination of this contract transmit to the Commission any classified matter in the possession of the Contractor or any person under the Contractor's control in connection with performance of this contract.

(2) Regulations. The Contractor agrees to conform to all security regulations and requirements of the Commission.

(3) Definition of Restricted Data. The term "Restricted Data", as used in this article, means all data concerning (1) design, manufacture, or utilization of atomic weapons; (2) the production of special nuclear material; or (3) the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to section 142 of the Atomic Energy Act of 1954.

(4) Security Clearance of Personnel. Except as the Commission may authorize, in accordance with the Atomic Energy Act of 1954, the Contractor shall not permit any individual to have access to Restricted Data until the designated investigating agency shall have made an investigation and report to the Commission on the character, associations, and loyalty of such individual and the Commission shall have determined that permitting such person to have access to Restricted Data will not endanger the common defense and security. As used in this paragraph, the

term "designated investigating agency" means the United States Civil Service Commission or the Federal Bureau of Investigation, or both, as determined pursuant to the provisions of the Atomic Energy Act of 1954.

(5) Criminal Liability. It is understood that disclosure of information relating to the work or services ordered hereunder to any person not entitled to receive it, or failure to safeguard any Restricted Data or any top secret, secret, or confidential matter that may come to the Contractor or any person under the Contractor's control in connection with work under this contract, may subject the Contractor, his agents, employees, and subcontractors to criminal liability under the laws of the United States. (See the Atomic Energy Act of 1954, 68 Stat. 919), (See also executive Order 10104 of February 1, 1950, 15 F. R. 597.)

(6) Subcontracts and Purchase Orders. Except as otherwise authorized in writing by the Contracting Officer, the Contractor shall insert provisions similar to the foregoing in all subcontracts and purchase orders under this contract.

b. The continuation by the Contractor of work found to involve restricted data will be subject to mutual agreement of the Commission and the Contractor and shall be covered by a modification of this agreement.

4. Disputes

Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. Within 30 days from the date of receipt of such copy, the Contractor may appeal by mailing or otherwise furnishing to the Contracting Officer a written appeal addressed to the Commission, and the decision of the Commission shall, unless determined by a court of competent jurisdiction to have been fraudulent, arbitrary, capricious, or so grossly erroneous as necessarily to imply bad faith, or is not supported by substantial evidence, be final and conclusive: Provided, That if no such appeal to the Commission is taken, the decision of the Contracting Officer shall be final and conclusive. In connection with any appeal proceeding under this clause, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal.

Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

5. Safety, Health and Fire Protection

The Contractor shall take all reasonable precautions in the performance of the work under this contract to protect the health and safety of employees and of members of the public and to minimize danger from all hazards to life and property, and shall comply with all health, safety, and fire protection regulations and requirements (including reporting requirements) of the Commission. In the event that the Contractor fails to comply with said regulations or requirements of the Commission, the Contracting Officer may without prejudice to any other legal or contractual rights of the Commission, issue an order stopping all or any part of the work; thereafter a start order for resumption of work may be issued at the discretion of the Contracting Officer. The Contractor shall make no claim for an extension of time or for compensation or damages by reason of or in connection with such work stoppage.

6. Officials Not to Benefit

No member of or delegate to Congress or resident commissioner shall be admitted to any share or part of this contract or to any benefit that may arise therefrom but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

7. Covenant Against Contingent Fees

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty, the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration the full amount of such commission, percentage, brokerage or contingent fee.

8. Convict Labor

In connection with the performance of work under this contract the Contractor shall not employ any person undergoing sentence of imprisonment at hard labor.

9. Termination

a. The Commission may at any time upon 120 days' written notice terminate this contract in whole or in part.

b. In the event of termination pursuant to subsection a., the Contractor shall submit a statement of costs incurred in performance of the work under the contract prior to such termination, and the Government shall pay to the Contractor that portion of the costs incurred which bears the same relationship to the total as the agreed Government support for the full term bears to the total of cost estimates for the full term, less the amount of all payments theretofore made. If the total payments theretofore made to the Contractor exceed the amount to which it is entitled hereunder, the Contractor shall promptly remit the amount of any such excess to the Government.

10. Eight-Hour Law

a. No laborer or mechanic doing any part of the work contemplated by this contract, in the employ of the Contractor or any subcontractor contracting for any part of said work contemplated, shall be required or permitted to work more than eight hours in any one calendar day upon such work, except upon the condition that compensation is paid to such laborer or mechanic in accordance with the provisions of this article. The wages of every laborer and mechanic employed by the Contractor or any subcontractor engaged in the performance of this contract shall be computed on a basic day rate of eight hours per day and work in excess of eight hours per day is permitted only upon the condition that every such laborer and mechanic shall be compensated for all hours worked in excess of eight hours per day at not less than one and one-half times the basic rate of pay. For each violation of the requirements of this article a penalty of five dollars shall be imposed upon the Contractor for each laborer or mechanic for every calendar day in which such employee is required or permitted to labor more than eight hours upon said work without receiving compensation computed in accordance with this article, and all penalties thus imposed shall be withheld for the use and benefit of the Government: Provided, that this stipulation shall be subject in all respects to the exceptions and provisions of the Eight-Hour Laws as set forth in 40 U.S.C. 321, 324, 325, 325a and 326, which relate to hours of labor and compensation for overtime.

b. This provision does not apply to work performed by employees of the Contractor if this contract is with a state or a state institution.

11. Nondiscrimination in Employment

a. In connection with the performance of work under this contract, the Contractor agrees not to discriminate against any employee or applicant for employment because of race, religion, color or national origin. The aforesaid provision shall include but not be limited to, the following: employment, upgrading, demotion, or transfer; recruitment or recruitment advertising, layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post hereafter in conspicuous places, available for employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of the nondiscrimination clause.

b. The Contractor further agrees to insert the foregoing provision in all subcontracts hereunder, except (i) subcontracts for standard commercial supplies or raw materials, (ii) subcontracts to be performed outside the United States where no recruitment of workers within the limits of the United States is involved, (iii) purchase orders on pocket-size forms similar to U. S. Standard Form 44, and (iv) subcontracts to meet other special requirements or emergencies, if recommended by the Committee on Government Contracts. In the case of purchase orders hereunder which do not exceed $5,000, the last sentence of paragraph a. above may be omitted.

12. Definitions

As used in this contract:

a. The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successor or any duly authorized representative of such person.

b. The term "Commission" means the United States Atomic Energy Commission or any duly authorized representative thereof, including the Contracting Officer except for deciding an appeal under the Article entitled "Disputes".

13. Fellowships

It is understood by the Contractor that none of the funds supplied by the Commission under this contract shall be used in any way to pay the stipend of any appointment for which commensurate services are not rendered under this contract; nor shall any of the funds be used to confer a fellowship, or to pay any part of the stipend of a fellowship, of any kind.

14. Foreign Travel

It is agreed that none of the funds supplied by the Commission under this contract shall be used to pay the expenses of foreign travel, except where such foreign travel is made with the prior approval of the Commission. "Foreign travel" as used herein means travel outside the continental United States, excepting, however, travel to Canada.

15. Buy American Act

In the event this contract provides for the acquisition of articles, materials, or supplies by the Government, the following provision shall apply with respect to such items: The Contractor agrees that there will be delivered under this contract only such unmanufactured articles, materials and supplies (which term "articles, materials and supplies" is hereinafter referred to in this clause as "supplies") as have been mined or produced in the United States, and only such manufactured supplies as have been manufactured in the United States substantially all from supplies mined, produced, or manufactured, as the case may be, in the United States. The foregoing provisions shall not apply (i) with respect to supplies exempted by the Commission from the application of the Buy American Act (41 U.S.C. 10a-d), (ii) with respect to supplies for use outside the United States, or (iii) with respect to the supplies to be delivered under this contract which are of a class or kind determined by the Commission not to be mined, produced, or manufactured, as the case may be, in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality, or (iv) with respect to such supplies, from which the supplies to be delivered under this contract are manufactured, as are of a class or kind determined by the Commission not to be mined, produced, or manufactured, as the case may be, in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality, provided that this exception (iv) shall not permit delivery of supplies manufactured outside the United States if such supplies are manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality.

1018258

APPENDIX "C"

REPORTS AND PROPOSALS
(FOR DIRECT AEC RESEARCH CONTRACTS)

		Date Due	Copies
1.	Progress Report	NOV 1	Six
2.	Renewal Proposal		Six
3.	200-word summary of purpose and scope with submittal date indicated thereon	Within 30 days after FEB 1	Three
4.	Complete Scientific Report	On contract expiration or termination	Six
5.	Radioisotopes Purchase Report	With renewal proposal if proposal is submitted, otherwise on contract expiration or termination	Three
6.	Brief reports or manuscripts may be submitted as desired by Senior Investigator		

NOTES:

All of the above should be addressed to:

Research and Development Division
Oak Ridge Operations Office
U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee

The progress report should briefly describe the scope of investigations undertaken and the significant results obtained. It should also explain any significant differences between the actual level of activity (expressed in the various categories of man-months, facilities procured, travel performed, etc.) and that contemplated in the contract. Technical reports and articles prepared for publication should be listed with bibliographic references. Reprints or preprints of all such material should be appended and material contained therein need not be duplicated in the report.

Renewal proposals, if any, should accompany the progress report and should contain the type of information outlined below unless the information is already contained in earlier proposals or in the accompanying progress report. Any contemplated change in program or scope for the additional work should be clearly explained and the cost estimated should be based upon past experience.

1018259

1. Title of the project.

2. The institution and department in which the work will be done.

3. Scientific background including literature relevant to the proposal, the significance, and the motivation. If the proposal is for continuation of work already in progress the extent of present support should be stated identifying amounts received from federal agencies.

4. Scientific scope of the proposed research, its objectives, its relation to present knowledge and to comparable work in progress elsewhere, and a plan of accomplishments for the work.

5. Scientific Personnel. Give the name, highest academic degree, position in the institution, scientific experience, publications and accomplishments of the Senior Investigator (the individual who will actively direct the research program) and of each regular staff scientist who it is proposed will engage in the work. Indicate the approximate fraction of the time of each to be devoted to the project. Scientific personnel to be newly employed for the project should be so designated, and professional records given if possible.

6. Other Personnel. The number of persons of each sub-professional grade and the fraction of the time of each to be devoted to the project should be listed. Graduate student employees should be identified as such if their thesis is to be related to the project.

7. Other Financial Assistance. If assistance for this or other activities involving the same personnel or facilities is to be proposed to, or received from other federal or non-university sources the extent of that assistance should be clearly stated, and the interplay of the arrangements should be fully explained.

8. Materials, Equipment and Facilities. List those already available for the work and justify the need for major items to be procured.

9. Travel and Other Items. Explain the purpose of the proposed travel, and of any other major items in the budget. Travel rates and the use of contract funds for attendance at regular scientific meetings should conform with the policy of the institution in the use of its own funds for these purposes.

10. Budget. This should list in detail all items of cost necessary to carry the project. It should include: a list of the individual salaries attributable to the project, supplies and services, equipment (defined as things individually costing more than $500 which will retain their utility for more than a year), travel, communication and publication, and the indirect costs allocable to the project. The basis for computing the indirect costs should be briefly explained. The budget should not include the stipend of fellows. All salaries chargeable to the project should be in accord with the established policies of the institution, or, if not, an explanation should be submitted.

1018260

11. Amount Requested. A statement of the part of the total amount listed in the budget which the institution is prepared to bear, and the amounts requested from the AEC, and a statement of any other sponsors of the project with the amounts contributed by each. The proposal should be signed by the Senior Investigator and endorsed by a responsible administrative officer of the institution.

12. Statement of Current Expenditures. A current statement of its expenditures for the project, and an estimate of expenses to be incurred. All expenditures will be reported according to the two categories "Operating Budget" and "Plant and Equipment Budget" used in the Budget in Appendix "A".

13. Residual Funds. Any difference in the scope of the work from that contemplated in the contract, as brought out in the report, may be reflected in the amount requested. If no new funds are required the contract may be renewed without funds. A proposal for such renewal should state the scope of the work proposed for use of residual funds.

The radioisotopes purchase report shall list all radioisotopes included in the budget at the regular price established by the Commission, but which are purchased, or will be purchased under the current budget, at a price less than the established price by utilizing the discount authorized by an AEC Discount Certificate issued to the Contractor. For each such purchase, the report shall state the price as established by the Commission, the price paid or to be paid using the discount, and the savings realized or to be realized. The report due on contract termination or expiration shall cover all such purchases actually made and not previously reported.

1018261

12/8

DATE: 12/07/78

TO : Addressees Listed Below

SUBJECT: CONTRACTUAL DOCUMENT FOR STAFF REVIEW

The document listed below is forwarded for your review, comments and initials. Upon completion of your review, please attach your comments, if any, and forward to next in line.

CONTRACT NO. DE-AS05-76EV02401 MODIFICATION NO. M028

WITH VANDERBILT UNIVERSITY

Addressee	Organization	Initials	Date	Remarks
1. Sylvia Galde*	RCP&R Branch Contract Div.	[illegible]	12-7-78	
~~2. W. K. Love*~~	"			
~~3. B. M. Mason*~~	"			
4. A. H. Frost, Jr., Chief,	RCP&R Branch Contract Div.	[illegible]	12/7/78	
5. H. S. Oster, Director,	Finance Div.	[illegible]	12/12/78	
6. W. L. Buchanan	Budget Div.	[illegible]	12/15/78	
~~7. Office of Chief Counsel~~				
8.				
9.				
RETURN TO	RCP&R Branch, Rm. 1011			

*Contract Specialist

DISTRIBUTION OF CONTRACTUAL DOCUMENT

Date Distributed _____

Signed Copy - Mailed to Contractor
Signed Copy & "Staffed Copy" - Legal File
1 Copy - Contract Administrator
1 Copy - Budget
1 Copy - Finance
1 Copy - Patents Group
2 Copies - HQS Program Office

1018262

Department of Energy
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tennessee 37830

NOV 27 1978

Charles W. Hill, Chief Counsel

REQUEST FOR CONTRACT ACTION

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

   ( ) Selection of New Contractor and/or Negotiation of Contract
   Number:
   Contractor:

   (X) Modification of Contract
   Number: DE-AS05-76EV02401 (Mod. M028)
   Contractor: Vanderbilt University

2. Nature of Services To Be Covered by Contract: Research
   Title: "Radioisotope Studies Utilizing a Low Level Whole Body Counter and Clinical Applications of Activation Analysis"

3. Type of Contract:
   (X) Support Agreement ( ) Cost Type ( ) Other

4. Amount of DOE Funds To Be Obligated by this CA: $54,037

5. DOE Percentage of Est. Total Cost To Be Shown by this CA: 100%

6. Description of Other Changes To Be Covered by this CA:

   Modify contract to cover research during period 11/01/78 thru 10/31/79. Increase cumulative DOE support ceiling from $618,537 to $672,574. Soviet-Bloc article applies. Title to property, if any, to vest in Contractor by P.L. 85-934.

7. Authority:
   PR #05-79EV02401-001

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR: SG

1018263

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: DE-AS05-76EV02401

For the contract period: November 1, 1978 through October 31, 1979

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct radioisotope studies utilizing a low level body counter and clinical applications of activation analysis. Most of the current work is directed toward the evaluation of radiation dose distributions from new radioactive tracers and new procedures.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 16% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages: $36,955

(2) Equipment to be purchased or fabricated by the Contractor: $ 2,785

a Equipment estimated to cost less than $1,000:

None

b Equipment estimated to cost in excess of $1,000:

CAMAC MM-816C 8192 16 Bit Word Memory Module

1018264

(3) Travel: $ 1,500

Domestic---------$ 1,500
Foreign----------$ 0

(4) Other direct costs: $ 9,158

(5) Indirect costs (based on a predetermined rate of 65% of salaries and wages): $24,021

(b) Items, if any, significant to the performance of this contract, but excluded from computation of support cost and from consideration in proportioning costs:

(1) Items to be contributed by Contractor:

None

(2) Items to be contributed by the Government:

None

(c) Time or effort of Principal Investigator(s) contributed by Contractor, but excluded from computation of support cost and from consideration in proportioning costs:

All costs including salary, fringe benefits, and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $ 74,419 ; DOE will pay 100 % of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and the Article entitled "Determination of Support Costs" in Appendix "B". The estimated DOE Support Cost for the contract period stated in this Appendix "A" is $ 74,419 .

1018265

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: DE-AS05-76EV02401

The estimated DOE Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$20,382
(b) New funds for the current period:	$54,037

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

1018266

VANDERBILT UNIVERSITY
NASHVILLE, TENNESSEE 37232 TELEPHONE (615) 322-7311
Director of Financial Management • Medical Center • Direct Phone 322-6684

July 27, 1978

FINANCIAL STATEMENT

Contract No. EY-76-S-05-2401

Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period. (11/1/77 - 10/1/78)	$ 26,627.62
2.	Estimated total cost for remainder of period.	$ 47,791.38
3.	Total actual and estimated cost chargable to ERDA for current period based on percentage of cost agreed upon as contained in A-111 of Appendix "A" to contract.	$ 74,419.00
4.	Accumulated costs chargeable to ERDA (include costs reported in certified statement for preceding period (s) and the costs stated in Item (3) above.).	$ 598,155.00
5.	Accumulated ERDA Support Celing as stated in Article III of Contract.	$ 618,537.00
6.	Total estimated ERDA funds remaining under contract (Subtract Item (4) from (5) which may be used to reduce amount of new funds required from ERDA for proposed renewal period.	$ 20,382.00

Macon Somerville
Assistant Director of Finance

A. Bertrand Brill, M.D.
Principal Investigator

1018267

Department of Energy
Washington, D.C. 20545

October 25, 1978

Dr. A. Bertrand Brill
Department of Radiology
Division of Nuclear Medicine
Vanderbilt University
Nashville, Tennessee 37232

Dear Dr. Brill:

I am pleased to inform you that the Office of Health and Environmental Research (formerly the Division of Biomedical and Environmental Research) has approved support for your renewal project, "Radioisotope Studies Utilizing a Low-Level Whole Body Counter and Clinical Applications of Activation Analysis," for an additional year. The recommended level of support will be at last year's level. You will be contacted in the near future by a representative from the Oak Ridge Operations Office regarding negotiations of the renewal contract.

Your next renewal period comes after the completion of 21 years of operation of this contract. For every multiple of three years, the Office requires a comprehensive report of the overall activities of the contract from the time of its initiation. In particular, the following items should be included in this report.

1. The main research accomplishments, with special reference to originally stated objectives.

2. Plans for the continuation of present objectives and possible new objectives in consideration of past results.

3. Graduate students trained, degrees granted, and post-doctoral tenures completed.

4. Bibliography, with titles of publications associated with this contract.

5. Your opinion as to the present state of knowledge in this area of research, its significance in the fields of biology and medicine, and needed future investigations.

6. The present division of federal support for your overall research program.

1018268

Six copies of the outlined request should be submitted in addition to the usual progress report to the Oak Ridge Operations Office.

Should you wish to renew your proposal for FY 1980, please submit your renewal proposal, with copies of the progress report, to:

Senior Procurement Official
U. S. Department of Energy
Washington, D. C. 20545

Since your proposal will be sent for outside evaluation next year, it is requested that you submit it four months prior to expiration of your contract.

Sincerely,

Donald W. Cole, Jr.
Human Health Studies Programs
Office of Health and
Environmental Research

bcc: OR

1018269

11-24-78

HQ PR for 11-1-78 thru 10-31-79

authorized:

new funds: $54,037

unexpended balance: 20,382

Total $74,419

Contractor Budget = $74,961

— 74,419

$542 difference

Telcon

Discussed above with Dr. A.B. Bull, Vanderbilt. He indicated reduction should be made in "Other direct costs."

Agade

11-24-78

1018270

PROCUREMENT COMMITMENT/OBLIGATION RECORD

TO : Budget Division DATE: 11/16/78

FROM: Contract Division

1. CONTROL NUMBER: CD-1018
2. ALLOTMENT SYMBOL: EV 90-91 OR
3. CONTRACT NUMBER: DE-AS05-76EV02401
4. MODIFICATION NUMBER: M028
5. ASSIGNED TO: S. Gelde ✓
6. NAME OF CONTRACTOR (IF KNOWN): Vanderbilt University
7. TYPE OF CONTRACT:
8. PROCUREMENT REQUEST NUMBER: 05-79EV02401.001
9. B&R NUMBER: HK 01 02 01
10. DOLLAR AMOUNT: $54,037
11. FUNDING AS STATED ABOVE IS AUTHORIZED:

W J Buchanan
SIGNATURE

11/21/78
DATE

1018271

DC AUGUST 1978

U. S. DEPARTMENT OF ENERGY

PROCU /FINANCIAL ASSISTANCE REQUES THORIZATION

1. TO Hart, R. L., Mgr
Oak Ridge Operations Office, Oak Ridge, TN 37830
2. FROM INITIATING OFFICE Human Health Studies Programs, OHER:EVA
Room E-201 Washington, D. C. 20545

3. INITIAL: [X] UPDATE: [ ] 4. PROCUREMENT: [X] FINANCIAL ASSISTANCE: [ ]
5. PR NUMBER: 05-79EV02401-001 6. PR CORRECTION LETTER: _ 7. RELATED PR NUMBER: _____

ACTION IDENTIFICATION

8. TITLE: Radioisotope Studies Utilizing a Low-Level Whole Body Counter and Clinical Applications of Activation Analysis
*Use of $20,382 in unexpended funds

9. UNSOLICITED PROPOSAL NO: UZ801613 10. PROJECT NO: 6105 11. CFDA NO: _____
12. PRODUCT OR SERVICE:* AIQ 13. SUPPORT SERVICES: YES [ ] NO [X] 14. CONSULTANT AWARD: YES [ ] NO [X]
15. CONTROLLED DELIVERABLE:* C6N 16. REPORT/DRAWING REQ: YES [X] NO [ ] IF YES, ATTACH DETAILS Per SRSA
17. CLASSIFICATION OF MATERIALS/WORK: U U — UNCLASSIFIED C — CONFIDENTIAL S — SECRET T — TOP SECRET
18. GOVERNMENT PROPERTY: N F — FURNISHED P — PURCHASED N — NOT INVOLVED IF CODE F OR P, ATTACH DETAILS.

AWARD PLANNING

19. AWARD AS ORDER UNDER BIN: _____
20. DESIRED AWARD DATE: 11 (MONTH) 01 (DAY) 78 (YEAR) 21. KIND OF AWARD ACTION:* 1Q 22. TYPE OF AWARD:* X IF CODE T, ATTACH DETAILS.
23. IF MULTI-YEAR AWARD, INDICATE NUMBER OF YEARS: _ 24. TYPE SOLICITATION INSTRUMENT:* UP
25. EXTENT OF COMPETITION:* __ IF COMPETITIVE, ATTACH TECHNICAL EVALUATION PLAN. IF NON-COMPETITIVE, ATTACH JUSTIFICATION. REF: DOE-PR 9-3.805.51 or 9-4.909(f).
26. SOURCE SELECTION PROCEDURE: 4 1 — A-E 2 — SEB 3 — OTHER 4 — NONE
27. FOR A-E, SHOW ESTIMATED CONSTRUCTION COST IN DOLLARS: N/A

AWARDEE

IF COMPETITIVE, HAS LIST OF SOURCES BEEN ATTACHED? YES [ ] NO [X] IF NON-COMPETITIVE, COMPLETE 28 - 31.
28. NAME: Vanderbilt University 29. ADDRESS: Nashville, TN 37232
30. DIVISION: Nuclear Medicine
31. GOCO/LAB: C A — GOCO/LAB B — GOCO/NON-LAB C — NON-GOCO/LAB D — NOT APPLICABLE

FINANCIAL

AWARD VALUE — DOLLAR AMOUNT
32. GOV'T SHARE 54,037
33. TOTAL _____
34. CONSIDERATION IN KIND, LOAN, OR LOAN GUARANTEE DATA REPORTED ON PR-799C: [ ]
35. PROJECT PERIOD: FROM 11 (MONTH) 01 (DAY) 78 (YEAR) THRU 10 (MONTH) 31 (DAY) 79 (YEAR)

CURRENT FY FUNDS COMMITTED

36. B&R NUMBER	37. FUND CLASS	38. DOLLAR AMOUNT
HK 01 02 01	E	54,037
_____	-	_____
_____	-	_____

39. FROM PR-799B (PART A) _____
40. TOTAL THIS PR 54,037
41. FUNDING PERIOD: FROM 11 (MONTH) 01 (DAY) 78 (YEAR) THRU 10 (MONTH) 31 (DAY) 79 (YEAR)
42. APPROPRIATION SYMBOL: 89X0210.91
43. ALLOTMENT SYMBOL: EV 90-91 OR
44. OBJECT CLASS: 250

PROJECT MANAGER

45. NAME: Cole, Donald W.
46. SIGNATURE: Donald W Cole
47. DATE: 10 (MONTH) 24 (DAY) 78 (YEAR) 48. OFFICE CODE: EVA
49. FTS TELEPHONE NUMBER: 233-3268

PROGRAM OFFICIAL

50. NAME: Liverman, James L.
51. SIGNATURE: James L. Liverman
52. DATE: 11 (MONTH) 3 (DAY) 78 (YEAR)

CERTIFYING OFFICIAL

53. NAME: Mayhew, D. D.
I HEREBY CERTIFY THAT THE FUNDS CITED IN ITEM 40 ARE AVAILABLE.
54. SIGNATURE: D D Mayhew
55. DATE: 10 (MONTH) 28 (DAY) 78 (YEAR)

NOV 3 1978

* SEE BACK OF FORM FOR CODES

1018272

m 028

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☒ ORIGINAL ☐ FOLLOWUP ☐ REVISION

☐ GRANT ☒ CONTRACT ☐ FELLOW ☐ OTHER

☐ NEW ☐ RENEWAL ☒ CONTINUATION

APPLICATION IDENTIFICATION NUMBER (If known)
ERDA E-(40-1) - 2401

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHEW policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Md 20014.

1. TITLE OF PROPOSAL OR ACTIVITY
Radioisotope Studies Utilizing a Low Level Whole Body Counter and Clinical Applications of Activation Analysis

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW
A. B. Brill, M.D., Ph.D., and Ronald R. Price, Ph.D.

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

☐ A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.)

☒ B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: ☒ NONE OF THE FOLLOWING, OR INCLUDING: ☐ MINORS, ☐ FETUSES, ☐ ABORTUSES, ☐ PREGNANT WOMEN, ☐ PRISONERS, ☐ MENTALLY RETARDED, ☐ MENTALLY DISABLED. UNDER SECTION 6. COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

☐ A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHEW THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF *DHEW Regulation 45 CFR 46*, THAT IT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHEW DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY.

☒ B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHEW ASSURANCE NUMBER G-0401)OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHEW. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF * IN ACCORDANCE WITH THE REQUIREMENTS OF THE *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46)*. THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM). Pending Review: August 2, 1978

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT:

EITHER ☐ HUMAN SUBJECTS WILL NOT BE AT RISK; OR ☒ HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION
Vanderbilt University Medical Center
21st and Garland, Nashville, TN 37232

8. TITLE OF INSTITUTIONAL OFFICIAL	TELEPHONE NUMBER
Assoc. Dean for Biomedical Sciences	(615) 322-2281
SIGNATURE OF INSTITUTIONAL OFFICIAL: John H Hash	DATE: 7-31-78

HEW-596 (Rev. 4-75)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY.

10827 13

Expenditure and Statement and Renewal Proposal

ERDA Contract EY-76-5-05-2401

I.

Radioisotope Studies Utilizing A Low Level Whole Body Counter

and

Clinical Applications of Activation Analysis

II.

Department of Radiology

Vanderbilt University School of Medicine

Nashville, Tennessee 37232

July 31, 1978

1018274

TABLE OF CONTENTS

III. Project Abstract

IV. Scientific Background

V. Scientific Scope

A. Specific Dosimetry Projects

1. Xenon-133 Long Term Organ Distribution Measurements

2. Dosimetry of Intraperitoneally Administered P-32 Colloid

3. Estimation of Fe-52 and Fe-55 Dosimetry from Fe-59 Kinetic Data

4. Environmental Monitoring--Nuclear Power Reactor

5. Radiation Sensitivity of the Thyroid after I-131 Therapy

6. Evaluation of the Standard Man Model for Dosimetry Calculations--Comparison with Laboratory Measurements

B. Supporting Systems Development

1. Hardware

a. Quantitative Longitudinal Tomographic System

b. Microprocessor Controlled Low-Level Whole Body Scanner

c. Compton Scattering Imaging System

d. High Speed-High Resolution Whole Body Imaging System Using One-Dimensional Position Sensitive Proportional Detectors

2. Software

a. Investigation of Real-Time Interpretive Systems for Nuclear Medicine Instrument Control

b. Specific Dosimetry Projects

c. SAAM

d. Sharing of Computer Programs in Nuclear Medicine

e. ORIS-11 Evaluation

VI. Scientific Personnel

VII. Other Personnel

VIII. Other Financial Assistance

1018275

IX. Premises, Facilities, Equipment, and Materials to be Furnished by Contract

X. Budget Estimated Requirements

XI. Authentication

XII. Appendix

Appendix I - Pho/Con Interface

Appendix II - Deconvolution Information Flow Software System

Appendix III - Software System for Quantitative Scanner

1018276

III. Project Abstract

Our work is directed toward the development of methods (hardware and software) for the quantitation of body and organ burdens of radioactivity. Initially, these studies were directed toward the estimation of low levels from fallout. These same facilities are now being prepared to make similar measurements for the purpose of monitoring environmental levels in human beings living near the proposed site of a new nuclear power reactor. Most of the current work is directed toward the evaluation of radiation dose distributions from new radioactive tracers and new procedures, such as bone mineral content, x-ray fluorescence, compton scattering imaging and neutron activation analyses used in nuclear medicine. The major problem that we face involves the meshing of our interests, capabilities and goals with the schedules and wishes of patients and referring physicians. Whenever the patient's problem and physical state permit sequential studies, we obtain additional data needed for dosimetry and metabolic kinetics studies. This includes multiple quantitative imaging studies, blood, and tissue samples (when available).

Continuing efforts are being directed toward the evaluation of the ORNL standard man model used for internal dosimetry calculations to determine the range of its validity in persons with different body/organ sizes and organ kinetics. We also continue to investigate the dosimetry from radio-iron labelled compounds in abnormals. In these studies, we investigate dose variations resulting from kinetic radioisotope distributions. The biological retention data obtained from measurements made with Fe-59 are now being used to determine the dosimetry of other radio-iron labels, specifically Fe-52 and Fe-55. As an extension of the study on the kinetics of I-131 administered in therapeutic quantities to patients with thyrotoxicosis, we are investigating the radiation sensitivity of the thyroid gland in Graves' Disease to radioiodine therapy. Iodine kinetic parameters and the iodine content of the gland, as measured by fluorescence scanning are being analyzed in an effort to identify potential sensitivity correlates.

In cooperation with the Department of Obstetrics and Gynecology, we are investigating the biological distribution and related dosimetry of P-32 labelled chromic phosphate colloid used in the treatment of ovarian cancer.

We are continuing to explore the potential of CAMAC for hardware and software standardization for nuclear medicine data acquisition and display systems. The benefits of CAMAC include standardization and modularity, the ability to replace defective systems modules without affecting the continued operation of the rest of the system, and the ability to incorporate new improved modules as they are developed. We will attempt to increase awareness in the nuclear medicine community of the benefits to be derived from CAMAC and hopefully will assist in insuring the general acceptance and survival of this important internationally accepted interfacing standard.

An autonomous crate controller which was acquired from the Fermi National Accelerator Laboratory and utilizes an Intel 8080 microprocessor is being interfaced to our quantitative whole-body scanner in an effort to reduce overhead on our general purpose computer system.

In cooperation with Oak Ridge National Laboratory we are investigating the feasibility of a high-speed, high-resolution whole-body imaging system which is based upon large one-dimensional position sensitive proportional counters. The impact of such an instrument on our work could be tremendous.

1018277

We continue to explore techniques for producing quantitative images from longitudinal tomographic scanners. The results of studies with phantoms and animals have been encouraging and are continuing. We are investigating both deconvolution and iterative techniques for producing quantitative images. The software systems that have been developed during the past year will be used with the Pho/Con scanner which is being provided to the project on loan from the Searle Corporation. The Pho/Con is the instrument of choice providing the optimum in speed and sensitivity for quantitating isolated distributions of radiopharmaceuticals.

The efforts of this project have been greatly strengthened by the arrival of David Rollo, M.D., Ph.D., Clinical Chief of Nuclear Medicine and Dr. Edward Siegel, Chief of Radiobiology. Dr. Rollo is a physicist as well as a physician and is well known for his work in Nuclear Medicine instrumentation evaluation. Dr. Siegel will be helping us analyze the results of the P-32 project. Dr. John Wikswo has joined the faculty of the Department of Physics as a Medical Physicist. We have already developed a number of areas of cooperative research with Dr. Wikswo.

The staff has achieved a scientific maturity and includes well respected, dedicated scientists. The problems on which we are concentrating our efforts are ones of biological significance and for which we have developed needed instrumentation capabilities. The dividends from our research investments are expected to increase now that a smaller share of effort goes into systems development. The major factor that determines the rate of progress of the biological studies is the number of subjects that fit into study categories and who are willing to participate. Progress is steady, and increasing cooperation from colleagues in other departments continues to accelerate our biological study output.

The work of the group is further reflected by commitments of key people to national efforts. These include the following responsible roles:

Dr. Price	MIRD Committee
Dr. Jones	NCRP Committee 55
Dr. Erickson	BCTIC--Directory Task Group
Dr. Brill	BCTIC--Advisory Committee to ORNL Chairman, NCRP Committee 32--Administered Radioactivity Member, NAS Subcommittee of Radioactivity in Drinking Water, and BEIR Committee Chairman, ANSI Committee 44--Medical Radiation Chairman, IEEE Committee on Nuclear Medical Scientists, 1975-76 Member, ORAU Human Investigations Committee

Thus the results of efforts sponsored by this ERDA contract at Vanderbilt are significant and contribute to the main stream of knowledge in an important area--patient dosimetry from nuclear medicine diagnostic procedures.

The work sponsored by this contract was originally directed to the evaluation of radiation exposures to humans from environmental contamination (due to fall-out from weapons testing). More recently we have developed methods to measure organ doses for radioactive isotopes administered to diseased human

subjects for diagnostic purposes. The techniques we have utilized permit the acquisition of sequential data from individuals so that ranges of dose can be assessed directly rather than being limited to extrapolations from animal studies. With increasing attention to the needs for additional and new energy sources, we plan to make our unusual facilities and resources available for establishing baselines and monitoring possible changes for new large power reactors being developed in our immediate area (Hartsville TVA plant). No money from this contract will be used to support that activity directly, unless supplemental funds are sought explicitly for specific projects. The collection and analysis of biological tissues (including placental tissue) before and following the opening of the plant is proposed, and could provide direct data on which to base discussions of risk verses benefits from needed new power sources.

1018279

IV. Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the costs of any of the research projects described in this proposal. Dr. A.B. Brill, Principal Investigator, is the Director of the Division of Radiological Sciences. Dr. R.R. Price is the Research Director within the Division. Dr. Parker and staff of the Environmental Engineering Group have collaborated with us in the design and conduct of experiments involving the use of radioactive and stable tracers for ecological studies. C. Bradshaw (acting Chairman of the Systems and Information Science Department and Director of Vanderbilt University Computer Center) and his staffs have contributed significantly to our work. None of the personnel in other departments is being supported financially by this contract, but the collaboration has strengthened our efforts and has led them to pursue research problems in our area. This should lead to the involvement of more graduate students from Engineering and Computer Science Departments in years to come. This, plus continuing support from the Physics Department has been of major importance in our research efforts. The Medical School has provided us with unusual facilities immediately adjacent to patient areas, which greatly enhances the opportunity to do meaningful work on both clinical service and research topics.

The recruiting and training of basic scientists, physicians, and technologists for careers in nuclear medicine and medical physics has been a major dividend from the research supported by this contract.

The development and application of analytical and experimental techniques for the conduct of quantitative organ dosimetry studies is the major accomplishment of our work. The use of these techniques for evaluation of patient radiation exposures by external counting permits the ascertainment of dose information in various disease states in man. Were it not for information from efforts such as these, we would be forced to rely on data extrapolated from rodents to man, or to rare circumstances where tissue data are available from autopsy or biopsy samples from diseased subjects. Further, we have designed and are carrying out studies which demonstrate the range of validity of the method most commonly used for model dose calculations, namely those using the "standard man" Monte Carlo methods developed by Snyder et. al. at ORNL.

1018280

A.1 Xenon-133 Long-Term Organ Distribution Measurements

New diagnostic Nuclear Medicine procedures for assessing regional pulmonary function require patients to breathe a mixture of radioactive Xenon and air from a closed system for periods of time up to and occasionally greater than 10 minutes. In our institution the procedure is called Gated Regional Spirometry (GRS). The GRS procedure is based on conventional Xenon lung scintigraphy which is used as a routine clinical procedure to estimate the topographical distribution of ventilation and perfusion and on a new modality of radionuclide imaging known as a multigated image acquisition (MUGA). Gated nuclear medicine technology was developed in 1974 to measure the ventricular ejection fraction and cardiac wall motion. The technique consists of imaging the changes in distribution of a radiotracer during an average physiological cycle of the function under study. The average physiological cycle is obtained by adding multiple cycles by means of synchronizing the data acquisition system with a physiological signal produced in each cycle.

The radiotracer used in GRS is most frequently either ^{127}Xenon or ^{133}Xenon which may either be inhaled or when disolved in saline it may be injected into an arm vein. The resulting distribution of radioactivity within the lungs is detected with a large field of view scintillation camera and data are registered in list mode by an on-line minicomputer. From the beginning of the procedure the subject rebreathes in a closed circuit in order to achieve a uniform concentration of Xenon throughout the system. Lung radioactivity is measured for approximately 3.5 minutes after the administration of the Xenon. During the first 3 minutes the subject is requested to perform a resting ventilation and during the last half minute he is requested to perform maximal ventilatory effort. Stored raw data are framed at a frequency of 5 frames per second and by selecting an area of interest around both lungs a time/activity curve within the lung can be obtained. The curve represents the changes in volume of the lungs and the peaks, corresponding to the beginning of inspiration, are used to trigger a MUGA program.

In this type of study, organs and tissues in the body which have very high solubility coefficients (fat primarily) are exposed to high concentrations of Xenon for relatively long times. These long exposure times result in the high solubility tissues becoming saturated with the radioxenon. The estimated radiation dose will thus depend upon the distribution of these tissues in the body, how long the xenon mixture has been breathed and the physical properties of the radionuclide.

There have been a number of studies on the retention of Krypton-85 and radon in animals, but there seems to be little information available on the retention and tissue distribution of noble gases which have been breathed to equilibrium by human subjects. A study by Susskind, et al. at Brookhaven National Laboratory measured the total body retention of Xe-127 breathed to equilibrium in 11 volunteers. They concluded that the clearance curve may contain up to 5 components; the longest had a $T_{\frac{1}{2}}$ of 7.6 - 17 hours and comprised 1.03 - 17.6% of the total lung activity at the start of the washout.

In our nuclear medicine clinic, we are performing GRS studies at the rate of two per week. We propose to carry out studies on at least 10 patients during the coming year to assess total body retention and the tissue distribution of the radioxenon. From this data, information will be obtained on how dose estimates, which have been made in the past by assuming a uniform distribution,

might be in error due to an inhomogeneous distribution of the radionuclide.

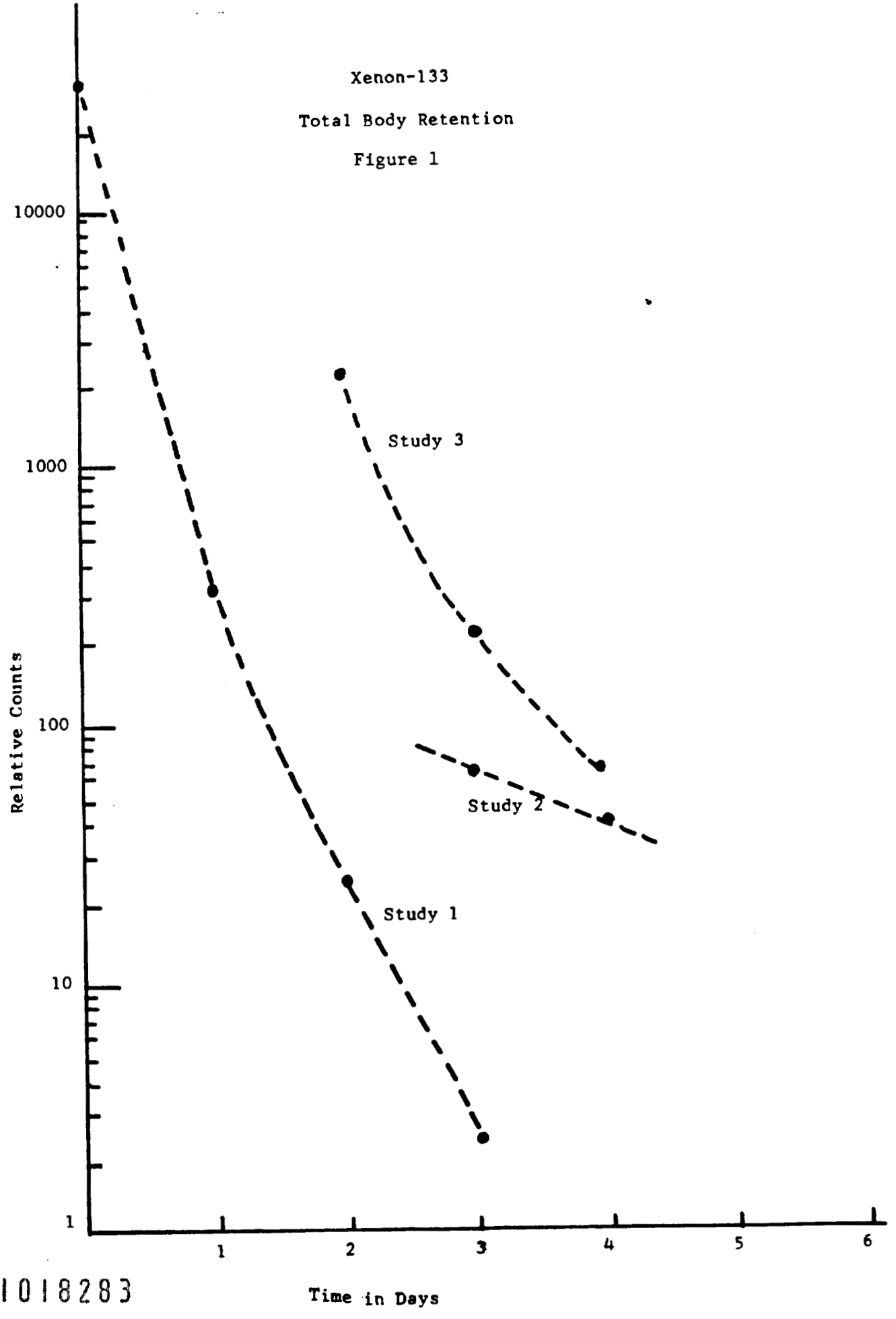
Preliminary kinetic measurements have been carried out in five normal individuals. Whole body counts were made on three of the five. Figure 1 shows that the $T_{\frac{1}{2}}$ of the long term retention component for these studies were approximately 8, 35, and 12 hours respectively for studies 1, 2, and 3. The 36 hour value was obtained from a young male who was not considered to be obese. Scan images were not obtained on this individual so that, unfortunately, no regional information was available. Preliminary calibration parameters were used to estimate the fraction of the administered dose residing in the (8-36) hour component. This calculation indicated that approximately 10% of the initial lung activity was accounted for by this component.

Scan images taken approximately 1 hour after being allowed to breathe room air for the remaining two individuals are shown in Figure 2. Even though both of these individuals were normal the Xenon images are obviously very different. It appears that the high concentrations of Xenon correspond to fat deposits in the mediastinum and mesentery in both individuals and in one individual (2) considerable xenon resides in what appears to be the liver and spleen. The total body activity was estimated to be from 1-2mCi at 1 hour. Each individual had breathed from a closed system ($\sim$ 10 liters including the patient) containing 30mCi of Xe-133 for a period of 3-5 minutes. From the scan images we estimated that approximately 25 -35% of the total body activity was in the mesentery region and from 20 -30% was in the mediastinum, liver/spleen area.

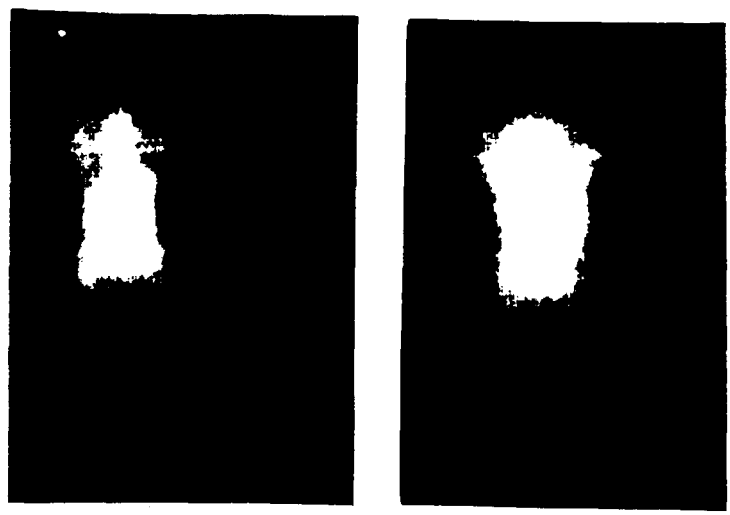
We propose to carry out a complete calibration of our scanner for Xe-133 using calibration techniques similar to those used previously for Tc-99m. This calibration procedure utilizes scans of point sources which have been placed in varying thicknesses of water to establish depth response and attenuation characteristics and a transmission scan which is used to determine the effective thickness of the body at each point of the scan field.

The total-body scanner system that will be configured about the position sensitive proportional detectors on loan from Oak Ridge National Laboratory (see Section B.1.d.) will be evaluated for possible use in this project.

1018282


Xenon-133
Total Body Retention
Figure 1
10000
1000
100
10
1
Relative Counts
Study 3
Study 2
Study 1
1
2
3
4
5
6
Time in Days

1018283



Patient 1 Patient 2

Figure 2: Total-body scans of two normal volunteers after Xe-133 pulmonary function test.

A.2 Dosimetry of Intraperitoneally Administered P-32 Colloid

We have completed the initial phase of the dosimetry study on P-32 colloid used in the therapy of ovarian cancer patients. The purpose of this type therapy is to deposit the colloid throughout the abdomen, where it can migrate along the same paths as ovarian metastases and deliver a tumoricidal dose without excessive damage to vital organs. To be effective, the colloid must follow all the migration paths in sufficient, but not excessive amounts. Thus the amount given and the method of administration are exceedingly important.

Our method was to surgically implant LiF dosimeters (TLD's) at selected sites in guinea pigs (diaphragm, parietal peritoneum, peri-aortic lymph node area, and lesser sac). Following recovery from surgery P-32 colloid was given, the animals sacrificed at various intervals, and the TLD's recovered and read-out to determine the radiation dose as a function of time. The purposes of this phase were to:

a) identify and correct experimental problems

b) determine approximate dose levels

c) monitor the deposition and movement of colloid

The results are shown graphically in Figures 1-2, where the dose (rads/microcurie given) is plotted versus time for the four sites. With all animals, the volume of colloid solution given was constant (2ml), the injected activity was approximately 100 microcuries (with different activities corrected for), and all injections were made in the mid-to-lower left quadrant of the abdomen.

Experimental Problems

The implantation of TLD's caused two significant problems; surgical complications, and animal reaction to the TLD's themselves. In order to implant the TLD's (a fairly delicate operation), it was necessary to distend the intestines. This procedure had an unknown and presumably variable effect on the abdominal peritoneum configuration and lymphatic drainage system. This could preclude accurate comparisons from one animal to another, which is an essential requirement for this study. Further, in the animals which did tolerate the surgery well, the recovered TLD's were enclosed in a thick membrane which shielded the TLD's from the P-32 beta radiation to some extent. Given the obvious scatter of the results in the figures, we felt these problems must be corrected.

Based on these experiences, we have decided not to implant dosimeters in future experiments. Instead, a small incision is made at the injection site, and a small catheter positioned in the abdomen. Following this minor surgery, the colloid is injected through the catheter, and the catheter removed. After a suitable period of time, the animal is sacrificed, tissue samples removed from the desired sites, and a set of TLD's exposed to the tissue samples. This surgery is expected to be well-tolerated by the animals and assures that the P-32 is injected into the abdominal cavity (not the intestines by accident). The TLD readings will give the activity of P-32 in the tissue samples, rather than a direct dose, but many tissue samples can be taken and several TLD's can be placed on a sample to check the uniformity of the P-32 deposition.

1018285

The main disadvantage to this method is that a direct dose measurement is not made, requiring a calculated estimate of the dose. Because of the complicated geometry of the in-vivo P-32 distribution, the calculation is subject to a number of errors. Our decision is to first establish the distribution of P-32 in normal animals and then to measure the dose in a surgically altered animal.

Approximate Dose Levels and Colloid Movement

Despite the scatter of the data, one can obtain some idea of the dose levels. The dose in the lesser sac appears to be the largest, reading a level of 33 rads/microcurie in three weeks. Next is the diaphragm at 12 rads/microcurie, at three weeks. The parietal peritoneum reaches a dose of 10 rads/microcurie within two weeks and appears to stay at that level, while the peri-aortic area dose is only 1-2 rads/microcurie. It must be emphasized that these estimates are for guinea pigs only; the inference for humans is unknown.

As mentioned before, the injection site was in the lower left quadrant of the abdomen. The TLD positions were:

a) lesser sac -- within the lesser sac in the mid-abdomen

b) parietal peritoneum -- along the right anterior body wall

c) peri-aortic area -- to the right of the midline at the peri-aortic lymph nodes in the lower abdomen

d) diaphragm -- along the diaphragm superior to the right lobe of the liver

The curves suggest that the colloid moves to the parietal peritoneum within two days, with some being drained through the peri-aortic area. Little reaches the diaphragm or lesser sac until five to seven days, but thereafter the dose to each increases rapidly. Within two weeks, little colloid remains in the parietal peritoneal area or the peri-aortic area, but irradiation of the lesser sac and diaphyragm continues. Data past three weeks are very doubtful because of the membranes that formed around the TLD's.

Colloid Distribution on Membranes

Tissue samples were removed from one animal and several TLD's exposed to each sample to check the uniformity of the P-32 deposition on the tissues. The results for parietal peritoneum, diaphragm, and mesenteric area samples are shown in Table 1. A very uneven distribution of colloid is apparent (the animal was sacrificed at 7 days post-administration). If so, large variations from one animal to another can be expected, making the dosimetry difficult. A more important implication is that the method of administration is inadequate; which if also true in humans, may compromise the effectiveness of the P-32 therapy.

We propose to continue the investigation of the dosimetry of P-32 colloid by removing tissue samples from guinea pigs and using TLD exposures to the samples to determine the activity of P-32 deposited on the samples. In addition, the uniformity of the P-32 deposition will be simultaneously checked. Because of experimental problems in measuring the dose directly, we have decided to divide the next part of the project into two distinct steps:

1018286

a) determine the distribution of P-32 activity, and

b) determine the dose levels more carefully.

Step (a) will utilize animal sacrifices and tissue sampling while step (b) will be a modified form of the procedure utilizing implanted TLD's. We feel that clinically important information will result from both steps, because both the activity of P-32 given and its method of administration are very important. In an effective therapy, the P-32 must cover all the paths followed by ovarian metastases, deliver a tumoricidal dose, but not excessively damage vital organs. Thus only a range of activities given will be effective, and the method of administration must be selected so as to give the most desirable distribution. Precisely what this desired distribution is, is not yet clear; the purpose of step (a) will be to find how the method of administration does affect the colloid deposition and movement.

When suitable method(s) of administration are decided upon, we will again implant dosimeters in a group of animals to redetermine the dose levels. This is essential, because calculated doses based upon activity measurements of tissue samples have too much uncertainty (e.g., the many folds of membranes in the lower sac mean that the dose at a point is due to the activity at that point plus the activity folded next to it; also, some activity in abdominal fluids contributes to the membrane dose but is not deposited on the membranes). Our past experiences with implantation, plus the knowledge obtained from step (a), should reduce the problems previously encountered with dosimeter implantations.

The ultimate goal of this project is to determine the P-32 activity and method of administration which will maximize the effects of the therapy in humans. Thus all animal results will be considered with the extension to humans in mind. In some respects this will be direct: the guinea pig abdomen is similar in shape, structure, and lymphatic drainage to the human abdomen. In other respects, the great size difference between humans and guinea pigs will pose problems when attempting to extrapolate the guinea pig dose to human dose. In cooperation with Drs. C. Julian and L. Burnett of the Department of Obstetrics and Gynecology, we are designing experiments for direct human measurements. These experiments include external measurements (Tc-99m sulfur colloid) and possibly limited implantation of TLD's. We will continue these considerations in an effort to reach our ultimate goal.

1018287

TABLE I

Relative TLD Readings of Tissue Samples (Arbitrary Units)

Perietal Peritoneum	Diaphragm	Mesentery
100	780	455
65	329	208
55	151	1600
59		1645
171		2212
159		2224

1018288

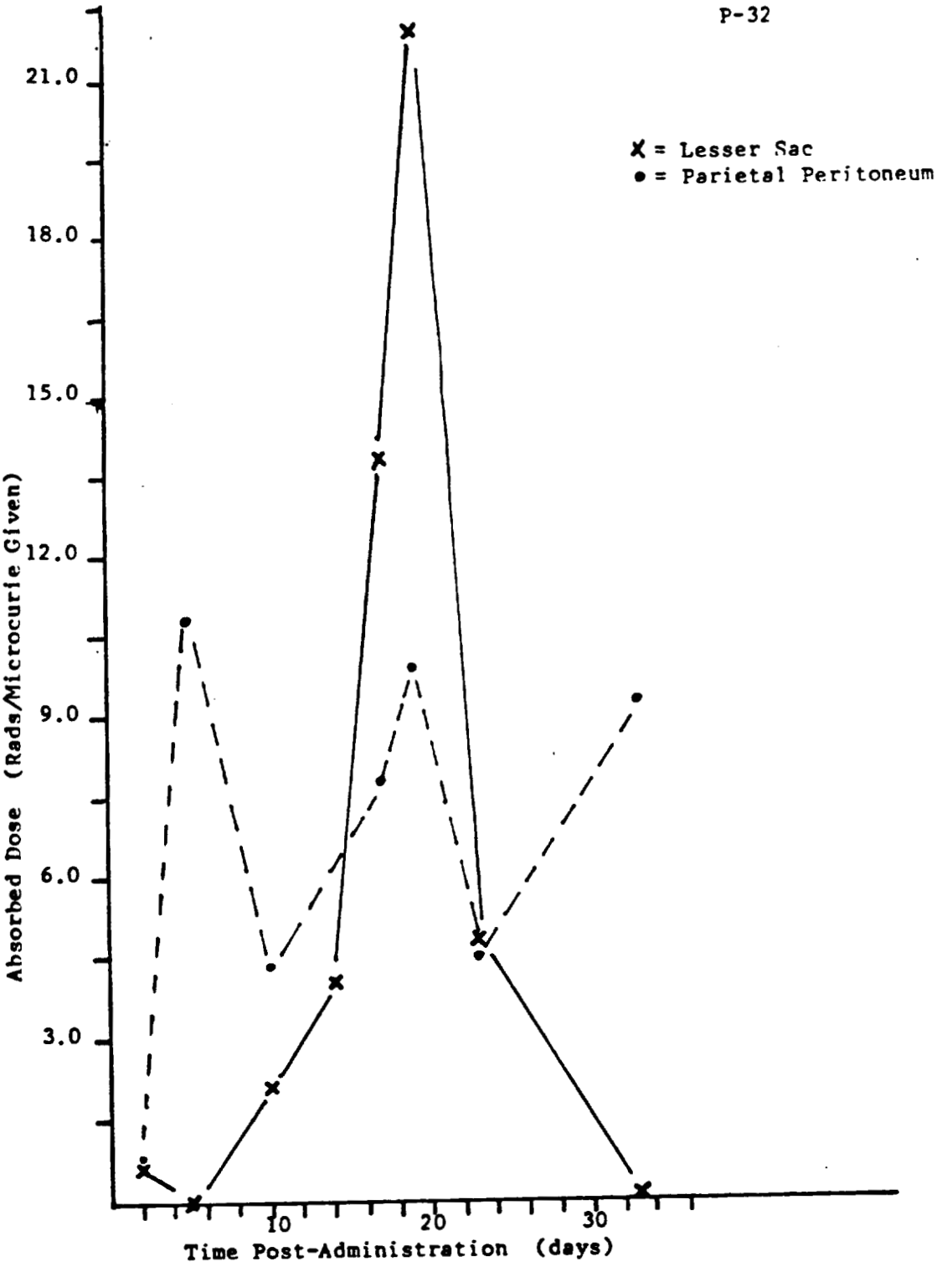


FIGURE 1

1018289

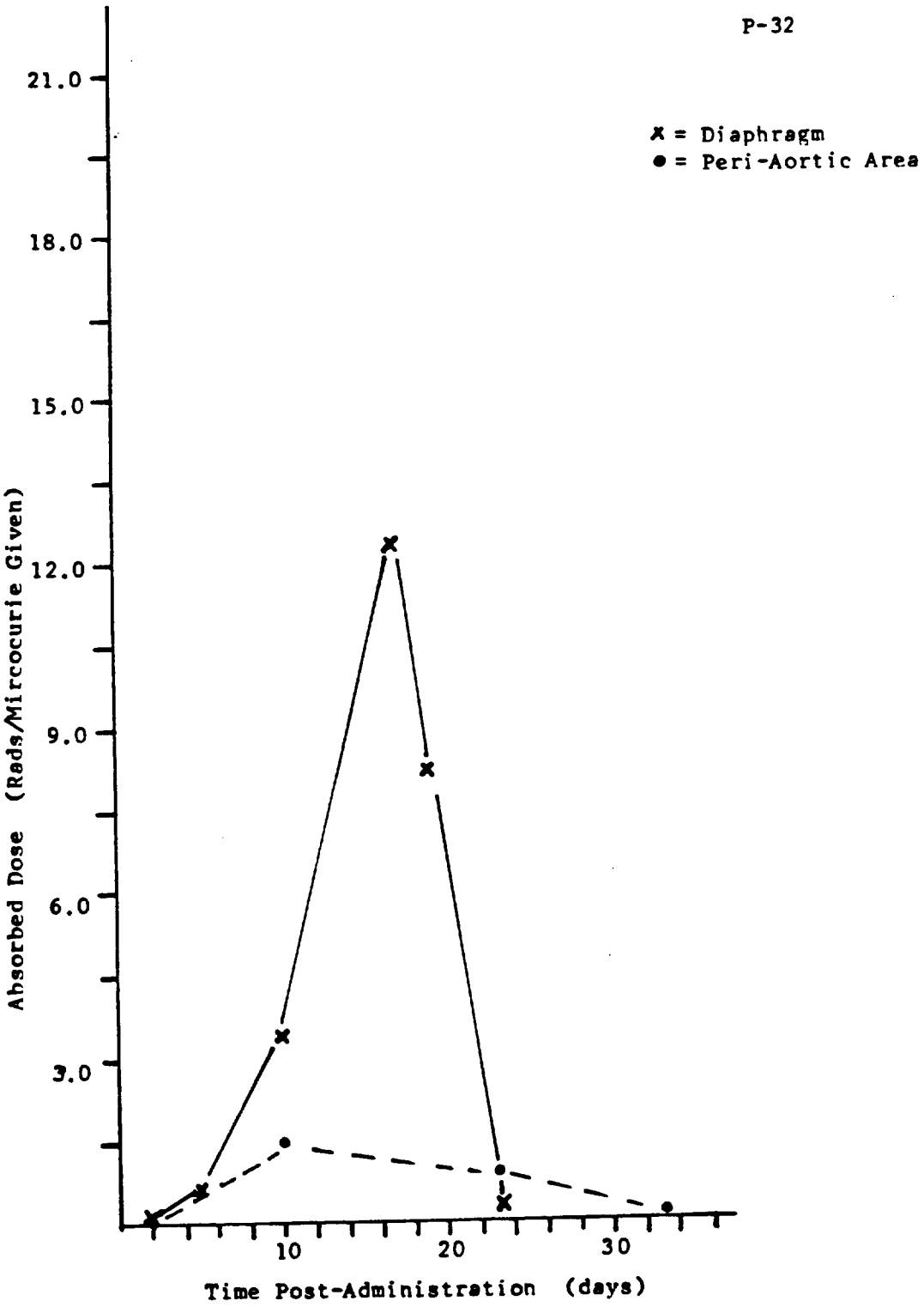


FIGURE 2

1018290

A.3 Estimation of Fe 52 and Fe-55 Dosimetry from Fe-59 Kinetic Data

This laboratory has worked for several years to build a unique data base of kinetic data from patients who had been administered tracer quantities of Fe-59 citrate. Calculations based upon these data have revealed average organ doses which may vary as much as an order of magnitude depending upon the disease state of the patient. Table 1 presents results from 16 of these patients as compared to a normal volunteer. In this work, we have taken advantage of the long half-life of Fe-59 to make external measurements of the iron distribution for time intervals as long as 250 days in some individuals. These long term measurements would not be possible with other isotopes of iron. During the next year we propose to utilize the kinetic data collected from the Fe-59 studies to make estimates of the radiation absorbed dose that might be expected from Fe-52 and Fe-55 studies.

Accelerator produced ^{55}Fe is carrier free. Reactor-produced ^{55}Fe and ^{59}Fe are available with specific activities of 2-50 Ci/g, each of these being slightly contaminated with the other isotope. ^{52}Fe is accelerator produced and is consequently available in only selected medical centers even through it possesses the most appealing imaging characteristics of any of the iron isotopes.

For the purpose of the present radiation absorbed dose calculations, 100% radionuclidic and radiochemical purity of the radiopharmaceutical will be assumed. However, ^{52}Fe decays to radioactive ^{52m}Mn and ^{52}Mn, some of which will be present with the ^{52}Fe as received. The ^{52m}Mn and ^{52}Mn produced by decay after injection will also add to the radiation dose. The dosimetry for each of these nuclides will be calculated separately.

The nuclear data for radioisotopes of iron and manganese that will be used are given in Table 2.

The problems associated with measuring the parameters of iron metabolism have been recognized for many years. The sizes of the iron storage pools have been particularly difficult to determine by tracer techniques because of the long term required for the equilibration of these pools with the circulating iron pools. Such long term studies of plasma radio-iron levels present two major problems: 1) plasma radio-iron levels become extremely low, giving large statistical errors in their measurement and, 2) measurement over extended periods is not practical in sick patients. Also, critically ill patients recieve numerous transfusions of whole blood and packed red cells which alter blood volumes and consequently the estimates of absolute circulating iron levels.

Through the use of compartmental modeling techniques, quantitative external measurements of the peripheral iron storage pools can be combined with the measurements of the circulating iron pools in a self-consistent manner. The ability to measure the turnover of slowly exchanging compartments directly, rather than inferring their kinetics from plasma clearance and red blood cell incorporation of the radio-iron, provides additional information on the anatomical distribution of these pools within the body and makes possible more reasonable dosimetric calculations.

Numerous models have been proposed to describe iron kinetics. The model used for the dose estimates in this report contains the salient features of the other models and is particularly useful for dosimetry purposes because the

1018291

NIH Simulation Analysis and Modeling computer program (SAAM) can directly provide the cumulated activities, $\tilde{A}$ μCi-hr, required for radiation absorbed dose estimates to the tissue. This model has been found to be useful in a majority of the abnormal cases as well as for describing normal kinetics.

A schematic of the compartmental model that is used for the dosimetric calculations along with the intercompartmental flow rates in a group of patients from our data base are shown in Figure 1 and Tables 3 and 4. The criterion for choosing this model over more complex ferrokinetic models is that this model was the simplest model found that was consistent with the measured data for the largest number of studies. In two patients with paroxysaml nocturnal hemoglobinuria (PNH) the model was inadequate to describe the kidney uptake and urinary excretion of iron. For these studies kidney and urine compartments were added to the model.

As a basis for estimating the $\tilde{A}$ values in normals, we will seek to derive analytical expressions for the time-activity curves for the various organs of interest (liver, spleen, marrow, red blood cells). The approach will be to first fit the observed data for individual subjects using the SAAM program and model. The "best fit" model parameters will then be used to generate noise free biological retention curves which will then be fitted to equations of the form of sums of exponentials. These biological retention curves will then be integrated over time using the appropriate physical decay parameters of the various isotopes to obtain the cumulative activity, $\tilde{A}$ in μCi-hr. The "S" factors for Fe-59, Fe-55, and Fe-52 as published by Synder, et al (ORNL-5000) in terms of m rad/μCi will be used along with cumulative activity results to make the dose estimates. The sources of activity will be taken to be in the liver, spleen, marrow and circulating red blood cells. In abnormals $\tilde{A}$ will be calculated individually for each patient using the SAAM program and his individual kinetic parameters.

1018292

TABLE 1

Total Absorbed Dose Fe-59 Citrate
(mrad/μCi)

	Diagnosis	Liver	Spleen	Marrow	Ovaries	Testes	Total Body
Q	Normal	77.4	174.6	40.6	25.3	23.2	25.2
A	Hemochromatosis	90.6	175.1	37.4	25.4	23.6	25.8
B	Leukemia	222.5	763.7	23.6	14.5	9.3	23.7
C	Refractory Anemia	258.7	760.4	16.8	10.8	5.3	21.7
D	Follicular Lymphoma	134.5	1295.5	42.5	28.5	24.2	35.8
E	Intestinal Bleeding	126.0	171.9	51.7	23.6	19.0	24.9
F	Sideroblastic Anemia	118.4	762.8	191.8	28.3	5.6	27.9
G	Refractory Anemia	426.3	313.4	19.1	12.2	4.5	25.9
H	Refractory Anemia	161.6	271.6	8.5	6.0	2.9	11.8
I	Suspected RCA	170.7	180.7	37.5	19.8	15.5	23.3
J	Remission RCA	175.2	169.7	26.7	19.4	16.4	23.3
K	Pure RCA	334.9	234.4	21.5	9.2	2.2	19.7
L	Refractory Anemia	175.0	169.5	32.4	19.6	15.9	23.4
M	Remission RCA	114.6	310.4	19.7	10.9	8.0	14.6
N	Suspected RCA	143.1	238.7	23.1	13.9	10.8	17.8
O	Pure RCA	335.6	309.8	14.5	9.0	2.8	20. 2
P	Suspected RCA	217.9	236.0	36.3	12.3	5.9	18.3

1018293

TABLE 2

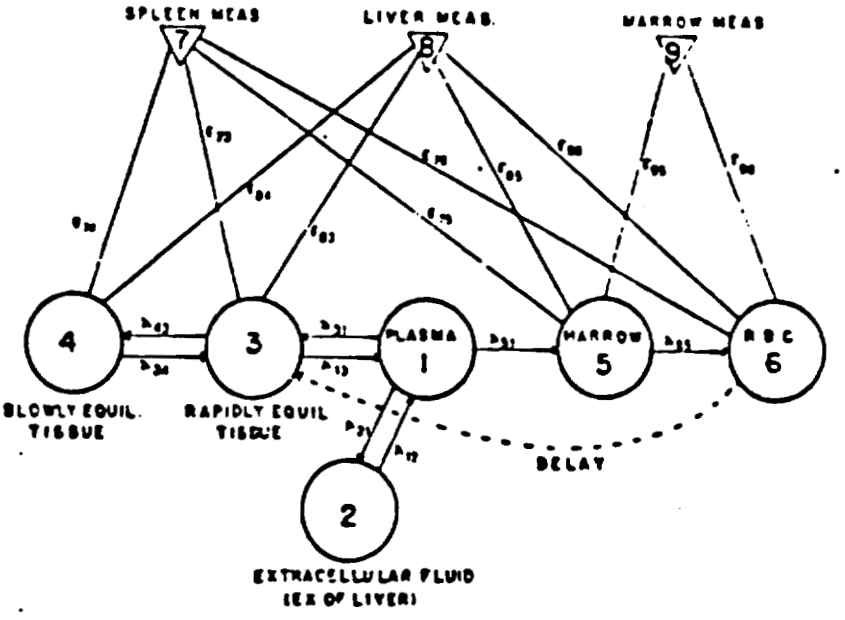
Nuclear Data

Radionuclide	^{52}Fe		^{55}Fe		^{59}Fe		^{52m}Mn		^{52}Mn	
Physical Half-Life	8.3h		2.7y		45d		21.3m		5.67d	
Mode of Decay	E.C. & β^+		E.C.		β^-		EC, β^+, IT		EC, β^+	
Equilibrium Dose Constant for Non-Penetrating Radiation (g-rad/μCi-h)	0.4375		0.0095		0.2511		2.4105		0.1642	
Principal Photons:	E_i	n_i	E_i	n_i	E_i	n_i	E_i	n_i	E_i	n_i
	0.169	0.993	0.0058	0.2339	0.1922	0.0292	1.434	0.98	0.744	0.90
	0.511	1.16			1.099	0.555	0.511	1.93	0.936	0.95
					1.292	0.441	0.378	0.19	1.434	1.00
									0.511	0.60

E_i, Energy (MeV); n_i, Mean Number/Dis

1018294

Diagram of SAAM Compartmental Model for Fe-59 Kinetics



Model Input Data

1) Fraction of administered activity in plasma

2) Fraction of activity in circulating red blood cells

3) Fraction of activity in liver from quantitative whole-body scan

4) Fraction of activity in spleen from quantitative whole-body scan

5) Fraction of activity in pelvis from quantitative whole-body scan

6) Fraction of circulating red blood cell pool in each region of the body (determined from ^{51}Cr-labeled red blood cell whole-body scan)

Figure 1

1018295

Table 3

Fe-59 Dosimetry

Intercompartmental Rate Constants
(fraction/hr)

	Plasma to Marrow	Marrow to RBC	Plasma to Rapid Stores	Rapid Stores to Slow Stores	Slow Stores to Rapid Stores	Rapid Stores to Plasma
Normal	8	0.23	2.3	0.53	0.05	0.20
Abnormal maximum	30.0	0.35	12.0	13.7	0.27	12.4
Abnormal minimum	0.24	0.004	0.27	0.02	0.001	0.001

1018296

TABLE 4

Fe-59 Dosimetry

Intercompartmental Rate Constants (fraction/day)

	Disease	Plasma to Marrow (λ_1)	Marrow to RBC (λ_2)	Plasma to Radid stores	Rapid stores to Slow Stores	Slow Stores to Rapid stores	Rapid Stores to Plasma
A	Hemachromatosis	30.0	0.30	12.0	0.10	0.12	0.82
B	Leukemia	9.6	0.17	6.2	3.0	0.005	0.10
C	Refractory Anemia	29.0	0.15	4.0	0.02	0.001	0.29
D	Follicular lymphoma	8.0	0.30	6.9	3.0	0.005	1.46
E	Intestinal bleeding	15.6	0.10	0.27	0.13	0.27	0.29
F	Refractory anemia (marrow storage)	28.7	0.01	6.16	1.55	0.56	0.74
G	Refractory anemia (liver storage)	4.2	0.07	10.5	0.74	0.01	0.44
H	Refractory anemia	2.7	0.20	6.8	0.45	0.03	0.001
I	RCA(suspected)	6.2	0.13	3.2	0.53	0.04	0.29
J	RCA(remission)	3.8	0.35	3.9	0.37	0.001	0.31
K	Pure RCA	0.65	0.004	4.0	0.73	0.08	0.12
L	Refractory anemia	5.3	0.19	2.7	0.11	0.19	0.18
M	RCA(remission)	24.8	0.14	1.8	13.7	0.66	0.001
N	RCA(suspected)	5.0	0.18	5.0	0.61	0.09	0.001
O	Pure RCA	0.24	0.04	2.3	0.65	0.11	0.001
P	RCA(suspected)	3.78	0.03	4.3	13.7	0.001	12.4
Q	Normal	8.00	0.23	2.3	0.53	0.05	0.20

1018297

4. Nuclear Power Reactors—Environmental Monitoring

Previous studies conducted in our laboratory have been directed toward the assessment of body burdens of environmental pollutants. In the early 1970's we collected over 1000 placentae from births in Nashville and assayed the content of heavy metals (Pb, Cd, Hg) and carried out neutron activation analysis to determine levels of other trace elements. Comparisons were made between levels found in placenta, blood, and hair samples in normal and abnormal births, in an attempt to identify potential etiological relationships. No gradients suggesting disease correlates were found, and levels were not elevated in this region. No concern has been raised locally with respect to potential hazards from these agents since data show no cause for concern.

We have contacted TVA representatives with respect to the possibility of mounting a similar study in the area of the Hartsville Nuclear Power Reactor. To date no firm arrangements or commitments have been made. A possible study design might consist of collecting placental tissues on a sampling basis from persons living at varying distances from the Hartsville plant, and analyzing these tissues for radionuclides that could be expected. Similarly, periodic low-level whole-body counts on selected individuals should also be taken. Assays should conducted by a laboratory expert on low level counting, and which has the capacity to handle such a volume. We would maintain the basic records, and do the temporal trend and epidemiologic analyses at Vanderbilt which should be considered a neutral observer. Collaboration between epidemiologists, statisticians, OB/GYN specialists, and community agencies should enable such a study to be conducted if sufficient interest suggests it is worth doing. Discussions concerning how our facilities and experience can be used in such studies are already underway.

The hazards whether imaginary or real of nuclear pollutants from nuclear power reactors has excited much public reaction. By virtue of the alleged increased incidence of cancer in people who are occupationally exposed to higher than average radiation backgrounds, we feel that it is partularly important that these data be collected in a systemic and scientific manner which will be able to withstand the most careful scientific scrutiny.

1018298

A.5 Radiation Sensitivity of the Thyroid During I-131 Therapy

Information on iodine uptake, the effective half-time of its retention in the thyroid and thyroid mass are used in calculating the amount of I-131 to be administered to patients in the treatment of hyperthyroidism. A major variable, however, which we have not yet learned how to assess is radiation sensitivity of the thyroid.

In our work on iodine kinetics, to date, we have evaluated iodine metabolism in large numbers of patients during treatment of thyrotoxicosis and have determined model parameters which are reasonable predictors of absorbed radiation dose to the thyroid, given knowledge of thyroid gland size.

To evaluate thyroid sensitivity, we need to measure a parameter that reflects damage to the thyroid. The rate of loss of iodine from the gland following therapy is due to altered rates of release from the gland and by diminution of uptake. We have measured the iodine content of the gland after therapy by means of x-ray fluorescence scanning in a large number of patients in an attempt to determine if predictions of hypothyroidism can be made from the early changes in iodine content after therapy. We are currently measuring iodine content and other thyroid function parameters in 52 patients who have received radioiodine therapy. The patients have been grouped into the following 5 categories based upon the course of therapy they received: (1) I-131 only, (2) drugs pre-I-131, (3) drugs post-I-131, (4) drugs pre-and post-I-131, and (5) previous surgery and I-131. These patients were studied at monthly intervals following I-131 therapy and the results of several quantitative fluorescent scans are shown in Figures 1 and 2. Figure 1 shows the 5 categories plotted as a function of the percentage of initial iodine content pre-therapy. There appears to be no significant difference in the categories when plotted in this fashion. All show a steep decline in iodine content between the second and third month post-therapy. Plotting the categories as a function of the absolute initial iodine content values in milligrams in Figure 2 shows that those patients with previous surgery before therapy had significantly lower initial iodine values than the other four categories. However, the course following therapy for the five categories is essentially the same. From these data, we have concluded that the course of treatment before I-131 therapy has very little, if any, effect on the rate of iodine loss following administration of I-131.

The data in Figures 3 and 4 show plots of the iodine content versus time post-I-131 therapy for 32 of the original 52 patients in which there was adequate follow-up to study the patients for a period of 12 months to a euthyroid status or to the time at which they became biochemically hypothyroid and were placed on replacements drugs or the time that they relapsed and were retreated. From these figures it is noteworthy that those patients who were destined to become hypothyroid had lower iodine content values at the 2-3 month interval that the other two groups. By closely analyzing the currently available data, we have arbitrarily chosen a value of 2mg as the level for making predictions on the outcome of therapy. Applying this separation criterion to the 43 patients in which adequate follow-up information was available as of June 1978 some interesting observations can be made as shown in the lower section of Table 1. Of the 21 patients who had iodine contents of 2 mg. or greater at the 2-3 month interval, only 3 became hypothyroid within 12 months. The remaining 18 either remained euthyroid or relapsed into hyperthyroidism within 12 months. On the other hand, of the 22 who had iodine

1018299

contents of less than 2 mg at the 2-3 month interval, 18 became hypothroid within 12 months. From these data it appears that an iodine content of less than 2 mg at 2-3 months post therapy with I-131 predisposes the patient to early hypothyroidism. It also appears that these low iodine content values may precede biochemical hypothyroidism by several months and may serve as an early indicator of hypothyroidism. We plan to continue studying therapy patients using the results reported here to determine if we can, in fact, predict early hypothyroidism on the basis of the iodine content values at the 2-3 month interval.

We have attempted to obtain data on the iodine content at short intervals after therapy but have been unable to make valid measurements at times less than one month post-therapy due to the inability to resolve the iodine K x-rays (from the fluorescence of stable iodine) at 28.5 keV and the xenon K x-rays (from the daughter of I-131) at 29.7 keV with the lithium-drifted silicon detector system and associated electronics that have been used in the past. The addition of a new state-of-the-art linear amplifier to the system has imporved the energy resolution considerably at high counting rates. This improvement is such that separation of the two distributions may now be possible. We have developed a two window technique utilizing the computer for separating I-123 and stable iodine (I-127) distributions in a scanning situation and the applicability of the method to I-127 and I-131 studies will be explored. I-123 has a 27.5 keV x-ray that must be resolved from the I-127 fluorescent x-ray at 28.5 keV. An energy spectrum from separate and combined sources is shown in Figure 5. As long as the two peak heights do not differ by too great a magnitude, the distributions can be separated using a two window method of computerized data collection and processing. The mathematics for this separation technique are shown below.

FOR SIMULTANEOUS COUNTING OF I-127 AND I-123 WITH TWO SCALERS

1. I-127 Window Counts = Net I-127 Counts + (I-123 Counts in I-127 Window) + Bkgd(127 Window)
2. I-123 Window Counts = Net I-123 Counts + (I-127 Counts in I-123 Window) + Bkgd(123 Window)
3. I-123 Counts in I-127 Window = IF7 x Net I-123 Counts
4. I-127 Counts in I-123 Window = IF3 x Net I-127 Counts

where: IF7 = Fraction of I-123 Counts in I-127 Window
IF3 = Fraction of I-127 Counts in I-123 Window

IF7 and IF3 can be determined by counting separate distributions of I-123 and I-127 with the same geometry and count rates as will be observed in the simultaneous imaging situation.

Substituting Eq. 3 and 4 into Eq. 1 and 2 we can solve for Net I-127 and Net I-123 Counts.

EQUATIONS FOR SEPARATE DISTRIBUTIONS

$$\text{Net I-123 Counts} = \frac{(\text{I-123 Win. Cnts.} - \text{Bkgd(123 Win.)}) - \text{IF3} \times (\text{I-127 Win. Cnts.} - \text{Bkgd(127 Win.)}}{1 - \text{IF3} \times \text{IF7}}$$

$$\text{Net I-127 Counts} = \frac{(\text{I-127 Win. Cnts.} - \text{Bkgd(127 Win.)}) - \text{IF7} \times (\text{I-123 Win. Cnts.} - \text{Bkgd(123 Win.)}}{1 - \text{IF3} \times \text{IF7}}$$

These calculations can be performed easily point-by-point in the computer to provide images of the separate distributions of I-123 and I-127.

1018300

The distributions are imaged simultaneously with a window set to bracket the iodine fluorescent x-ray peak and the I-123 x-ray peak as shown in Figure 6 for a thyroid phantom containing stable iodine (I-127) and an S-shaped phantom containing I-123. Two syringes, one containing I-123 and the other containing I-127 are also imaged in the same scatter geometry as shown in the top of the two images. From the syringe data, correction factors are obtained to be used in separating the distributions to obtain the final images as shown in Figure 6. The applicability of this technique is further demonstrated in Figure 7 in imaging a thyroid phantom containing 20 mg. of I-127 and 60 micro-curies of I-123.

The problem of separating I-127 (28.5 keV) and I-131 (29.7 keV) should be the same as that for I-127 and I-123. Although this technique has problems when one peak is significantly different in magnitude from the other, it may be accurate enough to provide meaningful data to study the early changes in iodine content after therapy and determine if there is additional information available in this early phase.

We are attempting to obtain a high purity germanium detector on loan to make some measurements for the simultaneous I-123/I-127 studies. The advantage of this system would be better energy resolution thus yielding better separation of the two peaks. If this detector becomes available we will also explore its potential for the I-127/I-131 studies.

1018301

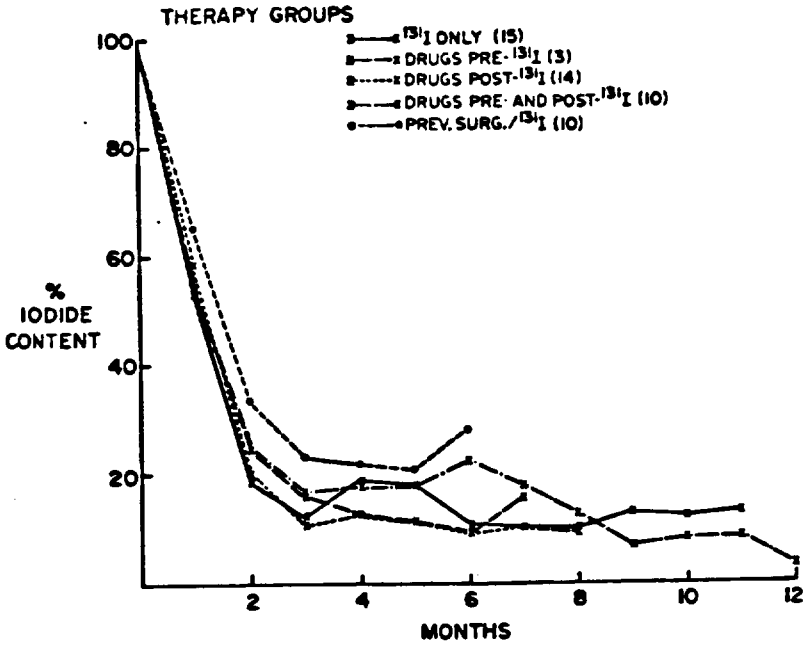


FIGURE 1

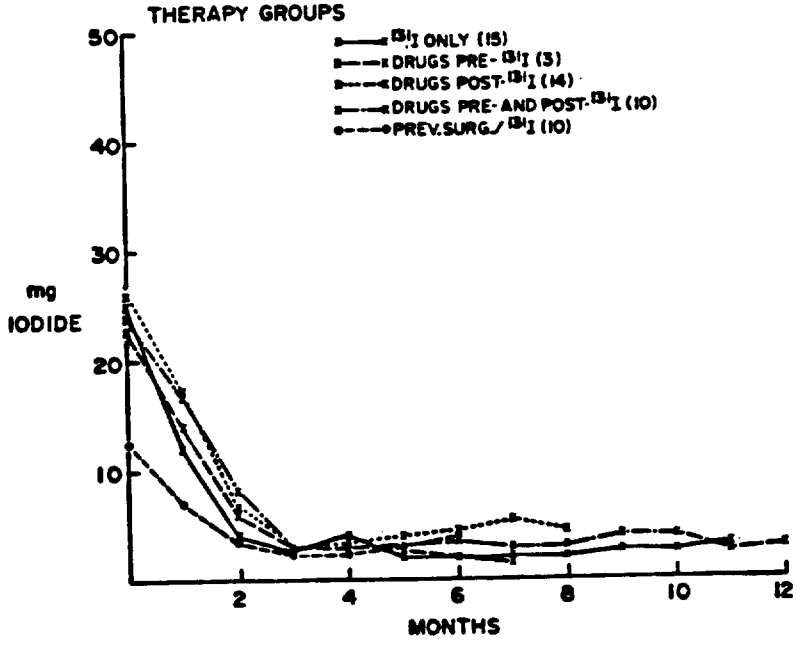


FIGURE 2

1018302

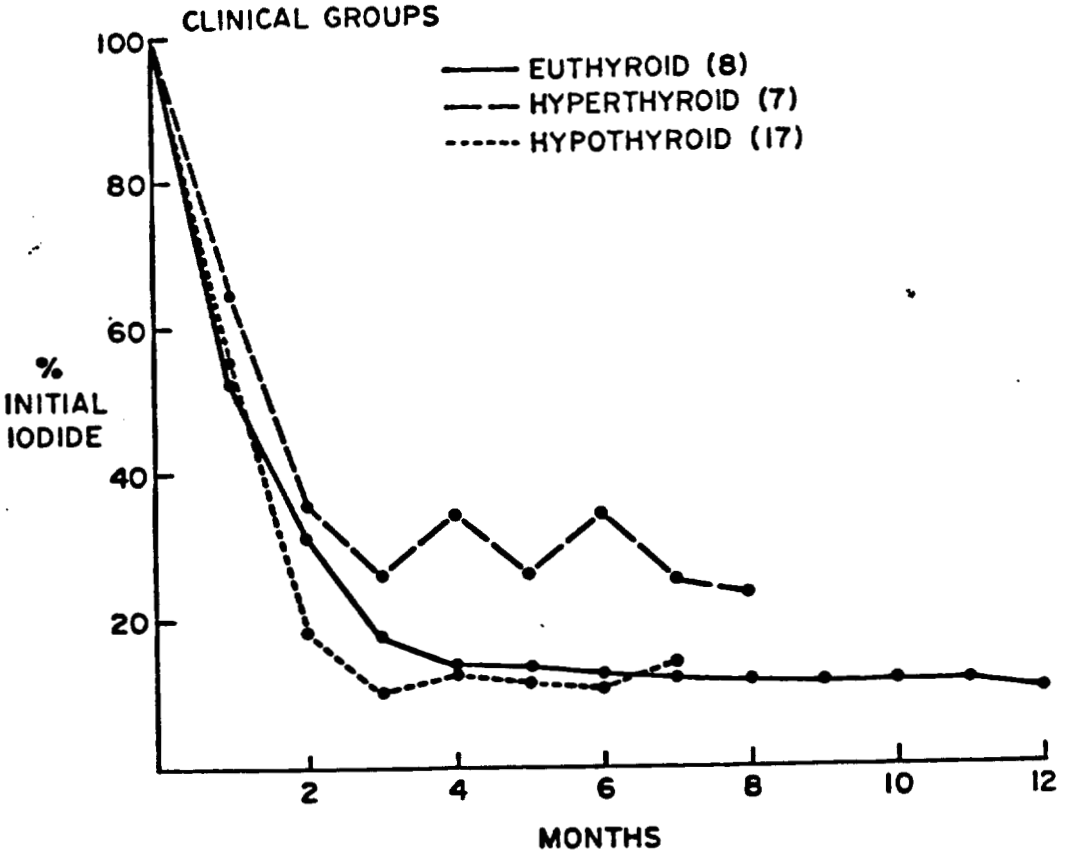
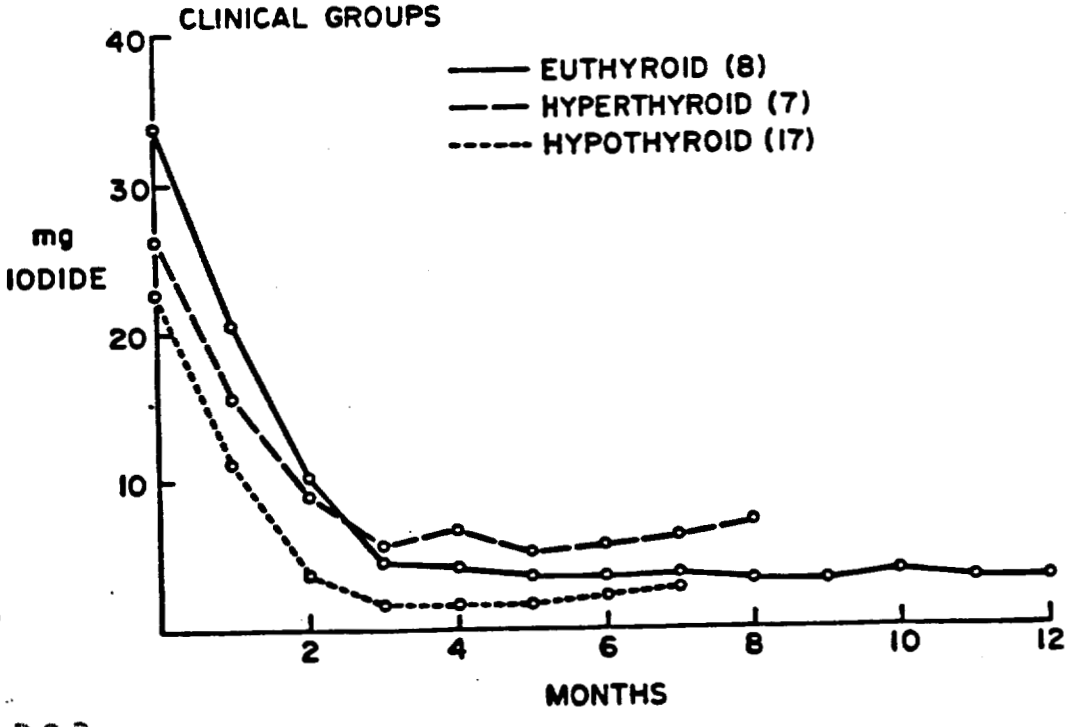


FIGURE 3



1018303

FIGURE 4

TABLE I

RELATIONSHIP OF LOW IODINE CONTENT TO EARLY HYPOTHYROIDISM

Thyroid Iodine at 2-3 Months	Hypothyroid Within 12 Months	Euthyroid at 12 Months or Relapse Within 12 Months	Total
< 2 mg.	14	2	16
≥ 2 mg.	3	13	16
Updated to 16 June 1978:			
< 2 mg.	18	4	22
≥ 2 mg.	3	18	21

Inadequate Followup: 9

1018304

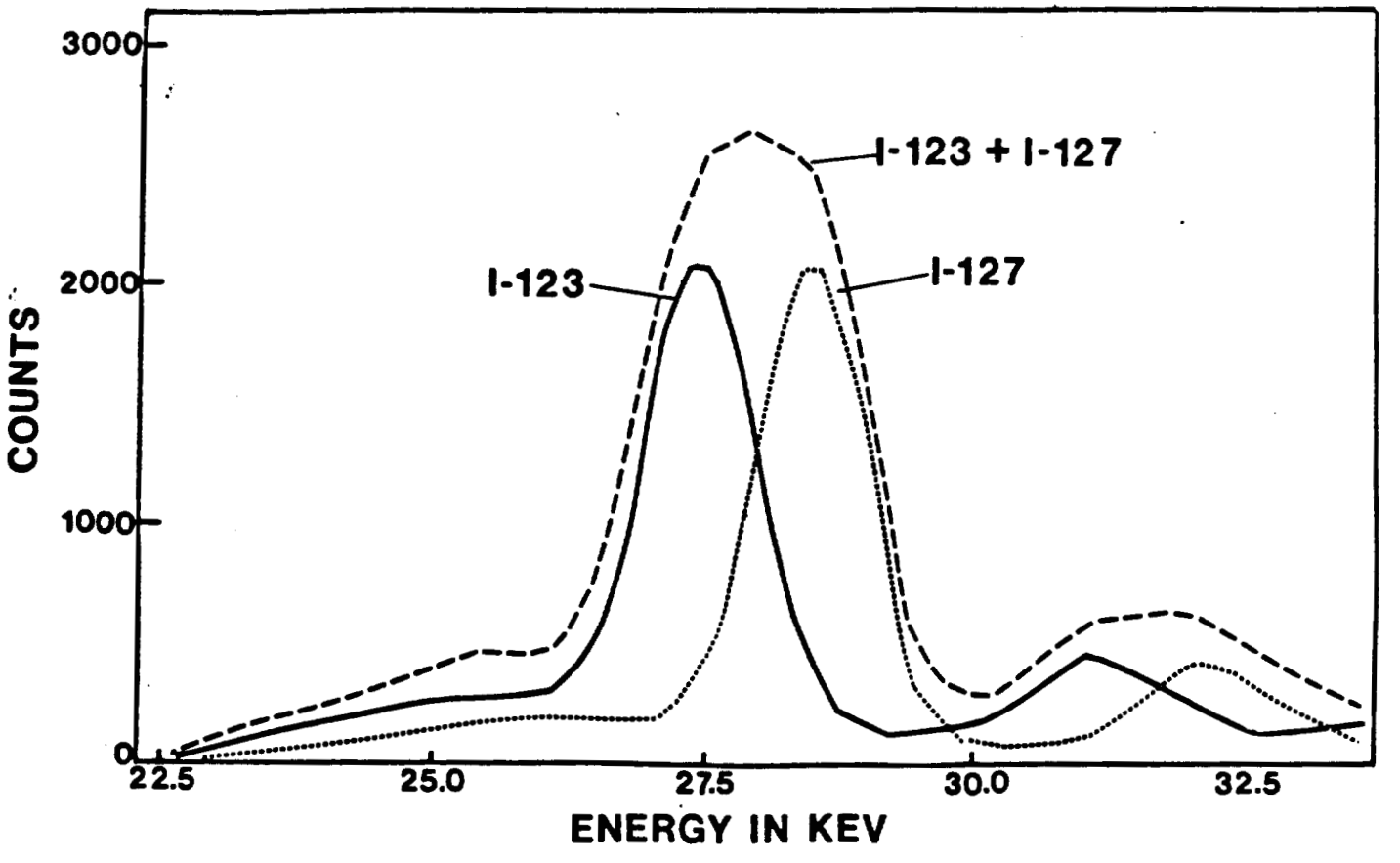


Figure 5 Energy spectrum from an I-123 source and a fluorescent energy spectrum from stable iodine (I-127) and a combined energy spectrum collected with the lithium-drifted silicon detector x-ray fluorescence system currently utilized for iodine content determinations of the thyroid.

1018305



Figure 6 Simultaneous scans of a thyroid phantom containing stable iodine (I-127) and radioactive iodine (I-123) and the distributions separated by computer techniques (Net I-127 and Net I-123).

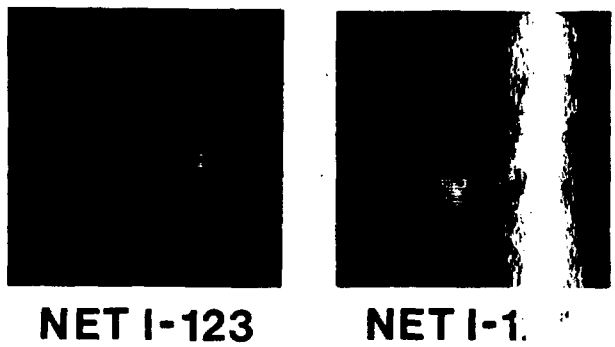


Figure 7 Separated distributions obtained by scanning a thyroid phantom containing 20 mg. of I-127 and 60 micro-Curies of I-123.

1018306

A.6 Evaluation of the Standard Man Model for Dosimetry Calculations--Comparison with Laboratory Measurements

One of our staff, Dr. Jerry Jones, is a member of NCRP Scientific Committee No. 55, charged to report on the accuracy of internal dosimetry calculations and make recommendations for further research. Although no official recommendations have been made as yet, discussion has been given to the following two projects:

1. Distribute replicas of the MR. ADAM phantom to various laboratories for both internal and external measurements.

2. Support the calculation of external photon energy spectra (due to internal sources), which could then be compared to spectral measurements on humans.

Further meetings of the committee will determine the plan of action.

One of the major factors affecting internal dosimetry calculations from external measurements is the effect of attenuation. Means currently exist for measuring attenuation coefficients or something related to them (CT numbers) in patients by using the whole-body x-ray computed tomography system.

In conjunction with the above work, we have developed programs which will allow us to read the magnetic tape of the Searle whole body CT system being used at Vanderbilt. The CT numbers from computed tomography images will be used to investigate the attenuation effects in patients as compared to the standard man model. Assuming a uniform distribution of activity within a body subregion, we can express the effects of self-attenuation in terms of attenuation coefficients and geometry (location and thickness of source as compared to total body thickness). The equations expressing these effects were originally derived to estimate Tc-99m activity in the liver from external scanning measurements. These equations can be used to compare the counts from activity in a patient to those from an equal amount of activity in the standard man model. The advantage of this approach is that one is only simulating the activity in the patient--no injections or emission scans are done. Similarly, there is no need to scan the standard man phantom, because its geometry is defined in MIRD Pamphlet No. 5 and related publications. Thus one is using the human and model geometries to compare their attenuation differences for uniform source distributions.

In our earlier reports we have shown how the use of absorption fraction from the standard man model can lead to erroneous results in patients who differ significantly in size form the standard man. In order to better estimate organ masses we are in the process of developing a system in which sequential transverse section slices through an organ produced by a standard B-mode ultrasound scanner can be used to yield organ volumes. The system utilizes a COLORADO VIDEO CVI-280 video digitizer which has been interfaced to our PDP-11 computer for the purpose of producing digitized ultrasonic images. Once the digitized images have been stored on disk in a Gamma-1 compatable format, the images can then be viewed one at a time and the organ boundaries outlined. The outlined boundary and the plane thickness can then be used to calculate the fractional volume residing in that plane. The total volume is then estimated by adding all of the planes together. This work is still in progress but preliminary studies have demonstrated the utility of the technique.

1018307

B.1.a Quantitative Longitudinal Tomographic System

The accuracy of many of our dose estimates have suffered because of an inability to separate overlying structures which contain activity from the activity within the organs of interest. In addition, frequently, our high sensitivity scanner is unable to spatially resolve closely adjacent organs. Both of these problems have been encountered in our recent work with the new I-131 labelled adrenal scanning agents. The adrenals are frequently obscured by activity in the liver, spleen, intestine, and kidneys. With the aid of a high resolution, high sensitivity, tomographic device, the problem would be simplified considerably.

Through arrangements made with the Searle Corporation, we are obtaining a Pho/Con tomographic scanner on loan. This system was to have been installed during the past year but difficulties were encountered as detailed in the report for contract year 1977-78. These difficulties have been overcome and the system should be arriving in August, 1978. This system consists of two 8 inch diameter by 1" thick sodium iodide crystals with focussed collimators operating as scintillation cameras (i.e. they are position sensitive). These detectors are mounted as if they were regular scintillation probes on a whole body rectilinear scanner. We had originally planned to interface the scanner to our PDP-11 computer using CAMAC and an interface was actually designed. However, Searle has agreed to fabricate the interface for us; therefore, we have designed a special purpose interface for this application (see Appendix 1).

Data from the interface will enter the PDP-11 computer either through a CAMAC input register or a DMA port and will be acquired in list mode with coordinates stored in relation to two coordinate systems as shown in Figure 1. The position of the center of the camera head will be recorded in relation to a camera coordinate system who's origin is at the center of the camera face. Thus an image of a particular plane can be constructed by back-projection techniques by simply translating the coordinates of each recorded scintillation within the camera coordinate system and adding them to the proper locations within the scanner coordinate system. The dimension and direction of the translations are determined by the location of the reconstructed plane in relation to the geometric focal plane as shown diagramatically in Figure 1. Thus it will be possible to reconstruct images of the radioisotope distribution in any plane by this technique. The software has already been developed at Vanderbilt to construct tomographic images from a longitudinal section scanning device similar to the Pho/Con system. This instrument is a 9 crystal intrinsic germanium detector system (ERDA Report No. ORO-2401-94) with multiple focussing collimators and the image reconstruction problem is a degenerate case of the Pho/Con reconstruction problem. A set of planes constructed by this back-projection technique for a dog with an induced myocardial infarction are shown in Figure 2 to demonstrate the image quality obtainable with this method. The Radiopharmaceutical used was Tc-99m pyrophosphate, a bone scanning agent that also accumulates in damaged heart muscle. The distances shown are in inches from the anterior surface of the dog. The knowledge gained in developing this software should greatly simplify the development of image reconstruction software for the new system.

1018308

The problem with this back-projection technique is that it is not quantitative (i.e. every detected event goes into the image of each plane). Our goal is to be able to quantitate the amount of activity in each reconstructed plane in order to improve the accuracy of our dose estimates by more accurately determining activity distributions within organs and background activities. We are therefore exploring new reconstruction techniques based on the techniques of deconvolution analysis. The Pho/Con tomographic scanner (as well as our prototype scanner) produces focal plane tomograms of the activity distribution in the object. Each tomogram reconstructed using the traditional back-projection technique includes not only the image of the true activity distribution in the selected plane but it also contains a superposition of the defocused images of the activity distributions at all other planes. Mathematically it is possible to remove the off-plane smearing thus producing a series of sharply-focused true object activity distributions. We are currently evaluating a pseudo-three-dimensional method proposed by Chang and MacDonald in which the defocused background is eliminated from the sequence of two-dimensional planes through the object using a deconvolution approach.

Using the symbols tj (x,y) to represent the matrix of the back-projected (blurred) tomogram at plane j and $o_i(x',y')$ to represent the "true" object activity distribution at plane i, the back-projection process can be expressed mathematically in the following manner:

$$tj(x,y) = \sum_{i}^{n} \int\int_{x'y'} o_i\,(x',y')\; h_{ij}\;(x - x',\; y - y')\; dx'dy',$$

where $h_{ij}\;(x - x',\; y - y')$ is the system response function and gives the response at point (x,y) in plane j to a point source at the point (x',y') in plane i. In this formulation the object is reconstructed in a sequence of n planes. If one takes the Fourier transform of the above equation it becomes:

$$Tj(f_x f_y) = \sum_{i} O_i\;(fxfy) \cdot H_{ij}(fxfy)$$

where the capital letters denote the transformed quantity and fx and fy denote the component frequency variables. In Fourier space the above equation represents a set of n simultaneous linear equations with n unknown (O_i's) at each frequency. The formal solution being given by:

$$Oi\;(fxfy) = \sum_{j} Tj\;(fxfy) \cdot H_{ij}^{-1}\;(fxfy).$$

We have created the H_{ij} matrix by scanning a point source in each of the planes to be reconstructed and then back-projecting it onto each other plane. The back-projected tomograms are then transformed using a Fast Fourier Transform program and then used to construct H(fxfy). Images of the point source response from each of the 9 planes used in the reconstruction process is shown in Figure 3 . The software system that we have developed to carry out these calculations in Appendix 2. Data for the point source response are shown in Tables I and II.

1018309

In addition to the Fourier techniques we are currently building into the image reconstruction programs the ability to perform uniformity corrections to correct for variations in sensitivity of the detector system and also attenuation corrections to make allowances for source depth. As soon as this software package is completed we plan to perform quantitative evaluations in phantoms before attempting quantitative tomography in patients.

We feel that the Pho/Con system meets our needs for being able to separate overlying and underlying structures which contain activity from the activity within the organs of interest. The Pho/Con will also prove to be an important instrument helping us to obtain quantitative information on organ distribution from the primary diagnostic procedure without requiring additional measurements. This is essential especially for very sick individuals and children.

1018310

TABLE I

POINT SOURCE DATA FOR HIGH PURITY GERMANIUM DETECTOR ARRAY.
NORMALIZED MAXIMUM COUNT VALUES FOR EACH DETECTOR IN EACH PLANE.

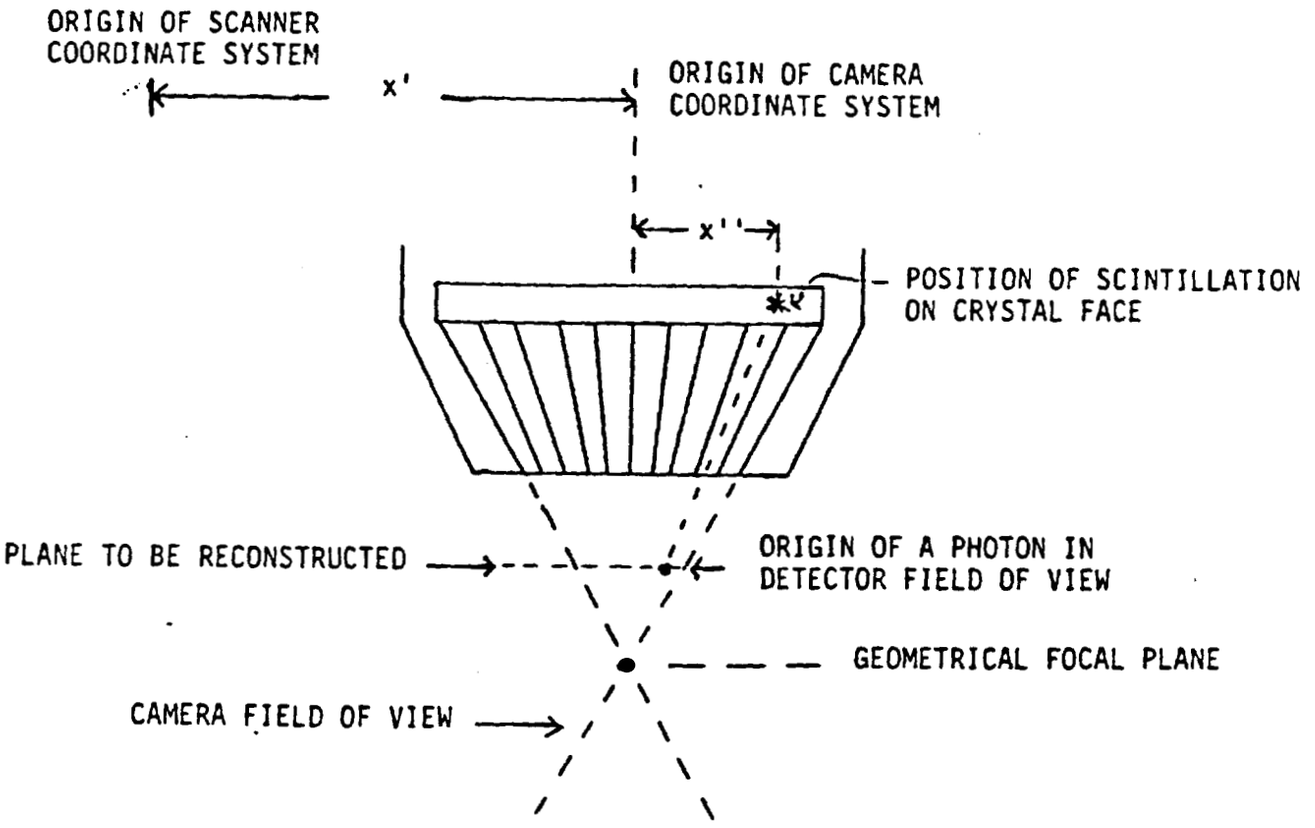
PLANE/DETECTOR	1	2	3	4	5	6	7	8	9
1	0.918	0.968	0.886	0.958	1.436	0.941	0.747	1.255	0.897
2	1.045	1.195	0.731	1.159	1.273	0.736	0.659	1.205	0.998
3	1.178	1.036	0.749	1.227	1.229	0.754	0.732	1.213	0.972
4	0.795	1.293	0.697	1.287	1.230	0.808	0.744	1.329	0.817
5	0.953	0.897	0.857	1.392	1.023	0.862	0.873	1.409	0.735
6	1.064	1.223	0.417	1.389	1.183	0.998	0.459	1.443	0.825
7	0.805	0.897	0.831	0.884	0.893	0.858	0.894	1.875	1.063
8	1.022	1.098	0.971	1.091	1.017	0.975	0.878	1.037	0.910
9	1.014	1.162	0.905	1.167	1.030	0.918	0.747	1.265	0.793

TABLE II

POINT SOURCE DATA FOR HIGH PURITY GERMANIUM DETECTOR ARRAY.
NORMALIZED TOTAL COUNTS FOR EACH DETECTOR IN EACH PLANE.

PLANE/DETECTOR	1	2	3	4	5	6	7	8	9
1	0.990	1.163	0.737	1.278	0.996	0.822	0.735	1.304	0.974
2	1.113	1.175	0.715	1.261	0.974	0.761	0.874	1.183	0.943
3	1.041	1.048	0.786	1.217	1.252	0.697	0.803	1.213	0.944
4	0.908	1.074	0.820	1.404	1.113	0.743	0.785	1.211	0.943
5	1.059	1.079	0.740	1.244	1.191	0.771	0.777	1.265	0.873
6	1.012	1.047	0.727	1.321	1.093	0.714	0.709	1.419	0.959
7	0.959	1.024	0.816	1.142	1.120	0.838	0.951	1.136	1.012
8	1.158	1.080	0.883	1.130	1.203	0.872	0.924	0.946	0.804
9	1.068	1.101	0.820	1.315	1.222	0.812	0.803	1.154	0.705

1018311



$X = x' + kx''$

X = traverse position of recorded event on image of reconstructed plane.

x' = traverse position of center of camera head in relation to scanner coordinate system.

x" = traverse position of scintillation on crystal face in relation to camera coordinate system.

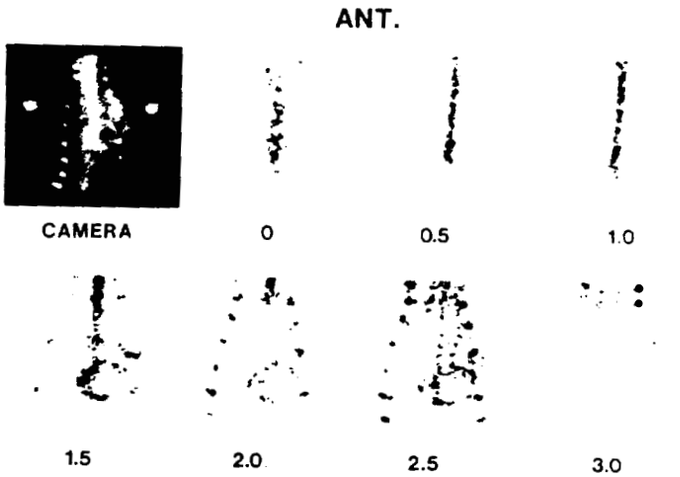
k = constant determined by distance and direction of reconstructed plane from geometrical focal plane.

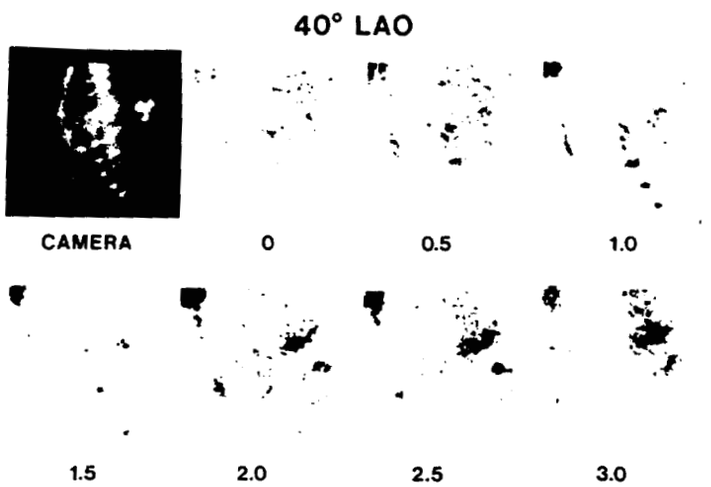
Similarly, the longitudinal position of the recorded event on the image of the reconstructed plane is given by:

$Y = y' + ky''$

FIGURE 1

1018312





Anterior and 40 degree LAO views of a dog with a surgically
infarction imaged with Tc-99m pyrophosphate using the scintillation
ınd the high purity germanium array in the tomographic mode. The
:s are in inches from the anterior surface of the dog. Note the
;eparation of the activity distributions in the tomographic images
: superimposed in the routine frontal plane images from the camera.

1018313

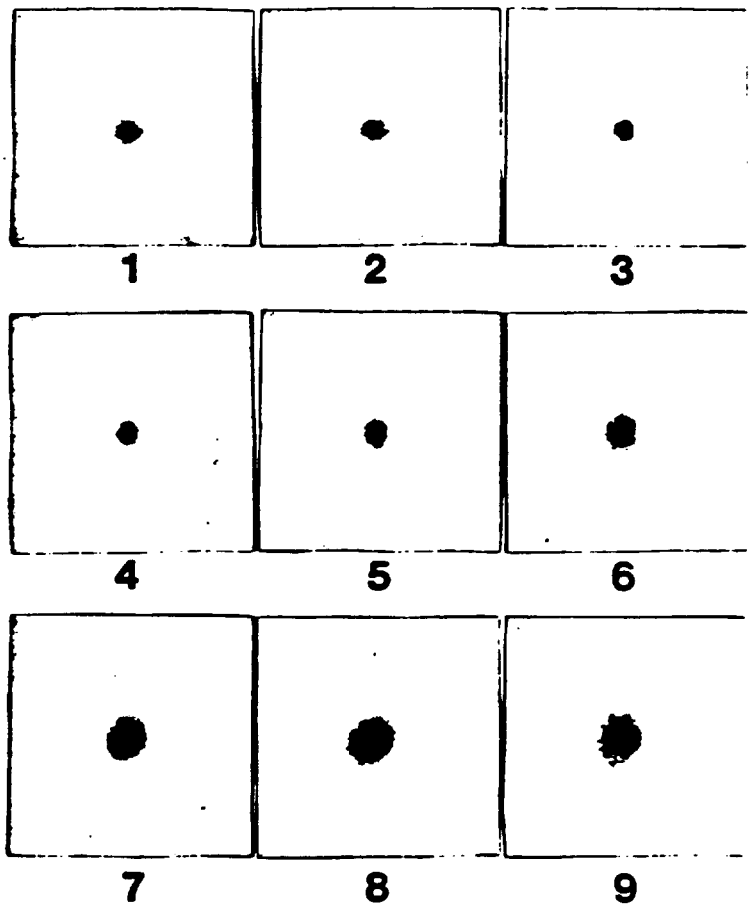


Figure 3 Point source response with Tc-99m (140 keV) for the high purity germanium array at 0.75 inch increments from 1.50 inches above the focal plane to 4.50 inches below the focal plane. Each image is a 64 x 64 array corresponding to a 6 x 6 inch scan field.

10183 14

B.1.b Microprocessor Controlled CAMAC Control of Low Level Counting Facility

During the coming year, we will begin phasing our PDP-9 computer out of its role as the primary data collection and control instrument for the low level counting facility. We intend to implement a data acquisition system using an autonomous CAMAC crate containing an 8080 microprocessor as the controlling device. This microprocessor controlled CAMAC crate which we have used in the past for other unrelated research projects will be configured as shown in Figure 1. The host computer will be used to develop and store the software which will be required for the collection system. A cross computer will be used to generate the operational code which will then be transmitted to the 8080 microprocessor via an RS-232 asynchronous serial data link. During the data collection procedure the CAMAC system will operate as a stand alone system with the collected data being stored in the MM816C memory module. Upon completion of the collection procedure the data will be transmitted to a larger computer system for permanent storage and analysis. This will be done using a high speed serial link at a 9600 Baud rate or higher. This will allow transferral of the entire 8192 word memory in less than 20 seconds. Error detection and correction protocols will be implemented to ensure the data integraty is maintained during the transfer.

Because the data link between the host computer and the satellite data collection is completely standard and non-machine specific any of the laboratories' larger computers can act as the host computer. This will of course require the writing of the appropriate software for handling the data link but it will not be necessary to design and construct specialized interface hardware.

The specific design specifications for the low level counting facility data collection system are based on the proposed utilization as an environmental monitering facility. The basic collection system will be implemented with the capability of controlling the scanner to provide a rectilinear scan while collecting data from at least four nuclear single channel analyzers. Using the memory module indicated in figure 1, we will be able to collect four 4096 byte images simultaneously. Because the system will be by an "intelligent" controller in the form of the 8080 microprocessor, we will be able to modify this storage configuration as required for specific studies or measurements. Based on our past experience in measurement of total body isotope distributions, we feel that the memory size indicated will accomodate 90% of our proposed studies. For the small number of measurements requiring more storage, it will be necessary to transfer data at intervals during collection. It is possible that this could be accomplished as collection is preceeding but because its scanning system is under control of the intelligent CAMAC crate, it is feasible to halt collection during data transfer and then resume it when the transfer is complete.

The implementation of this collection and control system will relieve our dependance on a single and somewhat unreliable computer, i.e. the PDP-9. Its implementation before the complete failure and removal of the present outdated computer, will allow the operation of the low level monitering facility to continue uninterupted.

1018315

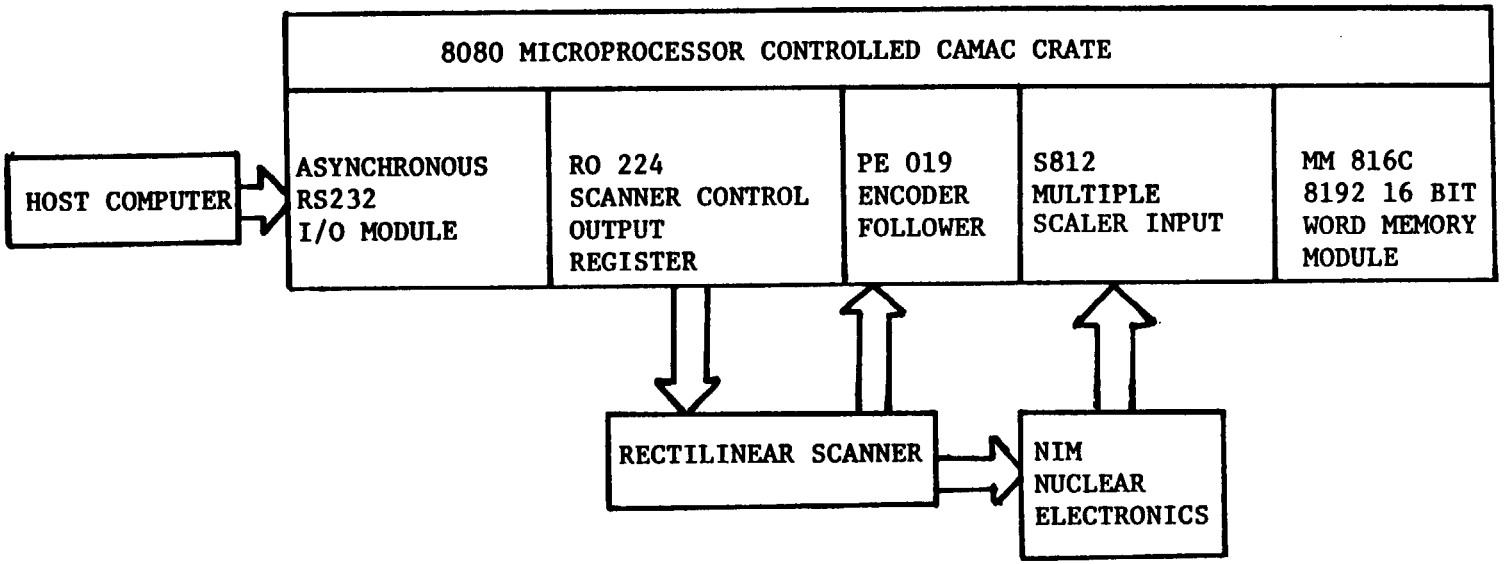


Figure 1: System diagram of microprocessor controlled scanner.

1018316

B.1.c Compton Scattering Imaging System

A new method of chest tomography using a gamma camera and an external gamma ray source has been demonstrated by Pistolesi, et al. (1) to permit the visualization of frontal and sagittal planes of the chest according to their tissue density. This technique involves the use of a line source of Hg-203 (279 KeV) to irradiate the chest from either the back or the side as shown in Figure 1. The detector system consists of a large-field-of-view scintillation camera with a parallel hole collimator positioned at a right angle (90 degrees) from the line of irradiation. The spectrometer of the scintillation camera is set to bracket the 90 degree Compton-scattered photon peak from the patient at 180 KeV. The investigators have shown that high quality chest tomograms can be obtained in 3-5 minutes using a 1 Curie source with relatively small radiation dose to the patient.

We plan to study this technique with the goals of optimizing the irradiation source on the basis of energy, half-life, radiation absorbed dose and cost as well as the design of the source configuration. Some of the sources that have been suggested and that will be explored for this application, in addition to Hg-203, are Tc-99m (140 KeV) and Ir-192 (296-317 KeV complex).

We have already initiated discussions with Neil Case at the Oak Ridge National Laboratory regarding the fabrication of such sources. We will work closely with him in an effort to arrive at the optimum system configuration. Once a practical system design has evolved we will seek permission to have the appropriate source fabricated at ORNL. Using a standard radiographic whole-body phantom, we will then measure the radiation absorbed dose distribution within the phantom for various studies using LiF thermoluminescent dosimeters.

1018317

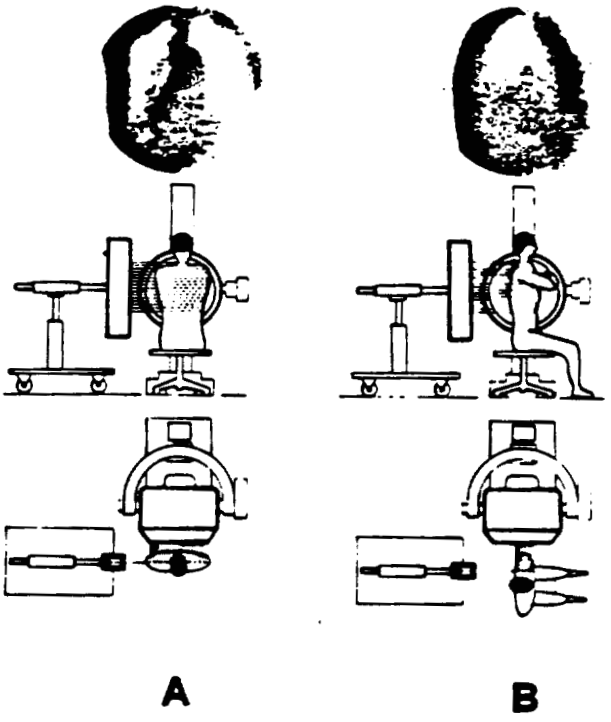


Figure 1 Schematic representation of external gamma source and gamma camera positioned for frontal chest tomogram(A) and sagittal tomogram(B). (From Pistolesi, et.al. Chest Tomography by Gamma Camera and External Gamma Source: Concise Communication, Journal of Nuclear Medicine, 19:94-97,1978.)

1018318

B.1.d High-Speed, High-Resolution Whole Body Imaging System Using One-Dimensional Position Sensitive Proportional Counters (PSPC)

In our whole-body scanner, as is the case for all imaging systems, there must be a trade-off between resolution and sensitivity. Because of our design criterion of rapid whole-body scans at low administered doses our scanner has suffered from relatively poor resolution. In some cases, this has made the differentiation of closely adjacent organs very difficult. To increase the resolution of our current system while maintaining the needed scan speed would be a very expensive undertaking requiring the addition of additional NaI detectors and a modification of the scanner main frame.

Recently we have become aware of the advancements in PSPC design being made at the Oak Ridge National Laboratory by the instrumentation development group of Nowlin, Kopp, Harter, and Borkowski. In collaboration with the ORNL group our clinical colleagues have already initiated an evaluation of a two-dimensional PSPC as a high resolution nuclear medicine imaging system for low-energy nuclides. Similarly, we are proposing to undertake a project to evaluate the idea of using groups of 1-D PSPC's to configure a high-speed high-resolution whole body imaging system. We propose to obtain the PSPC's and associated electronics on loan from ORNL for this evaluation study. The detectors will be mounted on our model 84 Ohio-Nuclear large-bed whole body scanner and the data will be acquired by the CAMAC modules and the mircroprocessor controller described in section B.1.b.

PSPC's have traditionally been confined to the detection of low-energy photons. However, the cylindrical cathode configuration of the 1-D detectors makes it easy to pressurize the gas filled chambers thereby increasing their detection efficiency for the 140KeV photons of Tc-99m to the neighborhood of 90% at pressures of 20-30 atmospheres.

A prototype system utilizing a single PSPC has been described by Borkowski, et al. in the IEEE Transaction of Nuclear Science, Vol. NS-22, No. 2, April 1975 (Figure 1).

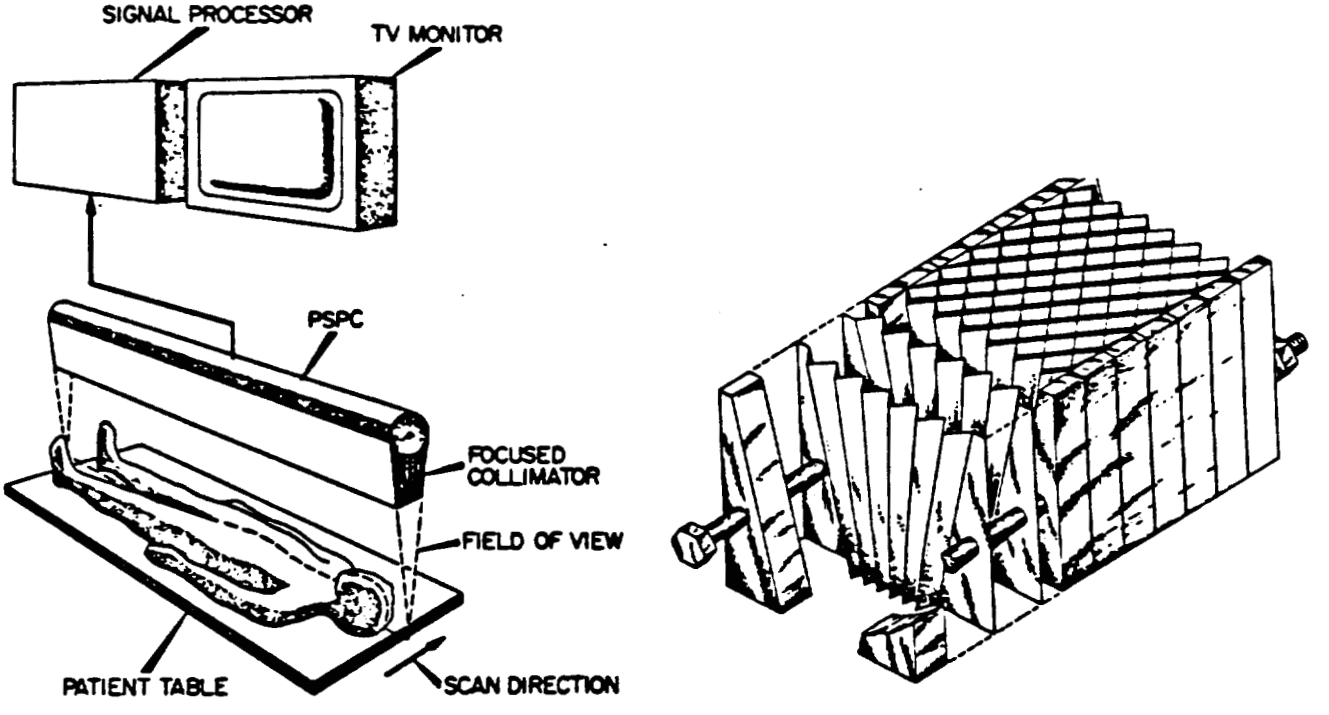
The initial system that we will configure will utilize two 60cm xenon filled PSPC's pressurized to 6 atmospheres and mounted in a dual opposed geometry on the Ohio-Nuclear scanner. The detectors will be mounted at right angles to the long axis fo the body with the mechanical motion of the scanner being only in one direction. The mechanical position of the scanner head will be monitored by shaft encoders (y-coordinate) and the resistance/capacitance (RC) readout from the signal processing electronics will provide the x-coordinate of the detected event. The position of each photon interaction in the PSPC is encoded by the RC-line characteristics of the anode and cathode (see reference above). Two signals are transmitted from the anode (corresponding to readout from each end) for each detected event. The time difference between the two signals is directly proportional to the position of the interaction. With the current detectors >1000 spatial elements can be resolved. With currently available collimators the resolution was measured to be approximately 2mm FWHM for Am-241. This prototype system will be used inititally as part of the Xenon-133 project described in Section A.1. The energy resolution was measured to be 16% for the 60KeV photon of Am-241.

1018319

If the prototype system utilizing the two 60cm long detectors proves to be practical, Dr. Nowlin has agreed to provide us with their large (~ 6 feet long) high pressure (20-30 atmosphers) detector for evaluation. With the increased size of these detectors we feel that it will be possible to develop a system which can carry out extremely rapid (1-2 min) whole-body survey scans while still maintaining good resolution. Ideally these large PSPC detectors would also be mounted in an opposed geometry. But rather than perpendicular, they would be mounted parallel to the long axis of the body and would have mechanical motion only perpendicular to this axis.

The possible benefit of this type of system to this project would be tremendous. It would not only provide us with the capability of obtaining more rapid samples to better define the kinetic data but it would give us better access to patients who could not ordinarily tolerate long studies and this group would include children specifically. Dosimetry and corresponding organ distribution estimates in children have been traditionally arrived at by extrapolating adult data. This instrument will provide us with a tool which will help us collect these types of data.

1018320



A B

Figure 1 A) Prototype system utilizing a single PSPC as described by Borkowski, et. al. IEEE Tran. of Nuc. Sc., Vol. NS-22, No. 2, April, 1975. B)Focused collimator used for radionuclide imaging (same reference).

1018321

2.a Investigation of Real-Time Interpretive Systems for Nuclear Medicine Instrumentation Control

During the next year we plan to install a real time Basic Interpreter on the PDP-11/55 computer system. This interpreter is one especially designed for processor control applications using CAMAC. It was originally designed and implemented at the Hahn-Meitner Institute for Nuclear Research in Berlin and will be provided to us at no charge. This particular interpreter (called Multi-User-Multi-Task-Interpreter or MUMTI) appears to be especially attractive to our laboratory since it allows multiple users to function simultaneously in the RSX 11/M operating system environment without requiring a detailed knowledge of the system as would be required if they were working in the standard task oriented manner. It will allow the development of data collection and control functions through CAMAC without requiring us to develop a complex general purpose CAMAC device driver for RSX-11M.

Once installed in our system, we plan to investigate its utility as a base for routine collection processes. It is unknown at this time exactly how useful it will be in the dual role as a developmental tool and a routine data collection interface.

2.b Specific Dosimetry Projects

We have continued to develop and test new kinetic models in order to gain a better understanding of the organ and tissue retention of medically administered radioactive materials. Solutions to these models have been sought generally through the compartmental modelling techniques of the NIH (Berman) computer program SAAM. In our current work SAAM is being used to analyze Fe-59 citrate, I-131 Iodocholesterol, In-111 citrate and I-131 Hippuran data. The advantage of SAAM over other programs is its ease and its provision to include data from external measurements. The uniqueness of this work is the use of quantitative external measurements to supplement the routine kinetic data from excretion and blood sample data.

2.c SAAM

The SAAM program that we are currently using was converted from the NIH-IBM/360 version to run on our Xerox Sigma 7 computer. The NIH has now developed an interactive version of SAAM which runs on the PDP-10 computer. During the coming year we will attempt to acquire this version and implement it on Vanderbilt PDP-10 system. The ability to interact with the program makes it possible to reduce the solution time considerably and also provides a teaching aid for understanding the behavior of the model.

On April 28-31, 1977 we organized and co-sponsored a seminar-workshop for SAAM users. The meeting was attended by approximately 40 people from throughout the country. Dr. Price was elected as the coordinator of the group. During the coming year we propose to investigate whether or not a second SAAM workshop should be organized. These workshops will serve as a mechanism for people who are working in the area of kinetic modelling to gather and discuss current topics and share ideas.

1018322

2.d Sharing of Computer Programs in Nuclear Medicine

We continue to work closely with the personnel of the Biomedical Computing Technology Information Center (BCTIC) at Oak Ridge. Dr. Brill is a member of the Advisory Committee and Dr. Erickson co-directed the production of a Nuclear Medicine Computing Directory. The first directory contained documentation on over 80 U.S. and 20 foreign nuclear medicine computer installations. The second edition of the directory is currently in production. This document greatly facilitates the interchange of software and provides software, hardware and clinical contacts at the various institutions.

The SAAM program (IBM-360 version) has now been added to the BCTIC library and is now being distributed. The Sigma-7 version of SAAM has been sent to St. Jude's Childrens Hospital in Memphis, Tennessee and we are currently working with them to help implement it on their system.

2.e ORIS-11 Evaluation

The Oak Ridge Imaging System (ORIS) has been successfully translated from the original PDP-8 language to the PDP-11 language by Drs. Bell and Dougherty of ORNL. The resulting ORIS-11 version 01 system was designed to operate on a clinical DEC GAMMA-11 nuclear medicine imaging system. ORIS-11 is not a stand alone system but is used to process raw-data images which have been acquired and stored on disk by the GAMMA-11 system. ORIS-11 version 01 has been implemented on the Vanderbilt clinical GAMMA-11 system and will be evaluated and tested during the coming year. Of particular interest to us are the two-dimensional Fast-Fourier transform (FFT) programs which are available in ORIS. These programs will be used to replace similar FFT programs which are now being used as part of the quantitative tomographic reconstruction programs.

ORIS-11 V01 runs as a separate task under the RT-11 monitor. It enhances the limited data processing capabilities of the GAMMA-11 system by providing the following image processing procedures:

1. Nonlinear least-squares polynomial smoothing and bounding.

2. Quickbound, a procedure to remove grossly aberrant data points.

3. Antiscatter and antipenetration correction to remove the effects of gamma ray scattering in the patient and gamma ray penetration of the walls of the camera collimator.

4. Two-dimensional Fast Fourier transform processing for image filtering and also for detection of imaging system defects which otherwise may grow unnoticed for a long time.

5. An adaptive filter disk. A nonlinear smoothing applied in the spatial frequency domain of the Fourier transform.

6. Time smoothing for dynamic study sequences. Essentially a Hanning filter applied in the time domain to the sequence to improve the statistical strength of the sequence without affecting its spatial resolution. As dynamic studies are of low counts per picture element, this is often quite helpful.

1018323

7. The NTMAX functional images for brain perfusion studies. Time relationship and maximum perfusion images are summarized from the whole study.

8. Symmetry images produced from static images or from sums of frames from dynamic studies. These enhance any cotralateral dissymmetry.

1018324

Appendix 1

Pho/Con--Computer Interface

The computer interface to be constructed is shown in Figure 1. This proposed system will handle the Pho/Con digital output which provides probe position informaton as well as the analog signals from the nuclear detectors. The data to be collected from the scanning mechanism are the following:

1. X & Y positon of the scanner
2. X & Y position of interaction in detector
3. Top or bottom detector
4. Isotope 1 or 2

These data will be collected in the following format in list mode for post-collection reconstruction. The position of the interaction in the detector will be digitized by a Dual ADC as with any scintillation camera and the X and Y coordinates combined into a single word of the format shown below.

Bit # =	0	1	2 - 8	9 - 15
	X	X	7 bits Y	7 bits X

Bit 0 = Detector Flag: 0 = Top, 1 = Bottom
Bit 1 = Isotope Flag: 0 = ISOTOPE 1, 1 = ISOTOPE 2

The position of the scanner mechanism will be obtained from encoders mounted on the X and Y axis of the instrument. These will be calibrated to provide a digital resolution equal to the detector digital resolution, i.e. 1.58mm/pt for 8" detector or 2.18mm/pt for 11 inch detector. As the scanner passes from one data cell to the next the bed coordinates will be inserted in the data list as a 3 word element in the following format:

Word 1 = FLAG WORD = ZERO

Word 2 = OSCILLATOR & X COORDINATES

Word 3 = Y COORDINATES

In the word containing the X coordinate of the scanner we will place a 7 bit value representing the output of a precision oscillator. If the scanner speed is stable the detector will remain in each data cell for a constant time period. If it is not stable the time spent in each data cell and therefore the sensitivity will vayy from cell to cell. By storing the oscillator counts, we can obtain an accurate monitor of scan speed stability for quantitative scanning studies.

The different data sets will be handled by a 4 to 1 multiplexor. When operating and not transmitting scanner position information, the 4 to 1 multiplexor will be controlled so as to select the output of the buffer registers on the dual ADC's which digitize scintillation data.

If either the X or Y scanner position changes (as indicated by a pulse called DELSCN), the following sequence takes place. The X and Y registers are latched. The two bit counter is cleared to cause the multiplexer to select a zero data word. When the DATA TAKEN pulse is returned, it increments

10183 25

the counter to select the scanner X position and transmits a second DATA RDY pulse. Upon acceptance of this data, the Scanner Y position is transmitted. After this data is accepted, the counter again selects the normal camera input but does not transmit the DATA RDY pulse. Thus the single flag word of all zeros and the 2 scanner position words are transmitted in sequence whenever either axis of the scanner changes. At all other times the single camera data word is transmitted.

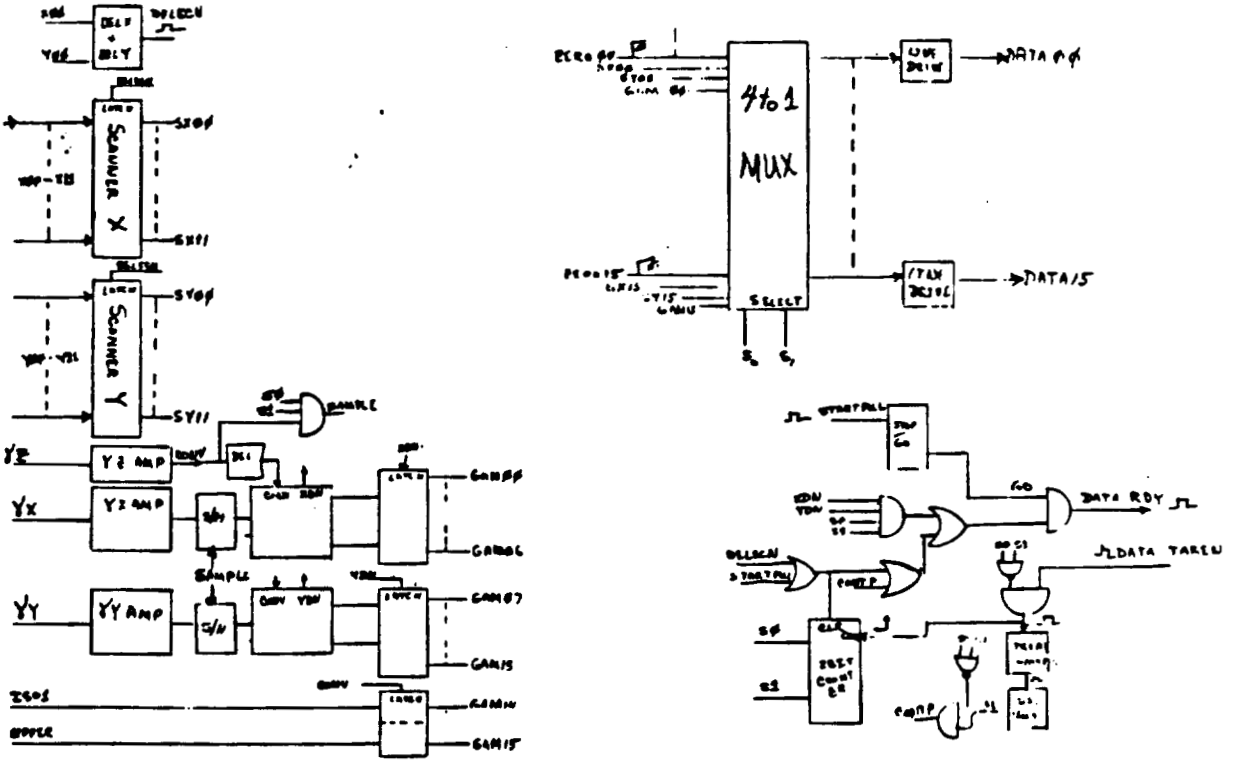
This method of data storage will result in a list of data which will be very amenable to reconstruction of tomographic images. The 3 word block with the leading flag word can be used for other information such as elapsed time for decay correction by use of a different flag word. This is possible since there are a large number of coordinates in 128 X 128 square array into which the circular detector image is digitized that are not used for image data. Any of these coordinates can be used for a flag word.

The data from the interface will enter the PDP-11 computer either through a CAMAC register or a DMA port and will be stored in list mode on disk. Image construction will then be performed after completion of the scan (See section B.2.a).

1018326

Figure 1

Computer Interface for Searle Pho/Con Scanner



1018327

Appendix 2

DECONVOLUTION INFORMATION FLOW

SOFTWARE DESCRIPTION

1. Point source data are obtained for a source at each of nine levels.

2. Tomographic blurred data are obtained for an object in a plane.

3. TRFRM2 converts each image plane and point source plane into its two dimensional Fourier domain representation.

4. Point source information is rearranged by SETUP for processing by HUGE.

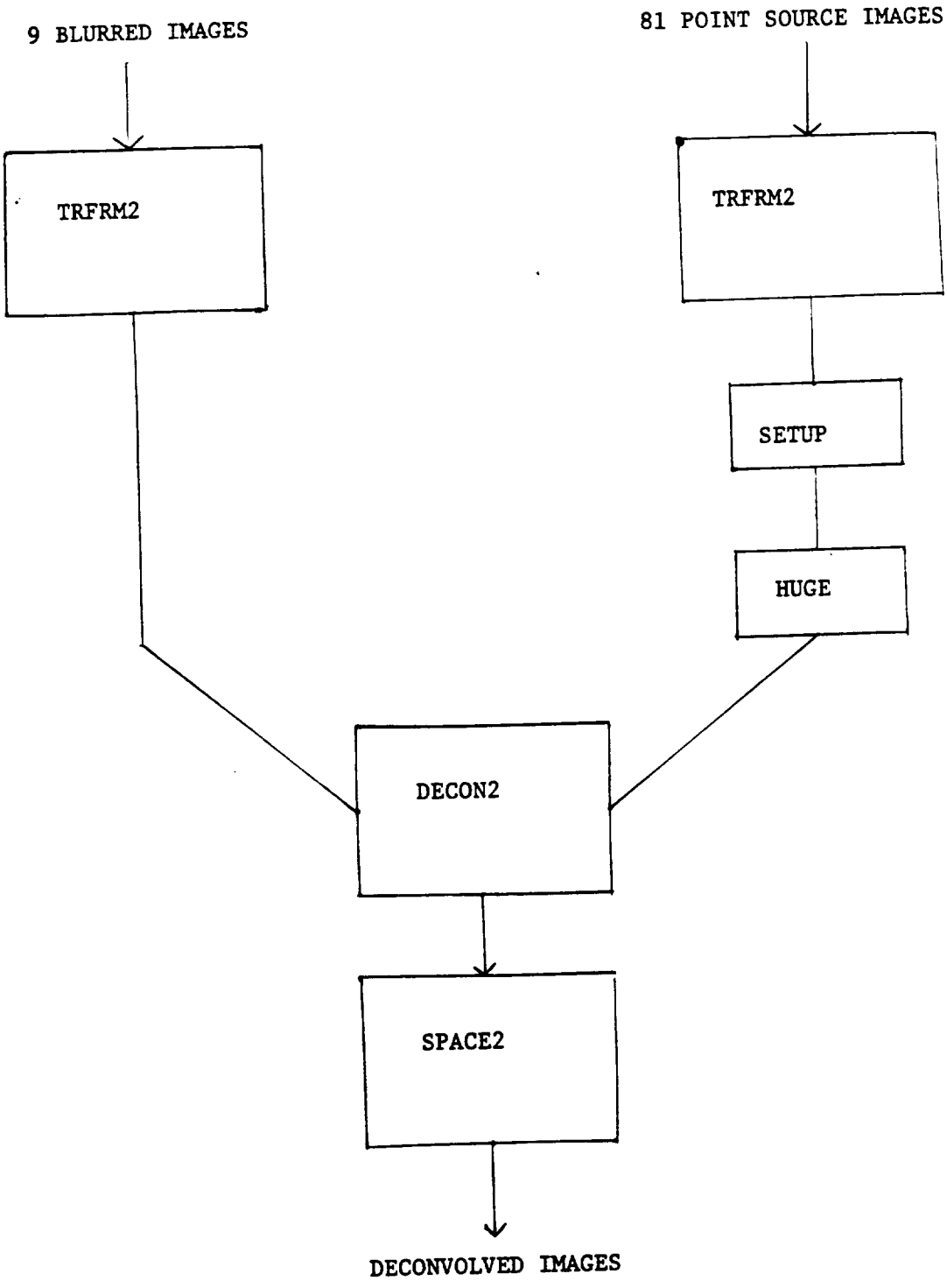
5. HUGE forms a single file containing all point source information which represents the system response and is used for each deconvolution.

6. In DECON2 the Fourier domain image response and the Fourier domain point source responses are used in the solution of the matrix equation AX = B, where A is a square matrix representing the point source response at a single spatial frequency, and B is a vector representing the tomographic image response at a single spatial frequency. X is a vector representing the desired deblurred object response at a particular spatial frequency.

7. The solution vectors produced by DECON2 are processed by SPACE2 which performs an inverse Fourier transformation. Nine images are returned representing each deblurred tomographic image.

1018328

DECONVOLUTION INFORMATION FLOW



1018329

TT:=DECON2.FOR

```
C       DECON2
C       DECONVOLUTION IN FREQ DOMAIN
C
        DIMENSION RI(9),AI(9),H(18,9)
        DIMENSION D(9,66,4)
        DIMENSION E(9,66)
        DOUBLE PRECISION HSQR(18,18),B(18)
        WRITE(7,20)
20      FORMAT(1X'INPUT FILE, PT. SRC RESP',$)
        CALL ASSIGN(1,'DK1:',-1,'RDO')
        DEFINE FILE 1(2112,324,U,KR)
        WRITE(7,30)
30      FORMAT(1X'INPUT FILE,IMAGE RESP ',$)
        CALL ASSIGN(3,'DK1:',-1,'RDO')
        WRITE(7,40)
40      FORMAT(1X'OUTPUT FILE ',$)
        CALL ASSIGN(2,'DK1:',-1)
        N=18
        KB=0
        DO 1000 JX=1,66,4
        READ(3)D
        DO 2 KNUM=1,4
        NNUM=0
        NUM=0
        DO 1 IX=1,33
        NNUM=NNUM+1
        DO 120 I=1,9
120     RI(I)=D(I,NNUM,KNUM)
        NNUM=NNUM+1
        DO 130 I=1,9
130     AI(I)=D(I,NNUM,KNUM)
C
C       REAL AND IMAGINARY PARTS OF B
C
        K1=9
        DO 3 K=1,9
        K1=K1+1
        B(K)=DBLE(RI(K))
3       B(K1)=DBLE(AI(K))
C
C       FORM REST OF COEF MATRIX H, 18X18
C
        KB=KB+1
        READ(1'KB)H
        J1=9
        DO 60 J=1,9
        J1=J1+1
        K1=9
        DO 60 I=1,9
        K1=K1+1
        HSQR(J,I)=DBLE(H(I,J))
        HSQR(J1,K1)=DBLE(H(I,J))
        HSQR(J,K1)=DBLE(-H(K1,J))
60      HSQR(J1,I)=DBLE(H(K1,J))
C
C       SOLVE LINEAR EQN AX=B BY GAUSSIAN ELIMINATION
C       SOLUTION RETURNED IN B
C
        CALL GAUSS(HSQR,B,N)
C
C       WRITE SOLUTION VECTOR
C
        K1=9
        DO 15 J4=1,9
        K1=K1+1
        RI(J4)=SNGL(B(J4))
        AI(J4)=SNGL(B(K1))
15      CONTINUE
        NUM=NUM+1
        DO 36 I=1,9
36      E(I,NUM)=RI(I)
        NUM=NUM+1
        DO 37 I=1,9
37      E(I,NUM)=AI(I)
1       CONTINUE
        WRITE(2)E
2       CONTINUE
        WRITE(7,202) JX
202     FORMAT(I5)
1000    CONTINUE
        CALL CLOSE(1)
        CALL CLOSE(2)
        CALL CLOSE(3)
        STOP
        END
C
C       SUBROUTINE SOLVES LINEAR EQN USING GAUSSIAN ELIMINATION
C       WITH PARTIAL PIVOTING
C
        SUBROUTINE GAUSS(H1,B,N)
        DOUBLE PRECISION H1(N,N),B(N),X(18)
        DOUBLE PRECISION D(18)
        DIMENSION IPIVOT(18)
        CALL FACTOR(H1,IPIVOT,D,N,IFLAG)
C
C       CHECK FOR SINGULAR MATRIX AT GIVEN FREQ
C       SET ALL X TO CONSTANT
        IF(IFLAG.EQ.2) GO TO 75
        CALL SUBST(H1,B,X,IPIVOT,N)
        DO 30 I=1,N
30      B(I)=X(I)
        GO TO 80
75      CONTINUE
        DO 80 IS=1,N
        B(IS)=1.0
80      CONTINUE
        RETURN
        END
$
```

TT:=SUBST.FOR

```
C       SUBST
C       SUBROUTINE TO PERFORM FORWARD-BACKWARD SUBSTITUTION
C
        SUBROUTINE SUBST(W,B,X,IPIVOT,N)
        DOUBLE PRECISION W(N,N),B(N),X(N),SUM
        DIMENSION IPIVOT(N)
        CALL SETERR (10,255)
        IF(N.GT.1) GO TO 10
        X(1)=B(1)/W(1,1)
        RETURN
10      IP=IPIVOT(1)
        X(1)=B(IP)
        DO 15 K=2,N
        IP=IPIVOT(K)
        KM1=K-1
        SUM=0.D00
        DO 14 J=1,KM1
14      SUM=W(IP,J)*X(J)+SUM
15      X(K)=B(IP)-SUM
21      X(N)=X(N)/W(IP,N)
22      K=N
        DO 20 NP1MK=2,N
        KP1=K
        K=K-1
        IP=IPIVOT(K)
        SUM=0.D00
        DO 19 J=KP1,N
19      SUM=W(IP,J)*X(J)+SUM
20      X(K)=(X(K)-SUM)/W(IP,K)
24      RETURN
        END
C       FACTOR
C       SUBROUTINE FORMS UPPER TRIANGULAR MATRIX
C
        SUBROUTINE FACTOR(W,IPIVOT,D,N,IFLAG)
        DOUBLE PRECISION W(N,N),D(N),ROWMAX,AW,COLMAX,AWIKOV,RATI
        DIMENSION IPIVOT(N)
8       DO 1200 I=1,N
8       WRITE(7,1000) I,(W(I,J),J=1,N)
1000    FORMAT(I3/6G13.6/6G13.6/6G13.6)
1200    CONTINUE
        IFLAG=1
C
C       INITIALIZE W,IPIVOT,B
C
        DO 10 I=1,N
        IPIVOT(I)=I
        ROWMAX=0.D00

        DO 9 J=1,N
        AW=DABS(W(I,J))
9       ROWMAX=DMAX1(ROWMAX,AW)
        IF(ROWMAX.EQ.0.)GO TO 999
        D(I)=ROWMAX
10      CONTINUE
C250    WRITE(7,1100) (D(I),I=1,18)
1100    FORMAT(1X,3(6G13.6/))
C       DO 1300 I=1,N
C       WRITE(7,1000) I,(W(I,J),J=1,N)
1300    CONTINUE
C
C       GAUSS ELIM W/ SCALED PARTIAL PIVOTING
C
        NM1=N-1
        IF(NM1.EQ.0.) RETURN
        DO 20 K=1,NM1
        J=K
        KP1=K+1
        IP=IPIVOT(K)
        COLMAX=DABS(W(IP,K))/D(IP)
        DO 11 I=KP1,N
        IP=IPIVOT(I)
        AWIKOV=DABS(W(IP,K))/D(IP)
        IF(AWIKOV.LE.COLMAX) GO TO 11
        COLMAX=AWIKOV
        J=I
11      CONTINUE
        IF(COLMAX.EQ.0.D00) GO TO 999
C
        IPK=IPIVOT(J)
        IPIVOT(J)=IPIVOT(K)
        IPIVOT(K)=IPK
        DO 20 I=KP1,N
        IP=IPIVOT(I)
        W(IP,K)=W(IP,K)/W(IPK,K)
        RATIO=-W(IP,K)
        DO 20 J=KP1,N
20      W(IP,J)=RATIO*W(IPK,J)+W(IP,J)
        IF(W(IP,N).EQ.0.D00) GO TO 999
        RETURN
999     IFLAG=2
C       WRITE(7,560)
550     FORMAT(' END FACTOR')
560     FORMAT(' END FACTOR, SMALL NO.')
        RETURN
        END
$
```

1018330

```
C
C       TRFRM2 TRANSFORMS 64X64 IMAGE FROM SPACE DOMAIN
C       TO FREQUENCY DOMAIN AND STORES ON DISK.
C       THIS PROGRAM MUST BE USED WITH DECON2
C       DAVE PEARSE  22-JUNE-78.
C
        COMMON DATA(4224),IC(64),DC(64)
        DIMENSION N(2), DI(9,64,4)
        DATA N(1),N(2)/64,64/
2       NDIM=2
        WRITE(7,5)
5       FORMAT(1X 'WRITE FILE! ',$)
        CALL ASSIGN(2,'DK1!',-1)
        CALL ASSIGN (3,'DK1!XYZ.DAT',0,'SCR')
        DO 100 IARY=1,9
        WRITE(7,7)IARY
7       FORMAT(1X 'READ FILE 0',I1,'  ',$)
        CALL ASSIGN(1,'DK1!',-1,'RDO')
        DO 10 I=4097,4224
10      DATA(I)=0.0
        K=1
        DO 20 J=1,64
        READ(1)IC
        DO 15 I=1,64
        DATA(K)=IC(I)
15      K=K+1
20      CONTINUE
        CALL FOUR2(N,NDIM,-1.0)
        CALL CLOSE(1)
        WRITE(3)DATA
        WRITE(7,70)IARY
70      FORMAT(1X ' ARRAY 0',I1,' FINISHED.')
100     CONTINUE
        ENDFILE 3
        DO 120 J=1,64,4
        REWIND 3
        NUM=(J-1)*64
        DO 110 I=1,9
        NM=NUM
        READ(3)DATA
        DO 110 M=1,4
        DO 110 K=1,64
        NM=NM+1
110     DI(I,K,M)=DATA(NM)
120     WRITE(2)DI
        CALL CLOSE(2)
        CALL CLOSE (3)
        STOP
        END
```

```
TTZ\Z\!=SETUP.FOR
C       SETUP
C       FROM REFORMATS H DATA FROM TRFRM2
C
        DIMENSION C(9,64,4),H(18)
1       WRITE(7,20)
20      FORMAT(' WRITE FILE',$)
        CALL ASSIGN(1,'DK1!',-1)
        WRITE(7,30)
30      FORMAT(' READ FILE',$)
        CALL ASSIGN(2,'DK1!',-1,'RDO')
        DO 120 I=1,16
        READ(2)C
        DO 120 IMAX=1,4
        K1=0
        DO 120 J1=1,33
        K=0
        DO 100 J3=1,2
        K1=K1+1
        DO 100 J2=1,9
        K=K+1
100     H(K)=C(J2,K1,IMAX)
        WRITE(1)H
120     CONTINUE
        CALL CLOSE(1)
        CALL CLOSE(2)
        GO TO 1
        STOP
        END
$
```

```
TT!=SPACE2.FOR
C       SPACE2
C       CONVERTS FROM FREQ. TO SPACE
C       THIS PROGRAM CAN ONLY BE USED
C       WITH DECON2
        DIMENSION NX(2),E(9,64)
        COMMON DATA(4224),IC(64),DC(64),HH(4096)
        DATA NX(1),NX(2)/64,64/
        WRITE(7,2)
2       FORMAT(1X' ENTER INPUT FILE ',$)
        CALL ASSIGN(1,'DK1!',-1,'RDO')
C       DO LOOP OVER 9 IMAGES
100     DO 1 M=1,9
        WRITE(7,5)M
5       FORMAT(1X,'WRITE FILE 0',I1,' ?',$)
        CALL ASSIGN (2,'DK1!',-1)
        NC=0
        DO 3 L=1,64
        READ(1)E
        DO 3 M=1,64
        NC=NC+1
        DATA(NC)=E(M,M)
3       CONTINUE
        NDIM=2
        CALL FOUR2(NX,NDIM,+1,-1)
D       AM=-1.
D       AMN=1.
D       DATA(1)=DATA(2)
D       DO 10 J=1,4096
D       AM=AMAX1(AM,DATA(J))
D       AMN=AMIN1(AMN,DATA(J))
D10     CONTINUE
D       R=AM-AMN
D       IF(R.NE.0.0) GO TO 30
D       DO 20 I=1,64
D       DO 15 J=1,64
D15     IC(J)=0
D20     WRITE(2)IC
D       GO TO 50
D30     CONTINUE
        NM=0
        DO 40 J=1,4096
        NM=NM+1
C       IC(NM)=(DATA(J)/100.)
D       IC(NM)=((DATA(J)-AMN)/R)*100
        IF(NM.NE.64) GO TO 40
        NM=0
        WRITE(2)IC
40      CONTINUE
50      CONTINUE
        CALL CLOSE(2)
        REWIND 1
1       CONTINUE
        STOP
        END
$
```

```
TT!=HUGE.FOR
C       HUGE
C       FROM TO REARRANGE 9 FILES FROM SETUP INTO A SERIES
C       OF FILES ORGANIZED 18X9X2112 READY FOR DECON2
C
        DIMENSION H(18),HPULSE(18,9)
        WRITE(7,10)
10      FORMAT(' ENTER OUTPUT FILENAME ',$)
        CALL ASSIGN(1,'DK1!',-1)
        DEFINE FILE 1(2112,324,U,KR)
        I1=0
        DO 30 I=11,19
        I1=I1+1
        WRITE(7,20)I1
20      FORMAT(' ENTER READ FILE FOR LEVEL',I2,1X,$)
        CALL ASSIGN(I,'DK1!',-1,'RDO')
30      CONTINUE
C
C       10 FILES OPEN! 9 READ, 1 WRITE
C       BEGIN READ/ REARRANGE/ WRITE! FILES BY FREQ 18X9X2112
C
        MM=0
        DO 150 KB=1,2112
        K=0
        DO 140 I=11,19
        K=K+1
        READ(I) H
        DO 120 J1=1,18
120     HPULSE(J1,K)=H(J1)
140     CONTINUE
        WRITE(1'KB)HPULSE
B       WRITE(6,141)HPULSE
D141    FORMAT(1X,9E12.5)
        MM=MM+1
        IF(MM.NE.20) GO TO 150
        NUM=KB/10
        WRITE(7,145)NUM
145     FORMAT(1X,I5)
        MM=0
150     CONTINUE
        DO 200 I=11,19
        CALL CLOSE(I)
200     CONTINUE
        CALL CLOSE(1)
        STOP
        END
$
```

1018331

```
      SUBROUTINE FOUR2(N,NDIM,ISIGN,IFORM)
        DIMENSION N(2)
        COMMON DATA(4224),IC(64),DC(66)
      NTOT=1
      DO 10 IDIM=1,NDIM
   10 NTOT=NTOT*N(IDIM)
      IF(IFORM)70,20,20
   20 NREM=NTOT
      DO 60 IDIM=1,NDIM
      NREM=NREM/N(IDIM)
      NPREV=NTOT/(N(IDIM)*NREM)
      NCURR=N(IDIM)
      IF(IDIM-1+IFORM)30,30,40
   30 NCURR=NCURR/2
   40 CALL BITRV(NPREV,NCURR,NREM)
D       WRITE(7,345)
345     FORMAT( ' AFTER BITRV ' )
      CALL COOL2(NPREV,NCURR,NREM,ISIGN)
D       WRITE(7,346)
346     FORMAT( ' AFTER COOL2 ' )
      IF(IDIM-1+IFORM)50,50,60
   50 CALL FIXRL(N(1),NREM,ISIGN,IFORM)
D       WRITE(7,347)
347     FORMAT( ' AFTER FIXRL ' )
      NTOT=(NTOT/N(1))*(N(1)/2+1)
   60 CONTINUE
D       WRITE(7,200) N(1),N(2),ISIGN,IFORM
      RETURN
   70 NTOT=(NTOT/N(1))*(N(1)/2+1)
      NREM=1
      DO 100 JDIM=1,NDIM
      IDIM=NDIM+1-JDIM
      NCURR=N(IDIM)
      IF(IDIM-1)80,80,90
   80 NCURR=NCURR/2
      CALL FIXRL(N(1),NREM,ISIGN,IFORM)
      NTOT=NTOT/(N(1)/2+1)*N(1)
   90 NPREV=NTOT/(N(IDIM)*NREM)
      CALL BITRV(NPREV,NCURR,NREM)
      CALL COOL2(NPREV,NCURR,NREM,ISIGN)
  100 NREM=NREM*N(IDIM)
D       WRITE(7,200) N(1),N(2),ISIGN,IFORM
200     FORMAT(1X,4I6)
      RETURN
      END
      SUBROUTINE COOL2(NPREV,N,NREM,ISIGN)
        COMMON DATA(4224),IC(64),DC(66)
D       WRITE(7,200)NPREV,N,NREM,ISIGN
200     FORMAT(1X,'COOL2 ',4I6)
        IF(N-2)
          TWOPI=6.283185*FLOAT(ISIGN)
        IP1=IPO*NPREV
        IP4=IP1*N
        IP5=IP4*NREM
        IP2=IP1
        NPART=N
   10   IF(NPART-2)50,30,20
   20   NPART=NPART/4
        GO TO 10
   30   IP3=IP2*2
        DO 40 I1=1,IP1,IPO
        DO 40 I5=I1,IP5,IP3
        JO=I5
        J1=JO+IP2
        TEMPR=DATA(J1)
        TEMPI=DATA(J1+1)
        DATA(J1)=DATA(JO)-TEMPR
        DATA(J1+1)=DATA(JO+1)-TEMPI
        DATA(JO)=DATA(JO)+TEMPR
   40   DATA(JO+1)=DATA(JO+1)+TEMPI
        GO TO 140
   50   IP3=IP2*4
        THETA=TWOPI/FLOAT(IP3/IP1)
        SINTH=SIN(THETA/2.)
        WSTPR=-2.*SINTH*SINTH
        WSTPI=SIN(THETA)
        WR=1.
        WI=0.
        DO 130 I2=1,IP2,IP1
        IF(I2-1)70,70,60
   60   W2R=WR*WR-WI*WI
        W2I=2.*WR*WI
        W3R=W2R*WR-W2I*WI
        W3I=W2R*WI+W2I*WR
   70   I1MAX=I2+IP1-IPO
        DO 120 I1=I2,I1MAX,IPO
        DO 120 I5=I1,IP5,IP3
        JO=I5
        J1=JO+IP2
        J2=J1+IP2
        J3=J2+IP2
        IF(I2-1)90,90,80
   80   TEMPR=DATA(J1)
        DATA(J1)=W2R*TEMPR-W2I*DATA(J1+1)
        DATA(J1+1)=W2R*DATA(J1+1)+W2I*TEMPR
        TEMPR=DATA(J2)
        DATA(J2)=WR*TEMPR-WI*DATA(J2+1)
        DATA(J2+1)=WR*DATA(J2+1)+WI*TEMPR
        TEMPR=DATA(J3)
        DATA(J3)=W3R*TEMPR-W3I*DATA(J3+1)
        DATA(J3+1)=W3R*DATA(J3+1)+W3I*TEMPR
   90   TOR=DATA(JO)+DATA(J1)
        TOI=DATA(JO+1)+DATA(J1+1)
        T1R=DATA(JO)-DATA(J1)
        T1I=DATA(JO+1)-DATA(J1+1)
        T2R=DATA(J2)+DATA(J3)
        T2I=DATA(J2+1)+DATA(J3+1)
        T3R=DATA(J2)-DATA(J3)
        T3I=DATA(J2+1)-DATA(J3+1)
        DATA(JO)=TOR+T2R
        DATA(JO+1)=TOI+T2I
        DATA(J2)=TOR-T2R
        DATA(J2+1)=TOI-T2I
        IF(ISIGN)100,100,110
  100   T3R=-T3R
        T3I=-T3I
  110   DATA(J1)=T1R-T3I
        DATA(J1+1)=T1I+T3R
        DATA(J3)=T1R+T3I
  120   DATA(J3+1)=T1I-T3R
        TEMPR=WR
        WR=WSTPR*WR-WSTPI*WI+TEMPR
  130   WI=WSTPR*WI+WSTPI*TEMPR+WI
  140   IP2=IP3
        IF(IP3-IP4)50,150,150
  150   RETURN
        END
        SUBROUTINE BITRV(NPREV,N,NREM)
          COMMON DATA(4224),IC(64),DC(66)
            IPO=2
        IP1=IPO*NPREV
        IP4=IP1*N
        IP5=IP4*NREM
        I4REV=1
        DO 60 I4=1,IP4,IP1
        IF(I4-I4REV)10,30,30
   10   I1MAX=I4+IP1-IPO
        DO 20 I1=I4,I1MAX,IPO
        DO 20 I5=I1,IP5,IP4
        I5REV=I4REV+I5-I4
        TEMPR=DATA(I5)
        TEMPI=DATA(I5+1)
        DATA(I5)=DATA(I5REV)
        DATA(I5+1)=DATA(I5REV+1)
        DATA(I5REV)=TEMPR
   20   DATA(I5REV+1)=TEMPI
   30   IP2=IP4/2
   40   IF(I4REV-IP2)60,60,50
   50   I4REV=I4REV-IP2
        IP2=IP2/2
        IF(IP2-IP1)60,40,40
   60   I4REV=I4REV+IP2
        RETURN
        END
        SUBROUTINE FIXRL(N,NREM,ISIGN,IFORM)
          COMMON DATA(4224),IC(64),DC(66)
        TWOFI=6.283185307*FLOAT(ISIGN)
D       WRITE(7,349)
349     FORMAT( ' ENTER FIXRL ' )
        IPO=2
        IP1=IPO*(N/2)
        IP2=IP1*NREM
        IF(IFORM)10,60,60
   10   J1=IP1+1
        DATA(2)=DATA(J1)
        J1=J1+IPO
        I2MIN=IP1+1
        DO 50 I2=I2MIN,IP2,IP1
        DATA(I2)=DATA(J1)
        J1=J1+IPO
        IF(N-3)40,40,20
   20   I1MIN=I2+IPO
        I1MAX=I2+IP1-IPO
        DO 30 I1=I1MIN,I1MAX,IPO
        DATA(I1)=DATA(J1)
        DATA(I1+1)=DATA(J1+1)
   30   J1=J1+IPO
   40   DATA(I2+1)=DATA(J1)
   50   J1=J1+IPO
   60   DO 80 I2=1,IP2,IP1
        TEMPR=DATA(I2)
        DATA(I2)=DATA(I2)+DATA(I2+1)
        DATA(I2+1)=TEMPR-DATA(I2+1)
        IF(IFORM)70,80,80
   70   DATA(I2)=DATA(I2)/2.
        DATA(I2+1)=DATA(I2+1)/2.
   80   CONTINUE
        IF(N-2)170,170,90
   90   THETA=TWOPI/FLOAT(N)
        SINTH=SIN(THETA/2.)
        ZSTPR=-2.*SINTH*SINTH
        ZSTPI=SIN(THETA)
        ZR=(1.-ZSTPI)/2.
        ZI=(1.+ZSTPR)/2.
        IF(IFORM)100,110,110
  100   ZR=1.-ZR
        ZI=-ZI
  110   I1MIN=IPO+1
        I1MAX=IPO*(N/4)+1
        DO 160 I1=I1MIN,I1MAX,IPO
        DO 150 I2=I1,IP2,IP1
        I2CNJ=N+IPO-2*I1+I2
C       WRITE(7,348)
348     FORMAT( ' BEFORE IF ' )
        IF(I2-I2CNJ)140,120,120
  120   IF(ISIGN+2*IFORM+1)130,150,150
  130   DATA(I2+1)=-DATA(I2+1)
        GO TO 150
  140   DIFR=DATA(I2)-DATA(I2CNJ)
        DIFI=DATA(I2+1)+DATA(I2CNJ+1)
        TEMPR=DIFR*ZR-DIFI*ZI
        TEMPI=DIFR*ZI+DIFI*ZR
        DATA(I2)=DATA(I2)-TEMPR
        DATA(I2+1)=DATA(I2+1)-TEMPI
        DATA(I2CNJ)=DATA(I2CNJ)+TEMPR
        DATA(I2CNJ+1)=DATA(I2CNJ+1)-TEMPI
  150   CONTINUE
C       WRITE(7,450)
450     FORMAT( ' AFTER CONTINUE ' )
        TEMPR=ZR-.5
        ZR=ZSTPR*TEMPR-ZSTPI*ZI+ZR
  160   ZI=ZSTPR*ZI+ZSTPI*TEMPR+ZI
        WRITE(7,321)
321     FORMAT( ' AFTER 160 ' )
  170   IF(IFORM)240,180,180
  180   I2=IP2+1
        I1=I2
        J1=IPO*(N/2+1)*NREM+1
        GO TO 220
  190   DATA(J1)=DATA(I1)
        DATA(J1+1)=DATA(I1+1)
        I1=I1-IPO
        J1=J1-IPO
  200   IF(I2-I1)190,210,210
  210   DATA(J1)=DATA(I1)
        DATA(J1+1)=0.
  220   I2=I2-IP1
        J1=J1-IPO
        DATA(J1)=DATA(I2+1)
        DATA(J1+1)=0.
        I1=I1-IPO
        J1=J1-IPO
        IF(I2-1)230,230,200
  230   DATA(2)=0.
D       WRITE(7,333)
333     FORMAT( ' LEAVE FIXRL ' )
D       WRITE(7,500)N,NREM,ISIGN,IFORM
500     FORMAT(1X,4I6)
  240   RETURN
        END
```

1018332

```
C       HPTOMB COLLECTS DATA FROM HPGE SYSTEM IN TOMO
C       MODE WITH SCANNING BED CONTROLLED BY COMPUTER.
C       J. PATTON  26-AUG-77.
C       THIS PROGRAM ASSUMES 90 PULSES/INCH AND 64 OR
C       128 POINTS PER LINE.
        COMMON IC(64),ID(128),IE(9,128),IG(9,128),IO(128)
C
C       COMMANDS FOR SCANNING BED CONTROL REGISTER
C
        ICLER=0          !CLEAR CONTROL REGISTER
        INTEN=1          !INTERRUPT ENABLE
        IRSTA=4          !READ STATUS REGISTER
        IXNEG=8          !GO XNEG.
        IXPOS=16         !GO XPOS.
        IYNEG=32         !GO YNEG.
        IYPOS=64         !GO YPOS.
C
C       CAMAC MODULE SLOT NUMBERS AND SUBADDRESSES
C
        ISLTS=8          !SLOT NO. OF SCLAERS 1--8.
        ISLT9=15         !SLOT NO. OF SCALERS 9 & 18.
        ISLT10=13        !SLOT NO. OF SCALERS 10-13.
        ISLT14=14        !SLOT NO. OF SCALERS 14--17.
        ISENC=6          !SLOT NO. OF ENCODER MODULE
        ISADX=0          !SUBADDRESS OF X ENCODER
        ISADY=1          !SUBADDRESS OF Y ENCODER
        ISLTO=18         !SLOT NO. OF OUTPUT REGISTER
        ISLTI=19         !SLOT NO. OF INPUT REGISTER
        ISADO=0          !SUBADDRESS OF OUTPUT REGISTER
        ISADI=0          !SUBADDRESS OF INPUT REGISTER
C
10      WRITE(7,20)
20      FORMAT(1X 'COUNT RATE(TIME IN SEC) OR SCAN(0)? ',$)
        READ(5,100)ICR
        IF(ICR.EQ.0)GO TO 60
        ISADS=0
        DO 30 IS=1,8
        IDATA=ICAMAC(2,ISLTS,ISADS)      !READ AND CLEAR SCALERS 1--8
30      ISADS=ISADS+1
        IDATA=ICAMAC(2,ISLT9,0)          !READ AND CLEAR SCALER 9
        ITIC=60*ICR
        IT=ITIME(0)                      !START CLOCK
40      IT=ITIME(1)                      !READ CLOCK
        IF(IT.LT.ITIC)GO TO 40
        ISUM=0
        ISADS=0
        DO 50 IS=1,8
        IDATA=ICAMAC(2,ISLTS,ISADS)      !READ AND CLEAR SCALERS 1--8
        ISUM=ISUM+IDATA
50      ISADS=ISADS+1
        IDATA=ICAMAC(2,ISLT9,0)          !READ AND CLEAR SCALER 9
        ISUM=ISUM+IDATA
        ISUM=ISUM/ICR
        WRITE(7,55)ISUM
55      FORMAT(1X 'TOTAL COUNT RATE = ',I5,' COUNTS/SEC.')
        GO TO 10
60      WRITE(7,70)
```

10-8333

```
70      FORMAT(1X     VERSE LINE LENGTH(F5.2)     $)
        READ(5,80)XLL
        WRITE(7,75)
75      FORMAT(1X 'LONG. LINE LENGTH(F5.2)? ',$)
        READ(5,80)XLLL
80      FORMAT(F5.2)
        IMX=0
        CALL LINDIS(IMX)          !CLEAR CRT, SET-UP DISPLAY,
C       AND DRAW FRAME.  NOTE:  CINIT PERFORMED IN LINDIS.
        WRITE(7,90)
90      FORMAT(1X 'MAX. VALUE TO NORM. DISPLAY? ',$)
        READ(5,100)IMX
100     FORMAT(I5)
        WRITE(7,120)
120     FORMAT(1X 'WRITE FILE NAME? ',$)
        CALL ASSIGN(2,'DK1:',-1)
        WRITE(7,140)
140     FORMAT(1X 'SPEED CORRECT? YES(1) OR NO(0) ',$)
        READ(5,100)ISP
        WRITE(7,150)
150     FORMAT(1X '64 OR 128 PTS/LINE? ',$)
        READ(5,100)INP
        XNP=INP
        XPUL=(90.0*XLL)/XNP + 0.5
        XLPUL=(90.0*XLLL)/XNP + 0.5
        IPPUL=XPUL
        IPULP=IPPUL-1             !PRELOAD FOR ENC COUNTING DOWN
        IPULM=-(IPPUL)   !PRELOAD FOR ENC COUNTING UP
        ILPUL=XLPUL
        ILPULM=-(ILPUL)
C       FIRST LINE ENC WILL COUNT UP, INIT. PT. IS LAST PT IN LINE
        IPRU=15          !UPPER 4 BITS OF ENC PRELOAD
        IPRL=IPULM                !LOWER 16 BITS OF ENC PRELOAD
        ILAM=12
        CALL CAMAC(17,ISENC,ISADX,ILAM) !ENABLE O.R. FLAGS
        CALL CAMAC(10,ISENC,2)          !CLEAR X O.R. FLAG
        CALL CAMAC(10,ISENC,3)          !CLEAR Y  O.R. FLAG
        CALL CAMAC(16,ISENC,ISADX,IPRU,IPRL)    !PRELOAD X ENC
        WRITE(7,200)
200     FORMAT(1X 'ONE OR TWO WINDOWS? ',$)
        READ(5,100)INW
        IF(INW.EQ.1)GO TO 215
        WRITE(7,210)
210     FORMAT(1X 'DISPLAY WINDOW #1 OR #2? ',$)
        READ(5,100)IDWN
215     WRITE(7,220)
220     FORMAT(1X 'SWITCH BED CONTROL TO AUTO')
        IDIR=-1                   !INIT. BED DIRECTION FORWARD
C       INIT. PROBE DIR. REVERSE
        IPT=128                   !INIT. POINT TO BE PLOTTED
        IXDIR=IXPOS               !DIRECTION REGISTER
        DO 1000 ILIN=1,INP
        ISADS=0
        DO 250 IS=1,8
        IDATA=ICAMAC(2,ISLTS,ISADS)     !READ AND CLEAR SCALERS 1--8
250     ISADS=ISADS+1
        IDATA=ICAMAC(2,ISLT9,0)         !READ AND CLEAR SCALER 9
        IDATA=ICAMAC(2,ISLT9,2) !READ AND CLEAR OSCILLATOR
        IF(INW.EQ.1)GO TO 350           !ONLY ONE WINDOW?
        IDATA=ICAMAC(2,ISLT9,1)         !NO, READ AND CLEAR SCALER 18
        ISADS=0
```

```
      DO 300 IS=1,4
      IDATA=ICAMAC(2,ISLT10,ISADS)     !READ AND CLEAR SCALERS 10--13
      IDATA=ICAMAC(2,ISLT14,ISADS)     !READ AND CLEAR SCALERS 14--17
300   ISADS=ISADS+1
350   CALL CAMAC(16,ISLTO,ISADO,IXDIR)          !START BED FORWARD
      DO 500 JPT=1,INP
C
C     X OVER-RANGE (O.R.) FLAG CHECKER
C
360   IF(IQCMD(8,ISENC,2).NE.0)GO TO 370
      CONTINUE
      GO TO 360
370   CALL CAMAC(10,ISENC,2)           !CLEAR O.R. FLAG
      ISADS=0
      DO 380 IS=1,8
      IE(IS,IPT)=ICAMAC(2,ISLTS,ISADS)          !READ AND CLEAR SCALERS 1--
380   ISADS=ISADS+1
      IE(9,IPT)=ICAMAC(2,ISLT9,0)      !READ AND CLEAR SCALER 9
      IO(IPT)=ICAMAC(2,ISLT9,2)        !READ AND CLEAR OSCILLATOR
      ID(IPT)=ISUM
      IF(INW.EQ.1)GO TO 400
      ISADS=0
      DO 390 IS=1,4
      IG(IS,IPT)=ICAMAC(2,ISLT10,ISADS)         !READ AND CLEAR SCALERS 10-
      ISS=IS+4
      IG(ISS,IPT)=ICAMAC(2,ISLT14,ISADS)        !READ AND CLEAR SCALERS 14-
390   ISADS=ISADS+1
      IG(9,IPT)=ICAMAC(2,ISLT9,1)      !READ AND CLEAR SCALER 18
400   IPT=IPT+IDIR
      IF(JPT.EQ.INP)GO TO 500
      CALL CAMAC(16,ISENC,ISADX,IPRU,IPRL)      !PRELOAD X-ENC
500   CONTINUE
C
C     INDEX PROCESSOR
C
      CALL CAMAC(16,ISLTO,ISADO,ICLER)          !STOP BED
      IF(ISP.EQ.0)GO TO 550
C
C     DO SPEED CORRECTION HERE
C
      IF(ILIN.GT.1)GO TO 520
      IST=1
      IF(INP.EQ.64)IST=65
      XS=0
      DO 510 I=IST,128
      XO=IO(I)
510   XS=XS+XO
      XNP=INP
      XS=XS/XNP
520   DO 530 J=1,9
      DO 530 I=IST,128
      XE=IE(J,I)
      XO=IO(I)
      XE=(XE*XS)/XO
530   IE(J,I)=XE
      IF(INW.EQ.1)GO TO 550
      DO 540 J=1,9
      DO 540 I=IST,128
      XG=IG(J,I)
```

```
          XO=IO(I)
          XG=(XG*XS)
  540     IG(J,I)=XG
  C
  C       SET-UP FOR DISPLAY OF ONE LINE OF DATA
  C
  550     IF(INF.EQ.64)GO TO 590
          L=1
          DO 580 I=1,128,2
          K=I+1
          ISUM=0
          DO 570 J=1,9
          IF(IDWN.EQ.2)GO TO 560
          ISUM=ISUM+IE(J,I)+IE(J,K)
          GO TO 570
  560     ISUM=ISUM+IG(J,I)+IG(J,K)
  570     CONTINUE
          IC(L)=ISUM
  580     L=L+1
          GO TO 625
  590     L=65
          DO 620 I=1,64
          ISUM=0
          DO 610 J=1,9
          IF(IDWN.EQ.2)GO TO 600
          ISUM=ISUM+IE(J,L)
          GO TO 610
  600     ISUM=ISUM+IG(J,L)
  610     CONTINUE
          IC(I)=ISUM
  620     L=L+1
  625     CALL LINDIS(IMX)          !DISPLAY LINE OF DATA(64 PTS)
          WRITE(2)IE
          CALL CAMAC(28,ISENC,ISADY)
          ILLO=ICAMAC(0,ISENC,ISADY)
          IPULY=ILPULM+ILLO
          IF(IPULY.GT.-1)IPULY=-1
          IF(INW.EQ.1)GO TO 630
          WRITE(2)IG
  630     CALL CAMAC(16,ISENC,ISADY,015,IPULY)     !PRELOAD Y-ENC
          CALL CAMAC(16,ISLTO,ISADO,IYPOS)         !START BED INDEXING
  C
  C       Y OVER-RANGE(O.R.) FLAG CHECKER
  C
  640     IF(IQCMD(8,ISENC,3).NE.0)GO TO 650
          CONTINUE
          GO TO 640
  650     CALL CAMAC(16,ISLTO,ISADO,ICLER)         !STOP BED
          CALL CAMAC(10,ISENC,3)           !CLEAR O.R. FLAG
  660     CALL CAMAC(28,ISENC,ISADX)
          ILOW=ICAMAC(0,ISENC,ISADX)
          IF(IDIR.EQ.1)GO TO 690  !I.E. BED MOVES FOR. NEXT LINE
          IF(INF.EQ.64)GO TO 670           !HERE BED MOVES REVERSE NEXT LINE
          IPT=1
          GO TO 680
  670     IPT=65
  680     IPRU=0
          IPRL=IPULP
          IPRT=IPULP+ILOW
          IXDIR=IXNEG
          GO TO 700
```

```
690       IPT=128
          IPRU=15
          IPRL=IPULM
          IPRT=IPULM+ILOW
          IXDIR=IXPOS
700       CALL CAMAC(16,ISENC,ISADX,IPRU,IPRT)     !PRELOAD X-ENC
          IDIR=-IDIR
1000      CONTINUE
          ENDFILE 2
          STOP
          END

*
```

VI. Scientific Personnel--Curriculum Vitae on File ERDA

Principal Investigator:

A. B. Brill, M.D., Ph.D. SS# 131-20-0970
Professor of Medicine & Radiology, Director of Radiological Sciences

Co-Principal Investigator:

R. R. Price, Ph.D. SS# 401-62-0402
Associate Professor, Radiology

Research Scientists:

J. J. Erickson, Ph.D. SS# 502-40-2283
Assistant Professor, Radiology

J. A. Patton, Ph.D. SS# 401-62-0385
Assistant Professor, Radiology

J. P. Wikswo, Ph.D. SS# 224-62-5499
Assistant Professor, Physics

J. E. Lagan SS# 409-58-5467
Electronics Engineer

J. P. Jones, Ph.D. SS3 401-66-008
Research Associate

F. D. Rollo, M.D., Ph.D. SS# 101-26-5710
Associate Professor, Radiology

VII. Other Personnel

Graduate Students

David Pickens III SS# 414-78-0392

Secretary:

T. Shaw SS# 480-68-5547, 100%

Research Technician:

M. McConnell SS# 403-48-9866, 50%

VIII. Other Finanical Assistance--None

1018338

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 13,000 square feet adjacent for conference, library, clinical imaging, and instrument development and modification	100 percent
3D Imaging Systems (Radiology Dept.) 1 EMI Head Scanner 1 Searle Body Scanner 2 Gray Scale Ultrasound 2 Real Time Ultrasound	
Animal Radiographic Research Lab	
Computer Center	As Required
Clinical Research Center	As Patients Present
Clinical Radioisotope Laboratory	Radiochemistry and counting facilities as needed
Animal House	Maintenance and primary care of animals used in tracer experiments
Medical, Chemistry, Biology, Engineering, Physics and Joint University Libraries	Access to books
Medical Illustrations	Drawings, slides, photographs for presentations and publications

1018339

RENEWAL PROPOSAL

ERDA EY-77-S-05-2401 November 1, 1978 through October 31, 1979

X. Budget Estimated Requirements		ERDA	University	TOTAL
1. Salaries & Wages Name, Title, Monthly rates, % effort				
A. B. Brill, M.D. Ph.D. SS # 131-20-0979 Professor Medicine & Radiology	16%	-0-	$9,761	$9,761
Co-Prinicpal Investigator R. R. Price, Ph.D. Associate Professor Radiology $2,069/mo %20		$4,966	------	$4,966
Research Associates:				
J. J. Erickson, Ph.D. Ass't Professor Radiology $1,656/mo 15%		$2,987	-----	$2,987
J. A. Patton, Ph.D. Ass't Professor Radiology $1,786/mo 20%		$4,286		$4,286
F. D. Rollo, M.D., Ph.D. Assoc. Professor Radiology 15%		-0-	-0-	-0-
J. E. Lagan Electronics Engineer $1,589/mo 10%		$1,907	-----	$1,907
J. P. Jones, Ph.D. Research Scientist $1,371/mo 25%		$4,113	------	$4,113
Secretary, T. Shaw, 100%		$8,028	-----	$8,028
Res. Technician M. McConnell, 50%		$5,138	------	$5,138
Fringe Benefits (not fixed % of salaries. Varies with employee status and option)		$5,530	$1,287	$6,817
TOTAL SALARIES & FRINGE BENEFITS		$36,955	$11,048	$48,003
INDIRECT COSTS (65% S & W)		$24,021	-----	------

1018340

2. SUPPLIES AND MATERIALS

Books, Periodicals, Journals	$500		
Computer Supplies (line printer paper, magnetic tapes)	$1,000		
Lab Supplies, Isotopes	$500		
Maintenance Service (computer only)	$500		
Office Supplies/Duplicating	$300		
Electronic Components & Replacement Parts	$6,900	Subtotal	$9,700

3. EQUIPMENT--Microprocessor Controlled Scanner

CAMAC MM-816C 8192 16 Bit Word Memory Module	$2,785	Subtotal	$2,785

4. TRAVEL--Domestic	$1,500	Subtotal	$1,500

TOTAL FUNDS REQUESTED ERDA	$74,961.00
UNIVERSITY CONTRIBUTION	$11,048.00

1018341

Projected Costs

Percentage & Amount, Vanderbilt University	13%	$11,048
Percentage & Amount, Requested ERDA	87%	$74,961

XI. AUTHENTICATION

A. B. Brill, M.D., Ph.D.
Principal Investigator

Paul Gazzerro, Jr.
Assoc. Vice-President for
Medical Affairs for Operations
and Fiscal Planning

NOTE: Studies described in the application, involving the investigational use of human subjects have been reviewed and approved by this Institutions's Clinical Investigation Committee. Annual review on the unchanged protocol is pending August 2, 1978 (see yellow Protection of Human Subjects form HEW-596).

1018342

"The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as the result of this application."

A. B. Brill

A. B. Brill, M.D., Ph.D.

Date: 1-28-78

1018343

TO : Addressees Listed Below DATE: January 16, 1978

FROM : F. O. Christie, Director, Contract Division, CRO

SUBJECT: CONTRACTUAL DOCUMENT(S) FOR REVIEW, COMMENTS AND INITIALING

The document(s) listed below (is) (are) forwarded for your review, comments and initials. Upon completion of your review, please attach your comments, if any, and forward to next in line. Expeditious handling of this matter will be appreciated.

Modification A027 to Contract EY-76-S-05-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. S. ~~L.~~ Phillips	Contract	SCP	1-16	
2. A. ~~M.~~ Frost, Jr.	Contract		1-16	
3. H. S. Oster, Jr.	Finance		1/17	
4. W. L. Buchanan	Budget		1/19/78	
5.				
6.				
RETURN TO Alice Brown, Contract Division, Room 109				

1018344

Routed by Research Contracts and Reports Branch Contract Division

FORM OR-133 (Rev. March 1975) F[illegible]er

ROUTE SLIP

- MANAGER
  - Deputy Manager
  - Assistant to Manager for Pub. Infor.
- CHIEF COUNSEL
  - Patent Group
- ASST. MGR. FOR ADMINISTRATION
- BUDGET AND REPORTS DIVISION
- CONTRACT DIVISION
  - Negotiated Contracts Branch
  - Research Contracts, Procedures, and Reports Branch
  - Procurement Branch
- FINANCE DIVISION
  - Systems & Cost Analysis Br.
  - Accounting Branch
    - Division Services Section
    - General Ledger Section
    - Government Payroll Sect.
  - Audit Branch
  - ADP Branch
    - ADP Service Center
- ORGANIZATION & PERSONNEL DIV.
  - Personnel & Management Analysis Br.
  - Industrial Personnel Branch
- SUPPLY DIVISION
  - Property Branch
  - Transportation Branch
  - Telecommunications Branch
    - Teletype Services
  - Office Services Branch
    - Mail Section
    - Repro., Distr. & Matls. Section
    - Photographic Services
    - Records Holding Area
- SECURITY DIVISION
  - Personnel Security Branch
  - Physical Security Branch
    - Oak Ridge Security Patrol
- ASST. MANAGER FOR OPERATIONS
- MANUFACTURING DIVISION
  - Quality Assurance Branch
  - Weapons Branch
- MATERIALS MANAGEMENT DIV.
  - Materials Management Br.
  - Nuclear Matls. Control Br.
- REACTOR DIVISION
- RESEARCH & TECH. SUPPORT DIV.
  - Classification & Tech. Services Br.
  - Research & Development Branch
  - Standards & Quality Assurance Branch
  - Waste Management Branch
- SAFETY & ENVIRONMENTAL CONTROL DIV.
  - Health Protection Branch
  - Ind. Safety & Fire Protection Br.
  - Nuclear Safety Br.
  - Environmental Prot. Br.
- URANIUM ENRICHMENT OPERATIONS DIVISION
  - Feed Materials Br.
  - Operations Branch
  - Power Branch
  - Toll Enriching Branch
- ASST. MGR. FOR DEVELOPMENT AND PLANNING
- INDUSTRIAL PARTICIPATION DIV.
- DEVELOPMENT DIVISION
- PLANNING DIVISION
  - Capacity Expansion Br.
  - Plans & Analysis Br.
  - Marketing & Revenue Br.
- ASST. MGR. FOR CONST. & ENGRG.
- CONSTRUCTION DIVISION
  - Administrative Branch
  - General Construction Branch
  - Special Projects Branch
- ENGINEERING DIVISION
  - Design Coordination Branch
  - Engineering Analysis Branch
- TECHNICAL INFORMATION CENTER
  - Office of Manager
  - Assistant Mgr. for Adm.
  - Asst. Mgr. for Info. Serv. & Systems
    - Science & Tech. Branch
    - Reference Branch
    - Computer Serv. Branch
  - Asst. Mgr. for Prod. & Doc. Mgmt.
    - Editorial Branch
    - Publishing Services Branch
    - Printing Branch
    - Document Mgmt. Branch
- CONTRACT COMPLIANCE OFFICE
  - (Southeastern Area)
- CONTROLLER REGIONAL AUDIT STAFF
- ATMOSPHERIC TURBULENCE & DIFFUSION LAB (NOAA)

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. BUDGET AND REPORTS DIVISION CONCURRENCE [illegible]

2. OFFICE OF CHIEF COUNSEL CONCURRENCE [illegible] 1-16-78

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

1018345

Department of Energy
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tennessee 37830

December 29, 1977

Charles W. Hill, Chief Counsel

REQUEST FOR CONTRACT ACTION

It is requested that you take the necessary steps to process the following described contract action (CA):

1. Nature of Action Requested:

   ( ) Selection of New Contractor and/or Negotiation of Contract
   Number:
   Contractor:

   (X) Modification of Contract
   Number: EY-76-S-05-2401 (Mod. A027)
   Contractor: Vanderbilt University

2. Nature of Services To Be Covered by Contract: Research
   Title: "Radioisotope Studies, Utilizing a Low Level Whole Body Counter and Clinical Applications of Activation analysis"

3. Type of Contract:
   (X) Support Agreement ( ) Cost Type ( ) Other

4. Amount of DOE Funds To Be Obligated by this CA: $74,419

5. DOE Percentage of Est. Total Cost To Be Shown by this CA: 100%

6. Description of Other Changes To Be Covered by this CA:
   Modify contract to cover research during period 11/01/77 thru 10/31/78. Increase Cumulative DOE Support Ceiling from $544,118 to $618,537. Soviet-Bloc article applies. Title to property, if any, to vest in Contractor by P.L. 85-934.

7. Authority:
   PR #P05-78-0116

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR: SLP

1018346

APPENDIX "A"

CONTRACTOR:. VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

For the contract period: November 1, 1977 through October 31, 1978

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct a study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 16% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages:	$36,089
(2) Equipment to be purchased or fabricated by the Contractor:	$ 3,282

a Equipment estimated to cost less than $1,000:

2 position encoders
FIFO Buffer

b Equipment estimated to cost in excess of $1,000:

Dual ADC, Bay Engineering PC11-AD

1018347

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

(3) **Travel:** $ 1,500

Domestic----------$ 1,500
Foreign----------$ 0

(4) **Other direct costs:** $ 9,369

(5) **Indirect costs (based on a predetermined rate of** 67% **of salaries and wages):** $24,179

[redacted]

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

The estimated DOE **Support Cost is funded as follows:**

(a) Estimated unexpended balance from the prior period(s):	$ 0
(b) New funds for the current period:	$74,419

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

1018349

UNITED STATES DEPARTMENT OF ENERGY

PROCUREMENT COMMITMENT/OBLIGATION RECORD

1. TO: Certifying Official	2. FROM: Procurement Office	3. Contract Number
BUDGET DIVISION	CONTRACT DIVISION	CD-594
		4. Date Negotiated

5. Allotment Symbol	6. Signature of Contracting Officer and Title	7. Telephone Number
EV 82-91(OR)	A. H. Frost, Jr. (SPhillips)	3-4105

8. Contract Number and TO/PA	9. Modification No.	10. Funding Period
EY-76-S-05-2401	A027	

11. Name of Contractor	12. Type of Contract
VANDERBILT UNIVERSITY	SRS&

13. Procurement Request Number	14. Budget and Reporting Classification	15. Object Class	16. Amount Of This Action
P05-78-0116	HK-01	=02-01	$74,419
			No notice of transfer of funds received
17. Total			

Funding as stated above is authorized.

18. Signature	19. Telephone Number	20. Date
WHB		12/30

21. Remarks

22. Negotiating Complete and Funds Reserved on:		23. Signed Contract Received and Effectively Obligated by Budget on:	
Date	Initials	Date	Initials
1/4/78	WHB		

1018350

FORM ERDA-799
(3-76)
EHDA-PR 9-16

U.S. Department of Energy

SP

PROCUREMENT REQUEST

*Please Type

(See Instructions on Reverse of Last Sheet)

1. TO: Procurement Office
R. J. Hart, Mgr., OR
Vanderbilt Univ.
Nashville, TN 37232
Dr. A. Bertrand Brill, P.I.

2. From
Activity Title: EV
Division: BER
Project: HHSP

3. Procurement Request Number
P-05-78:0116

4. ☐ Contract ☐ Grant ☒ Special Research Support Agreement (SRSA) ☐ Other
☐ Modification of
EY-76-S-05-2401 Contract Number TO/PA
☐ Change Order ☒ Supplemental Agreement

5. Priority Rating (Ref. FPR 1-1.311)
Routine

6. Desired Award Date
11 01 77

7. Security Classification (ERDAM APP. 3401)
☒ Unclass. ☐ Secret ☐ Conf. ☐ Top Secret

8. SERVICES, ARTICLES, MODIFICATIONS OR OTHER ACTION REQUIRED

TITLE Radioisotope Studies - Clinical Appl. of Act. Analysis

a. Item No.	b. Brief Description (As required, attach detailed Statement of work, including place(s) and time(s) of delivery(ies) or Schedule of work. State basis for estimated cost or price. Include detailed cost estimate, if available.)	c. Quantity	d. Estimated Cost or Price
	Study of radioisotope distribution and radiation absorbed dose from medical radionuclides. TERM: 11/01/77-10/31/78		

e. TOTAL ESTIMATED AMOUNT OF THIS ACTION $

9. Competitive Procurement ☐
Non-Competitive Procurement ☒
If competitive, attach technical evaluation plan.
If non-competitive, attach justification.
Ref.: FPR 1-3.101(d) & ERDA-PR 9-55.2

10. Is Source Evaluation Board Required?
☐ YES ☒ NO
Ref.: ERDA Source Evaluation and Selection Handbook

11. Procurement Request Resulting From Unsolicited Proposal
If yes, attach copy of proposal and determination Ref.: ERDA-PR 9-4.52 and 9-4.51 ☐ YES ☐ NO
U-77-02494
UNSOLICITED PROPOSAL NUMBER

12. Cost Sharing Contract
☐ YES ☒ NO
If yes, attach details of cost sharing.
Ref.: ERDA-PR 9-4.56

13. Government Furnished Equipment and Facilities Required?
If yes, attach details of requirements. ☐ YES ☐ NO

14. Recommended Source(s)
Attach name(s) and address(es) of source(s).

15. Report and Drawings Requirements
If yes, attach details of requirements. ☐ YES ☐ NO

16. Budget Activity Program, Subprogram, and Activity (ERDAM Appendix 1101, Part II)
HK 01 02 01
$ 74,419.
Amount of Funds Authorized

17. Requestor (*Typed name, title, location, telephone number, date*)
DEC 2 ...
Donald W. Cole, BER/HHSP x33268
(Name)
Donald W Cole 11-4-77
(Signature)

18. Authorizing Program Official (*Typed name, title, location, telephone number, date*)
James L. Liverman, ASEV
(Signature)

19. Certifying Official (*Typed name, title, location, telephone number, date*)
DEC 20 1977
(Date)
I hereby certify that funds in the amount here stated are available for such purposes under Allotment.
Approp. #89X0202.91
No. EV-82-91(OR)
(Signature)

PROCUREMENT OFFICE

1018351

VANDERBILT UNIVERSITY
NASHVILLE, TENNESSEE 37232
TELEPHONE (615) 322-7311
Division of Nuclear Medicine & Biophysics • School of Medicine • Direct phone 322-2394

FINANCIAL STATEMENT

Contract no. EY-76-S-05-2401

Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period. (8-01-76 thru 6-30-77)	$ 65,562.40
2.	Estimated total cost for remainder of period.	$ 27,461.60
3.	Total actual and estimated cost chargeable to ERDA for current period based on percentage of cost agreed upon as contained in A-111 of Appendix "A" to contract.	$ 93,024.00
4.	Accumulated costs chargeable to ERDA (include costs reported in certified statement for preceding period(s) and the costs stated in Item (3) above.).	$ 544,118.00
5.	Accumulated ERDA Support Celing as stated in Article III of contract.	$ 544,118.00
6.	Total estimated ERDA funds remaining under contract (Subtract Item (4) from (5) which may be used to reduce amount of new funds required from ERDA for proposed renewal period.	$ -0-

Macon Somerville
Assistant Director of Finance

A. Bertrand Brill, M.D.
Principal Investigator

1018352

A027

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☐ ORIGINAL ☐ FOLLOWUP ☐ REVISION

☐ GRANT ☒ CONTRACT ☐ FELLOW ☐ OTHER

☐ NEW ☐ RENEWAL ☒ CONTINUATION

APPLICATION IDENTIFICATION NUMBER *(If known)*

EY-76-S-05-2401

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHEW policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Md 20014.

1. TITLE OF PROPOSAL OR ACTIVITY

Radioisotope Studies Utilizing a Low Level Whole Body Counter and Clinical Application of Activation Analysis

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

A. B. Brill, M.D., Ph.D. and Ronald R. Price, Ph.D.

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

☐ A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.)

☒ B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: ☒ NONE OF THE FOLLOWING, OR INCLUDING: ☐ MINORS, ☐ FETUSES, ☐ ABORTUSES, ☐ PREGNANT WOMEN, ☐ PRISONERS, ☐ MENTALLY RETARDED, ☐ MENTALLY DISABLED. UNDER SECTION 6. COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

☐ A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHEW THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF *DHEW Regulation 45 CFR 46*, THAT IT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHEW DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY.

☒ B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHEW ASSURANCE NUMBER G-0401) OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHEW. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF * IN ACCORDANCE WITH THE REQUIREMENTS OF THE *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46)*. THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM).

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT: * Pending Review 8/17/77

EITHER ☐ HUMAN SUBJECTS WILL NOT BE AT RISK; OR ☒ HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION

Vanderbilt University Medical Hospital
21st and Garland, Nashville, TN 37232

8. TITLE OF INSTITUTIONAL OFFICIAL

John Hash, Ph.D.
Assoc. Dean, Biomedical Sciences

TELEPHONE NUMBER

615)322-2281

SIGNATURE OF INSTITUTIONAL OFFICIAL

John H Hash

DATE

7/29/77

HEW-596 (Rev 4-75)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY.

-10-8353

5. INVESTIGATIONAL NEW DRUGS - ADDITIONAL CERTIFICATION REQUIREMENT

SECTION 46.17 OF TITLE 45 OF THE Code of Federal Regulations states, "Where an organization is required to prepare or to submit a certification . . . and the proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 130.3(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received."

INVESTIGATIONAL NEW DRUG CERTIFICATION

TO CERTIFY COMPLIANCE WITH FDA REQUIREMENTS FOR PROPOSED USE OF INVESTIGATIONAL NEW DRUGS IN ADDITION TO CERTIFICATION OF INSTITUTIONAL REVIEW BOARD APPROVAL, THE FOLLOWING REPORT FORMAT SHOULD BE USED FOR EACH IND: (ATTACH ADDITIONAL IND CERTIFICATIONS AS NECESSARY).

- IND FORMS FILED: ☐ FDA 1571, ☐ FDA 1572, ☐ FDA 1573

- NAME OF IND AND SPONSOR IND 9222, Iodocholesterol - ^{131}I

- DATE OF 30-DAY EXPIRATION OR FDA WAIVER
  (FUTURE DATE REQUIRES FOLLOWUP REPORT TO AGENCY) June 8, 1977

- FDA RESTRICTION _____

- SIGNATURE OF INVESTIGATOR G. B. Brill DATE July 29, 1977

6. COOPERATING INSTITUTIONS - ADDITIONAL REPORTING REQUIREMENT

SECTION 46.16 OF TITLE 45 OF THE *Code of Federal Regulations* IMPOSES SPECIAL REQUIREMENTS ON THE CONDUCT OF STUDIES OR ACTIVITIES IN WHICH THE GRANTEE OR PRIME CONTRACTOR OBTAINS ACCESS TO ALL OR SOME OF THE SUBJECTS THROUGH COOPERATING INSTITUTIONS NOT UNDER ITS CONTROL. IN ORDER THAT THE DHEW BE FULLY INFORMED, THE FOLLOWING REPORT IS REQUESTED WHEN APPLICABLE.

USE FOLLOWING REPORT FORMAT FOR EACH INSTITUTION OTHER THAN GRANTEE OR CONTRACTING INSTITUTION WITH RESPONSIBILITY FOR HUMAN SUBJECTS PARTICIPATING IN THIS ACTIVITY: (ATTACH ADDITIONAL REPORT SHEETS AS NECESSARY).

INSTITUTIONAL AUTHORIZATION FOR ACCESS TO SUBJECTS

- SUBJECTS: STATUS (WARDS, RESIDENTS, EMPLOYEES, PATIENTS, ETC.) _____

NUMBER _____ AGE RANGE _____

NAME OF OFFICIAL (PLEASE PRINT) _____

TITLE _____ TELEPHONE _____

NAME AND ADDRESS OF COOPERATING INSTITUTION _____

- OFFICIAL SIGNATURE _____

NOTES: *(e.g., report of modification in proposal as submitted to agency affecting human subjects involvement)*

1018354

GPO · 1975 O - 574-84

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

IND 9222

JUN 8 1977

A. B. Brill, M.D., Ph.D.
Division of Nuclear Medicine and Biophysics
School of Medicine
Vanderbilt, Tennessee 37232

Dear Dr. Brill:

Please refer to your Notice of Claimed Investigational Exemption for ^{131}I-19-Iodocholesterol.

Reference is also made to your letter of May 6, 1976.

This IND is currently under review, and we have the following recommendations and requests:

MEDICAL

We have no objection if you proceed with your new studies. However, a more detailed protocol should be submitted and as agreed the same IND number (IND 9222) will be retained. This was discussed in a telephone conversation with Stephen Bartok, M.D. on May 13, 1977. Also, any deficiencies will be noted in a subsequent letter.

In addition, it is required that a sponsor of an IND forward a progress report of clinical investigation at reasonable intervals not exceeding a year. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. Your IND does not contain this information.

Your prompt written reply will be appreciated so we may continue our evaluation of your IND.

Sincerely yours,

William J. Gyarfas

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

1018355

Expenditure Statement and Renewal Proposal

ERDA Contract EY-76-5-05-2401

I.

Radioisotope Studies Utilizing A Low Level Whole Body Counter

and

Clinical Applications of Activation Analysis

II.

Department of Radiology

Vanderbilt University School of Medicine

Nashville, Tennessee 37232

July 31, 1977

1018356

Table of Contents

		Page
III.	Project Abstract	1
IV.	Scientific Background	4
V.	Scientific Scope	
	A. Specific Dosimetry Projects	5
	1. Comparative Dosimetry of Iodocholesterol Compounds	5
	2. Iron-59 Citrate Dosimetry in Diseased Human Subjects: Comparison to In-111	22
	3. Evaluation of ths Standard Man Model for Dosimetry Calculations--Comparison with Laboratory Measurements	28
	4. Radiation Sensitivity of the Thyroid During I-131 Therapy	29
	5. Nuclear Power Reactor--Environmental Monitoring.	35
	B. Supporting Systems Development	
	1. Hardware	36
	a. Mircoprocessor Controlled Quantitative Scanner	36
	b. Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies	38
	2. 2. Software	41
	a. Acquisition/reconstruction/display of Tomographic Data	41
	b. Software System for Quantitative Autoradiography (P-32) Microdosimetry	43
	c. Sharing Efforts	47
	i. Simulation and Modeling	47
	ii. Sharing of Computer Programs in in Nuclear Medicine	47
VI.	Scientific Personnel	49
VII.	Other Personnel	49
VIII.	Other Financial Assistance	49
IX.	Premises, Facilities, Equipment, and Materials to be Furnished by Contract	50
X.	Budget Estimated Requirements	51
XI.	Authentication	53
XII.	Appendix I: Studies on Red Cell Aplasia: Ferrokinetics During Remission of the Disease	
	Appendix II: Summary of Current Radiation Dose Estimates to Humans from 52-Fe, 55-Fe, and 59-Fe as Ferrous Citrate and Ferric Chloride (Draft)	
	Appendix III: Quantitation of Radioactivity for Irregular Geometric Shapes Using External Measurements	
	Appendix IV: Draft-Section for NCRP-55 Report	
	Appendix V: Simulation, Analysis, and Modelling (SAAM Workshop Program	
	Appendix VI: Vth International Conference on Information Processing in Medical Imaging	

1018357

III. Project Abstract

Our work is directed toward the development of methods (hardware and software) for the quantitation of body and organ burdens of radioactivity. Initially, these studies were directed toward the estimation of low levels from fallout. Our current work is directed toward the evaluation of radiation dose distributions from new radioactive tracers and new procedures, such as bone mineral content, x-ray fluorescence and neutron activation analyses used in nuclear medicine. The systems we have developed are well-suited to this task, but nonetheless, we continue to improve on the methods to diminish errors. The major problem that we face involves the meshing of our interests and capabilities with the schedules and wishes of patients and referring physicians. We stand by, ready to adjust our personnel and facility schedules so that we are able to answer the relevant questions concerning the patients' problems. Whenever the patient's problem and physical state permits sequential studies, we attempt to obtain additional data needed for dosimetry and metabolic kinetics studies. This includes multiple quantitative imaging studies, blood, and tissue samples (when available).

Continuing efforts are being directed toward the evaluation of the ORNL standard man model used for internal dosimetry calculations, to determine the range of its validity in persons with different body/organ sizes and organ kinetics. We will, also, continue to investigate Fe-59 citrate dosimetry in abnormals and its relationship to In-111 citrate used as a bone marrow scanning agent. In these studies, we investigate dose variations resulting from kinetic changes due to disease variations, to non-standard organ sizes, and inhomogenous radioisotope distributions. A new study is underway in cooperation with the Division of Endocrinology utilizing a new iodocholesterol adrenal scanning agent to compare its dosimetric properties to earlier compounds we have studied. As an extension of a study on the kinetics of I-131 administered in therapeutic quantities to patients with thyrotoxicosis, we are investigating the radiation sensitivity of the thyroid gland in Graves' Disease to radioiodine therapy. Iodine kinetic parameters and the iodine content of the gland, as measured by fluorescence scanning, will be analyzed in an effort to identify potential sensitivity correlates.

In cooperation with the Department of Obstetrics and Gynecology, we are developing a set of computer programs for the purpose of conducting quantitative analysis of autoradiographs. Initial measurements will be made in rats using P-32 labelled chromic phosphate colloid. The autoradiographs will be digitized using the department's existing quantitative video system. The development of this technique should provide valuable information on micro dosimetry questions concerning nonhomogenous distributions of radiopharmaceuticals.

We are continuing to explore the potential of CAMAC for hardware and software standardization for nuclear medicine data acquisition and display systems. The benefits of CAMAC include standardization and modularity, ability to replace defective systems modules without affecting the continued operation of the rest of the system, and the ability to incorporate new improved modules as they are developed. We will attempt to increase awareness in the nuclear medicine community of the benefits to be derived from CAMAC and hopefully will assist in insuring the general acceptance and survival of this important internationally accepted interfacing standard.

We have recently acquired an autonomous crate controller from the Fermi National Accelerator Laboratory. This controller utilizes an Intel 8080 micorprocessor and is now being interfaced to our quantitative whole-body scanner in an effort to cut down overhead on our general purpose computer system.

10183

The loan of a "Pho/Con" longitudinal tomographic scanner from the Searle Corporation will prove to be a boon to our ongoing iodocholesterol/adrenal dosimetry project. The Pho/Con is the instrument of choice providing the optimum in speed and sensitivity for quantitating isolated distributions of radiopharmaceuticals labelled with I-131.

During the past year, the Radiology Department has been greatly strengthened by the arrival of David Rollo, M.D., Ph.D., Clinical Chief of Nuclear Medicine and Dr. Edward Siegel, Chief of Radiobiology. Dr. Rollo is a physicist as well as a as a physician and is well known for his work in Nuclear Medicine instrumentatior evaluation. Dr. Siegel is equally well known for his work and will be helping us in developing our quantitative autoradiographic system. Dr. Craig Coulam, M.D., Ph.D. joined the faculty and is directing the computerized axial tomography clinical and research section in Radiology. He is a Radiologist with a Ph.D. in Bioengineering under Homer Warner, and is well known for his work at the Mayo Clinic with Earl Wood. We are currently awaiting the arrival of Dr. John Wikswo (Dept. of Physics, Stanford University) who will be joining the faculty of the Department of Physics as a Medical Physicist. We have already developed a number of areas of cooperative research with Dr. Wikswo. In order to coordinate the various scientific research programs, we have organized a new Division of Radiological Sciences, with Dr. Brill as Director (and Associate Director of Nuclear Medicine).

The staff has achieved a scientific maturity and includes will respected dedicated scientists. The problems on which we are concentrating our efforts are ones of biological significance and for which we have developed needed instrumental capabilities. The dividends from our research investments are expected to increase now that a smaller share of effort goes into systems development. The major factor that determines the rate of progress of the biological studies is the number of subjects that fit into study categories and who are willing to participate. Progress is steady, and increasing cooperation from colleagues in other departments continues to accelerate our biological study output.

The work of the group is further reflected by commitments of key people to national efforts. These include the following responsible roles:

Dr. Price	MIRD Committee
Dr. Jones	NCRP Committee 55
Dr. Erickson	BCTIC - Directory Task Group
Dr. Brill	BCTIC - Advisory Committee to ORNL
	Chairman, NCRP Committee 32 - Administered Radioactivity
	Member, NAS Subcommittee on Radioactivity in Drinking Water, and BEIR Committee
	Chairman, ANSI Committee 44 - Medical Radiation
	Chairman, IEEE Committee on Nuclear Medical Scientists, 1975-76
	Member, ORAU Human Investigations Committee

Thus, the results of efforts sponsored by this ERDA contract at Vanderbilt are significant and contribute to the main stream of knowledge in an important area - patient dosimetry from nuclear medicine diagnostic procedures.

The work sponsored by this contract was orginally directed to the evaluation of radiation exposures to humans from environmental contamination (due to fall out from weapons testing). More recently we have developed methods to measure organ doses for radioactive isotopes administered to diseased human subjects for diagnostic purposes. The techniques we have utilized permit the acquisition of sequential data from individuals so that ranges of dose can be assessed directly

1018359

rather than being limited to extrapolations from animal studies. With increasing attention to the needs for additional and new energy sources, we plan to make our unusual facilities and resources available for establishing baselines and monitoring possible changes for new large power reactors being developed in our immediate area (Hartsville TVA plants). No money from this contract will be used to support that activity directly, unless supplemental funds are sought explicitly for specific projects. The collection, and analysis of biological tissues (including placental tissue) before and following the opening of the plant is proposed, and could provide direct data on which to base discussions of risk verses benefits from needed new power sources.

1018360

A. Specific Dosimetry Projects

1. Comparative Dosimetry of Iodocholesterol Adrenal Scanning Agents

The development of I-131-19 iodocholesterol (19IC) as an adrenal scanning agent by Beierwaltes and colleagues at the University of Michigan provided an important tool for diagnosing and localizing adrenal disease. Unfortunately, photon densities are low and significant radiation doses are associated with the procedure.

In 1974, we carried out studies in 24 abnormals (adrenal disease) and 6 normals to measure the time-retention kinetics and associated radiation dose from 19IC. The results of this work were included in an earlier report. Since that time it has become apparent that the material obtained from the Pheonix Laboratories was contaminated with varying amounts of a second iodocholestrol compound, namely the ^{131}I-6-iodo methyl norcholestorol (6NC). These two compounds have now been separated, and Searle is planning to distribute the 19IC, while Phoenix Lab is preparing to distribute 6NC for adrenal visualization studies.

We have carried out studies on approximately 25 patients with various adrenal disorders using the Searle 19IC agent with approximately 10 of these patients having repeated studies after being placed on medical therapy. The results of the organ distribution measurements and the related radiation dose estimates are presented in Table 1-9 and Figures 1-7. Representative examples of the adrenal images are shown in Figure 8.

Recently we have acquired shipments of the 6NC compound and have made measurements on 4 patients. All four patients had been studied earlier with the Searle 19IC agent. The improvement of the diagnostic quality of the adrenal images (Figure 8) has been remarkable. However, the biological retention of the new agent relative to the 19IC agent appears to be significantly greater. (A comparison of the 19IC with the 6NC for the total body, liver, left upper quadrent, G.I., thyroid, and rectum and bladder regions can be found in Figures 1-7.)

Since the preliminary results with the 6NC compound look so promising from the clinical standpoint, it appears that this compound will become the favored adrenal imaging agent. In view of this with the added information from our preliminary studies that indicate a substantially increased radiation dose per unit of administered activity, we feel that it is essential to obtain a detailed knowledge of the organ distribution and metabolic fate of this new pharmaceutical. In cooperation with Dr. John Hollifield from the Department of Endocrinology, we are preparing to study an additional 20 patients using a revised protocol during the next year. The revised protocol is being implemented to ascertain whether or not diagnostic quality images can be obtained at earlier times than were required for the 19IC agent (7 to 11 days). If possible, we will propose a reduction of the administered activity which will result in a reduction in the radiation absorbed dose.

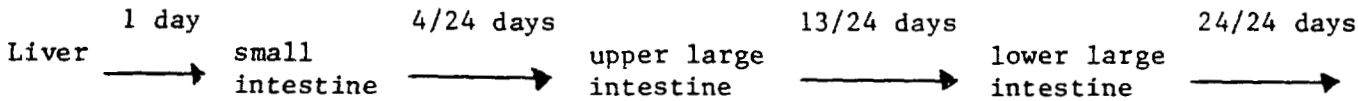
Radiation absorbed dose estimates have been completed on the 19IC compound. Preliminary dose calculations have also been made for the 6NC compound. It should be pointed out that the 6NC results are preliminary and are based on a limited number of measurements. More data will be forthcoming during the coming year.

The following two sections detail the biological data and develop the comparison of the organ distributions and corresponding dose estimates for the two compounds.

0-0836-1

I. ^{131}I-19-Iodocholesterol

Previous does estimates have been made using the model of cholesterol kinetics proposed by Bernard and Hayes. The model (shown below) is a catenary compartmental model which assumes instantaneous uptake of the material in the liver with an unidirectional flow in sequence through the small intestine first and then through the large intestine exiting in the feces. The model assumes no reflux, retention or transfer of activity across the intestine wall.



Utilizing the data presented in Figures 1-8, we have generated the data presented in Figure 9 in an effort to substantiate this model. In Figure 9, we have generated the liver and integrated entire G.I. tract activity curves. The curves were generated assuming the liver and right upper quadrant data on day 0 constituted liver activity and that the sum of the left upper quadrant, mid G.I., and the rectum at all other measurements constituted integrated G.I. activity. The resulting curves showed amazingly good agreement with the model prediction. The liver was found to have an uptake of approximately 72% with a monoexponential release of the activity with a half-life of approximately 1 day. The G.I. activity was observed to have a delayed peak occuring at day 1 with a subsequent monoexponential decay of approximately 1.5 days.

The total body retention curve also corroborates the liver measurement by displaying an exponential component with an approximately 2 day half-life and an intercept of approximately 70%. This is interpreted as the fraction of the material that is eliminated via the G.I. tract (72%). The remaining activity (28%) was assumed to be uniformly distributed in the total body and eliminated via the urine with a biological half-life of 1.5 days.

The thyroid data was used to estimate an average uptake of $\sim$ 1%. It was assumed to have an effective half-life equal to the physical half-life.

1018362

The adrenal activity was taken to be 0.1%. These data were based upon surgical samples and were assumed to come from a normal sized gland of 16 g. The effective half-live was also taken to be equal to the physical half-life. Having established the consistency of the model for the 19IC agent, the model was used to determine the following cumulative activities for the liver, small and large intestines.

Cumulative Activity

^{131}I-19IC

Organ	$\tilde{A}$ ($\frac{\mu Ci \cdot hours}{\mu Ci\ administered}$)
Total Body	12.7
Liver	22.5
Thyroid	2.8
Adrenals	0.28
Small Intestine	3.81
U. Large Intestine	11.02
L. Large Intestine	18.10

The cumulative activity was then used along with nuclear data shown Table 8 . To generate the continuation of the penetrating and non penetrating components of the absorbed dose. The results of these calculations are shown in table 2 and summarized in Table 3 .

1018363

Table 1

I-131-19-Iodocholesterol

(% of Administered Activity)

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Total Body	1.00	1.02 ± .71	.38 ± .06	.19 ± .07	.15 ± .07	---
Liver	.60 ± .05	.33	.08 ± .03	.04 ± .01	.03 ± .01	---
Upper Left Quadrant	.12 ± .03	.12	.06 ± .03	.04	.03 ± .01	---
Mid GI	.03	.05	.04 ± .02	.02 ± .01	.010 ± .006	---
Bladder & Rectum	.06 ± .01	.07	.05 ± .04	.027 ± .002	.02 ± .01	---
Thyroid	.05 ± .04	.03	.02 ± .01	.02 ± .01	.04 ± .02	---
Unaccounted For	.15 ± .06	.08 ± .06	.05 ± .03	.05 ± .03	.02 ± .01	---

	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Total Body	.16	.05 ± .02	.049 ± .009	.065	.04 ± .03	.017 ± .007
Liver	.032	.008 ± .004	.005	.008	.010	.003
Upper Left Quadrant	.02	.006 ± .005	.007 ± .004	.027	.002	.002 ± .001
Mid GI	.01	.004 ± .003	.004	.01	.003 ± .001	.002 ± .003
Bladder & Rectum	.01	.005	.005 ± .002	.001	.003	.002 ± .001
Thyroid	.06	.01 ± .01	.010 ± .017	.0006	.04	.006 ± .005
Unaccounted For	.02	.01 ± .01	.016 ± .008	.02	.010 ± .007	.004 ± .002

1018364

Table 1 Ctd.

I-131-19-Iodocholestero:

(% of Administered Activity)

Continued

	Day 12	Day 13	Day 14
Total Body	.015 ± .003	---	.008 ± .003
Liver	.003	---	.002
Upper Left Quadrant	.002	---	.001
Mid GI	.002 ± .001	---	.001
Bladder & Rectum	.001	---	.001
Thyroid	.002	---	.002 ± .003
Unaccounted For	.005 ± .002	---	.004

1018365

Table 2

19IC

Average Dose ($\bar{D}p$ rads/mCi)

(Penetrating Component)

Target/Source	Total Body	Liver	Small Intestine	ULI	LLI	Total (rads/mCi)
Total Body	0.049	0.107	0.020	0.058	0.096	0.330
Liver	0.059	1.600	0.020	0.060	0.017	1.756
S. I. Wall	0.068	0.102	0.330	0.374	0.046	0.920
ULI Wall	0.071	0.158	0.245	0.896	.0.214	1.584
LLI Wall	0.065	0.019	0.073	0.091	2.552	2.800

(Non-penetrating Component)

Organ	$\bar{D}np$
Total Body	0.075
Liver	5.06
S.I.	0.928
U.L.I.	10.90
L.L.I.	23.4
Thyroid	58.2
Adrenal	7.3

1018366

Dose Summary ($\bar{D}$ rad/mCi)
(19-IC)

Organ	$\bar{D}p$	$\bar{D}np$	$\bar{D}$ total
Total Body	0.330	0.075	0.405
Liver	1.756	5.06	6.82
S.I. Wall	0.920	0.928	1.848
ULI Wall	1.584	10.90	12.48
LLI Wall	2.800	23.4	26.2
Thyroid	---	58.2	58.2
Adrenal	---	7.3	7.3

1018367

Table 4

6 Nor Methyl

(% of Administered Activity)

	Day 0	Day 2	Day 4	Day 5	Day 7	Day 11
Total Body	1.00	.69 ± .10	.33 ± .01	.35	.22 ± .05	.16 ± .09
Liver	.53 ± .09	.20 ± .03	0.079 ± .002	.06	.05 ± .01	.04 ± .02
Upper Left Quadrant	.23 ± .02	.11 ± .01	.05 ± .01	.08	.05 ± .009	.02 ± .02
Mid GI	.05 ± .03	.06 ± .01	.032 ± .004	.08	.02 ± .01	.02 ± .02
Bladder & Rectum	.08 ± .02	.148 ± .022	.075 ± .002	.060	.05 ± .02	.03 ± .01
Thyroid	.03 ± .01	.023 ± .009	.023 ± .009	.014	.02 ± .02	.008 ± .002
Unaccounted For	.08 ± .04	.11 ± .01	.09 ± .02	.06	.05 ± .01	.028 ± .002

1018368

II. ^{131}I-6 Iodomethyl Norcholesterol (6NC)

Initial attempts at dose estimates for the 6NC agent paralleled the approach used for the 19IC agent, namely to use the model of Bernard and Hayes (see the section on 19IC). Further analysis indicated that the 6NC data were inconsistent with the model. Figure 11 is the equivalent data for the 6NC agent as was presented earlier for the 19IC agent in Figure 10. The liver in the compound exhibits a distinct two component behavior with the longer component being $\sim$ 7 days. Likewise the G.I. tract exhibits a similar long term transit ($T_{\frac{1}{2}} \sim 6$ days). These data are also corroborated by the total-body retention presented in Figure 1. The data suggest the presence of either another metabolically independent source of activity included in these regions of interest or a more complicated flow through the G.I. tract. Possible absorption or adherance of the compound in the intestines.

Because of these observations we are investigating other models in an effort to obtain a self consistent description of the data. With the lack of an appropriate model, we have made preliminary estimates of the dose to the total body, liver, adrenals, and thyroid using sums of exponentials to describe the retention functions.

$$\text{Total Body} = 9.24e^{\frac{-0.693}{1.5}t}$$

$$\text{Liver } (t) = 0.68e^{-\frac{0.693}{1.0}t} + 0.08e^{-\frac{0.693}{7.0}t}$$

$$\text{Thyroid} = 0.01e^{-0.0t}$$

Using the above retention equations and the nuclear data presented in Table 8 , radiation dose estimates were calculated. The results of these calculations are presented in summary in Table 5-6.

C. Comparison of 19IC and 6NC

A number of preliminary conclusions may be drawn based upon the comparison of the organ distribution and biological retention of the two compounds. It should be pointed out that the results of the 6NC compound are still preliminary and may change with additional measurements.

1. The 19IC compound appears to obey the classical cantonary model of G.I. transfer. The liver was observed to approximate a classical compartmental system with a monoexponential transit. The 6NC compound on the other hand presented a liver retention displaying at best a two component clearance making it inconsistent with the classical mode. The question arises as whether metabolic paths have been included in the liver region of interest. In particular does the increased adrenal activity now interfere with the liver measurement. As will be discussed later, we are attempting to resolve the liver from the adrenal using a longitudinal tomographic scanner. The doses we have calculated have assumed the liver measurement to be free of other overlapping pools.

2. The 6NC appears to have a larger fraction of the material going to the G.I. system. This fact coupled with the increased retention (due to what ever reason) all serves to increase the dose per unit of administered activity

0018369

relative to the 19IC agent. As shown in Table 7, the dose to the liver from the 6NC is increased by approximately a factor of 1.6 over the liver dose from 19IC. We anticipate a commercially increased dose to the samll and large intestines.

3. The uptake of the 6NC in the adrenals is much greater than that of the 19IC. Although this leads to larger doses if one continues to use the same level of injected dose--the natural course is to reduce the level of the administered activity.

Table 5

Cumulative Activity

6NC

Organ	$\sim \frac{\mu Ci \cdot hour}{\mu Ci}$ A
Total Body	10.9
Liver	33.0
Thyroid	2.8
Adrenal	---

Table 6

Dose Summary

($\overline{D}$ rad/mCi)

6NC

Organ	$\overline{Dp}$	$\overline{Dnp}$	$\overline{D}$ total
Total Body	0.121	0.064	0.19
Liver	2.40	7.59	9.99
Thyroid	---	58.2	58.2

Table 7

Dose Comparison

$\overline{D}$ (rad/mCi administered)

Organ	19IC	6NC
Total Body	0.045	0.19
Liver	6.82	9.99
Thyroid	58.2	58.2
S.I.	1.85	---
U.L.I.	12.5	---
L.L.I.	26.2	---

I018371

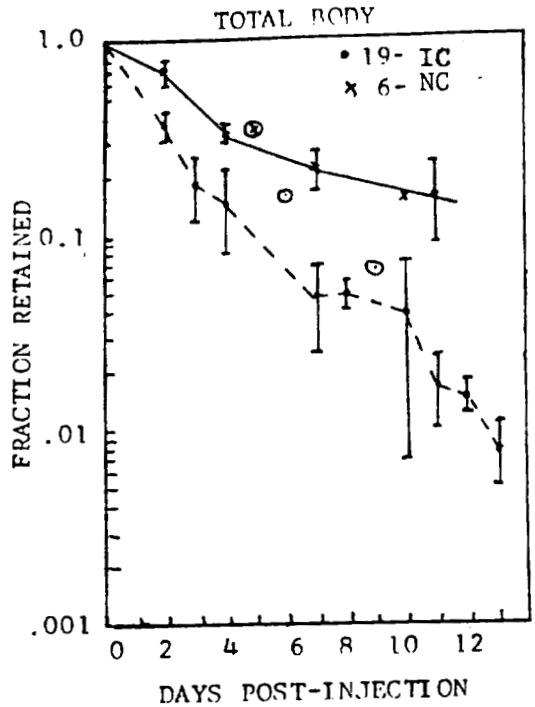


FIGURE 1

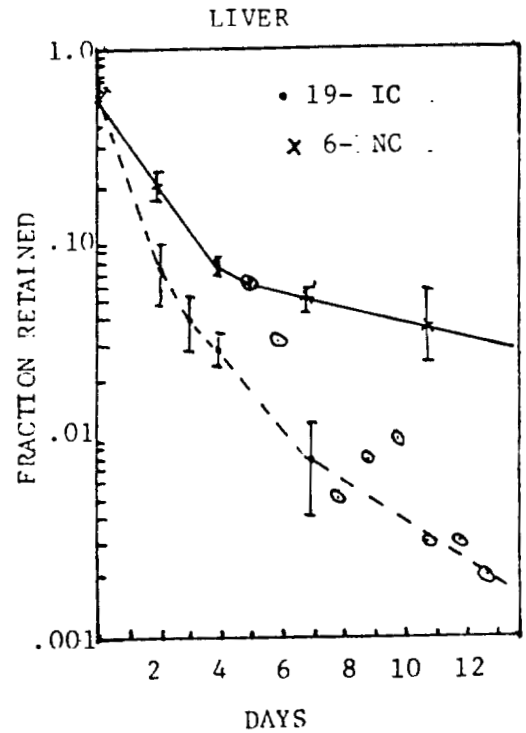


FIGURE 2

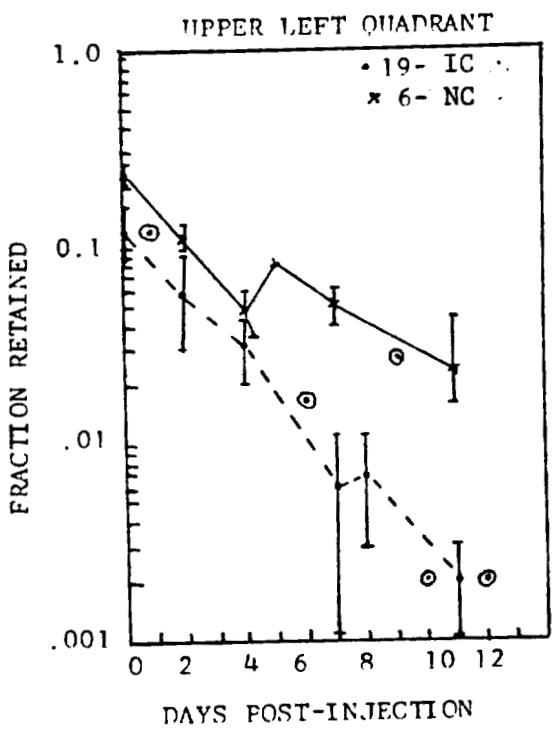


FIGURE 3

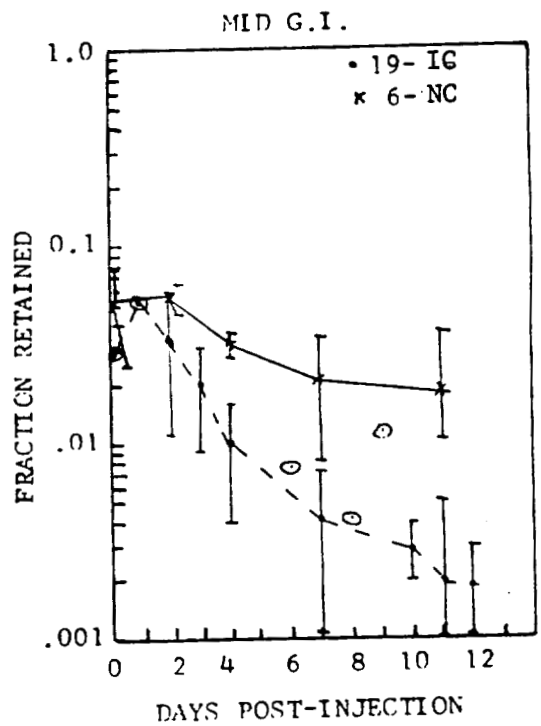


FIGURE 4

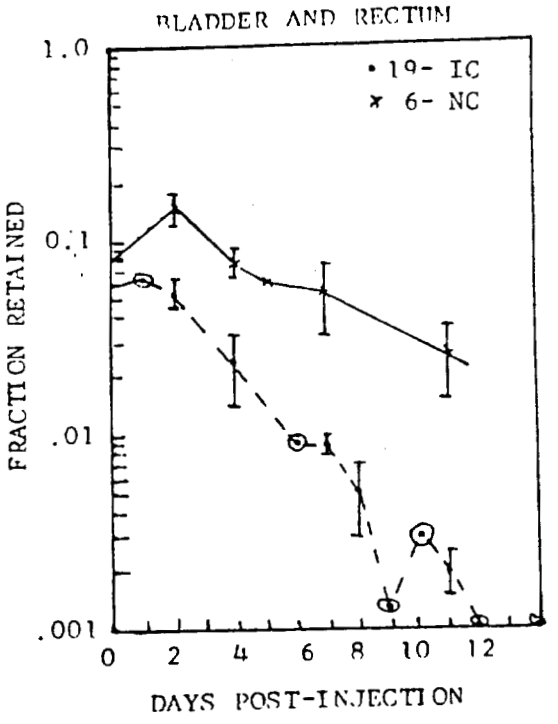


FIGURE 5

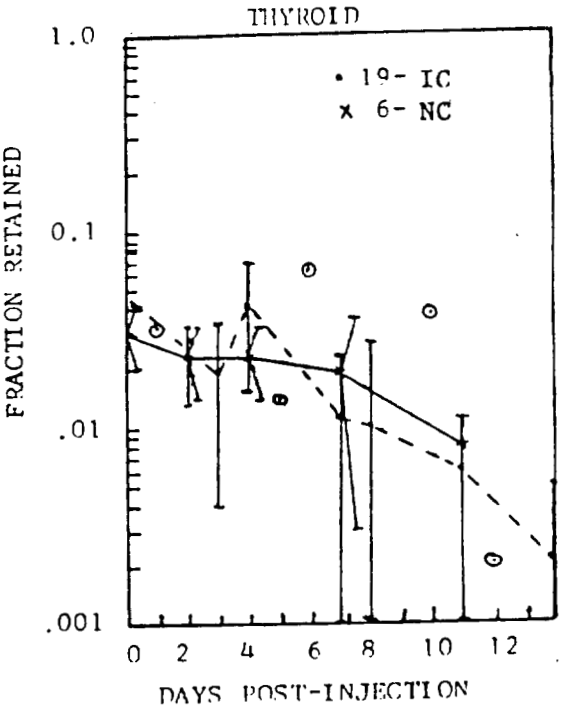


FIGURE 6

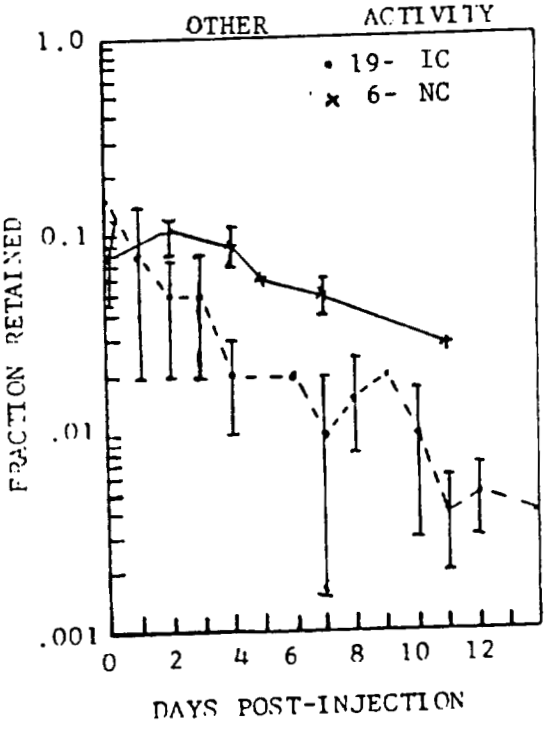
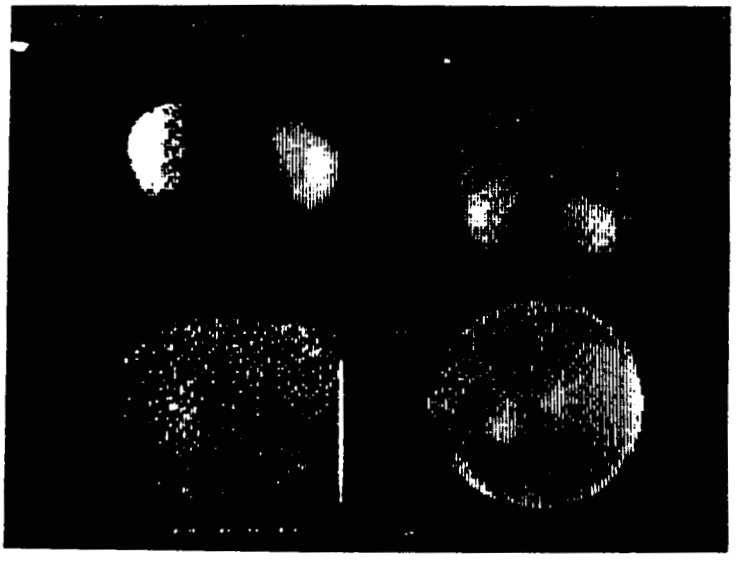


FIGURE 7

1018373

DAY 7

19 IC 6 NC

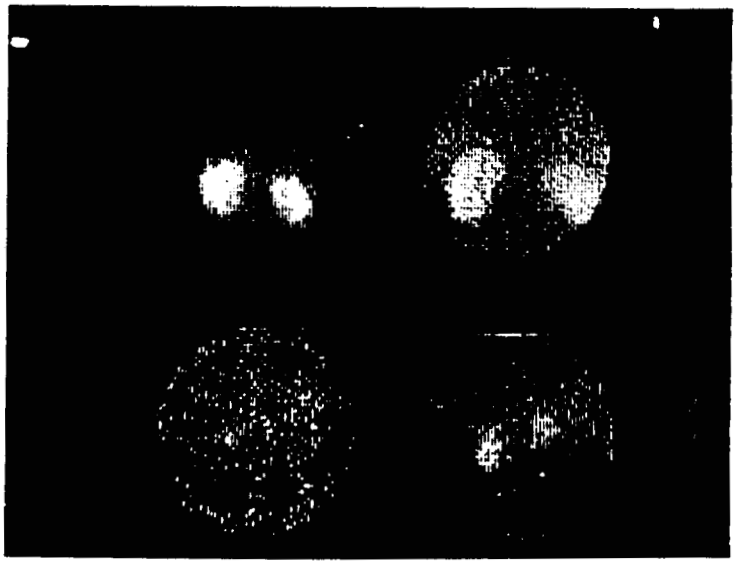


KIDNEY
Tc-DMSA

ADRENAL

DAY 11

19 IC 6 NC



KIDNEY

ADRENAL

FIGURE 8

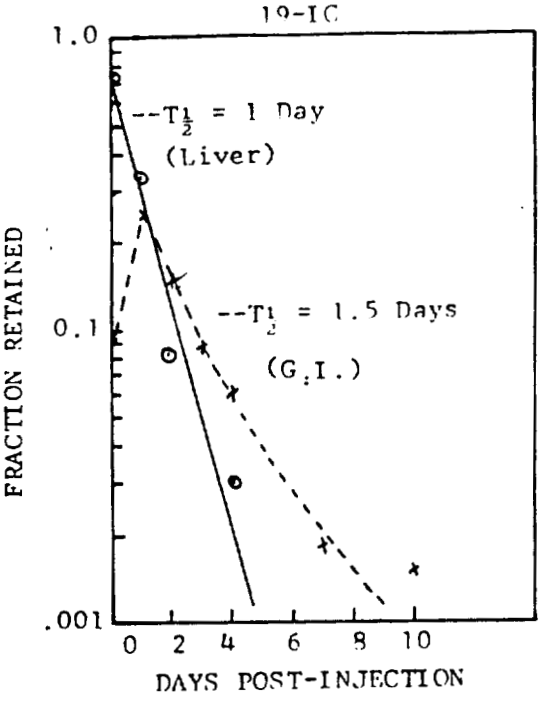


FIGURE 9

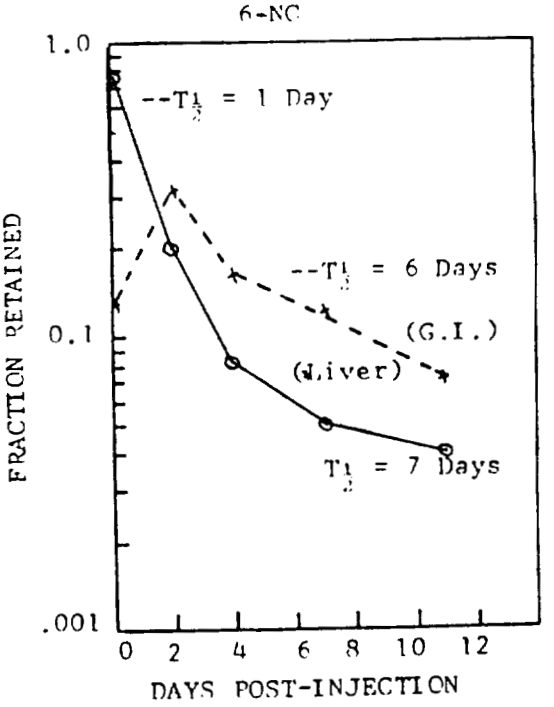


FIGURE 10

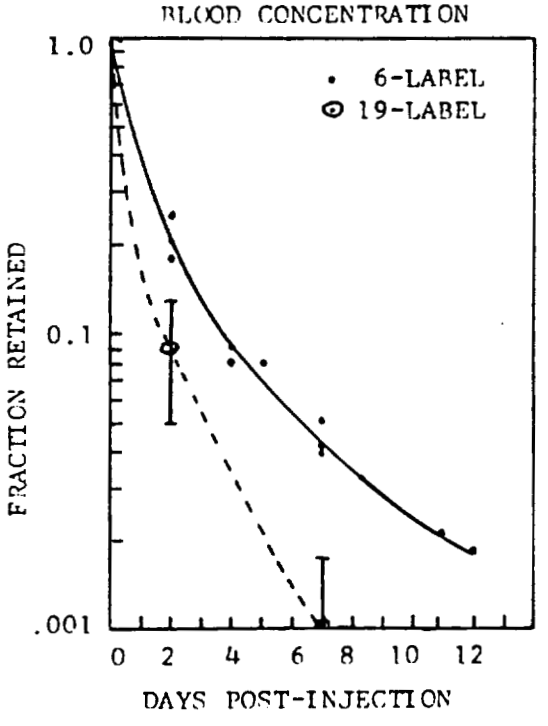


FIGURE 11

Table 8

Nuclear Data (MIRD Pamphlet No. 2)

Radionuclide	^{131}I
Physical half-life	8.05 days
Decay Constant	3.59×10^{-3} hours $^{-1}$
Δ (equiliberium dose constant for nonpentrating radiation)	$0.4135 \frac{g \cdot rad}{\mu Ci \cdot hour}$

Prinicple Photons

	Ei	Δi
Ei, energy	0.0801	0.0030
	0.1772	0.0005
Δi (equilibruim)	0.2843	0.0288
(dose constant)	0.365	0.6477
	0.5 - 0.72	0.1211
	K X-rays	0.0030

1018376

Table 9

Blood Levels

(% of Administered Dose)

Compound	Day 0	Day 2	Day 3	Day 4	Day 7	Day 11
19IC	100	---	9.3 ± 4.2	---	1.0 ± 0.5	0.3 ± 0.1
6NC	100	21.2 ± 3.6	---	8.5 ± 0.7	4.4 ± 0.6	2.0 ± 0.1

1018377

2. Iron-59 Citrate Dosimetry in Abnormal Human Subjects

During the past year, we have continued our work to make quantitative measurements of the absolute organ distribution of intravenously administered Fe-59 citrate in abnormal subjects. In cooperation with Dr. Sanford Krantz of the Department of Hematology, we are carrying out detailed studies on a selected group of patients with suspected and proved red-cell aplasia. Our work has allowed us to observe how the kinetics of the radioiron and the resulting organ distributions may vary greatly from patient to patient depending upon the stage of the disease. The kinetic data we have collected and are using to make dosimetric estimates are also proving useful to Dr. Krantz as an aid to establishing the stage of the disease.

A draft of a paper describing the results of our work on a group of patients who were in remission of the disease has been included as an appendix to our current report. The paper is entitled "Studies on Red Cell Aplasia: Ferro-kinetics During Remission of the Disease". In this paper we have attempted to compute the marrow retention curve of the radioiron in six (6) patients who are in remission of the disease. Dosimetrically, we have determined that the red marrow is the critical organ for patients in full remission while the liver and spleen are the critical organs at other stages of the disease. During remission we have observed great expansions of the active red marrow sites to the knees, ankles, elbows and the long bones of the arms and legs. We have also observed that the expanded marrow sites may also be accompanied by a prolonged transit time for the radioiron resulting in an increased radiation dose to the marrow. We have attempted to estimate the total marrow radioiron retention curve for each of the patients in this group. The results of these measurements are seen in Figure 1-3. These curves are also used to estimate the marrow dose from radioiron within the marrow.

Time-activity curves were generated for the pelvic marrow at approximately one day intervals for an average period of 10 days. Images of the total-body distribution of the radioiron were also made on a daily basis. The time-activity curves for the total marrow were estimated from the direct measurements of the pelvic marrow space. The pelvic marrow transit curve at 24 hours was taken to be equal to the total-body radioiron content minus the liver and spleen content. Two assumptions were that there was no significant circulating level of radioiron at 24 hours and that the liver and spleen constituted the entire storage pool exclusive of marrow. Based upon time-activity curves generated in this manner marrow transit-times were determined. The transit-time was defined as the time interval between the 50% levels of the maximum radioiron uptake in the marrow that occurred during the uptake and release phases. In a manner similar to that described by Finch the plasma clearance and red cell utilization curves were also used to estimate the total marrow activity curves. In this method one assumes the marrow uptake of the radioiron to be proportional to the inverse of the plasma clearance and the marrow release of the radioiron to be proportional to the inverse of the red cell incorporation curve. The curve is then normalized to the maximum activity incorporated into the circulating red cells. An assumption of this method is that the maximum circulating red cell activity is equal to the maximum uptake in the erythropoietically active marrow pool.

The patients in our current study group were classified into three groups with respect to their marrow transit curves. We have observed that the transit curves frequently exhibit two distinct transfer components. We have chosen to describe these two components as (1) erythropoietic (rapid, T-1/2 approximately 3 days) and (2) storage (T-1/2 approximately ∞).

0018378

In the normal the second (storage) component is extremely small while in some abnormals the reverse is true. It is the presence and magnitude of the storage components that is the prime contributor to the dose. As shown in Table 1 the three classes have been defined as follows:

A. No significant storage component
B. No significant erythropoietic component
C. Both components present

We have investigated the variation in the radiation dose to the marrow between these three groups. The results of these calculations are shown in Table 2. As seen in the table the marrow dose may be as much as a factor of 19 higher in those patients with significant marrow storage of the radioiron. We hope to be able to extend these measurements and calculations to a larger patient population.

The MIRD Committee in the United States has created a task group to gather dosimetric information from the medical uses of Fe-59 citrate. Dr. Price is a member of this task group and we are working in cooperation with Dr. Pollycove at the Donner Laboratory of the University of California and Dr. Johnston at the University of North Carolina to create a single data base. Vanderbilt's SAAM-25 iron kinetics model has been chosen to be used for the calculation of the cumulative organ activity (A) for the compiled normal and abnormal studies. The results of these measurements and calculations will be published by MIRD. A draft of this document is included as an appendix to our current report.

During the coming year, we propose to continue our relationship with Dr. Krantz and staff of the Division of Hematology and will study approximately 10 more patients in an effort to categorize the dosimetry and kinetics of different disease states.

Dose estimates to date have been made assuming a standard man model. For many of these disease states, the liver and spleen may be enlarged in addition to an expanded or diminished red marrow volume. The effects of these volume differences could be significant and will be investigated. Liver and spleen volume estimates will be made using ultrasonic scans, or with CAT body scans whenever possible. Estimates of the regional marrow volume will be made using the projected area from the Fe-59 scans.

It is known that the marrow spaces in some abnormal states contain a significant amount of the iron storage component. To resolve the functioning marrow components from the storage components using external marrow measurements, we propose to use simultaneous scans of In-111 transferrin and Fe-59. The assumption is that the In-transferrin communicates only with the ferritin hemosiderin (storage) pools and not with the hemoglobin (erythropoietic) pool, and thus, we can use the In-111 distribution to measure the storage pools of the marrow sites for Fe-59. The dosimetric implications of the separation are significant since the kinetics of the two components are so different. Fe-59 labelled to hemosiderin but residing in the marrow space would have an essentially infinite biological half life, whereas Fe-59 labelled hemoglobin leaves the marrow in a matter of a few days. We have proposed to study 10 new subjects this year and will carry out the simultaneous In/Fe study whenever possible.

1018379

Table 1

Cumulative Activity

$\tilde{A}$ ($\frac{\text{uCi days}}{\text{uCi adm.}}$)

	Patient Group	$\tilde{A}$
A	Patients with no significant storage component	2.40 - 3.66
B	Patients with no significant erythropoietic component	19.4
C	Patients with both storage and erythropoietic function	40.0

Table 2

Average Radiation Dose to the Red Marrow

($\bar{D}$ rad/uci adm.)

Group	$\bar{D}$np (nonpenetrating)	$\bar{D}$p (penetrating)	$\bar{D}$ (total)
A	0.008 - 0.012	0.003 - 0.005	0.011 - 0.017
B	0.066	0.027	0.093
C	0.136	0.055	0.191

1018380

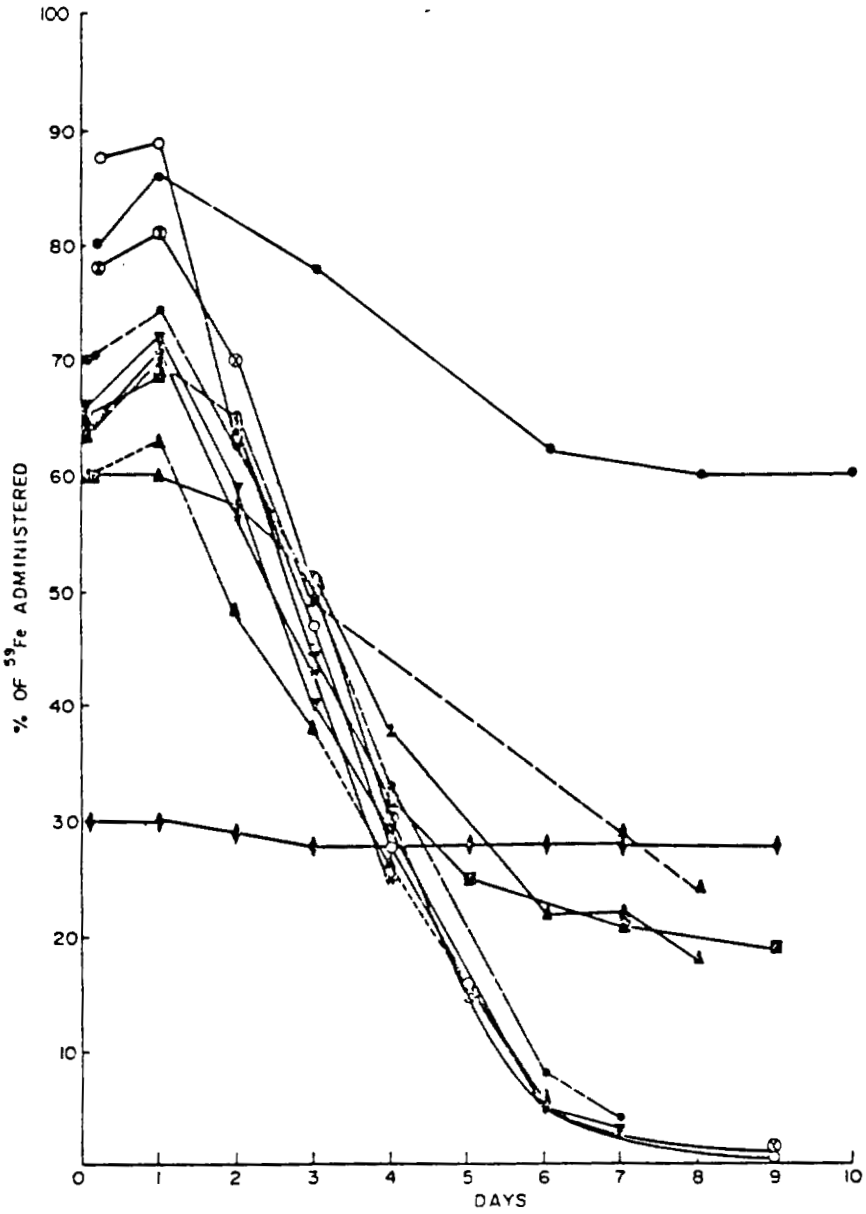


Figure 1. Marrow radioiron transit time curves. Normal volunteers o - o and o——o. Patient number 6 with PRCA ◊—◊. Patients with PRCA in remission: number 1, Oct., 74 △—△, June, 75 △- - -△, and Nov., 76 △—△, number 2, Nov., 73 o——o and Aug., 76 o- - -o; number 3, □—□; number 4, ▽—▽; number 5, *——*.

PRCA = pure red cell aplasia

1018381

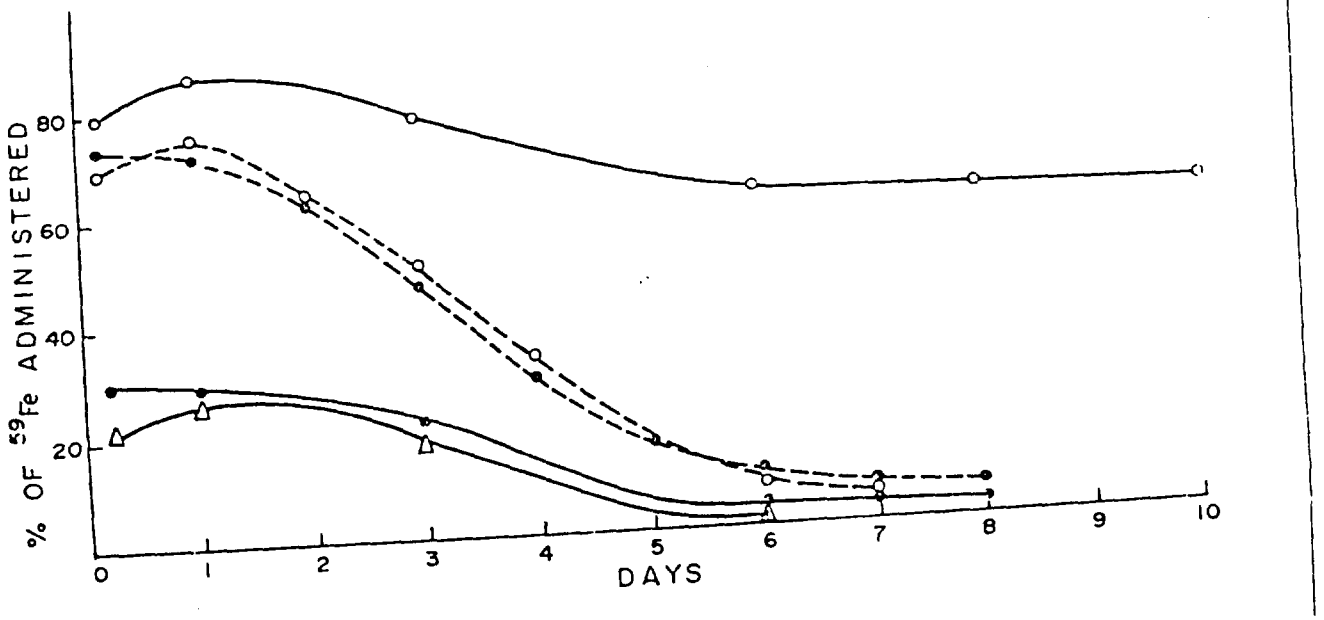


Figure 2. Comparison of marrow transit time curves for patient number 2 determined by two methods. Transit time curves derived by direct measurement of radioiron activity in the pelvis are compared with curves calculated from circulatory levels of radioiron in the plasma and red cells (14). Measurements were made in 1973 shortly after remission of PRCA and in 1976. Direct measurement Nov., 1973 (o——o); calculated from blood levels Nov., 1973 (o——o); direct measurement Aug., 1976 (o---o); calculated from blood levels Aug., 76 (o---o). Direct measurement of Nov., 1973 after subtracting day 10 activity (Δ——Δ).

1018382

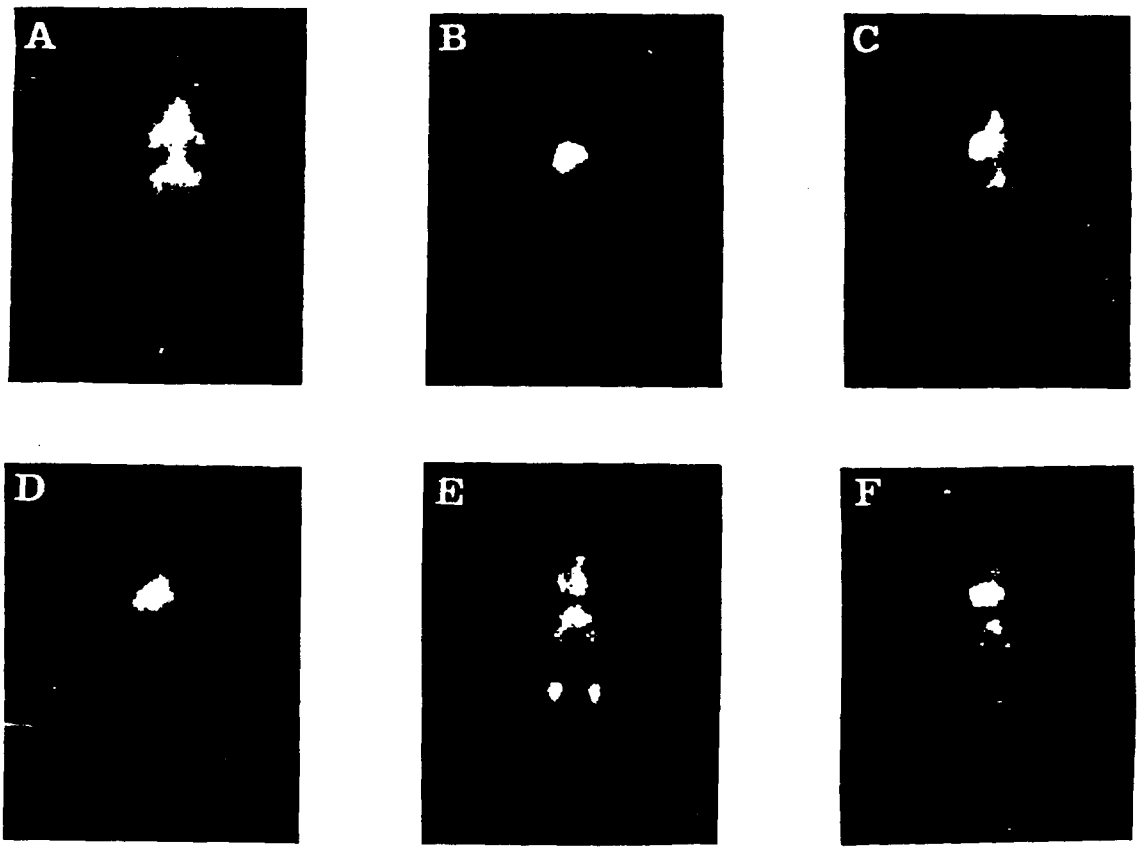


Figure 3. Surface organ scanning (A) Normal volunteer. (B) Patient number 6 with PRCA. (C,D,E,F) Patients with PRCA in remission showing (C) normal marrow distribution of ^{59}Fe in patient number 3, (D) moderate extension of bone marrow into lower extremities in patient number 5, (E) marked extension of bone marrow in patient number 2 in first study after remission, and (F) reduction of marrow extension in patient number 2 three years later.

PRCA - pure red cell aplasia

0018383

3. Evaluation of the Standard Man Model for Dosimetry Calculations - Comparison with Laboratory Measurements

One of our staff, Dr. Jerry Jones, is a member of NCRP Scientific Committee No. 55, charged to report on the accuracy of internal dosimetry calculations and make recommendations for further research. Although no official recommendations have been made, some discussion has been given to the following two projects:

1. Distribute replicas of the MR. ADAM phantom to various laboratories for both internal and external measurements.

2. Support the calculation of external photon energy spectra (due to internal sources), which could then be compared to spectral measurements on humans.

We plan to pursue the acquisition of such model spectra for various radiopharmaceutical distributions through committee members and researchers at Oak Ridge National Laboratory. There are several reasons why calculated spectra are desirable. The dose per emitted photon to a detector placed external to a human can be determined from the spectrum for a wide range of detectors (TLD's or ionization devices). This would give researchers greater flexibility in the choice of detector, while allowing them to make meaningful comparisons between their measured doses and doses calculated from models. Also, the small doses received by external detectors on nuclear medicine patients (usually less than 50 mrads) put severe limits on the accuracy of dose measurements with many types of detectors. However, spectroscopy detectors such as NaI(Tl) and Ge(Li) are commonly used at very low dose levels, so measurements of photon spectra emerging from nuclear medicine patients should be relatively quick and easy to perform. Either spectral measurements or dose measurements can be analyzed to evaluate the effects of different human sizes, shapes, and medical conditions (including children) on the applicability of model calculations, and with a minimum of discomfort for the human subjects.

In conjunction with this work, we also plan to use our graphics hardware and software with computed tomography images to investigate the attenuations effects in patients as compared to the standard man model. Assuming a uniform distribution of activity within a body subregion, we can express the effects of self-attenuation in terms of attenuation coefficients and geometry (location and thickness of source as compared to total body thickness). The equations expressing these effects were originally derived to estimate Tc-99m activity in the liver from external scanning measurements. These equations can be used to compare the counts from activity in a patient to those from an equal amount of activity in the standard man model. The advantage to this approach is that one is only simulating the activity in the patient--no injections or emission scans are done. Similarly, there is no need to scan the standard man phantom, because its geometry is defined in MIRD Pamphlet No. 5 and related publications. Thus one is using the human and model geometries to compare their attenuation differences for uniform source distributions. In addition, volume determinations of organs in patients are part of the currently available software. There is also considerable interest among the physicians in our department in liver and kidney volume determination and this will help assure an adequate supply of patients from whom data can be obtained.

1018384

A. 4. Radiation Sensitivity of the Thyroid During I-131 Therapy

Information on iodine uptake, the effective half-time of its retention in the thyroid and thyroid mass are used in calculating the amount of I-131 to be administered to patients in the treatment of hyperthyroidism. A major variable, however, which we have not yet learned how to assess is radiation sensitivity of the thyroid.

In our work on iodine kinetics, to date, we have evaluated iodine metabolism in large numbers of patients during treatment of thyrotoxicosis and have determined model parameters which are reasonable predictors of absorbed radiation dose to the thyroid, given knowledge of thyroid gland size.

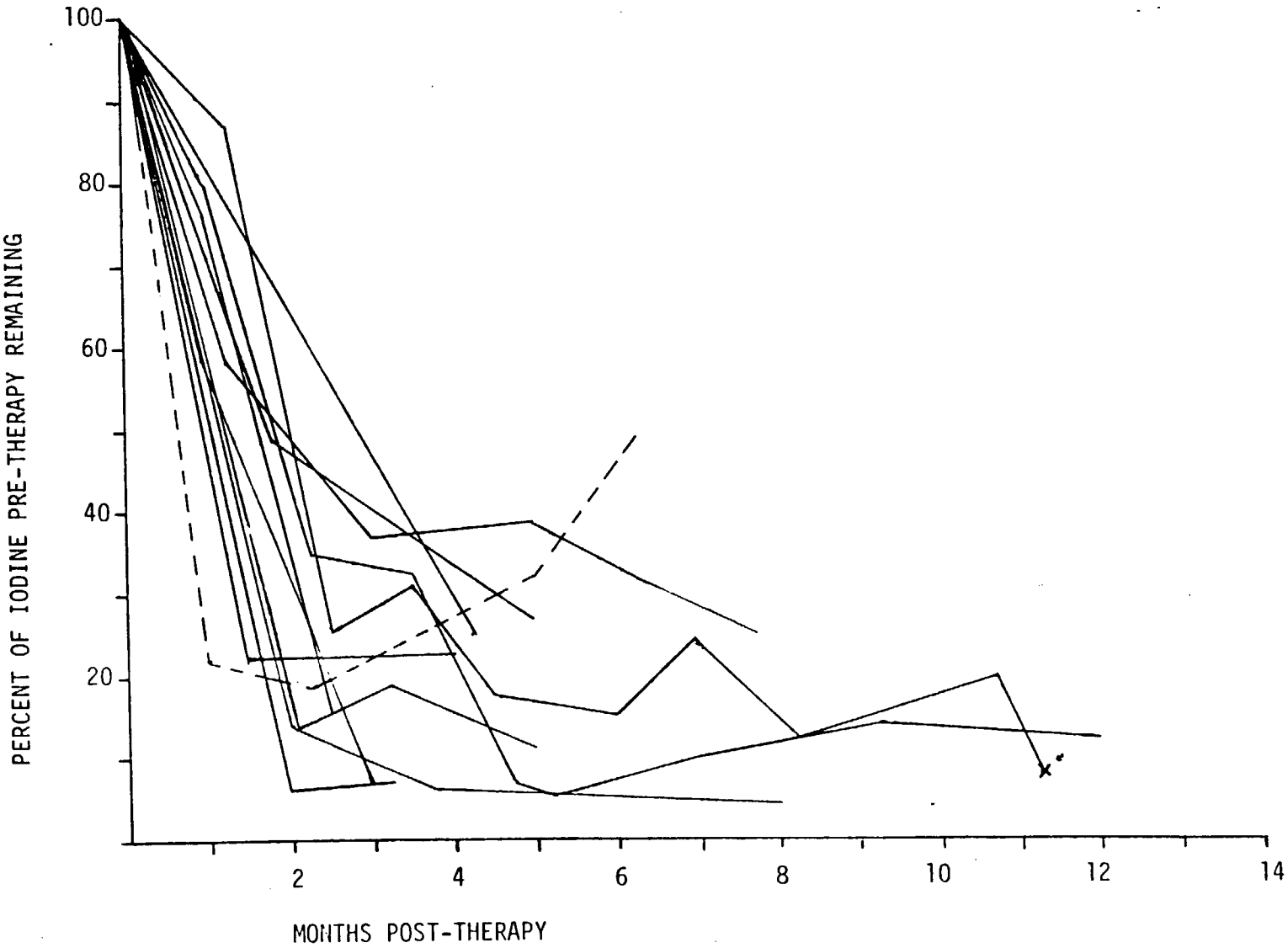
To evaluate thyroid sensitivity, we need to measure a parameter that reflects damage to the thyroid. The rate of loss of iodine from the gland following therapy is due to altered rates of release from the gland and by diminution of uptake. We have measured the iodine content of the gland after therapy by means of x-ray fluorescence scanning in a large number of patients in an attempt to determine if predictions of hypothyroidism can be made from the early changes in iodine content after therapy. We are currently measuring iodine content and other thyroid function parameters in 45 patients who have received radioiodine therapy. These patients have been followed for as long as 14 months post-therapy. These data are shown in Figures 1 - 4. The data are separated in two ways. Figures 1 and 2 show the data grouped in two categories, one with initial iodine content less than 15.5 mg. (1 standard deviation above the normal mean) and the other greater than 15.5 mg. The x at the end of a particular patient's curve indicates that the patient became hypothyroid and was placed on replacement medication at that time. We currently have six patients in that category. The second grouping is shown in Figures 3 and 4. These figures separate the patients into those who had anti-thyroid medication before and after therapy and those who did not. Two patients relapsed into hyperthyroidism (shown by dashed lines in the figures) and received a second therapy dose. We have collected blood samples from many of these patients throughout their course of study. These samples have been frozen until the thyroglobulin radioimmunoassay is established. We will then determine thyroglobulin and TSH levels and correlate these with the iodine content data to attempt to predict which patients will become hypothyroid on the basis of these data.

From the data shown in Figure 1 - 4, it appears that the loss of iodine from the gland is very rapid with most of the glands reaching a minimum in about two months. We have attempted to obtain data on the iodine content at short intervals after therapy but have been unable to make valid measurements at times less than one month post-therapy due to the inability to resolve the iodine K_α x-rays (from the fluorescence of stable iodine) at 28.5 keV and the xenon K_α x-rays (from the daughter of I-131) at 29.7 keV. These early changes in iodine content should be studied and we will attempt to develop techniques to do this in the coming year. At the time an iodine content measurement is performed by x-ray fluorescence, an energy spectrum will also be collected

in a multichannel analyzer. By utilizing spectral analysis techniques, we should be able to determine the contribution in the iodine x-ray window due to the detection of xenon x-rays and thus obtain a factor to be used in correcting the iodine content measurements. We should then be able to study the early changes in iodine content after therapy and determine if there is additional information available in this early phase.

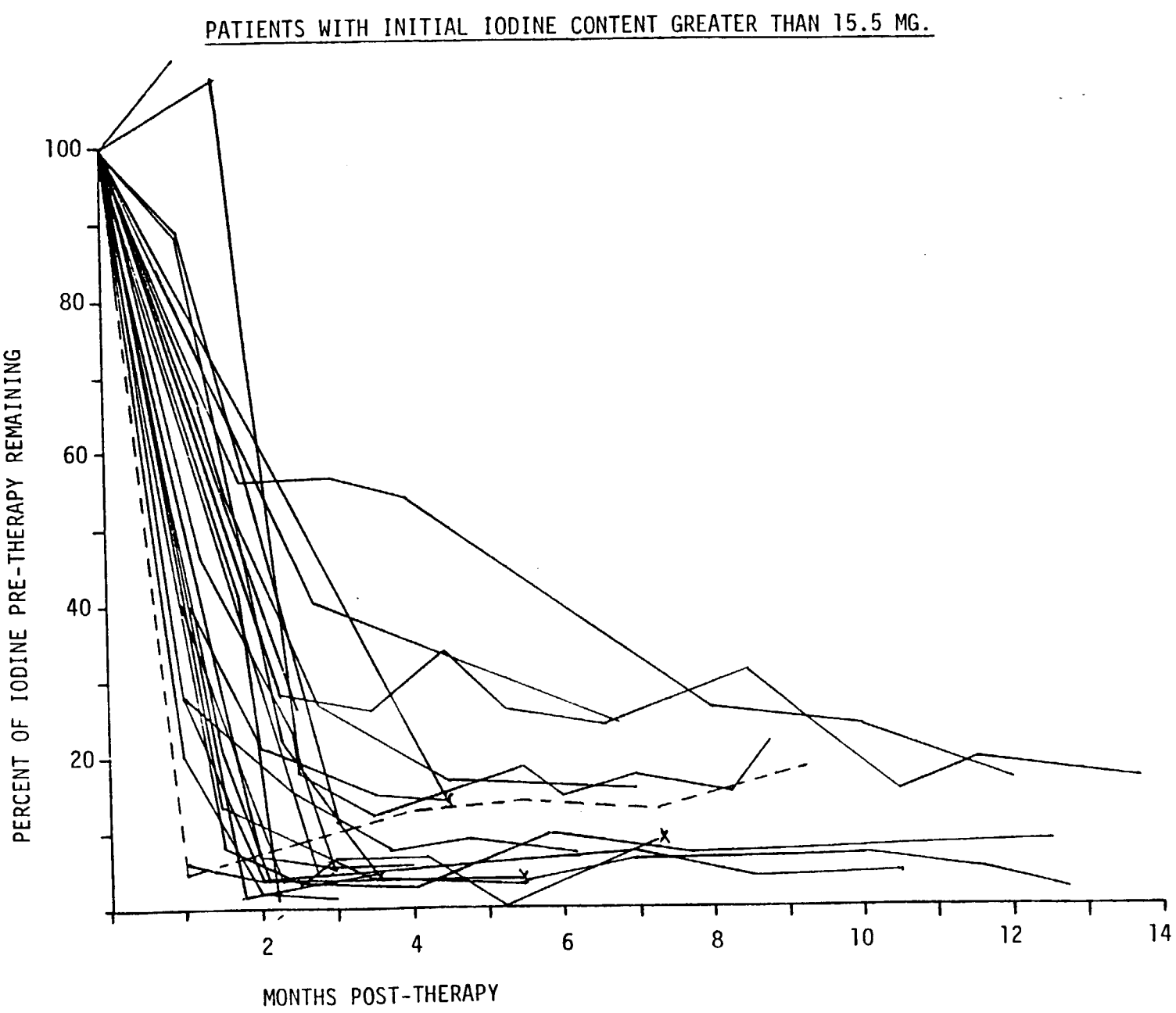
1018386

PATIENTS WITH INITIAL IODINE CONTENT LESS THAN 15.5 MG.



1018387

Figure 1



1018388

Figure 2

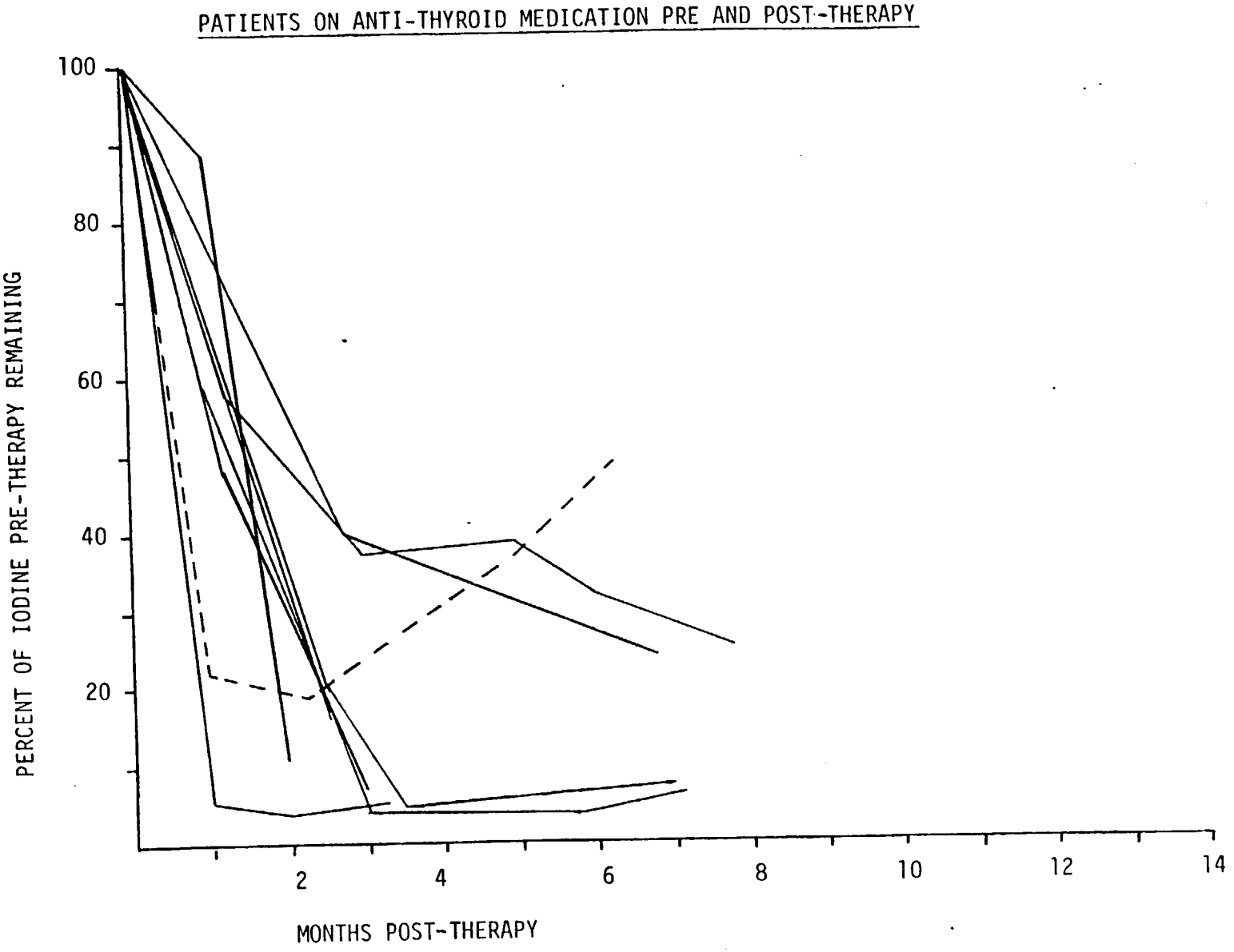
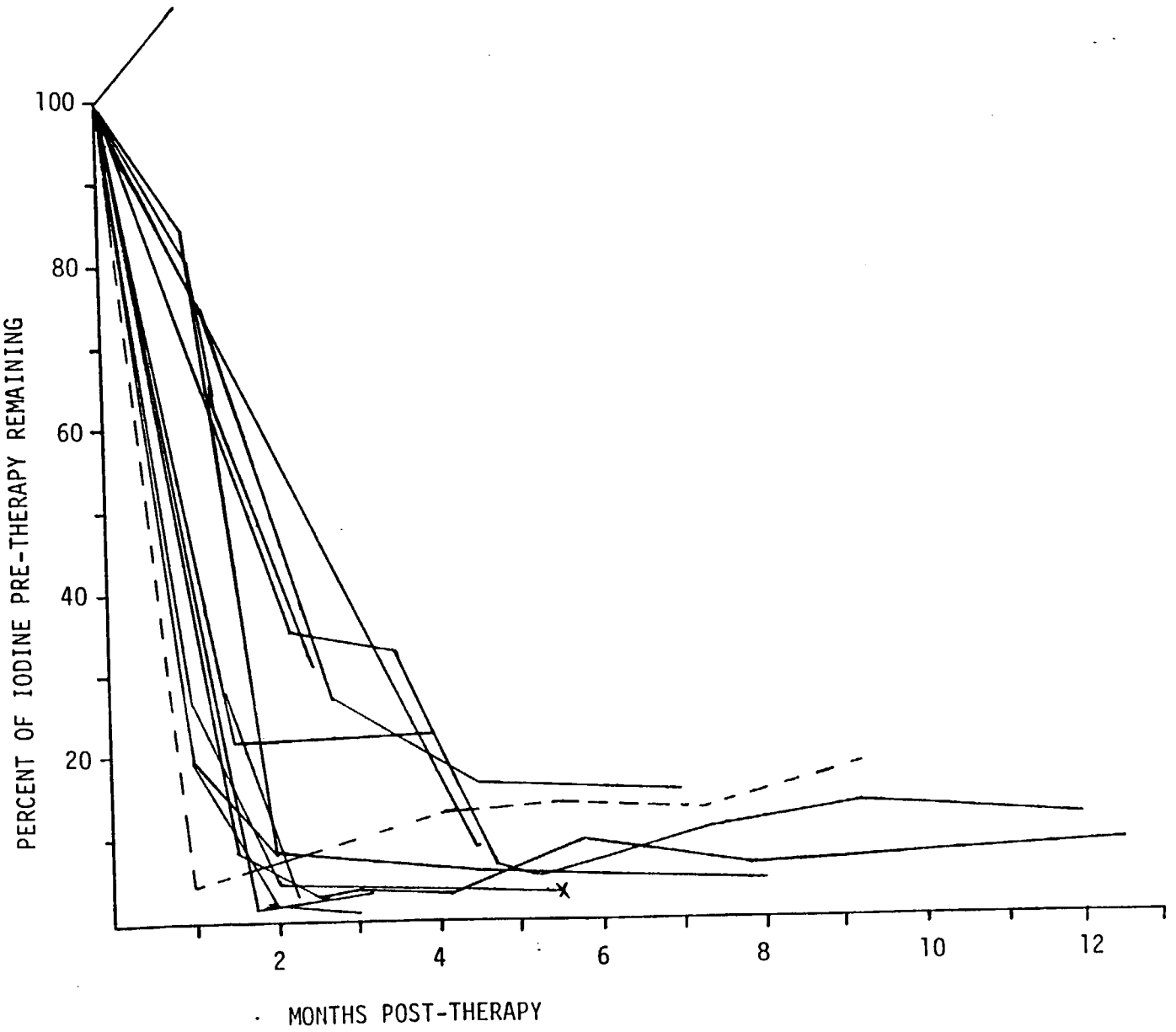

PATIENTS ON ANTI-THYROID MEDICATION PRE AND POST-THERAPY
100
80
60
40
20
PERCENT OF IODINE PRE-THERAPY REMAINING
2
4
6
8
10
12
14
MONTHS POST-THERAPY

Figure 3

PATIENTS ON NO ANTI-THYROID MEDICATION PRE AND POST-THERAPY



1018390

Figure 4

5. Nuclear Power Reactors--Environmental Monitoring

Previous studies conducted in our laboratory have been directed toward the assessment of body burdens of environmental pollutants. In the early 1970's we collected over 1000 placentae from births in Nashville and assayed the content of heary metals (Pb, Cd, Hg) and carried out neutron activation analysis to determine levels of other trace elements. Comparisons were made between levels found in placenta, blood, and hair samples in normal and abnormal births, in an attempt to identify potential etiological relationships. No gradients suggesting disease correlates were found, and levels were not elevated in this region. No concern has been raised locally with respect to potential hazards from these agents since data show no cause for concern.

We have been discussing with TVA representatives the possibility of mounting a similar study in the area of the Hartsville Nuclear Power reactor. We are exploring the feasibility of collecting placental tissues on a sampling basis from persons living at varying distances from the Hartsville plant, and analyzing these tissues for radionuclides that could be expected. Assays should be conducted by a laboratory expert on low level counting, and which has the capacity to handle such a volume. We would maintain the basic records, and do the temporal trend and epidemiologic analyses at Vanderbilt which should be considered a neutral observer. Collaboration between epidemiologists, statisticians, OB/GYN specialists, and community agencies should enable such a study to be conducted if sufficient interest suggests it is worth doing. We intend to pursue these discussions so that a study can be mounted utilizing our facilities and experience in such studies, and ERDA assistance may be sought, if it proves feasible to proceed.

1018391

B. Supporting Systems Development

1. Hardware

a. Microprocessor Controlled Scanner

During the coming year, we plan to impliment a data collection system for a rectilinear scanner using an autonomous CAMAC crate controller. The use of a computer to collect data from a scanner is a relatively easy task both from a hardware and a software standpoint. However, if the standard CAMAC configuration is used with a large minicomputer computer with CAMAC crate on its I/O bus, the data gathering system is dependent on the computer being interupted to service the crate at each data point in the scan line. This was not a problem in a single user system as operated in the PDP-9. But our laboratory is rapidly approaching the point where it is no longer feasible to operate single user systems. Both financial and personnel time constraints are causing us to switch to more powerful multi user systems available for the PDP-11 systems (RSX 11 M/V3) which will supplant our PDP-9's in the future.

While powerful in regard to the number of users it can support, it is not reasonable to expect it to be able to service the CAMAC crate under the time constraints involved in rectilinear scan control and data collection. For these reasons, we plan to use the autonomous CAMAC crate to perform the actual data collection procedure. We have considerable experience in this procedure with our current on-line crate and so the time required for software development should be minimal.

Figure 1 illustrates the configuration which we intend to impliment. The CAMAC crate will follow the scanner by means of incremental encoders mounted on the scanner. The counting data will be collected through the CAMAC scaler modules and stored in an 8K by 16 bit CAMAC Memory Module (Standard Engineering MM-816C). For small area scans or large scans with coarse spatial resolution this memory will be sufficient to store the entire scan for transmittal to the host processor at a later time. If the scan requires more memory than this module can provide, the data can be concentrated in the memory module and transmitted during the end of line turn around. This can be accomplished Utilizing a Kinetic systems model 3340 Communications interface module. This module contains a 128 word FIFO buffer which may be loaded by block transfer and emptied by data transmission at the rate selected for communication of data. By using standard modules, we will be able to impliment a system which can use any of our present computers as host systems. The PDP-11 systems will use standard DL11-C asynchronous data ports for acceptance of data from the autonomous crate. In order to utilize the DMA port of the PDP-9 for this purpose we plan to construct a UART driven deserializer to receive the data.

Operating the serial data link at 9600 baud, we expect to be able to transfer a 64 X 64 by 8 bit image in less than 5 seconds. Single line data 128 characters in length can be transmitted in less than 1/5 of a second.

1018392

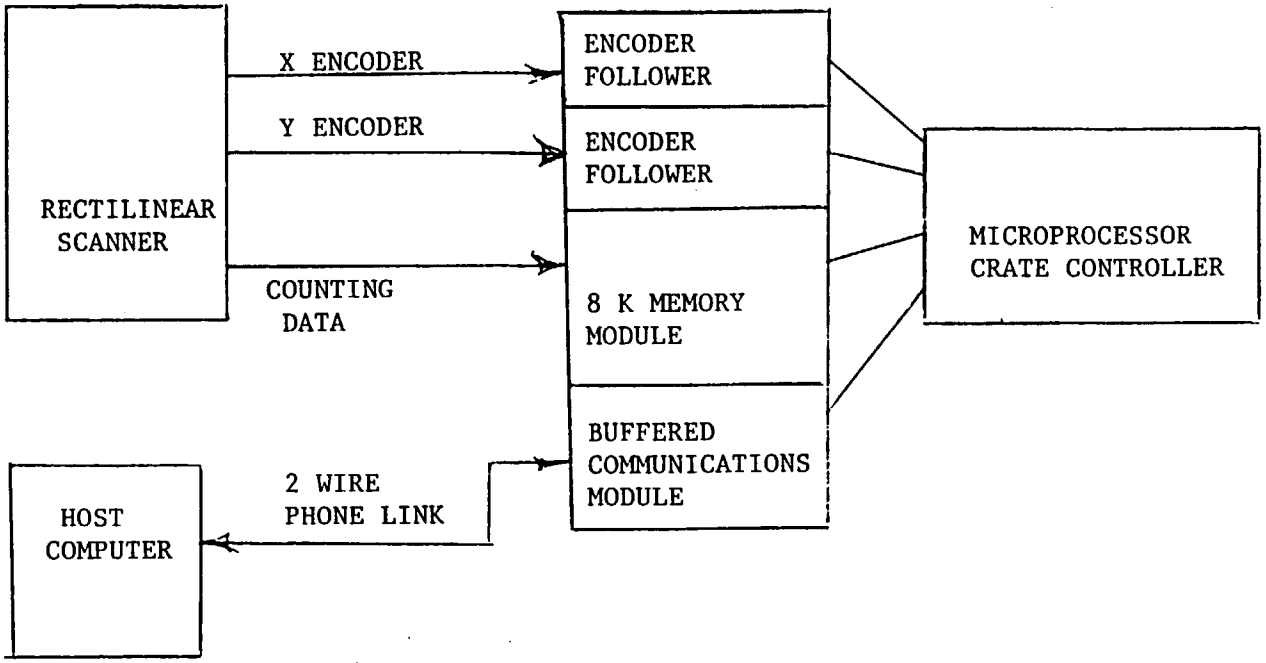


Figure 1. Proposed autonomous CAMAC crate based system for gathering data from a rectilinear scanner with subsequent transmittal to a host computer over a standard telephone line.

1018393

B.1.b. Digital Computer Interface for a Longitudinal Tomographic Scanner for Human Dosimetry Studies

The accuracy of many of our dose estimates have suffered because of an inability to separate overlying structures which contain activity from the activity within the organs of interest. In addition, frequently, our high sensitivity scanner is unable to spatially resolve closely adjacent organs. Both of these problems have been encountered in our recent work with the new I-131 labelled adrenal scanning agents. The adrenals are frequently obscured by activity in the liver, spleen, intestine, and kidneys. With the aid of a high resolution, high sensitivity, tomographic device, the problem would be simplified considerably.

In discussions with the Searle Corporation, we are in the process of securing one of the Pho-Con tomographic scanners on loan. We feel that this instrument will meet the needs described above. The techniques of acquiring truly quantitative data from tomographic slices are not completely understood and will be one of our areas of investigation during the next year. The Pho-Con will also prove to be an important instrument helping us to obtain quantitative information on organ distribution from the primary diagnostic procedure without requiring additional measurements. This is essential especially for very sick individuals and children.

The initial task in regard to the Pho-Con scanner is the interfacing of the instrument to a digital computer. This task will be carried out during the coming year.

The computer interface which we propose to build is shown in Figure 2. . We will implement the interface using a CAMAC system in order to allow the data collection to proceed without using significant amounts of memory and CPU time fromthe computer. The data to be collected from the scanning mechanism is the following:

1. X & Y position of the scanner
2. X & Y position of interaction in detector
3. Top or bottom detector
4. Isotope 1 or 2

These data will be collected in the following format in list mode for post-collection reconstruction. The position of the interaction in the detector will be digitized by a Dual ADC as with any scintillation camera and the X and Y coordinates combined into a single word of the format.

1	1	2 - 8	9 - 15
X	X	7 bits Y	7 bits X

bit 0 - Detector Flag: 0 = TOP, 1 = BOTTOM

BIT 1 = Isotope FLAG: 0 = ISOTOPE 1, 1 = ISOTOPE 2

The position of the scanner mechanism will be obtained from encoders mounted on X and Y axis of the instrument. These will be calibrated to provide a digital resolution equal to the detector digital resolution i.e.,

1018394

1.58 mm/pt for 8" detector or 2.18 mm/pt for 11 inch detector. As the scanner passes from one data cell to the next the bed coordinates will be inserted in the data list as a 3 word element in the following format:

Word 1	FLAG WORD = ZERO
Word 2	OSCILLATOR & X COORDINATES
Word 3	Y COORDINATES

In the word containing the X coordinate of the scanner (word 2) we will place a 7 bit word representing the output of a precision oscillator. If the scanner speed is stable the detector will remain in each data cell for a constant time period. If it is not stable the time spent in each data cell and therefore the sensitivity will vary from cell to cell. By storing the oscillator counts we can obtain an accurate monitor of scan speed stability for quantitative scanning studies.

This method of data storage will result in list mode data which will be very amenable to reconstruction of tomographic images. The 3 word block with the leading flag word can be used for other information such as elapsed time for decay correction, by use of a different flag word. This is possible since there are a large number of coordinates in 128 x 128 square array into which the detector image is digitized which are not used for image data. Any one of these coordinates can be used for a flag word.

By using the two 256 word FIFO Buffer modules one has buffers for data collection without using main memory. Data will be collected in one module until it becomes full at which time it can be transferred under program control to the computer for permanent storage on disc. A preliminary monitor image could also be constructed during this transfer. During transfer from the first buffer, data will be stored in the second so that no data loss will be incurred.

1018395

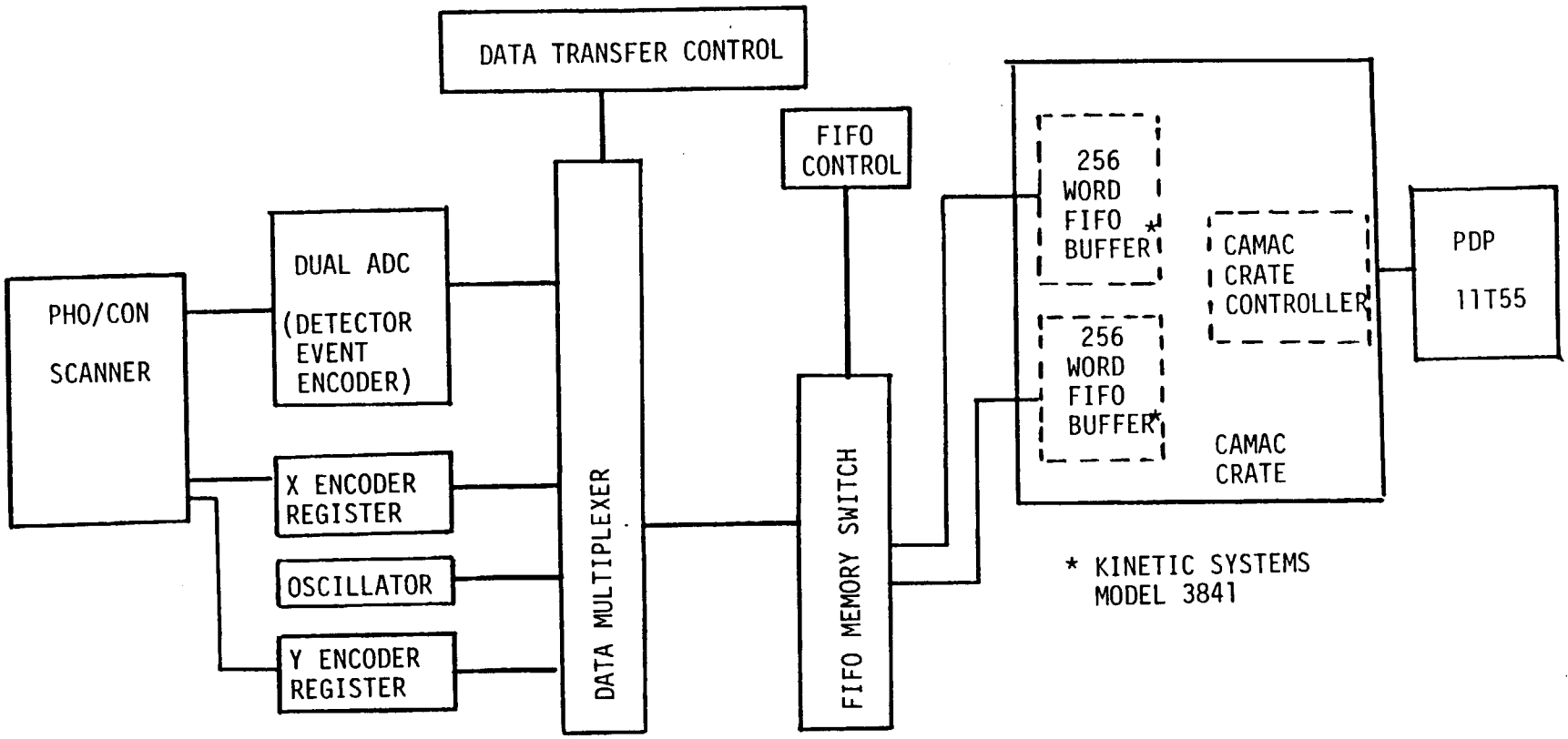


Figure 2. Proposed computer interface for collection of data from a Searle PHO/CON tomographic scanner.

1018396

2. Software

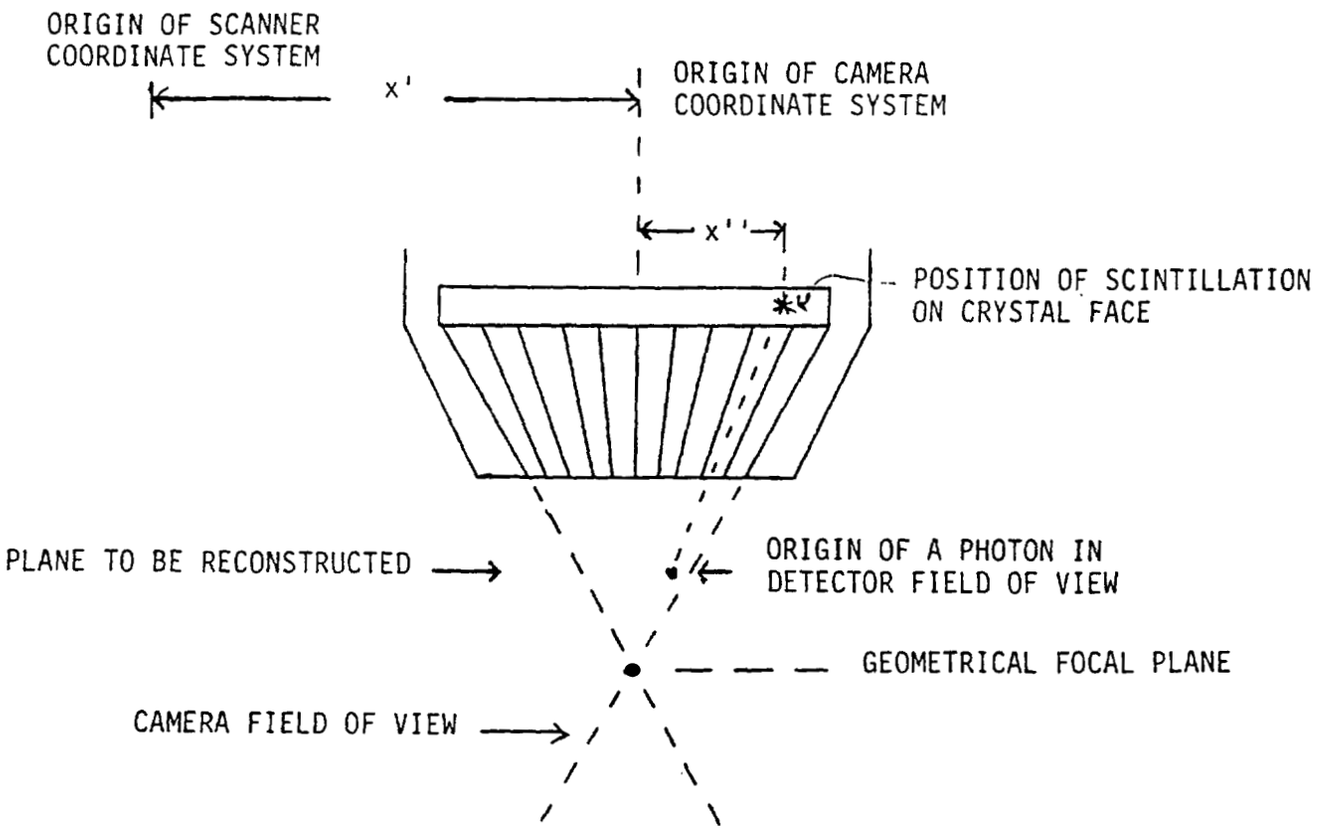
B. 2. a. Acquisition/Reconstruction/Display of Tomographic Data

Data for tomographic image construction will be acquired in list mode using the digital computer interface described in section B.1.b. Coordinates will be stored in relation to two coordinate systems as shown in Figure 1 . The position of the center of the camera head will be recorded in relation to the scanner coordinate system and the position of each scintillation on the camera face will be recorded in relation to the camera face. Thus in order to construct the image of a particular plane after completion of the data collection process it is necessary to simply perform translations of the coordinates of the scintillation within the scanner coordinate system. The dimension and direction of the translation will be determined by the location of the reconstructed plane in relation to the geometric focal plane as shown diagramatically in Figure 3 . Thus it will be possible to reconstruct images of the radioisotope distribution in any plane by this technique. The software has already been developed at Vanderbilt to construct tomographic images from a longitudinal section scanning device similar to the Pho/Con system. This instrument is a 9 crystal intrinsic germanium detector system (ERDA Report No. ORO-2401-94) with multiple focussing collimators and the image reconstruction problem is a degenerate case of the Pho/Con reconstruction problem. The knowledge gained in developing this software should greatly simplify the development of image reconstruction software for the new system.

Display systems available for image presentation include a high resolution CRT computer-controlled display for photographic purposes and a high quality AMC electrostatic printer. We also plan to explore ways of enhancing the information from a particular plane by removing the blurred off-plane activity which reduces contrast. This can be performed with deconvolution techniques using the point spread function as described by Chang et. al. (1)

1. Chang, L.T., MacDonald, B., and Perez-Mendez, V.: Axial Tomography and Three Dimensional Image Reconstruction, IEEE Transactions on Nuclear Science, Vol. NS-23, No. 1, Feb. 1976, pp. 568-572.

1018397



$X = x' + kx''$

X = traverse position of recorded event on image of reconstructed plane.

x' = traverse position of center of camera head in relation to scanner coordinate system.

x" = traverse position of scintillation on crystal face in relation to camera coordinate system.

k = constant determined by distance and direction of reconstructed plane from geometrical focal plane.

Similarly, the longitudinal position of the recorded event on the image of the reconstructed plane is given by:

$Y = y' + ky''$

Figure 1

2.b. Software System for Quantitative Autoradiography Measurements (P-32 Micro Dosimetry)

The Department of Obstetrics and Gynecology at Vanderbilt employs chromic phosphate (P-32) in treatment of patients with ovarian cancer, and they are interested in cooperating in a dosimetry study of P-32 labelled chromic phosphate colloid in animal studies. The colloid as used in therapy is injected intraperitoneally, where it spreads through the abdomen, with some adhering to abdominal membranes and some draining through abdominal lymph nodes. This is also a frequent course for ovarian metastases, and the colloid is believed to deliver a tumoricidal dose to abdominal metastases without excessive dose to vital organs, such as liver, kidneys, and gut.

We have met with Drs. Burnett and Julian (Professors and Chairmen of OB/GYN) and have proposed a pilot project to investigate the P-32 kinetics using guinea pigs. The animals will be injected intraperitoneally, with serial sacrificing of group members. The carcasses will then be cut into sections for autoradiography, giving a visual description of the P-32 distribution as a function of location and time. Radioautographs will be developed and these films will be digitized for quantitative evaluation, and with proper calibration, both activity and dose determined for each section.

The necessary first step is to assure that accurate calibrations can be made. We plan to use fabricated P-32 sources of known activity to investigate the effects of source thickness of know activity, and to evaluate the film system. As a cross-check, we also plan to expose TLD's to the sources and compare their response to both a calculation of the beta dose (using information in MIRD Pamphlet No. 7) and a gamma ray exposure. The next step will be to control exposure conditions so as to obtain reproducible results, which may require extra care for quantitative β-particle autoradiography. Then the animal data will be collected and analyzed to obtain the desired dosimetric information.

The film exposures will be to a known intensity source as well as animal sections containing P-32 of unknown strength and distributions. We have written numerous programs for the analysis of digitized video images from films, some of which are outlined in Table 1.

The general method of analysis will be to select a film background area, digitize it, and store both the area and average density. Then the density due to the known source will be likewise determined and stored. Finally, a section of film corresponding to the P-32 area will be digitized. After background correction, the activity at all points within the P-32 area will be computed and written onto the line printer (both numbers and grey scale plot). Calibration exposures will be treated in a similar way to determine the density vs. dose relationship for the film being used.

The routines need for this will include CURSRW, GETCVI, IMGDEF, IMGSET, IMAGE, GRLYLIN, and DATHAN. Thus the main programming effort required is a main control program to oversee the data flow and use of these routines, all of which are callable from standard FORTRAN.

1018399

TABLE I

(A) Systems Programs.

CURSRW (IX, IY, IZ)

This subroutine uses the high speed CAMAC ADC to monitor 2 analog control knobs (X and Y) and displays a point corresponding to their setting on the video monitor. In response to striking a key on the teletype the subroutine returns the X and Y coordinates of the point as well as the video intensity at that point.

GETCVI (IX, IYO, IY1, ADDR)

This digitizes a column of video information at horizontal position IX. The data from scan line IYO to line IY1 is obtained and stored in core starting at location ADDR.

CVPLOT (N, IX(1), IY1)

Displays N points through the Colorado Video Digitizer. The coordinates of the points are in lists beginning at IX (1), and IY (1).

CVDOT (IX, IY, IZ)

Digitizes point specified by IX, IY and returns video intensity IZ.

CVCURS

Utilizing console teletype for positioning the curser marker (as described in CURSRW) via commands from the TTY.

ADCIN (IDATA, ICHAN, MODE)

Reads high speed CAMAC ADC and returns data in IDATA. Any one of 4 input channels to the ADC may be specified by the variable ICHAN. Mode controls the time fo digitization.

RDCHK (ICHAR)

Used by other subroutines to determine whether or not a key has been stuck on the console TTY. If so the ASCII character is returned in ICHAR.

IMGDEF (N, IMAX, IMAY)

Defines a virtual image space with maximum X and Y dimensions of IMAX, IMAY and labels the image with number N.

IMGSET (N, I, J, IVAL)

Sets the I Jth point in virtual image #N to the value specified by IVAL.

K=IMAGE (N, I, J)

Set K to the value fo the I, Jth point in the virtual image N.

GRYLN (IARR, NUM, MAX, MIN)

Prints one grey scale representation of the line beginning at IARR. The number of data points is specified by NUM, the 10 step grey scale is spread over the numerical range from MIN to MAX.

1018400

DATHAN (IARR, NUM, IMNUM, INOUT, IRWD)

Stores and retrieves data from virtual image IMNUM and stores them in the array IARR. INOUT specifies the direction of data flow. Data is retrieved from or stored in the image at the location of a pointer that is initialized by the rewind switch IRWD to the start of the virtual image. Each successive call moves the pointer forward through the virtual image NUM points.

B. Applications Programs.

DIAM (IARR, IT, IB, IDIAM, MAX, IBK, NUM, ISTAT, NOPRT)

Accept array of data NUM points long representing a column of video data which includes the image of a blood vessel. The array is smoothed and corrected for non equal background at each side of the vessel image. The background IBK and peak value MAX are determined by an iterative technique to lessen the effects of abberant points in the data. The equation

$$D_c = -\log\left(10^{-BKG} + \frac{1}{7}\left(10^{-MAX} - 10^{-BKG}\right)\right)$$

is used to calculate the cutoff value which determines the vessel diameter. In case of failure to determine the edges IT and IB the variable ISTAT is set nonzero. A diagnostic printout of the raw and smoothed, adjusted data is permitted or suppressed by the variable NOPRT.

SPOT

A routine that is designed to average densities over a predetermined area around a specified point at the scene.

ENHANCE

The routine takes a digitized image, background subtracted, and gives values 0 or 1 when the value of the density at the center of a specified window is lower or higher respecitively than the average value over the window.

GRAD

Takes a digitized image, background subtracted. Calculates the difference between adjacent elements of the image along x and y directions. Assign values of 0 or 1 for the cases where the above difference value is respectively, higher or lower than a predetermined value.

DILATE

Calculates diameters along a vessel using a theoretical criterion relating the density of a curve's peak value with its width. Plots the vessel shape across its section at the specified site.

FILTER

Edge-enhances a digitized image using either 'GRAD' or 'ENHANCE' subroutines plots the resulting edge-enhanced image.

FLOW

A general purpose subroutine that performs:

(i) accumulation of densitometric data across vessel section located on specified sites along the vessel. Subtracts background and calculates the time center of gravity of the density vs time

1018401

curve at the various sites. Differences in the time average between adjacent sites yield the mean transit time of the bolus required for blood velocity determination.

(ii) makes use of 'DIAM' subroutine to calculate and plot the diameter at the specified site.

(iii) enables the calibration of linear dimension in the object plane in terms of x-y digitized point number.

1018402

2.c. Sharing Efforts

i. Simulation and Modelling

(a) Specific Dosimetry Projects

We are continuing to develop and test new kinetic models in an effort to understand better the total body and organ retention of these medically administered radioactive materials. Solutions to these models have been sought generally through the use of Berman's SAAM computer program. Our efforts have been directed toward improving model accuracy through the use of external quantitative measurements as supplemental to routine kinetic data. Models are currently being used to analyze data from studies of Fe-50, I-131 Iodocholesterol and iodine kinetics in addition to a number of new radiopharmaceuticals. The details of these models and model calculations have been discussed in the preceeding sections dealing with the specific material.

(b) SAAM Workshop

During the past year, we organized and co-sponsored a Seminar-Workshop for users of the Simulation, Analysis and Modelling Program (SAAM) developed by Dr. Mones Berman at the NIH. The SAAM program is well known and widely used as a tool for analyzing radiopharmaceutical kinetic data for the purpose of determining organ retention curves and cumulative activities. The SAAM workshop was held this past year at the Oak Ridge Associated Universitites Headquarters building on April 28-31. The other sponsors were the Biomedical Computing Technology Information Center and Dr. Mones Berman's group at the Laboratory of Theoretical Biology, NCI. The meeting covered the current features and uses of the SAAM program and was attended by approximately 40 people from throughout the country. A list of the attendees and a copy of the program have been included as an appendix to our current report.

During the meeting a SAAM users group was created with R. Price being chosen as the coordinator. During the coming years, we are proposing to sponsor seminar--workshops on SAAM and related simulation problems on a regular (hopefully, annual basis). These workshops will serve as a mechanism for people who are working in the area of kinetic modelling to gather, discuss current topics and disseminate new ideas.

ii. Sharing of Computer Programs in Nuclear Medicine

During the coming year we plan to intensify our efforts to assist ORNL in the demonstration of the utility of their newly formed information center for the exchange of nuclear medicine software packages. We are working with the personnel of the Biomedical Computing Technology Information Center (BCTIC) in Oak Ridge at several levels. Dr. Brill is a member of the Advisory Committee. Dr. Erickson is co-directing the production of a Nuclear Medicine Computing Directory. This directory of nuclear medicine computers users was first published in July 1976. A copy has been included as an appendix to our current report. At present, it contains descriptions of over 80 U.S. and 20 foreign installations where research is being carried out in the application of computers to nuclear medicine problems. This will greatly facilitate the interchange of software since it describes available computer systems and provides available computer systems and provides software, hardware and clinical contacts at the various institutions. We will continue to submit appropriate software packages to BCTIC for distribution to interested installations. Any new software which we develop--especially in regard to the autonomous CAMAC crate and the various dosimetry studies, will be designed with the intention of their being shared with other interested scientists. In addition, we will continue to assist in identifying available software of relevance to nuclear medicine and will assist

0048 01

in obtaining its submission ot BCTIC and in its subsequent testing prior to distribution.

1018404

VI. Scientific Personnel - Curriculum Vitae on file ERDA

Principal Investigator:

A.B. Brill, M.D., Ph.D. SS# 131-20-0970
Professor of Medicine & Radiology, Director of Radiological Sciences

Co-Principal Investigator:

R.R. Price, Ph.D. SS# 401-62-0402
Assistant Professor, Radiology

Research Scientists:

J.J. Erickson, Ph.D. SS# 502-40-2883
Assistant Professor, Radiology

J.A. Patton, Ph.D. SS# 401-62-0385
Assistant Professor, Radiology

J.P. Wikswo, Ph.D. SS# 224-64-5499
Assistant Professor, Physics

J.E. Lagan SS# 409-58-5467
Electronics Engineer

J.P. Jones, Ph.D. SS# 401-66-008
Research Associate

F.D. Rollo, M.D., Ph.D. SS# 101-26-5710
Associate Professor, Radiology

VII. Other Personnel

Graduate Students:

R. Hudepohl SS# 400-68-6152

K. Larsen, SS# 264-72-8555

Secretary:

T. Shaw SS# 480-68-5547, 100%

Research Technician:

M. McConnell SS# 403-48-9866, 50%

VIII. Other Financial Assistance - None

1018405

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 13,000 square feet adjacent for conference, library, clinical imaging, and instrument development and modification	100 percent
3D imaging Systems (Radiology Dept.) 1 EMI Head Scanner 1 Varian Body Scanner 2 Gray Scale Ultrasound 2 Real Time Ultrasound	
Animal Radiographic Research Lab	
Computer Center	As required
Clinical Research Center	As patients present
Clinical Radioisotope Laboratory	Radiochemistry and counting facilities as needed
Animal House	Maintenance and primary care of animals used in tracer experiments
Medical, Chemistry, Biology, Engineering, Physics and Joint University Libraries	Access to books
Medical Illustrations	Drawings, slides, photographs for presentations and publications

1018406

RENEWAL PROPOSAL

ERDA EY-76-S-05-2401 November 1, 1977 through October 31, 1978

X. Budget Estimated Requirements	ERDA	University	TOTAL
1. Salaries & Wages Name, Title, Monthly rates, % effort			
A.B. Brill, M.D., Ph.D. SS# 131 20 0970 Professor Medicine & Radiology, 16%	-0-	$9000.	$9000.
Co-Principal Investigator R.R. Price, Ph.D. Ass't Professor Radiology $1952/mo, 25%	$5973.	---	$5973.
Research Associates:			
J. Erickson, Ph.D. Ass't Professor Radiology $1566/mo, 20%	$3833.	---	$3833.
J.A. Patton, Ph.D. Ass't Professor Radiology $1685/mo, 25%	$5156.	---	$5156.
F. David Rollo, M.D., Ph.D. Assoc Professor Radiology 15%	-0-	-0-	-0-
J. E. Lagan Electronics Engineer $1328/mo, 10%	$1625.	---	$1625.
J.P. Jones, Ph.D. Research Scientist $1043/mo, 25%	$3193.	---	$3193.
Secretary, T. Shaw, 100%	$7235.	---	$7235.
Res. Technician, M. McConnell, 50%	$4752.	---	$4752.
Fringe Benefits (not fixed % of salaries. Varies with employee status and option)	$4322.	$1163.	$6648.
TOTAL SALARIES & FRINGE BENEFITS	$36,089.	10,163.	47,415.
INDIRECT COSTS (67% S & W)	$24.179.	---	---

1018407

2. SUPPLIES AND MATERIALS

Books, Periodicals, Journals	500.	
Computer Supplies (line printer paper, magnetic tapes)	1000.	
Lab Supplies, Isotopes	500.	
Maintenance Service (computer only)	500.	
Office supplies/duplicating	500.	
Electronic Components & Replacement Parts	6900.	Subtotal $9900.

3. EQUIPMENT--PHO/CON INTERFACE

2 position encoders H. H. Contols Optach Model 512 @ 150	300	
Dual ADC Bay Engineering PC11-AD	2000	
*FIFO Buffer Kinetic systems 3841-F1A	982.	Subtotal $3282.

4. Travel--domestic	1500	Subtotal $1500.

TOTAL FUNDS REQUESTED ERDA	$74,950.00
UNIVERSITY CONTRIBUTION	$10,163.00

* only one FIFO Buffer is requested since there is already one module in the laboratory which will be devoted to the project.

1018408

Projected Costs

Percentage & Amount, Vanderbilt University	12%	$10,163.00
Percentage & Amount, Requested ERDA	88%	$74,950.00

XI. AUTHENTICATION

A.B. Brill, M.D., Ph.D.
Principal Investigator

Paul Gazzerro, Jr.
Assoc. Vice-Chancellor for
Medical Affairs for Operations
and Fiscal Planning

NOTE: Studies described in the application, involving the investigational use of human subjects have been reviewed and approved by this Institution's Clinical Investigation Committee.

1018409

"The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as the result of this application."

A. B. Brill

A. B. Brill, M.D.

DATE: 7/29/77

1018410

Appendix I

STUDIES ON RED CELL APLASIA. IX.

FERROKINETICS DURING REMISSION OF THE DISEASE

By

Saengsuree Wibulyachainunt, Ronald Price, A. Bertrand Brill and Sanford B. Krantz

From

The Departments of Medicine and Radiology,

Vanderbilt University School of Medicine and

Veterans Administration Hospital

Nashville, Tennessee 37203

This research was supported by the Medical Research Service of the Veterans Administration, National Institutes of Health Grants #AM-15555 and RR-95 from the General Clinical Research Centers Program of the Division of Research Resources and ERDA Contract ERDA E-(40-1)-2401

Send reprint requests to: Sanford B. Krantz, M.D.
Chief, Hematology Section
Veterans Administration Hospital
1310 24th Avenue South
Nashville, Tennessee 37203

1018411

ABSTRACT

Ferrokinetic studies and surface organ scanning were performed on five patients with pure red cell aplasia (PRCA) in remission. One patient had erythroid hyperplasia and ineffective erythropoiesis shortly after remission occurred. This was indicated by a markedly short ^{59}Fe clearance rate and reduced red cell ^{59}Fe incorporation; a marked increase of the erythron iron turnover over the fixed red cell iron turnover; and a prolonged marrow transit time. These indices were nearly normal three years later. Two patients had an extended marrow distribution. Four patients had normal effective erythropoiesis while in remission. These studies suggest that some cases of primary refractory anemia with erythroid hyperplasia and ineffective erythropoiesis may be related pathogenetically to PRCA because of the evolution from one state into the other.

1018412

INTRODUCTION

Pure red cell aplasia (PRCA) is characterized by a normochromic, normocytic anemia with reticulocytopenia, and normal white blood cell and platelet concentrations. The bone marrow usually is normocellular with normal granulopoiesis and megakaryocytopoiesis, but is virtually devoid of erythroblasts (1-2). Many of the acquired primary cases of PRCA appear to have an immune pathogenesis. These patients have immunoglobulin inhibitors of the marrow erythroid cells or of the hormone, erythropoietin, and may have a favorable response to immunosuppressive drugs such as corticosteroids, 6-mercaptopurine, azathioprine, cyclophosphamide, or antilymphocyte globulin (3-9) or to splenectomy (2, 10). However, in many cases the red cell aplasia recurs at a later time (6). Few ferrokinetic studies have been reported in patients with treated PRCA in apparent clinical remission to determine if the patients had normal erythropoiesis during this period (8, 9). At the onset of PRCA, the ^{59}Fe clearance rate is markedly prolonged; there is no significant accumulation of ^{59}Fe in the sacral marrow, and the red cell ^{59}Fe incorporation is extremely low (11-14). Böttiger and Rausing (8) reported a case of PRCA successfully treated with immunosuppressive drugs. A ferrokinetic study after the patient was in remission showed a rapid clearance of plasma ^{59}Fe and low red cell iron utilization. Marmont and his colleagues (9) studied the ferrokinetics of two patients with PRCA before and after treatment. The observations after treatment were similar to those reported by Böttiger and Rausing. We report here the ferrokinetic studies and surface organ scanning five PRCA patients in remission and demonstrate the finding of normal erythropoiesis in four

and ineffective erythropoiesis in one patient who was in apparent clinical remission at the time of study.

METHODS

Blood Volume Measurement and Erythrocyte Survival. ^{51}Cr red cell mass and blood volume were determined by standard methods (15, 16) on the day preceding the injection of radioiron. The base-line sample for the ^{51}Cr red cell survival was taken 24 hours after injection of the labeled erythrocytes.

Iron Kinetics Studies. Traditional iron kinetics data were obtained and analyzed by standard methods (13, 17). Ten μCi of ferrous citrate with a specific activity of 18 to 20 μCi/mg iron was incubated for a period of 30-60 minutes in the patient's serum and injected intravenously on day 0. Blood samples were taken at frequent intervals throughout the study for evaluation of plasma and whole blood radioactivity.

External Measurements of Radioiron Distribution. Quantitative external measurements of radioiron were carried out by previously published methods (18). A heavily shielded scanner coupled to a digital data acquisition system was used to collect quantitative whole-body scans of the radioiron. This system utilized two opposed 5-inch diameter sodium iodide crystals fitted with single-hole tapered-bore collimators which were designed to achieve high counting efficiency. The detector signals were amplified and the characteristic energy of ^{59}Fe was selected by single channel analyzers.

Calibration procedures developed for the PDP-9 computer permits quantitation of the absolute amount of ^{59}Fe contained within any selected region of the whole-body scan. The calibration procedure attempts to correct for variation in body thickness, source volume and depth of the source

within the body. Measurements made on volunteers given known amounts of radioactivity showed the regional assessment technique to be accurate to ± 10%.

In order to correct the external measurements for the circulating blood background, the fraction of the circulating blood compartment included in the region of interest was measured by a quantitative ^{51}Cr whole-body scan taken one hour after injection of ^{51}Cr-labeled red cells.

Time-activity curves were generated for the pelvic marrow at approximately one day intervals for an average period of 10 days. Images of the total-body distribution of the radioiron were also made on a daily basis. The time-activity curves for the total marrow were estimated from the direct measurements of the pelvic marrow space. The pelvic marrow transit curve at 24 hours was taken to be equal to the total-body radioiron content minus the liver and spleen content. Based upon time-activity curves generated in this manner marrow transit-time were determined. The transit-time was defined as the time interval between the 50% levels of the maximum radioiron uptake in the marrow that occurred during the uptake and release phases. In a manner similar to that described by Finch et. al. (13) the plasma clearance and red cell utilization curves were also used to estimate the total marrow activity curves. In this method one assumes the marrow uptake of the radioiron to be proportional to the inverse of the plasma clearance and the marrow release of the radioiron to be proportional to the inverse of the red cell incorporation curve. The curve is then normalized to the maximum activity incorporated into the circulating red cells. This calculation yields the marrow transit time and the maximum uptake in the erythropoietically active marrow pool.

Case Studies

In all the patients, the blood chemistries, lupus erythematosus preparations, antinuclear antibody, latex fixation for rheumatoid factor, hepatitis-associated antigen, and Coombs' tests were normal. Skin testing for anergy (intermediate strength PPD, mumps and Histoplasmosis) did not show this abnormality. Protein electrophoresis, immunoelectrophoresis and quantitative immunoglobulin levels showed diffuse hypergammaglobulinemia in all of these patients. serum folic acid level was low in all, the serum B_{12} was normal in 2 (Patient number 1 and 2) and was not measured in 1 (Patient number 5). Serum complement (C_3) activity measured by radial immunodiffusion and

In all patients the diagnosis of PRCA was confirmed by our personal review of the pertinent marrow slides. These studies were approved by the Vanderbilt Committee for the Protection of Human Subjects.

Patient number 1 is a 54-year-old diabetic white male

who was treated with insulin.

In 1970, in an attempt to decrease the insulin requirement, Diabinese was administered for 3 months without any benefit. It was then stopped, but his hemoglobin was noted to be 9 g/l and he was treated with oral iron. In 1971 his hemoglobin was 12.5 g/l and he felt well until August 1972 when he had a 6 week course of Griseofulvin for a small fungal infection. He began to feel weak and was found to have a hemoglobin of 5.5 g/l with a total absence of reticulocytes. A bone marrow aspiration showed no erythroid precursors. Prednisone was tried for one month without any benefit. He also had a therapeutic trial of an androgenic hormone, cyclophosphamide (50 mg per day), and growth hormone, for 1 month each without any response. He was treated with frequent blood transfusions (approximately 3 units of blood every 3 weeks) to maintain his hematocrit and developed

serum hepatitis in April 1973. He was referred to Vanderbilt University Clinical Research Center for further evaluation of his anemia in January, 1974. On physical examination he had a bronze skin, palmar erythema, a palpable liver 2 cm below the right costal margin and a spleen tip palpable at the left costal margin. The chest roentgenogram and tomograms did not reveal a thymoma. The hematocrit was 0.364; the white cell count was 6.5 x 10^9/l with a normal differential; the platelets were 289 x 10^9/l and no reticulocytes were seen. The serum (SGOT) and alkaline phosphatase were increased. Bone marrow particle smears and sections again demonstrated PRCA with a marked increase in iron. The patient was treated with cyclophosphamide 150 mg and prednisone 30 mg per day and folic acid 1 mg per day and soon responded with normal erythropoiesis. The folic acid was continued throughout his course. Prednisone was stopped in April, 1974 and cyclophosphamide was stopped in July, 1974. Phlebotomies of 500 cc of blood every 2-3 weeks were begun and continued thereafter whenever possible. After February, 1974 he was able to maintain his hemoglobin at 13-14 g/l with 3-4 phlebotomies per month. In October, 1974 a repeat bone marrow showed slightly increased erythropoiesis and increased numbers of large lymphoid follicles. The first ferrokinetic study was performed at this time. He was then placed on maintenance cyclophosphamide 150 mg per day. He continued to be phlebotomized once a month and still maintained his hemoglobin at 14 g/l. He did well until March, 1975, when his hemoglobin fell to 12 g/l with a normal white cell count and he could no longer respond normally to phlebotomy. In May, 1975 a bone marrow was normal except for some megaloblastic changes of the erythroblasts. Cyclophosphamide was increased to 200 mg per day for 3 weeks and the patient responded with an increased hematocrit. The

white cell count dropped to 3.0 x 10^9/l and the cyclophosphamide was reduced to 150 mg per day and then discontinued on June 20, 1975. The patient was readmitted to Vanderbilt University Clinical Research Center in June, 1975. The white cell count was 3.5 x 10^9/l; the hemoglobin was 10.8 g/l and the platelets were 104 x 10^9/l. The bone marrow had a greatly reduced number of erythroblasts at 0.5% with normal granulocyte maturation. The second ferrokinetic study was performed at this time. Splenectomy was performed afterwards on June 30, 1975. Post-operatively the bone marrow aspirate on July 8 showed numerous islands of erythroid precursors with good maturation. He was discharged on July 24 with an increasing hemoglobin of 11.1 g/l and reticulocytes of 7.6%. He has maintained his hemoglobin of 12.8 g/l with a regular phlebotomy of 2 units of blood for 21 months. When last seen in November, 1976 his blood counts were completely normal. The bone marrow particle sections showed erythroid hyperplasia and a third ferrokinetic study was performed.

Patient number 2 is a 21-year-old white female who [redacted] in August, 1969, was found to have a hematocrit of 0.11 and was transfused to raise her hemoglobin to 9 g/l. In September, 1969 her hematocrit again fell to 0.10 with a reticulocyte count of 0.2%. The white cell count was 3.6 x 10^9/l; the platelets were 159 x 10^9/l. A bone marrow aspirate showed a profound erythroid hypoplasia. She was treated with vitamin B_{12}, folic acid, pyridoxine, riboflavin and prednisone without any response. She continued to require 2-3 units of blood transfusion every 2-3 weeks. In March, 1971 cyclophosphamide was administered for [redacted] months but was then discontinued after a severe automobile accident.

She was referred to [redacted]

Vanderbilt University Clinical Research Center in October, 1972 for further evaluation of her anemia. Physical examination was normal except for a gray-bronze skin. Chest roentgenogram and tomograms were normal. The hemoglobin was 9.4 g/l; the hematocrit was 0.278; the white cell count was 4.0×10^9/l with a normal differential; the platelets were 160×10^9/l; the reticulocyte count was 0.1%. Bone marrow particle smears and sections showed a hypercellular marrow. Only very early proerythroblasts were present. She received blood transfusions which raised her hemoglobin to 11 g/l. Folic acid 1 mg per day was administered because of a low serum folate. In February, 1973 she was found to have a hematocrit between 0.32-0.35 and no longer required blood transfusions. Phlebotomies of one unit of blood every 2-3 weeks were begun and continued whenever possible. However, it was noted that her reticulocyte count was always low for the level of her subnormal hematocrit following phlebotomy in spite of a hypercellular marrow with erythroid hyperplasia. A clinical diagnosis of ineffective erythropoiesis was made and the first ferrokinetic study was performed. In December, 1974, and thereafter, the patient's reticulocyte counts were noted to be appropriate for the hematocrit following phlebotomy. The second ferrokinetic study was performed in August, 1976. At that time the hematocrit was 0.453; the white cell concentration was 8.5×10^9/l; the reticulocyte count was 1.5%; the platelets were 180×10^9/l, and the marrow was normal except for increased stainable iron.

A case report concerning patient number 3 has already been published (7). The patient is a 41-year-old white man who had PRCA for two years, requiring 2-3 units of blood every 2-3 weeks, before he responded to cyclophosphamide and prednisone with a remission of the disease in April 1972.

He remained in remission, requiring no transfusions for 4 months, but was then found to have a hematocrit of 0.25 and a reticulocyte count of 0.3%. Cyclophosphamide and prednisone were reinstituted and once again a remission of the disease was produced. The cyclophosphamide and prednisone were once again discontinued. In April, 1973 his hematocrit was 0.39 and the reticulocyte count was 5.7%. Periodic phlebotomies were instituted to remove excess iron stores. In an attempt to sustain the remission he was started on maintenance cyclophosphamide 50 mg per day.

The patient again relapsed in November, 1973. The cyclophosphamide was increased and prednisone was reinstituted. Once again a remission of the PRCA was produced with normal blood counts by June, 1974. The cyclophosphamide was decreased to 150 mg/day which he continued to take up to the time of the ferrokinetic study, At that time his hematocrit was 0.42; the white cell concentration was $3.3 \times 10^9/l$; the reticulocyte count was 3.5%; the platelets were $87 \times 10^9/l$; and the marrow was slightly hypocellular with adequate numbers of erythroid precursors.

Patient number 4 is a 56-year-old white female who had been in good health until August, 1964 when she was found to be anemic with a hematocrit of 0.32. From 1964 to October, 1970 she was treated with many different hematinics without any success, but did not require blood transfusions. In October, 1970 she was started on prednisone 40 mg per day. This dose was decreased over a period of several months and by February, 1971 she was maintained on prednisone 20 mg every other day and sustained a hematocrit of 0.37. In an attempt to decrease the Cushinoid phenomena from steroids, she was begun on dexamethasone in December, 1971. She needed between 2.5 and 3 mg of dexamethasone every day to maintain a hematocrit in the range of 0.30. She discontinued this drug for a few days in February, 1973 and

promptly dropped her hematocrit to 0.21. She responded nicely to reinstitution of dexamethasone and did well until March, 1975 when a bone marrow showed PRCA. Her hematocrit dropped to 0.24 despite an increase of the dexamethasone to 6 mg daily. Cyclophosphamide was added at a dose of 50 mg daily initially, and later 100 mg daily while the dexamethasone was slowly discontinued. By August, 1975 her hematocrit was 0.40 with a 1.7% reticulocyte count on maintenance cyclophosphamide of 100 mg per day. During this period she only required 6-8 units of blood. The cyclophosphamide was decreased to 50 mg per day in October, 1975 due to leukopenia and slight thrombocytopenia, and was discontinued in January 1976 when her hematocrit remained in the range of 0.40. She was admitted to the Vanderbilt University Clinical Research Center in August, 1976 for study. Physical examination on admission was essentially normal. The hemoglobin was 14 g/l; the hematocrit was 0.45; the white cell count was $6.1 \times 10^9/l$ with a normal differential; the platelets were $240 \times 10^9/l$. Chest roentgenograms and tomograms were normal. Bone marrow particle smears and sections showed a normal cellularity with slightly increased erythropoiesis and increased iron. Ferrokinetic studies were performed and the patient was discharged to be followed by her local physician.

A case report concerning patient number 5 has already been published (10). She had PRCA occurring with viral hepatitis. The patient failed to respond to cyclophosphamide and prednisone, but went into remission following a splenectomy in September, 1972. A bone marrow aspirate obtained at the time of remission showed hypercellularity with extremely active granulopoiesis and erythropoiesis. The patient subsequently maintained a normal hematocrit without red cell transfusions, but with periodic phlebotomies to relieve the transfusion siderosis. She was

last seen at the Vanderbilt University Clinical Research Center in December, 1974 at which time ferrokinetic studies were performed. At that time her hematocrit was 0.469; the white cell concentrations was 12.1 x 10^9/l; the reticulocyte count was 1.6%; the platelets were 359 x 10^9/l; and the bone marrow particle smear showed a slight erythroid hypoplasia. The patient left the hospital prematurely which did not allow adequate completion of all the studies.

Patient number 6 is a 63-year-old white male who was in good health until April, 1973 when he started to feel tired while playing golf. He was found to have a hemoglobin of 6.6 g/l with a hematocrit of 0.179; the white cell count was 3.4 x 10^9/l and the platelet count was 520 x 10^9/l. He was treated with many different hematinics without any success. He was referred to Vanderbilt University Clinical Research Center in March, 1974 for further evaluation. Physical examination was essentially normal except for pallor. The hematocrit was 0.22; the white blood cell count was 3.6 x 10^6/l; the platelet count was 420 x 10^9/l. No reticulocytes were seen. Chest roentgenograms did not reveal a thymoma. Bone marrow particle smears showed an almost complete absence of erythroid precursors with normal granulopoiesis and normal numbers of megakaryocytes. He was treated with Prednisone 30 mg per day and cyclophosphamide 50 mg per day which was gradually increased to 150 mg per day. His hematocrit was stable at 0.30 without any transfusions and he had a reticulocyte count between 0.8 - 1%; but his white cell count was decreased to 1.5 x 10^6/l. The cyclophosphamide was discontinued and prednisone was tapered. No remission of the red cell aplasia occurred. Splenectomy was performed in January, 1975 without any complication and also without any remission

of the PRCA. At the time of the ferrokinetic study his hematocrit was 0.27; the white cell concentration was 3.4 x 10^9/l and platelet count was 60 x 10^9/l. The bone marrow was slightly hypercellular with increased numbers of granulocytic cells and markedly reduced numbers of erythroblasts.

Results

The ferrokinetic studies on all of the patients are shown in Table 1. Patient number 6 had a very prolonged plasma ^{59}Fe clearance rate and virtually no incorporation of ^{59}Fe into the red cells whereas most of the remaining PRCA patients in remission had ^{59}Fe clearance rates that were normal or only slightly prolonged. Patient number 2 had a markedly shortened ^{59}Fe clearance rate. The red cell incorporation of ^{59}Fe by these patients in remission was also greatly improved. In patients numbers 1 and 2, it was below normal shortly after remission occurred, but approached the normal level after two to three years. Patient number 3 had a red cell incorporation just below the normal level, after several years of phlebotomies. Patient number 4 had a normal red cell ^{59}Fe incorporation shortly after remission. Patient number 2, who had a very short ^{59}Fe clearance rate also had a marked increase of the erythron iron turnover over the fixed red cell iron turnover, which was clearly indicative of ineffective erythropoiesis, in her first study after remission of the PRCA.

Figure 1 shows the marrow transit time curves of these patients and two normal volunteers. The study performed on one patient (number 6) with PRCA showed very little incorporation into the marrow at any time. patient number 2, in her first study after remission of the PRCA, had a prolonged marrow transit time. A repeat study three years later revealed that her marrow transit time had become normal. The remaining patients in remission had normal marrow transit times.

1018423

A comparison of the transit time curves derived from direct measurements of the radioiron activity in the pelvis, to the transit time curves calculated from the circulating levels of radioiron in the plasma and red cells for PRCA patient number 2 is shown in Figure 2. Measurements were made in 1973 shortly after remission of the disease and again in 1976. The initial study revealed a discrepancy in the transit time curves estimated by the two different methods. The second study revealed a close agreement of the two methods. It was found that the two methods agreed in the initial study if a constant level of activity (equal to the activity as measured on day 10) were subtracted from each measurement. The resulting subtracted curve is also shown in Figure 3, and it is very close to the curve calculated from the blood levels of radioiron.

Figure 3 shows the external total-body scan of a normal volunteer and patients with PRCA in remission. Patient number 6 had very little uptake of ^{59}Fe into his marrow with only visualization of the liver. Patient number 3 had a normal ^{59}Fe scan of the marrow with increased ^{59}Fe uptake into the liver. Patient number 5 had a moderate extension of the isotope uptake into the lower extremities. Patient number 2 had a markedly extended marrow distribution in her first study of 1973, which improved by the time of the second study in 1976.

DISCUSSION

Quantitative measurements in iron metabolism studies have been generally confined to the determination of the concentration of a radioactive tracer in the circulating blood pool as a function of time (13, 17). Some investigators have also included measurements with stationary scintillation probes placed over selected organs or marrow sites as part of the study (14).

Information from isolated probe measurements, though containing considerable information, is not adequate to define regional kinetic parameters. Blood sampling alone can only provide information on total-body average parameters of marrow function or iron storage and cannot detect altered distribution patterns of either. Sequential total body scans of radioiron have allowed us to measure and visualize the body's changing iron distribution in a quantitative manner. The kinetic parameters of a selected marrow site has been measured directly. This measurement can then be coupled with measurements of the circulating blood pool to form a self-consistent description of the total-body iron kinetics.

The primary limitation of the external measurement technique is due to the problem of overlapping organs and kinetic pools. In the determination of kinetics of selected marrow sites, the question is simply how much of the radioiron detected is due to the tracer activity in the blood pool? We have solved this problem by carrying out dual tracer measurements. The second tracer was ^{51}Cr-labelled red blood cells. From the whole-body scan for ^{51}Cr-labelled red cells, we were able to determine the relative "circulating" blood pool for each region of the body. This information combined with the daily red cell incorporation level of the radioiron made it possible to subtract the correct fraction of the activity of each site that was due to "circulating" activity. This subtraction was carried out at each point in time to yield the "net" activity. Measurements of marrow function were taken over the pelvis to eliminate the problem of significant overlap from known iron storage pools such as the liver and spleen.

The marrow transit curves derived from the direct external measurements agreed well with the marrow transit curves estimated from the blood activity

measurements in most cases (Brill and Price, unpublished observations). In the case where there was disagreement (Figure 3), the direct measurements revealed a long term component in the marrow's release of the radioiron. By subtracting the long term component we were able to arrive very near to the marrow transit curve predicted on the basis of the circulating red cell measurements.

Some of the PRCA patients had normal or slightly prolonged clearance rates of ^{59}Fe with low ^{59}Fe incorporation into their red cells. This could be due to failure of the isotope to bind properly with transferrin and loss of ionized tracer iron from the plasma (19). For this reason, the volume of distribution of ^{59}Fe labelled transferrin was determined and it was identical to the volume of distribution of ^{125}I-labelled albumin suggesting that the ^{59}Fe was bound to transferrin and was not free in the plasma. Therefore, no detectable ^{59}Fe was lost into the extravascular space. In addition, using the same methodology, further studies on the same patients revealed red cell ^{59}Fe incorporations of 67-74% indicating that the method was adequate for this index. The low red cell incorporation in several PRCA patients in remission might occur for the following reasons: (1) dilution of ^{59}Fe from increased iron stores, (2) decreased erythropoiesis; or (3) ineffective erythropoiesis.

Prior ferrokinetic [illegible] on PRCA patients in remission have been limited to a determination of the ^{59}Fe clearance rates and red cell ^{59}Fe incorporation (8, 9). In our studies the degree of ineffective erythropoiesis was determined by the difference between erythron iron turnover and the fixed red cell iron turnover (20, 21). Values greater than 0.07 mg/100 ml blood/day generally indicate significant ineffective

erythropoiesis (20). However, one of our patients (number 4) had a negative value of -0.13 and the calculated error of this procedure in our hands was . For this reason, small values of 0.10 - 0.18 may not indicate a significant degree of ineffective erythropoiesis using our methodology. However, a value of 1.11 is clearly significant. Thus, one patient with PRCA in remission (number 2) clearly had a marked degree of ineffective erythropoiesis in her first study, while the other 4 patients had little ineffective erythropoiesis. The presence of ineffective erythropoiesis in patient number 2 was supported by a very fast ^{59}Fe clearance rate with low reticulocytes (low production index (22) , and a marrow with a marked erythroid hyperplasia in the presence of low reticulocytes. Finally, the marrow transit time was greatly prolonged in this patient as measured by direct marrow scanning and normal in the other PRCA patients who had a remission of the disease. An expanded marrow was found in 2 out of 5 patients with PRCA. This has been reported in 1 previous patient with PRCA in remission (23). The low red cell incorporation of ^{59}Fe in the remaining patients with PRCA in remission was probably due to dilution of the isotope by increased iron stores since the patients had sufficient erythropoiesis to maintain a normal hematocrit and since the red cell incorporation of ^{59}Fe improved after multiple phlebotomies.

The significance of our observations seems two-fold. First, the presence of ineffective erythropoiesis while in remission did not appear to have a poor prognostic significance in patient number 2. Without any therapy her marrow evolved from a state of ineffective erythropoiesis to normal erythropoiesis and she has remained normal for 4 years. Second, the fact that some patients with PRCA in remission may have profound ineffective erythropoiesis, while other patients may have normal marrow

erythropoiesis in terms of effective red cell production, suggests that some cases of ineffective erythropoiesis may be related pathogenetically to PRCA. The state of ineffective erythropoiesis was less severe than the original state of PRCA and this could have been due to a reduction in the basic pathogenetic process. The patient was able to maintain a normal hematocrit during this time. Indeed, the peripheral blood counts gave no clue to the presence of ineffective erythropoiesis in this patient. It was only the discrepancy between the blood counts and the marrow erythroid hyperplasia plus the lack of a normal reticulocyte response to phlebotomy that led us to consider a state of ineffective erythropoiesis. With this patient we were unable to demonstrate using an in vitro method previously described (3), that the patient's plasma inhibited heme synthesis by her own marrow cells (Krantz, unpublished observations). Therefore, we cannot be sure that this patient had an immunologic inhibition of her marrow and could not quantitate the pathogenetic process while she had PRCA and while she was in remission.

One patient with a refractory anemia and ongoing erythropoiesis has been studied for a plasma inhibitor of marrow cell function using the plasma clot method (24). It was found that this patient's serum inhibited new erythroid colonies by her own marrow cells. Another patient with primary refractory anemia, ringed sideroblasts, and apparent ineffective erythropoiesis responded on two occasions to treatment with azathiopine, a cytotoxic immunosuppressive drug (25). The fact that some patients with PRCA have antibodies that inhibit their marrow cell function in vitro (3, 4), and that the PRCA often responds to treatment with cytotoxic, immunosuppressive drugs(3, 4, 6-9), taken together with the above case reports (24, 25) suggests that an evolution from a state of PRCA to a

state of ineffective erythropoiesis may occur. Our ferrokinetic study also suggests that in some cases PRCA and the ineffective erythropoiesis of a primary refractory anemia may be related. Further investigation is necessary into an immune pathogenesis of some refractory anemias with ineffective erythropoiesis in order to delineate the mechanism for this anemia and to distinguish those cases that may be related to PRCA and, possibly, susceptible to a similar mode of treatment.

REFERENCES

1. Jacobs EM, Hutter RVP, Pool JL, Ley AB: Benign thymoma and selective erythroid aplasia of the bone marrow. Cancer 12:47, 1959.
2. DiGiacomo J, Furst SW, Nixon DD: Primary acquired red cell aplasia in the adult. J Mt Sinai Hosp 53:382, 1966.
3. Krantz SB, Kao V: Studies on red cell aplasia. I. Demonstration of a plasma inhibitor to heme synthesis and an antibody to erythroblast nuclei. Proc Natl Acad Sci USA 58:493, 1967.
4. Krantz SB, Moore WH, Zaentz SD: Studies on red cell aplasia. V. Presence of erythroblast cytotoxicity in IgG-globulin fraction of plasma. J Clin Invest 52:324, 1972.
5. Krantz SB: Studies on red cell aplasia. III. Treatment with horse anti-human thymocyte gamma globulin. Blood 39:347, 1972.
6. Krantz SB: Pure red cell aplasia. N Engl J Med 291:345, 1974.
7. Zaentz SD, Krantz SB, Brown EB: Studies on pure red cell aplasia. VIII. Maintenance therapy with immunosuppressive drugs. Br J Haematol 32:47, 1976.
8. Bottiger LE, Rausing A: Pure red cell anemia: Immunosuppressive treatment. Ann Intern Med 76:593, 1972.
9. Marmont A, Peschle C, Sanguinetti M, Condorelli M: Pure red cell aplasia (PRCA). Response of these patients to cyclophosphamide and/or antilymphocyte globulin (ALG) and demonstration of two types of serum IgG inhibitors to erythropoiesis. Blood 45:247, 1975.
10. Zaentz SD, Krantz SB, Sears DA: Studies on pure red cell aplasia. VII. Presence of proerythroblasts and response to splenectomy: A case report. Blood 46:261, 1975.

11. Pollycove M, Mortimer R: The quantitative determination of iron kinetics and hemoglobin synthesis in human subjects. J Clin Invest 40:753, 1961.

12. DiGuliemo R, Miliani A, Citi S. Eritroblastoftisi aequisita. Studio clinico, citomorfologico, umorale e radioisotopico. Boll Soc It Emat 11:35, 1963.

13. Finch CA, Deubelbeiss K, Cook JD, Eschbach JW, Harker LA, Funk DD, Marsaglia G, Hillman RS, Slichter S, Adamson JW, Ganzoni A, Giblett ER: Ferrokinetics in man. Medicine 49:17, 1970.

14. Pollycove M, Tono M: Studies of the erythron. Semin Nucl Med 5: 11, 1975.

15. Read RC: Studies of red-cell volume and turnover using radio-chromium. Description of a new "closed" method of red cell volume measurement. N Engl J Med 250:1021, 1954.

16. Lajtha LG: The Use of Isotopes in Haematology. Blackwell Scientific Publications Ltd. Oxford, 1961, pp 8-30.

17. Bothwell TH, Finch CA: Iron Metabolism (ed. 1). Boston, Little, Brown and Co., 1962.

18. Price RR, Johnston RE, Brill AB, Watts JR: Estimation of radioactive content of body organs combining direct measurements and distribution models. Proc. of Symp. on the Assessment of Radioactive Organ and Body Burdens. Stockholm, Sweden. IAEA-SM-150/31, Vienna, 1971, pp. 46-57.

19. Loeffler RK, Rappaport DA, Collins VP: Radioiron citrate as tracer to determine disappearance rate of plasma iron in normal subjects. Proc Soc Exp Biol Med 88:441, 1955.

20. Alexanian R, Alfrey CP: Erythrokinetics and androgens in bone marrow cancer. Cancer 38:833, 1976.

21. Cook JD, Marsaglia G, Eschbach JW, Funk DD, Finch CA: Ferrokinetics: A biologic model for plasma iron exchange in man. J Clin Invest 49: 197, 1970.

22. Bothwell TH, Hurtado AV, Donohue DM, Finch CA: Erythrokinetics. IV. The plasma iron turnover as a measure of erythropoiesis. Blood 12: 409, 1957.

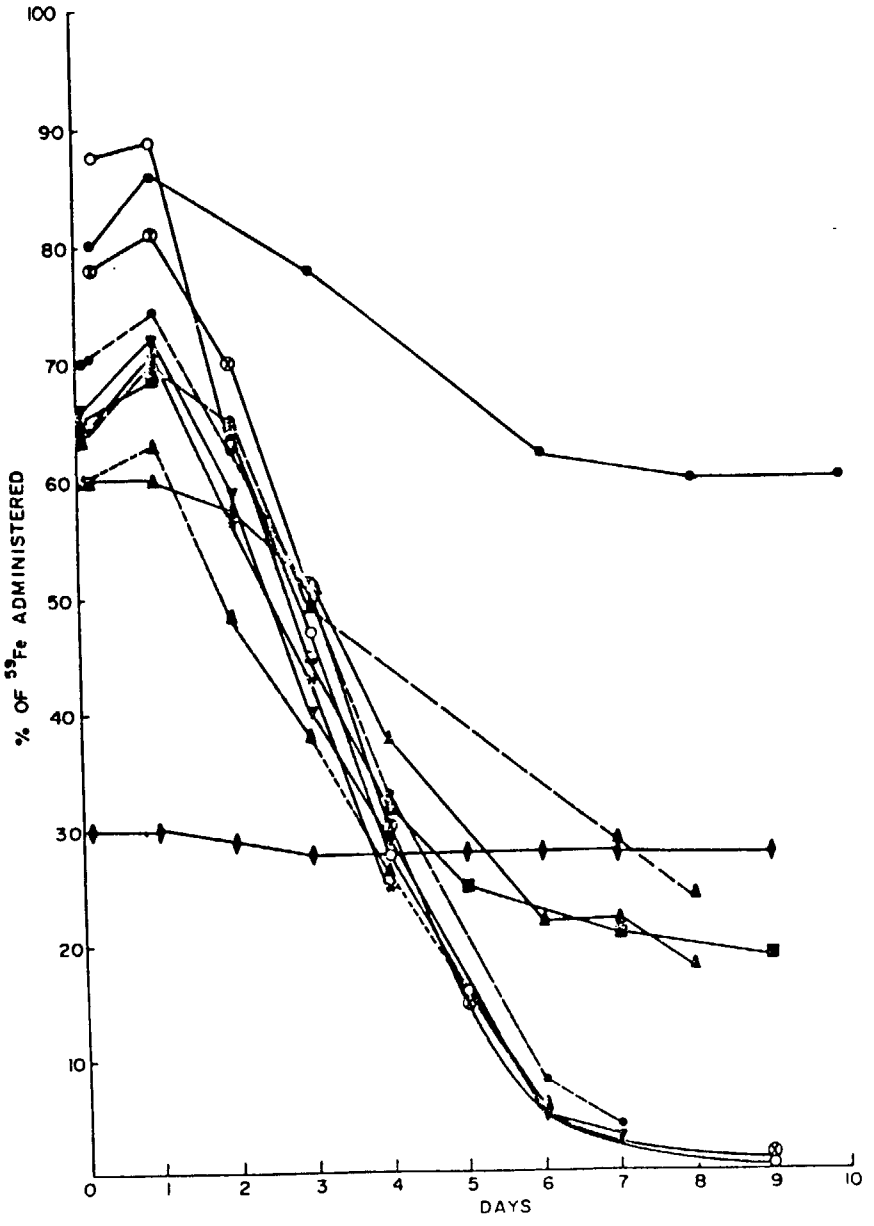
23. Bunn HF, McNeil BJ, Rosenthal DS, Krantz SB: Bone-marrow imaging in pure red cell aplasia. Arch Intern Med 136:1169, 1976.

24. Browman GP, Freedman MH, Blajchman MA, McBride JA: A complement independent erythropoietic inhibitor acting on the progenitor cell in refractory anemia. Am J Med 61:572, 1976.

25. Zervas J, Geary CG, Oloesky S: Sideroblastic anemia treated with immunosuppressive therapy. Blood 44:117, 1974.

Figure 1. Marrow radioiron transit time curves. Normal volunteers o - - o and o——o. Patient number 6 with PRCA ◊——◊. Patients with PRCA in remission: number 1, Oct., 74 ▲——▲, June, 75 ▲- - -▲, and Nov., 76 ▲——▲, number 2, Nov., 73 ●——● and Aug., 76 ●- - -●; number 3, ■——■; number 4, ▼——▽; number 5, *——*.

1018433


100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
DAYS
% OF ^{59}Fe ADMINISTERED

1018434

Figure 2. Comparison of marrow transit time curves for patient number 2 determined by two methods. Transit time curves derived by direct measurement of radioiron activity in the pelvis are compared with curves calculated from circulating levels of radioiron in the plasma and red cells (13). Measurements were made in 1973 shortly after remission of PRCA and in 1976. Direct measurement Nov., 1973 (o——o); calculated from blood levels Nov., 1973 (o——o); direct measurement Aug., 1976 (o- - -o); calculated from blood levels Aug., 76 (o- - -o). Direct measurement of Nov., 1973 after subtracting day 10 activity (Δ——Δ).

1018435

Fig. 2

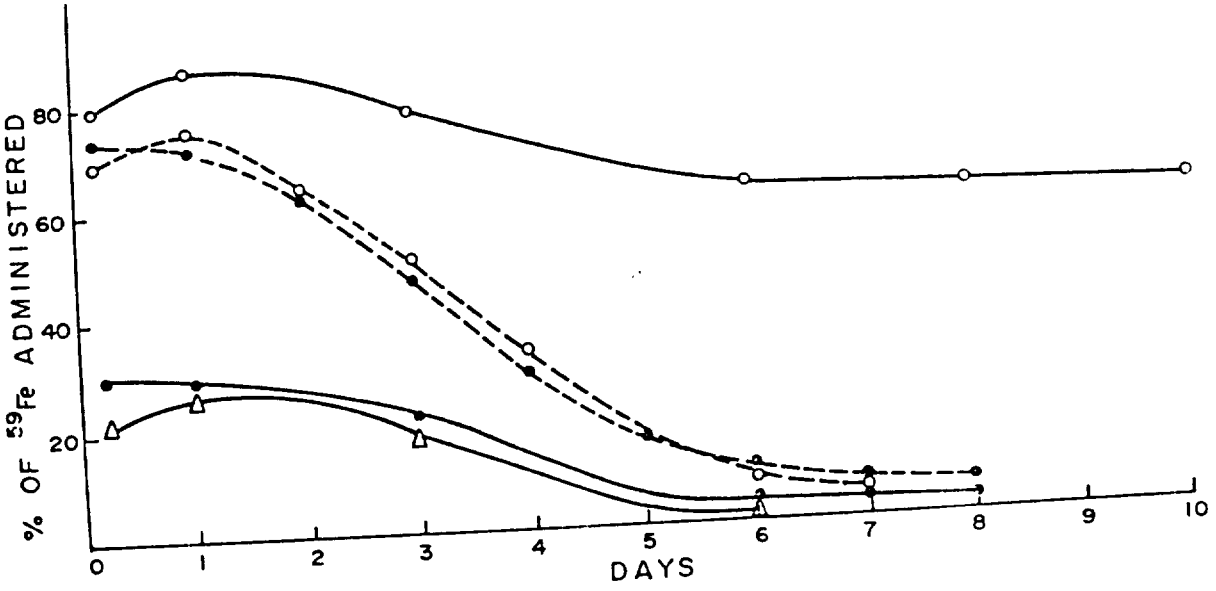
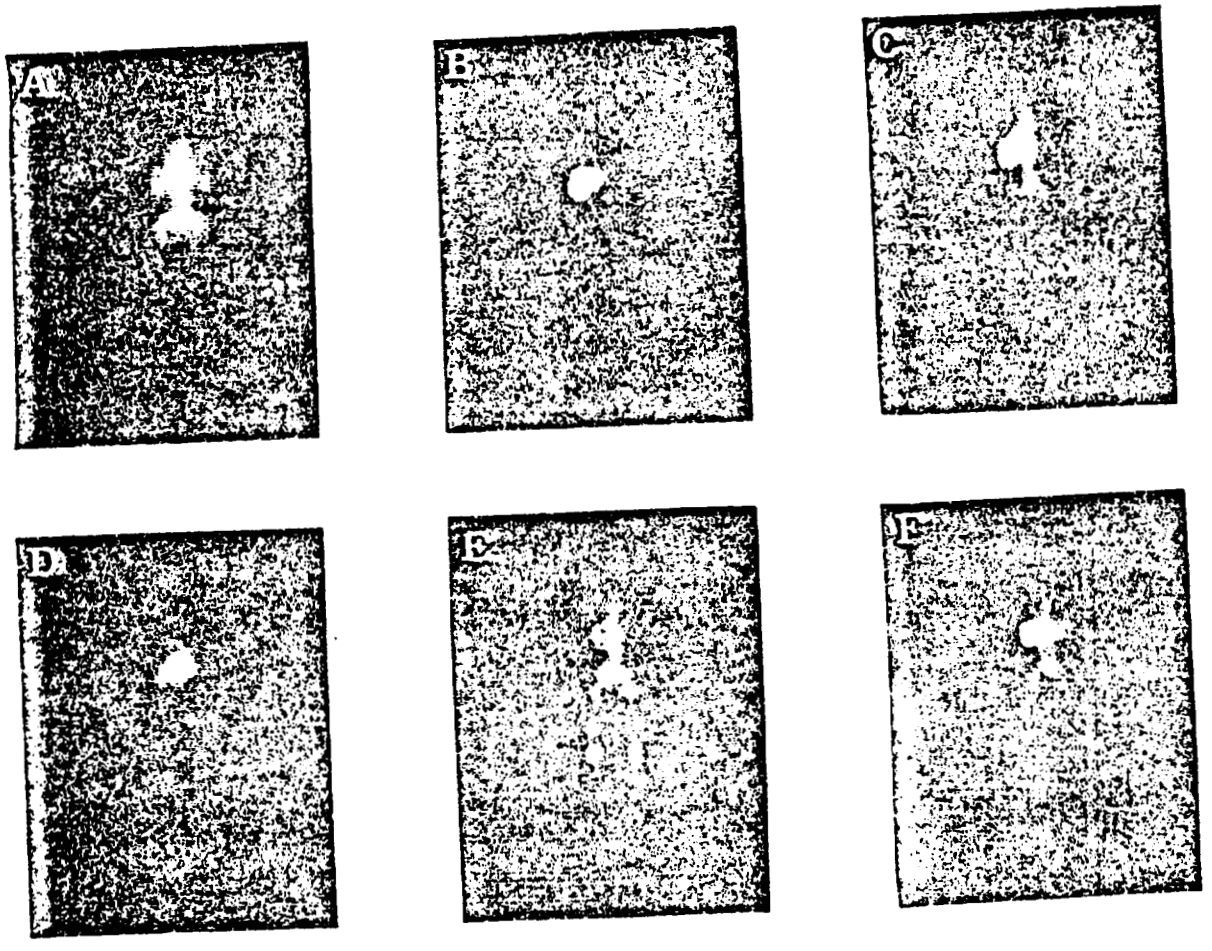


Figure 3. Surface organ scanning (A) Normal volunteer. (B) Patient number 6 with PRCA. (C,D,E,F) Patients with PRCA in remission showing (C) normal marrow distribution of ^{59}Fe in patient number 3, (D) moderate extension of bone marrow into lower extremities in patient number 5, (E) marked extension of bone marrow in patient number 2 in first study after remission, and (F) reduction of marrow extension in patient number 2 three years later.

1018437

Fig. 3



SUMMARY OF CURRENT RADIATION DOSE ESTIMATES TO HUMANS FROM 52-Fe, 55-Fe, and 59-Fe AS FERROUS CITRATE AND FERRIC CHLORIDE

RADIOPHARMACEUTICAL

Radioiron as a radiopharmaceutical is supplied in an acidic solution of ferrous citrate or ferris chloride with a specific activity of approximately 5 to 30 mCi per ug of iron. The production methods for radioisotopes of iron, 52-Fe, 55-Fe and 59-Fe yield carrier free products. For the purpose of these dose calculations the radionuclide and radiochemical purity of the radiopharmaceutical have been assumed to be 100%.

NUCLEAR DATA

Nuclear data for the radioisotopes of iron considered in this report are given in Table I.

BIOLOGICAL DATA

The data for human tissue distribution data for radioiron on which this report is based were obtained from the literature and from studies by M. Pollycove and H.S. Winchell at the Donner Laboratory of Medical Physics, University of California and the Clinical Laboratories, San Francisco General Hospial, San Francisco, California, and R. Price at Vanderbilt University, Nashville, Tennessee.

The iron kinetics dosimetry model was derived based upon these data. The basic model has been found to be useful for describing normal kinetics as well as in a mojority of the abnormal cases. The model is not purported to be complete and final model for iron kinetics but is considered to be adequate to provide radiation dose estimates to the tissues.

The problems associated with the measurements of the parameters of iron metabolism have been recognized for many years. The sizes of the

iron storage pools have been particularly difficult to determine by tracer techniques because of the long time required for the equilibration of these pools with the circulating iron pools. In order to adequately characterize the storage pools of the liver and slpeen by means of plasma levels of the radioiron (the most commonly used technique), measurements over extended time intervals would be required. The extended time periods present two major problems: 1) plasma levels of radioiron are extremely low making the statistical errors associated with the measurements large and, 2) measurements over extended periods are not practical especially for critically ill patients. Critically ill patients receive numerous transfusions of whole blood and packed red cells which tend to alter blood volumes and consequently the estimates of absolute circulating iron levels. Quantitative external measurements of the peripheral iron storage pools can be combined with the measurements of the circulating iron pools in a self consistent manner using compartmental modelling techniques. The ability to measure the turnover of these slowly exchanging compartments directly, rather than inferring their kinetics from plasma clearance and red blood cell incorporation of radioiron, provides additional information on the anatomical distribution of these pools within the body and makes possible more reasonable dosimetric calculations.

A schematic of the compartmental model that used for the dosimetric calculations is shown in Appendix I. The criterion for choosing this model over more complex ferrokinetic models is that this model was the simplest model we were able to find that was consistent with

the meausred data for the largest number of studies. With this model we have successfully fit kinetic data on three normals and 16 abnormals. The presumed diagnosis of the 16 abnormals is shown in Table II. In two patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) the model was inadequate to descibe the kidney uptake and urinary

excretion of iron. For these studies a more complex model was employed which included kidney and urine compartments. (The NIH Simulation Analysis and Modelling program SAAM was used for these calcuations).

A. Normal Kinetics

Iron compounds following intravenous injection are rapidly bound to transferrin and most of the administered tracer radioiron moves from plasma to bone marrow for hemoglobin synthesis in erythroblasts and reticulocytes. Much less of the iron is exchanged between plasma and extracellular fluid such as is contained in viscera other than liver. Plasma iron is exchanged to and from rapidly equilibrating tissue iron pools such as the cellular heme enzyme, and to and from tissue iron stores.

In normal iron kinetics the decrease in plasma radioiron occurs as a multicomponent exponential curve. The slower components are a result of feedback into the plasma of iron from the extracellular fluid and storage iron. Circulating RBC accumulation of radioactivity mirrors the release of radioactivity from the marrow and reaches a plateau within ten days.

Numerous models have been proposed to describe iron kinetics (4,5). The model used for the dose estimates in this report (6,7), contains the salient features of the other models and is particularly useful for dosimetry purposes because the computer program (SAAM),(8) can directly provide the cumulated activities, $\tilde{A}$ μCi-hr.

The time retention curve of administered radioiron within the liver, spleen and red marrow were determined from external counting measurements. The fraction of activity in these organs was derived from the literature and experimentally confirmed from external counting measurements combined with a computer program (SAAM) to determine the most probable value for net content of radioactivity in an organ where the measurement is a superposition of several compartments.

The percent of administered radioiron in the liver reaches an equilibrium level of 20-30% within 10-15 days, 15-25% of which is due to activity in the circulaitng RBC. The spleen reaches an equilibrium level of 8-12% within 10-15 days with 8-10% of the activity being accounted for by the circulating RBC. A maximum of 70-90% is reached in the red marrow within 24 hours and is released with a mean time of 3-5 days. Upon release from the marrow, the radioiron becomes incorporated in the RBC reaching a maximum of 80-90% in 10 to 15 days. The remaining 4-5% of administered radioiron is assumed to be distributed uniformly throughout the body. Total body radioactivity measurements (1,2,3) indicate an iron loss on the order of 0.01 to 0.1% per day. The radiation dose estimates in this report are based upon the assumption that there is no loss from the body.

In order to conform to earlier MIRD publications, we have sought to derive analytical expressions for the time activity curves in normals for the various organs of interest (liver, spleen, marrow, red blood cells). The approach was to first fit the observed data using the SAAM program and model. The "best fit" model parameters were then used to generate noise free retention curves which were then fit to equations of the form of sums of exponentials. These activity rentention curves were then integrated over time to obtain the cumulative and activity $\tilde{A}$ μCi-hr in terms of μCi·days/μCi. The S factor for Fe-59 as published by Snyder, et al (Table III) in terms of m rem/μCi·day were then used along with cumulative activity results to make the dose estimates. The sources of activity were taken to be only in the liver, spleen, marrow and circulating red blood cells.

For the normal kinetics we have fit the average data from three young male volunteers. The resulting intercompartmental rate constants are shown as patient Q in Table II. The analytical expressions resulting from these calculations of the liver, spleen, circulating red blood cells

1018442

and marrow are shown below. The units of the activity retention curves are in percent of the administered activity (i.e. μCi retained per μCi administered)with the time unit in days.

$$\text{liver } (t) = 25.2 - 17.5e^{-0.160t} + 4.66e^{-1.11t}$$

$$\text{spleen}(t) = 10.7 - 8.9e^{-0.224t} + 0.69e^{-0.76t}$$

$$\text{RBC } (t) = 98.2\ (e^{-0.005t} - e^{-0.160t}) - 50.0e^{-3.63t}$$

$$\text{Marrow } (t) = 90.2e^{-0.195t} - 13.4e^{-0.134t}$$

The liver and spleen time-activity curves were estimated by determining the fraction of the slowly equilibrating storage compartments and the circulating blood pool compartments necessary to reproduce the external measurements. Those fractions were found to be:

$$\text{Liver} = 0.67\ (\text{fast stores}) + 0.15\ (\text{slow stores}) + 0.26\ (\text{RBC})$$

$$\text{Spleen} = 0.15\ (\text{fast stores}) + 0.15\ (\text{slow stores}) + 0.10\ (\text{RBC})$$

The cumulative activity curves for the liver and spleen included the fraction of the circulating RBC compartment indicated in the above equations. These calculations assume no recirculation of the iron following the death of circulating red blood cells.

B. Abnormal

We have carried out the calculations for $\tilde{A}$ μCi-hr for the marrow, RBC, liver and spleen for each of the abnormal studies. The resulting $\tilde{A}$'s are shown in Table IV. Using these values we have estimated the average radiation doses to the red marrow, RBC, liver spleen, gonads and total body using direct numerical integration of the compartment contents using the SAAM program. The results of these calculations are shown indetailed in Appendix II.

E4484 0181

Table V summarizes the results of our dosimetric studies on 16 abnormal subjects. We have catagorized the results of the radiation dose estimates with respect to disease state. More complex tables such

as this can be used by physicians to estimate what radiation doses might be expected as the result of a diagnostic procedure. Even from this rather small sampling of disease states, strong disease dependence is obvious.

1018444

REPOSITORY Oak Ridge Operations Office
COLLECTION Reading Room
BOX No. RHA Shipment 9162 Box 6+7 PART 3 of 4
FOLDER New York Times FOIA Requests 88-91

OFFICE OF CHIEF COUNSEL
FILE
No papers will be removed therefrom
without special authority

1018445

Contract No. DE-AS05-76EV02401
VANDERBILT UNIVERSITY
Modification No. M028

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 26th day of December, 1978, effective the 1st day of November, 1978, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the SECRETARY OF ENERGY (hereinafter referred to as the "Secretary"), the statutory head of the DEPARTMENT OF ENERGY (hereinafter referred to as "DOE"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the Contractor and the Government, represented by the Secretary of the Department of Energy, have heretofore entered into Contract No. EY-76-S-05-2401 and Modifications No. 1 through A027 providing for the Contractor's performance of certain research; and

WHEREAS, the Contractor and DOE desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Department of Energy Organization Act (P. L. 95-91), and other applicable law, including Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. The contract designation number "EY-76-S-05-2401" is hereby changed to "DE-AS05-76EV02401."

2. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date October 31, 1978, is changed to October 31, 1979.

3. In Paragraph (a) of ARTICLE III - CONSIDERATION, the sum of $54,037 is added, increasing the sum $618,537 to $672,574.

4. The attached Appendix "A" is made applicable to the period indicated thereon.

5. The attached Appendices "B", "C" and "D" replace the Appendices "B", "C" and "D" attached to Modification No. A027 to the contract.

1018446

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: SECRETARY OF ENERGY

BY: _____

TITLE: _____

VANDERBILT UNIVERSITY

BY: _____

James S. Kramer

TITLE: Assistant Vice President for Medical Affairs

I, Thomas W. Haines (Attester), certify that I am the Director, Sponsored Research & Programs (Title) of the Contractor named under this contract; that James S. Kramer (Signatory) who signed this contract on behalf of said Contractor was then Assistant Vice President (Title) for Medical Affairs of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt University School of Medicine

Contract No.: Modification No. M028 to Contract No. DE-AS05-76EV02401

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: DE-AS05-76EV02401

For the contract period: November 1, 1978 through October 31, 1979

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct radioisotope studies utilizing a low level body counter and clinical applications of activation analysis. Most of the current work is directed toward the evaluation of radiation dose distributions from new radioactive tracers and new procedures.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 16% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages: $36,955

(2) Equipment to be purchased or fabricated by the Contractor: $ 2,785

a Equipment estimated to cost less than $1,000:

None

b Equipment estimated to cost in excess of $1,000:

CAMAC MM-816C 8192 16 Bit Word Memory Module

1018448

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: DE-AS05-76EV02401

(3) Travel: $ 1,500

Domestic---------$ 1,500
Foreign----------$ 0

(4) Other direct costs: $ 9,158

(5) Indirect costs (based on a predetermined rate of 65% of salaries and wages): $24,021

(b) Items, if any, significant to the performance of this contract, but excluded from computation of support cost and from consideration in proportioning costs:

(1) Items to be contributed by Contractor:

None

(2) Items to be contributed by the Government:

None

(c) Time or effort of Principal Investigator(s) contributed by Contractor, but excluded from computation of support cost and from consideration in proportioning costs:

All costs including salary, fringe benefits, and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $ 74,419 ; DOE will pay 100 % of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and the Article entitled "Determination of Support Costs" in Appendix "B". The estimated DOE Support Cost for the contract period stated in this Appendix "A" is $ 74,419 .

1018449

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: DE-AS05-76EV02401

The estimated DOE Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$20,382
(b) New funds for the current period:	$54,037

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

1018450

TABLE OF CONTENTS

APPENDIX "B"---GENERAL PROVISIONS

Article No.		Page No.
I	DEFINITIONS	1
II	INSPECTION, REPORTS, RECORDS, AND ACCOUNTS	1
III	PUBLICATION OF RESULTS	2
IV	DISCLOSURE OF INFORMATION	2
V	PATENT RIGHTS	3
VI	RIGHTS IN TECHNICAL DATA	5
VII	RIGHTS TO PROPOSAL DATA	7
VIII	AUTHORIZATION AND CONSENT	7
IX	NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT	7
X	REPORTING OF ROYALTIES	8
XI	RESPONSIBILITY FOR THE WORK	8
XII	PROPERTY ITEMS	8
XIII	TERMINATION FOR CONVENIENCE OF THE GOVERNMENT	10
XIV	PAYMENTS	12
XV	EQUAL OPPORTUNITY	14
XVI	CONVICT LABOR	16
XVII	CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION	16
XVIII	DISPUTES	17
XIX	OFFICIALS NOT TO BENEFIT	17

1018451

rticle No.		Page No.
XX	COVENANT AGAINST CONTINGENT FEES	18
XXI	EXAMINATION OF RECORDS BY COMPTROLLER GENERAL	18
XII	BUY AMERICAN ACT	19
III	ASSIGNMENT: SUBCONTRACTING	20
XIV	REPORTS AND RENEWAL PROPOSALS	20
XV	FOREIGN TRAVEL	21
VI	PRIORITIES, ALLOCATIONS, AND ALLOTMENTS	21
VII	UTILIZATION OF LABOR SURPLUS AREA CONCERNS	21
III	UTILIZATION OF SMALL BUSINESS CONCERNS	22
XIX	UTILIZATION OF MINORITY BUSINESS ENTERPRISES	22
XX	SOVIET-BLOC CONTROLS	22
XXI	DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA	23
II	EMPLOYMENT OF THE HANDICAPPED	26
III	DETERMINATION OF SUPPORT COSTS	27
XIV	ADDITIONAL APPROVALS	28
XV	PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS	30
VI	CLEAN AIR AND WATER	30

1t of Energy.

used herein
ecretary, or
tary depart-
ized
er than
f the

executing this
er or civilian
; and the term
the authorized
limits of his

the term "sub-

OUNTS

nner and at
ies of the Con-
his contract.

ports in such
tled "Reports
uch other
contract, as

of account, in
and practices,
t Circular-
date of the
items included
rtherance of
ntractor con-
all maintain
the contri-
Article A-II(b),
n accordance
.b. of FMC 73-8.

1018452

(d) DOE shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, in accordance with the retention requirements referenced in the article entitled "Examination of Records By Comptroller General," of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

After compliance with the patent review requirements of Article B-V(g) below, research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by DOE. A copy of each article submitted by the Contractor for publication shall be promptly sent to DOE. The Contractor shall also inform DOE when the article is published and furnish six (6) copies of the article as finally published.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of DOE, and shall promptly inform DOE in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and DOE regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons,

1018453

the production of special nuclear material or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - PATENT RIGHTS

(a) Definitions.

(1) "Subject Invention" means any invention or discovery of the Contractor conceived or first actually reduced to practice in the course of or under this contract, and includes any art, method, process, machine, manufacture, design, or composition of matter, or any new and useful improvement thereof, or any variety of plants, whether patented or unpatented, under the Patent Laws of the United States of America or any foreign country.

(2) "Patent Counsel" means the DOE Patent Counsel assisting the procuring activity.

(b) Invention disclosures and reports.

(1) The Contractor shall furnish the Patent Counsel (with notification by Patent Counsel to the Contracting Officer):

(i) A written report containing full and complete technical information concerning each Subject Invention within 6 months after conception or first actual reduction to practice whichever occurs first in the course of or under this contract, but in any event prior to any on sale, public use, or public disclosure of such invention known to the Contractor. The report shall identify the contract and inventor and shall be sufficiently complete in technical detail and appropriately illustrated by sketch or diagram to convey to one skilled in the art to which the invention pertains a clear understanding of the nature, purpose, operation, and to the extent known, the physical, chemical, biological, or electrical characteristics of the invention;

(ii) Upon request, but not more than annually, interim reports on a DOE-approved form listing Subject Inventions for that period and certifying that all Subject Inventions have been disclosed or that there were no such inventions; and

(iii) A final report on a DOE-approved form within 3 months after completion of the contract work listing all Subject Inventions and certifying that all Subject Inventions have been disclosed or that there were no such inventions.

1018454

(2) The Contractor agrees that the Government may duplicate and disclose Subject Invention disclosures and all other reports and papers furnished or required to be furnished pursuant to the contract.

(c) Allocation of principal rights.

(1) Assignment to the Government. The Contractor agrees to assign to the Government the entire right, title, and interest throughout the world in and to each Subject Invention, except to the extent that rights are retained by the Contractor under subparagraphs (c)(2) and (d) of this article.

(2) Greater rights determinations. The Contractor, or the employee-inventor with authorization of the Contractor, may request greater rights than the nonexclusive license and the right to request foreign patent rights provided in paragraph (d) of this article on identified inventions in accordance with the procedure and criteria of 41 CFR 9-9.109-6. A request for a determination of whether the Contractor or the employee-inventor is entitled to retain such greater rights must be submitted to the Patent Counsel at the time of the first disclosure of the invention pursuant to subparagraph (b)(1) of this article or not later than 9 months thereafter or such longer period as may be authorized by the Patent Counsel (with notification by Patent Counsel to the Contracting Officer) for good cause shown in writing by the Contractor. The information to be submitted for a greater rights determination is specified in 41 CFR 9-9.109-6(e).

(d) Minimum rights to the Contractor. The Contractor reserves a revocable, nonexclusive, paid-up license in each patent application filed in any country on a Subject Invention and any resulting patent in which the Government acquires title. Revocation shall be in accordance with the procedure of subparagraphs (c)(2) and (3) of the article in 41 CFR 9-9.107-5(a). The Contractor also has the right to request foreign rights in accordance with the procedures of subparagraph (c)(4) of the article in 41 CFR 9-9.107-5(a).

(e) Employee and Subcontractor agreements. Unless otherwise authorized in writing by the Contracting Officer, the Contractor shall:

(1) Obtain patent agreements to effectuate the provisions of the Patent Rights article from all persons in its employ who perform any part of the work under this contract except nontechnical personnel, such as clerical employees and manual laborers.

1018455

(2) Unless otherwise authorized or directed by the Contracting Officer the Contractor shall include the Patent Rights article of 41 CFR 9-9.107-5(a) or 41 CFR 9-9.107-6, as appropriate, modified to identify the parties in any subcontract hereunder, having as a purpose the conduct of research, development, or demonstration work; and

(3) Promptly notify the Contracting Officer in writing upon the award of any subcontract containing a Patent Rights article by identifying the Subcontractor, the work to be performed under the subcontract, and the dates of award, and estimated completion. Upon the request of the Contracting Officer, the Contractor shall furnish a copy of the subcontract to such requestor.

(f) Atomic energy.

(1) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(2) Except as otherwise authorized in writing by the Contracting Officer, the Contractor will obtain patent agreements to effectuate the provisions of paragraph (f)(1) of this article from all persons who perform any part of the work under this contract, except nontechnical personnel such a clerical employees and manual laborers.

(g) Publication.

In order that information concerning scientific or technical developments conceived or first actually reduced to practice in the course of or under the contract is not prematurely published so as to adversely affect patent interest of DOE, the Contractor agrees to submit to the Patent Counsel for patent review a copy of each paper 60 days prior to its intended publication date. The Contractor may publish such information after expiration of a 60-day period following such submission or prior thereto if specifically approved by Patent Counsel, unless the Contractor is informed in writing within the 60-day period, that in order to protect patentable subject matter, publication must be further delayed. In this event, publication shall be delayed up to 100 days beyond the 60-day period or such longer period as mutually agreed to.

ARTICLE B-VI - RIGHTS IN TECHNICAL DATA

(a) Definitions.

The definitions of terms set forth in 41 CFR 9-9.201 apply to the extent these terms are used herein.

(b) Allocation of rights.

(1) The Government shall have:

(i) Unlimited rights in technical data first produced or specifically used in the performance of this contract;

(ii) The right of the Contracting Officer or his representatives to inspect at all reasonable times up to three (3) years after final payment under this contract all technical data first produced or specifically used in the contract (for which inspection the Contractor or its subcontractor shall afford proper facilities to DOE);

(iii) The right to have any technical data first produced or specifically used in the performance of this contract delivered to the Government as the Contracting Officer may from time to time direct during the progress of the work or in any event as the Contracting Officer shall direct upon completion or termination of this contract.

(2) The Contractor shall have:

The right to use for its private purposes, subject to patent, security or other provisions of this contract, technical data it first produces in the performance of this contract provided the data requirements of this contract have been met as of the date of the private use of such data. The Contractor agrees that to the extent it receives or is given access to proprietary data or other technical, business or financial data in the form of recorded information from DOE or DOE contractor or subcontractor, the Contractor shall treat such data in accordance with any restrictive legend contained thereon, unless use is specifically authorized by prior written approval of the Contracting Officer.

(c) Copyrighted material.

(1) The Contractor agrees to, and does hereby grant to the Government, and to its officers, agents, servants and employees acting within the scope of their duties:

(i) A royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use, and dispose of and to authorize others so to do, all copyrightable material first produced or composed in the performance of this contract by the Contractor, its employees or any individual or concern specifically employed or assigned to originate and prepare such material; and

1018457

(ii) a license as aforesaid under any and all copyrighted or copyrightable works not first produced or composed by the Contractor in the performance of this contract but which are incorporated in the material furnished under the contract, provided that such license shall be only to the extent the Contractor now has, or prior to completion or final settlement of the contract may acquire, the right to grant such license without becoming liable to pay compensation to others solely because of such grant.

(2) The Contractor agrees that it will not knowingly include any material copyrighted by others in any written or copyrightable material furnished or delivered under this contract without a license as provided for in subparagraph (1)(ii) hereof, or without the consent of the copyright owner, unless it obtains specific written approval of the Contracting Officer for the inclusion of such copyrighted material.

ARTICLE B-VII - RIGHTS TO PROPOSAL DATA

Except for technical data contained on pages _____ of the Contractor's proposal dated _____ which are asserted by the Contractor as being proprietary data, it is agreed that as a condition of the award of this contract, and notwithstanding the provisions of any notice appearing on the proposal, the Government shall have the right to use, duplicate, and disclose and have others do so for any purpose whatsoever, the technical data contained in the proposal upon which this contract is based.

ARTICLE B-VIII - AUTHORIZATION AND CONSENT

The Government hereby gives its authorization and consent for all use and manufacture of any invention described in and covered by a patent of the United States in the performance of this contract or any part hereof or any amendment hereto or any subcontract hereunder (including any lower-tier subcontract).

ARTICLE B-IX - NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT

The provisions of this article shall be applicable only if the amount of this contract exceeds $10,000.

(a) The Contractor shall report to the Contracting Officer, promptly and in reasonable written detail, each notice or claim of patent or copyright infringement based on the performance of this contract of which the Contractor has knowledge.

(b) In the event of any claim or suit against the Government on account of any alleged patent or copyright infringement arising out of the performance of this contract or out of the use of any supplies furnished or work or services performed hereunder, the Contractor shall furnish to the Government when requested by the Contracting Officer, all evidence and information in possession of the Contractor pertaining to such suit or claim. Such evidence and information shall be furnished at the expense of the Government except where the Contractor has agreed to indemnify the Government.

(c) This article shall be included in all subcontracts.

ARTICLE B-X - REPORTING OF ROYALTIES

If this contract is in an amount which exceeds $10,000 and if any royalty payments are directly involved in the contract or are reflected in the contract price to the Government, the Contractor agrees to report in writing to the Contracting Officer or Patent Counsel during the performance of this contract and prior to its completion or final settlement the amount of any royalties or other payments paid or to be paid by it directly to others in connection with the performance of this contract together with the names and addresses of licensors to whom such payments are made and either the patent numbers involved or such other information as will permit identification of the patents or other basis on which the royalties are to be paid. The approval of DOE of any individual payments or royalties shall not stop the Government at any time from contesting the enforceability, validity or scope of, or title to, any patent under which a royalty or payments are made.

ARTICLE B-XI - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves an DOE license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-XII - PROPERTY ITEMS

(a) Except as otherwise provided in this Paragraph (a) and Paragraph (b) of this article, title to all material, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto: And, provided, There is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities,

1018459

the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to Paragraphs (b), (c), (d), (e), and (f) of this article.

(b) Subject to the mutual agreement of DOE and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government Property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain, at all times and in a manner satisfactory to DOE, records showing the use and disposition of Government property. Such records shall be subject to DOE inspection at all reasonable times and DOE shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by DOE, the Contractor shall use Government property only for the purposes of this contract: Provided, however, That the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use: (1) Does not interfere with its work under this contract; (2) is not prohibited by provisions of the other Federal agreements; and (3) is promptly reported by the Contractor to DOE under this contract.

(d) The Contractor shall promptly notify DOE of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of DOE.

(e) With the written approval of DOE, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may mutually be agreed upon in writing by the Contractor and DOE. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of DOE payments to be made under this contract, as DOE may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to DOE upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

ARTICLE B-XIII - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination, the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the Notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

1018461

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by DOE's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under Paragraph (c) shall be governed by the contract cost principles and procedures in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3) in effect on the date of this contract, except that if the Contractor is not an educational institution any costs claimed, agreed to, or determined pursuant to Paragraphs (c) or (e) hereof shall be in accordance with Subpart 1-15.2 of the Federal Procurement Regulations (41 CFR 1-15.2) in effect on the date of this contract.

(e) Subject to the provisions of Paragraph (c) above, and subject to any review required by DOE's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate established by the Secretary of the Treasury pursuant to Public Law 92-41 (50 U.S.C. App. 1215(b)(2)) for the Renegotiation Board, beginning 30 days from the date of such demand.

10184462

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XIV - PAYMENTS

(a) DOE shall make payments to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of 45 percent of the new funds as set forth in Article A-III(b) of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional 45 percent of the new funds as set forth in Article A-III(b) of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the new funds set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the DOE support cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report required by the article entitled "Reports and Renewal Proposals", in form and content satisfactory to DOE, and submission of a certified statement showing the support cost and evidencing the Contractor's performance under the contract and compliance by the Contractor with the patent provisions of this contract.

(b) The payments made pursuant to Paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to the article entitled "Termination for Convenience of the Government" hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of the article entitled "Termination for Convenience of the Government" shall be promptly returned to DOE.

(c) DOE, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) DOE shall issue a letter of credit as provided for by Treasury Fiscal Requirements Manual, Part VI, Section 1020, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the new funds as set forth in Article A-III(b) of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Fiscal Requirements Manual, Part VI, Section 1020, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in the Article entitled "Reports and Renewal Proposals," in form and content satisfactory to DOE, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission

1018464

by the Contractor to DOE of such invoices or vouchers as are satisfactory to DOE, DOE shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a payment voucher on letter of credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the new funds as set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the DOE support cost for the pertinent period and evidencing the Contractor's performance under the contract.

(2) DOE reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (c)(1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XV - EQUAL OPPORTUNITY

(The following article is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor [41 CFR, Ch. 60].)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity article.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity article, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by DOE and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity article of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of Paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as DOE may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by DOE, the Contractor may request the United States to enter into such litigation to protect the interest of the United States.

ARTICLE B-XVI - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment except as provided by Public Law 89-176, September 10, 1965 (18 U.S.C. 4082(c)(2)), and Executive Order 11755, December 29, 1973.

ARTICLE B-XVII - CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours and Safety Standards Act (40 U.S.C. 327-333), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder.

(a) Overtime Requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers, mechanics, apprentices, trainees, watchmen, and guards shall require or permit any laborer, mechanic, apprentice, trainee, watchman, or guard in any workweek in which he is employed on such work to work in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek on work subject to the provisions of the Contract Work Hours and Safety Standards Act unless such laborer, mechanic, apprentice, trainee, watchman, or guard receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; Liability for Unpaid Wages; Liquidated Damages. In the event of any violation of the provisions of Paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer, mechanic, apprentice, trainee, watchman, or guard employed in violation of the provisions of Paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of 8 hours or in excess of his standard workweek of 40 hours without payment of the overtime wages required by Paragraph (a).

(c) Withholding for Unpaid Wages and Liquidated Damages. The Contracting Officer may withhold from the Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor,

such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of Paragraph (b).

(d) Subcontracts. The Contractor shall insert Paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XVIII - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to DOE. The decision of DOE or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in Paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XIX - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XX - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XXI - EXAMINATION OF RECORDS BY THE COMPTROLLER GENERAL

(a) This article is applicable if the amount of this contract exceeds $10,000 and was entered into by means of negotiation, including small business restricted advertising, but is not applicable if this contract was entered into by means of formal advertising.

(b) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract unless the DOE authorizes their prior disposition, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(c) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract unless the DOE authorizes their prior disposition, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (1) purchase orders not exceeding $10,000 and (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(d) The periods of access and examination described in (b) and (c) above, for records which relate to (1) appeals under the "Disputes" article of this contract, (2) litigation or the settlement of claims arising out of the performance of this contract, or (3) costs and expenses of this contract as to which exception has been taken by the Comptroller General or any of his duly authorized representatives, shall continue until such appeals, litigation, claims, or exceptions have been disposed of.

(e) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XXII - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10a - 10d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which DOE determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which DOE determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XXIII - ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by the Contracting Officer. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by the Contracting Officer.

ARTICLE B-XXIV - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Research Contracts, Procedures, and Reports Branch, Contract Division, Oak Ridge Operations Office, United States Department of Energy, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports, preprints, and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three (3) months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as DOE may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

1018471

ARTICLE B-XXV - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer for each separate trip regardless of whether funds for such travel are contained in an approved budget. Foreign travel is defined as any travel outside of Canada and the United States and its territories and possessions.

ARTICLE B-XXVI - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Domestic and International Business Administration, Department of Commerce, in obtaining controlled materials and other products and materials needed to fill this contract.

ARTICLE B-XXVII - UTILIZATION OF LABOR SURPLUS AREA CONCERNS

(The following article is applicable if this contract exceeds $5,000.)

(a) It is the policy of the Government to award contracts to labor surplus area concerns that (1) have been certified by the Secretary of Labor (hereafter referred to as certified-eligible concerns with first or second preferences) regarding the employment of a proportionate number of disadvantaged individuals and have agreed to perform substantially (i) in or near sections of concentrated unemployment or underemployment or in persistent or substantial labor surplus areas or (ii) in other areas of the United States, respectively, or (2) are noncertified concerns which have agreed to perform substantially in persistent or substantial labor surplus areas, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy.

(b) In complying with Paragraph (a) of this article and with Paragraph (b) of the article of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (1) Certified-eligible concerns with a first preference which are also small business concerns; (2) other certified-eligible concerns with a first preference; (3) certified-eligible concerns with a second preference which are also small business concerns; (4) other certified-eligible concerns with a second preference; (5) persistent or substantial labor surplus area concerns which are also small business concerns; (6) other persistent or substantial labor surplus area concerns; and (7) small business concerns which are not labor surplus area concerns.

1018472

ARTICLE B-XXVIII - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXIX - UTILIZATION OF MINORITY BUSINESS ENTERPRISES

(a) It is the policy of the Government that minority business enterprises shall have the maximum practicable opportunity to participate in the performance of Government contracts.

(b) The Contractor agrees to use its best efforts to carry out this policy in the award of its subcontracts to the fullest extent consistent with the efficient performance of this contract. As used in this contract, the term "minority business enterprise" means a business, at least 50 percent of which is owned by minority group members or, in case of publicly owned businesses, at least 51 percent of the stock of which is owned by minority group members. For the purposes of this definition, minority group members are Negroes, Spanish-speaking American persons, American-Orientals, American-Indians, American-Eskimos, and American-Aleuts. Contractors may rely on written representations by subcontractors regarding their status as minority business enterprises in lieu of an independent investigation.

ARTICLE B-XXX - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, DOE shall have the right to change the listing of countries in Appendix "D" upon a determination by DOE that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to DOE if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by DOE pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018473

ARTICLE B-XXXI - DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA

(a) The Contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment, and otherwise treat qualified disabled veterans and veterans of the Vietnam era without discrimination based upon their disability or veterans status in all employment practices such as the following: Employment upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees that all suitable employment openings of the Contractor which exist at the time of the execution of this contract and those which occur during the performance of this contract, including those not generated by this contract and including those occurring at an establishment of the Contractor other than the one wherein the contract is being performed but excluding those of independently operated corporate affiliates, shall be listed at an appropriate local office of the State employment service system wherein the opening occurs. The Contractor further agrees to provide such reports to such local office regarding employment openings and hires as may be required.

State and local government agencies holding Federal contracts of $10,000 or more shall also list all their suitable openings with the appropriate office of the State employment service, but are not required to provide those reports set forth in Paragraphs (d) and (e).

(c) Listing of employment openings with the employment service system pursuant to this article shall be made at least concurrently with the use of any other recruitment source or effort and shall involve the normal obligations which attach to the placing of a bona fide job order, including the acceptance of referrals of veterans and nonveterans. The listing of employment openings does not require the hiring of any particular job applicant or from any particular group of job applicants, and nothing herein is intended to relieve the Contractor from any requirements in Executive orders or regulations regarding nondiscrimination in employment.

(d) The reports required by Paragraph (b) of this article shall include, but not be limited to, periodic reports which shall be filed at least quarterly with the appropriate local office or, where the Contractor has more than one hiring location in a State, with the central office of the State employment service. Such reports shall indicate for each hiring location (1) the number of individuals hired during the reporting period, (2) the number of nondisabled veterans of the Vietnam era hired,

1018474

(3) the number of disabled veterans of the Vietnam era hired, and (4) the total number of disabled veterans hired. The reports should include covered veterans hired for on-the-job training under 38 U.S.C. 1787. The Contractor shall submit a report within 30 days after the end of each reporting period wherein any performance is made on this contract identifying data for each hiring location. The Contractor shall maintain at each hiring location copies of the reports submitted until the expiration of one (1) year after final payment under the contract, during which time these reports and related documentation shall be made available, upon request, for examination by any authorized representatives of the Contracting Officer or of the Secretary of Labor. Documentation would include personnel records respecting job openings, recruitment, and placement.

(e) Whenever the Contractor becomes contractually bound by the listing provisions of this article, it shall advise the employment service system in each State where it has establishments of the name and location of each such hiring location in the State. As long as the Contractor is contractually bound to these provisions and has so advised the State system, there is no need to advise the State system of subsequent contracts. The Contractor may advise the State system when it is no longer bound by this contract article.

(f) This article does not apply to the listing of employment openings which occur and are filled outside the 50 States, the District of Columbia, Puerto Rico, Guam, and the Virgin Islands.

(g) The provisions of Paragraphs (b), (c), (d), and (e) of this article do not apply to openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement. This exclusion does not apply to a particular opening once an employer decides to consider applicants outside of its own organization or employer-union arrangement for that opening.

(h) As used in this article:

(1) "All suitable employment openings" includes, but is not limited to, openings which occur in the following job categories: Production and nonproduction; plant and office; laborers and mechanics; supervisory and nonsupervisory; technical; and executive, administrative, and professional openings which are compensated on a salary basis of less than $25,000 per year. This term includes full-time employment, temporary employment of more than three days' duration, and part-time employment. It does not include openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union

1018475

hiring arrangement nor openings in an educational institution which are restricted to students of that institution. Under the most compelling circumstances an employment opening may not be suitable for listing, including such situations where the needs of the Government cannot reasonably be otherwise supplied, where listing would be contrary to national security, or where the requirement of listing would otherwise not be for the best interest of the Government.

(2) "Appropriate office of the State employment service system" means the local office of the Federal State national system of public employment offices with assigned responsibility for serving the area where the employment opening is to be filled, including the District of Columbia, Guam, Puerto Rico and the Virgin Islands.

(3) "Openings which the Contractor proposes to fill from within its own organization" means employment openings for which no consideration will be given to persons outside the Contractor's own organization (including any affiliates, subsidiaries, and the parent companies) and includes any openings which the Contractor proposes to fill from regularly established "recall" lists.

(4) "Openings which the Contractor proposes to fill pursuant to a customary and traditional employer-union hiring arrangement" means employment openings for which the Contractor proposes to fill from union halls, which is part of the customary and traditional hiring relationship which exists between the Contractor and representatives of its employees.

(i) The Contractor agrees to comply with the rules, regulations, and relevent orders of the Secretary of Labor issued pursuant to the Act.

(j) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Act.

(k) The Contractor agrees to post in conspicuous places available to employees and applicants for employment notices in a form to be prescribed by the Director, provided by or through the Contracting Officer. Such notice shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era for employment, and the rights of applicants and employees.

1018476

(l) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding that the Contractor is bound by terms of the Vietnam Era Veteran's Readjustment Assistance Act and is committed to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era.

(m) The Contractor will include the provisions of this article in every subcontract or purchase order of $10,000 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE B-XXXII - EMPLOYMENT OF THE HANDICAPPED

(a) The Contractor will not discriminate against any employee or applicant for employment because of physical or mental handicap in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment and otherwise treat qualified handicapped individuals without discrimination based upon their physical or mental handicap in all employment practices such as the following: employment, upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees to comply with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Rehabilitation Act of 1973, as amended.

(c) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations and relevant orders of the Secretary of Labor issued pursuant to the Act.

(d) The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices in a form to be prescribed by the Director, Office of Federal Contract Compliance Programs, Department of Labor, provided by or through the Contracting Officer. Such notices shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified handicapped employees and applicants for employment, and the rights of applicants and employees.

1018477

(e) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding, that the Contractor is bound by the terms of Section 503 of the Rehabilitation Act of 1973, and is committed to take affirmative action to employ and advance in employment physically and mentally handicapped individuals.

(f) The Contractor will include the provisions of this article in every subcontract or purchase order of $2,500 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to Section 503 of the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE B-XXXIII - DETERMINATION OF SUPPORT COSTS

(a) The term "support cost" as used in this contract means DOE's share 1/ of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to DOE in accordance with (b) below. The term "cumulative support cost" as used in this contract means the total of the support cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three (3) months after the end of each contract period set forth in Appendix "A", and within three (3) months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the

1/ In those cases in which there is no proportionate sharing of costs, DOE's "share" will be 100 percent. With respect to any period in which proportionate cost sharing is applicable pursuant to Article A-III, it is understood that the support cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110 percent of the estimated support cost set forth in Article A-III for that contract period except as otherwise approved by DOE.

extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of FMC 73-8, as constituted on the effective commencement date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The certified statement should be in agreement with the institution's financial records and shall reflect only expenditures actually made during the period covered, including transfers from inventory. It shall not include commitments, as a part of such expenditures, for goods or services on order, but not received, or those received but not paid for unless the Contractor is operating under an established and consistently applied system of accrual accounting. If this is the case, the certified statement shall be so footnoted. A combination of accrual and cash accounting for cost accumulation and reporting purposes shall not be used. The renewal proposal budget should be footnoted to show the estimated amount of outstanding commitments for property at the end of the current contract period. The certified statement contains space in which should be inserted the actual amount of outstanding commitments for property at the end of the period covered by the statement. This commitment amount is for information only and is not a part of the expenditure calculation. The Contractor understands that ERDA expects to rely on this certified statement for determining the support cost for the pertinent contract period. With respect to any period in which proportionate cost sharing is applicable, the support cost for the pertinent period will be determined by applying the percentage figure included in Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to DOE shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Paragraph (c) of the article entitled "Inspection, Reports, Records, and Accounts" to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(i).

ARTICLE B-XXXIV - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain DOE's approval for:

(1) A change of the principal investigator, co-investigator, or other key people as might be named in this contract or continuation of the research work for any one period in excess of three (3) months without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining DOE approval; however, a representative of the institution shall consult with the appropriate DOE's Headquarters program representative if the principal investigator plans to, or becomes aware that he will devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work and what modification to the contract, if any, may be appropriate.

(2) No change in the phenomenon or phenomena under study; i.e., broad category of the research under the contract shall be made without the specific written approval of DOE; ordinarily such changes, if approved by DOE, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in the contract: Provided, it gives DOE prompt notification of such changes; and the Contractor may continue to follow the new objectives while DOE determines whether it wishes to continue the program under the changed approach. Significant changes in methods or procedures employed in performing the research should be reported in the first technical progress report issued subsequent to the changes.

(3) Acquisition of:

(i) An item of equipment not itemized in Appendix "A", the cost of which is $1,000 or more. Approval is not required if the equipment is merely a different model of an item listed in Appendix "A"; or

(ii) An item or items of equipment the cost of which will cause the total equipment dollar level shown in Article A-II(a) of the contract to be in excess of 125 percent thereof (if plant and capital equipment funds are provided for the acquisition of equipment with title to be vested in the Government, the total cost of such shall not exceed the amount provided for such equipment unless prior DOE approval has been obtained).

(4) Purchase of any general-purpose equipment, such as office furniture, air conditioning, etc., not specifically provided for in Appendix "A".

(5) Incurring costs for items set forth in Article A-II(a), during the pertinent contract period stated in Appendix "A", in excess of 110 percent of the total estimated cost specified in Article A-III. Charges to DOE for any such costs incurred with the approval of DOE shall also be subject to the limitations of Article III.

(6) Any proposed foreign travel (see the article entitled "Foreign Travel").

(7) Expenditures for domestic travel in excess of $500, or 125 percent of the amount shown in Article A-II(a) for such travel, whichever is greater.

(8) Acquisition of excess personal property.

ARTICLE B-XXXV - PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS

(a) If an appeal is filed by the Contractor from a final decision of the Contracting Officer under the Disputes article of this contract, denying a claim arising under the contract, simple interest on the amount of the claim finally determined owed by the Government shall be payable to the Contractor. Such interest shall be at the rate determined by the Secretary of the Treasury pursuant to Public Law 92-41, 85 Stat. 97, from the date the Contractor furnishes to the Contracting Officer its written appeal under the Disputes article of this contract, to the date of (1) a final judgment by a court of competent jurisdiction, or (2) mailing to the Contractor of a supplemental agreement for execution either confirming completed negotiations between the parties or carrying out a decision of a board of contract appeals.

(b) Notwithstanding (a) above, (1) interest shall be applied only from the date payment was due, if such date is later than the filing of appeal, and (2) interest shall not be paid for any period of time that the Contracting Officer determines the Contractor has unduly delayed in pursuing its remedies before a board of contract appeals or a court of competent jurisdiction.

ARTICLE B-XXXVI - CLEAN AIR AND WATER

(Applicable only if the contract exceeds $100,000, or the Contracting Officer has determined that the orders under an indefinite quantity contract in any one year will exceed $100,000, or a facility to be used has been the subject of a conviction under the Clean Air Act (42 U.S.C. 1857c-8(c)(1)) or the Federal Water Pollution Control Act (33 U.S.C. 1319 (c)) and is listed by EPA, or the contract is not otherwise exempt.)

(a) Contractor agrees as follows:

(i) To comply with all the requirements of Section 114 of the Clean Air Act, as amended (42 U.S.C. 1857, et. seq., as amended by Public Law 91-604) and Section 308 of the Federal Water Pollution Control Act (33 U.S.C. 1251, as amended by Public Law 92-500), respectively, relating to inspection, monitoring, entry, reports, and information, as well as other requirements specified in Section 114 and Section 308 of the Air Act and the Water Act, respectively, and all regulations and guidelines issued thereunder before the award of this contract.

(ii) That no portion of the work required by this prime contract will be performed in a facility listed on the Environmental Protection Agency list of violating facilities on the date when this contract was awarded unless and until the EPA eliminates the name of such facility or facilities from such listing.

(iii) To use his best efforts to comply with clean air standards and clean water standards at the facilities in which the contract is being performed.

(iv) To insert the substance of the provisions of this article in any nonexempt subcontract, including this paragraph (iv).

(b) The terms used in this article have the following meanings:

(i) The term "Air Act" means the Clean Air Act, as amended (42 U.S.C. 1857 et. seq., as amended by Public Law 91-604).

(ii) The term "Water Act" means the Federal Water Pollution Control Act, as amended (33 U.S.C. 1251 et. seq., as amended by Public Law 92-500).

(iii) The term "clean air standards" means any enforceable rules, regulations, guidelines, standards, limitations, orders, controls, prohibitions, or other requirements which are contained in, issued under, or otherwise adopted pursuant to the Air Act or Executive Order 11738; an applicable implementation plan as described in Section 110(d) of the Clean Air Act (42 U.S.C. 1857c-5(d)); an approved implementation procedure or plan under Section 111(c) or Section 111(d), respectively, of the Air Act (42 U.S.C. 1857c-6(c) or (d)); or an approved implementation procedure under Section 112(d) of the Air Act (42 U.S.C. 1857c-7(d)).

(iv) The term "clean water standards" means any enforceable limitation, control, condition, prohibition, standard, or other requirement which is promulgated pursuant to the Water Act or contained in a permit issued to a discharger by the Environmental

Protection Agency or by a State under an approved program, as authorized by Section 402 of the Water Act (33 U.S.C. 1342), or by a local government to ensure compliance with pretreatment regulations as required by Section 307 of the Water Act (33 U.S.C. 1317).

(v) The term "compliance" means compliance with clean air or water standards. Compliance shall also mean compliance with a schedule or plan ordered or approved by a court of competent jurisdiction, the Environmental Protection Agency or an air or water pollution control agency in accordance with the requirement of the Air Act or Water Act and regulations issued pursuant thereto.

(vi) The term "facility" means any building, plant, installation, structure, mine, vessel, or other floating craft, location, or site of operations, owned, leased, or supervised by a contractor or subcontractor, to be utilized in the performance of a contract or subcontract. Where a location or site of operations contains or includes more than one building, plant, installation, or structure, the entire location shall be deemed to be a facility except where the Director, Office of Federal Activities, Environmental Protection Agency, determines that independent facilities are collocated in one geographical area.

1018483

APPENDIX "C"

UNITED STATES DEPARTMENT OF ENERGY

STATEMENT OF COSTS

1. Name and Address of Contractor: _____

_____.

2. Contract Number: _____.

3. Beginning and ending date of pertinent contract period: _____

_____.

4. Costs incurred during the pertinent contract period. [List only those costs which are to be reimbursed by DOE or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.]

	Cost categories 1/	Amount
a.	Salaries and wages----------	$_____
b.	Equipment---------- [List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from DOE.]	$_____
c.	Travel [Show amounts for both foreign and domestic. If none, state none.]	$_____
	Domestic----------	$_____
	Foreign----------	$_____
d.	Other direct costs----------	$_____
e.	Total direct expenditures----------	$_____
f.	Indirect charges ---------- [Indicate percent and expenditures to which percent is applied.]	$_____

1/ The listing of categories should be consistent with the itemization in Appendix "A".

5. Total costs for items under Article A-II(a) for pertinent contract period ---------- $_____

6. Support cost for the pertinent contract period set forth in Appendix "A", as defined in the article entitled "Determination of Support Costs" of the contract, chargeable to DOE for the pertinent contract period (percent of the total costs using percent shown in Article A-III of Appendix "A" for pertinent period of contract) ---------- $_____

7. Cumulative support cost (support cost under this statement plus support cost for previous periods of the contract)---------- $_____

8. Accumulated support ceiling in Article III of the contract ---------- $_____

9. The difference between lines 7 and 8 ---------- $_____

10. Provide information regarding contributions by the Contractor of items listed in Article A-II(b) of Appendix "A" during pertinent contract period. State the extent of the Contractor's actual contribution, the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II(b); e.g., time, dollar, etc. ---------- $_____

11. Actual outstanding commitments for property at the end of the period covered by this statement ---------- $_____

I hereby certify that to the best of my knowledge and belief this report is true and correct, that the costs listed herein were incurred in connection with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein, and that all contract requirements have been complied with. If an audit results in a disallowance of cost, the Contractor will make prompt reimbursement to DOE.

_____
(Name and title of an authorized representative)

_____ _____
(Signature) (Date)

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other DOE programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; and provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-Controlled area of Vietnam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)

North Korea
Outer Mongolia
Cuba

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of DOE on an individual case basis:

   a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by DOE.

   b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

   c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by DOE funds or are organized and directed by persons receiving financial support for such activities from DOE and acting in the name of DOE or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold DOE security clearance will be subject to the prior approval of DOE on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held DOE security clearance of DOE's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify DOE of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform DOE, in advance whenever feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc Countries or other countries shall be subject to the following policy and procedure:

   a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Paragraph 2, above, are made in the name of the Contractor or the individual scientist and not in the name of DOE;

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

(2) The transmittals to countries listed in Paragraph 2, above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Paragraph 2, above, are made in the name of the Contractor or the individual scientist and not in the name of DOE.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) requests for comprehensive and detailed unpublisned design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) official correspondence from any government other than the United States, its territories and possessions.

As used in this Paragraph 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within DOE programs, and available either from the Technical Information Center, Oak Ridge, Tennessee, DOE depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated

emulsions; etc., originating within DOE programs but which are not available from the Technical Information Center, Oak Ridge, Tennessee, DOE depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosure of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosures of any information that would adversely affect the patent interest of DOE in violation of the provisions of this contract.

1018489

Contract No. EY-76-S-05-2401
VANDERBILT UNIVERSITY
Modification No. A027

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 1st day of February, 1978, effective the 1st day of November, 1977, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the SECRETARY OF ENERGY (hereinafter referred to as the "Secretary"), the statutory head of the DEPARTMENT OF ENERGY (hereinafter referred to as "DOE"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the Contractor and the Government, represented by the Administrator of Energy Research and Development Administration, have heretofore entered into Contract No. EY-76-S-05-2401 and Modifications Nos. 1 through A026 providing for the Contractor's performance of certain research; and

WHEREAS, pursuant to the Department of Energy Organization Act (P. L. 95-91), the functions and authority vested by law in the Administrator of Energy Research and Development or ERDA were transferred to and vested in the Secretary; and

WHEREAS, the Contractor and DOE desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Department of Energy Organization Act (P. L. 95-91), and other applicable law, including Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. Wherever the terms "Energy Research and Development Administration" or "ERDA" appear in the original contract and any modifications thereto, such terms shall be deemed to refer to the Department of Energy or DOE and wherever the term "Administrator" is used it shall be deemed to refer to the Secretary. The term "Head of the Agency" or "Secretary" means the Secretary, the Under Secretary, any Assistant Secretary, or other Federal agency; and the term "his duly authorized representative" means any person or persons or board (other than the Contracting Officer) authorized to act for the Head of the Agency or the Secretary.

0 1 8 4 9 0

2. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date October 31, 1977, is changed to October 31, 1978.

3. In Paragraph (a) of ARTICLE III - CONSIDERATION, the sum of $74,419 is added, increasing the sum $544,118 to $618,537.

4. The attached Appendix "A" is made applicable to the period indicated thereon.

5. The attached Appendices "B", "C" and "D" replace the Appendices "B", "C" and "D" attached to Modification No. A025 to the contract.

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: SECRETARY OF ENERGY

BY: _____

TITLE: _____

VANDERBILT UNIVERSITY

BY: _____

TITLE: Paul Gazzerro, Jr., Associate Vice-Pres. for Med. Affairs, Operations and Fiscal Planning

I, Thomas W. Haines (Attester), certify that I am the Director, Sponsored Research & Programs (Title) of the Contractor named under this contract; that Paul Gazzerro, Jr. (Signatory) who signed this contract on behalf of said Contractor was then Assoc. Vice-Pres. Medical Affairs Operations and Fiscal Planning (Title) of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt University School of Medicine

Contract No.: Modification No. A027 to Contract No. EY-76-S-05-2401

1018491

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

For the contract period: November 1, 1977 through October 31, 1978

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct a study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 16% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages: $36,089

(2) Equipment to be purchased or fabricated by the Contractor: $ 3,282

a Equipment estimated to cost less than $1,000:

2 position encoders
FIFO Buffer

b Equipment estimated to cost in excess of $1,000:

Dual ADC, Bay Engineering PC11-AD

1018492

(3) Travel: $ 1,500

Domestic---------$ 1,500
Foreign----------$ 0

(4) Other direct costs: $ 9,116

(5) Indirect costs (based on a predetermined rate of 67.7% of salaries and wages): $24,432

(b) Items, if any, significant to the performance of this contract, but excluded from computation of support cost and from consideration in proportioning costs:

(1) Items to be contributed by Contractor:

None

(2) Items to be contributed by the Government:

None

(c) Time or effort of Principal Investigator(s) contributed by Contractor, but excluded from computation of support cost and from consideration in proportioning costs:

All costs including salary, fringe benefits and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $ 74,419 ; DOE will pay 100 % of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and the Article entitled "Determination of Support Costs" in Appendix "B". The estimated DOE Support Cost for the contract period stated in this Appendix "A" is $ 74,419 .

1018493

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

The estimated DOE Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$ 0
(b) New funds for the current period:	$74,419

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

1018494

TABLE OF CONTENTS

APPENDIX "B"---GENERAL PROVISIONS

Article No.		Page No.
I	DEFINITIONS	1
II	INSPECTION, REPORTS, RECORDS, AND ACCOUNTS	1
III	PUBLICATION OF RESULTS	2
IV	DISCLOSURE OF INFORMATION	2
V	PATENT RIGHTS	3
VI	RIGHTS IN TECHNICAL DATA	5
VII	RIGHTS TO PROPOSAL DATA	7
VIII	AUTHORIZATION AND CONSENT	7
IX	NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT	7
X	REPORTING OF ROYALTIES	8
XI	RESPONSIBILITY FOR THE WORK	8
XII	PROPERTY ITEMS	8
XIII	TERMINATION FOR CONVENIENCE OF THE GOVERNMENT	10
XIV	PAYMENTS	12
XV	EQUAL OPPORTUNITY	14
XVI	CONVICT LABOR	16
XVII	CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION	16
XVIII	DISPUTES	17
XIX	OFFICIALS NOT TO BENEFIT	17

1018495

Article No.		Page No.
XX	COVENANT AGAINST CONTINGENT FEES	18
XXI	EXAMINATION OF RECORDS	18
XXII	BUY AMERICAN ACT	19
XXIII	ASSIGNMENT: SUBCONTRACTING	20
XXIV	REPORTS AND RENEWAL PROPOSALS	20
XXV	FOREIGN TRAVEL	21
XXVI	PRIORITIES, ALLOCATIONS, AND ALLOTMENTS	21
XXVII	UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS	21
XXVIII	UTILIZATION OF SMALL BUSINESS CONCERNS	22
XXIX	UTILIZATION OF MINORITY BUSINESS ENTERPRISES	22
XXX	SOVIET-BLOC CONTROLS	22
XXXI	DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA	23
XXXII	EMPLOYMENT OF THE HANDICAPPED	26
XXXIII	DETERMINATION OF SUPPORT COSTS	27
XXXIV	ADDITIONAL APPROVALS	28
XXXV	PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS	30
XXXVI	CLEAN AIR AND WATER	30

1018496

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"---GENERAL PROVISIONS

ARTICLE B-I - DEFINITIONS

(a) The term "DOE" means the United States Department of Energy.

(b) The term "Head of the Agency" or "Secretary" means the Secretary, the Under Secretary, any Assistant Secretary, or any other head or assistant head of the executive or military department or other Federal agency and the term "his duly authorized representative" means any person or persons or board (other than the Contracting Officer) authorized to act for the Head of the Agency or the Secretary.

(c) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(d) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS, AND ACCOUNTS

(a) DOE shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in the article entitled "Reports and Renewal Proposals". The Contractor shall also make such other reports to DOE, with respect to its activities under this contract, as DOE may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted acccounting principles and practices, and consistent with the requirements of Federal Management Circular (FMC) 73-8, as constituted on the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a Contractor contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit DOE to determine the extent of the contribution. If professional staff members are included under Article A-II(b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of subsection J.7.b. of FMC 73-8.

(d) DOE shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the Contractor shall preserve such books and papers, without additional compensation therefor, in accordance with the retention requirements referenced in the article entitled "Examination of Records," of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by DOE. A copy of each article submitted by the Contractor for publication shall be promptly sent to DOE. The Contractor shall also inform DOE when the article is published and furnish six (6) copies of the article as finally published.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of DOE, and shall promptly inform DOE in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the mutual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and DOE regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons,

the production of special nuclear material or the use of special nuclear material in the production of energy, but shall not include data declassified or removed from the Restricted Data category pursuant to Section 142 of the Atomic Energy Act of 1954, as amended.

ARTICLE B-V - PATENT RIGHTS

(a) Definitions.

(1) "Subject Invention" means any invention or discovery of the Contractor conceived or first actually reduced to practice in the course of or under this contract, and includes any art, method, process, machine, manufacture, design, or composition of matter, or any new and useful improvement thereof, or any variety of plants, whether patented or unpatented, under the Patent Laws of the United States of America or any foreign country.

(2) "Patent Counsel" means the DOE Patent Counsel assisting the procuring activity.

(b) Invention disclosures and reports.

(1) The Contractor shall furnish the Patent Counsel (with notification by Patent Counsel to the Contracting Officer):

(i) A written report containing full and complete technical information concerning each Subject Invention within 6 months after conception or first actual reduction to practice whichever occurs first in the course of or under this contract, but in any event prior to any on sale, public use, or public disclosure of such invention known to the Contractor. The report shall identify the contract and inventor and shall be sufficiently complete in technical detail and appropriately illustrated by sketch or diagram to convey to one skilled in the art to which the invention pertains a clear understanding of the nature, purpose, operation, and to the extent known, the physical, chemical, biological, or electrical characteristics of the invention;

(ii) Upon request, but not more than annually, interim reports on an DOE-approved form listing Subject Inventions for that period and certifying that all Subject Inventions have been disclosed or that there were no such inventions; and

(iii) A final report on an DOE-approved form within 3 months after completion of the contract work listing all Subject Inventions and certifying that all Subject Inventions have been disclosed or that there were no such inventions.

(2) The Contractor agrees that the Government may duplicate and disclose Subject Invention disclosures and all other reports and papers furnished or required to be furnished pursuant to the contract.

(c) Allocation of principal rights.

(1) Assignment to the Government. The Contractor agrees to assign to the Government the entire right, title, and interest throughout the world in and to each Subject Invention, except to the extent that rights are retained by the Contractor under subparagraphs (c)(2) and (d) of this article.

(2) Greater rights determinations. The Contractor, or the employee-inventor with authorization of the Contractor, may request greater rights than the nonexclusive license and the right to request foreign patent rights provided in paragraph (d) of this article on identified inventions in accordance with the procedure and criteria of 41 CFR 9-9.109-6. A request for a determination of whether the Contractor or the employee-inventor is entitled to retain such greater rights must be submitted to the Patent Counsel at the time of the first disclosure of the invention pursuant to subparagraph (b)(1) of this article or not later than 9 months thereafter or such longer period as may be authorized by the Patent Counsel (with notification by Patent Counsel to the Contracting Officer) for good cause shown in writing by the Contractor. The information to be submitted for a greater rights determination is specified in 41 CFR 9-9.109-6(e).

(d) Minimum rights to the Contractor. The Contractor reserves a revocable, nonexclusive, paid-up license in each patent application filed in any country on a Subject Invention and any resulting patent in which the Government acquires title. Revocation shall be in accordance with the procedure of subparagraphs (c)(2) and (3) of the article in 41 CFR 9-9.107-5(a). The Contractor also has the right to request foreign rights in accordance with the procedures of subparagraph (c)(4) of the article in 41 CFR 9-9.107-5(a).

(e) Employee and Subcontractor agreements. Unless otherwise authorized in writing by the Contracting Officer, the Contractor shall:

(1) Obtain patent agreements to effectuate the provisions of the Patent Rights article from all persons in its employ who perform any part of the work under this contract except nontechnical personnel, such as clerical employees and manual laborers.

(2) Unless otherwise authorized or directed by the Contracting Officer the Contractor shall include the Patent Rights article of 41 CFR 9-9.107-5(a) or 41 CFR 9-9.107-6, as appropriate, modified to identify the parties in any subcontract hereunder, having as a purpose the conduct of research, development, or demonstration work; and

(3) Promptly notify the Contracting Officer in writing upon the award of any subcontract containing a Patent Rights article by identifying the Subcontractor, the work to be performed under the subcontract, and the dates of award, and estimated completion. Upon the request of the Contracting Officer, the Contractor shall furnish a copy of the subcontract to such requestor.

(f) Atomic energy.

(1) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(2) Except as otherwise authorized in writing by the Contracting Officer, the Contractor will obtain patent agreements to effectuate the provisions of paragraph (f)(1) of this article from all persons who perform any part of the work under this contract, except nontechnical personnel such a clerical employees and manual laborers.

(g) Publication.

In order that information concerning scientific or technical developments conceived or first actually reduced to practice in the course of or under the contract is not prematurely published so as to adversely affect patent interest of DOE, the Contractor agrees to submit to the Patent Counsel for patent review a copy of each paper 60 days prior to its intended publication date. The Contractor may publish such information after expiration of a 60-day period following such submission or prior thereto if specifically approved by Patent Counsel, unless the Contractor is informed that in order to protect patentable subject matter, publication must be further delayed.

ARTICLE B-VI - RIGHTS IN TECHNICAL DATA

(a) Definitions.

The definitions of terms set forth in 41 CFR 9-9.201 apply to the extent these terms are used herein.

10185-01

(b) Allocation of rights.

(1) The Government shall have:

(i) Unlimited rights in technical data first produced or specifically used in the performance of this contract;

(ii) The right of the Contracting Officer or his representatives to inspect at all reasonable times up to three (3) years after final payment under this contract all technical data first produced or specifically used in the contract (for which inspection the Contractor or its subcontractor shall afford proper facilities to DOE);

(iii) The right to have any technical data first produced or specifically used in the performance of this contract delivered to the Government as the Contracting Officer may from time to time direct during the progress of the work or in any event as the Contracting Officer shall direct upon completion or termination of this contract.

(2) The Contractor shall have:

The right to use for its private purposes, subject to patent, security or other provisions of this contract, technical data it first produces in the performance of this contract provided the data requirements of this contract have been met as of the date of the private use of such data. The Contractor agrees that to the extent it receives or is given access to proprietary data or other technical, business or financial data in the form of recorded information from DOE or DOE contractor or subcontractor, the Contractor shall treat such data in accordance with any restrictive legend contained thereon, unless use is specifically authorized by prior written approval of the Contracting Officer.

(c) Copyrighted material.

(1) The Contractor agrees to, and does hereby grant to the Government, and to its officers, agents, servants and employees acting within the scope of their duties:

(i) A royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use, and dispose of and to authorize others so to do, all copyrightable material first produced or composed in the performance of this contract by the Contractor, its employees or any individual or concern specifically employed or assigned to originate and prepare such material; and

(ii) a license as aforesaid under any and all copyrighted or copyrightable works not first produced or composed by the Contractor in the performance of this contract but which are incorporated in the material furnished under the contract, provided that such license shall be only to the extent the Contractor now has, or prior to completion or final settlement of the contract may acquire, the right to grant such license without becoming liable to pay compensation to others solely because of such grant.

(2) The Contractor agrees that it will not knowingly include any material copyrighted by others in any written or copyrightable material furnished or delivered under this contract without a license as provided for in subparagraph (1)(ii) hereof, or without the consent of the copyright owner, unless it obtains specific written approval of the Contracting Officer for the inclusion of such copyrighted material.

ARTICLE B-VII - RIGHTS TO PROPOSAL DATA

Except for technical data contained on pages _____ of the Contractor's proposal dated _____ which are asserted by the Contractor as being proprietary data, it is agreed that as a condition of the award of this contract, and notwithstanding the provisions of any notice appearing on the proposal, the Government shall have the right to use, duplicate, and disclose and have others do so for any purpose whatsoever, the technical data contained in the proposal upon which this contract is based.

ARTICLE B-VIII - AUTHORIZATION AND CONSENT

The Government hereby gives its authorization and consent for all use and manufacture of any invention described in and covered by a patent of the United States in the performance of this contract or any part hereof or any amendment hereto or any subcontract hereunder (including any lower-tier subcontract).

ARTICLE B-IX - NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT

The provisions of this article shall be applicable only if the amount of this contract exceeds $10,000.

(a) The Contractor shall report to the Contracting Officer, promptly and in reasonable written detail, each notice or claim of patent or copyright infringement based on the performance of this contract of which the Contractor has knowledge.

(b) In the event of any claim or suit against the Government on account of any alleged patent or copyright infringement arising out of the performance of this contract or out of the use of any supplies furnished or work or services performed hereunder, the Contractor shall furnish to the Government when requested by the Contracting Officer, all evidence and information in possession of the Contractor pertaining to such suit or claim. Such evidence and information shall be furnished at the expense of the Government except where the Contractor has agreed to indemnify the Government.

(c) This article shall be included in all subcontracts.

ARTICLE B-X - REPORTING OF ROYALTIES

If this contract is in an amount which exceeds $10,000 and if any royalty payments are directly involved in the contract or are reflected in the contract price to the Government, the Contractor agrees to report in writing to the Contracting Officer or Patent Counsel during the performance of this contract and prior to its completion or final settlement the amount of any royalties or other payments paid or to be paid by it directly to others in connection with the performance of this contract together with the names and addresses of licensors to whom such payments are made and either the patent numbers involved or such other information as will permit identification of the patents or other basis on which the royalties are to be paid. The approval of DOE of any individual payments or royalties shall not stop the Government at any time from contesting the enforceability, validity or scope of, or title to, any patent under which a royalty or payments are made.

ARTICLE B-XI - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves an DOE license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-XII - PROPERTY ITEMS

(a) Except as otherwise provided in this Paragraph (a) and Paragraph (b) of this article, title to all material, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto: And, provided, There is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities,

the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to Paragraphs (b), (c), (d), (e), and (f) of this article.

(b) Subject to the mutual agreement of DOE and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government Property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain, at all times and in a manner satisfactory to DOE, records showing the use and disposition of Government property. Such records shall be subject to DOE inspection at all reasonable times and DOE shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by DOE, the Contractor shall use Government property only for the purposes of this contract: Provided, however, That the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use: (1) Does not interfere with its work under this contract; (2) is not prohibited by provisions of the other Federal agreements; and (3) is promptly reported by the Contractor to DOE under this contract.

(d) The Contractor shall promptly notify DOE of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of DOE.

(e) With the written approval of DOE, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may mutually be agreed upon in writing by the Contractor and DOE. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of DOE payments to be made under this contract, as DOE may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to DOE upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

ARTICLE B-XIII - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination, the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the Notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by DOE's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under Paragraph (c) shall be governed by the contract cost principles and procedures in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3) in effect on the date of this contract, except that if the Contractor is not an educational institution any costs claimed, agreed to, or determined pursuant to Paragraphs (c) or (e) hereof shall be in accordance with Subpart 1-15.2 of the Federal Procurement Regulations (41 CFR 1-15.2) in effect on the date of this contract.

(e) Subject to the provisions of Paragraph (c) above, and subject to any review required by DOE's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate established by the Secretary of the Treasury pursuant to Public Law 92-41 (50 U.S.C. App. 1215(b)(2)) for the Renegotiation Board, beginning 30 days from the date of such demand.

1018507

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acguired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XIV - PAYMENTS

(a) DOE shall make payments to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of 45 percent of the new funds as set forth in Article A-III(b) of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional 45 percent of the new funds as set forth in Article A-III(b) of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the new funds set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the DOE support cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report required by the article entitled "Reports and Renewal Proposals", in form and content satisfactory to DOE, and submission of a certified statement showing the support cost and evidencing the Contractor's performance under the contract and compliance by the Contractor with the patent provisions of this contract.

(b) The payments made pursuant to Paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to the article entitled "Termination for Convenience of the Government" hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of the article entitled "Termination for Convenience of the Government" shall be promptly returned to DOE.

(c) DOE, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) DOE shall issue a letter of credit as provided for by Treasury Fiscal Requirements Manual, Part VI, Section 1020, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the new funds as set forth in Article A-III(b) of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Fiscal Requirements Manual, Part VI, Section 1020, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in the Article entitled "Reports and Renewal Proposals," in form and content satisfactory to DOE, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission

by the Contractor to DOE of such invoices or vouchers as are satisfactory to DOE, DOE shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a payment voucher on letter of credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the new funds as set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the DOE support cost for the pertinent period and evidencing the Contractor's performance under the contract.

(2) DOE reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (c)(1) of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XV - EQUAL OPPORTUNITY

(The following article is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor [41 CFR, Ch. 60].)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity article.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity article, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by DOE and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

(f) In the event of the Contractor's noncompliance with the Equal Opportunity article of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of Paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as DOE may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by DOE, the Contractor may request the United States to enter into such litigation to protect the interest of the United States.

ARTICLE B-XVI - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment except as provided by Public Law 89-176, September 10, 1965 (18 U.S.C. 4082(c)(2)), and Executive Order 11755, December 29, 1973.

ARTICLE B-XVII - CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours and Safety Standards Act (40 U.S.C. 327-333), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder.

(a) Overtime Requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers, mechanics, apprentices, trainees, watchmen, and guards shall require or permit any laborer, mechanic, apprentice, trainee, watchman, or guard in any workweek in which he is employed on such work to work in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek on work subject to the provisions of the Contract Work Hours and Safety Standards Act unless such laborer, mechanic, apprentice, trainee, watchman, or guard receives compensation at a rate not less than one and one-half times his basic rate of pay for all such hours worked in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; Liability for Unpaid Wages; Liquidated Damages. In the event of any violation of the provisions of Paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer, mechanic, apprentice, trainee, watchman, or guard employed in violation of the provisions of Paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of 8 hours or in excess of his standard workweek of 40 hours without payment of the overtime wages required by Paragraph (a).

(c) Withholding for Unpaid Wages and Liquidated Damages. The Contracting Officer may withhold from the Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor,

such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of Paragraph (b).

(d) Subcontracts. The Contractor shall insert Paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XVIII - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to DOE. The decision of DOE or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in Paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XIX - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XX - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XXI - EXAMINATION OF RECORDS

(a) This article is applicable if the amount of this contract exceeds $10,000 and was entered into by means of negotiation, including small business restricted advertising, but is not applicable if this contract was entered into by means of formal advertising.

(b) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract unless the DOE authorizes their prior disposition, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

(c) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract unless the DOE authorizes their prior disposition, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (1) purchase orders not exceeding $10,000 and (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(d) The periods of access and examination described in (b) and (c) above, for records which relate to (1) appeals under the "Disputes" article of this contract, (2) litigation or the settlement of claims arising out of the performance of this contract, or (3) costs and expenses of this contract as to which exception has been taken by the Comptroller General or any of his duly authorized representatives, shall continue until such appeals, litigation, claims, or exceptions have been disposed of.

(e) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XXII - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10a - 10d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which DOE determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which DOE determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XXIII - ASSIGNMENT: SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by DOE. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by DOE.

ARTICLE B-XXIV - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Research Contracts, Procedures, and Reports Branch, Contract Division, Oak Ridge Operations Office, United States Department of Energy, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports, preprints, and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three (3) months in advance of the expiration of the current contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as DOE may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

ARTICLE B-XXV - FOREIGN TRAVEL

Foreign travel shall be subject to the prior approval of the Contracting Officer for each separate trip regardless of whether funds for such travel are contained in an approved budget. Foreign travel is defined as any travel outside of Canada and the United States and its territories and possessions.

ARTICLE B-XXVI - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Domestic and International Business Administration, Department of Commerce, in obtaining controlled materials and other products and materials needed to fill this contract.

ARTICLE B-XXVII - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

(The following article is applicable if this contract exceeds $5,000.)

(a) It is the policy of the Government to award contracts to labor surplus area concerns that (1) have been certified by the Secretary of Labor (hereafter referred to as certified-eligible concerns with first or second preferences) regarding the employment of a proportionate number of disadvantaged individuals and have agreed to perform substantially (i) in or near sections of concentrated unemployment or underemployment or in persistent or substantial labor surplus areas or (ii) in other areas of the United States, respectively, or (2) are noncertified concerns which have agreed to perform substantially in persistent or substantial labor surplus areas, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy.

(b) In complying with Paragraph (a) of this article and with Paragraph (b) of the article of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (1) Certified-eligible concerns with a first preference which are also small business concerns; (2) other certified-eligible concerns with a first preference; (3) certified-eligible concerns with a second preference which are also small business concerns; (4) other certified-eligible concerns with a second preference; (5) persistent or substantial labor surplus area concerns which are also small business concerns; (6) other persistent or substantial labor surplus area concerns; and (7) small business concerns which are not labor surplus area concerns.

1018517

ARTICLE B-XXVIII - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXIX - UTILIZATION OF MINORITY BUSINESS ENTERPRISES

(a) It is the policy of the Government that minority business enterprises shall have the maximum practicable opportunity to participate in the performance of Government contracts.

(b) The Contractor agrees to use its best efforts to carry out this policy in the award of its subcontracts to the fullest extent consistent with the efficient performance of this contract. As used in this contract, the term "minority business enterprise" means a business, at least 50 percent of which is owned by minority group members or, in case of publicly owned businesses, at least 51 percent of the stock of which is owned by minority group members. For the purposes of this definition, minority group members are Negroes, Spanish-speaking American persons, American-Orientals, American-Indians, American-Eskimos, and American-Aleuts. Contractors may rely on written representations by subcontractors regarding their status as minority business enterprises in lieu of an independent investigation.

ARTICLE B-XXX - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, DOE shall have the right to change the listing of countries in Appendix "D" upon a determination by DOE that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to DOE if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by DOE pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

1018518

ARTICLE B-XXXI - DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA

(a) The Contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment, and otherwise treat qualified disabled veterans and veterans of the Vietnam era without discrimination based upon their disability or veterans status in all employment practices such as the following: Employment upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees that all suitable employment openings of the Contractor which exist at the time of the execution of this contract and those which occur during the performance of this contract, including those not generated by this contract and including those occurring at an establishment of the Contractor other than the one wherein the contract is being performed but excluding those of independently operated corporate affiliates, shall be listed at an appropriate local office of the State employment service system wherein the opening occurs. The Contractor further agrees to provide such reports to such local office regarding employment openings and hires as may be required.

State and local government agencies holding Federal contracts of $10,000 or more shall also list all their suitable openings with the appropriate office of the State employment service, but are not required to provide those reports set forth in Paragraphs (d) and (e).

(c) Listing of employment openings with the employment service system pursuant to this article shall be made at least concurrently with the use of any other recruitment source or effort and shall involve the normal obligations which attach to the placing of a bona fide job order, including the acceptance of referrals of veterans and nonveterans. The listing of employment openings does not require the hiring of any particular job applicant or from any particular group of job applicants, and nothing herein is intended to relieve the Contractor from any requirements in Executive orders or regulations regarding nondiscrimination in employment.

(d) The reports required by Paragraph (b) of this article shall include, but not be limited to, periodic reports which shall be filed at least quarterly with the appropriate local office or, where the Contractor has more than one hiring location in a State, with the central office of the State employment service. Such reports shall indicate for each hiring location (1) the number of individuals hired during the reporting period, (2) the number of nondisabled veterans of the Vietnam era hired,

(3) the number of disabled veterans of the Vietnam era hired, and (4) the total number of disabled veterans hired. The reports should include covered veterans hired for on-the-job training under 38 U.S.C. 1787. The Contractor shall submit a report within 30 days after the end of each reporting period wherein any performance is made on this contract identifying data for each hiring location. The Contractor shall maintain at each hiring location copies of the reports submitted until the expiration of one (1) year after final payment under the contract, during which time these reports and related documentation shall be made available, upon request, for examination by any authorized representatives of the Contracting Officer or of the Secretary of Labor. Documentation would include personnel records respecting job openings, recruitment, and placement.

(e) Whenever the Contractor becomes contractually bound by the listing provisions of this article, it shall advise the employment service system in each State where it has establishments of the name and location of each such hiring location in the State. As long as the Contractor is contractually bound to these provisions and has so advised the State system, there is no need to advise the State system of subsequent contracts. The Contractor may advise the State system when it is no longer bound by this contract article.

(f) This article does not apply to the listing of employment openings which occur and are filled outside the 50 States, the District of Columbia, Puerto Rico, Guam, and the Virgin Islands.

(g) The provisions of Paragraphs (b), (c), (d), and (e) of this article do not apply to openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement. This exclusion does not apply to a particular opening once an employer decides to consider applicants outside of its own organization or employer-union arrangement for that opening.

(h) As used in this article:

(1) "All suitable employment openings" includes, but is not limited to, openings which occur in the following job categories: Production and nonproduction; plant and office; laborers and mechanics; supervisory and nonsupervisory; technical; and executive, administrative, and professional openings which are compensated on a salary basis of less than $25,000 per year. This term includes full-time employment, temporary employment of more than three days' duration, and part-time employment. It does not include openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union

hiring arrangement nor openings in an educational institution which are restricted to students of that institution. Under the most compelling circumstances an employment opening may not be suitable for listing, including such situations where the needs of the Government cannot reasonably be otherwise supplied, where listing would be contrary to national security, or where the requirement of listing would otherwise not be for the best interest of the Government.

(2) "Appropriate office of the State employment service system" means the local office of the Federal State national system of public employment offices with assigned responsibility for serving the area where the employment opening is to be filled, including the District of Columbia, Guam, Puerto Rico and the Virgin Islands.

(3) "Openings which the Contractor proposes to fill from within its own organization" means employment openings for which no consideration will be given to persons outside the Contractor's own organization (including any affiliates, subsidiaries, and the parent companies) and includes any openings which the Contractor proposes to fill from regularly established "recall" lists.

(4) "Openings which the Contractor proposes to fill pursuant to a customary and traditional employer-union hiring arrangement" means employment openings for which the Contractor proposes to fill from union halls, which is part of the customary and traditional hiring relationship which exists between the Contractor and representatives of its employees.

(i) The Contractor agrees to comply with the rules, regulations, and relevent orders of the Secretary of Labor issued pursuant to the Act.

(j) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Act.

(k) The Contractor agrees to post in conspicuous places available to employees and applicants for employment notices in a form to be prescribed by the Director, provided by or through the Contracting Officer. Such notice shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era for employment, and the rights of applicants and employees.

(l) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding that the Contractor is bound by terms of the Vietnam Era Veteran's Readjustment Assistance Act and is committed to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era.

(m) The Contractor will include the provisions of this article in every subcontract or purchase order of $10,000 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE B-XXXII - EMPLOYMENT OF THE HANDICAPPED

(a) The Contractor will not discriminate against any employee or applicant for employment because of physical or mental handicap in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment and otherwise treat qualified handicapped individuals without discrimination based upon their physical or mental handicap in all employment practices such as the following: employment, upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees to comply with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Rehabilitation Act of 1973, as amended.

(c) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations and relevant orders of the Secretary of Labor issued pursuant to the Act.

(d) The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices in a form to be prescribed by the Director, Office of Federal Contract Compliance Programs, Department of Labor, provided by or through the Contracting Officer. Such notices shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified handicapped employees and applicants for employment, and the rights of applicants and employees.

(e) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding, that the Contractor is bound by the terms of Section 503 of the Rehabilitation Act of 1973, and is committed to take affirmative action to employ and advance in employment physically and mentally handicapped individuals.

(f) The Contractor will include the provisions of this article in every subcontract or purchase order of $2,500 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to Section 503 of the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE B-XXXIII - DETERMINATION OF SUPPORT COSTS

(a) The term "support cost" as used in this contract means DOE's share 1/ of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to DOE in accordance with (b) below. The term "cumulative support cost" as used in this contract means the total of the support cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three (3) months after the end of each contract period set forth in Appendix "A", and within three (3) months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the

1/ In those cases in which there is no proportionate sharing of costs, DOE's "share" will be 100 percent. With respect to any period in which proportionate cost sharing is applicable pursuant to Article A-III, it is understood that the support cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110 percent of the estimated support cost set forth in Article A-III for that contract period except as otherwise approved by DOE.

extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of FMC 73-8, as constituted on the effective commencement date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The certified statement should be in agreement with the institution's financial records and shall reflect only expenditures actually made during the period covered, including transfers from inventory. It shall not include commitments, as a part of such expenditures, for goods or services on order, but not received, or those received but not paid for unless the Contractor is operating under an established and consistently applied system of accrual accounting. If this is the case, the certified statement shall be so footnoted. A combination of accrual and cash accounting for cost accumulation and reporting purposes shall not be used. The renewal proposal budget should be footnoted to show the estimated amount of outstanding commitments for property at the end of the current contract period. The certified statement contains space in which should be inserted the actual amount of outstanding commitments for property at the end of the period covered by the statement. This commitment amount is for information only and is not a part of the expenditure calculation. The Contractor understands that ERDA expects to rely on this certified statement for determining the support cost for the pertinent contract period. With respect to any period in which proportionate cost sharing is applicable, the support cost for the pertinent period will be determined by applying the percentage figure included in Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to DOE shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Paragraph (c) of the article entitled "Inspection, Reports, Records, and Accounts" to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(i).

ARTICLE B-XXXIV - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain DOE's approval for:

(1) A change of the principal investigator, co-investigator, or other key people as might be named in this contract or continuation of the research work for any one period in excess of three (3) months without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining DOE approval; however, a representative of the institution shall consult with the appropriate DOE's Headquarters program representative if the principal investigator plans to, or becomes aware that he will devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work and what modification to the contract, if any, may be appropriate.

(2) No change in the phenomenon or phenomena under study; i.e., broad category of the research under the contract shall be made without the specific written approval of DOE; ordinarily such changes, if approved by DOE, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in the contract: Provided, it gives DOE prompt notification of such changes; and the Contractor may continue to follow the new objectives while DOE determines whether it wishes to continue the program under the changed approach. Significant changes in methods or procedures employed in performing the research should be reported in the first technical progress report issued subsequent to the changes.

(3) Acquisition of:

(i) An item of equipment not itemized in Appendix "A", the cost of which is $1,000 or more. Approval is not required if the equipment is merely a different model of an item listed in Appendix "A"; or

(ii) An item or items of equipment the cost of which will cause the total equipment dollar level shown in Article A-II(a) of the contract to be in excess of 125 percent thereof (if plant and capital equipment funds are provided for the acquisition of equipment with title to be vested in the Government, the total cost of such shall not exceed the amount provided for such equipment unless prior DOE approval has been obtained).

(4) Purchase of any general-purpose equipment, such as office furniture, air conditioning, etc., not specifically provided for in Appendix "A".

(5) Incurring costs for items set forth in Article A-II(a), during the pertinent contract period stated in Appendix "A", in excess of 110 percent of the total estimated cost specified in Article A-III. Charges to DOE for any such costs incurred with the approval of DOE shall also be subject to the limitations of Article III.

(6) Any proposed foreign travel (see the article entitled "Foreign Travel").

(7) Expenditures for domestic travel in excess of $500, or 125 percent of the amount shown in Article A-II(a) for such travel, whichever is greater.

(8) Acquisition of excess personal property.

ARTICLE B-XXXV - PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS

(a) If an appeal is filed by the Contractor from a final decision of the Contracting Officer under the Disputes article of this contract, denying a claim arising under the contract, simple interest on the amount of the claim finally determined owed by the Government shall be payable to the Contractor. Such interest shall be at the rate determined by the Secretary of the Treasury pursuant to Public Law 92-41, 85 Stat. 97, from the date the Contractor furnishes to the Contracting Officer its written appeal under the Disputes article of this contract, to the date of (1) a final judgment by a court of competent jurisdiction, or (2) mailing to the Contractor of a supplemental agreement for execution either confirming completed negotiations between the parties or carrying out a decision of a board of contract appeals.

(b) Notwithstanding (a) above, (1) interest shall be applied only from the date payment was due, if such date is later than the filing of appeal, and (2) interest shall not be paid for any period of time that the Contracting Officer determines the Contractor has unduly delayed in pursuing its remedies before a board of contract appeals or a court of competent jurisdiction.

ARTICLE B-XXXVI - CLEAN AIR AND WATER

(Applicable only if the contract exceeds $100,000, or the Contracting Officer has determined that the orders under an indefinite quantity contract in any one year will exceed $100,000, or a facility to be used has been the subject of a conviction under the Clean Air Act (42 U.S.C. 1857c-8(c)(1)) or the Federal Water Pollution Control Act (33 U.S.C. 1319 (c)) and is listed by EPA, or the contract is not otherwise exempt.)

(a) Contractor agrees as follows:

(i) To comply with all the requirements of Section 114 of the Clean Air Act, as amended (42 U.S.C. 1857, et. seq., as amended by Public Law 91-604) and Section 308 of the Federal Water Pollution Control Act (33 U.S.C. 1251, as amended by Public Law 92-500), respectively, relating to inspection, monitoring, entry, reports, and information, as well as other requirements specified in Section 114 and Section 308 of the Air Act and the Water Act, respectively, and all regulations and guidelines issued thereunder before the award of this contract.

(ii) That no portion of the work required by this prime contract will be performed in a facility listed on the Environmental Protection Agency list of violating facilities on the date when this contract was awarded unless and until the EPA eliminates the name of such facility or facilities from such listing.

(iii) To use his best efforts to comply with clean air standards and clean water standards at the facilities in which the contract is being performed.

(iv) To insert the substance of the provisions of this article in any nonexempt subcontract, including this paragraph (iv).

(b) The terms used in this article have the following meanings:

(i) The term "Air Act" means the Clean Air Act, as amended (42 U.S.C. 1857 et. seq., as amended by Public Law 91-604).

(ii) The term "Water Act" means the Federal Water Pollution Control Act, as amended (33 U.S.C. 1251 et. seq., as amended by Public Law 92-500).

(iii) The term "clean air standards" means any enforceable rules, regulations, guidelines, standards, limitations, orders, controls, prohibitions, or other requirements which are contained in, issued under, or otherwise adopted pursuant to the Air Act or Executive Order 11738; an applicable implementation plan as described in Section 110(d) of the Clean Air Act (42 U.S.C. 1857c-5(d)); an approved implementation procedure or plan under Section 111(c) or Section 111(d), respectively, of the Air Act (42 U.S.C. 1857c-6(c) or (d)); or an approved implementation procedure under Section 112(d) of the Air Act (42 U.S.C. 1857c-7(d)).

(iv) The term "clean water standards" means any enforceable limitation, control, condition, prohibition, standard, or other requirement which is promulgated pursuant to the Water Act or contained in a permit issued to a discharger by the Environmental

Protection Agency or by a State under an approved program, as authorized by Section 402 of the Water Act (33 U.S.C. 1342), or by a local government to ensure compliance with pretreatment regulations as required by Section 307 of the Water Act (33 U.S.C. 1317).

(v) The term "compliance" means compliance with clean air or water standards. Compliance shall also mean compliance with a schedule or plan ordered or approved by a court of competent jurisdiction, the Environmental Protection Agency or an air or water pollution control agency in accordance with the requirement of the Air Act or Water Act and regulations issued pursuant thereto.

(vi) The term "facility" means any building, plant, installation, structure, mine, vessel, or other floating craft, location, or site of operations, owned, leased, or supervised by a contractor or subcontractor, to be utilized in the performance of a contract or subcontract. Where a location or site of operations contains or includes more than one building, plant, installation, or structure, the entire location shall be deemed to be a facility except where the Director, Office of Federal Activities, Environmental Protection Agency, determines that independent facilities are collocated in one geographical area.

APPENDIX "C"

UNITED STATES DEPARTMENT OF ENERGY

STATEMENT OF COSTS

1. Name and Address of Contractor: _____
_____.

2. Contract Number: _____.

3. Beginning and ending date of pertinent contract period: _____
_____.

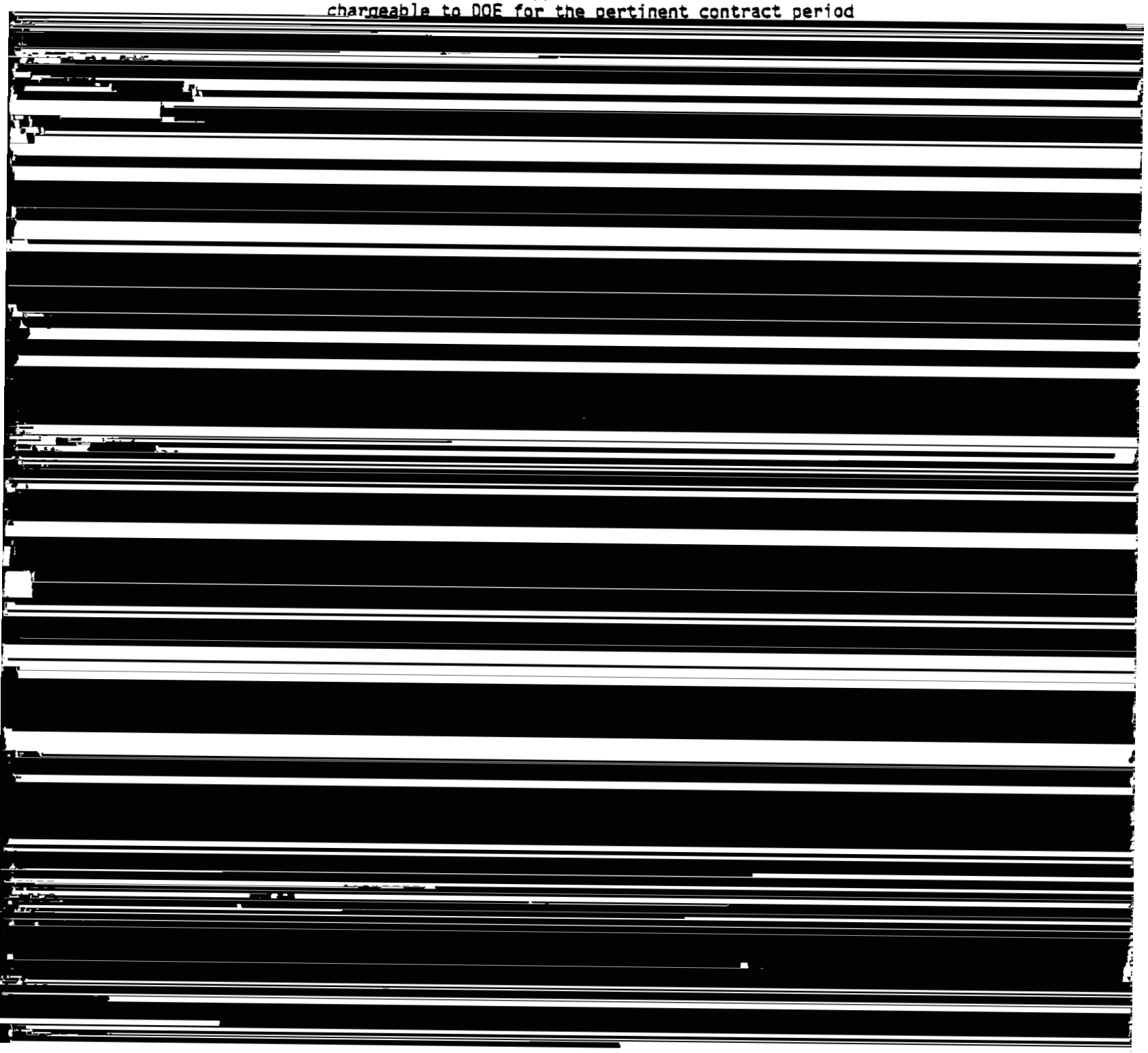
4. Costs incurred during the pertinent contract period. [List only those costs which are to be reimbursed by DOE or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.]

Cost categories 1/	Amount
a. Salaries and wages----------	$_____
b. Equipment---------- [List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from DOE.]	$_____
c. Travel [Show amounts for both foreign and domestic. If none, state none.]	$_____
Domestic----------	$_____
Foreign----------	$_____
d. Other direct costs----------	$_____
e. Total direct expenditures----------	$_____
f. Indirect charges ---------- [Indicate percent and expenditures to which percent is applied.]	$_____

1/ The listing of categories should be consistent with the itemization in Appendix "A".

5. Total costs for items under Article A-II(a) for pertinent contract period ---------- $_____

6. Support cost for the pertinent contract period set forth in Appendix "A", as defined in the article entitled "Determination of Support Costs" of the contract, chargeable to DOE for the pertinent contract period



APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate the the dissemination by the Contractor of the information developed under this contract and/or under other DOE programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Blox Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuris (includes Inner Mongolia; and provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-Controlled area of Vietnam
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)

North Korea
Outer Mongolia
Cuba

1018531

3. The following exchange activities between the Contractor and any of the Soviet-Bloc Countries shall be subject to the prior written approval of DOE on an individual case basis:

   a. Employees of the Contractor engaging in employment by activities of, or travel to, any of the Soviet-Bloc Countries where such employees' travel or other activity is financially supported by DOE.

   b. Employment of, or participation in activities of the Contractor by, nationals of any of the Soviet-Bloc Countries in furtherance of or in connection with work under this contract.

   c. Participation of nationals of any of the Soviet-Bloc Countries at U. S. conferences, meetings and symposia which are supported by DOE funds or are organized and directed by persons receiving financial support for such activities from DOE and acting in the name of DOE or the Contractor.

4. Unofficial travel to any of the Soviet-Bloc Countries by employees of the Contractor who hold DOE security clearance will be subject to the prior approval of DOE on an individual case basis.

5. The Contractor shall inform all of its employees who formerly held DOE security clearance of DOE's desire to be advised of their proposed unofficial travel to any of the Soviet-Bloc Countries. The Contractor shall notify DOE of all such proposed unofficial travel by its employees of which it becomes aware pursuant to the notification given in accordance with the provisions hereof.

6. The Contractor, if the contract herein is a cost-type rather than a fixed-price type, shall inform DOE, in advance whether feasible, of all proposed visits by nationals of any of the Soviet-Bloc Countries and shall furnish a report thereof in accordance with directions furnished by the Contracting Officer.

7. All correspondence and other communications relative to the exchange of information whether with Soviet-Bloc Countries or other countries shall be subject to the following policy and procedure:

   a. Transmittal of published information relating to the peaceful uses of atomic energy is permitted and encouraged provided the transmittals to countries listed in Group B of Paragraph 2, above, are made in the name of the Contractor or the individual scientist and not in the name of DOE;

1018532

b. Transmittal of unpublished information relating to the peaceful uses of atomic energy is permitted and encouraged provided:

(1) The information transmitted is made available to requesters in the United States. In order to insure availability to requesters in the United States, one copy of all such unpublished information (with the exception of personal correspondence covering informal scientific or technical opinion) shall be forwarded to the Contracting Officer;

(2) The transmittals to countries listed in Paragraph 2, above, are accompanied by a request for appropriate equally valuable material in return; and

(3) The transmittals to countries listed in Group B of Paragraph 2, above, are made in the name of the Contractor or the individual scientist and not in the name of DOE.

c. Requests for information not falling within the scope of the above-stated policy and any unusual requests for published and unpublished information shall be forwarded to the Contracting Officer. Examples of unusual requests for published and unpublished information include: (1) Requests for collections of published documents or for unpublished information which are not readily available to the recipient of the request; (2) requests for comprehensive and detailed unpublished design information and unpublished development information on major equipment, such as reactors, chemical processing plants, and accelerators; and (3) official correspondence from any government other than the United States, its territories and possessions.

As used in this Paragraph 7:

a. The term "published information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated emulsions; etc., originated within DOE programs, and available either from the Technical Information Center, Oak Ridge, Tennessee, DOE depository libraries, or other sources from which the public may obtain the above types of information by purchase or without cost.

b. The term "unpublished information" means all unclassified scientific and technical documents; internal and informal reports; reprints; preprints; page proofs of journal articles; engineering drawings; photographs; films; notes; irradiated

1018533

emulsions; etc., originating within DOE programs but which are not available from the Technical Information Center, Oak Ridge, Tennessee, DOE depository libraries, or from other sources from which the public may normally obtain the information by purchase or without cost.

8. In all exchanges of information, care should be taken that the release of the information does not result in the disclosure of Restricted Data or other classified information, or privileged information, in violation of applicable law and/or the provisions of this contract; or the disclosures of any information that would adversely affect the patent interest of DOE in violation of the provisions of this contract.

1018534

Contract No. EY-76-S-05-2401
VANDERBILT UNIVERSITY
Modification No. A026

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the 27th day of January, 1977, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the ADMINISTRATOR OF ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION (hereinafter referred to as "ERDA"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the Contractor and the Government, represented by the Administrator of Energy Research and Development Administration, have heretofore entered into Contract No. E(40-1)-2401 and Modifications Nos. 1 through 25 providing for the Contractor's performance of certain research; and

WHEREAS, the Contractor and ERDA desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Energy Reorganization Act of 1974 (P. L. 93-438), and other applicable law, including Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. The contract designation number "E(40-1)-2401" is changed to "EY-76-S-05-2401."

2. In Paragraph (a) of ARTICLE III - CONSIDERATION, the sum of $74,419 is added, increasing the sum $469,699 to $544,118.

3. The attached Appendix "A" (Revised) is made applicable to the period indicated thereon.

4. The Appendices "B", "C" and "D" attached to Modification No. 25 to the contract remain in effect.

1018535

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: ADMINISTRATOR OF ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

BY: _____

TITLE: _____
Contract Division

VANDERBILT UNIVERSITY

BY: _____

TITLE: Paul Gazzerro, Jr.
Associate Vice Chancellor for Medical Affairs Operations & Fiscal Planning

I, Thomas W. Haines, Ph D (Attester), certify that I am the Director, Sponsored Research & Programs (Title) of the Contractor named under this contract; that Paul Gazzerro, Jr. (Signatory) who signed this contract on behalf of said Contractor was then Associate Vice Chancellor for Medical Affairs Operations & Fiscal (Title) Planning of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt University School of Medicine

Contract No.: Modification No. A026 to Contract No. EY 76-S-05-2401

APPENDIX "A"
(Revised)

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

For the contract period: August 1, 1976 through October 31, 1977

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will conduct a study of radioisotope distribution and radiation adsorbed dose from medical radionuclides.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 16% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages:	$42,763
(2) Equipment to be purchased or fabricated by the Contractor:	$ 6,150

a Equipment estimated to cost less than $1,000:

Electronic components

b Equipment estimated to cost in excess of $1,000:

CAMAC ADC LRS
Module for autonomous crate controller

1018537

(3) Travel: $ 2,300

Domestic---------$ 2,300
Foreign----------$ 0

(4) Other direct costs: $15,297

(5) Indirect costs (based on a predetermined rate of 62% of salaries and wages): $26,514

(b) Items, if any, significant to the performance of this contract, but excluded from computation of support cost and from consideration in proportioning costs:

(1) Items to be contributed by Contractor:

None

(2) Items to be contributed by the Government:

None

(c) Time or effort of Principal Investigator(s) contributed by Contractor, but excluded from computation of support cost and from consideration in proportioning costs:

All costs including salary, fringe benefits and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $ 93,024; ERDA will pay 100 % of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and the Article entitled "Determination of Support Costs" in Appendix "B". The estimated ERDA Support Cost for the contract period stated in this Appendix "A" is $ 93,024.

1018538

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: EY-76-S-05-2401

The estimated ERDA Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$ 0
(b) New funds for the current period:	$93,024

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

1018539

Contract No. E(40-1)-2401
VANDERBILT UNIVERSITY
Modification No. 25

SUPPLEMENTAL AGREEMENT

THIS SUPPLEMENTAL AGREEMENT, entered into the _____ day of _____, 1976, effective the 1st day of August, 1976, between the UNITED STATES OF AMERICA (hereinafter referred to as the "Government"), acting through the ADMINISTRATOR OF ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION (hereinafter referred to as "ERDA"), and VANDERBILT UNIVERSITY (hereinafter referred to as the "Contractor");

WITNESSETH THAT:

WHEREAS, the Contractor and the Government, represented by the Administrator of Energy Research and Development Administration, have heretofore entered into Contract No. E(40-1)-2401 and Modifications Nos. 1 through 24 providing for the Contractor's performance of certain research; and

WHEREAS, the Contractor and ERDA desire to amend the contract further to provide for the continuance of this research and/or the performance of additional research; and

WHEREAS, this Supplemental Agreement is authorized by the Energy Reorganization Act of 1974 (P. L. 93-438), and other applicable law, including Public Law 85-934;

NOW, THEREFORE, the parties do mutually agree that the contract, as amended, is hereby further amended as follows:

1. In ARTICLE II - THE PERIOD FOR PERFORMANCE, the date July 31, 1976, is changed to October 31, 1977.

2. In Paragraph (a) of ARTICLE III - CONSIDERATION, the sum of $18,605 is added, increasing the sum $451,094 to $469,699.

3. The attached Appendix "A" is made applicable to the period indicated thereon.

4. The attached Appendices "B", "C" and "D" replace the Appendices "B", "C" and "D" attached to Modification No. 24 to the contract.

1018540

IN WITNESS WHEREOF, the parties have executed this Supplemental Agreement.

UNITED STATES OF AMERICA

BY: ADMINISTRATOR OF ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

BY: _____

TITLE: A. H. Eggert, Jr., Chief, Procurement Operations, Contract Division

VANDERBILT UNIVERSITY

BY: _____

Paul Gazzerro, Jr.

TITLE: Associate Vice Chancellor for Medical Affairs Operations & Fiscal Planning

I, Thomas W. Haines, Ph.D. (Attester), certify that I am the Director, Sponsored Research & Programs (Title) of the Contractor named under this contract; that Paul Gazzerro, Jr. (Signatory) who signed this contract on behalf of said Contractor was then Associate Vice Chancellor for Medical Affairs & Operations (Title) Fiscal Planning of said Contractor; that said contract was duly signed for and on behalf of said Contractor by authority of its governing body and is within the scope of its legal powers.

IN WITNESS WHEREOF, I have hereunto affixed my hand and the seal of said Contractor.

[Seal]

Contractor: Vanderbilt Universtiy School of Medicine

Contract No.: Modificaiton Number 25 to Contract Number E-(40-1)2401

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: E-(40-1)-2401

For the contract period: August 1, 1976 through October 31, 1977

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue to conduct a study of radioisotope distribution and radiation adsorbed dose from medical radionuclides.

The Principal Investigator, Dr. A. B. Brill, expects to devote approximately 25% of his time or effort to the project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages: $9,725

(2) Equipment to be purchased or fabricated by the Contractor: $1,750

a Equipment estimated to cost less than $1,000:

Electronic components

b Equipment estimated to cost in excess of $1,000:

None

1018542

(3) Travel: $ 800

Domestic---------$ 800
Foreign----------$ 0

(4) Other direct costs: $ 300

(5) Indirect costs (based on a predetermined rate of 62% of salaries and wages): $6,030

(b) Items, if any, significant to the performance of this contract, but excluded from computation of support cost and from consideration in proportioning costs:

(1) Items to be contributed by Contractor:

None

(2) Items to be contributed by the Government:

None

(c) Time or effort of Principal Investigator(s) contributed by Contractor, but excluded from computation of support cost and from consideration in proportioning costs:

All costs including salary, fringe benefits and related overhead.

ARTICLE A-III. The total estimated cost of items under A-II (a) above for the contract period stated in this Appendix "A" is $ 18,605; ERDA will pay 100 % of the actual costs of these items incurred during the contract period stated in this Appendix "A", subject to the provisions of Article III and the Article entitled "Determination of Support Costs" in Appendix "B". The estimated ERDA Support Cost for the contract period stated in this Appendix "A" is $ 18,605.

1018543

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: E-(40-1)-2401

The estimated ERDA Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$ 0
(b) New funds for the current period:	$18,605

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article entitled "Payments" in Appendix "B".

It is recognized that the substance of Articles A-II and A-III above relate specifically to only the first three months of the contract period. However, the Contractor shall proceed with the contract work as if the work were fully funded. It is anticipated that fiscal year 1977 funds will become available for additional funding of the work described in A-I above and that at such time, appropriate revision of Articles A-II and A-III will be made.

1018544

TABLE OF CONTENTS

APPENDIX "B"---GENERAL PROVISIONS

Article No.		Page No.
I	DEFINITIONS	1
II	INSPECTION, REPORTS, RECORDS, AND ACCOUNTS	1
III	PUBLICATION OF RESULTS	2
IV	DISCLOSURE OF INFORMATION	2
V	PATENT RIGHTS	3
VI	RIGHTS IN TECHNICAL DATA	5
VII	TECHNICAL DATA REQUIREMENTS	7
VIII	AUTHORIZATION AND CONSENT	9
IX	NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT	9
X	REPORTING OF ROYALTIES	9
XI	RESPONSIBILITY FOR THE WORK	10
XII	PROPERTY ITEMS	10
XIII	TERMINATION FOR CONVENIENCE OF THE GOVERNMENT	12
XIV	PAYMENTS	14
XV	EQUAL OPPORTUNITY	16
XVI	CONVICT LABOR	17
XVII	CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION	17
XVIII	DISPUTES	18
XIX	OFFICIALS NOT TO BENEFIT	19
XX	COVENANT AGAINST CONTINGENT FEES	19

1018545

Article No.		Page No.
XXI	EXAMINATION OF RECORDS	19
XXII	BUY AMERICAN ACT	20
XXIII	ASSIGNMENT: SUBCONTRACTING	21
XXIV	REPORTS AND RENEWAL PROPOSALS	21
XXV	FOREIGN TRAVEL	22
XXVI	PRIORITIES, ALLOCATIONS, AND ALLOTMENTS	22
XXVII	UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS	22
XXVIII	UTILIZATION OF SMALL BUSINESS CONCERNS	23
XXIX	UTILIZATION OF MINORITY BUSINESS ENTERPRISES	23
XXX	SOVIET-BLOC CONTROLS	24
XXXI	DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA	24
XXXII	EMPLOYMENT OF THE HANDICAPPED	27
XXXIII	DETERMINATION OF SUPPORT COSTS	28
XXXIV	ADDITIONAL APPROVALS	29
XXXV	PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS	31
XXXVI	CLEAN AIR AND WATER	31

1018546

SPECIAL RESEARCH SUPPORT AGREEMENT

APPENDIX "B"---GENERAL PROVISIONS

ARTICLE B-I - DEFINITIONS

(a) The term "ERDA" means the Energy Research and Development Administration, exercising the authority and performing the functions of the Administrator, the statutory head of that agency, or any duly authorized representative thereof, including the Contracting Officer, except for the purpose of deciding an appeal under the article entitled "Disputes."

(b) The term "Contracting Officer" means the person executing this contract on behalf of the Government and includes his successors or any duly authorized representative of any such person.

(c) Except as otherwise provided in this contract, the term "subcontracts" includes purchase orders under this contract.

ARTICLE B-II - INSPECTION, REPORTS, RECORDS, AND ACCOUNTS

(a) ERDA shall have the right to inspect, in such manner and at all reasonable times as it deems appropriate, all activities of the Contractor arising in the course of its undertakings under this contract.

(b) The Contractor shall make progress and other reports in such manner and at such times as specified in the article entitled "Reports and Renewal Proposals". The Contractor shall also make such other reports to ERDA, with respect to its activities under this contract, as ERDA may reasonably require from time to time.

(c) The Contractor agrees to keep records and books of account, in accordance with generally accepted acccounting principles and practices, and consistent with the requirements of Federal Management Circular (FMC) 73-8, as constituted on the effective commencement date of the contract period, covering its costs and expenditures for items included under Article A-II(a) of Appendix "A" and which are in furtherance of the research work under this contract. In the event a Contractor contribution is listed in Article A-II(b), the Contractor shall maintain records adequate to permit ERDA to determine the extent of the contribution. If professional staff members are included under Article A-II(b), the Contractor shall maintain records on such personnel in accordance with the payroll distribution procedure of subsection J.7.b. of FMC 73-8.

(d) ERDA shall at all reasonable times be afforded access to the premises and to these books and records and to related correspondence, receipts, vouchers, memoranda, and other data of the Contractor; and the

Contractor shall preserve such books and papers, without additional compensation therefor, in accordance with the retention requirements referenced in the article entitled "Examination of Records," of this contract.

ARTICLE B-III - PUBLICATION OF RESULTS

Research results obtained under this contract shall be made available to all through normal and accepted channels without restriction except that no Restricted Data as defined in the Atomic Energy Act of 1954, as amended, or other classified information shall be disclosed to unauthorized persons. Published results shall indicate that the research was supported by ERDA. A copy of each article submitted by the Contractor for publication shall be promptly sent to ERDA. The Contractor shall also inform ERDA when the article is published and furnish six (6) copies of the article as finally published.

ARTICLE B-IV - DISCLOSURE OF INFORMATION

(a) It is mutually expected that the activities under this contract will not involve Restricted Data or other classified information or material. It is understood, however, that if in the opinion of either party this expectation changes prior to the expiration or termination of all activities under this contract, said party shall notify the other party accordingly in writing without delay. In any event, the Contractor shall classify, safeguard, and otherwise act with respect to all Restricted Data and other classified information and material, in accordance with applicable law and the requirements of ERDA, and shall promptly inform ERDA in writing if and when Restricted Data or other classified information or material becomes involved. If and when Restricted Data or other classified information or material becomes involved, or in the actual judgment of the parties it appears likely that Restricted Data or other classified information or material may become involved, the Contractor shall have the right to terminate performance of the work under this contract and in such event the provisions of this contract respecting termination for the convenience of the Government shall apply.

(b) The Contractor shall not permit any individual to have access to Restricted Data, or other classified information, except in accordance with the Atomic Energy Act of 1954, as amended, and ERDA regulations or requirements.

(c) The term "Restricted Data" as used in this article means all data concerning the design, manufacture, or utilization of atomic weapons, the production of special nuclear material or the use of special nuclear

1018548

(2) The Contractor agrees that the Government may duplicate and disclose Subject Invention disclosures and all other reports and papers furnished or required to be furnished pursuant to the contract.

(c) Allocation of Principal Rights

(1) Assignment to the Government. The Contractor agrees to assign to the Government the entire right, title, and interest throughout the world in and to each Subject Invention, except to the extent that rights are retained by the Contractor under subparagraph (c)(2) and Paragraph (d) of this article.

(2) Greater Rights Determinations. The Contractor or the employee-inventor with authorization of the Contractor, may request greater rights than the nonexclusive license and the right to request foreign patent rights provided in Paragraph (d) of this article on identified inventions in accordance with the procedure and criteria of 41 CFR 9-9.109-6. A request for a determination of whether the Contractor or the employee-inventor is entitled to retain such greater rights must be submitted to ERDA at the time of the first disclosure of the invention pursuant to subparagraph (b)(1) of this article or not later than 3 months thereafter or such longer period as may be authorized by the Contracting Officer or Patent Counsel for good cause shown in writing by the Contractor. The information to be submitted for a greater rights determination is specified in 41 CFR 9-9.109-6(e).

(d) Minimum Rights to the Contractor. The Contractor reserves a revocable, nonexclusive, paid-up license in each patent application filed in any country on a Subject Invention and any resulting patent in which the Government acquires title. Revocation shall be in accordance with the procedure of subparagraphs (c)(2) and (3) of the article in 41 CFR 9-9.107-5(a). The Contractor also has the right to request foreign rights in accordance with the procedures of subparagraph (c)(4) of the article in 41 CFR 9-9.107-5(a).

(e) Employee and Subcontractor Agreements. Unless otherwise authorized in writing by the Contracting Officer, the Contractor shall:

(1) Obtain patent agreements to effectuate the provisions of the Patent Rights article from all persons in its employ who perform any part of the work under this contract except nontechnical personnel, such as clerical employees and manual laborers;

(2) Unless otherwise authorized or directed by the Contracting Officer in accordance with 41 CFR 9-9.107-4(f), the Contractor shall include the Patent Rights article of 41 CFR 9-9.107-5(a) or 41 CFR 9-9.107-6, as appropriate, modified to identify the parties in any subcontract hereunder; and

1018549

(3) Promptly notify the Contracting Officer in writing upon the award of any subcontract containing a Patent Rights article by identifying the Subcontractor, the work to be performed under the subcontract, and the dates of award, and estimated completion. Upon the request of the Contracting Officer the Contractor shall furnish a copy of the subcontract to such requestor.

(f) Atomic Energy

(1) No claim for pecuniary award or compensation under the provisions of the Atomic Energy Act of 1954, as amended, shall be asserted by the Contractor or its employees with respect to any invention or discovery made or conceived in the course of or under this contract.

(2) Except as otherwise authorized in writing by the Contracting Officer, the Contractor will obtain patent agreements to effectuate the provisions of subparagraph (f)(1) of this article from all persons who perform any part of the work under this contract, except such clerical and manual labor personnel as will not have access to technical data.

ARTICLE B-VI - RIGHTS IN TECHNICAL DATA

(a) Definitions.

(1) "Technical Data" means recorded information regardless of form or characteristic, of a scientific or technical nature. It may, for example, document research experimental, developmental, or demonstration, or engineering work, or be usable or used to define a design or process, or to procure, produce, support, maintain, or operate material. The data may be graphic or pictorial delineations in media such as drawings or photographs, text in specifications or related performance or design type documents or computer software or printouts. Examples of technical data include research and engineering data, engineering drawings, and associated lists, specifications, standards, process sheets, manuals, technical reports, catalog item identification, and related information. Technical data as used herein does not include financial reports, cost analyses, and other information incidental to contract administration.

(2) "Proprietary Data" means technical data which are trade secrets, such as may be included in design procedures or techniques, chemical composition of materials, or manufacturing methods, processes, or treatments.

(3) "Subject Data" means technical data resulting directly from performance of the contract and technical data which are specified to be delivered, or which are in fact, delivered pursuant to this contract.

1018550

(4) "Unlimited Rights" means rights to use, duplicate, or disclose technical data, in whole or in part, in any manner and for any purpose whatsoever, and to have others to do so, without any claim for compensation by the Contractor.

(b) General. The Government shall have:

(1) Unlimited rights in all Subject Data unless otherwise limited below; and

(2) The right at any time to modify, remove, or ignore any markings on Subject Data not authorized by this contract.

(c) Copyrights.

(1) The Contractor agrees to and does hereby grant to the Government, and to its officers, agents, servants, and employees acting within the scope of their official duties, (i) a royalty-free, nonexclusive, irrevocable license to reproduce, translate, publish, use, and dispose of, and to authorize others so to do, all copyrightable material first produced or composed under this contract by the Contractor, its employees or any individual or concern specifically employed or assigned to originate and prepare such material; and (ii) a license as aforesaid under any and all copyrighted or copyrightable work not first produced or composed by the Contractor in the performance of this contract but which is incorporated in the material furnished under the contract, provided that such license shall be only to the extent the Contractor now has, or prior to completion or final settlement of the contract, may acquire the right to grant such license without becoming liable to pay compensation to others solely because of such grant.

(2) The Contractor agrees that it will not include any copyrighted material in any written or copyrightable material furnished or delivered under this contract, without a license as provided for in subparagraph (1)(ii) hereof, or without the consent of the copyright owner, unless specific written approval of the Contracting Officer to the inclusion of such copyrighted material is secured.

(3) The Contractor agrees to report to the Contracting Officer or Patent Counsel promptly and in reasonable written detail any notice or claim of copyright infringement received by the Contractor with respect to any material delivered under this contract.

(d) Relation to Patents. Nothing contained in this article shall imply a license to the Government under any patent or be construed as affecting the scope of any licenses of other rights otherwise granted to the Government under any patent.

1018551

(e) Withholding of Proprietary Data. Proprietary data need not be furnished for items or processes, including minor modifications thereof, which were developed at private expense and which are incorporated as component parts in or to be used with the product or process being developed or furnished under this contract, if in lieu thereof the Contractor provides the Contracting Officer a list of such items or processes, and furnishes data for the purpose of identifying sources, size configuration, mating and attachment characteristics, functional charteristics and performance requirements ("form, fit and function" data).

(f) Inspection Rights. Except as specified in the contract schedule for specific items of proprietary data the Contracting Officer's representatives, at all reasonable times, may inspect at the Contractor's facility any proprietary data withheld pursuant to paragraph (e) of this article for the purposes of verifying that such data properly fell within the withholding provision of paragraph (e) or to evaluate work performance.

ARTICLE B-VII - TECHNICAL DATA REQUIREMENTS

(a) To the extent that the following technical data is not elsewhere required to be furnished to the Government under this contract, and is of the type customarily retained in the normal course of business, the Contractor, upon written request of the Contracting Officer, at any time during contract performance or within one year after final payment, shall furnish the following:

(1) A set of engineering drawings which will be sufficient to enable the manufacture of items or equipment furnished under this contract (other than components or items of standard commercial design, or items fabricated heretofore) by a firm skilled in the art of manufacturing items of equipment of the general type and character of the items or equipment furnished under this contract or a set of flow sheets and engineering drawings which will be sufficient to enable performance of any process developed under this contract by a firm skilled in the art of practicing processes of the general type and character of such process. Such set or sets of drawings and flow sheets shall incorporate all changes made in the equipment or process in the form in which it was delivered to the Government.

(2) Any of the following technical data which is necessary to explain or help Government technical personnel understand any equipment, items, or process developed under the contract and furnished to the Government:

(i) A copy of drawings and other technical data used in or prepared in connection with the development, practice, and testing of any process or processes required under the contract,

1018552

or with the development, fabrication, and testing of prototype models of equipment or items (other than items of standard commercial design or items fabricated heretofore), if required under the contract.

(ii) A report of all studies made in planning the work, and in developing background research for the work, including citation references to all such background research, and a copy of all compilations, digests, or analyses of such background research compiled in connection with the performance of this contract.

(iii) A copy of design, studies, research notes, parameter and tolerance studies, drawings, including Contractor's identification of symbols and markings, specifications, test results, and any other technical information used in any research, development, demonstration, design, engineering, and testing required in the performance of this contract, including test equipment and related items, together with any information as to safety precautions which may be necessary in connection with the manufacture, storage or use of the equipment, material, or process, if any, in the event that equipment, material, or process is the subject of research, development, or demonstration work under this contract.

The Contractor shall not be required to furnish any technical data which may be described in subparagraphs (ii) and (iii) above unless such data is essential and closely related to the contract work.

(b) All technical data which are required to be furnished by the Contractor under this provision are "Subject Data" within the meaning of the "Rights in Technical Data" article of this contract.

(c) Nothing contained in this "Technical Data Requirements" article shall require the Contractor to deliver (1) any technical data, the delivery of which is excused by paragraph (e) and not called for under paragraph (h), if included, of the article of this contract entitled "Rights in Technical Data"; or (2) technical data previously developed by parties other than the Contractor independently of this contract and acquired by the Contractor prior to this contract under conditions restricting the Contractor's right to disclose the same.

(d) In the event the Contracting Officer requests the delivery of technical data by the Contractor, as contemplated by paragraph (a) above, prior to final payment, such request shall be treated as a change under the article of this contract entitled "Changes" and an equitable a adjustment in the price, if this is a fixed-price contract, or estimated cost and any fixed fee, if this is a cost-type contract, shall be made

1018553

to cover the cost of preparing drawings called for in subparagraph (a)(1) above, and of collecting, preparing, editing, duplicating, assembling, and shipping the technical data requested under paragraph (a) above, but only to the extent that the Contractor warrants that such costs were not included in the price (or estimated cost and fixed fee) of the contract. The Contractor shall comply with requests of the Contracting Officer made under paragraph (a) above within one year following final payment, provided that suitable provision is made for reimbursement of the additional costs of complying with such request, together with a reasonable fee or profit thereon, such additional costs being limited to the costs set forth above, and warranted to have been excluded from the price (or estimated cost and fixed fee) of the contract. Any adjustment or payment under this paragraph shall not include any amount for the value or the technical data, as distinguished from the costs set forth above.

ARTICLE B-VIII - AUTHORIZATION AND CONSENT

The Government hereby gives its authorization and consent for all use and manufacture of any invention described in and covered by a patent of the United States in the performance of this contract or any part hereof or any amendment hereto or any subcontract hereunder (including any lower-tier subcontract).

ARTICLE B-IX - NOTICE AND ASSISTANCE REGARDING PATENT AND COPYRIGHT INFRINGEMENT

The provisions of this article shall be applicable only if the amount of this contract exceeds $10,000.

(a) The Contractor shall report to the Contracting Officer, promptly and in reasonable written detail, each notice or claim of patent or copyright infringement based on the performance of this contract of which the Contractor has knowledge.

(b) In the event of any claim or suit against the Government on account of any alleged patent or copyright infringement arising out of the performance of this contract or out of the use of any supplies furnished or work or services performed hereunder, the Contractor shall furnish to the Government when requested by the Contracting Officer, all evidence and information in possession of the Contractor pertaining to such suit or claim. Such evidence and information shall be furnished at the expense of the Government except where the Contractor has agreed to indemnify the Government.

(c) This article shall be included in all subcontracts.

ARTICLE B-X - REPORTING OF ROYALTIES

If this contract is in an amount which exceeds $10,000 and if any royalty payments are directly involved in the contract or are reflected in the contract price to the Government, the Contractor agrees to report

1018554

in writing to the Contracting Officer or Patent Counsel during the performance of this contract and prior to its completion or final settlement the amount of any royalties or other payments paid or to be paid by it directly to others in connection with the performance of this contract together with the names and addresses of licensors to whom such payments are made and either the patent numbers involved or such other information as will permit identification of the patents or other basis on which the royalties are to be paid. The approval of ERDA of any individual payments or royalties shall not stop the Government at any time from contesting the enforceability, validity or scope of, or title to, any patent under which a royalty or payments are made.

ARTICLE B-XI - RESPONSIBILITY FOR THE WORK

(a) The Contractor is solely responsible for the conduct of the work.

(b) In instances where the carrying out of the contract work involves an ERDA license, the provisions of the pertinent license shall prevail over any inconsistent provisions of this contract.

ARTICLE B-XII - PROPERTY ITEMS

(a) Except as otherwise provided in this Paragraph (a) and Paragraph (b) of this article, title to all material, supplies, and equipment purchased or otherwise acquired by the Contractor in the performance of its research activities shall be and remain in the Contractor. Said materials, supplies, and equipment shall be used for the benefit of research under this contract and any extensions or successor contracts hereto: And, provided, There is no interference with said research, shall be made available for use by investigators working on any Federal research agreement at the same location. Subject to these priorities, the materials, supplies, and equipment may be used as the Contractor wishes. Except as otherwise agreed in writing, title to any items of property listed as "Government property" shall pass directly to the Government; such property shall be subject to Paragraphs (b), (c), (d), (e), and (f) of this article.

(b) Subject to the mutual agreement of ERDA and the Contractor, the Government may furnish the Contractor items of equipment, materials, supplies, or facilities for use by the Contractor in the performance of the contract work; title to these items shall remain in the Government unless otherwise agreed in writing. Such items of property and the items of property listed elsewhere in this contract as Government property are hereinafter referred to as "Government Property." Title to Government property shall not be affected by the incorporation or attachment thereof to any property not owned by the Government nor shall any such property, or any part thereof, be or become a fixture or lose its identity as personalty by reason of affixation to any realty.

1018555

(c) To the extent practicable, the Contractor shall cause all items of Government property to be suitably marked with an identifying mark or symbol indicating that the items are the property of the Government. The Contractor shall maintain, at all times and in a manner satisfactory to ERDA, records showing the use and disposition of Government property. Such records shall be subject to ERDA inspection at all reasonable times and ERDA shall at all reasonable times have access to the premises wherein any items of Government property are located. Unless otherwise authorized in writing by ERDA, the Contractor shall use Government property only for the purposes of this contract: Provided, however, That the Contractor is hereby authorized to use items of equipment constituting Government property for other Federal research agreements to the extent such use: (1) Does not interfere with its work under this contract; (2) is not prohibited by provisions of the other Federal agreements; and (3) is promptly reported by the Contractor to ERDA under this contract.

(d) The Contractor shall promptly notify ERDA of any loss or destruction of or damage to Government property. It is understood that the Contractor shall not be liable for any such loss, destruction, or damage, unless same results from willful misconduct or lack of good faith on the part of any corporate officer of the Contractor, or of one or more of the Contractor's representatives having supervision or direction of all or substantially all of the activities under this contract. If the Contractor is liable for any such loss, destruction, or damage, it shall promptly account therefor, and is indemnified, reimbursed, or otherwise compensated for such loss, destruction, or damage, it shall promptly account therefor to the satisfaction of ERDA.

(e) With the written approval of ERDA, the Contractor may sell, transfer, or otherwise dispose of items of Government property to such parties and upon such terms as so approved, or itself acquire title to items of Government property upon such terms as may mutually be agreed upon in writing by the Contractor and ERDA. The proceeds of any such disposition, and any agreed price of any such Contractor acquisition, shall be paid by the Contractor to the Government, or credited on account of ERDA payments to be made under this contract, as ERDA may direct. Subject to the other provisions of this contract, the Contractor shall deliver Government property to ERDA upon request (suitably packed and shipped at the Government's expense).

(f) The Contractor shall utilize for the benefit of the work under this contract such items of property available to the Contractor by reason of its activities under other Federal research agreements as are appropriate for utilization under this contract pursuant to the provisions of the pertinent Federal agreements.

1018556

ARTICLE B-XIII - TERMINATION FOR CONVENIENCE OF THE GOVERNMENT

(a) The performance of work under this contract may be terminated, in whole or from time to time in part, by the Government whenever for any reason the Contracting Officer shall determine that such termination is in the best interest of the Government. Termination of work hereunder shall be effected by delivery to the Contractor of a Notice of Termination specifying the extent to which performance of work under the contract is terminated and the date upon which such termination becomes effective.

(b) After receipt of the Notice of Termination, the Contractor shall cancel its outstanding commitments hereunder covering the procurement of materials, supplies, equipment, and miscellaneous items. In addition, the Contractor shall exercise all reasonable diligence to accomplish the cancellation or diversion of its outstanding commitments covering personal services and extending beyond the date of such termination to the extent that they relate to the performance of any work terminated by the Notice. With respect to such canceled commitments, the Contractor agrees to (1) settle all outstanding liabilities and all claims arising out of such cancellation of commitments, with the approval or ratification of the Contracting Officer, to the extent he may require, which approval or ratification shall be final for all purposes of this article, and (2) assign to the Government, in the manner, at the time, and to the extent directed by the Contracting Officer, all of the right, title, and interest of the Contractor under the orders and subcontracts so terminated, in which case the Government shall have the right, in its discretion, to settle or pay any or all claims arising out of the termination of such orders and subcontracts.

(c) The Contractor shall submit its termination claim to the Contracting Officer promptly after receipt of a Notice of Termination, but in no event later than one year from the effective date thereof, unless one or more extensions in writing are granted by the Contracting Officer upon written request of the Contractor within such one-year period or authorized extension thereof. Upon failure of the Contractor to submit its termination claim within the time allowed, the Contracting Officer may, subject to any review required by ERDA's procedures in effect as of the date of execution of this contract, determine, on the basis of information available to him, the amount, if any, due to the Contractor by reason of the termination and shall thereupon pay to the Contractor the amount so determined.

(d) Any determination of costs under Paragraph (c) shall be governed by the contract cost principles and procedures in Subpart 1-15.3 of the Federal Procurement Regulations (41 CFR 1-15.3) in effect on the date of this contract, except that if the Contractor is not an educational institution any costs claimed, agreed to, or determined pursuant to Paragraphs

1018557

(c) or (e) hereof shall be in accordance with Subpart 1-15.2 of the Federal Procurement Regulations (41 CFR 1-15.2) in effect on the date of this contract.

(e) Subject to the provisions of Paragraph (c) above, and subject to any review required by ERDA's procedures in effect as of the date of execution of this contract, the Contractor and the Contracting Officer may agree upon the whole or any part of the amount or amounts to be paid to the Contractor by reason of the termination under this article, which amount or amounts may include any reasonable cancellation charges thereby incurred by the Contractor and any reasonable loss upon outstanding commitments for personal services which it is unable to cancel: Provided, however, That in connection with any outstanding commitments for personal services which the Contractor is unable to cancel, the Contractor shall have exercised reasonable diligence to divert such commitments to its other activities and operations. Any such agreement shall be embodied in an amendment to this contract and the Contractor shall be paid the agreed amount.

(f) The Government may from time to time, under such terms and conditions as it may prescribe, make partial payments against costs incurred by the Contractor in connection with the terminated portion of this contract, whenever, in the opinion of the Contracting Officer, the aggregate of such payments is within the amount to which the Contractor will be entitled hereunder. If the total of such payments is in excess of the amount finally agreed or determined to be due under this article, such excess shall be payable by the Contractor to the Government upon demand: Provided, That if such excess is not so paid upon demand, interest thereon shall be payable by the Contractor to the Government at the rate of 6 percent per annum, beginning 30 days from the date of such demand.

(g) The Contractor agrees to transfer title to the Government and deliver in the manner, at the times, and to the extent, if any, directed by the Contracting Officer, such information and items which, if the contract had been completed, would have been required to be furnished to the Government, including:

(1) Completed or partially completed plans, drawings, and information; and

(2) Materials or equipment produced or in process or acquired in connection with the performance of the work terminated by the notice.

Other than the above, any termination inventory resulting from the termination of the contract may, with the written approval of the Contracting Officer, be sold or acquired by the Contractor under the conditions prescribed by and at a price or prices approved by the Contracting

1018558

Officer. The proceeds of any such disposition shall be applied in reduction of any payments to be made by the Government to the Contractor under this contract or shall otherwise be credited to the price or cost of work covered by this contract or paid in such other manner as the Contracting Officer may direct. Pending final disposition of property arising from the termination, the Contractor agrees to take such action as may be necessary, or as the Contracting Officer may direct, for the protection and preservation of the property related to this contract which is in the possession of the Contractor and in which the Government has or may acquire an interest.

(h) Any disputes as to questions of fact which may arise hereunder shall be subject to the "Disputes" article of this contract.

ARTICLE B-XIV - PAYMENTS

(a) ERDA shall make payments to the Contractor with respect to the amount of consideration prescribed in Article III of this contract as follows:

(1) A maximum of 45 percent of the new funds as set forth in Article A-III(b) of this contract following execution of this contract (and following the effectuation of each extended period).

(2) A maximum of an additional 45 percent of the new funds as set forth in Article A-III(b) of this contract upon receipt of a request or requests from the Contractor evidencing that the amount requested is then required in connection with the work under the contract.

(3) If, following submission of an annual progress report, the contract is to be extended for an additional period of performance, an additional payment may be made at the time of execution of the extension which, when added to the payments already made under (1) and (2) above for the expiring period, will not exceed the new funds set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the ERDA support cost and evidencing the Contractor's performance under the contract.

(4) If the contract is not to be extended, the final payment of the consideration provided for in Article III of this contract shall be made following submission by the Contractor of a final report required by the article entitled "Reports and Renewal Proposals", in form and content satisfactory to ERDA, and submission of a certified statement showing the support cost and evidencing the Contractor's performance under the contract and compliance by the Contractor with the patent provisions of this contract.

1018559

(b) The payments made pursuant to Paragraph (a) above shall not prejudice or otherwise affect adversely any of the Government's rights under the contract. For purposes of settlement in the event of termination pursuant to the article entitled "Termination for Convenience of the Government" hereof, these payments shall not be construed as evidentiary, and any excess payment in the light of the article entitled "Termination for Convenience of the Government" shall be promptly returned to ERDA.

(c) ERDA, at its option, may invoke the following with respect to any amount of the contract consideration remaining to be paid at any given time:

(1) ERDA shall issue a letter of credit as provided for by Treasury Fiscal Requirements Manual, Part VI, Section 1020, under which payments to the Contractor with respect to the amount of consideration provided for in Article III of this contract will be made. The Contractor agrees that the first ninety (90) percent of the new funds as set forth in Article A-III(b) of the contract will be under the letter of credit and will be subject to the submission by the Contractor of a Payment Voucher on Letter of Credit (TUS 5401), in accordance with procedures based upon Treasury Fiscal Requirements Manual, Part VI, Section 1020, which are agreed to by the parties. Following submission by the Contractor of a final report provided for in the Article entitled "Reports and Renewal Proposals," in form and content satisfactory to ERDA, and submission of a certified statement showing the total expenditures and evidencing the Contractor's performance under the contract, and upon submission by the Contractor to ERDA of such invoices or vouchers as are satisfactory to ERDA, ERDA shall pay the Contractor the concluding payment of the consideration provided for in Article III of this contract, or said concluding payment will be included under the letter of credit and will be subject to submission by the Contractor of a payment voucher on letter of credit, in accordance with the procedure described above. If, following submission of an annual report, the contract is extended for an additional period of performance, an additional payment may similarly be made at the time of execution of the extension which, when added to the payments already made for the expiring period, will not exceed the new funds as set forth in Article A-III(b) for the expiring period; a concluding payment for the pertinent period, if appropriate, may be made following submission of a certified statement showing the ERDA support cost for the pertinent period and evidencing the Contractor's performance under the contract.

(2) ERDA reserves the right to increase, decrease, or cancel the amount covered by the letter of credit, provided that such action is required because of a change in the amount of consideration provided for in Article III or is taken pursuant to subparagraph (c)(1)

1018560

of this article. The issuance and use of a letter of credit and receipt of funds pursuant thereto shall not prejudice or otherwise adversely affect any of the Government's rights under the contract.

ARTICLE B-XV - EQUAL OPPORTUNITY

(The following article is applicable unless this contract is exempt under the rules, regulations, and relevant orders of the Secretary of Labor [41 CFR, Ch. 60].)

During the performance of this contract, the Contractor agrees as follows:

(a) The Contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. The Contractor will take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, color, religion, sex, or national origin. Such action shall include, but not be limited to, the following: Employment, upgrading, demotion, or transfer; recruitment or recruitment advertising; layoff or termination; rates of pay or other forms of compensation; and selection for training, including apprenticeship. The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices to be provided by the Contracting Officer setting forth the provisions of this Equal Opportunity article.

(b) The Contractor will, in all solicitations or advertisements for employees placed by or on behalf of the Contractor, state that all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, or national origin.

(c) The Contractor will send to each labor union or representative of workers with which it has a collective bargaining agreement or other contract or understanding, a notice, to be provided by the Contracting Officer, advising the labor union or workers' representative of the Contractor's commitments under this Equal Opportunity article, and shall post copies of the notice in conspicuous places available to employees and applicants for employment.

(d) The Contractor will comply with all provisions of Executive Order No. 11246 of September 24, 1965, and of the rules, regulations, and relevant orders of the Secretary of Labor.

(e) The Contractor will furnish all information and reports required by Executive Order No. 11246 of September 24, 1965, and by the rules, regulations, and orders of the Secretary of Labor, or pursuant thereto, and will permit access to its books, records, and accounts by ERDA and the Secretary of Labor for purposes of investigation to ascertain compliance with such rules, regulations, and orders.

1018561

(f) In the event of the Contractor's noncompliance with the Equal Opportunity article of this contract or with any of the said rules, regulations, or orders, this contract may be canceled, terminated, or suspended, in whole or in part, and the Contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in Executive Order No. 11246 of September 24, 1965, and such other sanctions may be imposed and remedies invoked as provided in Executive Order No. 11246 of September 24, 1965, or by rule, regulation, or order of the Secretary of Labor, or as otherwise provided by law.

(g) The Contractor will include the provisions of Paragraphs (a) through (g) in every subcontract or purchase order unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to Section 204 of Executive Order No. 11246 of September 24, 1965, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as ERDA may direct as a means of enforcing such provisions, including sanctions for noncompliance: Provided, however, That in the event the Contractor becomes involved in, or is threatened with, litigation with a subcontractor or vendor as a result of such direction by ERDA, the Contractor may request the United States to enter into such litigation to protect the interest of the United States.

ARTICLE B-XVI - CONVICT LABOR

In connection with the performance of work under this contract, the Contractor agrees not to employ any person undergoing sentence of imprisonment except as provided by Public Law 89-176, September 10, 1965 (18 U.S.C. 4082(c)(2)), and Executive Order 11755, December 29, 1973.

ARTICLE B-XVII - CONTRACT WORK HOURS AND SAFETY STANDARDS ACT--OVERTIME COMPENSATION

This contract, to the extent that it is of a character specified in the Contract Work Hours and Safety Standards Act (40 U.S.C. 327-333), is subject to the following provisions and to all other applicable provisions and exceptions of such Act and the regulations of the Secretary of Labor thereunder.

(a) Overtime Requirements. No Contractor or subcontractor contracting for any part of the contract work which may require or involve the employment of laborers, mechanics, apprentices, trainees, watchmen, and guards shall require or permit any laborer, mechanic, apprentice, trainee, watchman, or guard in any workweek in which he is employed on such work to work in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek on work subject to the provisions of the Contract Work Hours and Safety Standards Act unless such laborer, mechanic, apprentice, trainee, watchman, or guard receives compensation at a rate

1018562

not less than one and one-half times his basic rate of pay for all such hours worked in excess of 8 hours in any calendar day or in excess of 40 hours in such workweek, whichever is the greater number of overtime hours.

(b) Violation; Liability for Unpaid Wages; Liquidated Damages. In the event of any violation of the provisions of Paragraph (a), the Contractor and any subcontractor responsible therefor shall be liable to any affected employee for his unpaid wages. In addition, such Contractor and subcontractor shall be liable to the United States for liquidated damages. Such liquidated damages shall be computed with respect to each individual laborer, mechanic, apprentice, trainee, watchman, or guard employed in violation of the provisions of Paragraph (a) in the sum of $10 for each calendar day on which such employee was required or permitted to be employed on such work in excess of 8 hours or in excess of his standard workweek of 40 hours without payment of the overtime wages required by Paragraph (a).

(c) Withholding for Unpaid Wages and Liquidated Damages. The Contracting Officer may withhold from the Contractor, from any moneys payable on account of work performed by the Contractor or subcontractor, such sums as may administratively be determined to be necessary to satisfy any liabilities of such Contractor or subcontractor for unpaid wages and liquidated damages as provided in the provisions of Paragraph (b).

(d) Subcontracts. The Contractor shall insert Paragraphs (a) through (d) of this article in all subcontracts, and shall require their inclusion in all subcontracts of any tier.

(e) Records. The Contractor shall maintain payroll records containing the information specified in 29 CFR 516.2(a). Such records shall be preserved for three years from the completion of the contract.

ARTICLE B-XVIII - DISPUTES

(a) Except as otherwise provided in this contract, any dispute concerning a question of fact arising under this contract which is not disposed of by agreement shall be decided by the Contracting Officer, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to the Contractor. The decision of the Contracting Officer shall be final and conclusive unless within 30 days from the date of receipt of such copy, the Contractor mails or otherwise furnishes to the Contracting Officer a written appeal addressed to ERDA. The decision of ERDA or its duly authorized representative for the determination of such appeals shall be final and conclusive unless determined by a court of competent jurisdiction to have been fraudulent, or capricious, or arbitrary, or so grossly erroneous as necessarily to imply bad faith, or

1018563

not supported by substantial evidence. In connection with any appeal proceeding under this article, the Contractor shall be afforded an opportunity to be heard and to offer evidence in support of its appeal. Pending final decision of a dispute hereunder, the Contractor shall proceed diligently with the performance of the contract and in accordance with the Contracting Officer's decision.

(b) This "Disputes" article does not preclude consideration of law questions in connection with decisions provided for in Paragraph (a) above: Provided, That nothing in this contract shall be construed as making final the decision of any administrative official, representative, or board on a question of law.

ARTICLE B-XIX - OFFICIALS NOT TO BENEFIT

No member of or delegate to Congress, or resident commissioner, shall be admitted to any share or part of this contract, or to any benefit that may arise therefrom; but this provision shall not be construed to extend to this contract if made with a corporation for its general benefit.

ARTICLE B-XX - COVENANT AGAINST CONTINGENT FEES

The Contractor warrants that no person or selling agency has been employed or retained to solicit or secure this contract upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by the Contractor for the purpose of securing business. For breach or violation of this warranty the Government shall have the right to annul this contract without liability or in its discretion to deduct from the contract price or consideration, or otherwise recover, the full amount of such commission, percentage, brokerage, or contingent fee.

ARTICLE B-XXI - EXAMINATION OF RECORDS

(a) This article is applicable if the amount of this contract exceeds $2,500 and was entered into by means of negotiation, including small business restricted advertising, but is not applicable if this contract was entered into by means of formal advertising.

(b) The Contractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under this contract, have access to and the right to examine any directly pertinent books, documents, papers, and records of the Contractor involving transactions related to this contract.

1018564

(c) The Contractor further agrees to include in all its subcontracts hereunder a provision to the effect that the subcontractor agrees that the Comptroller General of the United States or any of his duly authorized representatives shall, until the expiration of three years after final payment under the subcontract, have access to and the right to examine any directly pertinent books, documents, papers, and records of such subcontractor, involving transactions related to the subcontract. The term "subcontract" as used in this article excludes (1) purchase orders not exceeding $2,500 and (2) subcontracts or purchase orders for public utility services at rates established for uniform applicability to the general public.

(d) The periods of access and examination described in (b) and (c) above, for records which relate to (1) appeals under the "Disputes" article of this contract, (2) litigation or the settlement of claims arising out of the performance of this contract, or (3) costs and expenses of this contract as to which exception has been taken by the Comptroller General or any of his duly authorized representatives, shall continue until such appeals, litigation, claims, or exceptions have been disposed of.

(e) Nothing in this contract shall be deemed to preclude an audit by the General Accounting Office of any transaction under this contract.

ARTICLE B-XXII - BUY AMERICAN ACT

(a) In acquiring end products, the Buy American Act (41 U. S. Code 10a - 10d) provides that the Government give preference to domestic source end products. For the purpose of this article:

(i) "Components" means those articles, materials, and supplies which are directly incorporated in the end products;

(ii) "End products" means those articles, materials, and supplies which are to be acquired under this contract for public use; and

(iii) A "domestic source end product" means (A) an unmanufactured end product which has been mined or produced in the United States and (B) an end product manufactured in the United States if the cost of the components thereof which are mined, produced, or manufactured in the United States exceeds 50 percent of the cost of all its components. For the purposes of this (a)(iii)(B), components of foreign origin of the same type or kind as the products referred to in (b)(ii) or (iii) of this article shall be treated as components mined, produced, or manufactured in the United States.

1018565

(b) The Contractor agrees that there will be delivered under this contract only domestic source end products, except end products:

(i) Which are for use outside the United States;

(ii) Which the Government determines are not mined, produced, or manufactured in the United States in sufficient and reasonably available commercial quantities and of a satisfactory quality;

(iii) As to which ERDA determines the domestic preference to be inconsistent with the public interest; or

(iv) As to which ERDA determines the cost to the Government to be unreasonable.

(The foregoing requirements are administered in accordance with Executive Order No. 10582, dated December 17, 1954.)

ARTICLE B-XXIII - ASSIGNMENT; SUBCONTRACTING

Neither this contract nor any interest therein nor claim thereunder shall be assigned or transferred by the Contractor, except as expressly authorized in writing by ERDA. The Contractor shall not subcontract any research or development work under this contract, except as expressly authorized in writing by ERDA.

ARTICLE B-XXIV - REPORTS AND RENEWAL PROPOSALS

The Contractor shall furnish six (6) copies of the following reports and renewal proposals, if any, addressed to the Research Contracts, Procedures, and Reports Branch, Contract Division, Oak Ridge Operations Office, Energy Research and Development Administration, Post Office Box E, Oak Ridge, Tennessee 37830:

(a) Progress Report. The progress report shall briefly describe the scope of investigations undertaken and the significant results obtained. It shall also indicate compliance with the contract requirements and any failures to comply. The report shall indicate the approximate percentage of time or effort which the principal investigator(s) has devoted to the project since the beginning of the current term of the agreement and indicate the amount of effort which is expected to be devoted during the remainder of the current term. Technical reports, preprints, and articles prepared for publication shall be listed with bibliographic references. Reprints of all such material not previously submitted shall be appended and material contained therein need not be duplicated in the report. Progress reports shall be submitted approximately three (3) months in advance of the expiration of the current

1018566

contract term and shall give the Contractor's best estimate of the probable events and occurrences in regard to the remainder of the current contract term. Except as ERDA may otherwise request, no further progress report will be required for any contract year unless there has been a significant change in scientific results or contract compliance between the latest progress report by the Contractor and its actual experience; this shall be reported promptly.

(b) Final Report. Upon termination or expiration of the total period of performance, the Contractor shall submit, promptly, a summary of its activities for the entire period, including a list of publications issued during the total term of the contract and copies of any reprints not previously submitted, as well as a comprehensive evaluation of progress in the area of research supported by the contract.

(c) Renewal Proposals. A renewal proposal, if any, shall be submitted along with the technical progress report, and each of the two documents shall be separately bound.

ARTICLE B-XXV - FOREIGN TRAVEL -

Foreign travel shall be subject to the prior approval of the Contracting Officer for each separate trip regardless of whether funds for such travel are contained in an approved budget. Foreign travel is defined as any travel outside of Canada and the United States and its territories and possessions.

ARTICLE B-XXVI - PRIORITIES, ALLOCATIONS, AND ALLOTMENTS

The Contractor shall follow the provisions of DMS Regulation 1 and all other applicable regulations and orders of the Domestic and International Business Administration, Department of Commerce, in obtaining controlled materials and other products and materials needed to fill this contract.

ARTICLE B-XXVII - UTILIZATION OF CONCERNS IN LABOR SURPLUS AREAS

(The following article is applicable if this contract exceeds $5,000.)

(a) It is the policy of the Government to award contracts to labor surplus area concerns that (1) have been certified by the Secretary of Labor (hereafter referred to as certified-eligible concerns with first or second preferences) regarding the employment of a proportionate number of disadvantaged individuals and have agreed to perform substantially (i) in or near sections of concentrated unemployment or underemployment or in persistent or substantial labor surplus areas or (ii) in other areas of the United States, respectively, or (2) are noncertified concerns which have agreed to perform substantially in persistent or

1018567

substantial labor surplus areas, where this can be done consistent with the efficient performance of the contract and at prices no higher than are obtainable elsewhere. The Contractor agrees to use its best efforts to place its subcontracts in accordance with this policy.

(b) In complying with Paragraph (a) of this article and with Paragraph (b) of the article of this contract entitled "Utilization of Small Business Concerns," the Contractor in placing its subcontracts shall observe the following order of preference: (1) Certified-eligible concerns with a first preference which are also small business concerns; (2) other certified-eligible concerns with a first preference; (3) certified-eligible concerns with a second preference which are also small business concerns; (4) other certified-eligible concerns with a second preference; (5) persistent or substantial labor surplus area concerns which are also small business concerns; (6) other persistent or substantial labor surplus area concerns; and (7) small business concerns which are not labor surplus area concerns.

ARTICLE B-XXVIII - UTILIZATION OF SMALL BUSINESS CONCERNS

(a) It is the policy of the Government as declared by the Congress that a fair proportion of the purchases and contracts for supplies and services for the Government be placed with small business concerns.

(b) The Contractor agrees to accomplish the maximum amount of subcontracting to small business concerns that the Contractor finds to be consistent with the efficient performance of this contract.

ARTICLE B-XXIX - UTILIZATION OF MINORITY BUSINESS ENTERPRISES

(a) It is the policy of the Government that minority business enterprises shall have the maximum practicable opportunity to participate in the performance of Government contracts.

(b) The Contractor agrees to use its best efforts to carry out this policy in the award of its subcontracts to the fullest extent consistent with the efficient performance of this contract. As used in this contract, the term "minority business enterprise" means a business, at least 50 percent of which is owned by minority group members or, in case of publicly owned businesses, at least 51 percent of the stock of which is owned by minority group members. For the purposes of this definition, minority group members are Negroes, Spanish-speaking American persons, American-Orientals, American-Indians, American-Eskimos, and American-Aleuts. Contractors may rely on written representations by subcontractors regarding their status as minority business enterprises in lieu of an independent investigation.

1018568

ARTICLE B-XXX - SOVIET-BLOC CONTROLS

In connection with the contract activities, the Contractor agrees to comply with the requirements set forth in Appendix "D" of this contract relating to the countries listed therein. From time to time, by written notice to the Contractor, ERDA shall have the right to change the listing of countries in Appendix "D" upon a determination by ERDA that such change is in conformance with national policy. The Contractor shall have the right to terminate its performance under this contract upon at least sixty (60) days' prior written notice to ERDA if the Contractor determines that it is unable, without substantially interfering with its policies as an educational institution or without adversely affecting its performance, to continue performance of the work under this contract as a result of a change in Appendix "D" made by ERDA pursuant to the preceding sentence. If the Contractor elects to terminate performance, the provisions of this contract respecting termination for the convenience of the Government shall apply.

ARTICLE B-XXXI - DISABLED VETERANS AND VETERANS OF THE VIETNAM ERA -

(a) The Contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment, and otherwise treat qualified disabled veterans and veterans of the Vietnam era without discrimination based upon their disability or veterans status in all employment practices such as the following: Employment upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees that all suitable employment openings of the Contractor which exist at the time of the execution of this contract and those which occur during the performance of this contract, including those not generated by this contract and including those occurring at an establishment of the Contractor other than the one wherein the contract is being performed but excluding those of independently operated corporate affiliates, shall be listed at an appropriate local office of the State employment service system wherein the opening occurs. The Contractor further agrees to provide such reports to such local office regarding employment openings and hires as may be required.

State and local government agencies holding Federal contracts of $10,000 or more shall also list all their suitable openings with the appropriate office of the State employment service, but are not required to provide those reports set forth in Paragraphs (d) and (e).

(c) Listing of employment openings with the employment service system pursuant to this article shall be made at least concurrently with

1018569

the use of any other recruitment source or effort and shall involve the normal obligations which attach to the placing of a bona fide job order, including the acceptance of referrals of veterans and nonveterans. The listing of employment openings does not require the hiring of any particular job applicant or from any particular group of job applicants, and nothing herein is intended to relieve the Contractor from any requirements in Executive orders or regulations regarding nondiscrimination in employment.

(d) The reports required by Paragraph (b) of this article shall include, but not be limited to, periodic reports which shall be filed at least quarterly with the appropriate local office or, where the Contractor has more than one hiring location in a State, with the central office of the State employment service. Such reports shall indicate for each hiring location (1) the number of individuals hired during the reporting period, (2) the number of nondisabled veterans of the Vietnam era hired, (3) the number of disabled veterans of the Vietnam era hired, and (4) the total number of disabled veterans hired. The reports should include covered veterans hired for on-the-job training under 38 U.S.C. 1787. The Contractor shall submit a report within 30 days after the end of each reporting period wherein any performance is made on this contract identifying data for each hiring location. The Contractor shall maintain at each hiring location copies of the reports submitted until the expiration of one (1) year after final payment under the contract, during which time these reports and related documentation shall be made available, upon request, for examination by any authorized representatives of the Contracting Officer or of the Secretary of Labor. Documentation would include personnel records respecting job openings, recruitment, and placement.

(e) Whenever the Contractor becomes contractually bound by the listing provisions of this article, it shall advise the employment service system in each State where it has establishments of the name and location of each such hiring location in the State. As long as the Contractor is contractually bound to these provisions and has so advised the State system, there is no need to advise the State system of subsequent contracts. The Contractor may advise the State system when it is no longer bound by this contract article.

(f) This article does not apply to the listing of employment openings which occur and are filled outside the 50 States, the District of Columbia, Puerto Rico, Guam, and the Virgin Islands.

(g) The provisions of Paragraphs (b), (c), (d), and (e) of this article do not apply to openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement. This exclusion does not apply to a particular opening once an employer decides to consider applicants outside of its own organization or employer-union arrangement for that opening.

J018570

(h) As used in this article:

(1) "All suitable employment openings" includes, but is not limited to, openings which occur in the following job categories: Production and nonproduction; plant and office; laborers and mechanics; supervisory and nonsupervisory; technical; and executive, administrative, and professional openings which are compensated on a salary basis of less than $25,000 per year. This term includes full-time employment, temporary employment of more than three days' duration, and part-time employment. It does not include openings which the Contractor proposes to fill from within its own organization or to fill pursuant to a customary and traditional employer-union hiring arrangement nor openings in an educational institution which are restricted to students of that institution. Under the most compelling circumstances an employment opening may not be suitable for listing, including such situations where the needs of the Government cannot reasonably be otherwise supplied, where listing would be contrary to national security, or where the requirement of listing would otherwise not be for the best interest of the Government.

(2) "Appropriate office of the State employment service system" means the local office of the Federal State national system of public employment offices with assigned responsibility for serving the area where the employment opening is to be filled, including the District of Columbia, Guam, Puerto Rico and the Virgin Islands.

(3) "Openings which the Contractor proposes to fill from within its own organization" means employment openings for which no consideration will be given to persons outside the Contractor's own organization (including any affiliates, subsidiaries, and the parent companies) and includes any openings which the Contractor proposes to fill from regularly established "recall" lists.

(4) "Openings which the Contractor proposes to fill pursuant to a customary and traditional employer-union hiring arrangement" means employment openings for which the Contractor proposes to fill from union halls, which is part of the customary and traditional hiring relationship which exists between the Contractor and representatives of its employees.

(i) The Contractor agrees to comply with the rules, regulations, and relevent orders of the Secretary of Labor issued pursuant to the Act.

(j) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Act.

1018571

(k) The Contractor agrees to post in conspicuous places available to employees and applicants for employment notices in a form to be prescribed by the Director, provided by or through the Contracting Officer. Such notice shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era for employment, and the rights of applicants and employees.

(l) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding that the Contractor is bound by terms of the Vietnam Era Veteran's Readjustment Assistance Act and is committed to take affirmative action to employ and advance in employment qualified disabled veterans and veterans of the Vietnam era.

(m) The Contractor will include the provisions of this article in every subcontract or purchase order of $10,000 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE 8-XXXII - EMPLOYMENT OF THE HANDICAPPED

(a) The Contractor will not discriminate against any employee or applicant for employment because of physical or mental handicap in regard to any position for which the employee or applicant for employment is qualified. The Contractor agrees to take affirmative action to employ, advance in employment and otherwise treat qualified handicapped individuals without discrimination based upon their physical or mental handicap in all employment practices such as the following: employment, upgrading, demotion or transfer, recruitment, advertising, layoff or termination, rates of pay or other forms of compensation, and selection for training, including apprenticeship.

(b) The Contractor agrees to comply with the rules, regulations, and relevant orders of the Secretary of Labor issued pursuant to the Rehabilitation Act of 1973, as amended.

(c) In the event of the Contractor's noncompliance with the requirements of this article, actions for noncompliance may be taken in accordance with the rules, regulations and relevant orders of the Secretary of Labor issued pursuant to the Act.

(d) The Contractor agrees to post in conspicuous places, available to employees and applicants for employment, notices in a form to be prescribed by the Director, Office of Federal Contract Compliance Programs, Department of Labor, provided by or through the Contracting

1018572

Officer. Such notices shall state the Contractor's obligation under the law to take affirmative action to employ and advance in employment qualified handicapped employees and applicants for employment, and the rights of applicants and employees.

(e) The Contractor will notify each labor union or representative of workers with which it has a collective bargaining agreement or other contract understanding, that the Contractor is bound by the terms of Section 503 of the Rehabilitation Act of 1973, and is committed to take affirmative action to employ and advance in employment physically and mentally handicapped individuals.

(f) The Contractor will include the provisions of this article in every subcontract or purchase order of $2,500 or more unless exempted by rules, regulations, or orders of the Secretary issued pursuant to Section 503 of the Act, so that such provisions will be binding upon each subcontractor or vendor. The Contractor will take such action with respect to any subcontract or purchase order as the Director of the Office of Federal Contract Compliance Programs may direct to enforce such provisions, including action for noncompliance.

ARTICLE B-XXXIII - DETERMINATION OF SUPPORT COSTS

(a) The term "support cost" as used in this contract means ERDA's share 1/ of the sum of costs incurred by the Contractor for items included under Article A-II(a) of Appendix "A" which are in furtherance of the work hereunder, which are incurred in accordance with the provisions of this contract, and which are reported to ERDA in accordance with (b) below. The term "cumulative support cost" as used in this contract means the total of the support cost incurred during the initial contract period plus any extension periods of the contract.

(b) Within three (3) months after the end of each contract period set forth in Appendix "A", and within three (3) months after the termination or expiration of the total period of performance, the Contractor shall furnish a certified statement, executed by an official of the Contractor showing the Contractor's cost, and evidencing its performance under the contract, during the contract term just completed. The statement shall show all costs incurred during the pertinent contract term set

1/ In those cases in which there is no proportionate sharing of costs, ERDA's "share" will be 100 percent. With respect to any period in which proportionate cost sharing is applicable pursuant to Article A-III, it is understood that the support cost for that specified period will equal the stipulated percent of the sum of costs incurred by the Contractor during the stated period for items under A-II(a) of Appendix "A", not to exceed 110 percent of the estimated support cost set forth in Article A-III for that contract period except as otherwise approved by ERDA.

1018573

forth in Appendix "A" for items under Article A-II(a) of Appendix "A", including the Contractor's share, if any, of such costs, and show the extent of the Contractor's contribution of items listed under Article A-II(b)(1) of Appendix "A". Costs included in the certified statement may include the following: Expenditures of cash; the cost of material and supplies transferred from stores inventory; and the amount due the Contractor for indirect costs in accordance with the rate and factor or factors shown in Appendix "A" of the contract for the pertinent contract period. The costs for the pertinent contract period shall be consistent with the principles of FMC 73-8, as constituted on the effective commencement date of said period. The certified statement shall be in the form set forth in Appendix "C".

(c) The certified statement should be in agreement with the institution's financial records and shall reflect only expenditures actually made during the period covered, including transfers from inventory. It shall not include commitments, as a part of such expenditures, for goods or services on order, but not received, or those received but not paid for unless the Contractor is operating under an established and consistently applied system of accrual accounting. If this is the case, the certified statement shall be so footnoted. A combination of accrual and cash accounting for cost accumulation and reporting purposes shall not be used. The renewal proposal budget should be footnoted to show the estimated amount of outstanding commitments for property at the end of the current contract period. The certified statement contains space in which should be inserted the actual amount of outstanding commitments for property at the end of the period covered by the statement. This commitment amount is for information only and is not a part of the expenditure calculation. The Contractor understands that ERDA expects to rely on this certified statement for determining the support cost for the pertinent contract period. With respect to any period in which proportionate cost sharing is applicable, the support cost for the pertinent period will be determined by applying the percentage figure included in Article A-III for the pertinent period, to the certified cost of items included under Article A-II(a) incurred during the pertinent contract period. All charges to ERDA shall be subject to the approval requirements of this contract. The Contractor is expected to maintain auditable records as contemplated by Paragraph (c) of the article entitled "Inspection, Reports, Records, and Accounts" to substantiate the costs incurred for items under Article A-II(a) and to show the extent of the Contractor's contribution of items listed under Article A-II(b)(i).

ARTICLE B-XXXIV - ADDITIONAL APPROVALS

(a) In addition to such approvals as are specifically required by other provisions of this contract, the Contractor shall obtain ERDA's approval for:

(1) A change of the principal investigator, co-investigator, or other key people as might be named in this contract or continuation of the research work for any one period in excess of three

1018574

(3) months without direction by an approved principal investigator. The principal investigator may increase or decrease the amount of effort which he devotes to the project without obtaining ERDA approval; however, a representative of the institution shall consult with the appropriate ERDA's Headquarters program representative if the principal investigator plans to, or becomes aware that he will devote substantially less effort to the work than anticipated in Article A-I. The purpose of such consultation will be to determine what effect, if any, the anticipated change will have on the research work and what modification to the contract, if any, may be appropriate.

(2) No change in the phenomenon or phenomena under study; i.e., broad category of the research under the contract shall be made without the specific written approval of ERDA; ordinarily such changes, if approved by ERDA, will be accomplished through a new contract or a mutually agreed-to modification. The Contractor may change the specific objectives in the research work described in the contract: Provided, it gives ERDA prompt notification of such changes; and the Contractor may continue to follow the new objectives while ERDA determines whether it wishes to continue the program under the changed approach. Significant changes in methods or procedures employed in performing the research should be reported in the first technical progress report issued subsequent to the changes.

(3) Acquisition of:

(i) An item of equipment not itemized in Appendix "A", the cost of which is $1,000 or more. Approval is not required if the equipment is merely a different model of an item listed in Appendix "A"; or

(ii) An item or items of equipment the cost of which will cause the total equipment dollar level shown in Article A-II(a) of the contract to be in excess of 125 percent thereof (if plant and capital equipment funds are provided for the acquisition of equipment with title to be vested in the Government, the total cost of such shall not exceed the amount provided for such equipment unless prior ERDA approval has been obtained).

(4) Purchase of any general-purpose equipment, such as office furniture, air conditioning, etc., not specifically provided for in Appendix "A".

(5) Incurring costs for items set forth in Article A-II(a), during the pertinent contract period stated in Appendix "A", in excess of 110 percent of the total estimated cost specified in Article A-III. Charges to ERDA for any such costs incurred with the approval of ERDA shall also be subject to the limitations of Article III.

1018575

(6) Any proposed foreign travel (see the article entitled "Foreign Travel").

(7) Expenditures for domestic travel in excess of $500, or 125 percent of the amount shown in Article A-II(a) for such travel, whichever is greater.

(8) Acquisition of excess personal property.

ARTICLE B-XXXV - PAYMENT OF INTEREST ON CONTRACTOR'S CLAIMS

(a) If an appeal is filed by the Contractor from a final decision of the Contracting Officer under the Disputes article of this contract, denying a claim arising under the contract, simple interest on the amount of the claim finally determined owed by the Government shall be payable to the Contractor. Such interest shall be at the rate determined by the Secretary of the Treasury pursuant to Public Law 92-41, 85 Stat. 97, from the date the Contractor furnishes to the Contracting Officer its written appeal under the Disputes article of this contract, to the date of (1) a final judgment by a court of competent jurisdiction, or (2) mailing to the Contractor of a supplemental agreement for execution either confirming completed negotiations between the parties or carrying out a decision of a board of contract appeals.

(b) Notwithstanding (a) above, (1) interest shall be applied only from the date payment was due, if such date is later than the filing of appeal, and (2) interest shall not be paid for any period of time that the Contracting Officer determines the Contractor has unduly delayed in pursuing its remedies before a board of contract appeals or a court of competent jurisdiction.

ARTICLE B-XXXVI CLEAN AIR AND WATER

(Applicable only if the contract exceeds $100,000, or the Contracting Officer has determined that the orders under an indefinite quantity contract in any one year will exceed $100,000, or a facility to be used has been the subject of a conviction under the Clean Air Act (42 U.S.C. 1857c-8(c)(1)) or the Federal Water Pollution Control Act (33 U.S.C. 1319 (c)) and is listed by EPA, or the contract is not otherwise exempt.)

(a) Contractor agrees as follows:

(i) To comply with all the requirements of Section 114 of the Clean Air Act, as amended (42 U.S.C. 1857, et. seq., as amended by Public Law 91-604) and Section 308 of the Federal Water Pollution Control Act (33 U.S.C. 1251, as amended by Public Law 92-500), respectively, relating to inspection, monitoring, entry, reports, and information, as well as other requirements specified in Section 114 and Section 308 of the Air Act and the Water Act, respectively, and all regulations and guidelines issued thereunder before the award of this contract.

1018576

(ii) That no portion of the work required by this prime contract will be performed in a facility listed on the Environmental Protection Agency list of violating facilities on the date when this contract was awarded unless and until the EPA eliminates the name of such facility or facilities from such listing.

(iii) To use his best efforts to comply with clean air standards and clean water standards at the facilities in which the contract is being performed.

(iv) To insert the substance of the provisions of this article in any nonexempt subcontract, including this paragraph (iv).

(b) The terms used in this article have the following meanings:

(i) The term "Air Act" means the Clean Air Act, as amended (42 U.S.C. 1857 et. seq., as amended by Public Law 91-604).

(ii) The term "Water Act" means the Federal Water Pollution Control Act, as amended (33 U.S.C. 1251 et. seq., as amended by Public Law 92-500).

(iii) The term "clean air standards" means any enforceable rules, regulations, guidelines, standards, limitations, orders, controls, prohibitions, or other requirements which are contained in, issued under, or otherwise adopted pursuant to the Air Act or Executive Order 11738; an applicable implementation plan as described in Section 110(d) of the Clean Air Act (42 U.S.C. 1857c-5(d)); an approved implementation procedure or plan under Section 111(c) or Section 111(d), respectively, of the Air Act (42 U.S.C. 1857c-6(c) or (d)); or an approved implementation procedure under Section 112(d) of the Air Act (42 U.S.C. 1857c-7(d)).

(iv) The term "clean water standards" means any enforceable limitation, control, condition, prohibition, standard, or other requirement which is promulgated pursuant to the Water Act or contained in a permit issued to a discharger by the Environmental Protection Agency or by a State under an approved program, as authorized by Section 402 of the Water Act (33 U.S.C. 1342), or by a local government to ensure compliance with pretreatment regulations as required by Section 307 of the Water Act (33 U.S.C. 1317).

(v) The term "compliance" means compliance with clean air or water standards. Compliance shall also mean compliance with a schedule or plan ordered or approved by a court of competent jurisdiction, the Environmental Protection Agency or an air or water pollution control agency in accordance with the requirement of the Air Act or Water Act and regulations issued pursuant thereto.

1018577

(vi) The term "facility" means any building, plant, installation, structure, mine, vessel, or other floating craft, location, or site of operations, owned, leased, or supervised by a contractor or subcontractor, to be utilized in the performance of a contract or subcontract. Where a location or site of operations contains or includes more than one building, plant, installation, or structure, the entire location shall be deemed to be a facility except where the Director, Office of Federal Activities, Environmental Protection Agency, determines that independent facilities are collocated in one geographical area.

1018578

APPENDIX "C"

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

STATEMENT OF COSTS

1. Name and Address of Contractor: _____

_____.

2. Contract Number: _____.

3. Beginning and ending date of pertinent contract period: _____

_____.

4. Costs incurred during the pertinent contract period. [List only those costs which are to be reimbursed by ERDA or proportionately shared by the parties in accordance with Article A-II(a) and Article A-III.]

Cost categories 1/	Amount
a. Salaries and wages	$_____
b. Equipment [List separately the cost of each piece of equipment separately listed in Appendix "A" to the contract or for which separate approval was obtained from ERDA.]	$_____
c. Travel [Show amounts for both foreign and domestic. If none, state none.]	$_____
Domestic	$_____
Foreign	$_____
d. Other direct costs	$_____
e. Total direct expenditures	$_____
f. Indirect charges [Indicate percent and expenditures to which percent is applied.]	$_____

1/ The listing of categories should be consistent with the itemization in Appendix "A".

1018519

5. Total costs for items under Article A-II(a) for pertinent contract period---------- $_____

6. Support cost for the pertinent contract period set forth in Appendix "A", as defined in the article entitled "Determination of Support Costs" of the contract, chargeable to ERDA for the pertinent contract period (percent of total costs using percent shown in Article A-III of Appendix "A" for pertinent period of contract)---------- $_____

7. Cumulative support cost (support cost under this statement plus support cost for previous periods of the contract)---------- $_____

8. Accumulated support ceiling in Article III of the contract---------- $_____

9. The difference between lines 7 and 8---------- $_____

10. Provide information regarding contributions by the Contractor of items listed in Article A-II(b) of Appendix "A" during pertinent contract period. State the extent of the Contractor's actual contribution, the measure of such contributions should be in the same terms as the Contractor's commitment under Article A-II(b); e.g., time, dollar, etc.---------- $_____

11. Actual outstanding commitments for property at the end of the period covered by this statement---------- $_____

I hereby certify that to the best of my knowledge and belief this report is true and correct, that the costs listed herein were incurred in connection with the performance of the research provided for under this contract and in accordance with the terms and conditions set forth therein, and that all contract requirements have been complied with. If an audit results in a disallowance of cost, the Contractor will make prompt reimbursement to ERDA.

_____
(Name and title of an authorized representative)

_____ _____
(Signature) (Date)

1018580

APPENDIX "D"

REQUIREMENTS RELATING TO EXCHANGES OF INFORMATION

1. The requirements set forth herein relate to the dissemination by the Contractor of the information developed under this contract and/or under other ERDA programs to countries by or through exchange activities, including but not limited to employment, work participation, visits and correspondence. The term "countries" (including where used in the term "Soviet-Bloc Countries"), as used in this Appendix "D", includes all nations (other than the United States, its territories and possessions), the embassies, consulates, and agencies of such nations, and individuals and organizations of such nations.

2. For the purpose of these requirements the Soviet-Bloc Countries consist of:

Group A

Albania
Bulgaria
Czechoslovakia
Estonia
Hungary
Latvia
Lithuania
Poland and Danzig
Rumania
Union of Soviet Socialist Republics

Group B

China, including Manchuria (includes Inner Mongolia; the provinces of Tsinghai and Sikang, Tibet; the former Kwantung Leased Territory, the present Port Arthur Naval Base Area and Liaoning Province) and excluding Taiwan (Formosa)
Communist-Controlled area of Vietnam.
East Germany (Soviet Zone of Germany and the Soviet Sector of Berlin)

North Korea
Outer Mongolia
Cuba

1018581