Table 1

TRANSPLANT KIDNEY MODEL PARAMETERS

FOR NORMAL FUNCTION

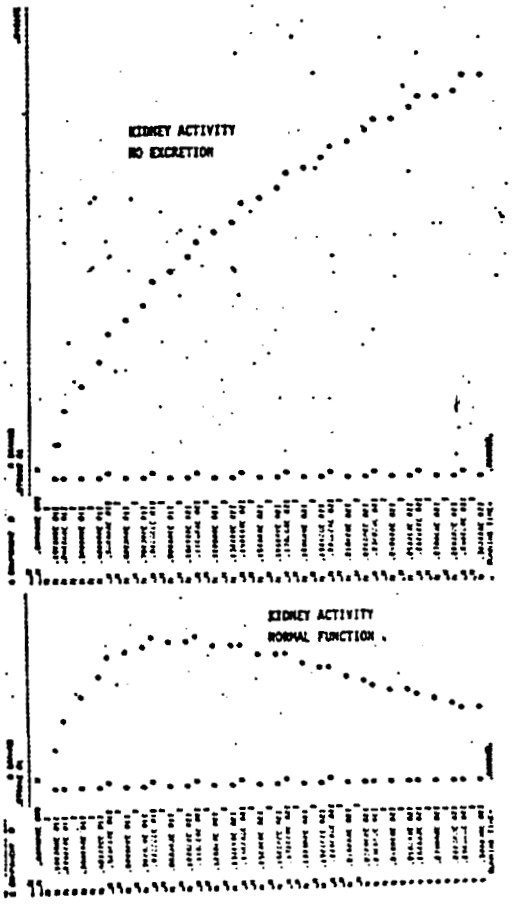
λ_{12}	0.095/min
λ_{21}	0.072
λ_{31}	0.092
λ_{43}	0.388
λ_{54}	0.500

Table 2

I-131 HIPPURAN RENOGRAM

(50μCi Dose)

	Dose in rads to the kidney
Normal Function	0.078
No Excretion	44.9



1037395

Figure 1.

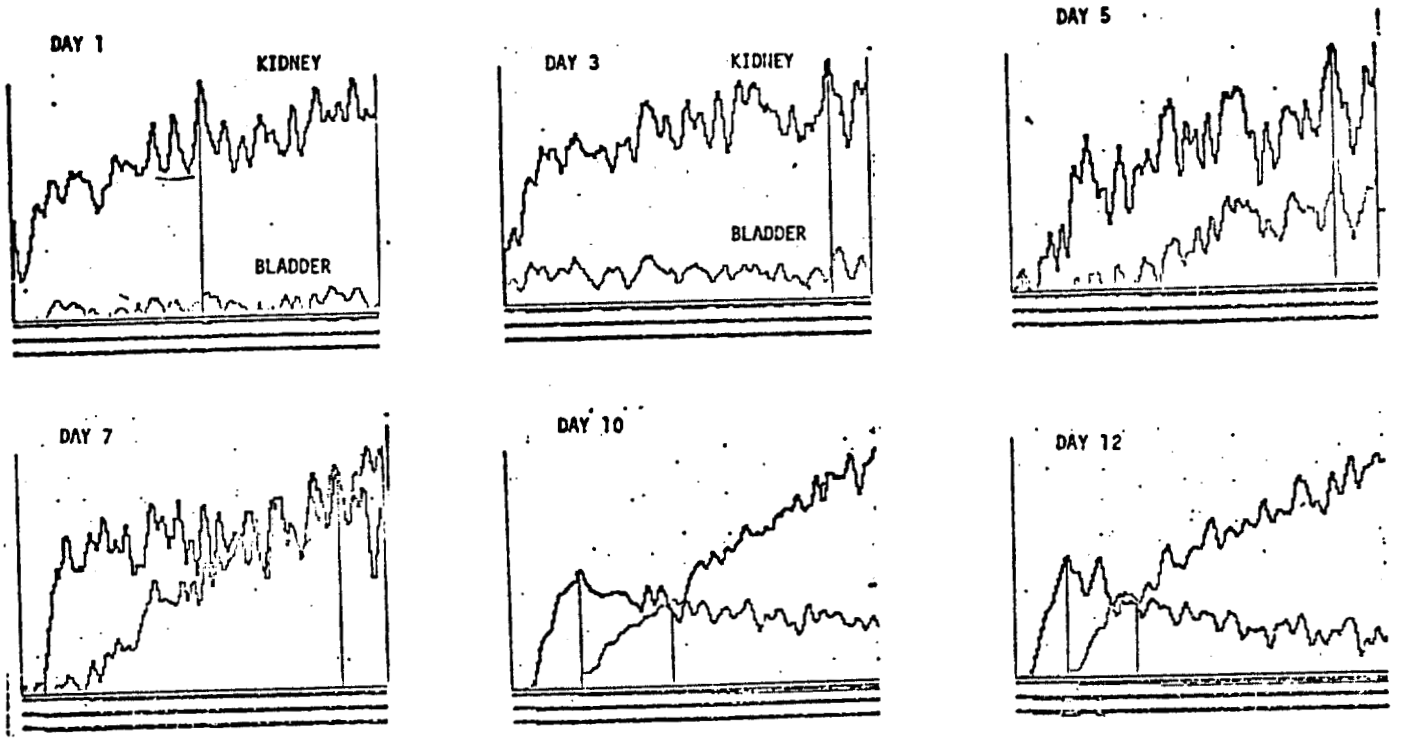


Figure 2. Transplant Renograms

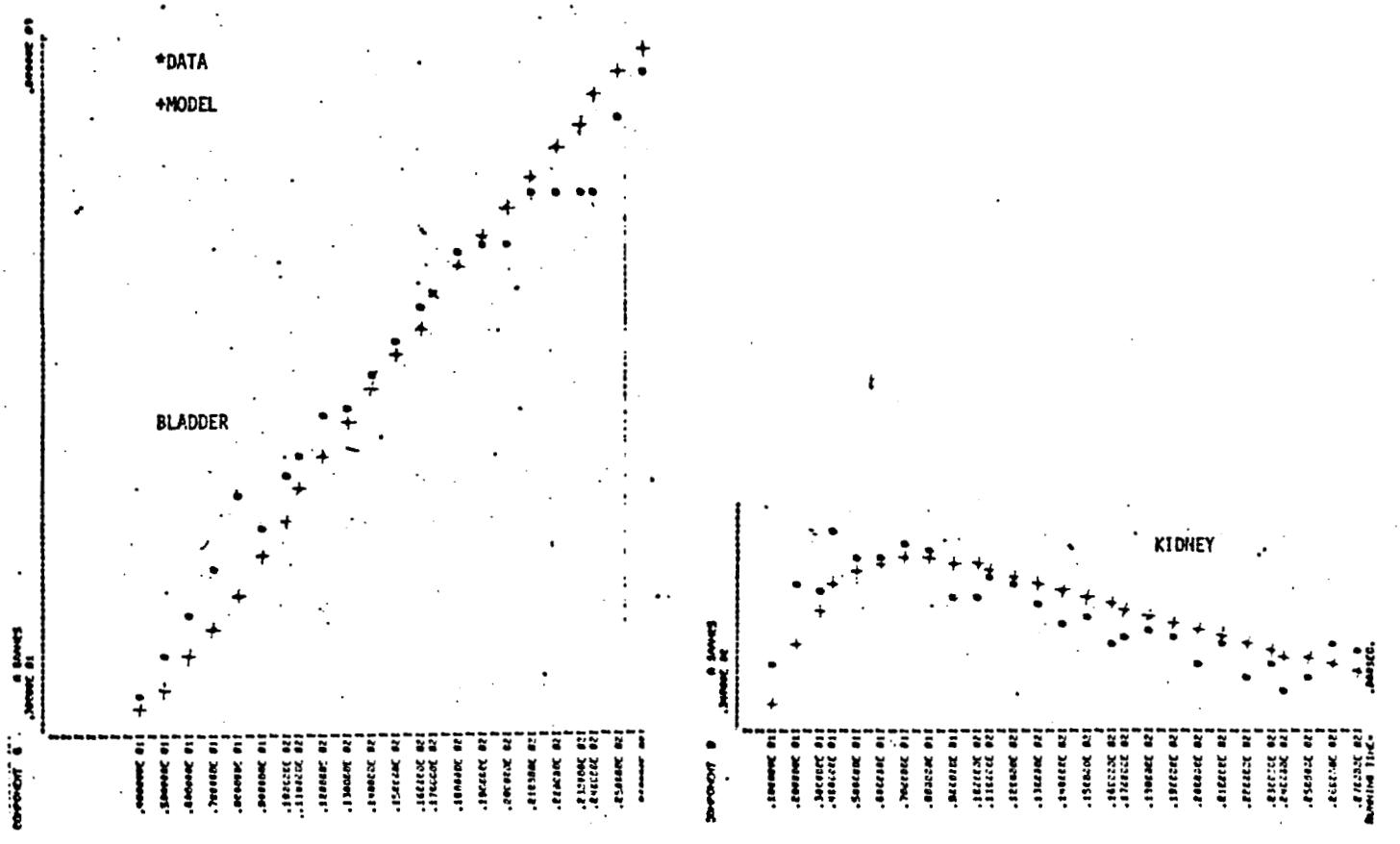


Figure 3.

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STATIONARY PROBE DATA
CORRESPONDING TO PREVIOUS FIGURE

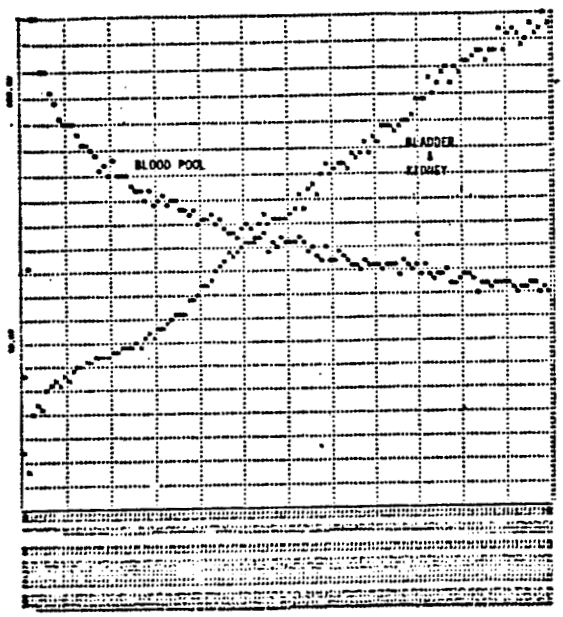


Figure 4.

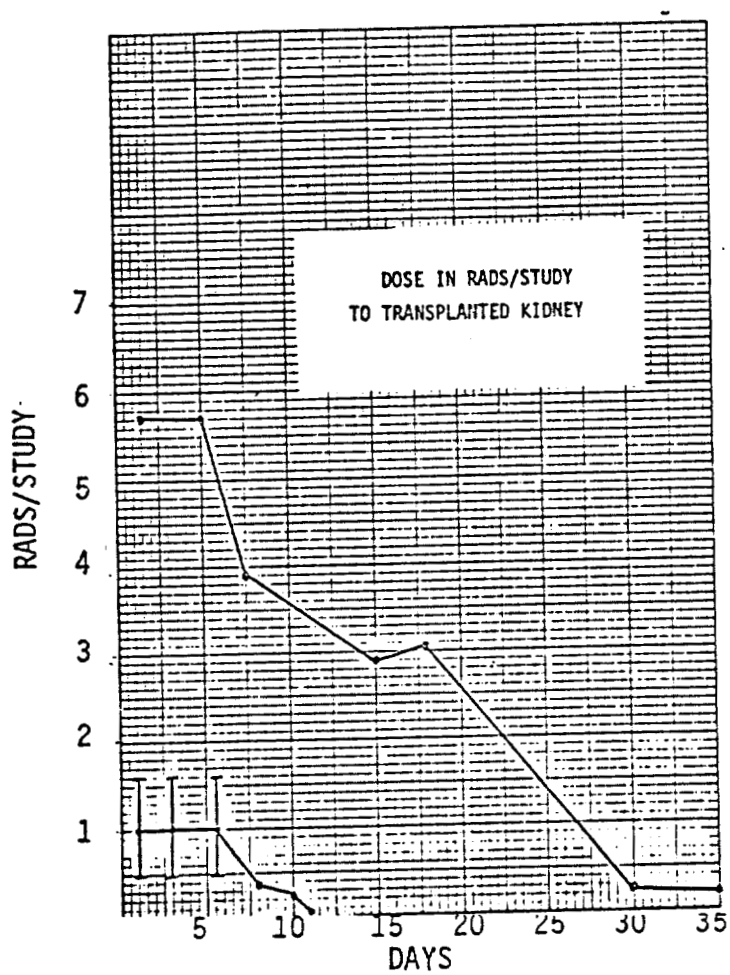


Figure 5.

1037397

d. Dosimetry of Tc-99m Labelled Pyrophosphates

Much interest has been shown recently in Tc-99m Pyrophosphate as both a new bone scanning agent and as an agent for assessing myocardial infarctions. Initial data indicate that the blood to bone ratio may be improved for Tc-pyrophosphate relative to the more routinely used agent Tc-polyphosphate. Initial data on short term blood clearance and urinary excretion exist; however, long term biological retention data are not available. We propose to study 8-10 volunteers during the next year according to the protocol shown in Table 1. These volunteers will be selected from patients referred to the Division of Nuclear Medicine for routine bone scans. After informed consent has been obtained the patient will be followed for 48 hours post injection using the whole body counter, whole body scanner, blood samples, and scintillation camera images. Preliminarily results from a pilot study are shown in Figures 1 and 2. These data reveal a multi component blood disappearance curve and a total body curve consisting of at least two components. The shortest of the two components for the total body has a $T_{\frac{1}{2}}$ of 3-6 hours while the longer is $\geq$ 72 hours.

Although both of the two preliminary studies showed similar behavior as to the number of exponential components or compartments and the sizes of the washout rate constants, the initial distribution of the pyrophosphate appears to be different. The fraction in the rapid compartment was 0.75 in one study while it was found to be 0.55 in the other. Similarly the slow compartments showed 0.25 and 0.45, respectively. Preliminary dose estimates assuming the radioactivity to be uniformly distributed in the total body dose of 75-90 mrem/mCi administered or 0.75-0.90 rem per study with an administered dose of 10mCi.

These studies are just beginning and as more data becomes available the radiation dose to the gonads, skeleton, bladder, red marrow in addition to the total body will be determined.

TABLE 1

PYROPHOSPHATE PROTOCOL

Step 1. Determine plasma volume with I-125.

Step 2. Inject ^{99m}Tc-pyrophosphate (15 mCi) and collect data as per protocol below.

TIME	BLOOD SAMPLE	W.B. SCAN	W.B. COUNT	PIN-HOLE CAMERA THYROID & ANKLE
15-20 minutes			X	X
2 hours	X	X		
6-8 hours	X		X	X
24 hours	X		X	X
48 hours	X		X	X

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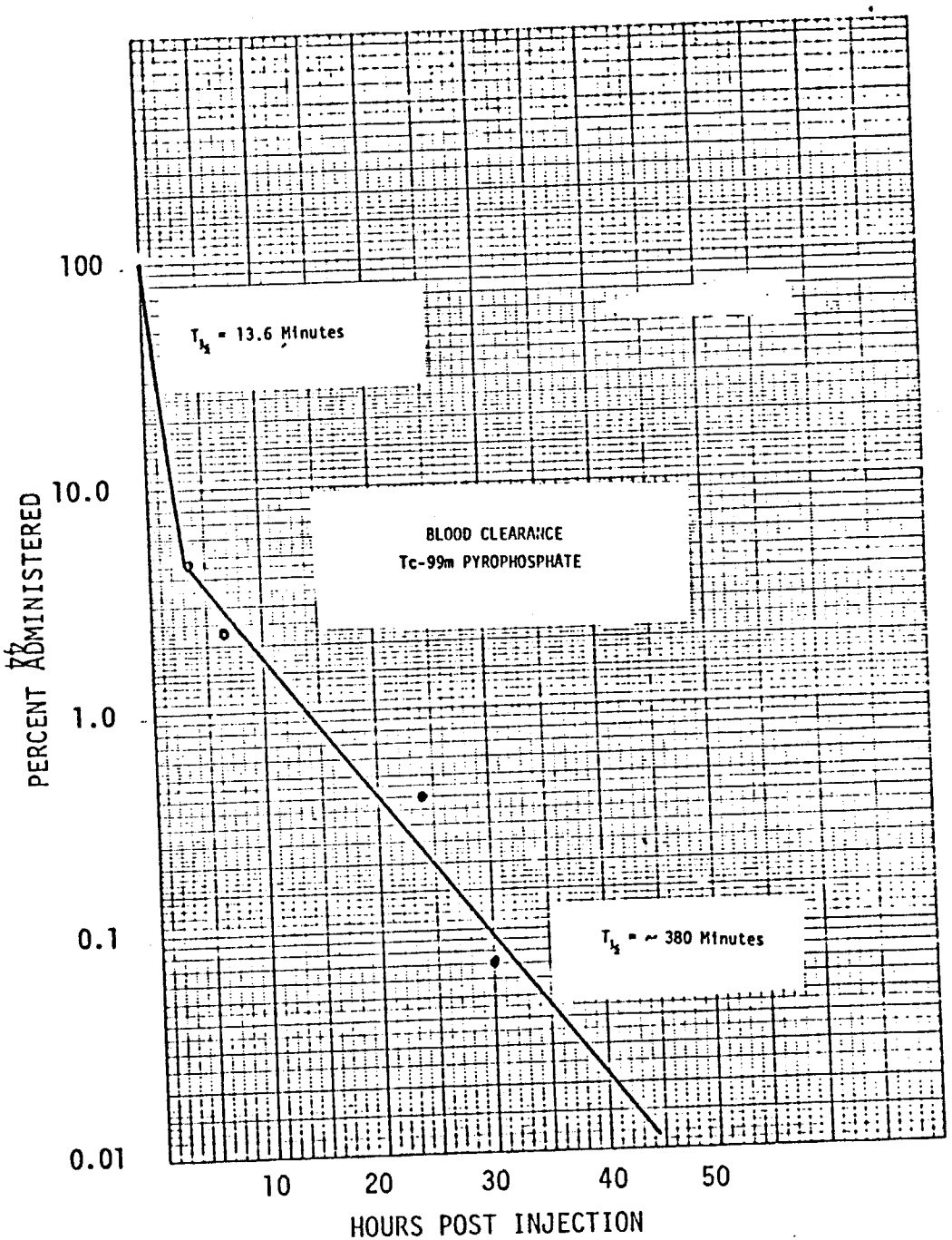


Figure 1

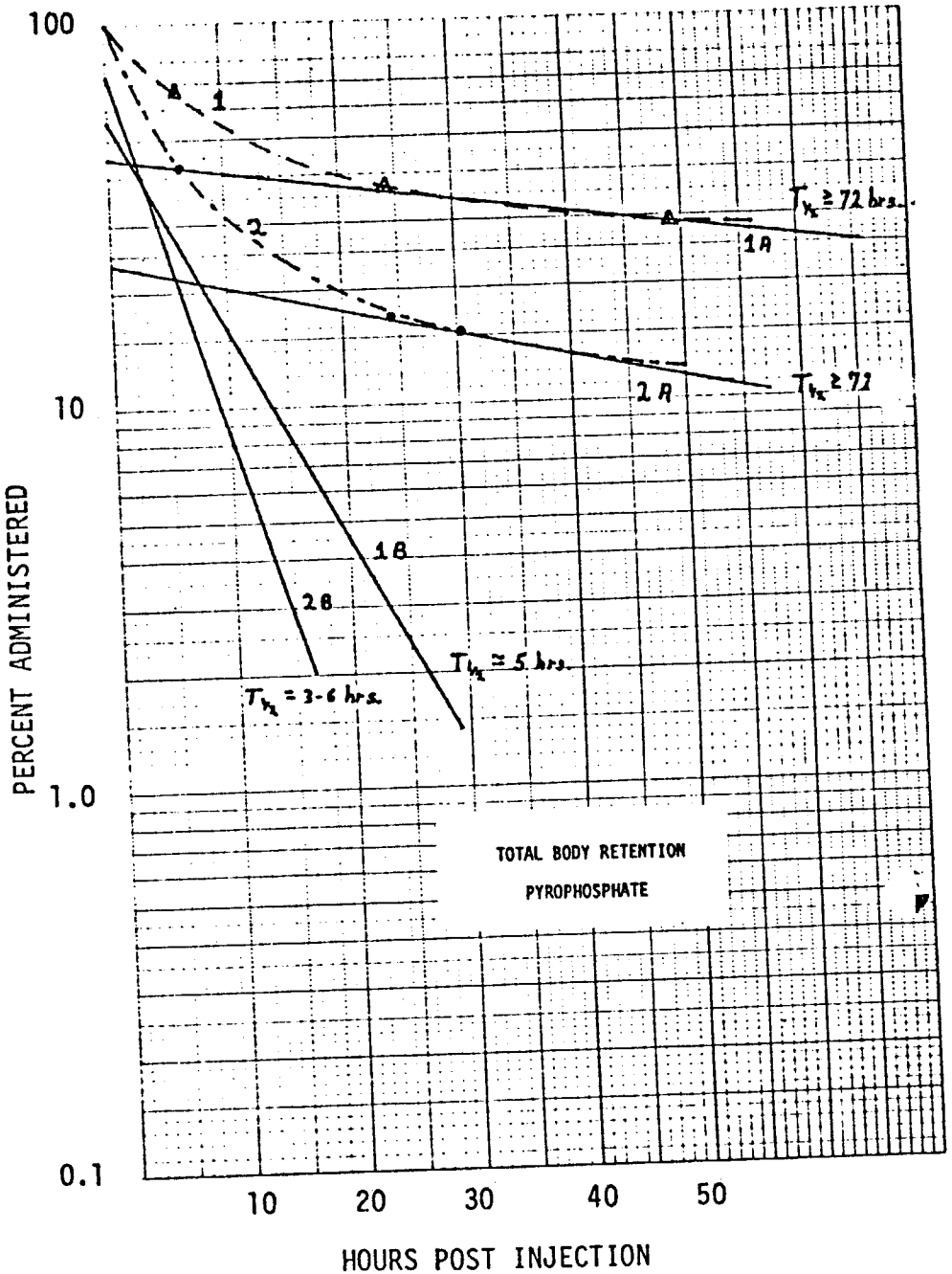


Figure 2

1037399

e. Monitoring of Cs-137 Levels in Man

Almost four years ago we resumed a program started in 1959 by Meneely et.al. to monitor Cs-137 levels in a population of normal individuals. Last year we measured 52 individuals from the Middle Tennessee area and included a small group of young male subjects who were studied earlier by Meneely.

During the coming year we propose to remeasure as many of the group measured last year as possible and continue to monitor this population every second year. The mean value for last year's measurements was found to be 3.00 ± 1.40 nanocuries. Figure 1 shows the comparison of the measurements made to date at Vanderbilt as compared to measurements made at Oak Ridge National Laboratory.

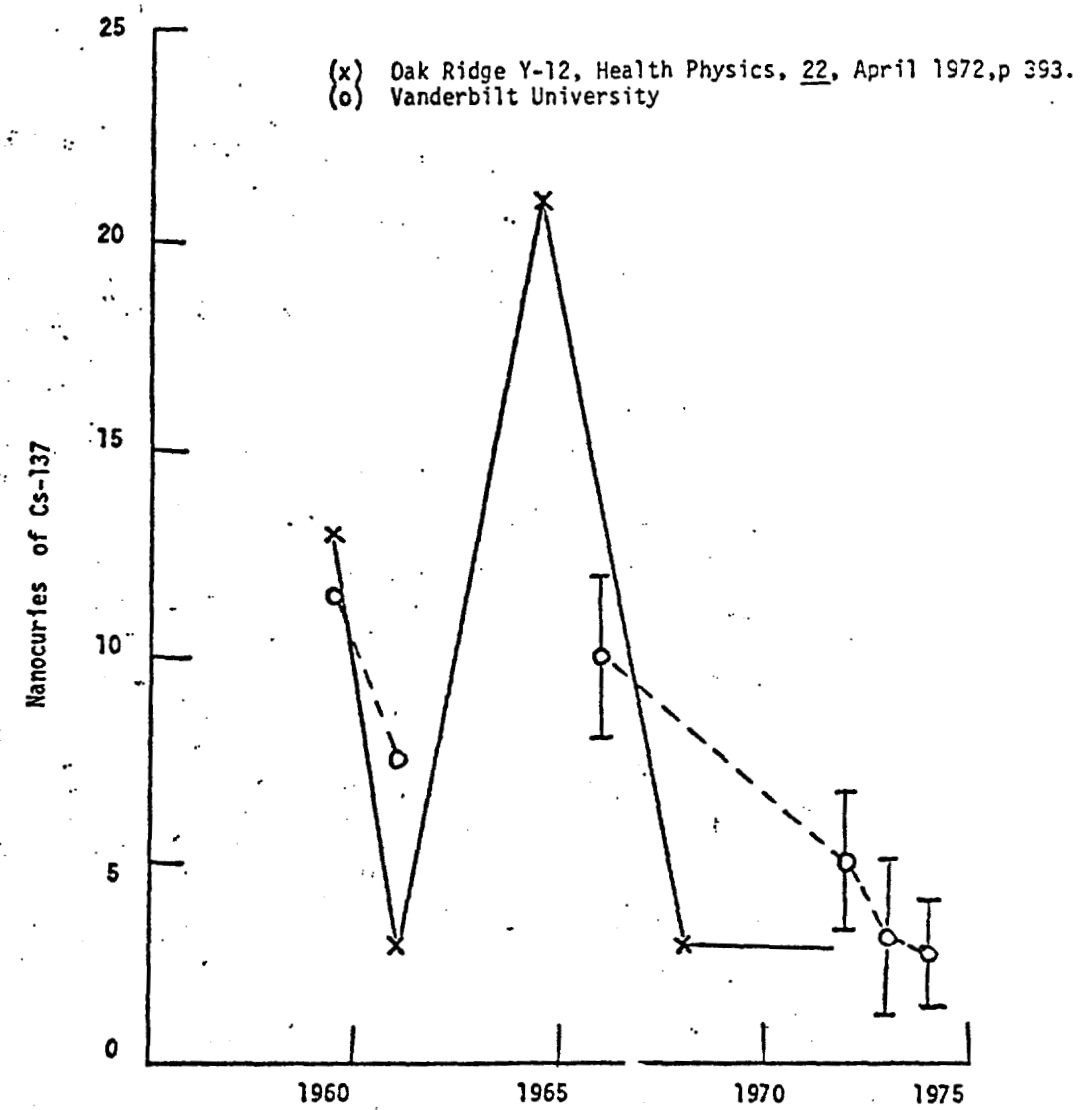


Fig. 1. Body burdens of Cs-137.Whole body counter measurements:

1037400

f. Iodine Metabolism and Dosimetry in I-131 Therapy

One year ago the Bureau of Radiological Health supported a study to obtain dosimetry data on patients included in the PHS(BRH)-sponsored cooperative thyrotoxicosis therapy follow-up study. The calculations of the radiation-absorbed dose to the thyroid were carried out by means of non-linear compartmental modelling analysis using the SAAM-25 model shown in Figure 1. The model parameter describing the uptake rate of radio-iodine in the thyroid was assumed to be a function of the number of active thyroid cells. The number of cells was, in turn, assumed to be dependent upon the cumulative radiation dose.

The dosimetry calculations made for the BRH were based upon data from approximately 80 patient studies obtained from the BRH archives. The problems with these data were incompleteness of sample collections and, most importantly, only a very few studies were carried out more than one week post therapy. It became apparent to us that the effects of the therapy, as manifested in the measurements of the circulating levels of PBI, thyroid uptake and excretion, only become important at periods greater than one week. Consequently, the dose dependent parameters of the model were poorly determined in most cases. In order to make accurate estimates of the kinetic parameters, it is essential that we have long-term follow-up data for our analysis. As mentioned earlier in section A. 1. b. 1., we are proposing to establish a collaborative project with the Nuclear Medicine Division of the National Atomic Energy Commission in Buenos Aires, Argentina, to receive such long term iodine kinetics data. The investigators in Buenos Aires are collecting complete and long term follow-up data on all of their I-131 therapy cases (25-30 studies per year). Follow-up is frequently carried out to 6-8 weeks. This collaboration is important to Buenos Aires since they do not have the necessary computational facilities to carry out these analyses.

Dose estimates to the gonads and total body in addition to the thyroid will be made and tabulated. From these analyses the relative radiation dose sensitivity of the thyroid for different disease states may be studied, possibly making prior dose estimates more accurate.

Work on a revised model to accomodate data made available to us by Dr. Brown Dobyns of the Cleveland Memorial General Hospital is currently under way. These data include measurements on blood levels of MIT, DIT and thyroglobulin (TG) in addition to the measurements of PBI, T3, T4, urine and thyroid activity. The importance is that the kinetics of MIT, DIT, and TG reflect thyroid radiation damage directly and consequently may yield more reliable information on the time course of radiation damage and the degree of biological sensitivity of the thyroid gland.

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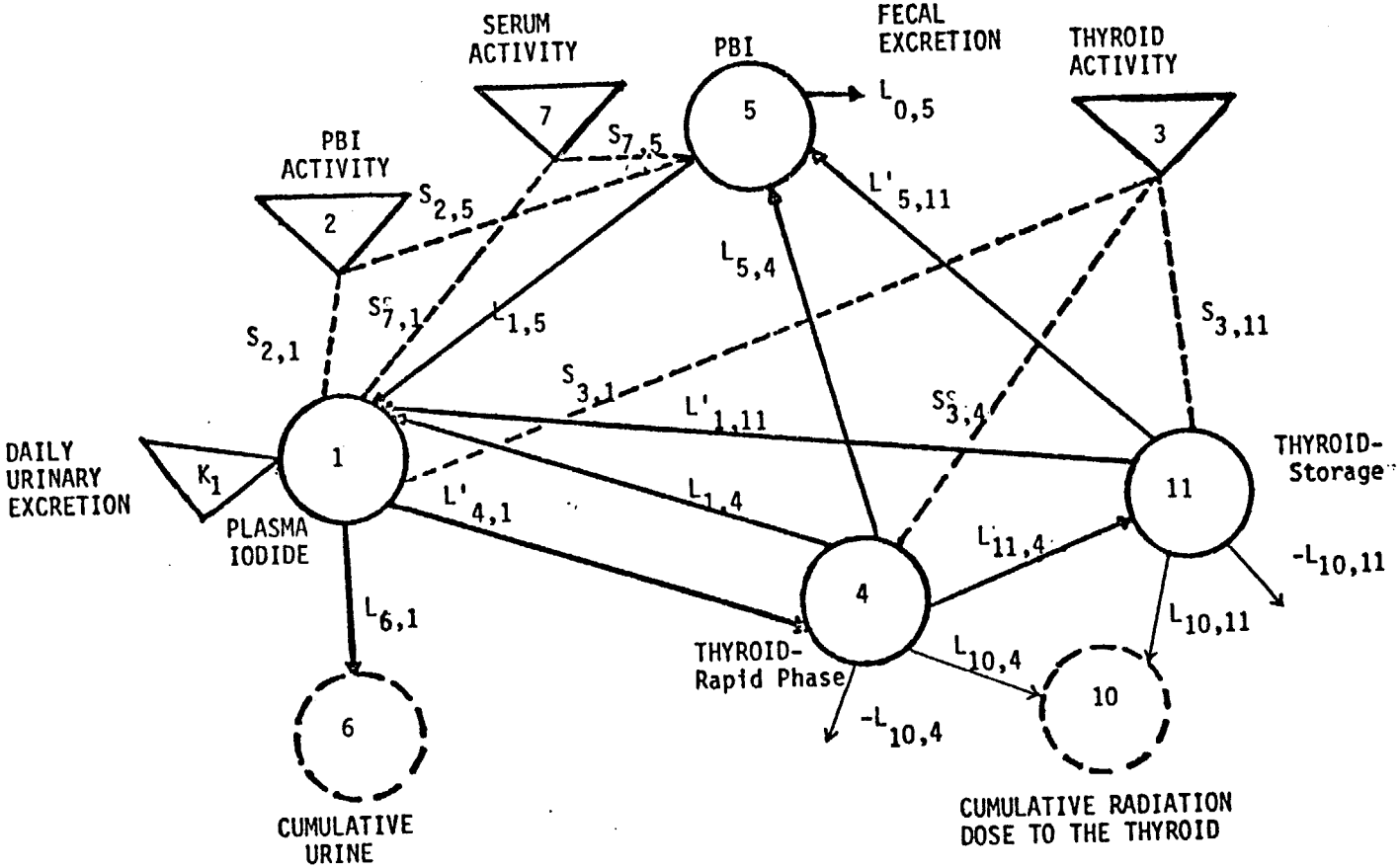


FIG. 1. THE FOUR-COMPARTMENT DOSE-DEPENDENT MODEL.

1037402

B. Clinical Applications of Activation Analysis

1. Measurement of Deuterium and Deuterium Labelled Compounds Using the (γ,n) Reaction

One of the more important tracers used in medicine involves the isotopes of hydrogen. Although deuterium is stable and several commercially available detection systems are currently in use, tritium is often the preferred isotope due to the relative ease of its detection. Tritium is radioactive, emitting a low-energy Beta and possessing a half-life of approximately 12.5 years.

We believe that deuterium would be used more routinely by many more institutions if a convenient counting method were available for its detection.

Several groups have suggested the use of the $D(\gamma,n)H$ reaction as a possible method for the detection of deuterium. We intend to pursue this idea and develop a clinically useful system that will allow its use in routine studies and stimulate further development of Deuterium Tracer Kinetics. This method looks like a particularly promising photo reaction as the threshold energy is very low (2.23 MeV) and therefore one may easily produce this reaction before other photoneutron reactions turn on. Thus, background neutrons should not be a problem.

If one chooses to count the neutrons produced, then the variable parameters are the source detectors and geometry.

We have done some preliminary investigations into these parameters.

A. Sources:

Several sources exist which emit photons of energy greater than the threshold energy. Table 1 lists these with some pertinent characteristics. A bremsstrahling source would appear at first to be the natural source in a hospital environment as many large hospitals possess these type sources in their Radiotherapy Center. However, several disadvantages are apparent.

1. Higher energy linacs activate most everything
2. The useful flux from lower energy clinical linacs is lower than isotopic sources.
3. Although physically nearby, they are not always available in a busy radiotherapy department.
4. It is sometimes difficult to use "borrowed" equipment.

Na-24 would appear an ideal source except for the very short half-life. High activity sources are very easy to produce with a reactor. Therefore it is possible to consider having a facility in the immediate reactor vicinity. This has been proposed by others and we have done some preliminary work along these lines.

Ga-72 is notably more difficult to obtain than Na-24 and also has a short $T_{\frac{1}{2}}$.

Th"C" (from a natural decay series) would be very expensive if not impossible to obtain in the quantities required.

CO-56 would also appear unreasonable at first as it is not reactor produced. However, it may be possible to produce significant size sources caused in the (p,n) reaction on iron near large accelerators, and LAMPF is considering making it available. Having a 77 day half-life it would appear much more attractive than Na-24 although it emits many other γ's besides the useful ones. We are in contact with LASL concerning the possibility of their producing this type source.

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B. Detectors:

Our requirements on detection demand high efficiency and low γ-sensitivity. Several type neutron counters are available. Regardless of the type, all high efficiency neutron detectors require that the neutrons first be thermalized (as thermal neutron crossections can be 4-5 orders of magnitude larger than fast neutron crossections). The only reasonable moderator is a hydrogenous material. All other moderators would require so much material as to significantly lower the geometric efficiency. Of course, all hydrogenous moderators will contain deuterium (0.015% natural abundance). This could lead to a large background number of neutrons if the moderator is placed in a large flux high γ-energy field. Solving this problem should also resolve any problem concerning γ-sensitivity of detectors.

We have done some preliminary work with indium foils, and although the efficiency of these foils is very large, due to the inconvenience of having a two step process (activating then counting), we have for the moment discontinued experimenting with them.

The two other most common neutron detectors are BF_3 and He proportional counters. We feel either would be appropriate. Helium counters are more efficient; however, they are more expensive and more γ-noise susceptible. Therefore, we are currently working with BF_3 proportional counters.

C. Current Design Ideas

We are currently of the belief that the best way to obtain a maximum sensitivity facility is to use as large a γ source as may be safely produced and used with the sample positioned next to the source. This would all be in a lead cask of sufficient thickness so as to reduce the γ-flux to a tolerable limit. As the produced neutron flux is being reduced by $1/R^2$ and the γ-flux is being attenuated by both $1/R^2$ and exponentially, by using several counters, we should be able to overcome any loss in geometric efficiency.

D. Preliminary Experiment:

We have conducted a preliminary experiment in collaboration with the Isotopes Technology Division of ORNL. They have modified a lead cask 80 cm in diameter so a large (~200Ci) Na-24 source may be placed in its center and a test tube may be positioned next to it. A BF_3 proportional counter 2" diameter - 12¼" Active length) borrowed from the Analytical Chemistry group at ORNL was used on the outside of the cask. A 1-3/4" thick block of paraffin was used as moderator. Positioning of the deuterated water samples was the major source of error leading to uncertainties much larger than statistics. However we were able to determine an approximate sensitivity of 70 cpm/mg of D_2O. We believe that we can improve this by a factor greater than 20 by optimizing moderator thickness, pulse height discrimination and using more detectors. Background counting rates in a neutron free area is ~7 cpm. Therefore, we feel that these sensitivities will allow us to conduct several experiments,

1. We intend to first attempt total body water dilution studies on animals and then people. We expect samples to be in the milligram of D_2O range and therefore straight forward to do.
2. Recent papers have suggested that Deuterium can be used in bile salt metabolism in infants. We will need µg sensitivity here.
3. Possible other studies including Lipid or fatty acid metabolism studies, and kidney function studies might be possible.

Although it is envisioned that a large Na-24 source facility could only be available near a reactor, thereby not being available for emergency studies, this facility would allow routine studies of various nature to be done with little difficulty and excellent sensitivity.

1037404

2. Cf-252 Neutron Activation Facility

During the past year we have been in contact with ERDA making the necessary arrangements for the loan of a Cf-252 source for evaluation. The irradiation chamber in which the source will be housed has already been delivered to Vanderbilt and is on loan from the Oak Ridge National Laboratory. Funds for the transportation of the Cf-252 source from the Savannah River Laboratory are being requested. The transportation of the source requires the use of a special carrier belonging to the Savannah River Laboratory. The carrier is designed to transport neutron sources and the Laboratory must be repaid for its use. During the next year we hope to accept delivery of this source and begin preliminary sensitivity studies using prepared in-vitro samples of known elemental content and then extending the measurements to laboratory animals.

In conjunction with this work we are investigating two different techniques to measure bone mineral content. The first, which we now have operational, is the dual isotope regional and whole body transmission scan using 153-Gd. This method allows us to measure the total mineral content (calcium and phosphorous) of the bone. The other technique utilizing the Cf-252 source is in-vivo partial body neutron activation analysis. Using this method, the calcium content of bone will be measured by activating Ca-48 and then counting the γ-rays given off by Ca-49. We propose to use both methods on the forearm to find the calcium-to-total mineral ratio. If a total body transmission scan is also done, the total body calcium content can then be estimated. We are also studying the feasibility of using the neutron activation facility for in-vitro activation and neutron radiography. Our present design of this facility is shown in Figure 1. We plan to use six 2mg Cf-252 sources. Calculations[1] have shown that in order to obtain the maximum thermal neutron flux at the center, the sources are arranged in a ring (radius = 2.5) and are surrounded by a polyethylene sphere (4.5 cm radius) which acts as a moderator. This is then surrounded by a 35 cm radius graphite reflector with lead and borated polyethylene shielding on the outside. The whole facility will be located beneath the floor to provide additional shielding.

A collimator with its inlet at the center of the ring of sources and axis perpendicular to the plane of sources will provide a beam of neutrons which will be used for arm activation and neutron radiography. A tube may be inserted into the collimator for activation of samples in-vitro at the center of the sources where the flux is a maximum and uniform. Additional tubes may be placed around the outside of the ring of sources for long-term sample activation.

Using the activation facility, we plan to investigate the use of stable tracers. In the past we have used the stable tracers Fe-58 and Cr-50. However, the samples had to be sent to a reactor and then returned to us for analysis. Because of the time delay, this procedure is not suitable for routine clinical studies. With the on site activation facility, this type of study could possibly replace studies that are now done using radioactive tracers thereby elimating the radiation dose to the patient. The main difficulty is that the thermal neutron flux we expect from our proposed (10^{13} thermal neutron/sec). We have done some calculations to determine the minimum levels of some tracers that we will be able to detect in a sample. The results of these calculations are shown in Table 1. To determine whether a particular study is feasible, we will need to know how much of the element can be safely given to the patient and approximately

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how much we would expect to find in a sample. A comparison of this with the values in Table 1 will determine whether or not useful information can be obtained by such a study.

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[1]Dan Kedem, Soreq Nuclear Research Centre, Yavne, Israel, personal communication.

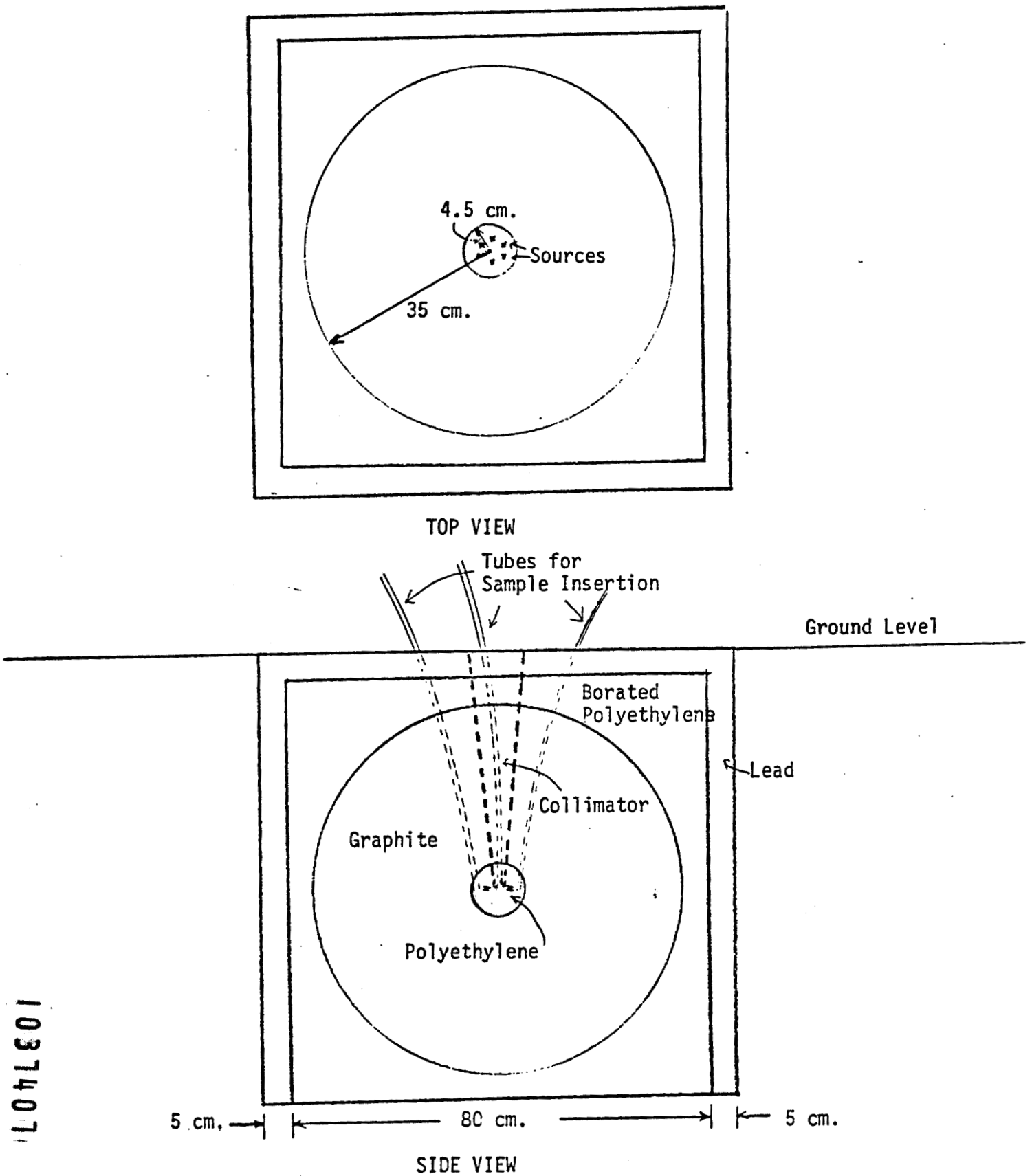


Figure 1 Proposed Cf-252 Neutron Irradiation Facility.

Table 1

Mass of Various Elements that may be Measured In-Vitro with Proposed Neutron Activation Facility

ISOTOPE[1]	MASS (mg)[2]	ISOTOPE[1]	MASS (mg)[2]
Ne-22	1.0	Ag-107	5.0
Na-23	0.7	Cd-116	0.3
Mg-26	4.0	In-115	0.002
Al-27	3.0	Sn-122	0.3
Si-30	1000.0	Sb-121	1.0
S-36	5.0	Te-130	0.4
Cl-37	0.6	I-127	0.1
Ar-40	0.2	Xe-136	10.0
K-41	4.0	Cs-133	0.3
Ca-48	0.5	Ba-138	0.7
Sc-45	5.0	La-139	0.7
Ti-50	0.7	Ce-142	3.0
V-51	0.1	Pr-141	8.0
Cr-50	7.0	Nd-148	0.09
Mn-55	0.01	Sm-154	0.02
Fe-58	100.0	Eu-151	0.002
Co-59	0.1	Gd-160	0.6
Ni-64	0.3	Tb-159	6.0
Cu-65	2.0	Dy-164	0.003
Zn-70	20.0	Ho-165	0.02
Ga-71	0.2	Er-170	0.08
Ge-74	2.0	Tm-169	30.0
As-75	0.5	Yb-168	0.006
Se-74	3.0	Lu-175	0.08
Br-81	0.8	Hf-178	0.8
Kr-84	1.0	Ta-181	3.0
Rb-87	10.0	W-186	0.3
Sr-86	0.1	Re-187	0.1
Y-87	80.0	Os-189	30.0
Nb-93	200.0	Ir-193	0.1
Mo-100	1.0	Pt-198	0.2
Ru-104	2.0	Au-197	0.05
Rh-103	0.003	Hg-196	0.02
Pd-108	2.0		

[1] If the natural abundance of the isotope if less than 90%, it is assumed that it is enriched to 90%.

[2] Mass that could be detected when irradiated for 1 hour and counted for 1 hour assuming 10,000 counts collected with no interference from other isotopes.

1037408

Appendix I

The Method of Activity Determination in Patients

In order to set up the formalism, imagine the scan field to be divided up into a large number of rectangles, or cells, as shown in Figure 1. The length of each cell is equal to the distance moved by the scanner when counts are recorded for one data point, and the width of each cell is equal to the distance between scan lines. When the detectors traverse the length of a cell, the counts accumulated in that time are recorded by a computer, thus giving a data point corresponding to that cell.

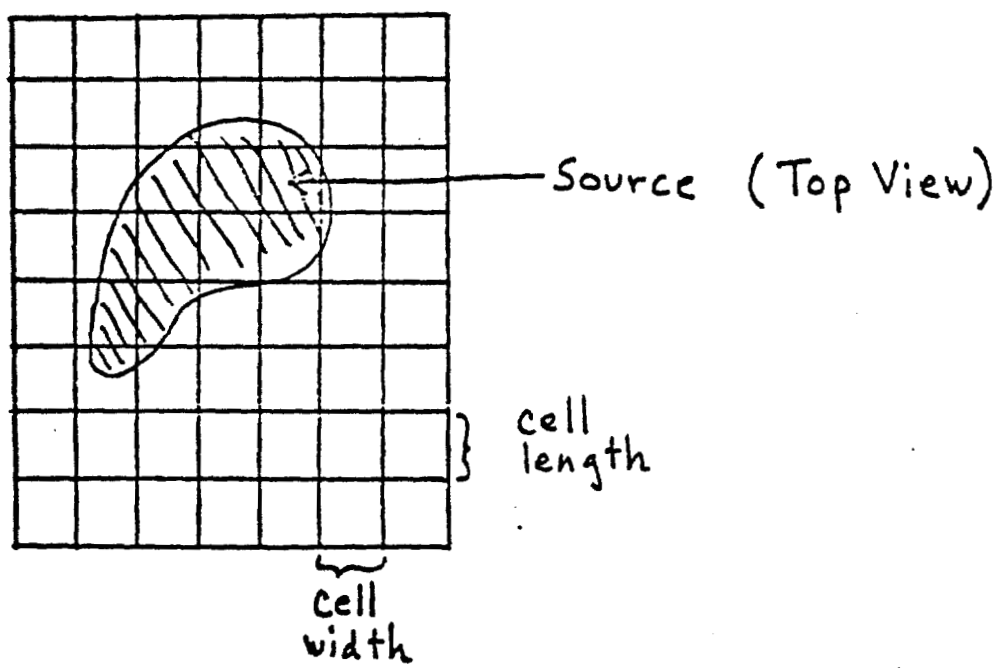


Figure 1. The division of the scan field. The size of the cells is greatly exaggerated for clarity. In this case, there are 56 cells in the scan field. In the usual case, there are 4096.

To calibrate the scanner, a "point" source of known activity is placed in a constant-thickness phantom and scanned. We define

$$S_{ij}(d,z) = \frac{\text{counts recorded in data point } i \text{ due to activity in cell } j}{\text{activity in cell } j} \qquad (1)$$

where d is the phantom thickness and z the height of the source from the bed. In order that this be a well-defined parameter, one must have the cell sizes much smaller than the area of the collimator field of view. Otherwise, the precise x-y location of the "point" source within a given cell would be important.

There would be a calibration factor of the form of (1) for each detector, but wherever possible, an explicit distinction between top and bottom detector functions will not be made, for the sake of brevity.

The calibration function for each detector is

$$f(d,z) = \sum_{i}^{n} S_{ij}(d,z) \qquad (2)$$

and there is an $f_T(d,z)$ for the top detector, and $f_B(d,z)$ for the bottom one. Experimentally, these functions are found by summing the counts over the scan image, and dividing by the source activity. These functions were found to have the form

$$f_T(d,z) = a\, e^{-\mu(d-z)} \qquad f_B = f_B(z) = b\, e^{-\mu z} \qquad (3)$$

where a, b, and μ are constants. These represent exponential attenuation of the photons being counted (see figure 2).

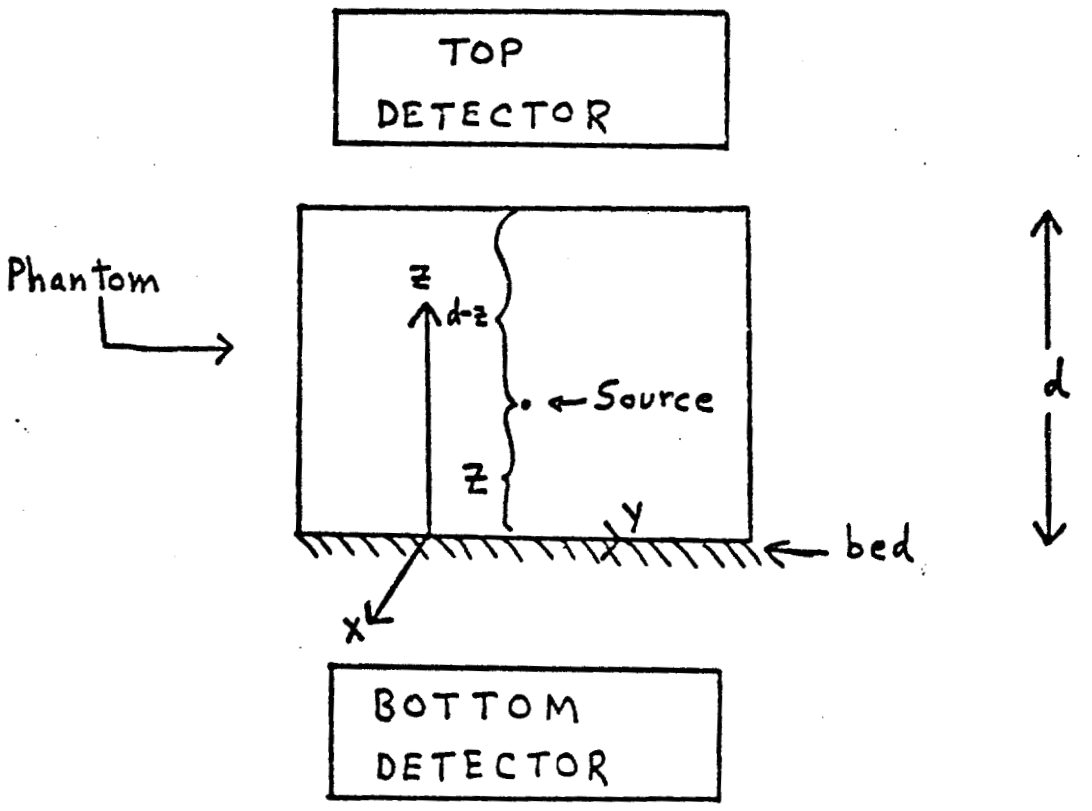


Figure 2. The coordinate system used. A point source at height z in a phantom of thickness d is shown.

Now consider the case of a uniform source of varying thickness located in a phantom of varying thickness. This is assumed to be the case for patients. The uniform source is assumed largely because a better assumption is not known, but it should be adequate, especially for healthy patients.

The counts in data point i due to the activity A_j in cell j is given by

$$C_{ij} = \left(\frac{A_j}{t_j}\right) \int_{z_{j1}}^{z_{j2}} S_{ij}(?, z_j)\, dz_j \qquad (4)$$

where t_j is the source thickness in cell j, and the ? means that the correct phantom thickness to use is unknown. In general, this would depend upon all the cell thicknesses, because of Compton scattering, but it is assumed here that d_j (phantom thickness in cell j) is the primary factor. This should be a good approximation because patient thickness does not change much from one cell to another (except along the sides of the trunk, where little or no activity is located), and the exponential form of (3) implies that not too much scatter is being counted anyway. Then (4) becomes

$$C_{ij} = \left(\frac{A_j}{t_j}\right) \int_{z_{j1}}^{z_{j2}} S_{ij}(d_j, z_j)\, dz_j$$

and the total counts in data point i is

$$C_i = \sum_j^m C_{ij} = \sum_j^m \left(\frac{A_j}{t_j}\right) \int_{z_{j1}}^{z_{j2}} S_{ij}(d_j, z_j)\, dz_j \,. \qquad (5)$$

In order to write the scan results in terms of the calibration function given by (2), we must sum (5) over the image of the source:

$$C = \sum_i^l C_i = \sum_j^m \left(\frac{A_j}{t_j}\right) \int_{z_{j1}}^{z_{j2}} \sum_i^l S_{ij}(d_j, z_j)\, dz_j \qquad (6)$$

or

$$C = \sum_j^m \left(\frac{A_j}{t_j}\right) \int_{z_{j1}}^{z_{j2}} f(d_j, z_j)\, dz_j \qquad (7)$$

where the fact that l>n does not matter because the S_{ij} which make the major contribution to (6) are the same S_{ij} which appear in (2). Substituting (3) into (7) gives

$$C_T = a \sum_j^m A_j e^{\mu z_{j1}} e^{\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} e^{-\mu d_j} \qquad (8)$$

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$$C_B = b \sum_j^m A_j e^{-\mu z_{j1}} e^{-\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \qquad (9)$$

for the top and bottom detectors, respectively. The apparent activity $\bar{A}$ is given by

$$\bar{A} = (C_T C_B)^{1/2} \Big/ \left[f_T(d, z_0)\, f_B(d, z_0) \right]^{1/2} \qquad (10)$$

where z_0 is a dummy variable (the denominator of (10) is independent of it with the functions in (3)), and d is some sort of average phantom thickness to be specified. Using (8), (9), and (3), (10) becomes

$$\bar{A} = \frac{\left[\sum_j^m A_j e^{\mu z_{j1}} e^{\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} e^{-\mu d_j} \sum_j^m A_j e^{-\mu z_{j1}} e^{-\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right]^{1/2}}{e^{-\mu d/2}} \qquad (11)$$

This equation is hard to evaluate, because the t_j and d_j are uncorrelated (they are measured with different instruments), and because the z_{j1} are difficult to find even with an ultrasonic scan. However, this equation can be reduced with the Schwarz Inequality:

$$\sum_j^m X_j^2 \sum_j^m Y_j^2 = \left(\sum_j^m X_j Y_j \right)^2, \text{ if } \frac{Y_j}{X_j} \text{ is independent of } j \qquad (12a)$$

$$\sum_j^m X_j^2 \sum_j^m Y_j^2 > \left(\sum_j^m X_j Y_j \right)^2, \text{ otherwise.} \qquad (12b)$$

With the definitions

$$X_j^2 = A_j e^{\mu z_{j1}} e^{\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} e^{-\mu d_j}$$

$$Y_j^2 = A_j e^{-\mu z_{j1}} e^{-\mu t_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)},$$

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(11) and (12) give

$$\bar{A} = e^{\mu d/2} \sum_j^m A_j \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} e^{-\mu d_j/2}, \quad \text{if } e^{-\mu d_j} e^{2\mu z_{j1}} e^{\mu t_j} \text{ is independent of } j \tag{13a}$$

$$\bar{A} > e^{\mu d/2} \sum_j^m A_j \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} e^{-\mu d_j/2}, \quad \text{otherwise.} \tag{13b}$$

This can be written in terms of the total source activity, since the source is uniform:

$$A_j / t_j = A / \sum_j^m t_j, \qquad \left(A = \sum_j^m A_j\right)$$

which implies that

$$\bar{A}/A = e^{\mu d/2} \sum_j^m e^{-\mu d_j/2} \left(\frac{t_j}{\sum_j^m t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}, \quad \text{if the same ratio is independent of } j \tag{14a}$$

$$\bar{A}/A > e^{\mu d/2} \sum_j^m e^{-\mu d_j/2} \left(\frac{t_j}{\sum_j^m t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}, \quad \text{otherwise.} \tag{14b}$$

Unfortunately, (14a) is also hard to evaluate, again because the d_j and t_j are not correlated. However, d remains to be picked as well, and we will see that the proper choice of d will lead to an accurate approximation to (14a). To see what this choice is, consider the special case in which all the t_j are the same. For that, (14a) would be

$$\bar{A}/A = e^{\mu d/2} \left(\frac{1}{m} \sum_j^m e^{-\mu d_j/2}\right) \frac{\sinh(\mu t/2)}{(\mu t/2)},$$

which will reduce to the self-attenuation correction (the last term) if d is chosen so that

$$e^{-\mu d/2} = \frac{1}{m} \sum_j^m e^{-\mu d_j/2}. \tag{15}$$

This expression for d will be used for the source of varying thickness as well.

To obtain a suitable approximate expression from (14a), the exponentials are combined and expanded in a power series:

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$$\bar{A}/A = \sum_j^m \left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} - \frac{\mu d}{2} \sum_j^m \left(\frac{d_j}{d}-1\right)\left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}$$

$$+ \left(\frac{\mu d}{2}\right)^2 \frac{1}{2!} \sum_j^m \left(\frac{d_j}{d}-1\right)^2\left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} - \left(\frac{\mu d}{2}\right)^3 \frac{1}{3!} \cdot \qquad (16)$$

$$\sum_j^m \left(\frac{d_j}{d}-1\right)^3\left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} + \left(\frac{\mu d}{2}\right)^4 \frac{1}{4!} \sum_j^m \left(\frac{d_j}{d}-1\right)^4\left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} - \cdots$$

The first term is easily evaluated with ultrasonic data, but the other terms still require correlated ultrasonic and transmission scan data. The approximation, then, is to ignore these other terms, and replace the entire series by the first term only. To see if this is valid, first note that all the values of $\sinh(\mu t_j/2)(\mu t_j/2)$ will be in range from 1.0 - 1.3 for the values of μt to be encountered here, so to within an order of magnitude, and maybe even better, this series becomes

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 - \frac{\mu d}{2} \frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right) + \left(\frac{\mu d}{2}\right)^2 \frac{1}{2!} \frac{1}{m} \cdot \right. \qquad (17)$$

$$\left. \sum_j^m \left(\frac{d_j}{d}-1\right)^2 - \left(\frac{\mu d}{2}\right)^3 \frac{1}{3!} \frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)^3 + \left(\frac{\mu d}{2}\right)^4 \frac{1}{4!} \frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)^4 - \ldots \right],$$

where $\sinh(\mu t/2)/(\mu t/2)$ is an average of the individual values of this function. Each of the terms in brackets was computed for each patient study done thus far, and gave results similar to those in Table 1.

Table 1.

Computer calculations of the terms in (14) from transmission scan data of patients.

d = 9.83"

First Sum = 0.015 = $\frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)$

Second Sum = 0.025 = $\frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)^2$

Third Sum = 0.00114 = $\frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)^3$

Fourth Sum = 0.00161 = $\frac{1}{m} \sum_j^m \left(\frac{d_j}{d}-1\right)^4$

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For this value of d, $\mu d = 3$, so that (17) becomes

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 - \frac{3}{2}(.015) + \frac{9}{8}(.025) - \frac{27}{48}(.00114) + \frac{81}{16.24}(.00161) - \ldots\right]$$

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 - .0225 + .0281 - .000641 + .000340 - \ldots\right]$$

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 + .0056 - .000301 - \ldots\right].$$

Evidently, this is a very good approximation, because the term after the 1 is about two orders of magnitude less. This was surprising, since the standard deviation of these d_j values is about 15.4% of their average. To check this, another calculation was done with the same data, only

$$\bar{d} = (1/m) \sum_j^m d_j$$

was used in place of d. This gave

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 - 0 + \frac{9}{8}(.0237) - \frac{27}{48}(.000025) - \frac{81}{16.24}(.00149) - \ldots\right]$$

$$\bar{A}/A \sim \frac{\sinh(\mu t/2)}{(\mu t/2)} \left[1 + .0267 - .0000127 + .000315 - \ldots\right],$$

indicating a somewhat larger, but still acceptable error in truncating the series. More importantly, the value of d given by (15) has the advantage of being somewhat less than $\bar{d}$, so that the first two sums in (17) tend to cancel each other. With $\bar{d}$ the first sum is zero, so this does not happen. Thus, d picked by (15) is a better value to use than $\bar{d}$, because of this cancellation effect.

Therefore, if (14a) is valid, it can be evaluated to a good approximation by the expression.

$$\bar{A}/A = \sum_j^m \left(\frac{t_j}{\sum_j t_j}\right) \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)},$$

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where d is picked from (15). But if (14a) is not valid, the value of A computed in this way will be an upper limit to the true activity, as can be seen from (14b). Consequently, we turn our attention to the validity of (14a).

The condition which must be met is

$$e^{-\mu d_j}\, e^{+2\mu z_{j1}}\, e^{\mu t_j} = K,$$

where K is independent of j. This is equivalent to the condition

$$d_j - 2 z_{j1} - t_j = k, \qquad \left(k = -\frac{1}{\mu} \ln K \right)$$

or

$$d_j - (z_{j1} + z_{j2}) = k. \tag{18}$$

To interpret this equation physically, imagine that the cells are so small that d_j, z_{j1}, and z_{j2} can be expressed as functions of the position variables x and y, i.e., the cells are infinitesimal. Then $d_j = d(x,y)$, and similarly for z_{j1} and z_{j2}, so that (18) has the form

$$d(x,y) - \left(z_1(x,y) + z_2(x,y) \right) = k.$$

Defining $z_0(x,y)$ as the average of z_1 and z_2, this equation can be written in the differential form

$$d\left[d(x,y) \right] - 2\, d\left[z_0(x,y) \right] = 0,$$

where d [ ] means the differential of the quantity in brackets. Using the chain rule, this becomes

$$\frac{\partial d(x,y)}{\partial x}\, dx + \frac{\partial d(x,y)}{\partial y}\, dy - 2\, \frac{\partial z_0(x,y)}{\partial x}\, dx - 2\, \frac{\partial z_0(x,y)}{\partial y}\, dy = 0$$

$$\left(\frac{\partial d(x,y)}{\partial x} - 2\, \frac{\partial z_0(x,y)}{\partial x} \right) dx + \left(\frac{\partial d(x,y)}{\partial y} - 2\, \frac{\partial z_0(x,y)}{\partial y} \right) dy = 0$$

$$\underline{\nabla} \left(d(x,y) - 2 z_0(x,y) \right) \cdot d\underline{r} = 0,$$

where ∇ is the gradient operator, and $d\underline{r} = dx\hat{i} + dy\hat{j}$. This last equation states that the directional derivative of the phantom thickness must equal twice that of the source midpoint, for a given direction in the x-y plane and given set of (x,y) values. Further, this must be true over the entire extent of the source. This condition is probably not exactly true for patients, although large organs (such as the liver) may tend to follow the general body shape. So it is important to see how sensitive (14a) is to this condition being met.

This has been investigated as well. The method of investigation is to first examine the Schwarz Inequality in a general way, and then make a specific examination with the functions in (11) and (12). The first examination is fairly simple, and will be shown here, while the other is more involved, so only an outline of it will be given.

First, suppose that the condition for equality is violated by only a small amount. That is,

$$x_j = c\,y_j + \epsilon_j$$

where c is a constant, and ϵ_j represents the violation of each term. Then

$$\sum_j^m x_j^2 \sum_j^m y_j^2 = \sum_j^m (c\,y_j + \epsilon_j)^2 \sum_j^m y_j^2 =$$

$$\left(c^2 \sum_j^m y_j^2 + 2c \sum_j^m y_j\,\epsilon_j + \sum_j^m \epsilon_j^2\right) \sum_j^m y_j^2 \approx \qquad (19)$$

$$c^2 \left(\sum_j^m y_j^2\right)^2 + 2c \sum_j^m y_j\,\epsilon_j \sum_j^m y_j^2 \,,$$

where the last step follows because ϵ_j^2 will be negligible. This represents the left side of either (12a) or (12b). The right side is simply

$$\left(\sum_j^m x_j\,y_j\right)^2 = \left(\sum_j^m (c\,y_j + \epsilon_j)\,y_j\right)^2 = \left(\sum_j^m c\,y_j^2 + \sum_j^m \epsilon_j\,y_j\right)^2$$

$$= c^2 \left(\sum_j^m y_j^2\right)^2 + 2c \sum_j^m y_j^2 \sum_j^m \epsilon_j\,y_j + \left(\sum_j^m \epsilon_j\,y_j\right)^2 \qquad (20)$$

$$\approx c^2 \left(\sum_j^m y_j^2\right)^2 + 2c \sum_j^m \epsilon_j\,y_j \sum_j^m y_j^2 .$$

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Comparing the last step of (19) to that of (20) shows them to be equal. So to first order in ϵ_j, the Schwarz Inequality is still an equality. This is an important result, because it means that even if the condition for (14a) is not exactly met, (14a) is still valid, i.e., the Schwarz Inequality is not very sensitive to this condition. This gives hope that (14a) may be adequate for patient estimates.

If one does not neglect the ϵ_j^2 terms of (19) and (20), there results the condition

$$\sum_j^m Y_j^2 \sum_j^m \epsilon_j^2 \geq \left(\sum_j^m Y_j \epsilon_j \right)^2 , \tag{21}$$

where the equality holds if (14a) is true, and the > holds otherwise. For the functions in (11),

$$X_j^2 = A_j e^{-\mu d_j} e^{\mu t_j/2} e^{\mu z_{j1}} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}$$

$$Y_j^2 = A_j e^{-\mu t_j/2} e^{-\mu z_{j1}} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} ,$$

from which $\epsilon_j = X_j - C Y_j$ can be found, and hence ϵ_j^2. Substituting these expressions into (21) finally results in

$$\left(\sum_j^m A_j e^{-\mu t_j/2} e^{-\mu z_{j1}} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right) \left(\sum_j^m A_j e^{-\mu d_j} e^{\mu t_j/2} e^{\mu z_{j1}} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right) \geq \left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right)^2 . \tag{22}$$

At this point, use is made of (18), giving it the form

$$d_j - 2 z_{j1} - t_j = h + \delta_j$$

where δ_j is the violation corresponding to ϵ_j. Solving this for z_{j1} and

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substituting into (22) finally gives

$$\left(\sum_j^m A_j e^{-\mu d_j/2} e^{\mu \delta_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right) \left(\sum_j^m A_j e^{-\mu d_j/2} e^{-\mu \delta_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right) \geq \left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right)^2 .$$

By using the definitions of the sinh and cosh functions, the $\exp(\mu \delta_j/2)$ and $\exp(-\mu \delta_j/2)$ can be eliminated to give

$$\left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \cosh(\mu \delta_j/2) \right)^2 -$$

$$\left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \sinh(\mu \delta_j/2) \right)^2 \geq \left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh^{(23)}(\mu t_j/2)}{(\mu t_j/2)} \right)^2$$

This is still not in the desired form. Each term on the left side of (23) can be reduced by applying the Schwarz Inequality:

$$\left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \cosh(\mu \delta_j/2) \right)^2 \leq \sum_j^m A_j^2 e^{-\mu d_j} \left(\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right)^2 \sum_j^m \cosh^2(\mu \delta_j/2)$$

$$\left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \sinh(\mu \delta_j/2) \right)^2 \leq \sum_j^m A_j^2 e^{-\mu d_j} \left(\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \right)^2 \sum_j^m \sinh^2(\mu \delta_j/2)$$

Because the left side of (23) is a difference of two terms, substituting these expressions into it would lead to ambiguity, in general. However, we will make these substitutions anyway, and then show that this procedure is actually correct.

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Making this substitution gives

$$\sum_j^m A_j^2 e^{-\mu d_j} \left(\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2 \left[\sum_j^m \cosh^2(\mu\delta_j/2) - \sum_j^m \sinh^2(\mu\delta_j/2)\right]$$
$$\overset{?}{\geq} \left(\sum_j^m A_j e^{-\mu d_j/2} \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2, \tag{24}$$

where the ? indicates the ambiguity.
The quantity in brackets is just equal to m, the number of terms in the sum, because of a well-known identity of the cosh and sinh functions. So, dividing both sides of (24) by m^2 gives

$$\frac{1}{m}\sum_j^m A_j^2 e^{-\mu d_j}\left(\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2 \overset{?}{\geq} \left(\frac{1}{m}\sum_j^m A_j e^{-\mu d_j/2}\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2. \tag{25}$$

For simplicity, make the definition

$$E_j \equiv A_j e^{-\mu d_j/2}\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)},$$

so that (25) is

$$\frac{1}{m}\sum_j^m E_j^2 \overset{?}{\geq} \left(\frac{1}{m}\sum_j^m E_j\right)^2. \tag{26}$$

Regarding the E_j values as a statistical set of numbers, the variance of this set would be given by

$$\sigma^2 = \frac{1}{m}\sum_j^m E_j^2 - \left(\frac{1}{m}\sum_j^m E_j\right)^2,$$

and is a positive definite quantity. Thus, in (26), the left side is truly greater than the right, so that the ? can be removed. Continuing on back, it can also be removed from (25) and (24), showing that the substitution made into (23) is actually correct; there is no ambiguity.

Equation (25), without the ?, is the equation to be analyzed further. Removing A_j in favor of A, as was done with (13a), multiplying both sides by $e^{\mu d}$ and taking the square root gives

$$\left[\frac{1}{m}A^2\sum_j^m\left(\frac{t_j}{\sum_j t_j}e^{-\mu(d_j-d)}\cdot\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2\right]^{1/2}\geq\frac{1}{m}A\sum_j^m\frac{t_j}{\sum_j t_j}e^{-\mu(d_j-d)/2}\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}$$

$$\left[\frac{1}{m}\sum_j^m\left(\frac{t_j}{\sum_j t_j}e^{-\mu(d_j-d)/2}\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}\right)^2\right]^{1/2}\geq\frac{1}{m}\sum_j^m\frac{t_j}{\sum_j t_j}e^{-\mu(d_j-d)/2}\frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}. \quad (27)$$

The right side of this expression is just the right side of (14a), which, as was shown in (17), can be evaluated accurately by replacing the exponentials by 1. This will also be true of the left side, since it has practically the same form. So, the same patient data as before can be used to test the inequality above, in exactly the same way that (17) was used to test the approximation of (14a). One has, to within an order of magnitude (possibly better):

$$\frac{\sinh(\mu t/2)}{(\mu t/2)}\left[1-.0450+.0562-.001282+.000680\right]^{1/2}\gtrsim$$

$$\frac{\sinh(\mu t/2)}{(\mu t/2)}\left[1-.0225+.0281-.000641+.000340\right],$$

or

$$(1+.0112-.00060)^{1/2}\gtrsim 1+.0056-.000301$$

$$\sqrt{1.0106}\gtrsim 1.0053,$$

and these two numbers are practically equal. This, and equation (27) are extremely important results, because they mean that when one is checking the approximate method of evaluation of (14a), he is also checking on the validity of (14a) as compared to the validity of (11). If the approximate method of evaluating (14a) is seen to be adequate, then (14a) is a good approximation to (11). If the approximate method gives a poor result, then (14a) is about an equally poor approximation to (11), and one must decide upon other methods to evaluate (11), or use a different method of activity determination.

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VI. Scientific Personnel - Curriculum Vitae on file ERDA

Principal Investigator:

A.B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Director, Division of Nuclear Medicine & Biophysics and the Clinical Radioisotope Center

Co-Investigators:

R.R. Price, Ph.D. [redacted]
Assistant Professor, Radiology

Research Associates:

J.J. Erickson, Ph.D. [redacted]
Assistant Professor, Radiology

J.A. Patton, Ph.D. [redacted]
Assistant Professor, Radiology

J.F. Parker, M.S. [redacted]
Computer Engineer

J.E. Lagan, [redacted]
Electronics Engineer

Jerome Wagner, Ph.D. [redacted]
Assistant Professor, Physics

VII. Other Personnel

Graduate Students:

J. Jones, [redacted]
K. Larsen, [redacted]

Secretary:

Deborah Ruff, [redacted], 100%

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VIII. Other Financial Assistance - None

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 8,000 square feet adjacent for conference, library clinical scanning, and instrument development and modification	100 percent
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

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RENEWAL PROPOSAL

1 August 1975 through 31 July 1976

X. Budget Estimated Requirements	ERDA	University	Total
1. Salaries and Wages Name, title monthly rate, % effort			
Principal Investigator: A.B. Brill, M.D., Ph.D. [redacted] Professor Medicine & Radiology, 25%	-0-	---	-0-
Co-Principal Investigator: R.R. Price, Ph.D. Instructor, Radiology @ $1435/mo, 34%	$6783.	---	$6783.
Research Associates: J. Erickson, Ph.D. Instructor, Radiology @ $1400/mo, 67%	9744.	---	9744.
J.A. Patton, Ph.D. Instructor Radiology @ $1435/mo, 29%	5166.	---	5166.
J.F. Parker, M.S. Computer Engineer @ 672/mo.,	8062.	---	8062.
J.E. Lagan Electronics Engineer @ $1168/mo, 41%	5748.	8220.	13,968.
J. Wagner, Ph.D. Assistant Professor @ $1493/mo, 2 mos. only	2987.	---	2987.
Graduate Students: (2) @ $100/mo	2400.	---	2400.
Secretary, D. Ruff, 100%	6246.	---	6246.
Research Tech., E. Block, 50%	3099.	---	3099.
Fringe Benefits (not fixed % of salaries. Varies with employee status and option)	6325.	820.	7145.
TOTAL SALARIES & FRINGE BENEFITS	56,560.	$9040.	65,600.
Indirect Costs (44% S & W)	24,886.		

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2. Supplies and Materials

Animal Purchases	$ 250.
Books, Periodicals, Journals	1000.
Chemicals & Glassware	300.
Computer Supplies (line printer paper, magnetic tapes)	1000.
Lab Supplies, Radioisotopes	2000.
Maintenance Service (computer only)	1000.
Office Supplies	800.
Equipment rental	1300.
Electronic Components & Replacement parts	9000.
Subject Participation	500.

3. Equipment

CAMAC Input Register Module	525.
CAMAC Output Register Module	575.

4. Publications and Duplicating	1200.	
5. Travel - Domestic	2000.	
6. Other:		
Steel Room Patient Hoist Mechanism (shop costs)	1100.	
Steel Room Patient Positioning apparatus (shop costs)	825.	
Transportation costs for Cf-252	500.	
	$23,875.	
TOTAL FUNDS REQUESTED ERDA		105,321.
UNIVERSITY CONTRIBUTION		9,040.
		114,361.

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Projected Costs

Percentage & Amount, Vanderbilt University	$9040.	8%
Percentage & Amount, Requested ERDA	$105,321.	92%

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Paul Gazzerro, Jr.
Assoc. Vice-Chancellor for
Medical Affairs for Operations
and Fiscal Planning

NOTE: Studies described in this application, involving the investigational use of human subjects, have been reviewed and approved by this Institution's Clinical Investigation Committee.

1037426

"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."

G. P. Bruce
(signed)

Date 4-28-75

1037427

TO : Addressees Listed Below DATE: September 29, 1975

FROM : F. O. Christie, Director, Contract Division, ORO

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 23 to Contract E(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~Lamar Medley~~	~~Contract~~		9/29/75	
2. ~~A. H. Frost, Jr.~~	Contract		9/29/75	
3. ~~A. E. Miller~~	~~Budget~~		9/30	
4. H. S. ~~Oster, Jr.~~	~~Finance~~		10/2	
5.				
6.	7508			

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Alice Brown | Contract Division | Tel.: 3-4105

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Form OR-133 (Rev. June 1973)

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  - Audit Branch
  - ADP Branch
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  - Equal Opportunity Branch
- SUPPLY DIVISION
  - Property Branch
  - Transportation Branch
  - Telecommunications Branch
  - Office Services Branch
    - Mail Section
    - Repro., Distr. & Mtls. Sect.
    - Photographic Services
    - Records Holding Area
- SECURITY DIVISION
  - Personnel Security Branch
  - Physical Security Branch
    - AEC Patrol

- ASST. MANAGER FOR OPERATIONS
- MANUFACTURING DIVISION
  - Quality Assurance Branch
  - Weapons Branch
- MATERIALS MANAGEMENT DIV.
  - Materials Management Br.
  - Nuclear Matls. Control Br.
  - New Brunswick Laboratory
- RESEARCH & TECH. SUPPORT DIV.
  - Classification & Tech. Services Br.
  - Research & Development Branch
  - Standards & Quality Assurance Branch
  - Waste Management Branch
  - Puerto Rico Area Office
- 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
  - Cincinnati Area Office
  - Paducah Area Office
  - Portsmouth Area Office
- 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
- RRD-OSR (ORNL)
- CONTRACT COMPLIANCE OFFICE
  - (Southeastern Area)
- CONTROLLER REGIONAL AUDIT STAFF

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

~~1. BUDGET AND REPORTS DIVISION~~ CONCURRENCE W E Miller Jr

~~2. OFFICE OF CHIEF COUNSEL~~ CONCURRENCE J. J. [illegible] 5234

USAEC Technical Information Center, Oak Ridge, Tennessee

1037429

UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

September 18, 1975

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: E-(40-1)-2401
   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 ERDA Funds To Be Obligated by this CA: $17,388

5. ERDA Percentage of Est. Total Cost To Be Shown by this CA: 90%

6. Description of Other Changes To Be Covered by this CA:

   Modify contract to provide for the performance of additional research during the period August 1, 1975 through October 31, 1975. ERDA Support Ceiling will be increased from $376,675 to $394,063. Title to equipment, if any, shall vest in the Contractor under authority of PL 93-438.

7. Authority:

   Form AEC-481 (CA) from J. L. Liverman, DBER, HQ dated Aug. 7, 1975.

A. H. Frost, Jr., Chief
Research Contracts, Procedures and Reports Branch
Contract Division

ACR: LM

1037430

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: E-(40-1)-2401

For the contract period: August 1, 1975 through October 31, 1975

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 25% of his time or effort to the research project.

ARTICLE A-II. WAYS AND MEANS OF PERFORMANCE

(a) Items included in total estimated cost:

(1) Salaries and wages: $8,940

(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

1037431

(3) Travel: $ 500

Domestic--------$ 500
Foreign---------$ 0

(4) Other direct costs: $5,951

(5) Indirect costs (based on a predetermined rate of 44 % of salaries and wages): $3,934

(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:

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 $ 19,325 ; ERDA will pay 90 % 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 ERDA Support Cost for the contract period stated in this Appendix "A" is $ 17,388 .

1037432

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:	$17,388

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article B-X.

1037433

Form AEC-481
(9-72)

AECPR 9-4.81 U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
	BER-76-110

3.A. TO
Robert J. Hart, Manager
Oak Ridge Operations Office

3.B. FROM
James L. Liverman, Director
Division of Biomedical and Environmental Research

4.A. CONTRACTOR *(Name, Address, Department, etc.)*
Vanderbilt University
Nashville, Tennessee 37203
Department of Radiology

4.B. PRINCIPAL INVESTIGATOR(S)
A. Bertrand Brill

5. ☐ NEW CONTRACT ☐ RENEWAL ☒ OTHER — Extension

6. TERM OF CONTRACT
8/1/75 - 10/31/75

7. CONTRACT NUMBER
E(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)
☐ COST REIMBURSEMENT
☐ FIXED PRICE ☐ OTHER

9. PROPERTY TITLE TO VEST IN:
☐ AEC
☒ CONTRACTOR-DETERMINED TO BE IN THE PROGRAMMATIC INTEREST OF THE AEC

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE Radioisotope Studies Utilizing a Low-Level Whole Body Counter and Clinical Applications of Activation Analysis

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 17,388
Estimated AEC Balance From Prior Term, if any	$ -
Total Estimated AEC Support Cost for New Term	$ 17,388
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$
Estimated Project Cost, For Pertinent Budget Period	$

Budget and Reporting Classification: RT 01 03
Allotment Transfer: 06-60-91 (24)

B. PLANT AND CAPITAL EQUIPMENT ..... $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

Being extended pending results of site visit.

15. SCOPE OF WORK Study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

5946

AUG 11 1975

1037434

TO : Addressees Listed Below DATE: September 20, 1974

FROM : F. O. Christie, Director, Contract Division, ORO

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 22 to Contract AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. Damar Medley	Contract		9-20-74	
2. A. H. Frost, Jr.	Contract		9/20/74	
3. A. E. Miller	Budget		9/23/74	
4. W. H. Henderson	Finance		9/21	
5.				
6.				
RETURN TO: Alice Brown	Contract Division			Tel.: 3-4105

1037435

Routed by

C C & R Branch

n OR-133 (Rev. June 1973)

number

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.
	Government Personnel Branch
	Industrial Personnel Branch
	Organization & Management Branch
	Equal Opportunity Branch

	SUPPLY DIVISION
	Property Branch
	Transportation Branch
	Telecommunications Branch
	Office Services Branch
	Mail Section
	Repro., Distr. & Mtls. Sect.
	Photographic Services
	Records Holding Area

	SECURITY DIVISION
	Personnel Security Branch
	Physical Security Branch
	AEC Patrol

	ASST. MANAGER FOR OPERATIONS

	MANUFACTURING DIVISION
	Quality Assurance Branch
	Weapons Branch

	MATERIALS MANAGEMENT DIV.
	Materials Management Br.
	Nuclear Matls. Control Br.
	New Brunswick Laboratory

	RESEARCH & TECH. SUPPORT DIV.
	Classification & Tech. Services Br.
	Research & Development Branch
	Standards & Quality Assurance Branch
	Waste Management Branch
	Puerto Rico Area Office

	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
	Cincinnati Area Office
	Paducah Area Office
	Portsmouth Area Office

	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

	RRD-OSR (ORNL)

	CONTRACT COMPLIANCE OFFICE
	(Southeastern Area)

	CONTROLLER REGIONAL AUDIT STAFF

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ ~~CONCURRENCE~~ A Miller for

2. OFFICE OF CHIEF COUNSEL CONCURRENCE 4584

USAEC Technical Information Center, Oak Ridge, Tennessee

1037436

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

September 13, 1974

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: AT-(40-1)-2401
   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 Application of Activation Analysis."

3. Type of Contract:

   [X] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: $69,550

5. AEC Percentage of Est. Total Cost To Be Shown by this CA: 90.5%

6. Description of Other Changes To Be Covered by this CA:

   See Attachment "A"

7. Authority:
   Form AEC-481 (CA)
   from J. L. Liverman, D-BER, HQ,
   dated August 7, 1974.

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR: LM

037437

ATTACHMENT "A"

Modify contract to provide for the performance of additional research during the period August 1, 1974 through July 31, 1975. AEC Support Ceiling will be increased from $307,125.00 to $376,675.00. Title to the equipment, if any, shall vest in the Contractor under authority of Atomic Energy Act of 1954. Delete the "Government Property" listed in the contract since the property has been sold by UCC-ND Purchasing and the proceeds remitted to the AEC through the OROO Finance Division.

1037438

Form AEC-481
(9-72)

AECPR 9-4.81

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
AUG 7 1974	BER-75-182

3.A. TO
Robert J. Hart, Manager
Oak Ridge Operations Office

3.B. FROM
James L. Liverman, Director
Division of Biomedical and Environmental Research
Charles W. Bast, Acting for

4.A. CONTRACTOR *(Name, Address, Department, etc.)*
Vanderbilt University
Nashville, Tennessee 37203
Department of Radiology

4.B. PRINCIPAL INVESTIGATOR(S)
A. Bertrand Brill

5.
☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER

6. TERM OF CONTRACT
8/1/74 - 7/31/75

7. CONTRACT NUMBER
AT(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)
☐ COST REIMBURSEMENT
☐ FIXED PRICE ☐ OTHER

9. PROPERTY TITLE TO VEST IN:
☐ AEC
☒ CONTRACTOR-DETERMINED TO BE IN THE PROGRAMMATIC INTEREST OF THE AEC

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE Radioisotope Studies Utilizing a Low-Level Whole Body Counter and Clinical Application of Activation Analysis

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen WH Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 69,550
Estimated AEC Balance From Prior Term, if any	$ 0
Total Estimated AEC Support Cost for New Term	$ 69,550
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$
Estimated Project Cost, For Pertinent Budget Period	$

Budget and Reporting Classification: RX 01 03
Allotment Transfer: 06-51-91 (24)

B. PLANT AND CAPITAL EQUIPMENT $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

15. SCOPE OF WORK

Study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

F 5365
AUG 12 1974

1037439

APPENDIX "A"

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: AT-(40-1)-2401

For the contract period: August 1, 1974 through July 31, 1975

ARTICLE A-I. RESEARCH TO BE PERFORMED BY CONTRACTOR

The Contractor will continue the study of radioisotope distribution 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 fringe benefits: $48,753

(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

1037440

(3) Travel: $ 1,500

Domestic--------$ 1,500
Foreign---------$ 0

(4) Other direct costs: $ 5,193

(5) Indirect costs (based on a predetermined rate of 44 % of salaries and wages and fringe benefits): $21,450

(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:

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 $ 76,896; the Commission will pay 90.5 % 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 $ 69,550.

1037441

CONTRACTOR: VANDERBILT UNIVERSITY
CONTRACT NO.: AT-(40-1)-2401

The estimated AEC Support Cost is funded as follows:

(a)	Estimated unexpended balance from the prior period(s):	$ 0
(b)	New funds for the current period:	$69,550

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article B-XI.

1037442

EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

AEC CONTRACT AT-(40-1)-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

April 30, 1974

F 2505

MAY 1 1974

1037443

OMB No. 68-R1143

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

TIF TION NUMBER (If known)
AT-(40-1) 2401

PROTECTION OF HUMAN SUBJECTS CERTIFICATION

☒ Contract ☐ New
☐ Grant ☒ Renewal
☐ Fellowship ☐ Continuation

STATEMENT OF POLICY: Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the DHEW is the responsibility of the institution which receives or is accountable to the 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 the Department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an appropriate institutional committee. (References: "Institutional Guide to DHEW Policy on the Protection of Human Subjects.")

1. TITLE OF PROPOSAL

Application of Activation Analysis Radioisotopes Studies Utilizing Low Level Whole Body Counter & Clinical

2. PROJECT DIRECTOR/PROGRAM DIRECTOR/FELLOW

POSITION TITLE A. B. Brill, M.D.

3. INSTITUTIONAL COMPONENT OR DEPARTMENT

Radiology

4. CHECK ONE OF THE FOLLOWING STATEMENTS AS APPLICABLE:

☐ A. This application does not propose any activities that would involve human beings who might be considered subjects, human material, or personal data from primary or secondary sources.

☐ B. This is to CERTIFY that this application which does propose activities involving human subjects has been reviewed and approved by our institutional committee on the date of _____ in accordance with the DHEW policy and the institutional assurance on file with the DHEW. (The review date should be recent; certification is invalid if review date would precede award date by more than one year.)

☒ C. This is to CERTIFY that this application which proposes to involve human subjects is pending review on the date of May 23, 1974 in accordance with the DHEW policy and the institutional assurance on file with the DHEW. If the committee does not review and approve the proposal by or on the date certified, the agency office requesting this certification will be notified immediately by telephone, telegraph, or mail. (Review date should precede requested or planned date of award by at least one month whenever possible.)

☐ D. This application proposes to involve human subjects. This institution does not now have an active assurance on file with the DHEW. I understand that information on the assurance procedure will be received should the application become eligible for an award.

5. SIGNATURE OF INSTITUTIONAL OFFICIAL AUTHORIZED TO SIGN PROPOSALS

D. B. Ramsey

DATE 4/26/74

6. TITLE Assoc. Dean Clinical Sciences

TELEPHONE NO. (Code, No., Extension) (615) 322-2145

7. NAME AND ADDRESS OF INSTITUTION (Street, City, State, zip code)

Vanderbilt University
Nashville, Tennessee 37232

NOTE TO AGENCY: This form should NOT be included with application forms that have provision for human subject certification. It may be used to request certification, or correction of certification.

HEW 596 (Formerly NIH 1611)
6-72

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO THE AGENCY REQUESTING ITS COMPLETION

1037444

1-SIE-78a

PUBLICATION BY AEC AUTHORIZED ☐

NOTICE OF RESEARCH PROJECT
SCIENCE INFORMATION EXCHANGE
SMITHSONIAN INSTITUTION
U.S. ATOMIC ENERGY COMMISSION

SIE NO.

AEC CONTRACT NO.

SUPPORTING DIV. OR OFFICE:

NAME & ADDRESS OF CONTRACTOR OR INSTITUTION: (State the division, department, or professional school, medical, graduate or other, with which this project should be identified.)

Vanderbilt University
Department of Radiology, Division of Nuclear Medicine
21st Avenue South
Nashville, Tennessee 37232

TITLE OF PROJECT:

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

NAMES, DEPARTMENT, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS AND OTHER PROFESSIONAL SCIENTIFIC PERSONNEL: (not including graduate students) engaged on the project, and fraction of man-year devoted to the project by each person.

A. B. Brill, M.D., Ph.D.--Radiology--Professor--Principal Investigator,
R. R. Price, Ph.D.--Radiology--Instructor--Co-Principal Investigator,
J. J. Erickson, Ph.D.--Radiology--Instructor--Research Associate,
J. A. Patton, Ph.D.--Radiology--Instructor--Research Associate,
J. F. Parker, M.S.--Radiology--Research Associate,
J. E. Lagan--Radiology--Research Associate

NO. OF GRADUATE STUDENTS ON PROJECT: 2 NO. OF GRADUATE STUDENT MAN-YEARS: 2

SUMMARY OF PROPOSED WORK: (200-300 words, omit Confidential Data). Summaries are exchanged with government and private agencies supporting research, are supplied to investigaters upon request, and may be published in AEC documents. Make summaries substantive, giving initially and for each annual revision the following: OBJECTIVE; SCIENTIFIC BACKGROUND FOR STUDY; PROPOSED PROCEDURE; TEST OBJECTS AND AGENTS.

The main emphasis of these studies is the development of instrumentation and analytical techniques for the acquisition and analysis of isotope tracer kinetic data, emphasizing dosimetry. Tracer turnover studies involve both radioactive and stable tracers. We continue to explore ways of using neutrons for activation analysis in an attempt to minimize radiation exposure to the patient while obtaining needed diagnostic information.

We are attempting to validate assumptions in dosimetry calculations. We are collecting quantitative data on diagnostic tracers administered to patients and analyzing these results with currently accepted methods. Berman's computer programs for simulation and modelling (SAAM 25) and dosimetry calculations (RADOS) are used in these studies, in addition to Monte Carlo programs being run at ORNL.

Dosimetry and clinical studies will be carried out on patients using new, approved radiopharmaceuticals where dosimetry data are lacking. These will include I-131 19-iodocholesterol and new radiolabelled compounds used in lung scanning.

We participate in the IAEA/WHO study of tissue levels of trace elements in ischemic heart disease, and plan to develop an on-site activation analysis capability using Cf-252.

RESULTS TO DATE: We have developed instrumentation and analytical techniques for radiation dosimetry and tracer kinetic studies. The data obtained on Fe-59 and Ca-47 kinetics in normal and diseased patients revealed rad/mCi dose estimates in normals which agreed with previous estimates. Absorbed doses in abnormal subjects deviated greatly and such estimates are being extended. Activation analysis studies in newborn infants showed that intracranial hemorrhages in hyaline membrane disease are a post-partum effect. Detailed presentations of results are published or in press.

	PROGRAM CATEGORY NO.
BUDGET	
PRIMARY	
SECONDARY	

A. B. Brill
Signature of Principal Investigator

DATE: April 30, 1974

INVESTIGATOR – DO NOT USE THIS SPACE

1037445

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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 used in nuclear medicine. The systems we have developed are well suited to this task, but nonetheless, we continue to work to improve on the methods to diminish errors. The major problem that we face involves the integration of our interests and capabilities with those of the patients and their physicians. We stand by ready to adjust our personnel and facility schedules so that we are able to answer patients' problems as they arise and from careful sequential studies arrive at information that is needed for patient diagnosis and management and at the same time provide the needed data for dosimetry and metabolic kinetics studies.

We continue to work on methods to reduce patient exposures to the minimum needed to answer specific diagnostic problems. In this search, we have developed stable tracer techniques utilizing remote radiation sources and on-site counting and analysis facilities including high resolution solid state detectors and interactive computer systems. These facilities have been used also for sample composition studies trying to identify unusual trace elements in patients with ischemic heart disease. We are now developing methods using whole body counting and transmission scanning and neutron activation analysis to ascertain body composition changes in patients with various diseases on parenteral nutrition and in patients with massive obesity following surgical bypass of large segments of small bowel. Bone mineral content measurements are being made on patients with osteoporosis

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on various therapies using a two-photon technique and Gd-153. In the coming year we propose to develop an on-site neutron irradiation facility for small-animal and sample analysis using a Cf-252 source and a neutron irradiator developed at ORNL and currently on loan to Vanderbilt. The configuration being developed will permit small-animal whole-body activation analyses. Partial-body irradiation of human beings in future years will be evaluated if analysis techniques and exposures turn out to make this extension feasible. These facilities will be used in collaboration with researchers in many different departments at Vanderbilt for body composition studies in the management of patients (and experimental animals) with different syndromes and therapeutic regimens and for radiotracer kinetic studies. Continuing efforts will be devoted to specific projects in which we have a long history of interest. These include body composition in patients with massive obesity, iron metabolism in various disease states, calcium metabolism in abnormals, iodine metabolism and dosimetry in I-131 therapy patients, monitoring of Cs-137 levels and the dosimetry associated with diagnostic uses of new radiopharmaceuticals.

We are developing an 8-detector mosaic intrinsic germanium system in collaboration with Lawrence Berkeley Radiation Laboratory under NIH sponsorship for high resolution tumor scanning. The system will be evaluated for this and other applications by our staff, and dosimetry associated with new nuclides used in these applications will be performed. The utility of solid state detectors requires increased sensitivity, and we are hopeful that the results of AEC-sponsored work on intrinsic germanium detector technology will prove to be useful in nuclear medicine.

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The staff has achieved a scientific maturity and is a stable group of 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 promises to accelerate our biological study output.

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 are continuing to extend our system to acquire data from additional diagnostic instruments. 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.

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IV. Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the operation of the Vanderbilt Low Level Counting Facility. Dr. A. B. Brill, Principal Investigator, is the Director of the Division of Nuclear Medicine and Biophysics. Dr. R. Price is the Research Director within the division. Dr. J. Wagner, Physics Department (vice R. Baglan) has contributed many ideas and assistance in the direction of graduate student thesis research. 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. Dr. W. Rowan and staff of the Information Science Program and C. Bradshaw, Director of the Vanderbilt University Computer Center, and his staff have contributed significantly to our work. DuPont employees at the Old Hickory, Tennessee, and Wilmington, Delaware, plants have been of great assistance to us in working with Berman's SAAM 25 and RADOS computer programs. None of the personnel in other departments have been 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 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.

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V. Scientific Scope

A. Dosimetry and tracer kinetics

1. Methodology

a. Correlation studies between calculated and TLD measurements of radiation dose

Previous reports have described the instrumentation and analytical formalisms we have developed for quantitative external counting studies. The data obtained from these systems is used for organ and regional tracer kinetic and dosimetry analyses. Important information on radiation dosimetry in normal and abnormal subjects is obtained with these techniques. We have attempted to determine the accuracy of these systems by various means. From studies with encapsulated single point sources of known amounts of I-131, we determined that the accuracy of the system was better than 10%, and these values were reproducible. We have subsequently realized that methodologic errors may be encountered in the counting of distributed sources. We previously reported that the geometric mean value of the counts from two opposed detectors runs into difficulty when used to estimate the activity of two point sources counted together. This method tends to overestimate the total activity of the two point sources, although the overestimate is small ($\leq$ 10%). We have now found that this overestimate will probably occur for any distribution of activity (except a single point source), and is caused by the fact that we fail to take into account attenuation within the source. In practical situations, however, the procedures we are using provide estimates of the activity of distributed sources which are sufficiently accurate for dosimetry calculations. We have also found that when we write expressions which properly account for attenuation within the source, ordinarily there is insufficient information to solve the relationships uniquely. (In order to solve the equations uniquely, knowledge of the depth distribution of the

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activity itself is required.)

This methodologic error arises in the following way. The top detector views the distributed source as if it were an equivalent point source (EPS) at a location (depth) X_T, relative to the scanning bed. The bottom detector views the distributed source as an EPS located at X_B. But because of self-attenuation within the source, X_T and X_B are not equal. Thus the detectors do not agree upon where a single EPS should be located. Our established procedures correct for the effects of photon attenuation by the scattering medium around the source, but not for self-attenuation within the source. As a result, the activity is overestimated; but because the self-attenuation of the source is small in many practical situations, the overestimate is small, especially for photon energies greater than 140 keV (Tc-99m).

We have now developed a mathematical formalism which allows for the effects of self-attenuation for any distribution of activity and any specified functional form of calibration data. Using this formalism, we can predict the magnitude of the overestimate.

In a dosimetry study using Tc-99m sulfur colloid in liver and spleen, the expected overestimate is about 10%, and in order to correct for this, the anterior-posterior thickness of the liver needs to be known as a function of location along the liver. This can be found by tomographic scans or ultrasonic B-scan techniques. We have performed ultrasonic scans in several patients and are attempting to develop methods to utilize these two types of data for improved dosimetry analyses.

The calibration procedure for the TLD's has also been evaluated. This calibration consists of calculating the dose to a TLD lying on the face of a cube filled with Tc-99m water solution. Dr. Snyder of Oak Ridge National Laboratory has calculated the dose per unit activity to the TLD in this geometry, allowing one to relate the TLD output to radiation dose. Since

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good accuracy of this calculated dose is crucial, an experiment was run to check for agreement between this dose and our methodology. It was found that the experimentally estimated dose (based upon ionization chamber readings) exceeded Dr. Snyder's calculated dose by a factor of 3. Our experimentally estimated doses have a fairly large uncertainty (±30%), but not a factor of three. We are now working with Dr. Poston (Dr. Snyder's replacement following his retirement in March) to find the cause of this discrepancy.

The computer program to calculated the absorbed fraction for the TLD's (liver, spleen ⟶ TLD) is being rewritten to include analytical absorption terms in addition to the standard Monte Carlo calculations. The program has not been used in this fashion before. The calculation is done in this way because a complete Monte Carlo computation would require excessive computer time, due to the small size of the target region. Until satisfactory results are obtained for the calibration geometry, the program for the patient geometry will not be run. However, we have collected some patient data and are continuing to collect more, and will begin analyzing it when the discrepancy for the calibration geometry is resolved.

Although some patient data have been obtained to test the dose equation, more is needed to test the accuracy of the factors that go into the dose equation, which is

$$D = \tilde{A} \sum_i \Delta_i \Phi_i \qquad (1)$$

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Here, D is absorbed dose, $\tilde{A}$ the time cumulated activity ($\int A dt$), Δ_i the equilibrium dose constant for i-type radiation, and Φ_i the specific absorbed fraction for i-type radiation and a given source-target configuration. The source-target configuration being used in this experiment has the liver and spleen as sources, and a section of skin anterior to and overlaying the liver as target (see last year's proposal). TLD's placed on the skin measure the target dose; the activity in the liver and spleen is measured by scanning techniques, and the specific absorbed fraction has been calculated by Dr. Walter Snyder (ORNL) using his "standard man" model. This work is being extended in collaboration with Dr. Poston. Since we are experimentally checking the equality implied by equation (1), it is important to measure the dose and activity very carefully.

The accuracy of the dose measurement depends upon the accuracy of the TLD calibration and the reproducibility of the TLD outputs. The accuracy of the calibration (the calculated dose for the experimental cube geometry) has been checked in the following way:

(a) Measure the dose rate from a "point" source of Tc-99m with an ionization chamber.

(b) Expose the TLD's to this source.

(c) Read out the TLD's and compute their sensitivity (i.e., TLD counts/dose). The dose here is inferred from the reading of step (a).

(d) Put a known activity of Tc-99m in the cube and stir it to assure a uniform distribution of activity.

(e) Expose the TLD's to the cube source.

(f) Read out the TLD's and again compute their sensitivity. Here, the dose is inferred from the computer calculations for the cube.

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If our TLD methodology is correct, and if the doses for both the point source and cube source are correct, the sensitivity in step (c) above should be equal (within experimental error) to the sensitivity found in step (f). The calibration procedure will be considered accurate if this is the case.

To insure the reproducibility of TLD outputs, several steps (in addition to normal procedures) are followed during TLD readout:

(a) The photomultiplier tube gain is checked before and after each readout to assure that gain drift has been small ($\leq$1%). For the readout system being used (Model TLR-S TLD reader, Eberline Instrument Company), the shift in gain is about 1% per ten TLD readings.

(b) The reflectivity of the heating pan is checked before and after each readout. We have observed that the pan must be kept clean, or else an oxide will form on it. This oxide is not as reflective as the silver pan, and can easily cause a 5% - 10% reduction in the TLD reading. Thus, the pan is carefully cleaned before each readout, and its reflectivity monitored before and after each readout. From this procedure, small changes in reflectivity can be corrected for.

(c) Dirt and other contaminants on the TLD's can greatly affect their reading. To minimize these effects, the TLD's are individually wrapped in Mylar (0.008" thick). This thickness of Mylar also provides for electron equilibrium of the TLD's when exposed to Tc-99m gamma rays.

(d) Because individual TLD's show small to moderate differences in sensitivity, each one is individually calibrated.

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(e) The TLD's are read out between 24 and 48 hours after exposure. If they are read out sooner, short-lived thermoluminescent peaks can make an appreciable and variable contribution to the TLD reading ($\geq$5%). But after 24 hours, these peaks have decayed away, making the TLD readouts more consistent.

Using all these steps, two TLD's were exposed and read out ten consecutive times. None of the readings deviated by more than $\pm$1% from the average. Also, another set of exposures showed that if any of these steps were omitted, the reproducibility of the readings was no better than $\pm$5%.

The cumulated activity of A is found by measuring the activity at different times, and then integrating this empirical curve. There are also several steps we will take to help assure the accuracy of this measurement:

(a) Both the transmission scan and emission scan are collected simultaneously. This was felt to be necessary because of difficulties in correlating the thickness data with the emission scan when these scans are done separately. When they are collected simultaneously, inaccuracies due to patient positioning and visual correlations are eliminated. Corrections for dead-time losses, chance coincidences, and differential fields of view of the opposed detectors will be obtained from calibration studies.

(b) Because of the large size of the liver and the relatively low energy of Tc-99m photons, the self-attenuation in the liver needs to be taken into account. In order to do this, the thickness of the liver must be found, which will be accomplished by ultrasonic scanning.

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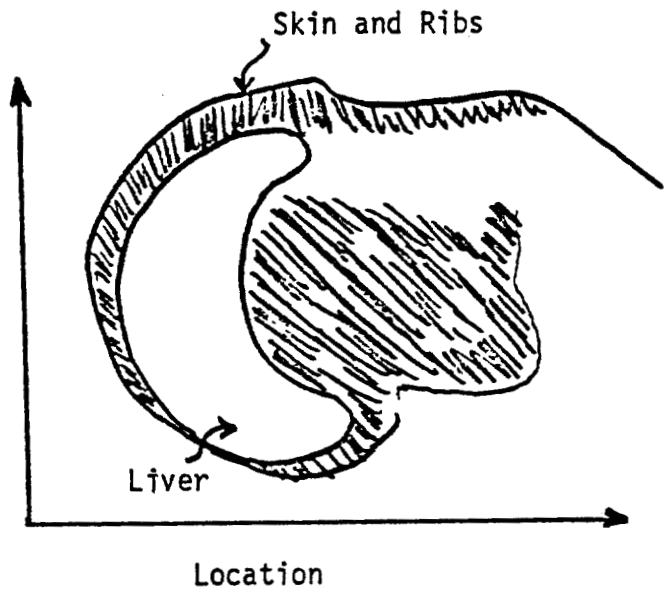


Figure 1. An ultrasonic scan of the liver is on the left, and an interpretive sketch is shown on the right. A distance of one centimeter on the picture corresponds to four centimeters in the patient.

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The ultrasonic scan gives a cross-section view of the liver (Fig. 1), so several transverse sections will be scanned in order to represent the liver thickness adequately. It can be shown that the total overestimate of the activity in a liver scan is a weighted average of the overestimates of each cell, with the weighting factor being the fraction of the total liver activity that is contained in each cell. If the liver activity is uniformly distributed, the amount of activity in each cell will be proportional to the thickness of the cell, so that only an average liver thickness is needed to correct for the effects of its self-attenuation. This eliminates the need to make a cell-by-cell correlation between the ultrasonic scans and the transmission scans, and the errors associated with this correlation. Further, the ultrasonic scans are clear enough that accurate measurement of the thickness (to within $\pm$0.5 cm) can be made, as shown in the figure below.

The ultrasonic scanner is calibrated to give the thickness of water, and for the purpose of calculating the activity in the liver, a water-equivalent thickness is desired. However, one must take care that the water-equivalent thickness of liver is the same for both ultrasound and gamma rays. For gamma rays, the linear attenuation coefficients for liver and water are approximately equal while the speed of ultrasound through liver is about 5% greater than through water (Wells, P.N.T., Physical Principles of Ultrasonic Diagnosis, Academic Press, 1969, pp. 5-6), so that these equivalent water thicknesses will be similar.

With these procedures, we feel that the dose and activity can be determined with improved accuracy. Thus, the possible effects of factors such as a non-uniform distribution of activity, or patients of different size and shape than the "standard man" model can be investigated.

The scan data from the patients studied thus far are shown in the following table. Each patient received two scans, and the entries are

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activity estimates in mCi.

TABLE 1

	t(hrs)	Liver	Spleen	Total
Patient A, Scan #1	0	1.400	.210	1.610
#2	24.	.085	.012	.097
Patient B, Scan #1	0	1.000	.988	1.988
#2	19.	.101	.106	.207
Patient C, Scan #1	0	.956	1.130	2.086
#2	22.	.068	.083	.151

Tc-99m sulfur colloid is expected to stay in the liver and spleen, and thus have an effective half-life of about 6 hours (the physical half-life of Tc-99m). This was checked using the data above and is presented in the table below. A(2) is the total activity from scan #2, and A(1) that from scan #1. The quantity exp $(-\lambda\Delta t)$ is the physical decay of Tc-99m, where Δt is the elapsed time between the two scans, and $\lambda = 0.1155$ hr.$^{-1}$.

TABLE 2

Patient	Δt	exp $(-\lambda\Delta t)$	Observed A(2)/A(1)	% Dev. (O-E)
A	24:09	.0614	.0602	-2.0%
B	19:12	.1088	.1041	-4.3%
C	22:29	.0745	.0724	-2.8%

If the decay of activity were due entirely to the physical decay of Tc-99m, the observed and expected columns would be equal. This is seen to be approximately true, although the fact that all three observed values are slightly smaller indicates that a small amount of the activity was biologically

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eliminated. However, this is so small that it is not expected to create any problems in evaluating the dose equation.

b. Data analysis

(1) Software developments

(a) Simulation and modelling

We are continuing to develop and test new kinetic models in an effort to understand better the total body and organ retention of medically administered radioactive materials. Solutions to these models have been sought generally through the use of Berman's SAAM 25 computer program. Our efforts are being 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 iron, calcium and iodine kinetics in addition to a number of new radiopharmaceuticals. The details of these models and model calculations will be discussed in the following sections dealing with the specific material.

(b) Multi-instrument executive for data collection and display

As the usage of the instrumentation connected to the PDP-9 continued to rise, it became urgent to find some means to operate these devices concurrently. Routine use of the low level counting facility with the computer, for instance, places a relatively low average data rate burden upon the PDP-9 yet requires rapid response from the computer to control the position of the scanner without introducing positional skew due to dead time. Similar situations occur with other devices, whether the data acquisition and display instruments are interfaced through the AEC standard CAMAC system or through dedicated pre-CAMAC hardware.

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Consequently, a supervisory executive program consisting largely of real time closed subroutines was written to run under the "Background Foreground Monitor" supplied by Digital Equipment Corporation. As presently in operation, this substantial program (over 3000 lines of source code, much of this in "macro instructions") will permit the simultaneous and asynchronous utilization of the following devices:

1. The low level whole body counting facility in a rectilinear scanning mode.
2. The electrical storage tube video buffer for local and remote graphic and image display.
3. A multichannel analyzer in a frame mode of image acquisition.
4. Via CAMAC:
   a. Position encoders for two independent and autonomous rectilinear scanners.
   b. Event sensors from remote locations, such as QRS-complex discriminator or beginning-of-procedure indications from the Cardiac Catheterization Facility.
   c. Multiple scaler/counter units which capture physiological information from the the patients under study.

The executive program is very modular in architecture so as to facilitate new requirements. Extensive use is made of the CAMAC macro instructions to enhance the initial programming task, to guard against obsolescence, and to promote the sharing of technology. It is anticipated that additional data acquisition and display capabilities can be added readily. Documentation of the executive is complete and reports on these systems will be presented annually to the Oak Ridge Symposia on the Sharing of Computer Technology in Nuclear Medicine.

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During the coming year it is planned to extend the executive program to include the following:

1. Industry standard magnetic tape for data storage and retrieval as well as data communication with other digital systems.
2. Scanning Anger-type camera (via CAMAC).
3. Multiple-probe tomography system (via CAMAC).
4. Multiplexed ADC for use with slowly varying inputs, such as physiological data (via CAMAC).

As the computer requirements increase, it is expected that it will become necessary to devise an overlay structure to allow the software to be brought into the memory of the PDP-9 from disc storage only when required. This revision should not require major rewriting of the subroutines because of the modular nature of the executive and the capabilitites of the operating system. Similarly, no problems are anticipated with the executive in the conversion from a basic CAMAC system with a dedicated controller in accordance with AEC standard TID-25875 to a CAMAC "branch highway" system conforming to TID-25876, since most of the changes will be accomodated by redefining the CAMAC macro instruction expansions.

(c) Sharing of computer programs in nuclear medicine

In collaboration with Dr. Berman and his associate Mrs. Weiss at the NIH, we modified and adapted the March 22, 1972 version of the simulation, analysis and modelling program, SAAM-25, to run on the Vanderbilt University computer. Since the time when this conversion was completed, we have made source versions of the program available to a number of users throughout the country. The 1972 version of SAAM had a number of minor problems and at least one major problem which affected our ability to utilize time delays

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in long-term iron-kinetics dosimetry studies. In order to use time delays in the past, we had to simulate the delay by a series of compartments. This technique increased the solution time considerably and also did not yield a true delay function. Mrs. Weiss has recognized this problem and has spent the past year implementing an analytical delay. The analytical delay required major modifications to the majority of the over 200 subroutines making up the SAAM program.

The new version of SAAM will be released by the NIH within the next few weeks. We propose to adapt this version to run on the university's computer so that the iron kinetics studies may continue at an accelerated rate. A number of other problems in the program have been solved, and numerous new features have been added to the new version of SAAM.

The SAAM program represents the results of many years of continuing effort by a very talented research team. It is sufficiently general in the types and sizes of problems that it can solve that it should be of general utility to a large number of people. Unfortunately, it is not easy to use, and hence it has not been used as widely or effectively as it should have been.

Utilizing our close ties with the Society of Nuclear Medicine Computer Committee, the Radiation Shielding Information Center (RSIC) at the Oak Ridge National Laboratory, and the experience we have gained through the use of the SAAM program, we are co-sponsoring a conference on the sharing of computer programs and technology in nuclear medicine (fourth in a series we have co-sponsored to date). This conference will, in part, be used to introduce prospective users to SAAM and will help current users to utilize SAAM to its highest potential. Problems concerning the use of SAAM and unique model solutions will also be discussed.

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(2) Hardware development

(a) CAMAC: multiple energy aperture camera

We propose to collect image data required for the multi-energy aperture image correction techniques from the scintillation camera through the CAMAC data acquisition system (described in section 2.a.). We propose to collect data for these studies by combining the electronics we designed and constructed for use with a scanning bed/imaging system with a single channel analyzer and a third ADC. The data will be collected in the following manner: the undiscriminated energy signal from the scintillation camera will be fed into an SCA whose window will be adjusted to bracket the potential energy range of interest. The output of this SCA will then be used to cause analog to digital conversion of the X, Y and Z signals from the camera. These three digitized values will then be transferred through CAMAC input registers to the PDP-9 to be stored in list mode on magnetic tape. A block diagram of this system is shown below (Fig.2).

The extra SCA is required in this instance because the energy window width of the camera's SCA is limited to 35% of the center photopeak energy, and this is not sufficient to bracket the wider contemplated window widths, for example, using Ga-67.

(b) CAMAC: branch highway

The CAMAC instrumentation system offers various levels of standardization and modularity. The AEC specification TID-25875 covers the basic interface, and by means of a single crate and a dedicated controller, the utility of this level of standardization in medical instrumentation is apparent to us but remains to be accepted by the medical community. The Vanderbilt PDP-9 CAMAC controller design was largely lifted intact from automatic backplane wiring specifications

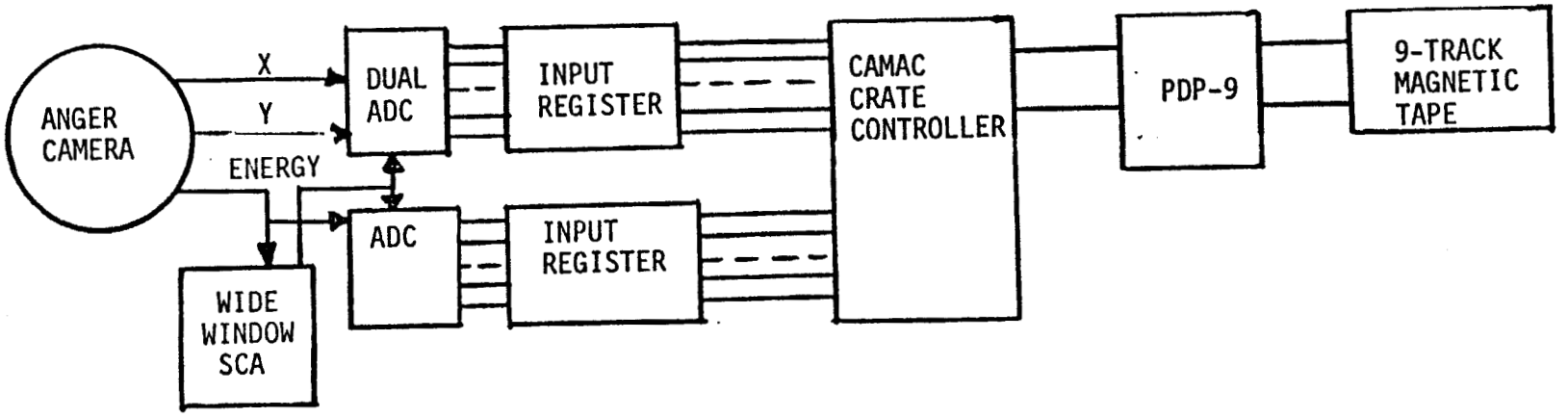


Figure 2. Block diagram of the data acquisition system for use with the multiple energy aperature camera

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already in use at Argonne National Laboratories. Commercially available modules from various manufacturers are being used in our system for data acquisition tasks.

The growth of the CAMAC use at Vanderbilt increases the worth of standardizing at the next level, that of the "branch highway" as specified in TID-25876. Such a level of standardization covers the interconnection of more than one CAMAC crate. Reliability increases substantially with this standardization for two reasons:

1. The developmental systems can be confined to a crate which is separate from routinely used modules, reducing the chance that defective components will damage good components.
2. The crate controller is no longer specific to the computer employed and is less expensive, making a spare cost justifiable.

While both of these savings will normally be felt only at medical facilities involved in research, the possibility of maintenance by module replacement is important in all health care delivery situations.

Consequently, funds are requested to augment the CAMAC system on the PDP-9 so as to add a second crate and to bring it into conformity at a higher level of the AEC standards. Specifically, this means the addition of a branch highway driver as a peripheral device on the PDP-9, the addition of a second crate, the acquistion of standard "type A-1" crate controllers, and the necessary connectors and terminators. These items are spelled out in the financial section of this application.

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The justifications for upgrading our CAMAC system include:

(1) The ability to test new devices and concepts in a second "experimental" crate without risk of damage to devices for routing functions being carried out in the first crate.

(2) Higher data rate capability than provided by present home-made type crate controller.

(3) Improved carry over from our experience with standard modules/configurations for sharing with other laboratories attempting to use CAMAC in nuclear medicine.

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(c) Interactive display: organ boundary identification

An important part of our data collection and analysis system is the PEP-400 silicon target electrical storage tube which is interfaced to the PDP-9. Although photographs can be generated using the computer's CRT, the electrical storage tube is useful for displaying intermediate results of an image processing sequence on video monitors. This device is presently used to display various types of computer-generated graphical information, but high quality images with a wide range of gray shades have been difficult to obtain. Good images are required for organ boundary delineation for dosimetry studies for region-of-interest definition. Several hardware modifications are being made which should improve the fidelity of images written on the storage tube. These changes will make it possible to write good images on the tube at slow speeds (under control of the executive in the background/foreground system). The versatility of the silicon storage tube display is enhanced by a software character generator. This subroutine forms characters by writing 5x7 arrays of data on the storage tube. Axes of graphs can be labelled, and numerical data can be added to images or graphs which are to be viewed on video monitors at remote locations.

A coordinate digitizer interfaced through a teletype port is now being used to interact with video images from the storage tube or the video disc recorder. A more convenient method of interaction is a video light pen which is being built. This will have much improved linearity over the coordinate digitizer. Both of these devices will be useful in delineating regions of interest and calculating dimensions of anatomical structures.

We have developed a general purpose image analysis system using equipment made available from NASA. This system is being used in our dosimetry and tracer kinetics studies. A system for the purpose of

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determining organ boundaries from video disc or hard copy images. The system is composed of a 600-frame stop-action video disc (Data Disc), a mechanical coordinate digitizer (Numonic), an electrical storage tube (PEP), and a PDP-9 computer (DEC). The system was designed primarily for high data rate image intensifier studies (x, gamma, and neutron images) and is being used for ventricular volume determinations from bi-plane video-cardioangiograms obtained during routine cardiac catheterization. However, the system will also be used for boundary determination of any organ for which a video or hard copy image can be obtained. (This includes video-displayed images from the computer via the PEP display system.)

The procedure is simply to trace around the image with the digitizer as the coordinates are read into the computer. Upon completion, the coordinates obtained are displayed by the computer in graphical form on the PEP. (Hardware modifications are being made to enable the display of these data on the same T.V. monitor as the one displaying the image.) The computer then calculates the organ volume using Simpson's rule, and after a few seconds the value is then displayed on a TV monitor from the electrical storage tube (PEP).

A computer algorithm has been developed by Homer Warner and is being modified for use here in our studies. This algorithm automatically recognizes even pulsating organ borders for all video frames throughout the cardiac cycle, and should be very useful for organ boundary identification in general. We have spent one week in Dr. Warner's laboratory learning the details of their system and are now implementing their algorithm for our organ boundary identification studies.

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(d) High resolution NaI vs. Ge(Li) detectors

Numerous studies have been made to examine the feasibility and applicability of semiconductor detectors for radioisotope studies. The superior energy resolution of these detectors makes it possible to discriminate more effectively against scattered radiation and thus to obtain higher quality images of radioisotope distributions. Significant advances have also been made in NaI(Tl) detector technology. These warrant careful evaluation. Improvements in electronic component miniaturization procedures, the availability of new, high quality photomultipliers, and improvements in crystal growth and couplings in integral line assemblies now make it possible to obtain a complete detector package with excellent energy resolution capabilities at a modest price.

We have recently obtained from RCA 12 developmental prototype NaI(Tl) assemblies at no cost to this contract. Each detector consists of a Bicron 1-3/4 x 1/2 inch NaI(Tl) crystal optically coupled to a high sensitivity, high resolution 2 inch photomultiplier. Mounted on the base of each tube is a dynode string, high voltage supply, pre-amplifier, linear amplifier, and single channel analyzer. The entire detector package is an integral line assembly approximately the size of a normal crystal photomultiplier pre-amplifier assembly. The only external electronics that are required for the operation of the assembly are a $\pm$12-volt supply, a +5-volt supply, and 3 resistive pots for adjustment of the analog output voltage, and single channel analyzer baseline and window selection. The evaluation of these detectors was designed to measure the resolution, sensitivity, stability, and reliability. In the course of these evaluations, it was found that significant warm-up times (> 2 hours) were required in order for the analog output to stabilize. This has been identified as a problem in the high voltage power supply. After each detector was allowed to stabilize, the

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analog output was adjusted to 4 volts maximum for 140 keV and a differential spectrum was collected at integral count rates of 1000, 2000, 4000, 8000, 12,000, and 20,000 counts/second from a source of Tc-99m (140 keV). Resolution and photopeak position measurements were made at each count rate. The results of this study are shown in Table 1. The resolution measurements shown are the averages of the 1000, 2000, and 4000 counts/second measurements. Excluding detector numbers S10214/C947 and K15706, which have been returned to RCA for repair, the average resolution was 10.1%±0.4%, and the average photopeak shift was 1.8%±0.8%. At count rates above 20,000 counts/second, significant degradations in resolution and photopeak stability were encountered. However, these count rate limitations should not prove to be of consequence with the photon fluxes that are currently available from radionuclide distributions in patients. The resolution and stability results are good, but the resolution was not as good as had been hoped for (8-9% at 140 keV).

In order to evaluate the effect of the superior resolution of the new NaI(Tl) detectors, we collected line spread functions at multiple depths in water from collimated detectors with a Tc-99m line source. Two experiments were performed. In the first, data were collected at 2, 3, and 4 inches from a 16mm. planer Ge(Li) detector with excellent energy resolution (0.5% at 140 keV), a standard 1-1/2" x 1/2" NaI(Tl) detector (18.4% at 140 keV), and one of the new NaI(Tl) detectors (9.1% at 140 keV), using a 7-hole collimator (VU7) focused at 4 inches with high spacial resolution and relatively uniform response (see figure 1). Energy spectra for each detector are shown in Figure 2. Optimum energy baselines of 139.5 keV, 126 keV, and 134 keV were chosen for the Ge(Li), NaI(Tl), and new NaI(Tl) detectors, respectively. The results of the line spread measurements shown in Figure 3 and the modulation transfer functions calculated from these line spread data (Figure

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4) show that only very slight improvements in scatter discrimination can be obtained with the new NaI(Tl) detectors for very high spatial resolution collimators. Thus in order to take full advantage of this type of collimator, one needs ultra-high resolution detectors that can only be obtained with small semiconductors. We repeated the experiment with a 53 mm Ge(Li) detector (3.1% at 140 keV) and a coarse resolution 19-hole collimator (ACRH) focused at 4 inches (see Figure 1). An energy baseline of 136 keV was used for the Ge(Li) detectors, and the same baselines as in the previous study were used for the NaI(Tl) detectors. The line spread functions shown in Figure 5 and the modulation transfer functions calculated from these line spread data (Figure 6) show significant improvements in scatter discrimination with the new NaI(Tl) detectors, although the data obtained with Ge(Li) are still considerably better.

It can be concluded that the use of high resolution NaI(Tl) detectors should permit higher quality images with coarse resolution collimators through better scatter discrimination. However, for studies with high spacial resolution collimators, one still needs semiconductor detectors to obtain significant improvements.

Within the next few months we will be obtaining a 4x2 mosaic of 1-inch diameter intrinsic germanium detectors at no cost to this contract. We will evaluate the image quality obtainable with this system and compare it to the quality obtained with similar arrays of high resolution NaI(Tl) detectors (to be constructed for evaluation purposes). It is necessary to use arrays of semiconductor detectors in order to overcome the sensitivity limitations that are inherent in these small detectors. The use of this array for imaging of radionuclide distributions in patients and animals should prove extremely useful in obtaining more accurate information on organ uptakes and distributions for dosimetry measurements and evaluations

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of new radiopharmaceuticals. However, small high resolution NaI(Tl) detectors in arrays may prove to be more practical because of their higher sensitivity and lower cost. Detailed comparisons of the imaging ability of these two types of arrays will be performed in phantoms and animals to evaluate their practical utility.

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TABLE 1

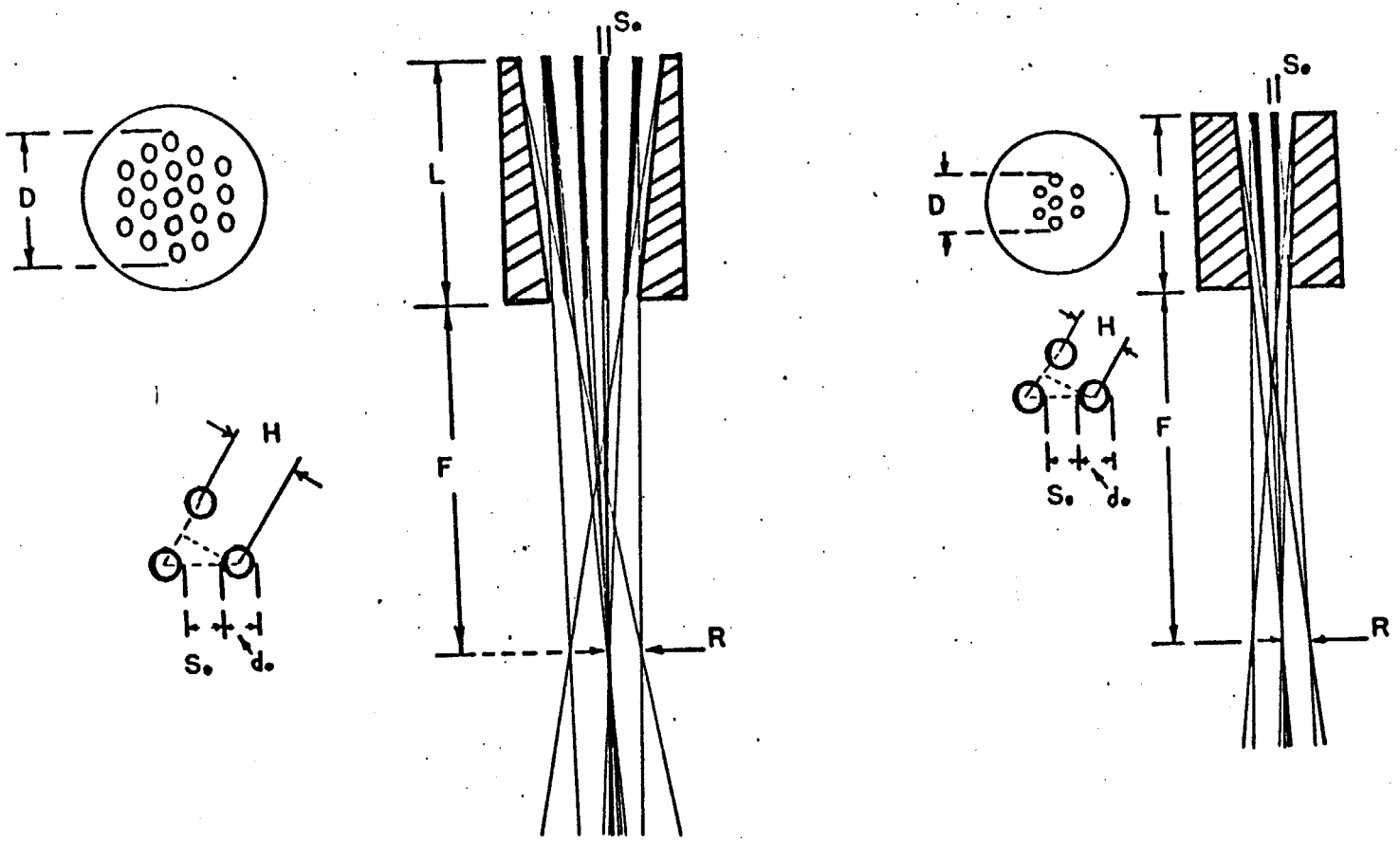
R.C.A. Integral Line Assembly Evaluation

TUBE NO.	% RESOLUTION V.U.	PHOTOPEAK SHIFT	NOTES
S85585	9.8%	1.0%	
S85563	10.2%	1.8%	
S85499	11.5%	1.6%	
S85567	10.8%	2.5%	
S10213	9.4%	0.6%	
S10214/C947	13.6%	1.2%	Returned for repair
K15700	9.4%	2.6%	
K15702	10.2%	1.1%	
K15696	10.1%	1.3%	
K15704	9.4%	3.3%	
K15706	9.0%	6.7%	Returned for repair
K15703	9.8%	2.1%	
Average	10.1%±0.4%	1.8%±0.8%	

Photopeak Shift = Max. shift observed from 1000 to 20,000 CPS Integral

% Resolution = Average of 3 measurements at 1000, 2000, and 4000 CPS

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DIMENSIONS IN CM.

	D	L	F	R	d_0	S_0	H
ACRH	4.65	6.75	10.1	1.01	0.84	0.11	0.82
VU	1.5	5.0	10.	0.5	0.43	0.1	0.46

Fig. 1.. Collimators used for line spread function determinations.

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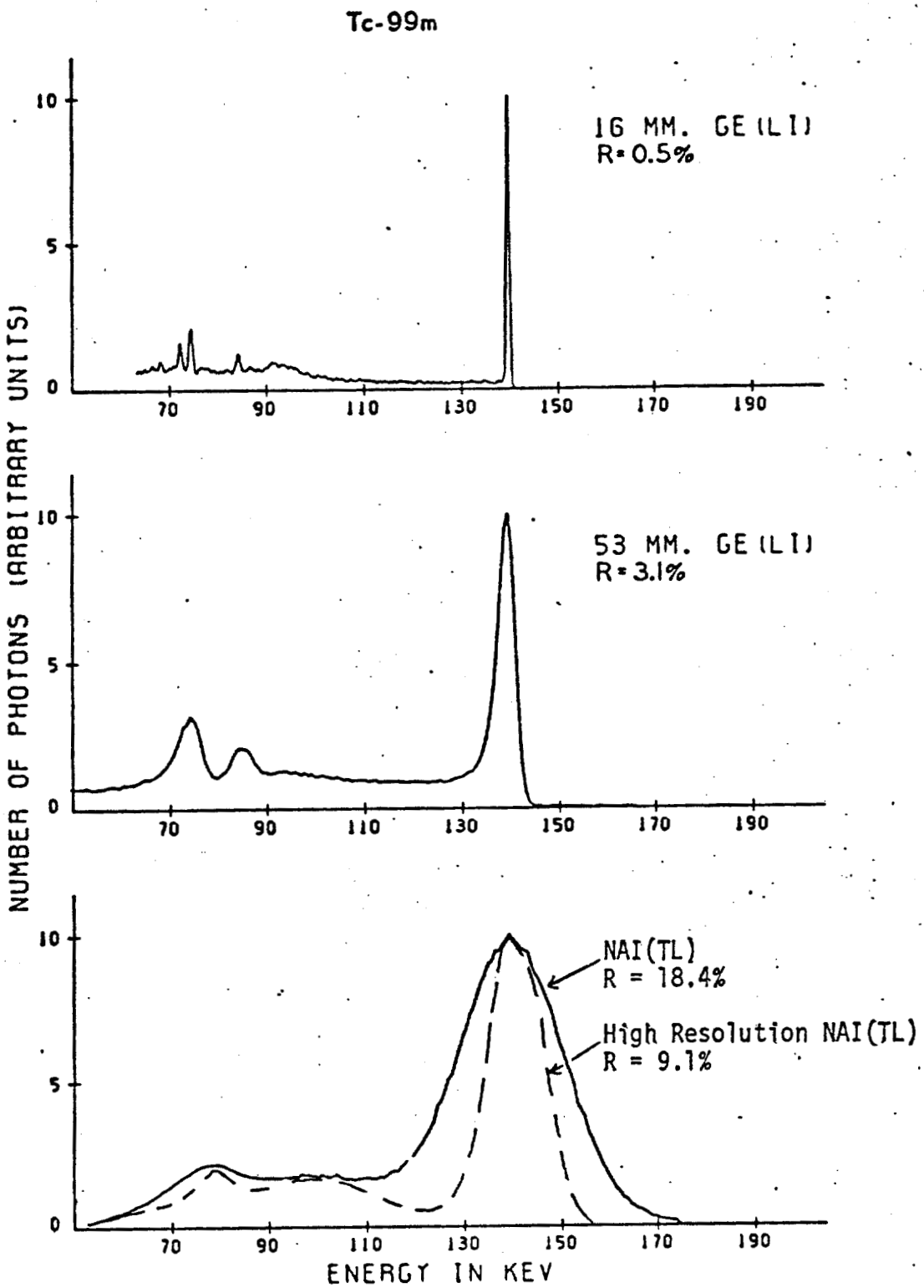


Figure 2. Energy Spectra collected from a source of Tc-99m

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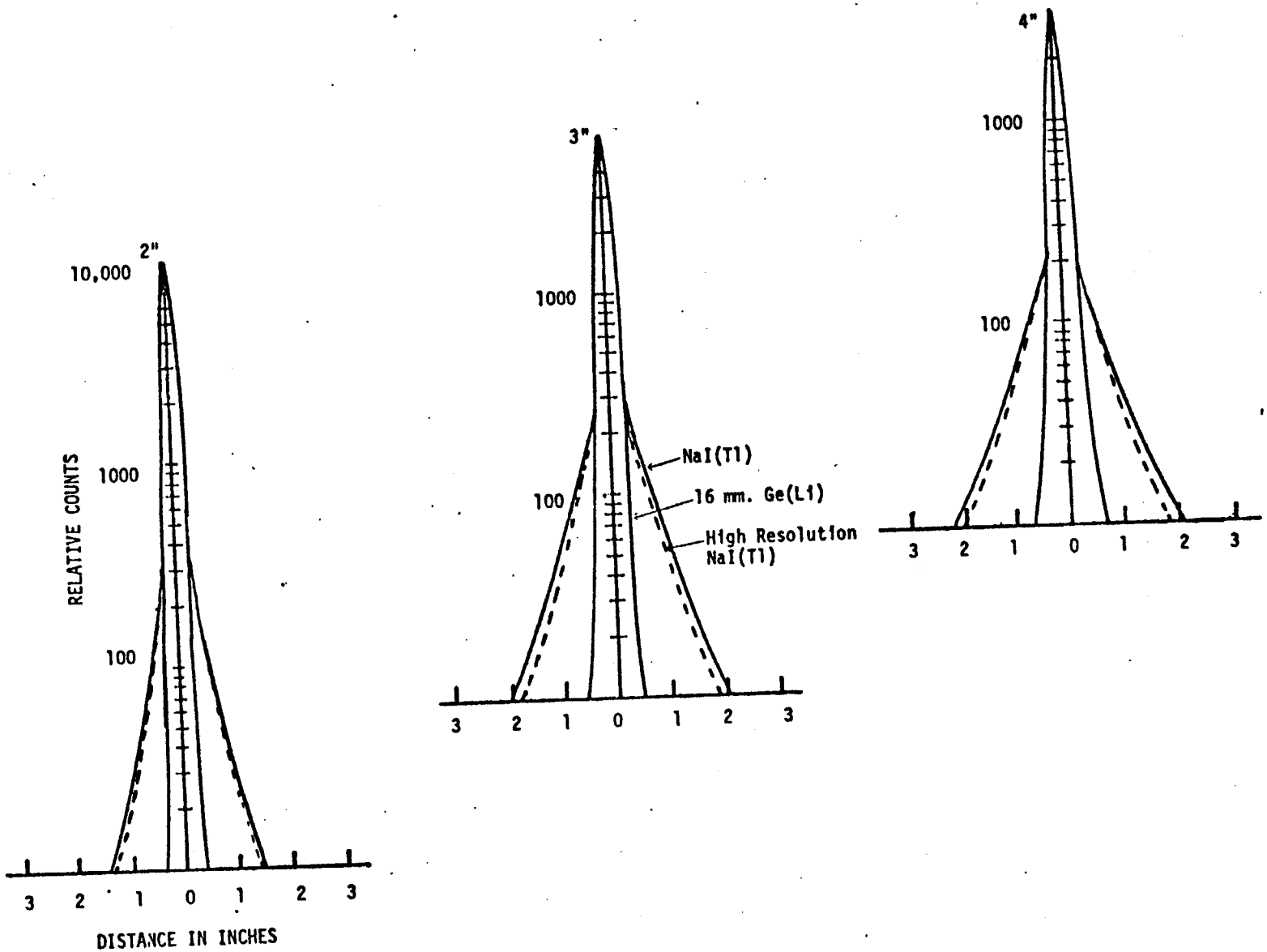


Fig. 3. Line spread functions measured at 2, 3, and 4 inches with Tc-99m in water using the high resolution 7 hole VU7 collimator.

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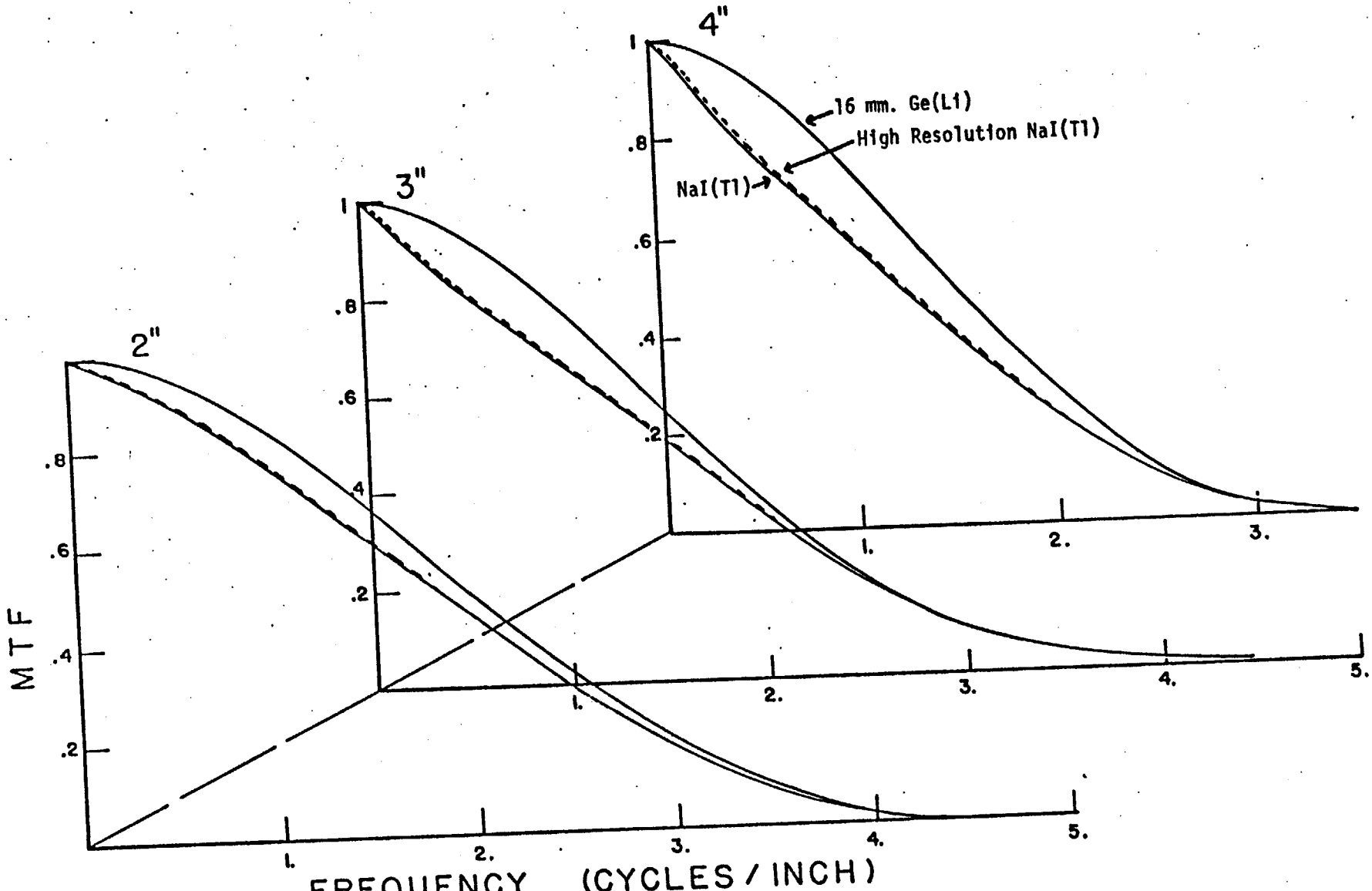


Fig. 4. Modulation Transfer Functions calculated from line spread functions measured at 2, 3, and 4 inches with Tc-99m in water using the high resolution 7 hole VU7 collimator.

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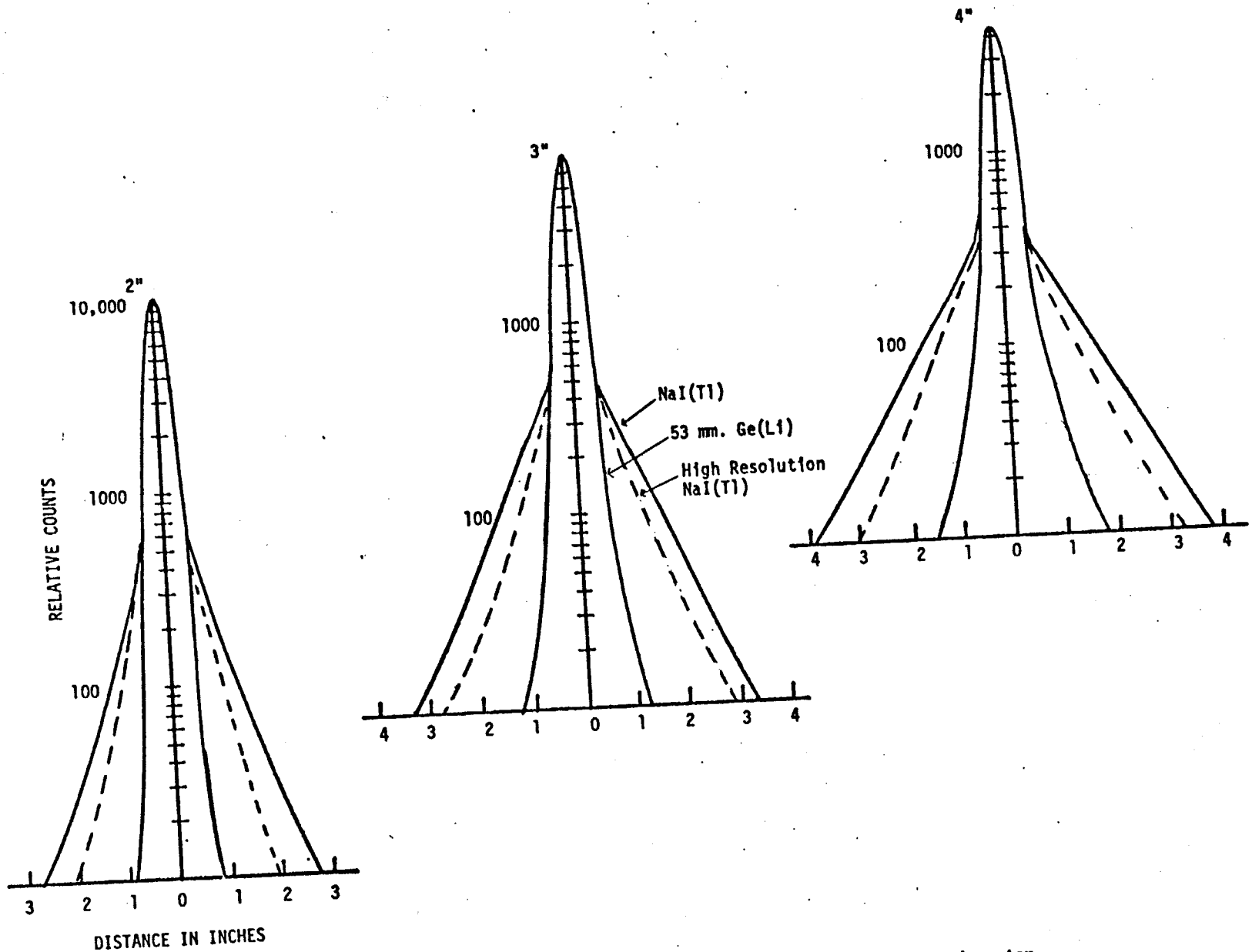


Fig. 5. Line spread functions measured at 2, 3, and 4 inches with Tc-99m in water using the coarse resolution 19 hole ACRH collimator.

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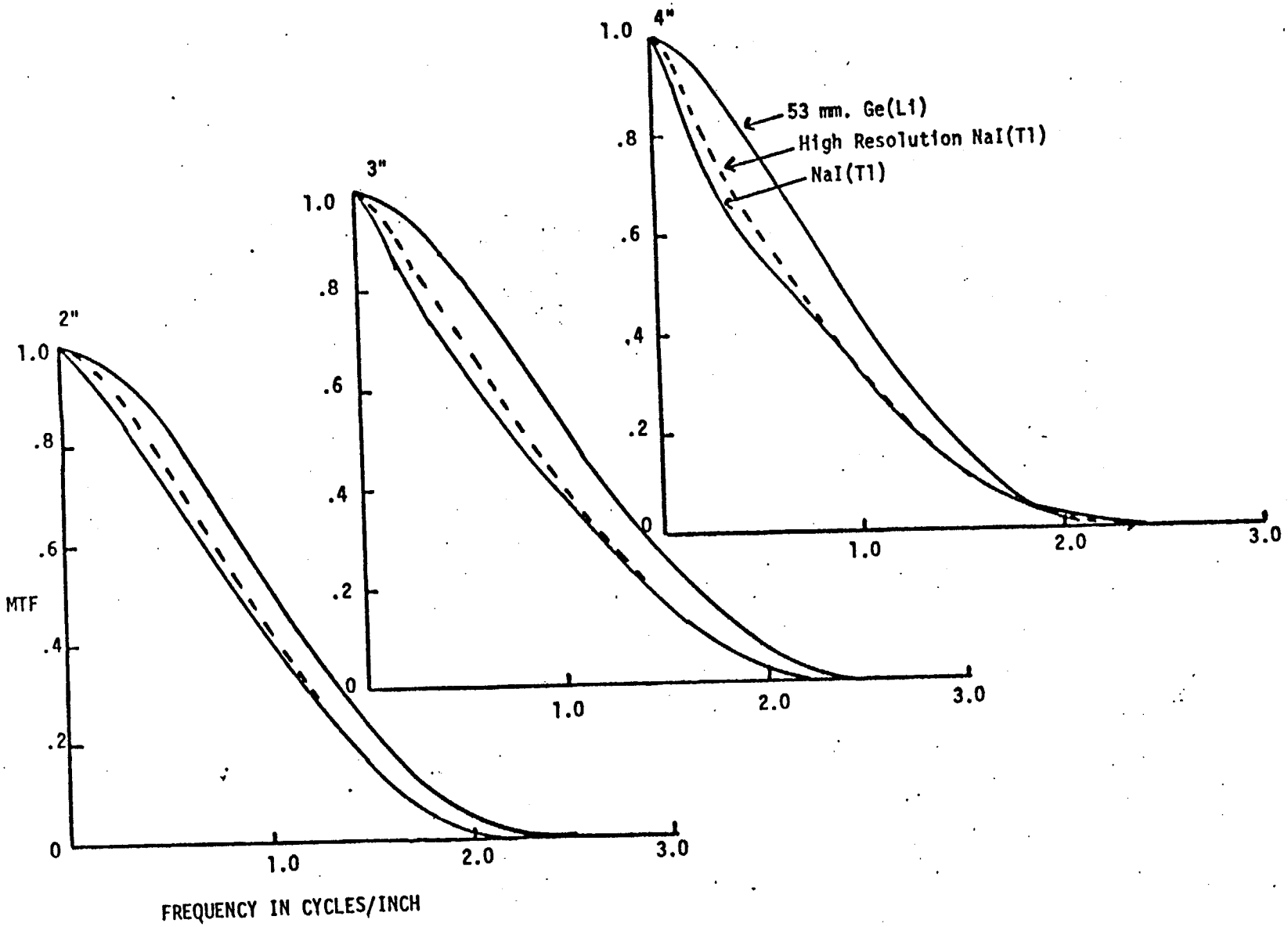


Fig. 6. Modulation Transfer Functions calculated from line spread functions measured at 2, 3, and 4 inches with Tc-99m in water using the coarse resolution 19 hole ACRH collimator.

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(3) Optimum use of energy spectrum for nuclear medicine images

When one collects images of radioisotope distributions in patients to be used in dosimetry calculations, accurate representations of the actual distribution are needed. However, the images are usually degraded due to (1) the effects of scattered radiation, (2) the presence of a blood background in most imaging situations, (3) the inability to make full use of some transitions in radionuclides with complex gamma-ray spectra, (4) limited photon densities, and (5) other imaging difficulties, including non-unique information on source depth. The data collection hardware that we have developed permits us to study ways of reducing the effects of some of these interferences. Using the executive operating system with the CAMAC data acquisition system, we are now able to collect data from multiple energy apertures simultaneously from the rectilinear scanners in our laboratory. (In the past it required dedication of our entire system for hours to do such a study.) With the development of the multiple energy aperture camera (section (2)(a)), this type of information will also be available from the Anger camera (stationary and moving). We plan to use this hardware and software capability to make the following studies.

(a) Scatter reduction

There have been several methods presented to reduce the effects of scattered radiation on the quality of radioisotope images. Some of these have actually been implemented and others are only theoretical proposals at the present. We plan to study the more promising of these techniques, to compare their advantages and disadvantages, and finally to implement the procedure that proves to be most useful. At present, we plan to study the penetration and scatter correction algorithm developed by P. R. Bell of the Medical Instrumentation Group at Oak Ridge National Laboratory,

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the multiple energy aperture weighting algorithm proposed by R. N. Beck at the Argonne Cancer Research Hospital, and the least-squares minimization techniques used at the Donner Laboratory by Budinger, et al. Other techniques will be studied as they are developed, and the best will be incorporated into our systems.

(b) Blood background subtraction

The presence of a blood background interferes to some degree in most imaging situations. With our system it is possible to reduce this effect by tagging the blood pool with a suitable radiopharmaceutical (such as early images following In-113m chloride injection), collecting photopeak counts from the radioisotope being imaged simultaneously with the In-113m, and subtracting the latter after suitable normalization. We plan to study this technique first in patients receiving Tc-99m polyphosphate bone scans where blood background causes some difficulties in interpretation. High quality photographs of the subtracted image will be generated on the computer CRT to evaluate the utility of the technique. Three factors may contribute to positive bone scans: bone uptake, blood pool effects, and blood flow. We will attempt to separate these factors in patients in whom this distinction becomes important by three isotope studies, simultaneously. Systems studies will be carried out in animals to develop the methods, and later extended to humans if warranted.

(c) Radionuclide with complex gamma-ray spectra

To image radionuclides with complex gamma-ray spectra such as Ga-67, Rb-81, Se-75, and In-111 with most instruments, one generally sets an energy aperture on the most intense photopeak and does not make use of photopeaks of lesser intensity. With a multiple energy aperture system we

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can make use of the less intense peaks to obtain images of higher statistical quality than the single aperture system. Other researchers have demonstrated the utility of the technique using rectilinear scanners; however, little work has been done in evaluating the utility of a multiple energy aperture camera system. We will apply this technique to the above-mentioned radionuclides which we are using in our clinical research and compare the images to those obtained with the single aperture systems.

1037485

2. Specific Studies

Radiation dosimetry measurements ordinarily have been made in animals where large numbers of normals are sacrificed at different times following tracer injection. Extrapolations from these data to men are used until human experience is collected. Human data are usually obtained from analyses of blood disappearance and whole body retention curves supplemented by occasional biopsy and autopsy samples. The MIRD Committee in the United States is collecting data from laboratories doing dosimetry studies and analyzing the new data along with well-documented literature reports. We have supplied the MIRD Committee with extensive data on Fe-59, I-131 iodocholesterol, and I-131 albumen (cysternography). This and other information is currently being reviewed and summarized by a number of different groups. This includes MIRD, a group from the Free University of Berlin, and NCRP-32 (chairman, A. B. Brill). The report being prepared by the NCRP Committee includes a discussion of the decision factors relating to the choice of the particular tracer and the amount administered in an attempt to maximize diagnostic information while minimizing radiation dose. A major deficiency in the presently available information is the lack of data for abnormal patients. At Vanderbilt, we are using our low level whole body scanner to obtain organ retention data by external counting and computing dose information for patients with different disorders. These studies are difficult to conduct especially in very sick patients, but such studies are badly needed.

We have been studying patients with disorders of iron and calcium metabolism for several years. The dose estimates from these studies are shown in tables 1 and 2, along with comparison values reported in ICRP 17 and from the Free University of Berlin. New data that have been accumulated are described in the following sections. Dose calculations are preliminary

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as are the clinical correlations.

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TABLE 1

Radiation Dose in mrad per μCi of
Fe-59 Ferrous Citrate Administered I.V.

	Liver	Spleen	Kidneys	Total Body
Normal	114	377	X	23
Sideroblastic Anemia	104	675	X	31
Refractory Anemia	440	377	X	23
PNH (Case 3)	21	173	321	
PNH (Case 5)	99	179	303	16.5
Hemochromatosis	93	379	X	25
Ineffective marrow (Leukemia)	206	671	X	23
Mild Bleeding	103	379	X	20.7
Summary				
Vanderbilt University	21-440	173-675	300-320	16-31
ICRP 17	--	140	--	--
Berlin (1973)	100	130	74	20

X Assumed to be approximately total body dose

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TABLE 2

Radiation Dose (mrad) per μCi from Intravenous Administration of Ca-47 Calcium Chloride

	Target Organ	
Disease	Skeleton	Total Body
Osteoporosis (H.W.)	7.7	1.6
Generalized Pagets (K.R.) (Before Therapy)	12.3	2.6
Generalized Pagets (K.R.) (After Therapy)	12.5	2.6
Localized Pagets (O.C.) (Before Therapy)	7.9	1.6
Localized Pagets (O.C.) (After Therapy)	4.1	0.9
Summary		
Vanderbilt University	4.1 - 12.5	0.9 - 2.6
ICRP 17	17. - 31.	--
Berlin (1973)	10.	3.2

1037489

a. Radiopharmaceuticals

(1) Tc-99m macroaggregated albumin

Results from pilot studies on patients receiving Tc-99m macroaggregated albumin for lung scans indicate that the time retention of the macroaggregates in the lungs is much longer than was previously believed. Since this is an important and routinely-used clinical procedure, it is imperative that the dosimetry be well known.

Preliminary data on one patient with normal lung function are shown in Table 1. These data indicate that the half-life of the particles in the lungs may be as long as 24 hours.

TABLE 1

Tc-99m Macroaggregated Albumin

% Administered Activity

	Total Body	Lungs	Liver	Spleen
1 hour	100	77	2	2
3 hours	95	64	2	3
6 hours	88	53	3	4
24 hours	85	50	6	5

In the following year we propose to study ten normal volunteers and as many abnormals as become available in accordance with the following protocol which we have followed in the pilot studies.

(a) Each volunteer will be given 0.5 millicuries (¼ the recommended dose) intravenously. The syringe used to give the radio pharmaceutical will be assayed before and after dosing and each value will be recorded on the data sheet. This will permit determination of the actual dose administered.

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(b) Immediately after injecting the volunteer, approximately 0.5 millicuries of pertechnetate will be withdrawn and injected into a 2000 ml volumetric flask. Again the syringe will be assayed before and after delivery of the pertechnetate and the values will be recorded on the data sheet. The volumetric flask contents will then be made up to 2 liters with distilled water.

(c) Blood samples (3-5ml) will be withdrawn 15 minutes, 1, 6, and 24 hours post injection; the samples will be marked and saved for radioassay.

(d) Scans will be performed on each subject at 1, 3, 6 and 24 hours post injection to determine the amount of administered dose retained in the lung, liver and total body.

(e) Duplicate one ml aliquots of the blood samples will be assayed in a scintillation spectrometer (peaked for Tc-99m, with a 10% window) in comparison with a one ml sample of the standard prepared in step (b). Values obtained will be entered on the data sheet.

(f) The amount of radionuclide will be calculated in terms of microcuries/ml and % dose/ml for each blood sample, and values will be entered on the data sheet.

(g) The concentration of radionuclide will be calculated in terms of microcuries/organ and % dose/organ for both the lungs and liver for each scan; values will then be entered on the assay sheet.

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(2) I-131 cholesterol

The development of I-131 19-iodocholesterol as an adrenal scanning agent by Beierwaltes and colleagues at the University of Michigan provides an important new tool for diagnosing and localizing adrenal disease. Professor Grant Liddle, Chairman of the Department of Medicine and Director of the Endocrinology Division of Vanderbilt University Hospital, is following a large number of patients with various adrenal disorders. These patients are studied in great detail. We obtain 10 mCi from the University of Michigan once or twice a month and inject 1 mCi/patient. We have studied approximately 50 patients during the last year, obtaining serial blood, urine and whole-body counts as well as Anger scintillation camera images. The image data are collected in the PDP-9 computer and are analyzed to determine the relative uptake of the right and left adrenal. We propose to continue this work so that a patient population adequate to define the metabolic parameters necessary for valid radiation dose calculations and efficacy data will be obtained. The evaluation of radiation dosimetry and efficacy of this potentially important new procedure will be carried out in collaboration with Dr. Liddle and his staff.

(3) Quality control of new radiopharmaceuticals

Since our investigations often involve the use of new radiopharmaceuticals which have existed for only a very short time as a commercially available product, we feel that it is important to monitor and document the radioactive and chemical integrity of these products.

(a) Spectral analysis assessment of radioactive impurities

Energy spectra using high resolution Ge(Li) detectors will be made for each new radiopharmaceutical batch we receive. The spectra will be analyzed for the presence and percent abundance of all impurities. This

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information is essential for dose estimations and will be tabulated for each new batch. Rubidium-81 is of particular interest to us. We are currently evaluating Rubidium as a myocardial scanning agent in dogs. In this case we found considerable contamination of Rb-82m, Rb-83, and Rb-84.

This represents a continuation of our work on radionuclidic impurities from technetium generators utilized throughout the southeastern region of the United States during a 6-month period. We will continue to evaluate breakthrough products in the generator systems used in our laboratories to determine the frequency of bad batches of Mo-99 distributed to our laboratory. We will process the earliest eluates promptly to determine the presence of unusual contamination early enough to determine whether or not a particular batch is contaminated. In our previous work, when we found one contaminated generator, all generators from that batch were also contaminated, and thus this information could be of general importance.

(b) Chemical assessment of pharmaceutical integrity

In addition to radioactive purity, one must also be aware of the percent of radioisotope that remains in the free state in any radiopharmaceutical preparation. Not only is the dosimetry of the procedure dependent upon this parameter but also the diagnostic interpretation of the study. For these reasons we propose to carry out a routine monitoring for chemical integrity in a manner similar to part (a). Of particular interest to us at this time is the I-131 19-iodocholesterol which ranges in free iodide from 5 to 25 percent in batches received to date.

1037493

b. Calcium kinetics and bone density

During the past year we have continued to make total-body and regional measurements of Ca-47 turnover in patients with osteoporosis and Paget's disease. In order to infer net organ time retention information and metabolic parameters from the external measurements, we have employed compartmental modelling analysis techniques. The models we have employed to date are shown in figures 1 and 2. As presented in last year's report (1973), we have been able to obtain model fits to these data thus allowing preliminary dose estimates to be made. However, the program has been unable to adequately estimate the parameters of the very slowly exchanging calcium pools. This problem arises from the fact that the time necessary for the slowly exchanging pools to equilibriate is long with respect to the time over which radioisotopic measurements can be made. In an effort to minimize these uncertainties, we have sought to place constraints on the model solutions by providing compartment volume information from the total body and regional calcium content measurements.

As represented in figure 1, we have characterized compartment 5 as "non-exchanging" bone with respect to the Ca-47 measurements. Calculations to date have not allowed us to estimate the flow rate from compartment 5 back to compartment 4 (λ_{45}). By utilizing data derived from the total body transmission scan, we will be able to estimate this flow rate in the following manner. The steady state solution requires that the mass flow of calcium into and out of compartment 5 be equal. That is,

$$M_4\lambda_{54} = M_5\lambda_{45}$$

$$\text{or} \quad \lambda_{45} = \frac{M_4}{M_5}\,\lambda_{54}$$

where M_4, M_5 are the masses of compartment 4 and 5 respectively, and λ_{54}

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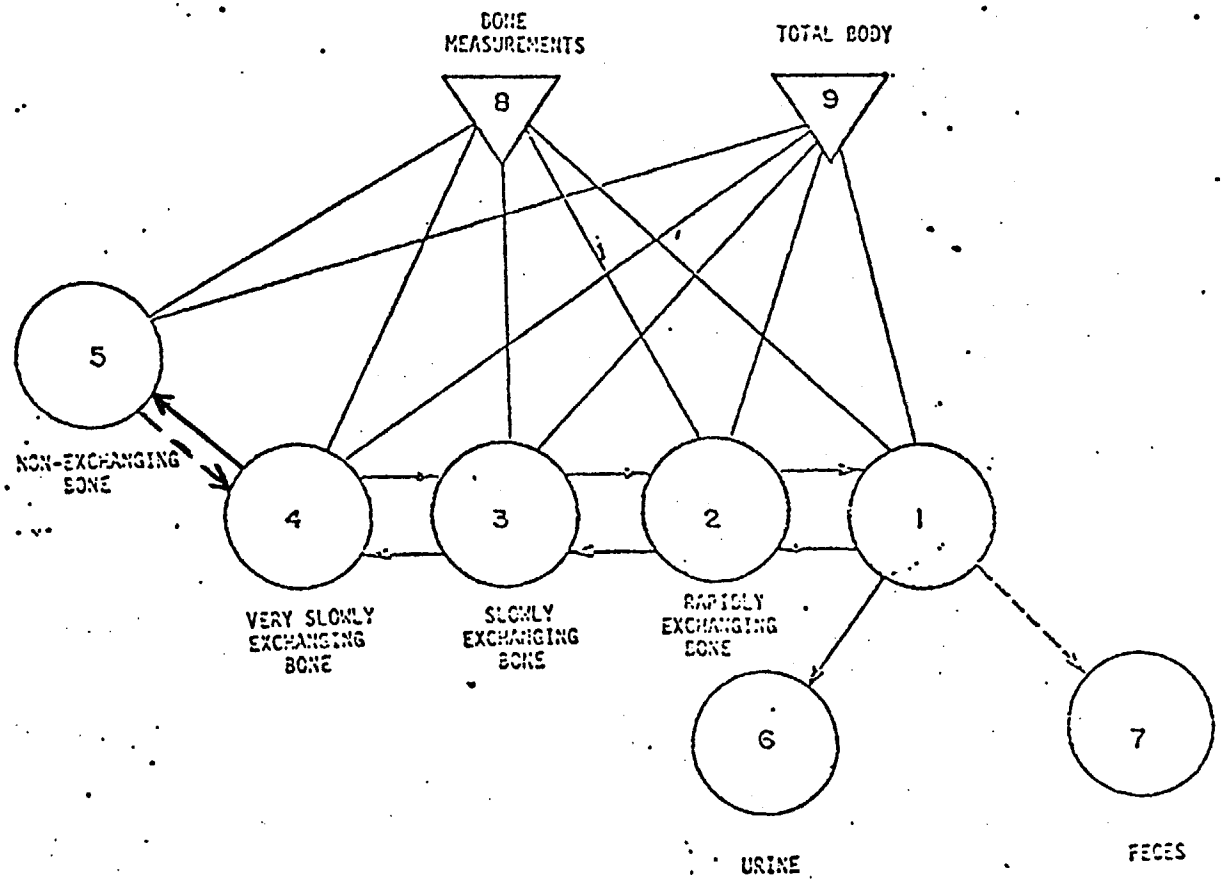


Fig. 1 Schematic of SAAM-25 calcium kinetics model used in osteoporosis studies.

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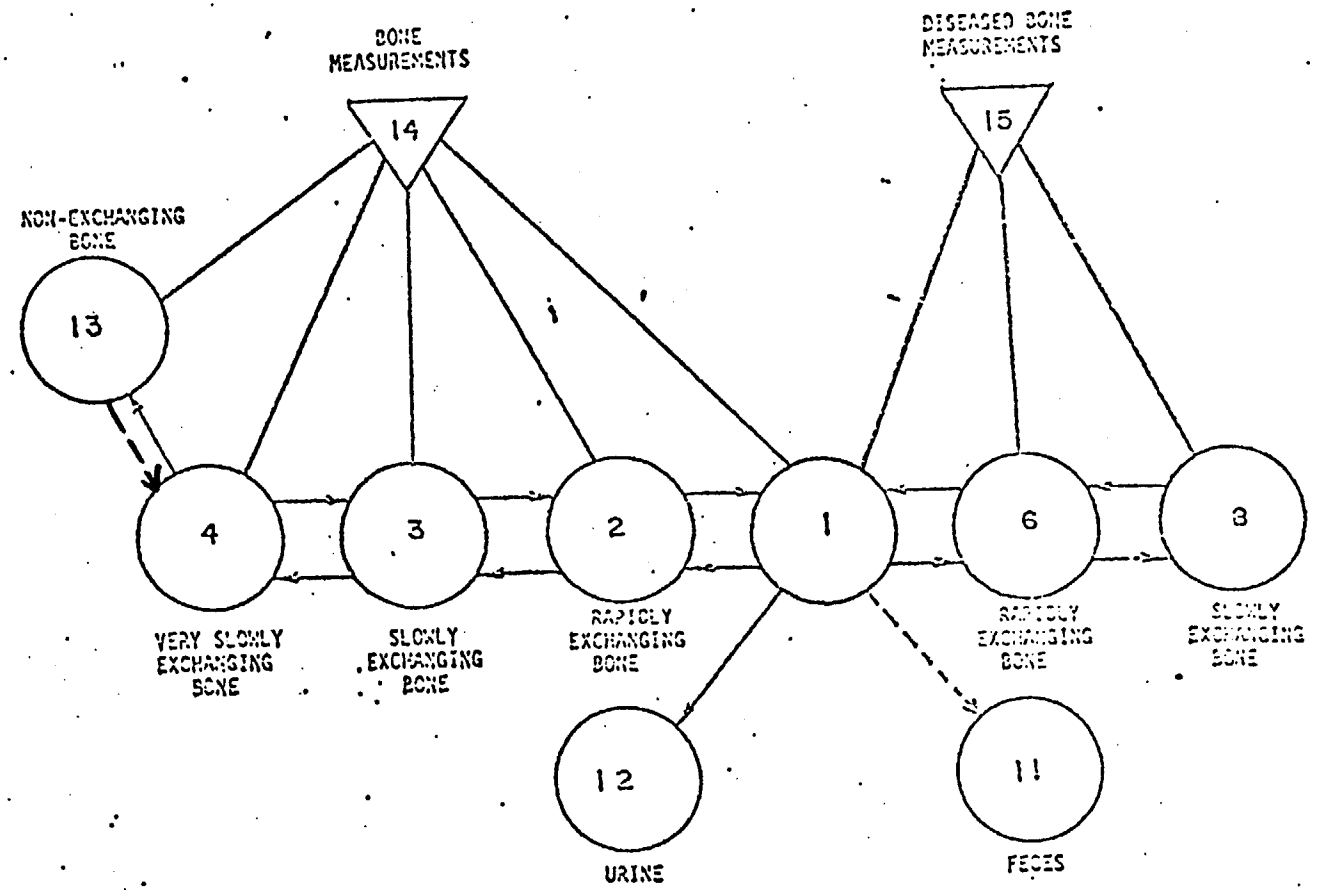


Fig. 2 SAAM-25 calcium kinetics model modified to be used in studies of patients with localized bone diseases.

is the flow rate from compartment 4 into 5. The values for M_4 and λ_{54} are derived from the model calculation, and M_5 is measured by the total-body transmission scan. The quantity M_5 represents the non-exchangeable calcium pool and is assumed to be 99.5 percent of the total body calcium.

The proportional contribution to the regional bone measurements from each compartment will be determined from the transmission scan. The proportionality constant will be set equal the fraction of the total body calcium found in the region of interest. Using these techniques, we will investigate the validity of extensions to the model shown in figure 1. These extensions will be similar to the model shown in figure 2. However, regional measurements will also be directed to assessing the differences in kinetics between weight-bearing and non-weight-bearing bones in addition to diseased and non-diseased bones as shown in figure 2.

In order to make these measurements, we have been making whole-body transmission scans using the low-level facility operating in the scanning mode. These scans employ the two-photon technique which makes it possible to separate the soft tissue contributions to the bone mineral content measurement in any selected region. An example is shown in Figure 3.

By assuming the body to be composed of two component materials (bone and soft tissue) with different properties with respect to photon attenuation, we can solve the simultaneous equations describing the attenuation of the two different energy photon beams for the bone thickness at each point of the rectilinear scan. The thickness $T_{x,y}$ (gm/cm^2) can then be integrated over any region of interest to yield total grams of bone mineral. The solution to these equations is as follows:

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$$T_{x,y}(gm/cm^2) = \frac{\ln \frac{I_o^L}{I_{x,y}^L} - \frac{\mu_E^L}{\mu_T^H} \ln \frac{I_o^H}{I_{x,y}^H}}{\mu_B^L - \frac{\mu_T^L \mu_B^H}{\mu_F^H}}$$

where superscripts L and H refer to low and high energy photon beams,

subscripts T and B refer to tissue and bone, respectively,

μ - mass attenuation coefficient

$I_{x,y}$ - beam intensity at region x,y

I_o - unattenuated beam intensity

Computer programs have been written and implemented on the PDP-9 computer to automatically evaluate $T_{x,y}$ for any selected region of the total-body transmission scan.

Much attention has been given to the development of suitable sources. At present, we are using a combination of I-125 (28-35 keV) and I-131 (365 keV) for the transmission source. Over the central portion of the body, the I-125 transmission is low, and hence large amounts (100 mCi of I-125) are used.

An isotopic source of particular interest to us is Gd-153. We have used this material for fluorescence and transmission scanning with success. The availability of two photons (99 keV gamma and 40 keV Eu x-ray) make it possible to do both bone and soft tissue determinations simultaneously with the same source.

The Isotopes Development Group at Oak Ridge National Laboratory has prepared an ultrahigh purity Gd-153 source (2Ci) and has made it available to us for evaluation. We are now making preliminary measurements with it and expect it to prove to be both more reliable and more convenient than currently used transmission sources.

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Figure 3. Dual-photon total-body transmission scans performed simultaneously with computer-controlled low-level scanner. Left (360 keV, I-131) Right (27 keV, I-125)

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A calibration of the whole-body transmission scan to determine the total-body and regional calcium content from the measurement of bone mineral has been carried out. Two of our staff have had total body calcium measurements made by whole-body neutron activation analysis at the Brookhaven National Laboratory. They have also had total body bone mineral measurements by transmission scanning at our facility. The factor relating the bone mineral content to the calcium content was found to be 0.538 for these normal subjects.

$$\text{BNL calibration factor} = 0.538 \frac{\text{gm calcium}}{\text{gm bone mineral}}$$

Results of measurements on four patients, two with osteoporosis and two with Paget's disease, are shown in table 1. The first entry in the table is the average value for the two normal volunteers. Although in every case the diseased states were found to have less calcium than the average normal, this should not be taken as meaningful diagnostic information since these measurements are not corrected for patient size. We are continuing to make these measurements in an effort to assess reproducibility and to test the assumption of a constant conversion factor for all parts of the body.

The opposed detectors used in these studies do not maintain perfect alignment as the scanner moves, and the excessive counting rate recorded by the large NaI detectors in the low level counting facility has led us to propose the construction of a new source/detector frame for these studies. The proposed system will use a computer-controlled scanning bed available in our clinic (for scanning camera studies) which we will use with a stationary high resolution high count rate NaI(Tl) detector. The C-frame configuration of the source-detector system assures perfect alignment at all points of the scan. The scanning bed is in the process of being inter-

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TABLE 1

WHOLE-BODY BONE MINERAL CONTENT MEASUREMENTS

	Bone Mineral Content (gm)	Calcium Content (BNL Calibration) (gm)
Normal	2011	1081
Paget's Disease #1	1874	1007
Paget's Disease #2	1510	811
Osteoporosis #1	1496	804
Osteoporosis #2	1604	861

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faced to the PDP-9 computer by means of CAMAC modules. The interface is expected to be operational within the very near future. The transmission source will be Gd-153.

Serial studies from the existing regional scanner have shown that the bone mineral measurements can be determined with an error of less than 2%. The high energy resolution of a Ge(Li) detector is not necessary for these studies since good geometry and a point source provides minimum of data with scattered radiation. Validation of our quantitative regional bone mineral counting techniques was carried out in conjunction with Dr. J. Connolly (Vanderbilt University Orthopedic Surgery Department). In these studies, dog bones were transmission scanned with an I-125 source and opposed Si(Li) detector. The bones were then ashed and the results of the two procedures compared. These studies were carried out for both intact and fractured bones, and preliminary results have been reported (1). Examples of data derived from these validation experiments are shown in figures 4 and 5. In these experiments fractures were stimulated electrically, and the degree of remineralization was determined by the regional scan. Figure 4 shows the time course of the mineralization in terms of the additional mineral gained above the unfractured opposed leg. With very poor statistics it appears that the additional mineral gained by the fractured bone reaches a maximum during the 5 - 7 week interval and then begins to resorb. Figure 5 shows that the mineral is asymmetrically distributed toward the cathode. The significance of this finding is not obvious at this time and is being studied further by the staff of the Department of Orthopedic Surgery.

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To date most of our measurements in humans have been focussed on the detection and quantitation of temporal changes in bone mineral content

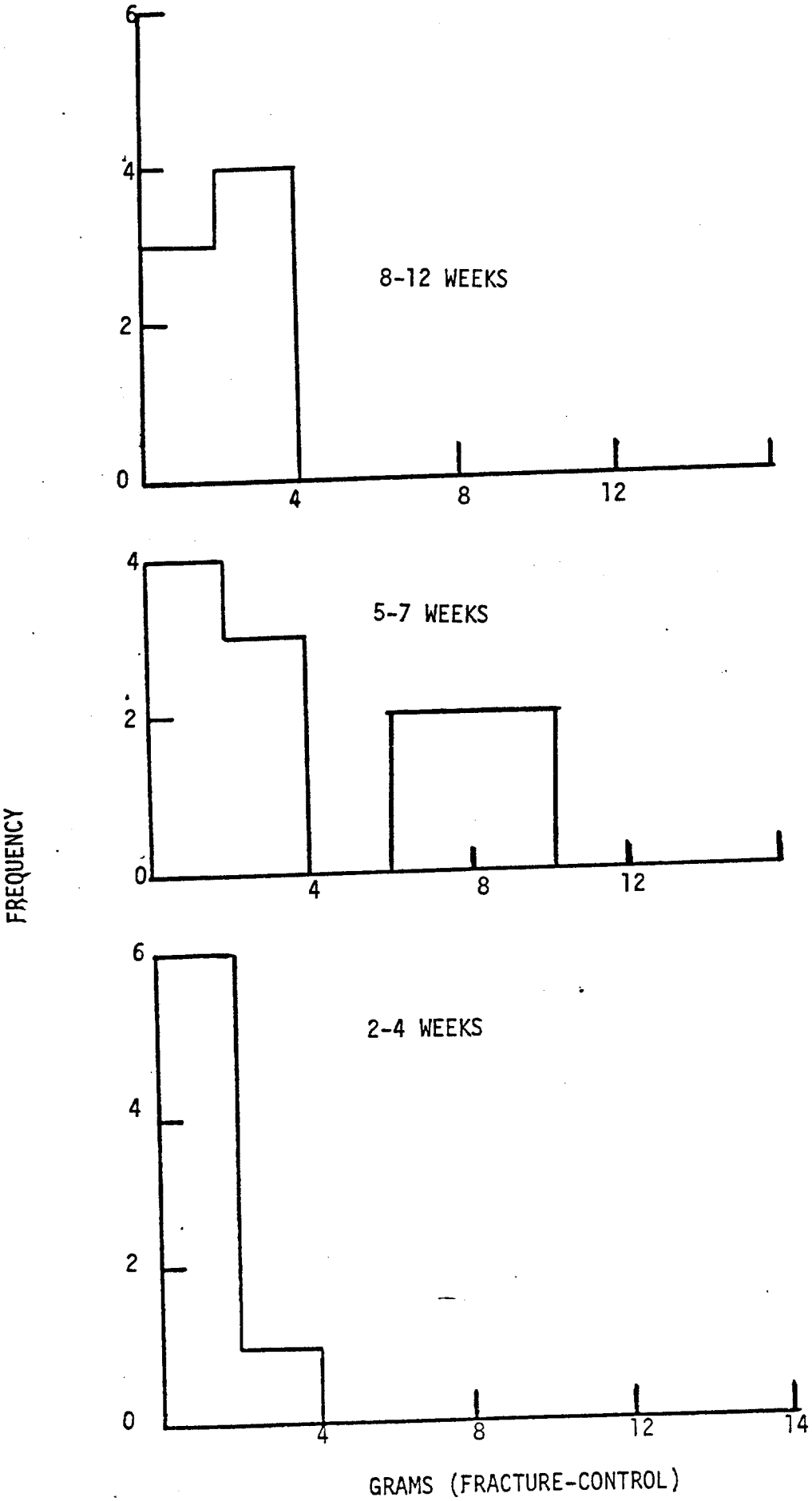


Figure 4. Bone mineral content in healing bone as a function of time after fracture

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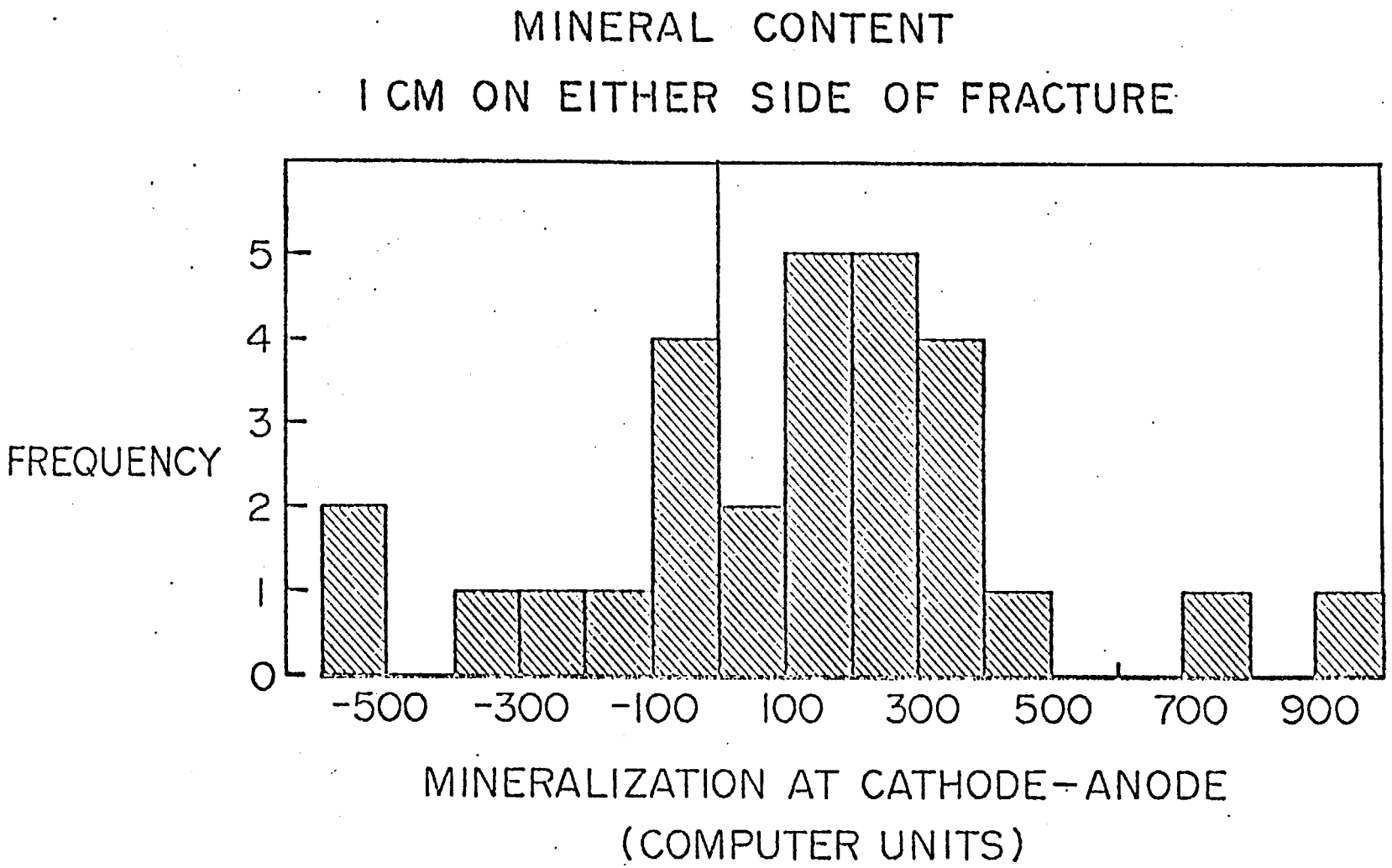


Figure 5. Bone mineral content of fractured dog bones undergoing electro stimulation healing

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changes in patients suffering from a variety of bone diseases, on and off therapy. During the next year we propose to continue these studies and increase the number of subjects studied considerably.

(1) Normals

Studies to date have largely been directed toward measuring the relative rate of bone mineral changes. We were restricted to relative measurements in part because we were using a single photon measurement. These measurements did not correct for soft tissue variations and could not be related to an absolute standard. The measurements we are now making utilize the dual photon properties of Gd-153; and, consequently, we are capable of making absolute estimates of bone mineral content independent of soft tissue variations. We propose to study a group of normal volunteers from the hospital staff and to begin establishing normal values of regional and total-body bone mineral content. These normal ranges must, of course, be functions of age, sex, weight and height.

(2) Osteoporosis and Paget's disease

We have been working closely with the physicians in the Department of Endocrinology, in particular Dr. McKenna, to study persons afflicted with disease resulting in bone demineralization. We propose to continue this relationship and to study as many patients as are made available to us. At this time we have made initial measurements and will continue to make monthly measurements on six patients. Results from these measurements are shown in Table 2. A plot showing the normal distribution of these quantities as measured at the University of Wisconsin is shown in figure 6 for comparison.

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Immobilized patients, such as paraplegics and quadriplegics, are known to lose body calcium at increased rates. In patients immobilized for long times, significant complications relating to calcium losses are

TABLE 2

BONE MINERAL CONTENT

PATIENT	AGE	BONE MINERAL MG/CM^2	NORMAL VALUE
A(OSTEOPOROSIS)	35	349	510
B(")	50	458	500
C(HYPERTHYROIDISM)	47	463	500
D(OSTEOPOROSIS)	61	597	450
E(")	70	444	400
F(OSTEOPOROSIS)	35	356	510

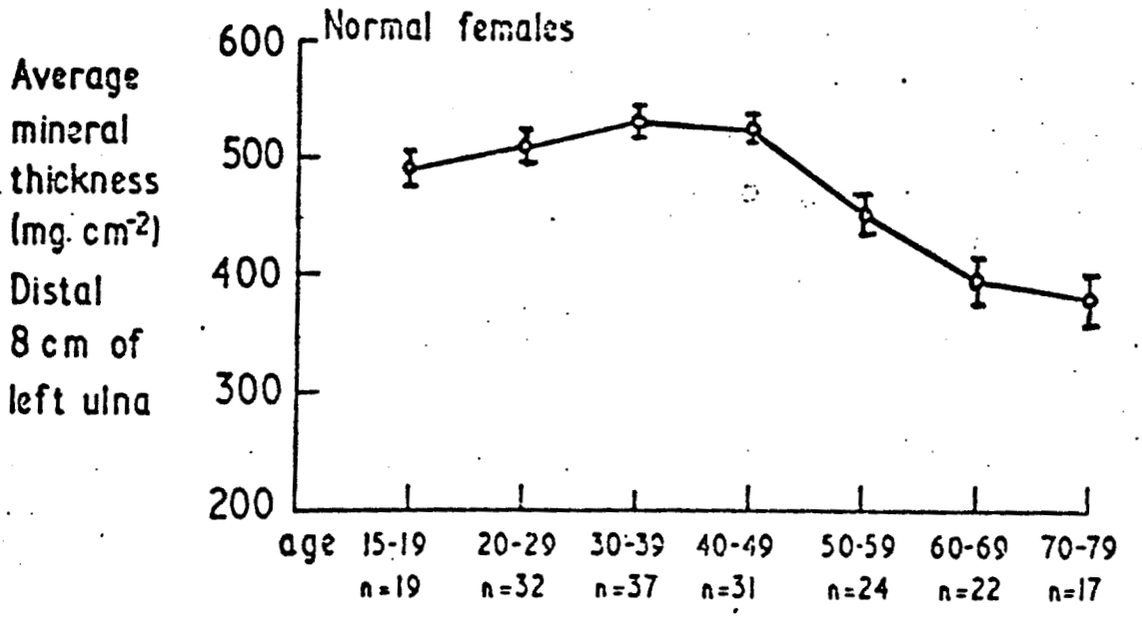
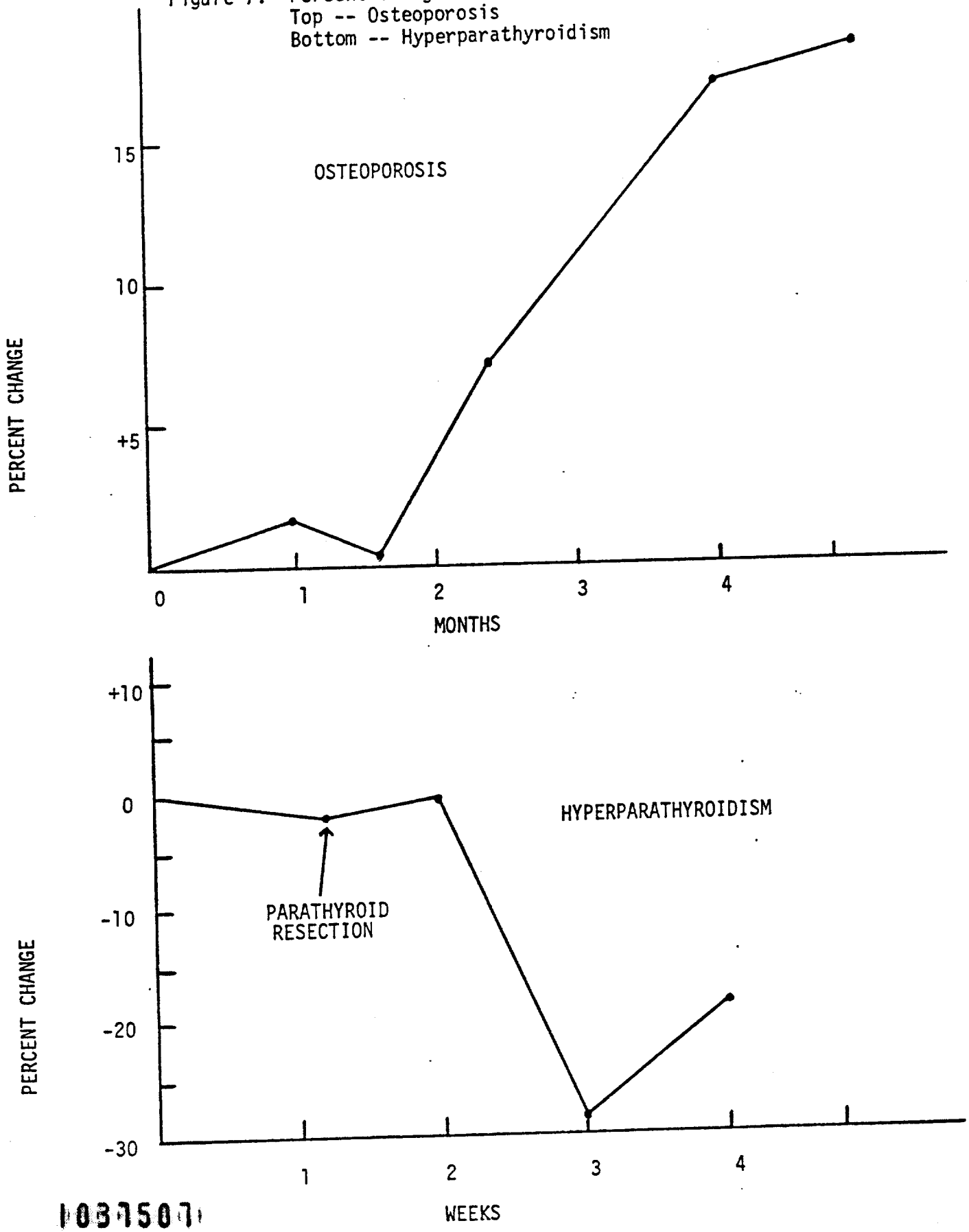


Figure 6

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Figure 7. Percent change of bone mineral content
Top -- Osteoporosis
Bottom -- Hyperparathyroidism



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encountered and suitable therapy, including mobilization, is needed to reverse this process. As an example of some of our studies, we are making a series of measurements in (1) a 61-year-old female osteoporotic and (2) a 47-year-old female with primary hyperparathyroidism. The results of these measurements are shown in figure 7 .

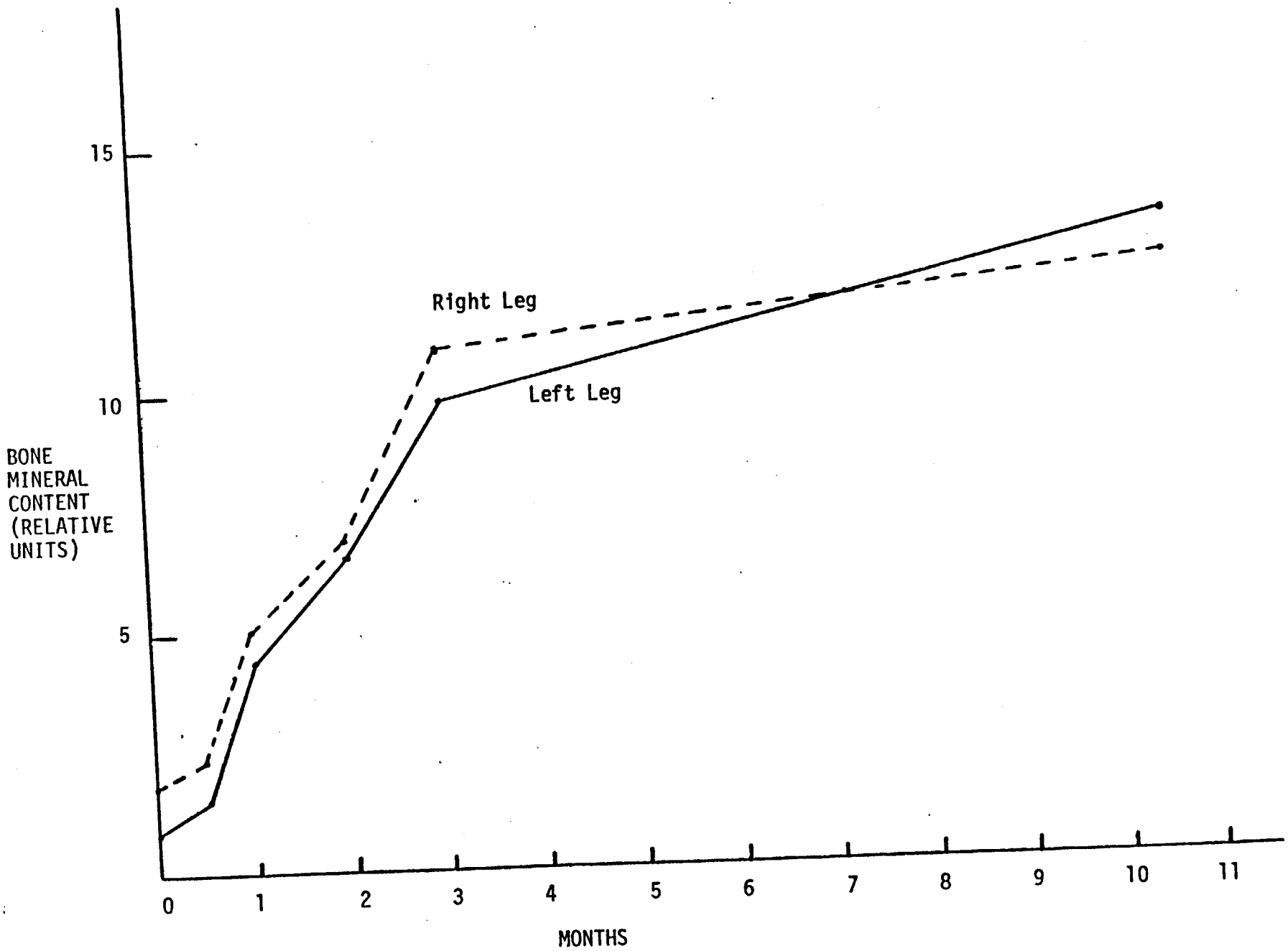
The osteoporotic patient was placed on fluoride containing compounds at the start of the measurement series and showed a progressive increase in bone mineral content. The second patient, having had her parathyroid gland removed shortly after the initial measurement, continued to lose calcium from her extremities for approximately one month. At that time she began to show increased mineralization. These studies will be continued and extended to as many disease states as become available to us.

(3) Osteogenesis imperfecta

During the last year we have been making sequential measurements on children suffering from osteogenesis imperfecta. Patients with this hereditary disease are subject to frequent bone fractures due to poor bone formation and composition. These patients are being followed in an attempt to assess the efficacy of treatment with fluoride-containing compound. Data on a 16-year-old female patient is shown in figure 8. This patient was maintained as an in-patient for the first month after the start of treatment with fluoride. She was then maintained on fluoride for the next ten months at a reduced level. During this time she remained at home except for short visits back to the hospital. The measurements show a dramatic increase of over 25% over the pretreatment value.

These measurements are very encouraging and will be continued in approximately ten patients during the next year. These studies will be carried out in collaboration with Dr. Joe McKenna of the Department of Endocrinology and Dr. Griffin of the Department of Orthopedic Surgery.

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Figure 8. Relative bone mineral content in 16-year-old female with osteogenesis imperfecta

c. Iron metabolism and dosimetry in abnormals

(1) Clinical utility of Fe-59

We have been carrying out research studies over the past three years using Fe-59 to determine ferrokinetic parameters in abnormal subjects. These efforts continue to yield rewarding clinical data. Although in the past this isotope has not been used widely for clinical studies because of difficulty in collimation and dosimetric considerations, we believe that with the use of proper instrumentation and analysis techniques it can be shown to be a clinically useful diagnostic agent for a variety of disease states. As an imaging agent it can be used to image the active bone marrow sites as well as identify abnormal liver or spleen activity. The same injection used for imaging can also be used for routine plasma disappearance and red blood cell incorporation measurements, which is not possible with Fe-52.

(2) Specific studies

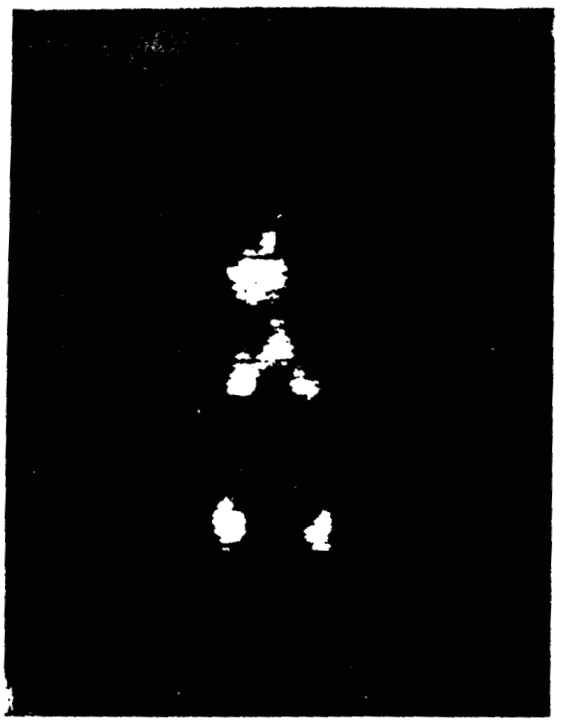
(a) Red cell aplasia

We have been working closely with Dr. Sanford Krantz in the Department of Hematology during the last year in an effort to study and characterize the early stages of the disease in patients with isolated red cell aplasia. Dr. Krantz has studied a number of patients with this rare disorder and has noted that the metabolism of iron and the symptoms presented by the disease change drastically with time. We propose to monitor individual patients (to determine metabolic parameters) periodically so that we might characterize iron metabolism in the different stages of the disease.

As an example of how different the disease may appear, figure 1 shows Fe-59 scans of two patients with known red cell aplasia. Scan A, representing an early phase, is characterized by symptoms of ineffective marrow function. The scans revealed poor marrow function, large liver

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(B)



(A)

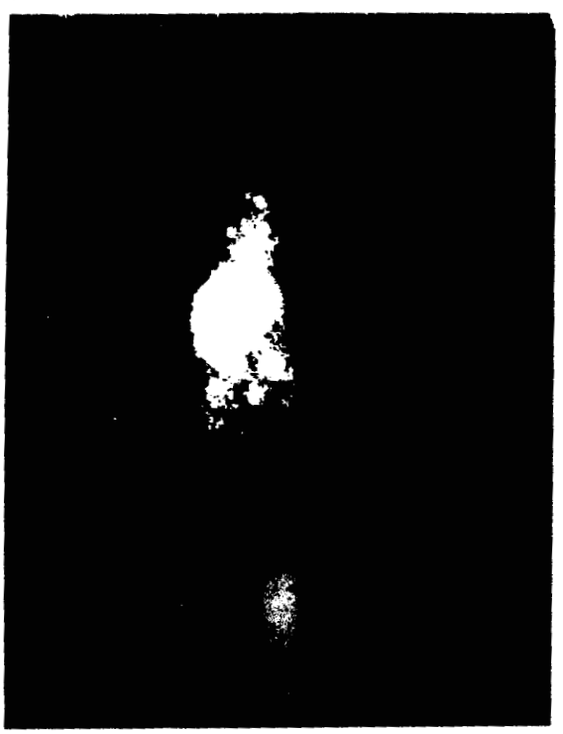


Figure 1. Red Cell Aplasia Patients (B) Late Stages and (A) Early Stages

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uptake and a plasma disappearance of almost two hours. Scan B represents a late phase where the patient presents no clinical symptoms, the iron turnover is increased (plasma disappearance of about 30 minutes), and there is expanded marrow function.

(b) Hodgkin's disease

We propose to investigate the usefulness of Fe-59 total body scans for the purpose of determining marrow function and assessing bone marrow reserve. This problem comes up repeatedly in the therapy of patients with tumors, especially Hodgkin's disease and malignant lymphomas when it is necessary to decide whether further radiation therapy or chemotherapy can be tolerated.

The combination of total body iron scans and RBC incorporation measurements provides an assessment of regional marrow function and efficacy of iron utilization.

We propose to measure these parameters in Hodgkin's patients prior to therapy and at times during and after therapy when management problems arise and patients are referred for evaluation.

(c) PNH

Vanderbilt (Division of Hematology) has a very large number of PNH patients under careful study. We have made long term measurements in two patients and have carried out an extensive SAAM-25 analysis. The model used for these studies is shown in figure 2.

We propose to continue these studies in cooperation with Dr. Krantz and Dr. Hartman in a number of new patients. The major question that we would like to answer is: What is the metabolism of the iron stored in the kidneys? The results of earlier studies indicated that this iron may be made available for reutilization, but this question has not been fully resolved and needs to be pursued further in a systematic manner in a larger

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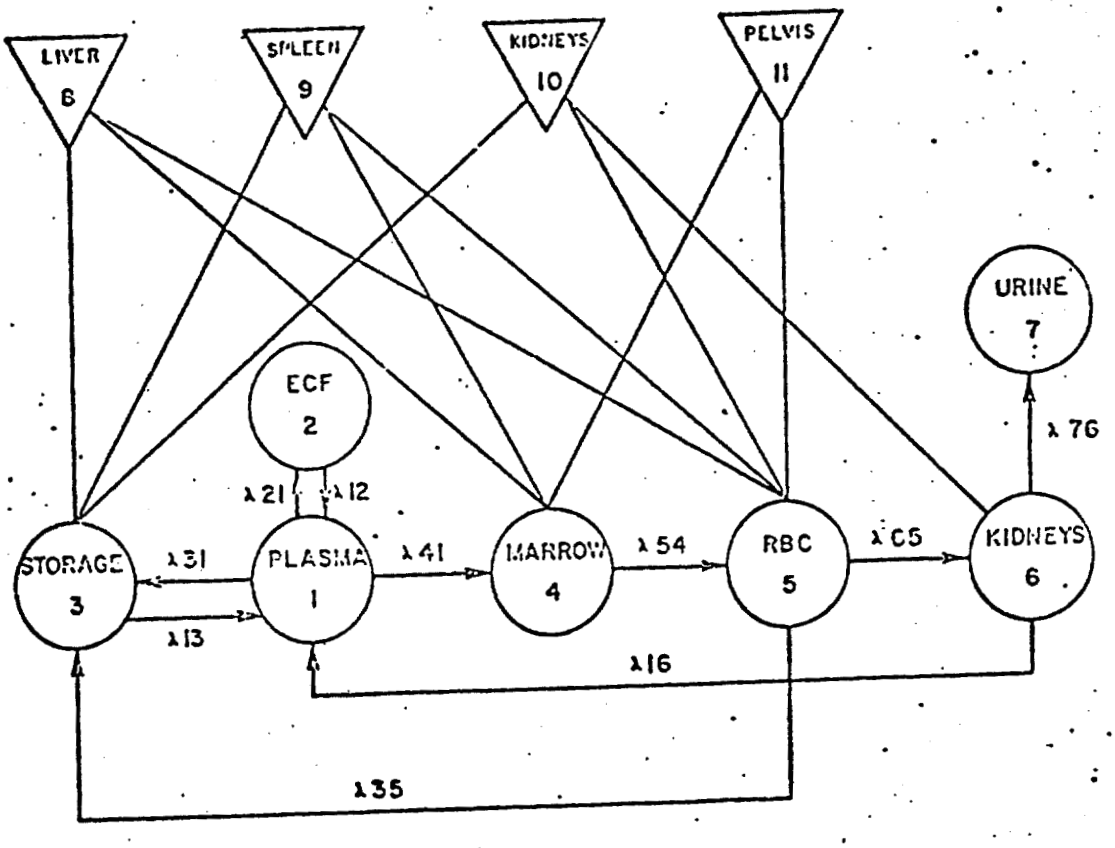


Fig. 2 . Schematic of SAAM-25 model used in PNH studies.

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number of patients. We propose to study an additional 2 - 5 patients with PNH in the coming year.

d. Iodine metabolism and dosimetry in I-131 therapy

During the past two years the Bureau of Radiological Health has supported a study whose goal was to obtain dosimetry data on carefully studied patients included in the PHS(BRH)-sponsored cooperative thyrotoxicosis therapy follow-up study. The calculation of the radiation-absorbed dose to the thyroid was carried out by means of non-linear compartmental analysis using SAAM-25. The model parameter describing the uptake rate of radioiodine in the thyroid was assumed to be a function of the number of active thyroid cells. The number of cells was, in turn, assumed to be dependent upon the cumulative radiation dose. The biological sensitivity function, chosen on the basis of a very limited amount of data, was initially assumed to be exponentially dependent upon the cumulative dose with exponential constant equal to 0.0001; i.e., the active thyroid tissue falls to 1/e or 37% of its initial value for a dose of 10,000 rads. Other functions are currently under investigation.

By and large we have achieved the stated goals of the study; however, in light of new data just made available to us, we feel these model calculations can be significantly improved. These new data were made available to us by Dr. Brown Dobyns of the Cleveland Memorial General Hospital and include measurements on blood levels of MIT, DIT and thyroglobulin (TG), in addition to the already available measurements of PBI, T3, T4, urine and thyroid activity. The importance is that the kinetics of MIT, DIT, and TG reflect thyroid radiation damage directly and consequently will not only yield a more reliable model calculation but will also yield valuable information on the time course of radiation damage and degree of biological sensitivity of the thyroid gland to radiation dose levels. We propose to in-

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vestigate these questions by extending the model we are currently using to include the additional measurements. The following paragraphs will briefly describe the current model and some of our progress to date.

We have fit data from 60 hyperthyroid patients undergoing I-131 therapy with a four-compartment, time-dependent, non-linear kinetic model which allows for diminution of thyroid uptake as a function of the cumulative radiation dose to the thyroid. The parameters deducible from this model are the estimated radiation dose to the thyroid, the thyroid uptake rate, PBI secretion rate, PBI degradation and fecal excretion rates and the daily iodide urinary excretion rate as well as the apparent volumes of distribution of the iodide and PBI pools. The data fitting was performed by the computer program SAAM-25 developed by Dr. Mones Berman and his associates for simulation, analysis, and modelling of biological data. The data used was made available by Dr. Brown Dobyns of the Cleveland Metropolitan General Hospital and the Bureau of Radiological Health.

The model of iodine kinetics is sketched below (Fig.1). The circles, arrows, triangles and dashed lines represent, respectively, the compartments, flow rates (λ_{ij}), observations and proportionality factors (σ_{ij}). Two compartments are used to simulate the thyroid: the rapid phase (compartment 4) and the storage phase (11). Both compartments provide hormone secretion as well as the "iodide leakage." A pseudo-compartment (10) has been included to calculate the cumulative radiation dose to the thyroid. This compartment is a mathematical device and does not affect the other model parameters. The meaning associated with each fractional flow rate is as follows:

$\lambda_{4,1}$ (iodide to rapid turnover compartment)
$\lambda_{1,4}$ (rapid leakage to iodide compartment)
$\lambda_{11,4}$ (rapid turnover to storage compartment)
$\lambda_{5,11}$ (delayed hormone secretion to PBI, from storage)
$\lambda_{1,11}$ (delayed leakage to iodide from storage)
$\lambda_{1,5}$ (deiodination of PBI)
$\lambda_{5,4}$ (rapid hormone secretion to PBI)

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The mean values and standard deviations of the various flow rates for the total group studied to date are shown in Table 1.

Extensive statistical calculations have been carried out investigating all possible correlations between the cumulative radiation dose to the thyroid and the derived model parameters.

Factor analysis calculations relating pairs of flow rates to the cumulative dose gave rise to three major factors characterizing the model results. These can roughly be summarized as 1) thyroid uptake rate, 2) hormone secretion rate, and 3) delayed thyroid-iodide leakage.

Regression analysis has yielded the most important relationships relating cumulative dose to model parameters. Of these the most useful for dosimetry purposes is the following:

$$\text{cumulative thyroid dose} = K \times (\lambda_{4,1})^{1/3}, \qquad (1)$$

where K is a constant and $\lambda_{4,1}$ is the flow rate from the iodide pool to the rapid thyroid compartment. This regression equation was found to account for approximately 95% of the variance and provides an extremely simple relationship which can be used to estimate radiation dose to the thyroid based upon information from a diagnostic kinetics study.

A number of statistical analyses have also been made relating the absorbed dose to diagnostic measurements. In general, we have investigated correlations between the radiation dose as estimated by the model calculation and the four quantities: thyroid uptake, PBI activity, serum activity and urinary excretion. The most significant relationship arising from the multiple regression analyses is the direct linear relationship between cumulative dose and the 24-hr thyroid uptake measurement. The formula:

Dose = constant x 24-hr thyroid uptake,

accounts for 97% of the total variance and leads to the relation:

$$\text{mCi/rad} = \frac{0.0012 \times \text{thyroid wt in grams}}{\%\ \text{24-hr uptake}} \qquad (2)$$

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The advantage of this equation over equation 1, in terms of simplicity, is obvious. In order to make dose estimates prior to radioiodine therapy, one needs only the diagnostic 24-hr uptake measurement and the mass of the thyroid. In fact, these calculations agree very closely with relationships calculated using classical formalism and assuming a 5.5-day effective half-time for iodine in the thyroid in hyperthyroidism. Until you go to very high doses, the disparity between dosimetry predictions based upon diagnostic studies and the actual behavior of the therapeutic dose is not of major importance, and certainly is less uncertain than the weight estimate for the thyroid gland.

Nonetheless, we do want to extend the model to include the effects of therapy upon release of MIT, DIT, and TG from the gland because this is a radiobiologically interesting problem.

The four-compartment model described above will be expanded by replacing the single compartment representing the single compartment representing PBI by a number of parallel compartments in order that the new data on T3, T4, MIT, DIT and butonal-insoluble thyroglobulin may be accomodated. The proposed seven-compartment model is shown in figure 2.

We will use the data obtained by Dr. Brown Dobyns for these studies and will attempt to correlate the findings obtained from the model studies with the extensive clinical information he has on these subjects.

e. Massive obesity

The jejunoileal bypass operation has been shown to be an effective means of causing weight loss in morbidly obese patients by inducing malabsorption. In collaboration with Dr. H. William Scott of the Department of Surgery, we have studied 62 patients who received different types of small-bowel-bypass operations in an effort to assess the effect on weight loss and body composition.

(03-81-11)

TABLE 1

IODINE KINETICS PARAMETERS

Flow Rate	Average Value	Standard Deviation
$\lambda_{4,1}$	2.42	2.20
$\lambda_{5,4}$	0.0495	0.0764
$\lambda_{1,4}$	0.173	0.225
$\lambda_{11,4}$	0.733	0.616
$\lambda_{5,11}$	0.0096	0.0096
$\lambda_{1,11}$	0.0367	0.0430
$\lambda_{1,5}$	0.087	0.004
$\lambda_{6,1}$	1.25	0.80
$\lambda_{0,5}$	0.12	0.08

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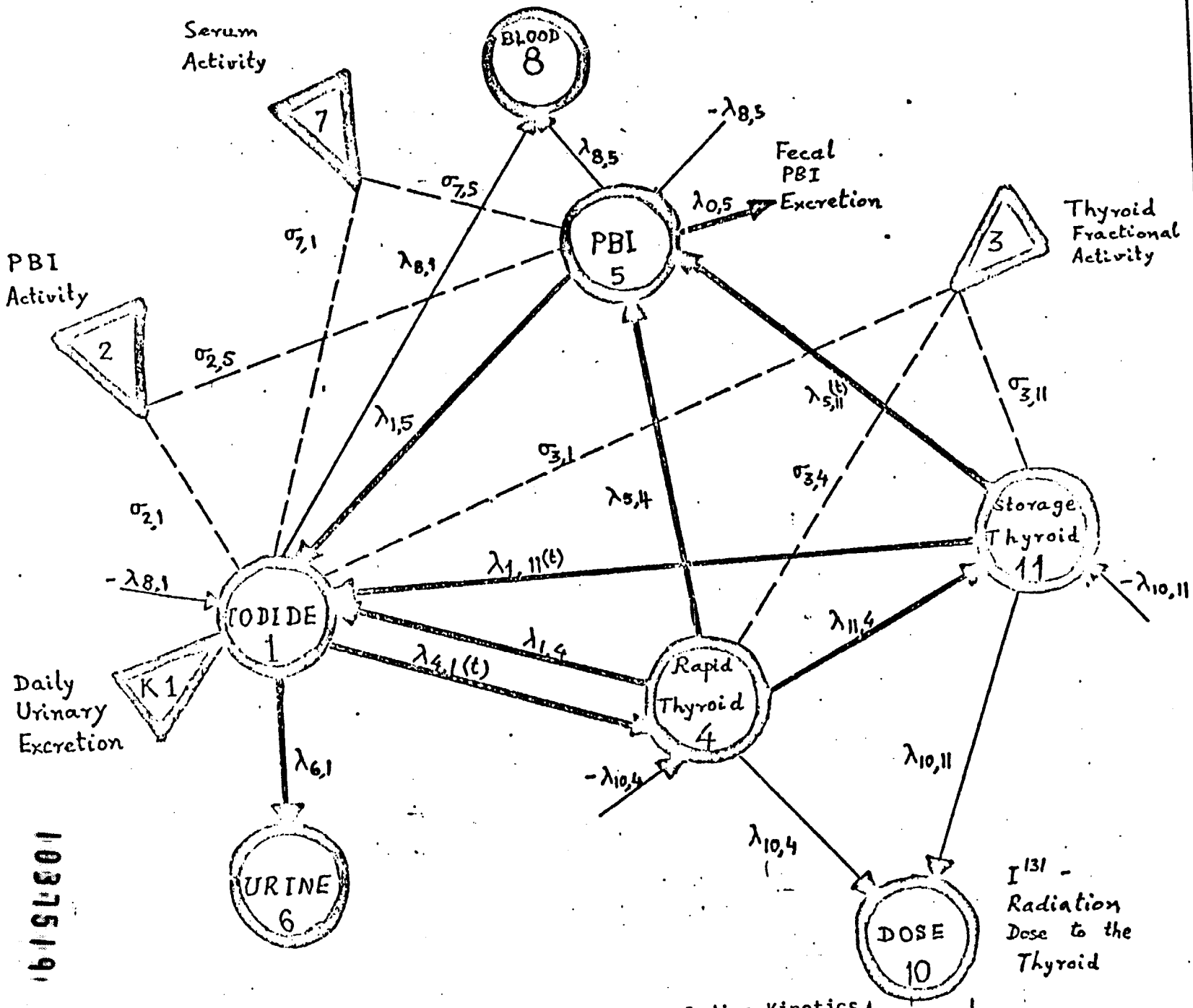


Figure 1. Four compartment SAAM-25 model for Iodine Kinetics.

$V_1 = 0.16\,\omega_b(\ell)$.

$V_5 = 0.06\,\omega_b(\ell)$.

$\sigma_{7,1} = 1/V_1$.

$\sigma_{7,5} = 1/V_5$.

$\sigma_{2,5} = 0.92\,\sigma_{7,5}$.

$\sigma_{3,4} = 1 = \sigma_{3,11}$.

$K1 = \lambda_{6,1}$.

$\lambda_{4,1}(t) = \lambda^{\circ}_{4,1} e^{-G_5 \int(\cdot,\cdot)} \cdot e^{-0.086t}$

$G_5 = 10^{-4}$.

$\lambda_{1,11}(t) = \lambda^{\circ}_{1,11} + G(2)$,

$\lambda_{5,11}(t) = \lambda^{\circ}_{5,11} + G(3)$,

$\frac{\lambda_{1,4}}{\lambda_{5,4}} = \frac{\lambda^{\circ}_{1,11}}{\lambda^{\circ}_{5,11}} = \frac{G(2)}{G(3)} = \tau$,

$G(2) = \zeta\, G_5\, \lambda_{10,11} \int(11,t) \times e^{-0.086t} e^{-G_5 \int(10,t)}$

where

$\zeta = \frac{\lambda_{1,4}}{\lambda_{1,4} + \lambda_{5,4}} = \frac{\tau}{1+\tau}$, $\tau = \frac{\lambda_{1,4}}{\lambda_{5,4}}$

τ : 0.1 – 25.0.

$\lambda_{10,4} = \lambda_{10,11} = y\,\sigma_{3,4}$,

$y = 10.6\,\frac{d(\mu Ci)}{\omega_{th}(g)}$.

$\lambda_{8,i} = \lambda^{\circ}_{8,i} e^{-0.086t}$

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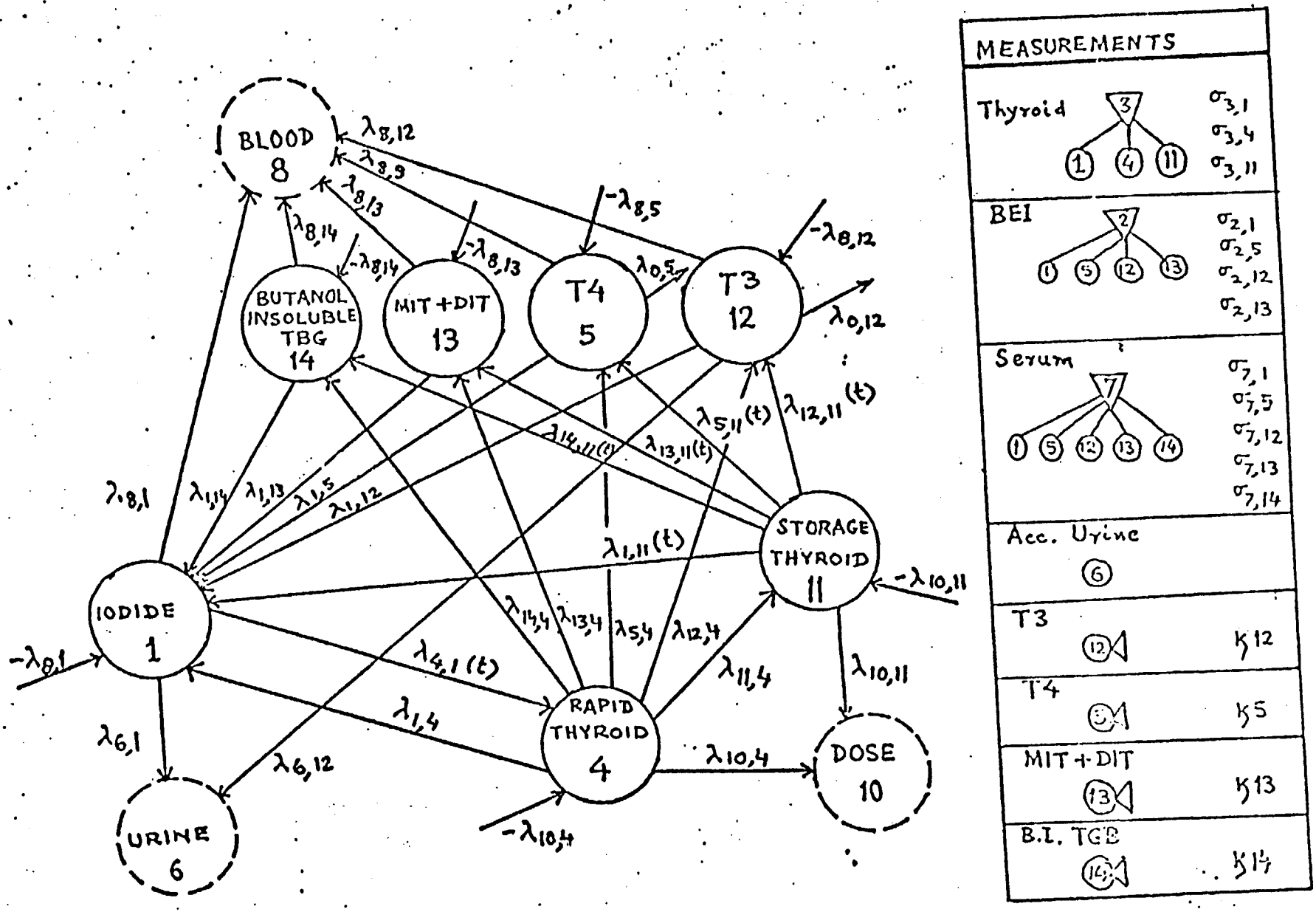


Figure 2. 7- Compartment Model.

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In addition to the usual methods of metabolic appraisal, lean body mass (LBM) was measured before and at intervals after jejunoileal bypass. Two types of measurement of LBM are being made: (1) from K-40 whole-body counting, and (2) from $^{3}H_2O$ spaces. LBM derived from K-40 whole-body counting has been found to be the preferred method because it is easy to measure on an outpatient basis and requires no added radiation dose.

As described in an earlier report (1969), the whole-body scanner operating in the exposed crystal mode has been calibrated with known amount of K-40 so that the cpm from a patient can be translated into milliequivalents of K and LBM (LBM in kg = mEq. K/68.1). In order to establish the reproducibility of the technique, daily measurements were made in a small group of normal subjects. The data from two of these subjects are shown in Figure 1. For subject A the coefficient of variation was 3.7% while the value was 5.1% for subject B.

To date five different surgical procedures have been used. Measurements are being made on patients grouped according to operation type. Group parameters describing weight loss and LBM as a function of time post-operation are being compared. The numbers of patients included in each study group are shown in Table 1.

TABLE 1

Operation Type	Number of Patients
I	9
II	9
III	2
IV	16
V	26

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Groups I through IV are currently under study and have had numerous follow-up measurements made. Group V patients have most recently undergone surgery and, at the present time, have had only baseline measurements. Group III included only two patients. For this reason we have chosen to present the data but will not include group III in the comparisons.

Figures 2, 4, 6 and 8 show the plot of the time course of the body weight as a percent of the pre-operative weight for patients in groups I through IV, respectively. The group average values are also indicated. All groups were found to lose weight dramatically during the first year after surgery. The group average for Type I tended to reach a plateau at about 70% of baseline weight by the second year. Groups II and IV, although having less follow-up data, appear to be following the same general pattern. There is some indication that group IV may reach a slightly lower plateau level (~65%).

Figures 3, 5, 7, and 9 are the graphs of the LBM as a fraction of the body weight. The behavior of the group mean values are summarized in Table 2. Initially, for all three types of operations, the LBM fraction increases with time. Types I and II measurements appear to reach a new elevated plateau during the third year after the operation. Type IV patients (based on measurements out to 20 months) appear to be increasing the LBM ratio at a faster rate and show no evidence of plateauing at this time.

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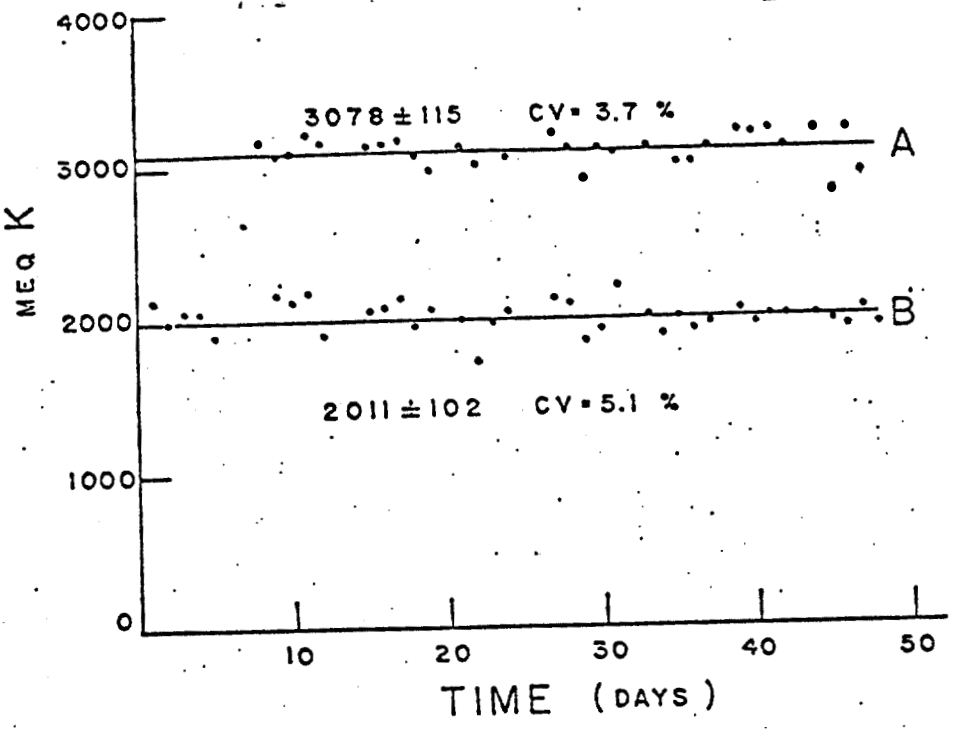
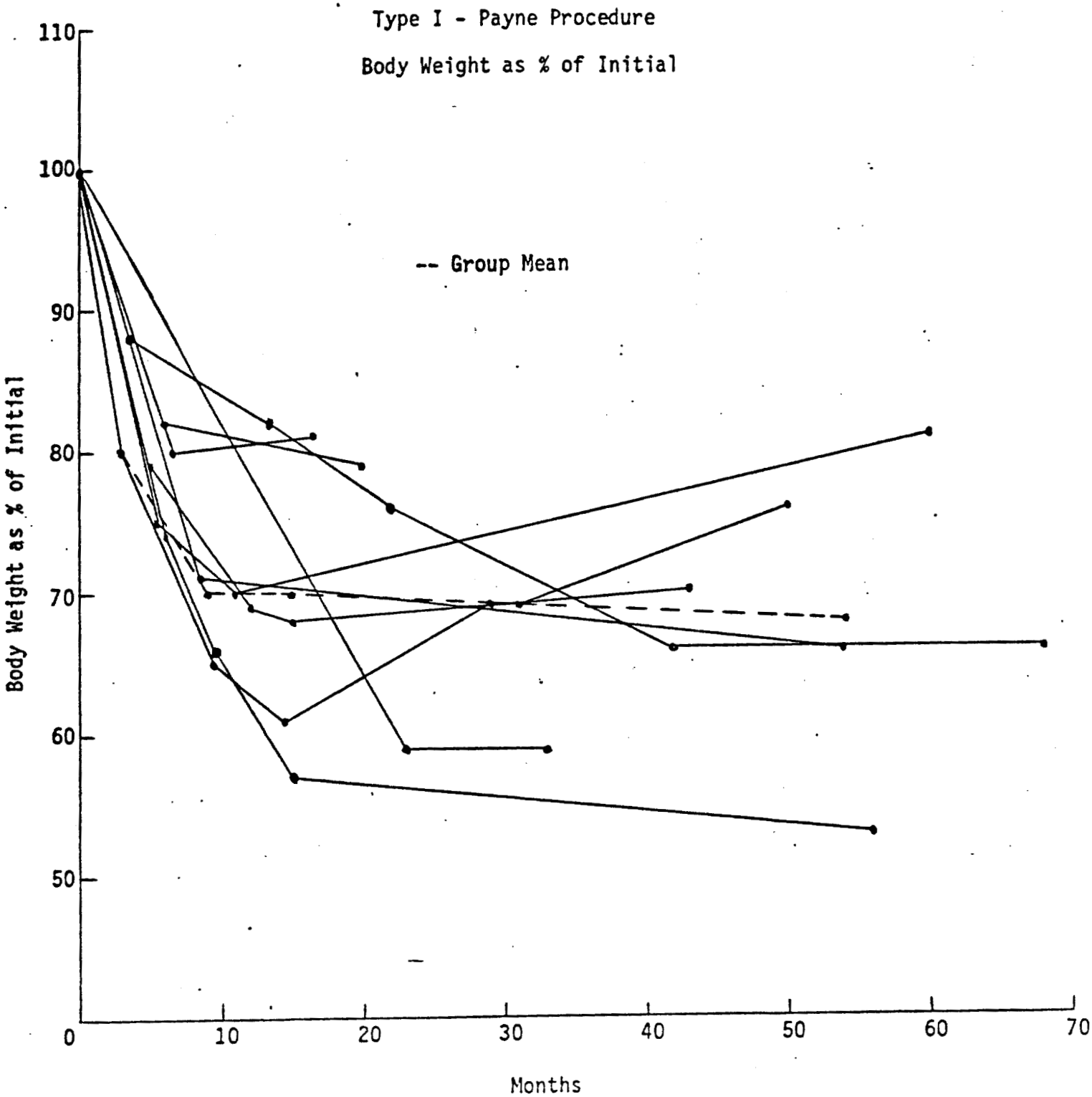


Fig. 1. Repeated measurements of total body potassium for two normal patients.

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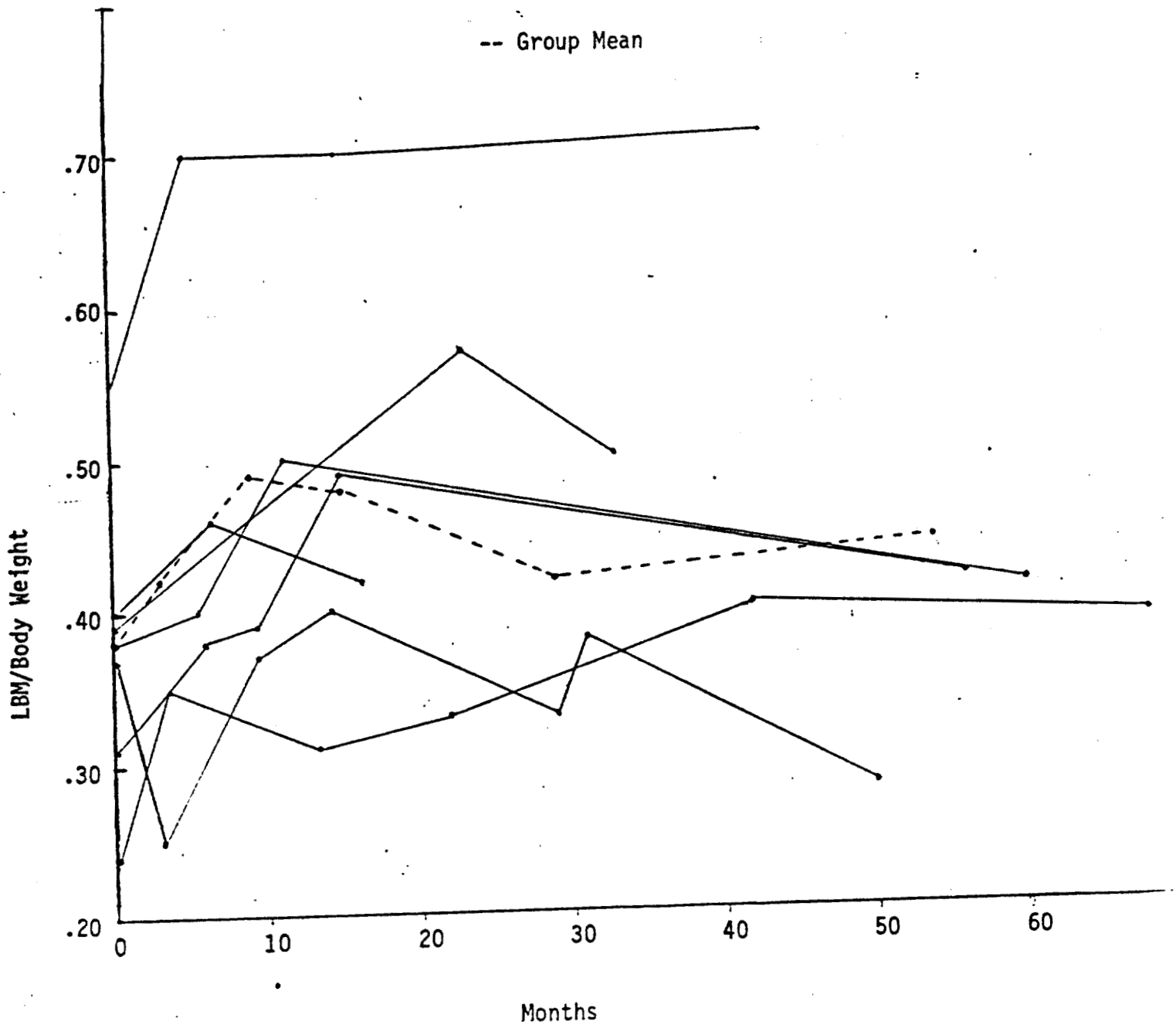


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Figure 2

Type I - Payne Procedure

LBM as Fraction of Body Weight



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Figure 3

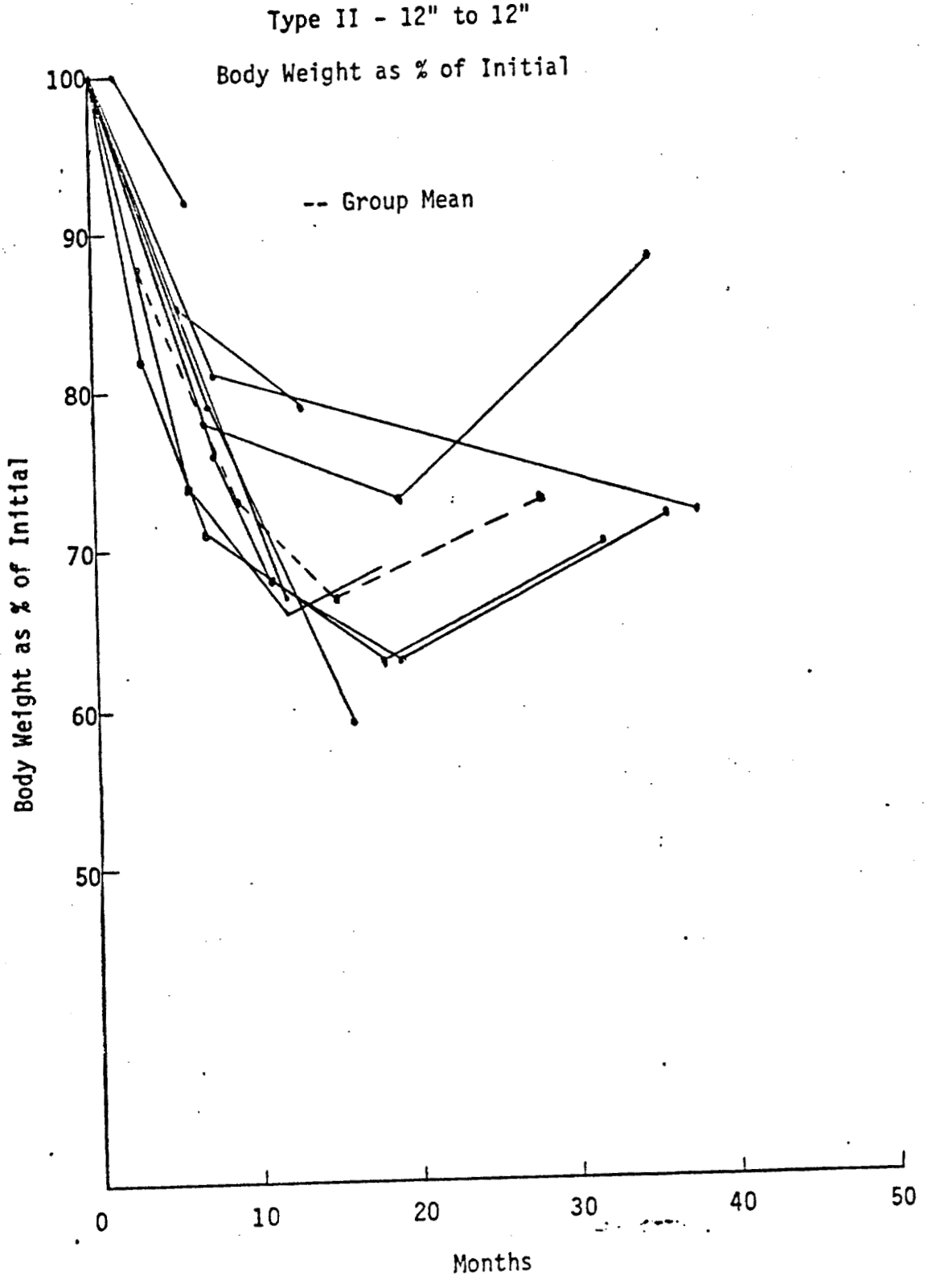
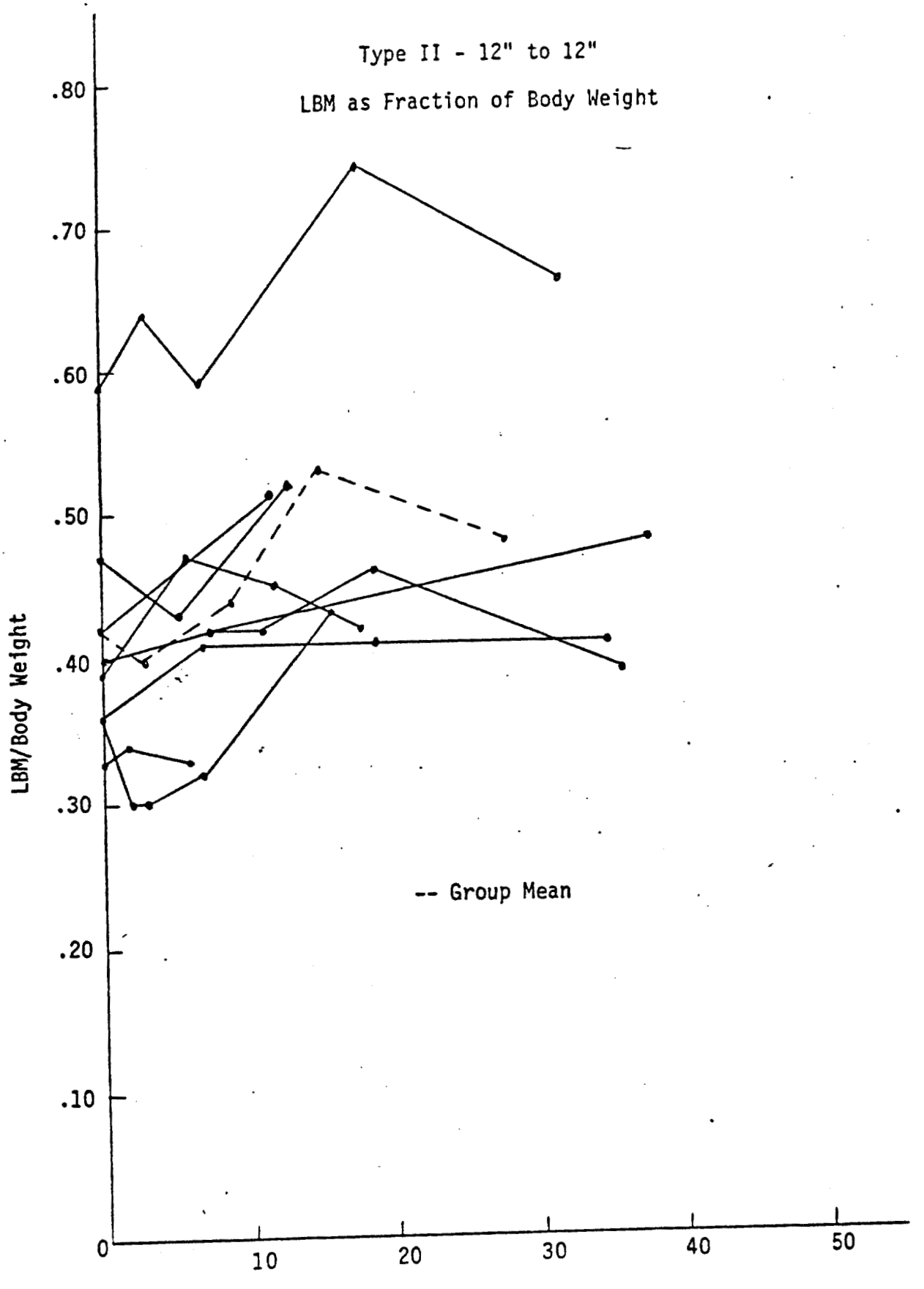


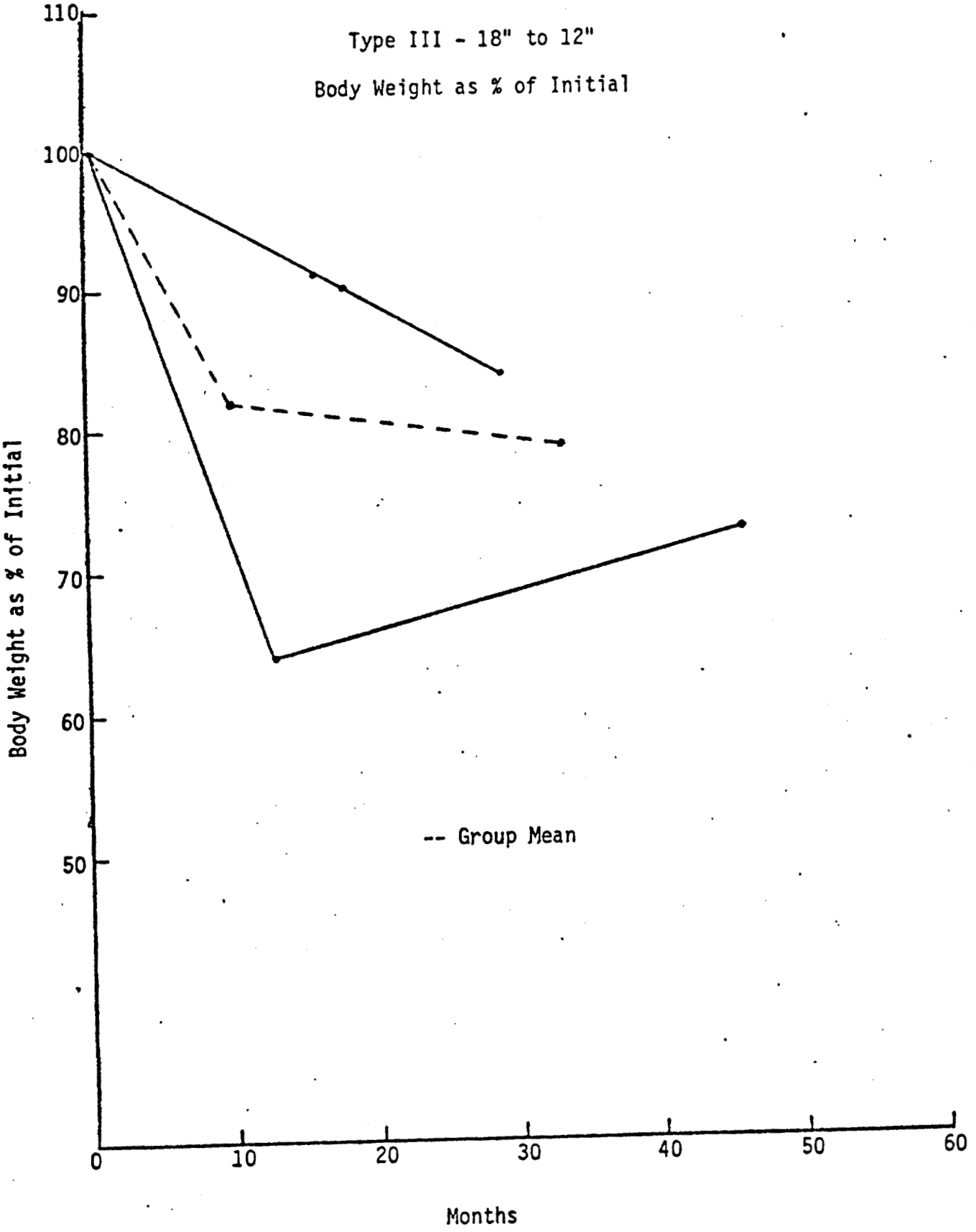
Figure 4

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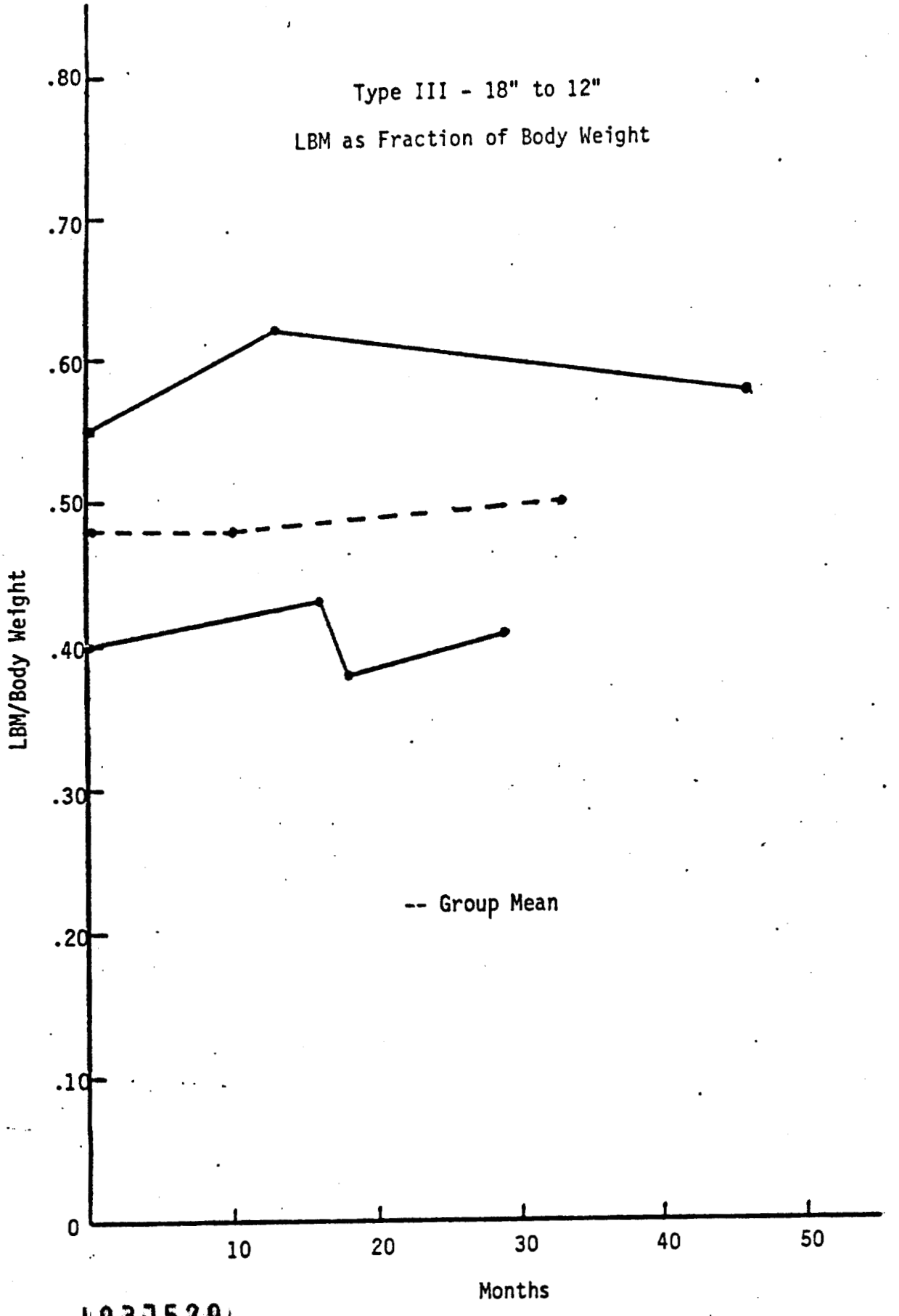
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Figure 5



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Figure 6



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Figure 7

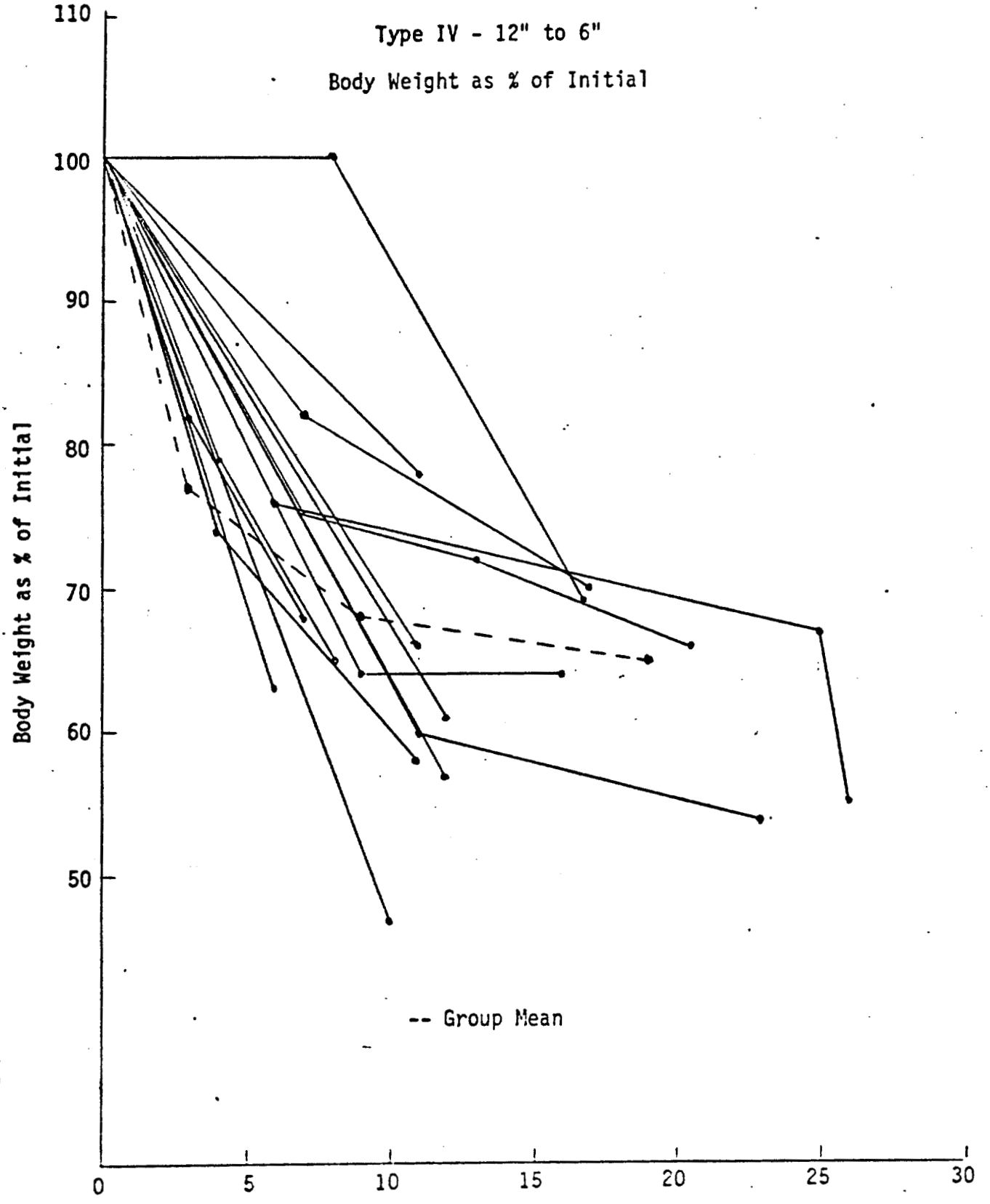

Type IV - 12" to 6"
Body Weight as % of Initial
Body Weight as % of Initial
110
100
90
80
70
60
50
0
5
10
15
20
25
30
Months
-- Group Mean

Figure 8.

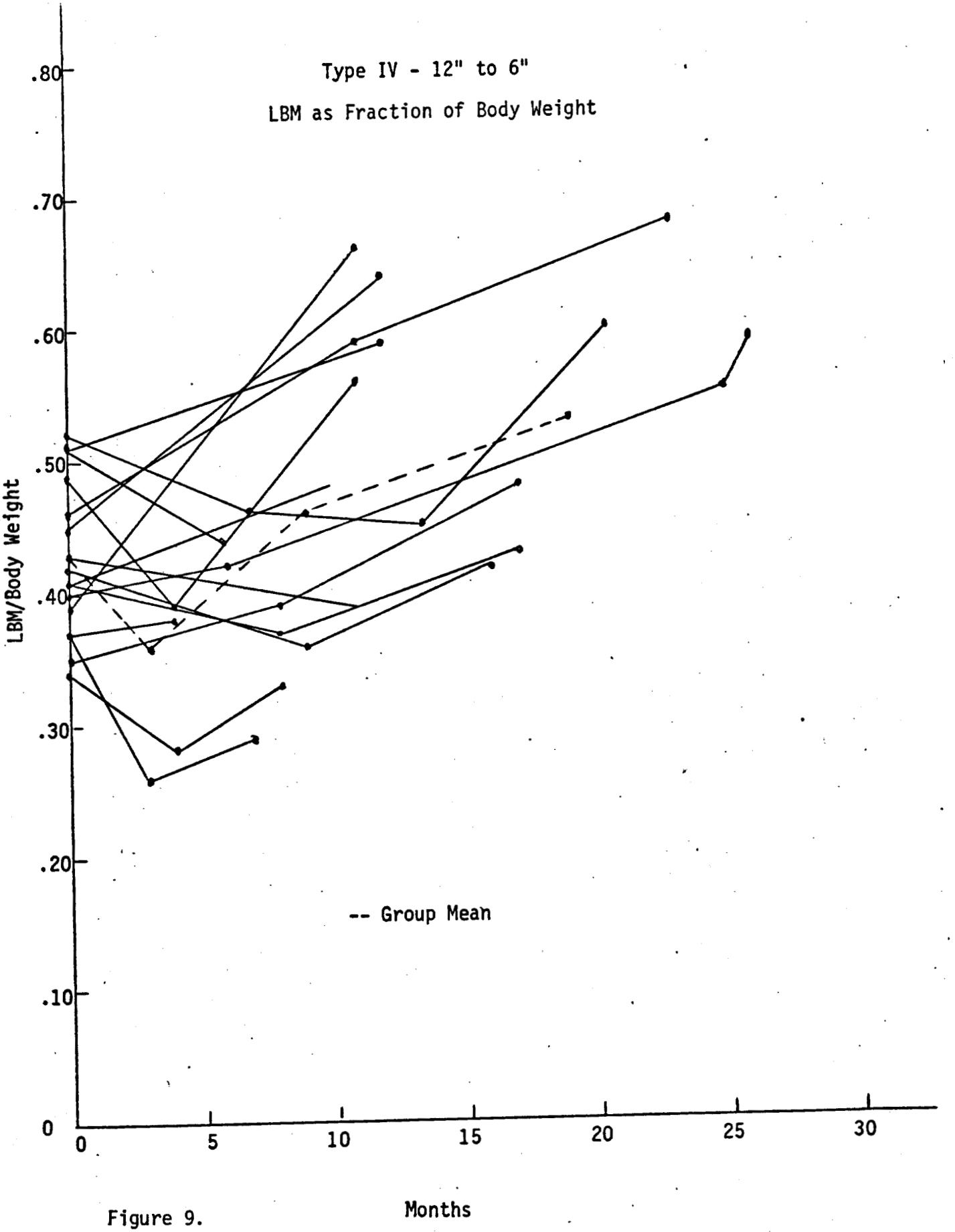

Type IV - 12" to 6"
LBM as Fraction of Body Weight
LBM/Body Weight
.80
.70
.60
.50
.40
.30
.20
.10
0
0
5
10
15
20
25
30
Months
-- Group Mean

Figure 9.

TABLE 2

LBM/BODY WEIGHT

	Initial	10 months	20 months	30 months
Type I	0.38	0.49	0.46	0.42
Type II	0.42	0.45	0.51	0.48
Type IV	0.43	0.47	0.53	--

We propose to continue to follow these patients during the next year. Thirty-month follow-up measurements will be made on patients receiving Type IV procedure, and more Type V follow-up data will become available. In addition, we propose to correlate fat-free body (FFB) as estimated for these patients from tritiated water measurements with the LBM measurements. This correlation should yield additional information on the compatibility of these two measurements.

f. Monitoring of Cs-137 levels in man

Almost three years ago we resumed a program started in 1959 by Meneely, et al to monitor the Cs-137 levels in a population of normal individuals. At that time we derived a preliminary calibration equation for the steel room whole-body scanner when used in the exposed crystal mode. We made measurements on a small group of young male subjects who were studied earlier by Meneely, et al. At that time we found about a twofold decrease in total body burden of Cs-137 from the 1966 Nashville population value.

Last year we recalibrated the system in order to make the most accurate measurements possible. In this recalibration procedure we used the Cs-137 levels as determined for three normal males by the Brookhaven National Laboratory's whole-body counting system as absolute normalization for our system. Using the new calibration equations, we have continued to monitor subjects from the middle Tennessee area including those from the

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earliest studies (1959). Our measurements shown in figure 1 are compared to data reported in Health Physics for Oak Ridge Y-12 employees. The mean values for the last three years continue to decrease from the Nashville 1966 value of approximately 10 nanocuries. The rate of fall during the past year is, however, diminished from the previous year's measurement thus suggesting that a plateau might have been reached. The mean value for the past year's measurements was found to be 3.00 ± 1.40 nanocuries. This value was based upon a study sample of 52 individuals.

We propose to continue these measurements and will make an effort to include as many studies as possible from the earliest (1959) study group. In addition, we will monitor those patients described in section e. The addition of this group will increase our statistics greatly.

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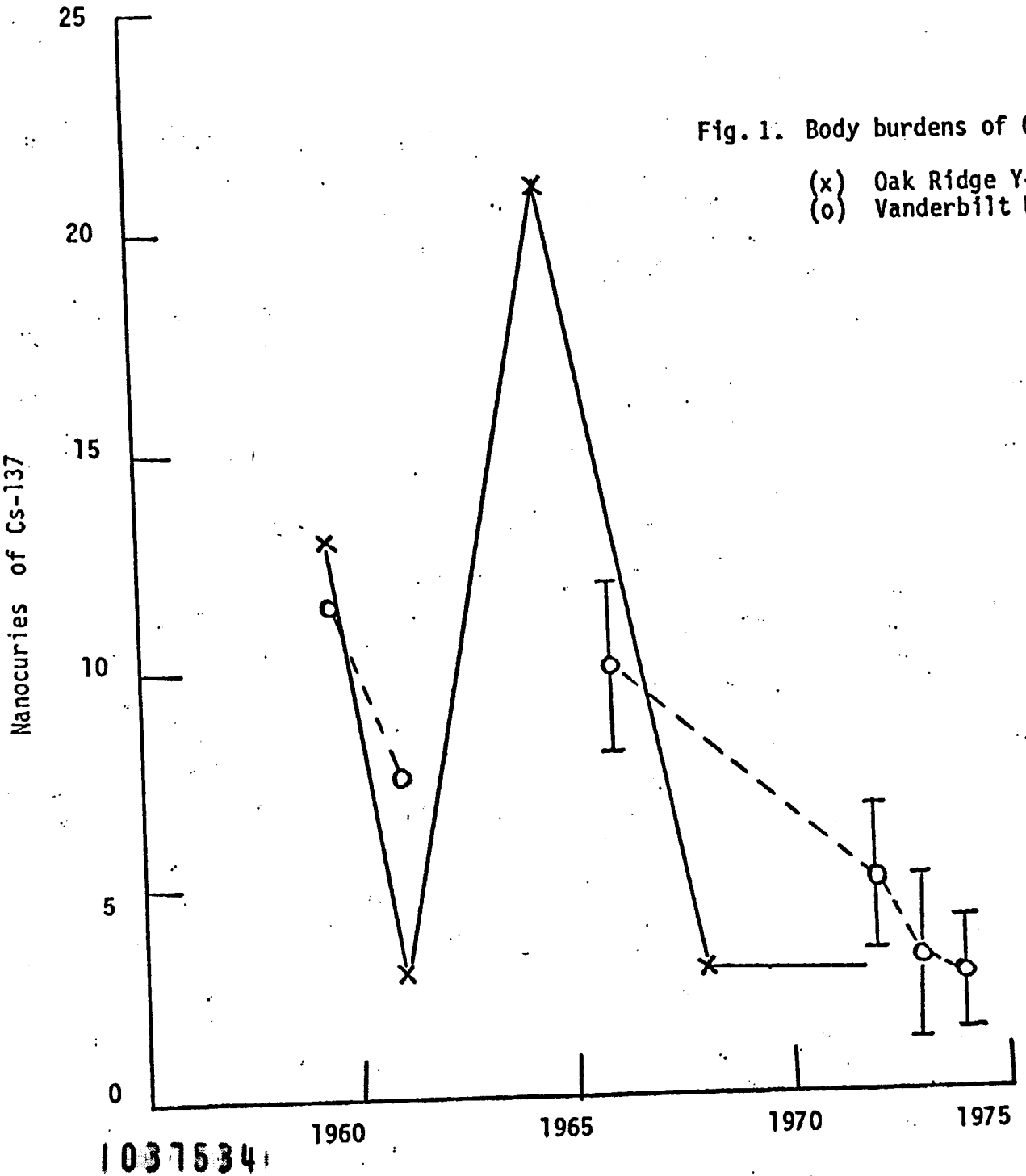


Fig. 1. Body burdens of Cs-137.Whole body counter measurements:

(x) Oak Ridge Y-12, Health Physics, 22, April 1972,p 393.
(o) Vanderbilt University

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B. Clinical applications of activation analysis

1. Californium feasibility studies

Knowledge of body/bone content of Calcium is of importance in the diagnosis and management of patients with many diseases. At present there is great interest in the measurement of changes in calcium content in bones in patients/astronauts who are immobilized for protracted periods. The evaluation of drugs used to reverse these processes is being pursued in several different laboratories with unique facilities such as we are using for pilot studies.

The only effective, non-destructive analytical technique for measuring in-vivo calcium content is neutron activation analysis (NAA). Whole-body NAA facilities exist in the U.S.A. at Brookhaven (Cohn, et al)(1,2) and at the University of Washington (Nelp, et al).(3) Total-body calcium levels have been determined at these facilities to within a few percent.

We propose to build a facility for use in small animal, in vitro sample, and partial body (arm) activation analysis. We now have a transmission scanning system that enables us to determine total bone mineral content (described in V.A.2.b. Calcium kinetics and bone density). Except for certain diseases where the calcium levels in a specific bone may be different from the levels in other bones, the ratio of calcium content to bone mineral content should be constant throughout the skeleton. Therefore, by irradiating a portion of the arm and determining the calcium content of that portion, the ratio of calcium-to-bone mineral can be calculated and the total body calcium determined.

To measure accurately the amount of an element using NAA, there must exist an isotope of the element that has certain properties:

(a) A sufficient amount of the isotope must be present.

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(b) It must have a relatively high thermal neutron capture cross section.

(c) The radioactive product of the (n,γ) reaction should have a half-life of a few minutes or hours. If the half-life is too short, most of the isotope will decay during the time the patient is being transferred from the irradiation facility to the counting facility. On the other hand, a long half-life may require a lengthy counting time and will result in an increased radiation exposure (other factors being equal).

(d) A gamma ray must be emitted by the daughter nucleus in its decay process. The energy of this gamma ray should not coincide with the gamma-ray energies emitted by isotopes of other elements that are present in the body. The gamma ray should also be emitted in a relatively large percentage of decays.

In the determination of calcium, the only useful isotope for NAA is Ca-48. This isotope has a cross section of 1.1 barns. The daughter, Ca-49, has a half-life of 8.8 minutes and emits a 3.10 MeV gamma ray in 89% of its decays.(4) This energy is higher than the energies of most gamma rays given off by other elements present in the body. A higher energy photon event may arise from the activation of Na-23. The induced Na-24 emits gamma rays with energies 1.369 MeV and 2.754 MeV in rapid succession in almost all decays. If these are detected simultaneously (chance coincidence), a (sum) peak at 4.123 MeV will occur. The Compton region from this peak will increase the background for the 3.10 MeV Ca-49 peak. Ca-49 itself emits two gamma rays with higher energies--one at 4.11 MeV in 10% of the decays and the other at 4.76 MeV in .3% of the decays--which will also contribute to the background at 3.1 MeV. The main problem with Ca-48 is its

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small isotopic abundance of 0.185%. This makes the determination of calcium content difficult: large neutron fluences are necessary for accurate analysis, but fluences must be kept below certain limits to restrict the dose to the patient.

Initial studies will be done on animals (rats and dogs) to determine the sensitivity and precision of this method of calcium determination. Phantoms will also be used to determine the accuracy of the method. The levels in the animals will be determined by NAA; then the animals will be sacrificed and the calcium levels determined using chemical methods. Similarly, arm phantoms with a known amount of calcium will be activated and counted to compare the experimentally-determined levels with known levels.

Calcium determinations with an accuracy of a few percent have been made by other investigators using accelerator-produced neutrons.(1,3,5,6) There are certain disadvantages in using this type of neutron source:

(a) The neutron energy spectrum often includes high energy neutrons (up to 14 MeV). These neutrons scatter off atoms in the body and lose energy during the scattering processes thereby contributing to the dose received by the patient. If this scattering has not slowed them down enough to be captured, they escape from the body and do not contribute to the activation process.

(b) The accelerators are too costly for use in dedicated projects of the type we are planning.

(c) Because of their complexity, they are not as reliable as isotopic neutron sources.

Therefore, portable neutron sources, usually involving the (α,n) reaction such as Pu-Be and Am-Be, are being investigated for in-vivo NAA.(2,7,8) Spontaneous fission sources, such as Cf-252, are superior to the (α,n) type

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N_A = Avogadro's number = 6.02×10^{23} atoms/gm mol.wt.,

P_{AB} = fraction of naturally occurring calcium that exists as Ca-48 = 0.00185,

P_{IN} = fraction of decays of Ca-49 in which a 3.10 MeV gamma ray is emitted = 0.89,

E = efficiency of the detector at 3.10 MeV $\simeq$ .10,

$\lambda = \ln 2 / T_{\frac{1}{2}}$, where $T_{\frac{1}{2}}$ = half-life of Ca-49 = 8.8 min.,

t_1 = time after irradiation that the count is begun,

t_2 = time after irradiation that the count is ended,

and A = atomic weight of calcium = 40.08.

By substituting reasonable values into this equation for all but one quantity (which may be t, t_1, t_2, C, or F), the unknown can be computed. The statistical error in counting is given by S.E. = $\sqrt{C}/C \times 100\%$. The dose equivalents (D.E.) for the various experimental procedures were also calculated from the equation (10)

$$\text{D.E.} = (0.122)\text{Ft mrem}$$

where F is the flux in $n/cm^2 \cdot sec$

and t is the irradiation time in hours.

The results of these calculations are shown in Table 2.

The value 0.122 $\frac{\text{mrem} \cdot \text{sec} \cdot \text{cm}^2}{\text{neutron} \cdot \text{hr}}$ for the neutron dose equivalent rate multiplied by $4\pi r^2$ is the value for unmoderated neutrons from the Cf-252 source. Since the probability for capturing a neutron is much higher at thermal energies than at the energies of unmoderated Cf-252 neutrons, we will place a moderating medium around the Cf-252 source. Data from the Lawrence Livermore Laboratory (11) indicate that the dose is reduced considerably using moderated neutrons (Table 3). In their calculations, a

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source was assumed to be at the center of a D_2O sphere and the dose equivalent rate was calculated outside the sphere. We plan to do similar calculations using a Monte-Carlo neutron transport computer program, the MORSE code, which we obtained from the Radiation Shielding Information Center at the Oak Ridge National Laboratory and adapted to the Sigma 7 computer system at Vanderbilt. This program will enable us to calculate neutron fluxes and spectra for various source positions and moderator designs. By using these values of neutron flux and estimating the dose from other radiations such as gamma rays from the source and moderator and beta and gamma rays from the decay of activated atoms in the arm, we will develop a procedure to determine the calcium levels as accurately as possible while attempting to keep the dose to the arm below 3 rem.

Since we plan to activate only a certain portion of the arm, it is necessary to be able to define accurately the portion of the bone that is irradiated. Since cadmium is an excellent absorber of thermal neutrons (σ_c = 20,000 for Cd-113), it can be wrapped around all but a certain length of arm to define the portion that will be irradiated. Measurements have been done using the small facility at the ORAU Special Training Division to determine the variation of neutron flux at the center of a paraffin cylinder. A sheet of cadmium was wrapped around part of the cylinder. Flux monitors were placed inside the cylinder and at two positions on the outside--facing the source, and on the side of the cylinder at 90° to the source-cylinder line. The monitors consisted of small cylinders approximately 1 cm long and .5 cm in diameter, each containing .1 to .3 gm of manganese. Three types of cylinders were used: aluminum, lucite and gelatin capsules. After irradiation, each cylinder was placed between two 3" x 3" NaI detectors.

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A window was set with a single channel analyzer to collect counts in a scaler from the 847 keV gamma ray emitted in the decay of Mn-56. We were then able to determine how the flux varied as a function of position along the center of the paraffin cylinder and how well the monitors placed on the outside could predict the flux distribution in the center. The results are shown in Figure 1. The flux does not fall off as sharply in the center and on the side at 90° to the source as it does on the side facing the source. This is because of the neutrons scattering in the paraffin.

We plan to do further studies with arm phantoms to develop techniques that will enable us to determine the flux at the bone. The arm phantoms will consist of a tissue-equivalent liquid containing enriched Ca-48 segments along the bone positions. Monitors will be placed on the outside of the phantom during activation and then counted separately. The calcium segments will also be counted separately. A relationship can then be established between the flux as measured on the outside and the flux at the bone. This will be done for different phantom sizes in order to determine how the shape of the arm affects this relationship. When an arm is activated, we will then be able to determine using monitors on the arm the flux at the bone as a function of position along the arm, F(x).

After irradiation, the arm will be placed between two 3" x 3" NaI detectors for pulse height analysis. Since the detectors will be viewing a length of arm, gamma rays emitted near the edge of the detector will be detected with a lower efficiency than those emitted near the center of the detector. We will, therefore, need to measure efficiency curves at various points along the face of the detector and determine the efficiency as a function of position along the arm, E(x).

If μ is the mass of calcium per unit length of bone, the mass of

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calcium in an incremental length, dx, of bone is

$$dm = \mu\, dx$$

The number of counts obtained from such an increment at a position x is given by

$$dC = \frac{\sigma N_A \mu P_{AB} P_{IN}}{\lambda A} \cdot (1 - e^{-\lambda t}) \quad (e^{-\lambda t_1} - e^{-\lambda t_2})\ F(x)E(x)dx$$

Assuming that μ is constant over the length of bone that contributes most of the counts, this expression can be integrated over the length of the arm:

$$C = \frac{\sigma N_A \mu P_{AB} P_{IN}}{\lambda A}\ (1 - e^{-\lambda t}) \quad (e^{-\lambda t_1} - e^{-\lambda t_2}) \quad \int_{arm} F(x)E(x)dx$$

From this expression, μ can be calculated. The mass of calcium in a length of bone, l, is then given by

$$m = \mu l$$

We also plan to do in-vitro NAA to determine concentrations of various element in samples. We have used this method to determine trace element concentrations in placentas and human blood (12) and for stable tracer studies.(13,14) It has been necessary, however, to send the samples to the Oak Ridge National Laboratory and the Georgia Institute of Technology for irradiation. This procedure has prohibited us from determining levels of elements with short half-lives.

For the in-vitro studies, a standard of known composition is irradiated under the same conditions as the sample. A pulse height spectrum is obtained for each. The peaks in the spectra correspond to the energies of gamma rays emitted from the elements that comprise the sample. The mass of a particular element in the sample is determined from the composition and spectrum of the standard. We have done some calculations to determine the

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minimum quantities of various elements we will be able to measure using six 1 mg Cf-252 sources. The results are summarized in Table 4. This table indicates that our proposed facility may permit us to measure small concentrations of Na, Cl, Mn, Co, As, Zn, I, Cd, and Br in samples. The known serum concentrations of Na and Cl indicate that we should be able to measure these concentrations accurately in a 2 ml sample. In addition, stable tracer studies using Br for the determination of the extra-cellular fluid space will be possible with NAA or XRF analyses.

A preliminary design of the facility that could be used for these studies is shown in figure 2. The facility could utilize a large aluminum tank we obtained on loan from the Oak Ridge National Laboratory. The tank is 5' high and 5' in diameter. It has a 33 cm hole in the top into which a cylinder containing the sources and an irradiation chamber can be inserted. The irradiation tank can be filled with water and placed underground so that radiation levels in the room can be minimized. Four to six 1 mg Cf-252 sources should provide an adequate flux for in-vitro sample activation. Samples will be inserted via a pneumatic transfer system so that they can be quickly transferred to the detector for counting. This would enable us to determine levels of elements half-lives as short as a few seconds.

Another tank containing water or paraffin as a moderator could be placed above this one. This tank would have two holes in the side--one 15-20 cm in diameter for arm and small animal activation and another 30-40 cm in diameter for large animal activation. The outside of this tank would be surrounded by a layer of Cd to absorb the thermal neutrons emerging from the tank and a layer of lead to absorb gamma rays. These layers and the moderator need to be designed to minimize the radiation received by the patient and the persons operating the system during in-vivo activation.

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On the basis of the findings we achieve in our continuing feasibility studies, we plan to develop a proposal for acquiring needed Cf-252 sources, modifying the irradiator and the room into which it would be placed, and obtaining partial salary support for a physics graduate student who will work with us on this project. The facility will be used initially for in-vitro studies and experimental animal studies. In future years, we plan to extend these measurements to human subjects when sensitivity, precision and safety data have been developed. The use of partial body extremity irradiation with neutrons will minimize bone marrow radiation exposure and may be more readily justified than whole body neutron exposures.

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Table 1

Calcium Content of Rat Bones

Type of Bone	Mass of Bone (mg)	Number of Counts	Mass of Calcium in bone (mg)	% Calcium in bone (by weight)
1. Tibia/fibula	445.0	693[a]	60.1	13.7
2. Femur	1197.2	900[b]	80.3	6.7
3. Tibia/fibula	426.2	599[b]	53.5	12.6

a - count time = 480 seconds

b - count time = 400 seconds

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Table 2: Counting Accuracies and Absorbed Radiation Doses for Different Experimental Procedures in NAA Determination of Calcium in a Human Arm

Irradiation Time (secs)	Wait Time (secs)	Count Time (secs)	Counts	Neutron Dose (REM)	Statistical Counting Error (%)
10.0	60.0	600.0	697	5.0	3.8
10.0	60.0	1200.0	1015	5.0	3.1
30.0	60.0	600.0	2066	14.9	2.2
30.0	60.0	1200.0	3005	14.9	1.8
74.7	60.0	600.0	5000	37.1	1.4
50.6	60.0	1200.0	5000	25.1	1.4
44.0	60.0	600.0	3000	21.8	1.8
29.0	60.0	600.0	2000	14.4	2.2
19.8	60.0	1200.0	2000	9.8	2.2

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Table 3

Ability of D_2O to Reduce Dose from 252Cf Neutrons

Radius of D_2O (cm)	6	15	25
$\frac{\text{mrem/hr}}{\text{n/cm}^2\text{-sec}}$	0.0809	0.0333	0.0128

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Table 4

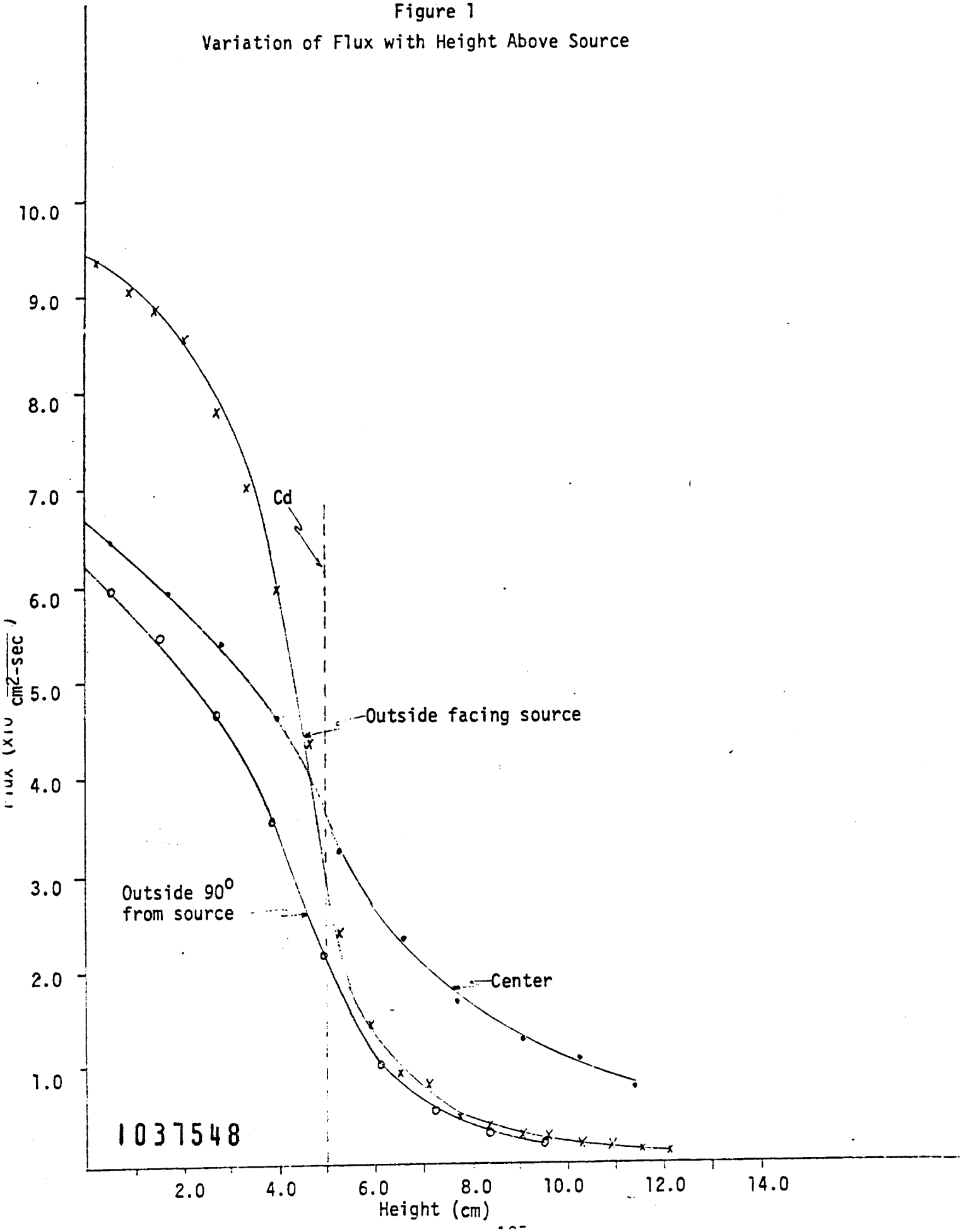
Minimum Amounts of Elements That can be Measured In vitro with Proposed NAA Facility
(At 1% Counting Accuracy)

Isotope	Natural Abundance of Isotope (%)	Mass of Element (mg)
^{23}Na	100.	2.18
^{41}K	6.77	93.2
^{37}Cl	24.47	4.55
^{48}Ca	0.185	447.
^{26}Mg	11.29	68.7
^{55}Mn	100.	0.022
^{36}S	0.014	6.88×10^{4}
^{19}F	100.	904.
^{58}Fe	0.31	6.34×10^{4}
^{59}Co	100.	0.241
^{50}Cr	4.31	347.
^{75}As	100.	1.14
^{68}Zn	18.56	6.09
^{80}Se	49.82	14.9
^{127}I	100.	0.217
^{110}Cd	12.39	9.28
^{196}Hg	0.146	23.0
^{204}Pb	1.40	34.6
^{79}Br	50.52	0.629

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Figure 1

Variation of Flux with Height Above Source



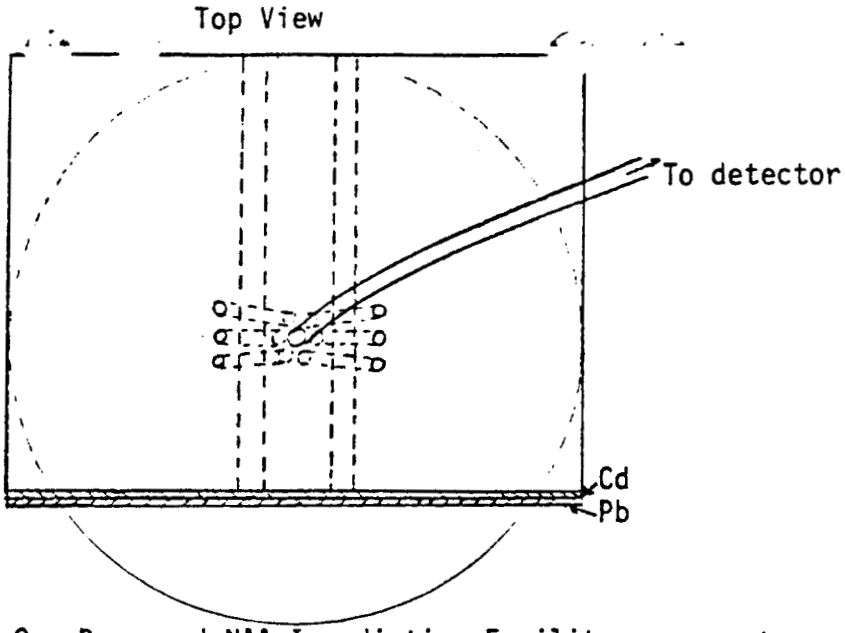
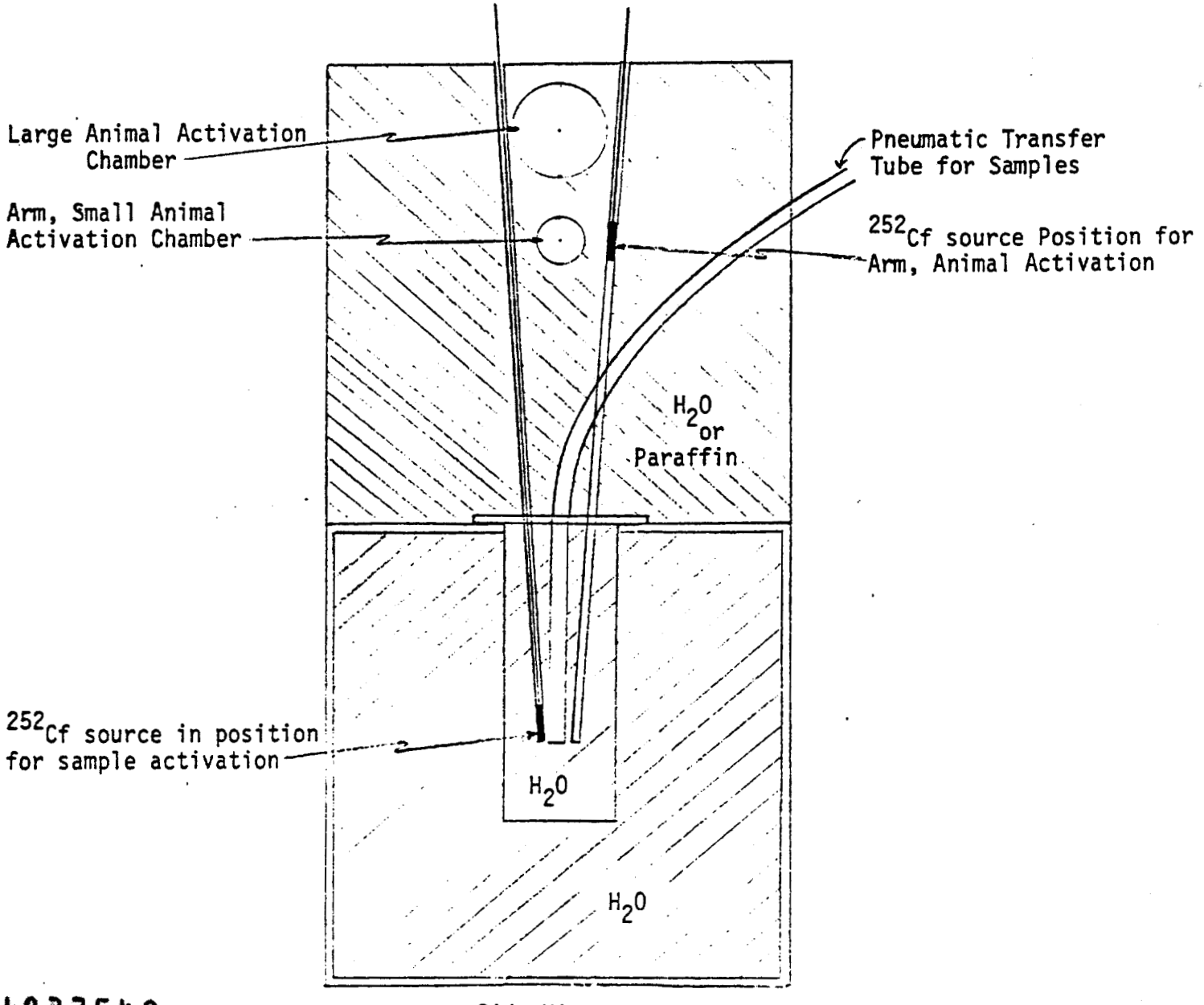


Figure 2: Proposed NAA Irradiation Facility



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References

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(14) Dyer, N.C., Brill, A.B., Tsiantos, A.K., Sell, E., Victorin, L.H., and Stahlman, M.T.: Timing of intracranial bleeding in newborn infants. J. Nucl. Med. 14: 807 (1973).

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2. Tissue levels of trace elements in ischemic heart disease

At the February 1973 meeting of the study participants, much attention was given to methodology in order to identify sources of errors in analysis and to estimate their magnitude. K. Heydorn (Danish Atomic Energy Commission) and R. Parr designed new forms which have just been distributed to study participants (copies in Appendix). An additional source of error identified in the Vienna IAEA working group meeting (1973) was from drugs/chemicals administered to patients. A listing of agents of importance that need to be identified from the patient history is now being formulated. During the interim, while new procedures are being established, we have collected samples from 5 patients who died acutely following a first infarct. These have not yet been processed, but are being held until we are sure of our methods, especially for chromium analysis. In addition to analyzing myocardial samples, we will attempt to analyze samples from the coronary artery and aorta. The published "Reports of the Conference on Trace Elements in Relation to Cardiovascular Disease," IAEA-157 (technical report), contains the papers presented at the Research Coordination meeting held in Vienna in February 1973, and includes copies of the protocols for the study.

Contacts have been made with staff at the NHLI and ABCC vis-à-vis obtaining samples from subjects in their study protocols. If they decide that they are interested and can fund such an effort, we will attempt to interest Japanese scientists working on neutron activation analysis for trace element identification in processing samples from ABCC and the Hawaii/California subjects in the ABCC Protocols (TR-12-71). By the time of the October 1974 Society of Nuclear Medicine meeting in Tokyo, we should be able to make contacts and follow-up on these in person while in Japan

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for the meeting (invited paper on CAMAC in nuclear medicine). Preliminary correspondence has been sent, and returns are awaited before we know how to proceed.

Results of our own samples will be processed at ORNL by our staff. We propose to interest Japanese scientists at Chiba in processing the ABCC samples, and support for their efforts is being explored with NIH staff in the NHLI.

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VI. Scientific Personnel--Curriculum Vitae on file AEC

Principal Investigator:

A. B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Director, Division of Nuclear Medicine & Biophysics and the Clinical Radioisotope Center

Co-Investigators:

R. R. Price, Ph.D. [redacted]
Instructor, Radiology

Research Associates:

J. J. Erickson, Ph.D. [redacted]
Instructor, Radiology

J. A. Patton, Ph.D. [redacted]
Instructor, Radiology

J. F. Parker, M.S. [redacted]
Computer Engineer

J. E. Lagan, [redacted]
Electronics Engineer

VII. Other Personnel

Graduate Students:

J. Jones, [redacted]
K. Larsen [redacted]

Secretary:

Carolyn R. Thompson, [redacted] 100%

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VIII. Other Financial Assistance -- None

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 8,000 square feet adjacent for conference, library, clinical scanning, and instrument development and modification	100 percent
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

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RENEWAL PROPOSAL

1 August 1974 - 31 July 1975

X. Budget Estimated Requirements	AEC	University	Total
1. Salaries and Wages Name, title, monthly rate, % effort			
Principal Investigator: A. B. Brill, M.D., Ph.D. [redacted] Professor Medicine & Radiology, 25%	-0-	---	---
Co-Principal Investigator: R. R. Price, Ph.D. Instructor Radiology @ $1246/mo., 35%	$ 5275.	---	$ 5275.
Research Associates: J. Erickson, Ph.D. Instructor Radiology @ $1234/mo., 67%	$ 6858.	$ 3110.	$ 9968.
J. A. Patton, Ph.D. Instructor Radiology @ $1231/mo., 29%	$ 4220.	---	$ 4220.
J. F. Parker, M.S. Computer Engineer @ $1062/mo., 33%	$ 4220.	---	$ 4220.
J. E. Lagan Electronics Engineer @ $1076/mo., 78%	$ 6858.	$ 3165.	$10023.
Graduate Students: Summer grad. student	$ 800.	---	$ 800.
Secretary, C. Thompson, 100%	$ 5803.	---	$ 5803.
Fringe Benefits (not fixed % of salaries. Varies with employee status and option)	$ 5585.	$ 1071.	$ 6656.
Total Salaries and Fringe Benefits:	$39,619.	$ 7346.	$46,965.

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	AEC	University	Total
2. Supplies and Materials			
Animal Purchases	$ 200.		
Books and Journals	$ 300.		
Chemicals and Glassware	$ 200.		
Computer Expense - on campus	$1000.		
Laboratory Supplies Radioisotopes	$2500.		
Machine Service Contracts	$3500.		
Office Supplies	$ 800.		
Equipment Rental	$1300.		
Electronic Components Maintenance and Repair	$6000.		
Subject Participation	$ 400.		
	$16,200.		$16,200.
3. Equipment			
1 NaI (2"x¼") RCA 8053 thin window integral line assembly (for transmission scanner)	$ 350.		
1 GEC Elliott PDP-9 Executive suite CAMAC controller (including data channel & API)	$9000.		
1 Type A controller	$ 895.		
1 CAMAC crate with power supply	$1395.		
1 Branch terminator	$ 195.		
2 cables (4 ft @)	$ 430.		
	$12,265.		$12.265.
4. Publications and Copying	$1600.		$ 1,600.
5. Travel - Domestic - scientific mtgs.	$1500.		$ 1,500.
CF 252 Evaluation	$ 500.		$ 500.
6. Other			
Steel Room Patient hoist mechanism (shop costs)	$1100.		
Steel Room patient positioning jigs (shop costs)	$ 825.		
	$1925.		$ 1,925.
7. Indirect Costs, 48% salaries and fringe benefits	$19,017.	$7346.	$19,017.
Budget Summary:			
Items 1-6	$73,609.	$7346.	$80,955.
7	$19,017.	---	$19,017.
Total	$92,626.	$7346.	$99,972.

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Projected Costs

Percentage & Amount, Vanderbilt University	$ 7,346	7.9%
Percentage & Amount, Requested AEC	$92,626	92.1%

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Lloyd H. Ramsey
Assoc. Dean for Clinical
Sciences

Paul Gazzerro, Jr.
Assoc. Vice-Chancellor for
Medical Affairs for Operations
and Fiscal Planning

NOTE: Studies described in this application, involving the investigational use of human subjects, have been reviewed and approved by this Institution's Clinical Investigation Committee.

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III. Project Abstract

The main emphasis of these studies is the development of instrumentation and analytical techniques for the acquisition and analysis of isotope tracer kinetic data , emphasizing dosimetry. Tracer turnover studies involve both radioactive and stable tracers. We continue to explore ways of using neutrons for activation analysis in an attempt to minimize radiation exposure to the patient while obtaining needed diagnostic information.

We are attempting to validate several key assumptions in dosimetry calculations in collaboration with staff of the Health Physics Division at ORNL. At the same time, we are collecting quantitative data on diagnostic tracers administered to patients and analyzing these results with currently accepted methods. Berman's computer programs for simulation and modelling (SAAM 25) and dosimetry calculations (RADOS) are used in these studies.

Efforts will be made to increase the effective use of SAAM-25 in medicine through the mechanism of a workshop we plan to sponsor on this topic during the coming year. We are actively involved in efforts to increase the utility of computers in Nuclear Medicine and are trying to demonstrate the role of CAMAC for data acquisition in medicine.

Advances in electronics and photomultiplier technology have resulted in the introduction of a new low cost NaI(Tl) detector, produced by RCA. The precise matching and tuning of components promises to deliver high resolution at low cost. These systems could be of great use in many applications, including mosaic detectors, and we will evaluate their properties and uses.

Dosimetry and clinical studies will be carried out on patients using new approved radiopharmaceuticals which appear promising. These include ^{111}In, ^{169}Yb, ^{99m}Tc bone seekers, ^{131}I-cholesterol and ^{206}Bi. These efforts are coor-

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dinated with those of the MIRD Committee (SNM) and the NCRP Committee-32 (Uses of Radiotracers in Medicine) by Drs. Johnston and Brill, who are senior members of these groups.

New emphasis will be placed on calcium metabolism and dosimetry studies in the coming year. Studies will be made on ^{47}Ca metabolism and bone mineral content (regional and total body). Different transmission sources will be studied, with particular emphasis on ^{153}Gd.

Evaluation of long term body composition changes in massively obese patients who receive different intestinal bypass operations will continue, as will monitoring of Cs-137 levels in man.

We will continue to participate in the IAEA/WHO study of tissue levels of trace elements in ischemic heart disease. In order to enhance our activation analysis capabilities we will conduct feasibility studies with ^{252}Cf. This would be of great use in our calcium metabolism studies, and fits into our facilities and staff interests very well. In addition to trained staff, we have a whole-body-counter and neutron radiography imaging system well-suited for these evaluations. Feasibility studies will be conducted at neighboring institutions and facility and experiment planning will be conducted during the coming year.

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IV. Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the operation of the Vanderbilt Low Level Counting Facility. Dr. A. B. Brill, Principal Investigator, is the Director of the Division of Nuclear Medicine and Biophysics. Dr. R. E. Johnston, receives salary support from the Veterans Administration. Dr. R. Baglan, Physics Department has contributed many ideas and assistance in the direction of graduate student thesis research. 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. Dr. W. Rowan and staff of the Information Science Program and C. Bradshaw, Director of the Vanderbilt University Computer Center, and his staff have contributed significantly to our work. Don Johnson, an Engineer at DuPont, Old Hickory, Tennessee, has been of great assistance to us in working with the SAAM 25 computer program. None of these personnel have been supported financially by this contract but the collaboration has strengthened our efforts and has led them to pursue research problems in our area. This will lead to the involvement of more graduate students from engineering and computer science 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 closely related 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.

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The staff has achieved a scientific maturity and is stronger today than ever before. 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 be even more profuse this coming year than ever before from this contract. 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 promises to accelerate our biological study output.

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V. Scientific Scope

A. Dosimetry

1. Methodology

a. Correlation studies between calculated and TLD measurement of radiation dose

We have developed a methodology and calibration technique to obtain quantitative measurements of radioactivity distributions within human subjects (AEC ORO #2401-44). We are now attempting to determine the adequacy and accuracy of these procedures by a careful evaluation of the measured parameters used. The first of these is the geometric mean value of the counts from two opposed detectors. A careful study shows that the GM has a previously unrecognized difficulty associated with it as illustrated in the following table:

Table 1

Phantom thickness	6"	6"	6"
Point Source Location From top detector	2"	4"	2" and 4"
GM, cts/mCi	8453	8336	8926

Thus, two point sources counted separately yield a different count/mCi value when summed. The calculated GM value for two sources is given by the following equations:

$$GM_{2+4} = 1/2 \left((GM_2)^2 + (GM_4)^2 + C_{T2} C_{B4} + C_{T4} C_{B2} \right)^{1/2} \quad (1)$$

Rather than the assumption that:

$$GM_{2+4} = 1/2 \left(GM_2 + GM_4 \right) \quad (2)$$

Experiments (AEC ORO# 2401-42) show that equation 1 is correct for point GM sources. These results imply important conclusions concerning the use of the GM to estimate activity in patients. The GM has the advantage of being relatively source location independent (within a given thickness), hence requiring fewer computations to obtain an activity estimate. However, for a distributed source

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of activity, the GM is a nonlinear function of the point source GM's, and this functional relationship cannot be found until the activity as a function of depth is known. Since this information cannot be found from a single two-dimensional scan, the estimate of activity in patients based upon point source GM's is likely to be in error.

To obtain an estimate of how bad this error would be in patients, several scans were run using $^{99}Tc^{m}$ sources in phantoms ranging from kidney size to liver size. It was found that the GM always overestimated the activity present (assuming a linear relationship), but never greater than 6%. We are continuing our efforts to evaluate the parameters associated with the radiation dose equation, $D = \tilde{A} \sum_i \Delta_i \Phi_i$. Studies are now underway to determine correlations between measured dose, D, and calculated dose.

The radioisotope selected for this study is $^{99}Tc^{m}$, for which Δ_i has been calculated by L.T. Dillman and is assumed to be correct (negligible uncertainty). The source organs are the liver and spleen ($^{99}Tc^{m}$ sulfur colloid), the target region a section of skin anterior to and overlaying the liver. For these conditions, Dr. Snyder (Health Physics Division ORNL) has agreed to calculate Φ_i using his "standard man" model. The stated uncertainty in Φ_i is statistical due to the statistical nature of the Monte Carlo method; but the applicability of Φ_i computed in this way to the estimate of radiation dose to human patients has not been estimated. A number of patients are being studied to check the effects of height, weight, and clinical condition on the dose estimates. Thus, if D and $\tilde{A}$ can be accurately measured, this study will provide some estimate of how well Dr. Snyder's "standard man" model approximates a patient for calculating absorbed fractions.

The dose, D, to the target region will be measured using LiF TLD's (TLD-100). The TLD's read relative dose, thus a calibration procedure for the TLD's

must be established to convert the reading to absolute units (rad). The TLD output depends upon geometry (due to electron equilibrium) and the energy of the primary photons, thus adding to the importance of calibration. For making the patient measurements, the TLD's are taped on the skin. The resulting geometry does not establish electron equilibrium with the environment. For this reason, it was decided to calibrate the TLD's by taping them on the surface of a cube filled with a $^{99}Tc^{m}$ water solution. Dr. Snyder (ORNL) has used his Monte Carlo program to calculate the absorbed fraction for this specific geometry. For this well defined geometry and known radioactivity (A), an accurate dose can be calculated and the TLD's calibrated. It is expected that the cube approximates a patient in that the TLD's "see" about the same gamma ray energy spectrum and secondary radiation energy spectrum in each case.

The cumulated activity $\tilde{A}$ will be determined with the low-level dual opposed scanning detector system. Each scan will determine the activity and distribution at that time. The cumulated $\tilde{A}$ will be determined by integrating the curve fitted to the data points (activity at time t). Because of the six hour half life of $^{99}Tc^{m}$, it is expected that only three values of activity can be obtained per patient, thus making the curve fitting somewhat inaccurate. Several steps have been taken to minimize this error:

1) Each scan will only take about 15 minutes, so that the $^{99}Tc^{m}$ will not decay appreciably while the scan is being taken. Further, the time assigned to this measured activity will be the time midpoint of the scan (time at 7 1/2 minutes into the scan) to help reduce this error.

2) $^{99}Tc^{m}$ sulfur colloid is taken up rapidly by the liver and spleen and is retained there (does not circulate throughout the body). Consequently the TLD's will not be put on a patient until the uptake of $^{99}Tc^{m}$ in the liver reaches its

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maximum. Then, the decay of activity in the liver and spleen should be primarily the physical decay of the isotope, which can be easily fit by an exponential function. We have begun making measurements on human subjects. A series of measurements will be made and correlations drawn between measured dose, calculated dose, and patient parameters such as height, weight, and disease state in the attempt to obtain estimates of the effects on calculated doses.

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b. Data analysis

i. Software simlulation analysis and modelling

In collaboration with Dr. Mones Berman and his associate Mrs. Marjorie Weiss at the NIH, we have modified the most recent version of the simulation, analysis and modelling program, SAAM-25, so that it could be run on the Vanderbilt University Computer. We have used this program extensively in calcium and iron metabolism studies, and for dosimetry calculations. This general purpose program permits the user to formulate a model, read in experimental data for measured compartments and obtain from the computer estimates of the model parameters.

The SAAM program represents the results of many years of continuing effort by a very talented research team. It is sufficiently general in the types and sizes of problems that it can solve, that it should be of general utility to a large number of people. Unfortunately, it is not easy to use and hence it has not been used as widely or effectively as it should have been.

Utilizing our close ties with the Society of Nuclear Medicine Computer Committee, and Radiation Shielding Information Center (RSIC) and the experience we have gained through the use of the SAAM program, we propose to organize a SAAM user's workshop in collaboration with RSIC. This workshop would introduce prospective users to SAAM and would help current users to utilize SAAM to its highest potential. Problems concerning the use of SAAM and unique model solutions would also be discussed.

It is our intention that this workshop be co-sponsored by the Society of Nuclear Medicine, RSIC (Oak Ridge National Laboratory) and Vanderbilt University. We will invite SAAM users and potential users to the workshop. We will attempt to get Dr. Mones Berman to participate

as senior faculty member , along with people who have worked extensively with SAAM. We will assist in preparations for and conduct of the conference but funds for the conference will be sought from other sources.

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b. Data Analysis

ii. Hardware development

1. CAMAC

We propose to concentrate our hardware development efforts on enhancing the effectiveness with which CAMAC standards can be employed in Nuclear Medicine for interfacing to computers. CAMAC is an internationally accepted standard, modular interfacing system which has proven to be effective for digital data acquisition, control, and display functions. Many modules are designed and commercially manufactured which now make it possible to interface computers to peripherals and computers to computers without need for additional signal conditioning or interface development. The cost of controllers and peripheral devices from computer manufacturers has remained relatively unchanged while the costs of the computer memory and main frame logic has fallen rapidly. The two major systems stumbling blocks for computers in medicine have been the high cost of interfacing specialized devices to the computer, and software to handle these devices and analyze the data. CAMAC promises to help in both these areas, but as yet is relatively little known in the United States, outside of high energy physics laboratories.

Computer applications in medicine have proven to be very costly of money and manpower. This is true both for management information and for data acquisition and display systems. The level of computer science competence available in most medical laboratories often is inadequate for the efficient solution of systems problems. Furthermore, functions implemented successfully on large systems are often so specialized to the facility for which they were designed that the translation between laboratories is very difficult. Characteristically, the level of documentation is poor and each laboratory starts over and designs its own system as if this were the first of its kind. This results in an in-

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ordinate duplication of costly effort. Thus it takes many years before these techniques are disseminated widely in medical facilities. CAMAC should shorten this time delay and reduce the probability of systems obsolescence from rapidly evolving technology.

Initial results from the use of an adapted Argonne National Laboratory interface between the PDP-9 computer and rectilinear scanner (such as the low-level whole body counter), static probes, and a tomographic scanner have been most encouraging. The efficiency with which this interface has utilized the power of the PDP-9 computer has been reduced due to the ad hoc way the ANL interface was connected to the computer. Hardware modifications to make use of the priority interrupt structure of the PDP-9 computer promise to solve this problem.

Pending is a substantial ($800 K over 5 yrs) grant application with HEW for the development of "A CAMAC Computer Resource in Nuclear Medicine." If that parallel effort is funded we will proceed to acquire the same CAMAC-based biomedical computer configuration as developed at the Los Alamos Meson Production Facility (LAMPF). The potentiality for hardware and software standardization will be explored for Nuclear Medicine data acquisition and display systems. The commonality of systems at Vanderbilt and LAMPF will facilitate bidirectional sharing of hardware and software. The Vanderbilt facilities will be a resource serving multiple investigators at Vanderbilt and neighboring institutions. CAMAC provides the possibility for sharing of computing resources by networking and minimizing the need for replication of expensive computer peripherals and data storage devices. It furthermore protects against obsolescence and makes it possible to protect against down time by its modular nature.

Whether or not the larger system is developed, we will attempt to demonstrate the benefits of CAMAC (standardization and modularity, ability to replace defective systems modules without affecting the continued operation of the rest of the system,

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ability to incorporate new improved modules as they are developed, etc.). We will extend our system to acquire data from additional diagnostic instruments, and will attempt to increase awareness in the Nuclear Medical 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.

2. INTERACTIVE DISPLAY (PEP)

The use of high resolution imaging devices combined with relatively high photon flux radiopharmaceuticals allows the acquisition of images containing large numbers of data points. This is especially true in the case of large area scanners such as our low level counting facility.

The presentation of such images to the user of the system becomes a significant problem in and of itself. We presently have the capability of producing high quality photographs but because of film costs and the long time periods involved this does not satisfy the requirements for an on line monitor during image manipulation procedures undertaken by the investigator. Also nearly all quantitative clinical studies or dosimetric investigations require the ability to select regions of interest in the image. Often these regions are irregularly shaped depending on the study findings and, thus, must be specified by the user at the time of analysis. We have attempted to solve the problem of high quality image display by means of an electrical storage tube system. While our work in this area has shown the feasibility of this approach, the images have been sub-optimum. We are currently updating the electrical storage tube system by replacing the tube itself as well as its deflection yoke. Along with several changes in the interface design this should significantly improve the image quality.

To provide the ability to flag regions of interest in the displayed images we have acquired a low cost coordinate digitizer. This device is normally used to digitize curves. For our use it will be suspended over the TV monitor displaying the image, and will transmit positional information into the PDP-9 through the LT-19 teletype multiplexer available on

our computer. The combination of these two devices will greatly enhance the quantitative imaging capabilities of our system and should prove to be of great value in future dosimetric investigations as well as routine clinical procedures.

3. High resolution NaI vs. GeLi detectors

Much discussion has been generated by the results of evaluations using Ge(Li) in radioisotope studies. The superior energy resolution of these detectors makes it possible to discriminate more effectively against scattered radiation and thus to obtain higher quality images of radioisotope distributions. Significant advances are also being made in NaI(Tl) detector technology which warrant careful attention. In particular, improvements in electronic component miniaturization procedures and the availability of new, high quality photomultipliers now make it possible to obtain a complete detector package with excellent energy resolution capabilities at a modest price. Within the next few months, we will be receiving from RCA 12 developmental prototype NaI(Tl) assemblies at no cost to this contract. Each detector will consist of a 1 3/4 x 1/2 inch NaI(Tl) crystal optically coupled to a high sensitivity, high resolution 2 inch photomultiplier tube. Mounted on the base of each tube will be a high voltage supply, pre-amplifier, linear amplifier, and single channel analyzer. The entire detector package will be an integral line assembly the size of a normal crystal-photomultiplier-preamplifier assembly. We will conduct a detailed evaluation of these detectors including resolution, stability, sensitivity, and reliability measurements along with images produced. The resolution of these detectors is approximately 9%* at 122 keV compared to 3 to 5% for large area Ge(Li) detectors. The availability of such high quality detector-electronics packages at moderate cost should make the utility of arrays of detectors feasible. One could then use collimators with very good spatial resolution (but low sensitivity) to increase the accuracy of in vivo quantitative measurements and also to increase the quality of diagnostic imaging procedures. Different mosaic configurations will be evaluated and results compared to those obtained with germanium detectors.

*based on experience with prototype model tested at RCA.

(iii) Scatter correction studies

We have been investigating a new approach for maximizing the diagnostic quality of Nuclear Medicine imaging procedures while minimizing patient exposure.

The general approach to the solution of this problem was to first develop an analytical description of the photon energy spectrum, then using the measured energy response of the system and a deconvolution calculation, derive factors which could be used to weight counts from multiple energy apertures during a scan.

In our work, during the last year, we have represented the energy spectrum $\phi(E)$ in the following manner:

$$\phi(E) = \alpha_0 \delta(E-E_0) + \sum_{j=1}^{N} \alpha_j f_j(E)$$

where the δ function represented the unscatter photons of energy E_0, and the α's are weighting factors. The scatter part of the spectrum (represented by the summation) was approximated by an explansion in polynomials of the energy, E. In our work we truncated the expansion to three terms.

We have assumed that the energy spectrum $\phi(E)$ is transformed into a pulse-height spectrum $\phi(h)$ by a linear transformation with the transformation matrix $A(h,E)$ being the response matrix of the system. The energy resolution and the relative contributions to four pulse height windows positioned above and below the photopeak were used to estimate $A(h,E)$ (ORO-2401-60: section C.b.). Several approximations went into this calculation in order to shorten the computer time, the effects of which must be re-evaluated.

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Since we feel that the image formed from photons which undergo no scatter is the best indication of the true isotope distribution we solve for α_o in terms of the D_i's and A^{-1}.

$$\alpha_o = \sum_i (A^{-1})_{oi} D_i$$

where D_i are the counts detected in the i^{th} energy aperture.

When the previous equation was solved using data from NaI(Tl) detectors the following relationship was found:

$$\alpha_o = -0.10 D_1 - 0.44 D_2 - 0.40 D_3 + 1.0 D_4$$

In the case of $^{99}Tc^m$, D_1=116-124 keV, D_2=124-132, D_3=132-140, and D_4=140-164.

The results to date have been somewhat disappointing in that the derived weighting factors are in conflict with our intuition and the generated scan images are not dramatically improved and may be inferior to other scatter correction methods we have used in the past.

The more efficient utilization of photon information from patient studies will permit the extraction of added diagnostic data without additional radiation exposure. Weighting factors can be chosen to maximize the signal to noise ratio, or to achieve maximum contrast. These factors will vary depending on size of objects, detector properties, and hot vs. cold sources.

Because of the magnitude and complexity of this problem we feel that a collaborative effort would be the most expedient and judicious approach to this problem. Mr. Robert Beck's theoretical studies first led to our interest in the general approach to this problem. Discussions with Mr. Beck

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(Argonne Cancer Research Hospital) have led us to propose a collaborative effort utilizing Mr. Beck's theoretical expertise and our systems capabilities to collect, analyze and display scan images that have been collected from multiple energy apertures. Mr. Beck's work along these lines is well known and respected. In addition to continuing the work along the lines we have started, we will investigate and test the experimental utility of various techniques suggested by Mr. Beck.

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2. Specific Studies

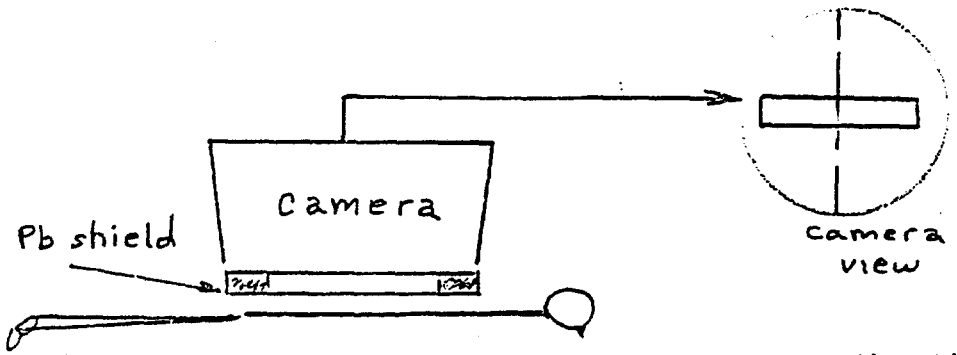
a. Radiopharmaceuticals

(i) Indium-111 DTPA

Indium-111 DTPA is used as an imaging agent to study cerebral spinal fluid flow dynamics. We have obtained data from 15 patients who were administered 400 uCi of In-111 DTPA for the purpose of estimating the radiation dose to the patient.

Measurements were made with the Pho Gamma III camera immediately after injection and at 4 to 6 hours, 24, 48 and 72 hours. The CSF region was divided into two 5 inch segments by dividing the camera field of view into two halves and positioning the patient so that the injection site was viewed in one half of the camera and the upper spinal column appeared in the other half. (see fig.)

Preliminary analysis of the data indicate that the distribution of activity throughout the CSF appears to be uniform by 4 hours after administration with no apparent "hot spot" over the injection site.



Preliminary estimates of the biological retention of the radioactivity in the CSF, blood and total body have been made and the results presented in Table 1. These values are averaged for about one half the patients studied and do not show the range of values for "normal" and different classes of "abnormal." A more complete analysis of all the data will

be made with attempts to estimate the range of values that might be expected for different disease states.

Radiation dose estimates will be made to the spinal cord and nerve roots as well as to the total body. For more realistic dose estimates to the spinal cord, special attention will be directed to the charged particle component of radiation and the source-target geometry. Methodology similar to that applied to RISA cisternography will be used.
(R. E. Johnston, E. V. Staab, A. B. Brill, J. H. Allen, Radiation Dosimetry Associated with the intrathecal administration of ^{131}I human serum albumin, Brit. J. Radiology , 45, 444, 1972).

TABLE 1

Biological Retention of ^{111}In DTPA
Introduced Intrathecally

CSF

T_1 = 1.5 hr. $a_1 = 0.644$

T_2 = 7 hr. $a_2 = 0.34$

T_3 = 88 hr. $a_3 = 0.016$

Whole Body

T_1 = 7.5 hr $a_1 = 0.58$

T_2 = 41 hr $a_2 = 0.42$

Blood

T_1 = 14 hr $a_1 = 0.025$

where $A(t) = a_1 e^{-\frac{0.693\,t}{T_1}} + a_2 e^{-\frac{0.693\,t}{T_2}} + a_3 e^{-\frac{0.693\,t}{T_3}}$

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(ii) Ytterbium- 169 DTPA

Yb-169 DTPA is another radiopharmaceutical which is injected intrathecally for the study of cerebrospinal fluid dynamics. We have recently added this agent to our protocols for CSF studies and are now proceeding to obtain sufficient data to make radiation dose estimates. The protocol is similar to that followed for In-111 DTPA. We will obtain blood samples, urine samples, whole body counts and spinal column images at 0, 4, 24 hours, then periodically over 5 or 6 days. Retention in the CSF blood activity and whole body retention will then be determined and radiation dose calculations made. We plan to study a minimum of 10 patients. Yb-169 has significant potential in view of its favorable energy for Anger camera studies, and its long shelf-life ($t_{\frac{1}{2}}$ = 31.8d). It will be used with increasing frequency in years to come, and radiation dose estimates are needed in order to determine its merit relative to the other tracers available for these studies.

iii. Technetium-99m bone seeking agents

The development of technetium polyphosphates as bone scanning radiopharmaceuticals which provide high quality images with low patient radiation response has been a major advance in nuclear medicine. The primary problem, however, has been due to difficulty in attaining a predictable bone uptake property for the polyphosphates--these materials seemed to vary in behavior for each lot prepared.

Because of the variable behavior of the polyphosphates, we are investigating factors influencing bone uptake patterns. Several types of studies have been undertaken. Biological uptake studies were initially carried out on rats. and have been extended with trimeta phosphate to selected human subjects under IND 9360 approved by the FDA.

Initial evaluation studies were conducted in rats based upon a determination of the fractional incorporation of labeled phosphate in selected leg bones as the index of merit, with maximum bone uptake being sought. The assay procedure developed involved sacrifice of the rat at selected time intervals after I.V. injection of the labeled material. Assay procedures and results of careful analyses of the major variables in labelling and toxicity are described in the Progress Report.* From these studies we were led to the development of $^{99}Tc^{m}$ labelled cyclic triphosphate as a bone scan agent. We have developed a kit system for labelling, evaluated toxicity,obtained an IND, and are now proceeding to test this agent in humans.

To date, evaluation of the Tc^{99m}-tin-trimeta-phosphate has been conducted in about 50 selected human subjects. By systematically varying experimental conditions, considerable information has been obtained concerning factors that effect optimum bone and lesion uptake.

* ORO-2401-60

Optimum time of scans

Limited studies indicate that optimum time for maximum lesion to bone ratios may be slightly less than maximum bone to soft tissue ratios. Patients have been scanned for time periods as short as 15 minutes after dosing and for periods up to 4 hours after dose administration. Maximum bone/soft tissue ratios are obtained at about 2-2 1/2 hours after dosing, but with some patients scanned 1 1/2 to 2 hours post injection, lesions appear to show quite prominently. Further studies are underway to validate these preliminary observations.

Optimum dose levels

Our animal studies indicated a 0.25-1.25 mg/kg dose level to be optimum. Also, commercial kits recommend 20-25 mgm 70kg adult doses. (0.29 - .36 mg/kg) In our studies we have given doses to selected adult patients at the 20, 15, 10, and 5 mg level, representing 0.29, 0.21, 0.15, and 0.07 mg/kg dosage. (In all cases a 10 millicurie/patient radionuclide dose was maintained). Visual evaluation of scans obtained indicate no detectable difference in scan quality throughout the range of dosages studies. However, since there may be inter-relationships between dose level and optimum scan time, studies are continuing so as to correlate these variables.

Effect of drugs on Tc^{99m} phosphate bone uptake

Preliminary investigation has indicated potential interference of Tc^{99m} phosphate bone uptake by medication being received by some subjects.

To date two patients, whose bone uptake pattern with Tc^{99m}-tin-trimeta phosphate was quite low, were found to be on cortisone medication. Unfortunately, repetition of the studies after discontinuation of the medication was not possible.

One patient, who twice showed low bone uptake when dosed with the technetium-tin-TMP radiopharmaceutical, was found to be on several types of medi-

cation. When the medication was discontinued and the patient was redosed with the radiopharmaceutical and again scanned, a normal amount of bone uptake was observed. The basis for this effect is uncertain but provides an important clue that we will pursue.

Comparative bone uptake patterns

Several studies have been done whereby the Tc^{99m}-tin-TMP bone lesion uptake pattern has been evaluated and compared to strontium-85 bone uptake patterns. Results indicate good correlation between the two agents. Furthermore, in some instances the Tc^{99m}-tin-TMP showed lesions that were not discernible with the Sr^{85} scans. In contrast, because of accumulation of activity in the bladder/kidneys, some lesions in the proximity of those organs were not detectable when the Tc^{99m}-tin-TMP was used.

The results of our efforts to date have resulted in preparations of high quality with minimum numbers of failures. The low toxicity of the TMP compound and simplicity of preparation make it an interesting agent that justifies additional evaluation. Dosimetry data have not yet been obtained on sufficient numbers of patients and these studies are still required. The role of oxidizing agents in poisoning of labelling reactions is under study along with prevention methods. These studies will be continued and pursued in detail in the coming year.

(iv) ^{131}Iodocholesterol:

The development of ^{131}I-19 iodocholesterol as an adrenal scanning agent, by Beierwaltes and colleagues at the University of Michigan, provides an important new tool for diagnosing and localizing adrenal disease. Professor Grant Liddle, Chairman of the Department of Medicine, and Director of the Endocrinology Division is following a large number of patients with various adrenal disorders. These patients are studied in great detail. We have filed an IND and are now approved to use ^{131}I-19 iodocholesterol. We obtain 10 mCi from the University of Michigan once or twice a month and inject 1 mCi/patient. We plan to study approximately 50 patients during the coming year, obtaining serial blood, urine and whole body counts as well as Anger scintillation camera iamges. The data will be collected in the PDP/9 computer. Images will be corrected for non-uniformity of camera response, data bounded, smoothed and display processed for presentation to clinicians for diagnostic judgements. Quantitative analysis of uptake in right and left adrenals will be obtained from scans performed in the low level whole body counter on day 10-14. The evaluation of radiation dosimetry and efficacy of this potentially important new procedure will be performed in collaboration with Dr. Liddle and his staff.

v. Bismuth-206 as a brain scan agent

For some time radioisotopes of bismuth have been known to have significant promise as tumor-localizing agents. The basis for this interest was derived from the results of studies with tumor-bearing rats (1) where tumor-to-blood ratio of 20 to 85 have been obtained. These results have been confirmed by others for a variety of tumors (2,3). If these large ratios hold true for man, bismuth could be a very valuable tumor-localizing agent. Of the several bismuth isotopes, ^{206}Bi appears to be the most favorable for scanning. It has a half-life of 6.2 days and emits multiple gamma rays with the more intense transitions lying in the 800-900 keV region.

The primary problem associated with imaging distributions of Bi-206 is the multiplicity of high energy gamma ray transitions with energies up to 1.6 meV. The presence of the high energy transitions produces severe problems in collimation due to penetration and also imaging problems due to scatter contributions to photopeak counts. Hoffer et.al., recently suggested that GeLi detectors could be used to advantage in mapping Bi-206 (IEEE Trans Ns-19, p.51.) To verify their suggestion we conducted studies to determine the optimum energy window and detector for scanning Bi-206. The results of these studies showed that the optimum window for imaging with a large (5X4 inch) NaI(Tl) detector should bracket the 800 keV family of peaks assuming adequate collimation (See AEC Report # 2401-60).

The Isotopes Development Group at Oak Ridge National Laboratory has developed methods of producing high purity Bi-206 for patient studies. At the time of this proposal we have received two shipments and have only limited patient data. One study involved a patient with a massive recurrent poorly vascularized meningioma near the midline of the brain. Technetium uptake was very poor. This patient was administered 250 uCi of Bi-206 intravenously and was scanned with steel room

high energy gamma scanner, 48 hours later with single channel analyzer windows bracketing the 800 keV family of photopeaks. The images obtained were of poor quality, however the presence of the lesion was demonstrated on the posterior view. The patient went to surgery 8 days after administration and tumor and blood samples were obtained. These samples were counted using a dual-opposed NaI(Tl) sample counting system. The tumor-to-blood ratio of 11.7 was much lower than expected and is thought to account for the poor tumor visualization in the scan images. A second patient with a cerebellar hemangioendothelioma was studied. This tumor could not be visualized with techneitum, and similarly Bi-206 was not imaged successfully. In this case there was no detectable difference in tissue and blood levels. These patients had both been operated upon previously. When S/S recurred they were restudied and when these were unsuccessful Bi-206 was then tried.

We plan to continue Bi-206 scanning of patients with tumors which are difficult to visualize using other isotopes. If these patients are scheduled for surgery, we will simultaneously administer tracer amounts of other isotopes (Tc-99m , Ga-67, etc.) for comparison purposes to determine the relative merits of Bi-206 for tumor localization in men. The continuation of this work will depend upon the continued availability of Bi-206 from ORNL.

1. C.M.E. Matthews and G. Molinaro. "A Study of the Relative Value of Radioactive Substances used for Brain Tumor Localization and of the Mechanism of Tumor/Brain Concentration in Transplantable Fibrosarcoma, Brain, and other Organs of the rat," British Journal of Experimental Pathology 44, (1963), p. 260.

2. J. Th. VanDerWerff, "Gamma Encephalography with Radioactive Bismuth-206" ACTA Radiol. 4:403-16, July, 1966.

3. F. Mundinger "Radioactive Bismuth (Bi-206), its Biological Basis and Results in the Localization and Possible Specific Diagnosis of Intracranial Expanding Lesions". Proceedings of Second International Congress of Neurological Surgery, 1962. p. E125.

(b) Calcium Metabolism Studies:

(i) Methodology:

1. Calcium-47 Kinetics:

Patients on a constant intake of calcium are administered approximately 35 uCi of ^{47}Ca, I.V. Plasma samples are obtained each hour for the first four hours post injection and then daily thereafter. Urine and stool collections are made daily in addition to a daily whole-body rectilinear scan out to day 7 to 10. To date, we have studied calcium kinetics in patients before and after various forms of therapy. The protocol for these studies includes pretreatment base-line kinetics, a repeat study after patients have been on calcitonin for several months, and again two weeks after withdrawal. Careful control of dietary calcium is assured as these patients are in the Clinical Research Center.

Although the hormone effect is complex, useful information can be obtained using compartmental analysis techniquesto calculate steady state compartment sizes, transfer rates between compartments and their fractional turnover rates. We have employed Berman's compartmental analysis digital computer program, SAAM 25, for data analysis.

Figure 1 shows a schematic of the compartmental model used to analyze the data from the Osteoporosis studies and in those patients with Paget's disease where the disease seemed to involve the whole body uniformly. This model was first used by Neer and Berman (1). Figure 2 is a schematic of the model used to analyze data from patients suffering from localized diseases, Paget's disease in particular. In the case of localized diseases we make direct measurements of the kinetics of the diseased regions in addition to normal regions. These data are treated as independent measurements by the SAAM-25 program.

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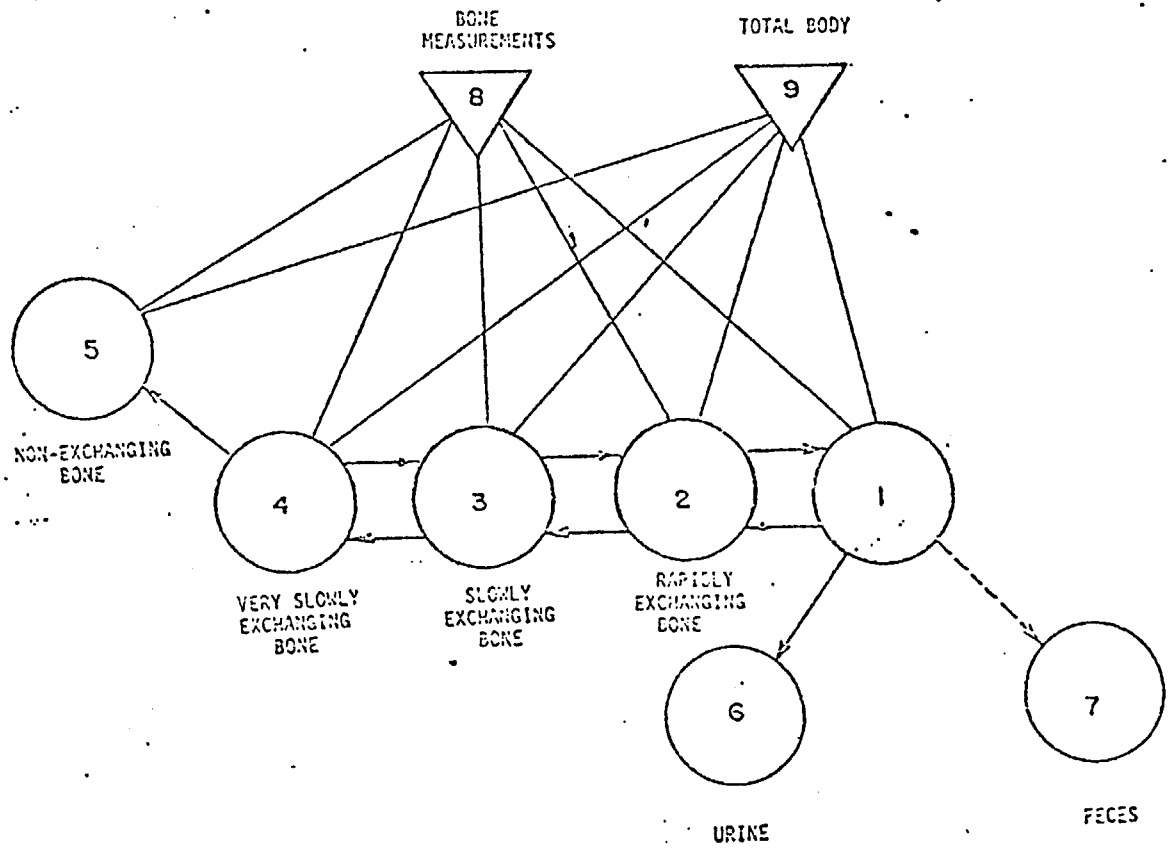
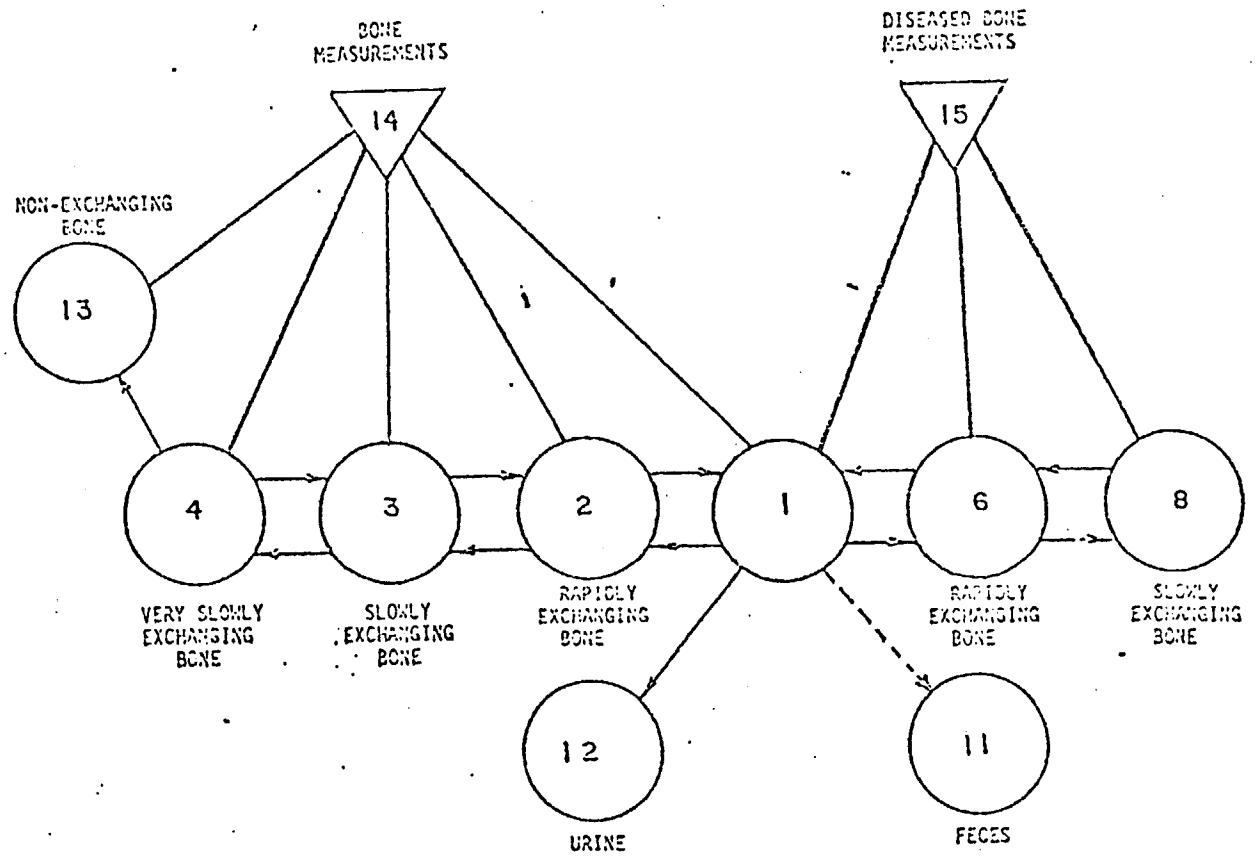


Fig. 1 Schematic of SAAM-25 calcium kinetics model used in osteoporosis studies.

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Fig. 2 SAAM-25 calcium kinetics model modified to be used in studies of patients with localized bone diseases.

We have found it necessary to modify the cumulative stool compartment by inserting a series of delaying compartments to simulate the intestinal transit time of the radiocalcium for the model shown in figure 1. We identify compartment 1 as that pool into which we inject the calcium and from which we withdraw our serum samples. We have found that the apparent volume of this pool in our studies varies from slightly below, to about 4 times as large as the average normal studied by Neer and Berman. Compartments 2,3,4,5 correspond to various stages of bone fixation with 5 corresponding to fixed bone. The short term of most of our studies does not allow us to detect bone reabsorption which would be estimated from the model calculation by the flow rate from the relatively non-exchanging bone (compartment 5) back to the very slowly exchanging bone compartment. This does not invalidate the calculation of ^{47}Ca radiation dose estimates since we assume infinite retention in that compartment, which results in a slight over-estimate of absorbed dose in bone.

In conjunction with the studies to be described in this section, we will modify the models and test them against experimental data collected whenever possible.

(1) R. Neer, M. Berman, et. al. J. Clinical Inv. 46, 8, 1967.

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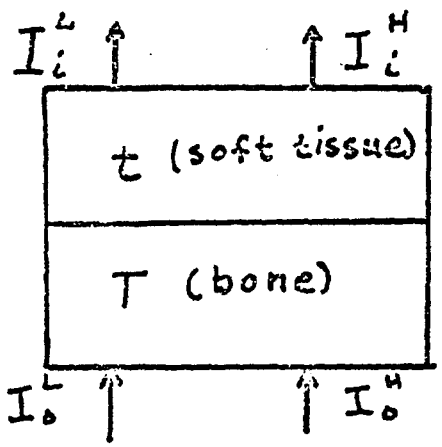
2. Bone Mineral Content Determinations

Cameron and others have developed transmission scanning techniques whereby bone mineral content can be measured with accuracies on the order of 2% and changes of 2% in the bone mineral content can be detected. In this procedure, a collimated beam from a radioactive source is passed through a patient and unattenuated photons are collected by a collimated detector. Attenuation is proportional to the density of material through which the beam is passing, and quantitative assessment of bone mineral content can be derived. (Cameron, et.al., Proceedings of Bone Measurement Conference, USAEC CONF-700515). Low energy isotopes such as ^{125}I, ^{241}Am, and ^{153}Gd have been used successfully for bone mineral determinations. Higher energy isotopes such as $^{99}Tc^{m}$, ^{131}I, and ^{85}Sr have been used to obtain anatomical information necessary with certain emission scanning procedures, particularly for dosimetry measurement. For example, organ location and relative thickness measurements are made in our laboratory by means of transmission scanning as a necessary part of our quantitation procedures with the whole body counter.

In order to determine the high Z elemental content of the body part chosen for study, two different techniques have been used. A material with the same electron density as soft tissue can be packed about the body part so that diminution in transmission over the bone has a properly normalized reference, i.e. equivalent soft tissue stopping power. Alternatively, several multiple energy transmission sources have been investigated. The usual energy output of dual isotope sources includes one transition $\leq$60 KeV and another $\geq$100KeV, the lower energy being preferentially attenuated by high Z elements, and the upper being indifferently attenuated by bone and soft tissue. For whole body bone mineral content determinations the dual isotope method is simpler and better accepted by patients.

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Unlike routinely used transmission scanning devices which assume the bone to be imbedded in a uniform field of soft tissue of constant thickness, the dual isotope method measures and corrects for soft tissue attenuation at each point of the rectilinear scan. Each region of the body can be thought of as containing a component of soft tissue of thickness t, and bone thickness T. The soft tissue may be located both outside and inside the bone. When this region is exposed to two monoenergetic beams of photons, one low energy I_o^L (28KeV), one high energy I_o^H (365 Kev) the following attenuation equations can be written:



$$I_i^H = I_o^H e^{-\mu_t^H t - \mu_B^H T}$$

$$I_i^L = I_o^L e^{-\mu_t^L t - \mu_B^L T}$$

These two simultaneous equations can then be solved for t and T in terms of the measured attenuation coefficients and densities. We have chosen photon energies so that the low energy beam has large differences in bone and soft tissue attenuation and the high energy beam has almost identical soft tissue and bone attenuation properties. This fact can be used to simplify the equation by setting $\mu_t^H = \mu_B^H$.

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$$T_i = \frac{\ln\left(\frac{I_0^L}{I_i^L}\right) - \frac{\mu_t^L}{\mu_t^H}\ln\left(\frac{I_0^{H2}}{I_i^{H1}}\right)}{\mu_B^L - \frac{\mu_t^L \mu_B^H}{\mu_t^H}}$$

for $\mu_B^H = \mu_t^H$

$$T_i = \frac{\ln\left(\frac{I_0^L}{I_i^L}\right) - \frac{\mu_t^L}{\mu_t^H}\ln\left(\frac{I_0^H}{I_i^H}\right)}{\mu_B^L - \mu_t^L}$$

The values of u will be measured on our system using packed bone and water to simulate soft tissue. The bone mineral content of the total body or any selected region is found by summing Ti. For Ti to be expressed in terms of mass the u should be replaced by u.p where p is the density.

The calibration of the whole-body transmission scan to determine the total body and regional calcium content from total bone mineral content is currently underway and will be continued. Three of our staff have had total body calcium measurements made by whole-body calcium activation analysis at the Brookhaven National Laboratory. We are now performing whole-body transmission scans on these volunteers and will develop calibration factors relating measured bone mineral content to calcium content.

Much attention has been given to the development of suitable sources. At present, we are using a combination of ^{125}I and ^{131}I (365KeV) for the transmission source. Over the central portion of the body, the ^{125}I transmission is low and hence large amounts (~100mCi of ^{125}I) are used.

An isotopic source of particular interest to us is ^{153}Gd. We have used this material for fluorescence and transmission scanning with success. The availability of two photons (99KeV γ and 40 KeV Eu X-ray) make it possible to do both bone and soft tissue determinations simultaneously with the same source.

The Isotopes Development Group at Oak Ridge National Laboratory is working on a method of preparing ultrahigh purity ^{153}Gd, and we are awaiting arrival of a high output source from them for use in these studies (at no cost to this contract). We plan to use this source in conjunction with our bone mineral content studies and to evaluate the radiation dose associated with transmission scanning techniques.

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(ii) Specific Studies

1. Osteoporosis and Paget's Disease

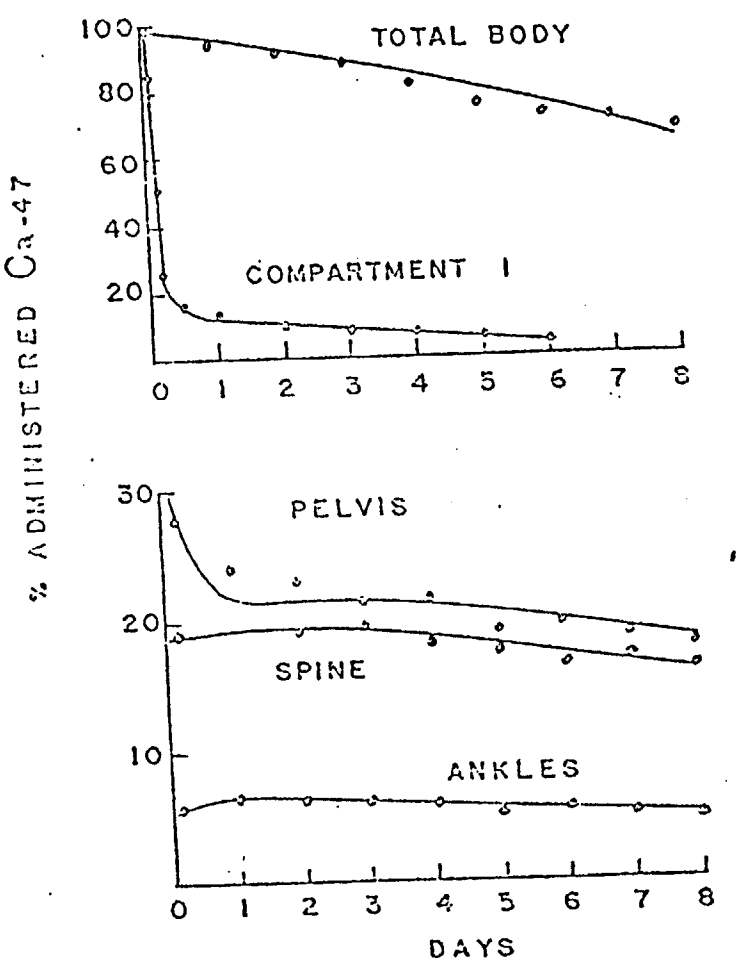
During the past year and a half we selected a group of nine patients who were to undergo calcitonin therapy. Of this group, 5 were suffering from Osteoporosis and 4 were afflicted with Paget's Disease. We have made baseline ^{47}Ca kinetic studies for all of these patients and have $\geq$4 months followup studies on three. Of these three patients, two (one with generalized Paget's disease and the other Osteoporosis) showed less marked changes in total body calcium distribution and SAAM 25 kinetic parameters while one patient suffering from localized Paget's disease showed striking differences in calcium uptake and turnover. The observed changes after therapy were restricted primarily to diseased bone sites while the kinetics of normal bone sites remained relatively unchanged. In the following paragraph we will described these data in more detail.

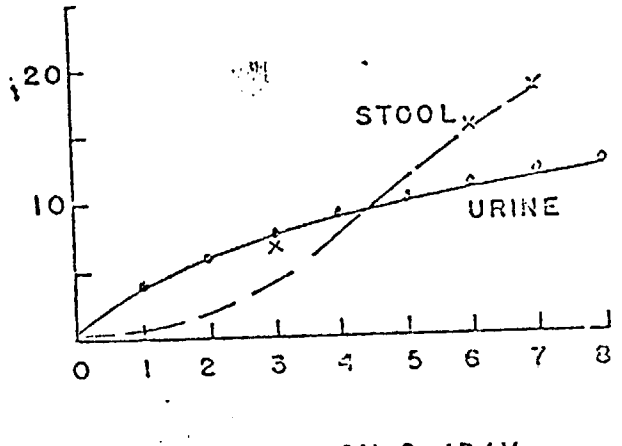
From the quantitative whole body scans for ^{47}Ca, we have selected bone sites such as the pelvis, spine, legs and ankles for measurements of the bone compartments. These bone measurements represented by triangles in the model diagram shown in section A(1) are assumed, in general, to represent a linear combination of the four compartments.

Figure 3 shows the results of the SAAM 25 model calculations as compared to the actual measurements for a typical osteoporosis patient. The kinetic parameters in this patient show a somewhat decreased turnover rate of compartment 1. No other parameters were found to be significantly different from normal. The apparent volume of distribution for compartment 1 was found to be normal to slightly decreased from noraml. The excretion rate was found to be within the normal range. Flow rates shown in Figure 3 are in units of grams per day.

—=mathematically generated fit
o,x =experimental data points

OSTEOPOROSIS





COMP 1 TO	MEASURED	NORMAL
BONE	18.8 ± 2.9	25 - 46
URINE	0.170 ± 0.005	0.13 - 0.41
FECES	0.63 ± 0.01	0.55 - 0.96

Fig. 3 SAAM-25 simulation calculations and corresponding external [illegible] from a typical osteoporosis patient.

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The total body retention measurement is a check on the completeness of stool and urine collections. Disagreements are attributed to incomplete stool collections, and the "corrected" data are used in the modelling calculations.

Figure 4 shows scans of the patient with generalized Paget's disease. The image on the left was made prior to thyrocalcitonin therapy. The image on the right was made after about 4 months of therapy. From the scan images alone it is difficult to detect or quantitate any difference. Figure 5 shows the results of the measured values and the corresponding model calculations for compartment 1 and the quantitative scan measurements of the spine, pelvis, legs and whole body.

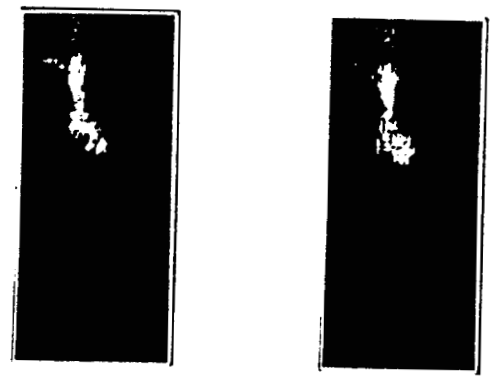
Over the study period before therapy, we found no appreciable loss of radiocalcium. After therapy there was a slight decrease in total body retention. Serum calcium levels (before and after) showed no significant change. However, there was a significant increase in the clearance rate of compartment 1. There was no significant change in urinary and fecal excretion rates. The bone measurements, in general, showed approximately equal initial uptakes. However, after therapy the bone measurements show increased contributions from the more rapidly exchanging bone compartments.

Figure 6 shows two scan images of a patient with localized Paget's disease. The image to the left was made prior to thyrocalcitonin therapy. The image on the right was made during our study at about four months after the start of therapy. In this case, the decreased uptake in the diseased region after therapy is more obvious.

To describe the kinetics of these studies, we have used the modified model described in section A(1) for the diseased bone which communicates with the normal pathways through compartment 1. We have investigated several

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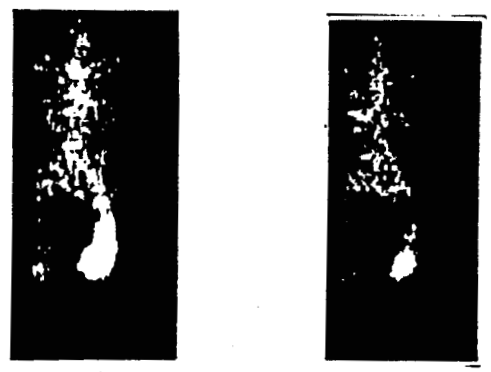
PAGET'S DISEASE



BEFORE AFTER

Fig. 4 ^{47}Ca whole body scans of patient with generalized Paget's disease made before and at approximately 5 months after the start of Calcitonin therapy.

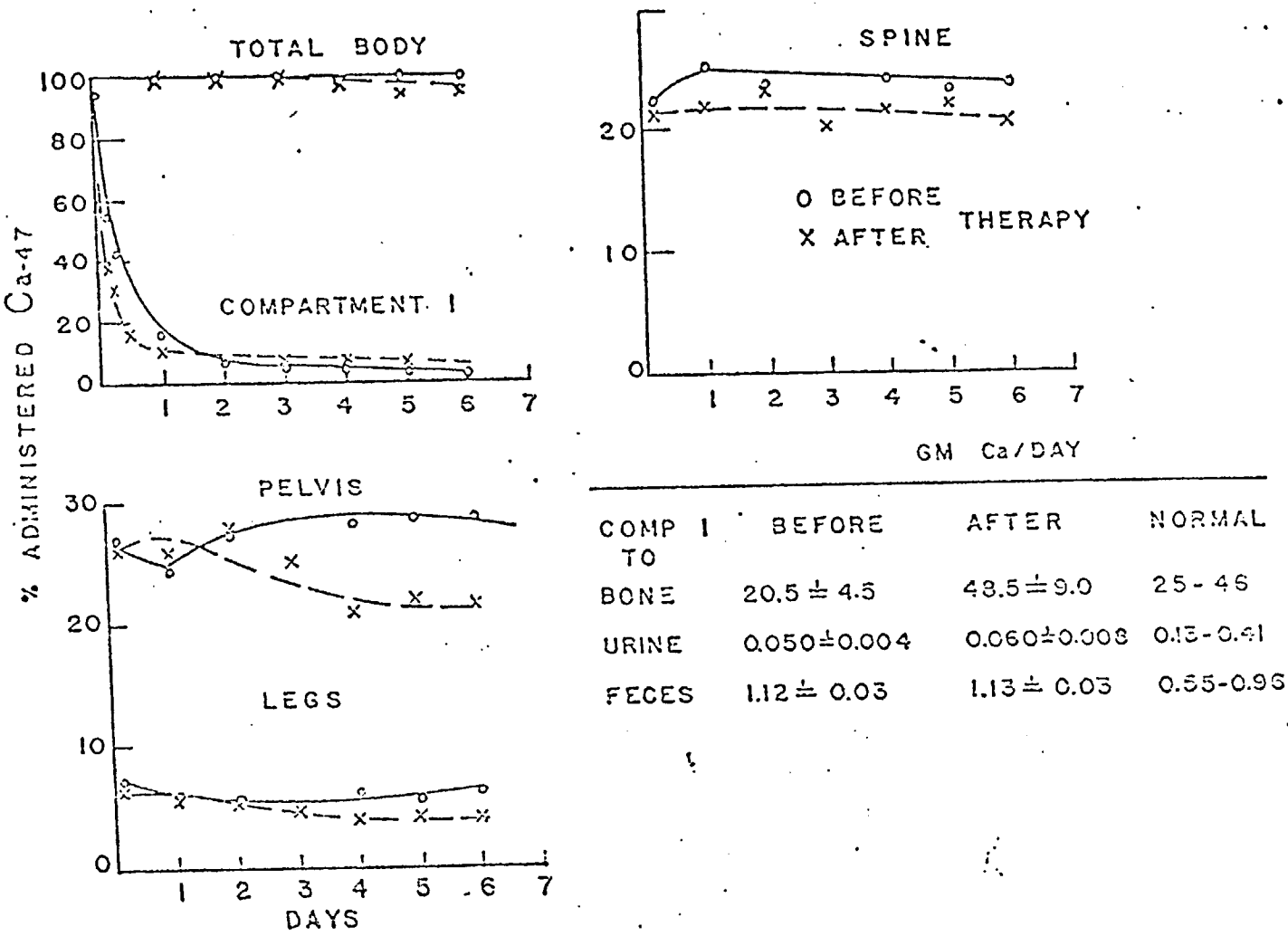
PAGET'S DISEASE



BEFORE AFTER

Fig. 6 ^{47}Ca whole body scan of a patient with localized Paget's disease made before and at approximately 4 months after the start of Calcitonin therapy.

PAGET'S DISEASE



COMP 1 TO	BEFORE	AFTER	NORMAL
BONE	20.5 ± 4.5	48.5 ± 9.0	25 - 46
URINE	0.050±0.004	0.060±0.008	0.13 - 0.41
FECES	1.12 ± 0.03	1.13 ± 0.03	0.55 - 0.96

Fig. 5 SAAM-25 simulation calculations and corresponding radiocalcium measurements for a patient with Paget's disease. The disease showed general bone involvement.

4S

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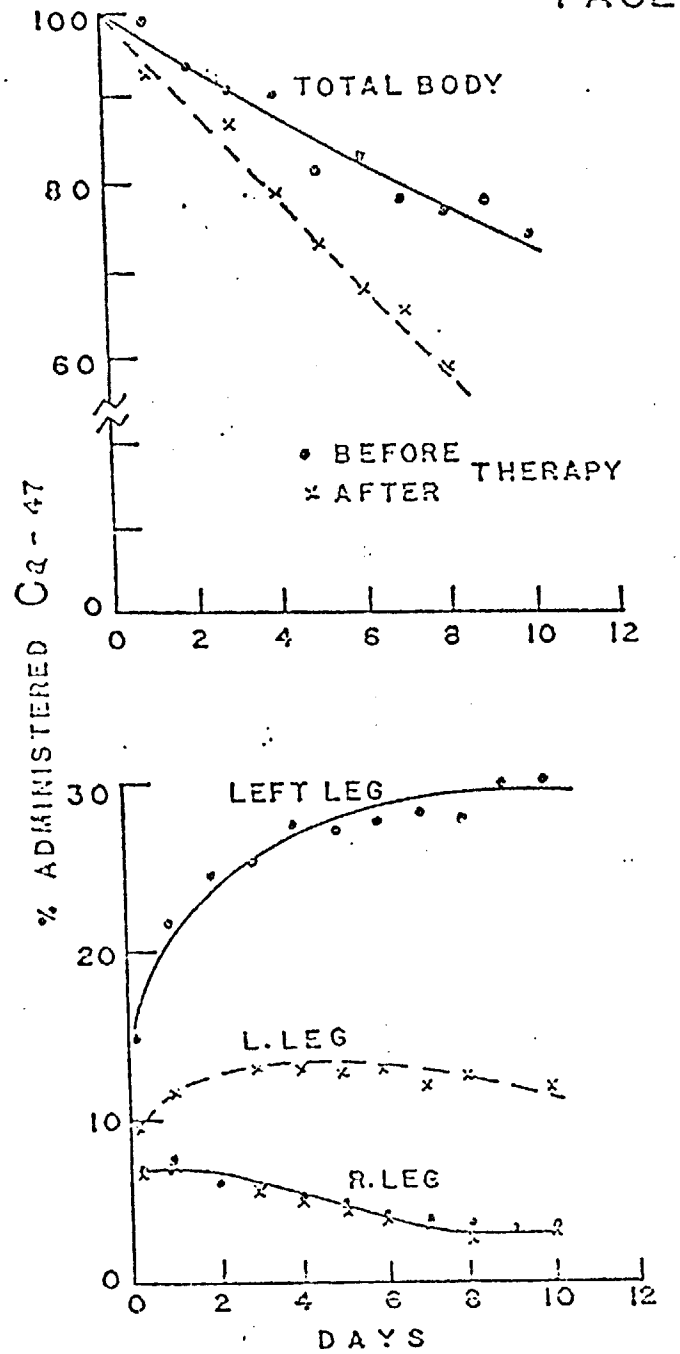
configurations of the diseased bone compartments, and have found that a two compartment system for the diseased region is the simplest configuration that gives good fits to the patients we have studied. We have constrained the size of these additional compartments to the measure value of the diseased area. Figure 7 shows some of our measurements and the corresponding model calculations for this patient.

Similar to the effects seen in the case with generalized Paget's disease therapy increased the tracer calcium disappearance rate from compartment 1. Contrary to observations in very short term studies, this patient had an increased urinary excretion rate after thyrocalcitonin therapy. There was no statistically significant difference in the fecal excretion rates. The increased excretion can easily be seen in the total body retention curve. The effects of therapy are seen most dramatically in comparison of the measurement of the diseased bone site versus a corresponding region in the normal leg. The diseased site was seen to reduce uptake of radiocalcium by about a factor of 2 while having no appreciable effect on the uptake in the normal leg. These results suggest that thyrocalcitonin has its greatest effect in regions of rapid bone turnover.

We are continuing to make radiocalcium turnover measurements and are investigating the possibility of using transmission scanning data as absolute measures of whole body and regional calcium content as normalizing constraints for our model simulations.

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PAGET'S DISEASE



COMP I TO	GM Ca / DAY BEFORE	AFTER	NORMAL
NORM. BONE	5.3 ± 3.0	35 ± 10	25 - 46
DIS. BONE	2.0 ± 0.2	1.5 ± 0.7	
URINE	0.21 ± 0.01	0.31 ± 0.01	0.13 - 0.41
FECES	0.62 ± 0.01	0.69 ± 0.02	0.55 - 0.96

Fig. 7 SAAM-25 simulation calculations and corresponding external ^{47}Ca measurements for a patient with Paget's disease involving the left leg.

1037601

2. Bone Mineral Content Determination

(a) Animal Studies

In collaboration with Dr. John Connolly of the Orthopedic Surgery Department, we are presently using I-125 transmission scanning techniques to study fracture healing in animals. Techniques developed in these studies will then be used to study fracture healing in humans.

In a large group of dogs, we have fractured the right radius and have allowed it to heal in a case for varying periods of time, usually from 3 to 10 weeks. At the end of the selected interval of time, the animal is sacrificed and both right and left legs are submitted to I-125 transmission scans. The bone mineral contents of the fracture region and the corresponding region of the normal bone are determined by the following equation:

$$\text{Bone Mineral Content} \approx \sum_j \ln\left(\frac{I_o}{I_j}\right)$$

where I is the unattenuated beam and I_j is the attenuated beam measured over the j^{th} region of the bone. The scan is carried out over a region that extends from approximately one-half inch above to one-half below the fracture site. A region of equal size is scanned in the normal bone. An index of healing is computed by taking the ratio of the control leg to the fractured leg.

After transmission scanning the bones are submitted to tests which measure the breaking torque and angle of break. Animals studied to date show that the breaking torque is apparently related to mineral content. This can be seen in Table I.

We propose to continue these transmission scanning studies in an effort to correlate rates of recalcification quantitatively with clinical radiological and ultrasonic estimation of fracture healing. Attempts to increase the rate of healing by type of fixation, mobilization, and electrical stimulation are under study in these collaborative continuing investigations. For

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these studies we have used a Si(Li) detector on a research scanner ordinarily used for thyroid fluorescence mapping studies. In the next year, we plan to build or acquire a scanning table so that the subject can be moved, and the detectors held stationary. In this way, perfect alignment of source and detector will be assured at all points in the scan.

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T A B L E I

BONE DENSITY MEASUREMENTS

Dog #	Time of Healing (weeks)	Bone mineral Ratio	Breaking Torque Ratio	Breaking angle Ratio
77	3	0.20	0.20	0.41
57	5	0.21	0.16	0.62
69	6	0.52	0.48	0.66
92	6	0.58	0.86	0.47

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(b) Human Studies

Immobilized patients are known to lose body calcium at increased rates. In patients immobilized for long times, such as paraplegics and quadriplegics, significant complications relating to calcium losses are encountered and suitable therapy, including mobilization, is needed to reverse this process. With the transmission scanning systems described in the experimental animal bone fracture studies, we are making a series of measurements in a young female paraplegic patient.

The results of these measurements are shown in figure 8 . During the first three weeks of the study scans were made twice weekly on successive days to insure reproducibility of measurements. We are now making measurements at approximately two week intervals and are attempting to correlate changes in bone mineral content with changes in therapeutic regimens. These studies will continue in this patient and in others in whom prolonged immobilization is required.

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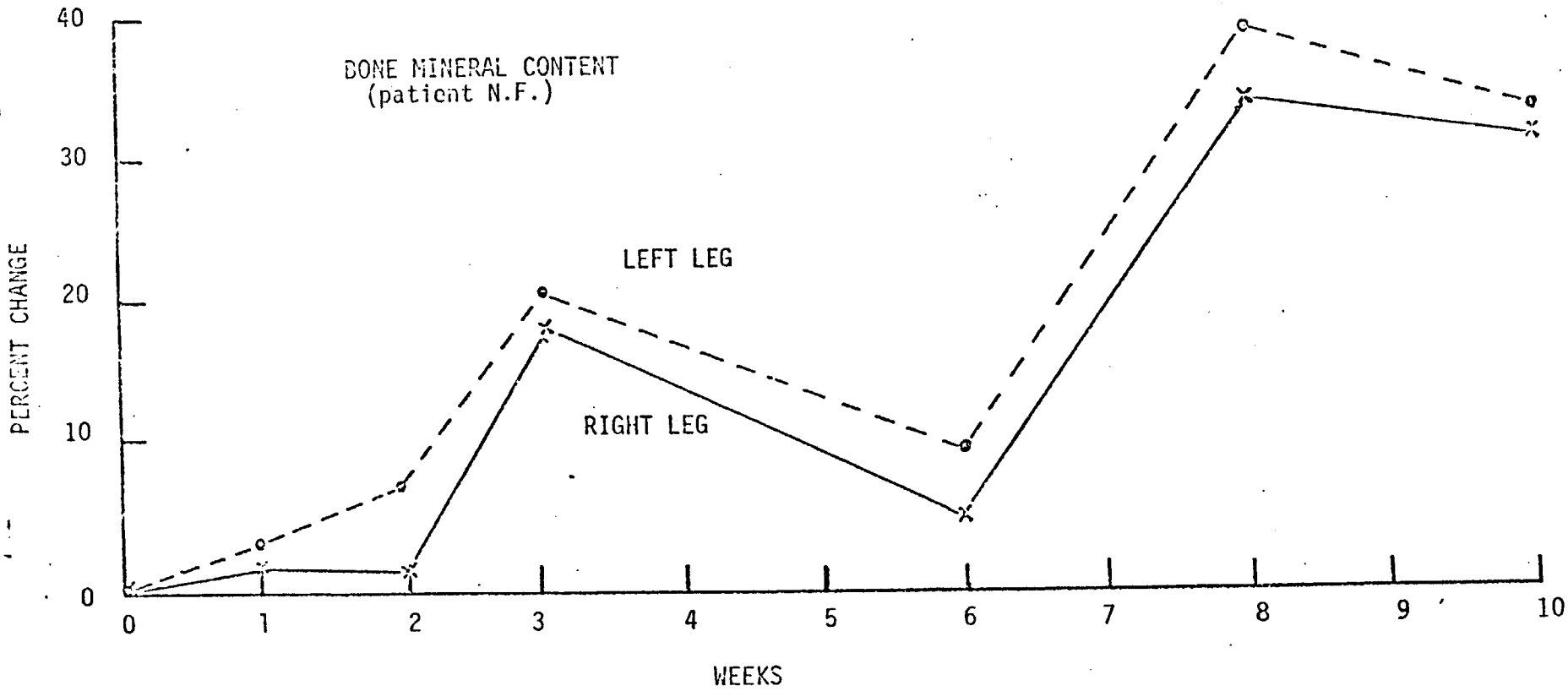

BONE MINERAL CONTENT
(patient N.F.)
LEFT LEG
RIGHT LEG
PERCENT CHANGE
WEEKS
0
10
20
30
40
0
1
2
3
4
5
6
7
8
9
10

Figure 8

3. Osteogenesis imperfecta

A relatively large number of patients with osteogenesis imperfecta are being followed and treated at VAnderbilt. Patients with this hereditary disease are subject to bone fractures due to the presence of thin brittle bones. A variety of drugs have been tried in the treatment of this disease, and presently at Vanderbilt, patients are being treated with fluoride containing compounds. In an attempt to determine whether there is appreciable increase in mineralization during therapy, patients will be studied at frequent intervals with bone mineral content measurements over selected sites. Regions will be chosen which are large enough to minimize repositioning uncertainties and small enough to minimize radiation exposures. Approximately 10 patients (varying from 2-18 years) will be studied per year, and these studies will be continued over several years. These collaborative studies will be conducted under the direction of Dr. Paul Griffin, Chairman of the Department of Orthopedic Surgery. Other biochemical and radiographic measurements will be make to evaluate other effects of treatment.

c. Massive obesity

The jejuno-ileal bypass operation has been shown to be an effective means of causing weight loss in morbidly obese patients by inducing malabsorption. In collaboration with Dr. H. William Scott of the Department of Surgery, we have been studying a number of patients undergoing different types of small bowel bypass operations in an effort to assess the effect on weight loss and body composition.

In addition to the usual methods of metabolic appraisal, lean body mass (LBM) is measured before and at intervals after jejunoileal bypass. Two types of measurement of LBM are being made: (1) from ^{40}K whole body counting, and (2) from $^{3}H_2O$ spaces. LBM derived from ^{40}K whole body counting has been found to be the preferred method because of its ease of measurement on an outpatient basis. In addition, these patients tend to be edematous and commonly have elevated total body water spaces. Elevated total body water values yield elevated estimates of the LBM since the calculation assumes that 73.2% of the LBM is equal to the total body water.

As described in an earlier report (1969), the whole-body scanner operating in the exposed crystal mode has been calibrated with known amount of K-40 so that the cpm from a patient can be translated into milliequivalents of K and LBM (LBM in kg = mEq. K/68.1). In order to establish the reproducibility of the technique, daily measurements were made in a small group of normal subjects. The data of two of these subjects are shown in Figure 1. For subject A the coefficient of variation was 3.7% while the value was 5.1% for subject B.

Reviewing the results of the patients studied to date, we have found striking loss of weight occurring during the early post-operative months (normally 6 months) followed by a period of more gradual weight loss (figure 2). From the K-40 whole body counts, we have found that total body

1037608

potassium (LBM) also decreased and approximately paralleled weight loss for the initial post-operative period (figure 2). This indicates that lean body mass and fat are being lost at equal rates. For the second period (6 months) most patients generally lose no further LBM but continue to lose weight, indicating loss of fat only.

We propose to continue to follow those patients who have undergone bypass operations during the past year and to start measurements on patients who are now being submitted to a modified operative procedure. In addition to monitoring LBM in each of these study groups, we will make group comparisons of the rate and magnitude of loss of LBM.

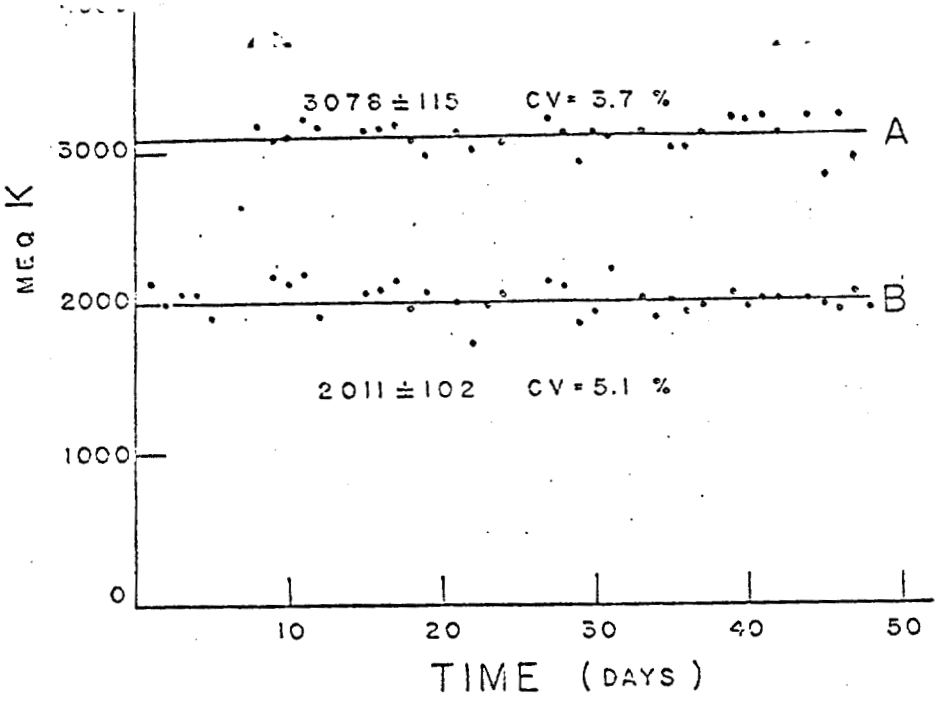


Fig. Repeated measurements of total body potassium for two normal patients.

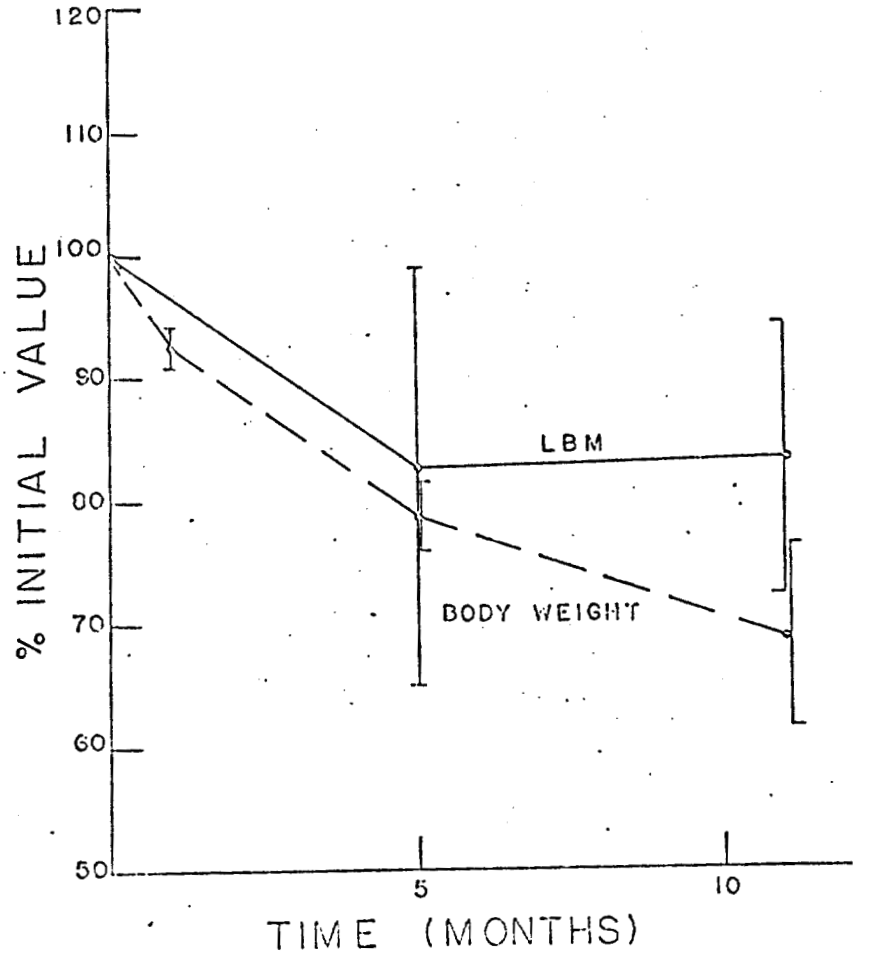


Fig. Comparison of loss of Lean Body Mass and body weight for a group of patients following by-pass operation.

1037610

d. Monitoring of ^{137}Cs Levels in Man

Over two years ago we resumed a program started in 1959 by Meneely, et al. to monitor the ^{137}Cs levels in a population of normal individuals. We made measurements on a small group of young male subjects who were studied earlier by Meneely. At that time we found about a twofold decrease in total body burden of ^{137}Cs from Meneely's 1966 value.

During the past year, we have recalibrated the system in order to make the most accurate measurements possible. In this recalibration procedure we have used the ^{137}Cs levels as determined for three normal males by the Brookhaven National laboratories whole-body counting system as absolute normalization for our system. The mean value for last year's measurements was found to 3.13 ± 2.12 nonocuries. This appears to be decreased from the previous year's value. We will continue to monitor Cs-137 levels in subjects from the middle-Tennessee area as part of our routine whole body counting program. We will also continue to attempt to remeasure a sample of those subjects from earlier studies in 1956.

1037611

B. Clinical Applications of Activation Analysis

1. Californium-252 Studies

In previous years, we have reported on the results of investigations using activation analysis for sample composition and stable tracer kinetic studies. In these studies we have attempted to achieve high sensitivity in order to study metabolism in normal individuals and pregnant women without the need to administer radioactive compounds or large amounts of stable materials. Stable tracers have been used in newborns to determine blood volume and to determine the time at which intracranial intraventricular hemorrhages occurred by analysis of head clot samples obtained at surgery. In view of the fact that we do not have access to neutron irradiation facilities on site we have had to irradiate samples at remote locations, i.e. ORNL and/or Georgia Tech. In order to circumvent this problem we have sought funds for on site accelerator facilities in the past, without success. These were joint ventures with the V.U. Physics Dept., focused initially on a small cyclotron and subsequently on the Wright-Patterson Van de Graaff facility. In order to utilize neutron activation analysis effectively, high output sources on site are needed so as to provide results in reasonable time periods. With the amounts of ^{252}Cf currently available, many elements cannot be quantitated. In principle, one can increase the sensitivity of the analyses by increasing the size of the source or irradiated samples (providing that flux depression corrections can be made). Similarly, the ability to do in-beam counting of prompt gammas, protons, and alphas may provide sufficient sensitivity for some biomedically important studies, if background levels are low. We propose to evaluate feasibility using ^{252}Cf sources in neighboring installations,

1037612

i.e. ORAU and elsewhere as needed. Pu(Be) and Am(Be) will also be investigated, since their higher neutron energy may be advantageous for whole body activation analysis.

We have been deeply involved with body composition measurements for many years, primarily involving studies that could be performed with our whole body counter. These included lean body mass from K-40 determinations, ECF (Br-82), TBW (T_2O), Red Cell mass (Cr^{51}) and PV (RISA) and more recently quantitative regional bone mineral content has been measured by transmission scanning. Our system has been calibrated by neutron activation of three of our staff followed by determination of total body calcium at BNL. We are actively involved in studying calcium kinetics in patients using radioactive tracers and transmission scanning in collaboration with orthopedic surgeons at Vanderbilt in an effort to evaluate the efficacy of different means of treating fractures, and managing patients with osteoporosis and Paget's disease. The availability of a sensitive method of measuring body calcium content would greatly enhance these studies.

Marshall Space Flight Center designed and built a neutron sensitive imaging system with an image intensifier with a neutron converter face plate and video camera coupled to a video disk storage system. This system has never been used and at present is not operational. We have obtained the system and with the assistance of MSFC staff, are now attempting to make it operational and to test the system with low light level inputs. We will subsequently test it with low yield neutron sources (PuBe) available at Vanderbilt. Routine neutron radiography studies would require higher output sources such as readily available from 1-5 mgm ^{252}Cf.

During the coming year we will evaluate the feasibility of using neutron sources in our facilities for the above applications and will design the needed shielding and irradiation facilities. Pilot studies will be conducted at existing neighboring facilities. Our own neutron radiography system will be made operational and tested. Funds for site modification and source configuration will then be sought. This will be the basis of either a small supplement request or a part of next year's proposal.

103614

2. Tissue Levels of Trace Elements in Ischemic Heart Disease

We plan to continue to participate in the IAEA protocol and to collect heart, liver and kidney specimens from patients with ischemic heart disease, and accidental death victims autopsied at Vanderbilt. We will obtain background medical and demographic history as required by the protocol and carry out analyses in collaboration with reactor based investigators participating in the IAEA/WHO study. For many of the analyses, one needs to look at short-lived nuclides and radiochemical on-site separations will be needed. Since we do not have these facilities, it seems best to have these analyses run by staff at other participating sties, and this will be arranged for analysis of samples currently being acquired.

Numerous methodological problems have been identified by the IAEA working group and many have been solved. Some technical problems involving how to collect uncontaminated samples still exist, but these are being solved. Inter-laboratory variations in assay procedures and accuracies will be a continuing problem, but these, too promise to be minimized by exchange of intercomparison standards.

A major problem arises from the fact that many of the principal investigators are analysts who have little contact with the medical sources of their samples. Thus, limited information is often available on patients in the study. Major problems involve drugs patients receive, including radioactive materials, and chelating agents which may transiently alter trace element distributions, residential and dietary histories which may be prime determinants of body content of trace elements. An even more significant problem arises from the fact that many study participants are unable to obtain materials from subjects who die in accidents since they may be infrequently autopsied. Because of regional

differences it is essential that "control" samples be available for comparison purposes. The possibility exists that suitable samples could be obtained from ABCC autopsy studies in accordance with IAEA/WHO protocols. Interest in cardiovascular studies at ABCC and traditional emphasis on geographical pathology in Japan should enhance the possibility that such a study would be considered seriously by ABCC and we will help to catalyze the process. I plan to explore this matter with former colleagues at ABCC informally and will proceed in accordance with their reaction and that of the ABCC Director.

1037616

VI. Scientific Personnel --Curriculum Vitae on file AEC

Principal Investigator:

A. B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Director Division of Nuclear Medicine & Biophysics and the Clinical Radioisotope Center, 25%

Co-Investigators:

R. E. Johnston, Ph.D. [redacted]
Assistant Professor, Radiology, 35%

R. Price, Ph.D. [redacted]
Instructor, Radiology, 35%

Research Associates:

J. Erickson, Ph.D. [redacted]
Instructor, Radiology, 67%

J. Patton, Ph.D. [redacted]
Instructor, Radiology, 29%

J. Parker, [redacted]
Computer Engineer, 33%

J. E. Lagan, Electronics Engineer
[redacted] 78%

VII. Other Personnel

Graduate Students:
J. Jones
K. Larsen

Secretary: C. Elam, [redacted] 100%

VIII. Other Financial Assistance -- Federal or Non-University

Co-Investigator, salary support from Veterans Administration, 35% effort this research.

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 8,000 square feet adjacent for conference, library, clinical scanning, and instrument development and modification	100 percent
Computer Center	As required
Clinical Research Center	As patients present
Clinical Radioisotope Laboratory	Radiochemistry and counting facilities as needed
Animal House	Maintenace 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

RENEWAL PROPOSAL
Contract At-(40-1)-2401
1 August 1973 - 31 July 1974

X. Budget Estimated Requimrents	AEC	University	TOTAL
1. Salaries & Wages Name, title, monthly rate, % effort			
Principal Investigator: A.B. Brill, M.D., Ph.D. [redacted] Professor, Medicine and RAdiology Salary support not included, proportionate sharing, 25%	-0-	---	---
Co-Investigators: R.E. Johnston, Ph.D. Asst. Professor Radiology Salary support, Veterans Administration, 35%	-0-	---	---
R. Price, Ph.D. Instructor Radiology @ $1,181, 35%	$ 5,000.	---	$ 5,000
Research Associates: J. Erickson, Ph.D. Instructor Radiology @ $1,114/mo, 67%	$ 6,500	$ 2,500	$ 9,000
J. Patton, Ph.D. Instructor Radiology @ 1,167,29%	$ 4,000	---	$ 4,000
J. Parker, Computer Engineer, @ $1,000, 33%	$ 4,000	---	$ 4,000
J.E. Lagan, Electronics Engineer,$1,020, 78%	$ 6,500	$ 3,000	$ 9,500
Graduate Students: J. Jones K. Larsen	$ 3,200 $ 3,200	--- ---	$ 3,200 $ 3,200
Secretary, C. Elam, 100%	$ 5,800		$ 5,800
Fringe Benefits (not fixed % of salaries. Varies with employee status & option)	$ 3,200	710	$ 3,910
TOTAL SALARIES & FRINGES:	$41,400	$ 6,210	$47,610

	AEC	University	TOTAL
2. Supplies & Materials			
Animal Purchases	$ 200		
Books & Journals	$ 200		
Chemicals & Glassware	$ 500		
Computer Expense - on campus	$1000		
Laboratory Supplies			
Radioisotopes	$2500		
Machine Service Contracts	$2500		
Office Supplies	$1200		
Equipment Rental	$1300		
Electronics Components (maintenance & repair)	$2700		
Subject Participation	$ 400		
	$12,500		$12,500
3. Equipment	-0-		-0-
4. Publications & copying	$ 800		$ 800
5. Travel			
Domestic - scientific meetings	$1000		$ 1,000
- Cf-252 Evaluation	$ 500		$ 500
6. Other	-0-		-0-
7. Indirect Costs, 44% salaries and fringe benefits	$18,216	2,732	$20,948
TOTAL PROJECTED COSTS	$74,416	$ 8,942	$83,358

1037620

Projected Costs

Percentage & Amount, Vanderbilt University	$ 8,942	10.7%
Percentage & Amount, Requested AEC	$74,416	89.3%

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Allan D. Bass
Associate Dean for Biomedical Sciences

Paul Gazzerro, Jr.
Assoc. Vice Chancellor for Medical Affairs for Operations and Fiscal Planning

NOTE: Studies described in this application, involving the investigational use of human subject, have been reviewed and approved by this Institution's Clinical Investigation Committee.

037621

VANDERBILT UNIVERSITY

NASHVILLE, TENNESSEE 37232 TELEPHONE 322-7311 AREA 615

Division of Nuclear Medicine & Biophysics • School of Medicine • Direct phone 322-2394

FINANCIAL STATEMENT

CONTRACT NO. AT-(40-1)-2401

Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period.	$ 42,447.
2.	Estimated total cost for remainder of period.	$ ~~30,302~~ 32,785
3.	Total actual and estimated cost chargeable to AEC for current period based on percentage of cost agreed upon as contained in A-111 of Appendix "A" to Contract.	$ ~~65,000~~ 67357
4.	Accumulated costs chargeable to AEC (include costs reported in certified statement for preceding period(s) and the costs stated in Item (3) above).	$ ~~307,125~~ 307,233.66
5.	Accumulated AEC Support Ceiling as stated in Article III of Contract.	$ 307,125.
6.	Total estimated AEC funds remaining under Contract (Subtract Item (4) from (5) which may be used to reduce amount of new funds required from AEC for proposed renewal period.	($ 108.66)

Macon Somerville

Macon D. Somerville
Assistant Director, Finance Acctg.

Above changes made per telecon with Mr. Somerville
5-3-74
R.T.H.
ORO

1037622

TO : Addressees Listed Below DATE: October 10, 1973

FROM : Ralph Elson, Director, Contract Division

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 21 to Contract AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~Lamar Medley~~	~~Contract~~	Emm	10-10-73	
2. ~~A. H. Frost, Jr.~~	~~Contract~~		10/10/73	
3. ~~A. E. Miller~~	~~Budget~~		10/16	
4. ~~W. H. Henderson~~	Finance		10/17	
5.				
6.				
RETURN TO				
Alice Brown	Contract Division			Tel.: 3-4105

1037623

Routed by

CONTRACT DIVISION

Form OR-133 (Rev. May 1972)

number

ROUTE SLIP

	MANAGER
	Deputy Manager
	Assistant to Manager for Pub. Infor.

	CHIEF COUNSEL
	Patent Group

	ASST. MANAGER FOR OPERATIONS

	MANUFACTURING DIVISION
	Quality Assurance Branch
	Weapons Branch

	PLANNING DIVISION
	Planning Branch
	Power Branch

	RESEARCH & TECH. SUPPORT DIV.
	Classification & Tech. Services Br.
	Research & Development Branch
	Standards & Quality Assurance Branch
	Waste Management Branch
	New Brunswick Laboratory
	Puerto Rico Area Office

	SAFETY & ENVIRONMENTAL CONTROL DIV.
	Health & Nuclear Safety Branch
	Ind. Safety & Fire Protection Branch
	Reactor & Facility Safety Branch
	Waste & Pollution Control Branch

	URANIUM ENRICHMENT DIVISION
	Nuclear Materials Control Branch
	Operations Branch
	Process Improvement Branch
	Toll Enriching Branch
	Cincinnati Area Office
	Paducah Area Office
	Portsmouth Area Office

	ASST. MGR. FOR ADMINISTRATION

	BUDGET AND REPORTS DIVISION
	Budget Analysis Branch
	Funds Control & Reports Branch

	CONTRACT DIVISION
	Negotiated Contracts Branch
	Research Contracts, Procedures, and Reports Branch
	Procurement Branch

	FINANCE DIVISION
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	Government Payroll Sect.
	Audit Branch
	ADP Branch
	ADP Service Center

	ORGANIZATION & PERSONNEL DIV.
	Government Personnel Branch
	Industrial Personnel Branch
	Organization & Management Branch
	Equal Opportunity Branch

	SUPPLY DIVISION
	Office Services Branch
	Records Holding Area
	Records Officer
	Supply & Maintenance Section
	Reproduction & Distr. Unit
	Stores Unit
	Mail Section
	Photographic Services
	Teletype Section
	Property Branch
	Transportation Branch

	SECURITY DIVISION
	Personnel Security Branch
	Physical Security Branch
	AEC Patrol

	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. Ser.
	Assistant Mgr. for Pro. Ser.
	Assistant Mgr. for Sci. Comm.
	Science & Tech. Branch
	Tech. Services Branch
	Assistant Mgr. for Comp. Processes & Mfg.
	Editorial Branch
	Graphics Arts Branch
	Printing Branch
	Assistant Mgr. for Doc. & Systems Dev.
	Document Mgmt. Branch
	Computer Operations Branch
	Program & Systems Dev. Branch

	RDT-OSR (ORNL)

	CONTRACT COMPLIANCE OFFICE (Southeastern Area)

	CONTROLLER REGIONAL AUDIT STAFF

	AECOP

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

~~1. BUDGET AND REPORTS DIVISION~~ ~~CONCURRENCE~~ O'Emilia

2. OFFICE OF CHIEF COUNSEL CONCURRENCE _____

4254

USAEC Technical Information Center, Oak Ridge, Tennessee

1037624

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

October 5, 1973

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: AT-(40-1)-2401
   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 Application of Activation Analysis"

3. Type of Contract:

   [X] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: $65,000

5. AEC Percentage of Est. Total Cost To Be Shown by this CA: 89.4%

6. Description of Other Changes To Be Covered by this CA:

   Modify contract to provide for the performance of additional research during the period August 1, 1973 through July 31, 1974. AEC support ceiling will be increased from $242,125 to $307,125. Title to the equipment, if any, shall vest in the Contractor under authority of Atomic Energy Act of 1954.

7. Authority:

   Form AEC-481 (CA) from J. L. Liverman, HQ, dated September 5, 1973.

A. H. Frost, Jr., Chief
Research Contracts, Procedures and Reports Branch
Contract Division

ACR: LM

1037625

APPENDIX "A"

VANDERBILT UNIVERSITY
CONTRACT NO. AT-(40-1)-2401

For the contract period August 1, 1973 through July 31, 1974

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 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 fringe benefits:	$42,979
(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:	$ 1,500
	Domestic--------$1,500 Foreign---------$ 0	
(4)	Other direct costs:	$ 9,359
(5)	Indirect costs (based on a predetermined rate of 44% of salaries and wages and fringe benefits):	$18,911

1037626

(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:

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 $72,749; the Commission will pay 89.4% 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 $65,000.

The estimated AEC Support Cost is funded as follows:

(a) Estimated unexpended balance from the prior period(s):	$ 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.

1037627

VANDERBILT UNIVERSITY

NASHVILLE, TENNESSEE 37232 TELEPHONE 322-7311 AREA 615

Division of Nuclear Medicine & Biophysics • School of Medicine • Direct phone 322-2394

September 28, 1973

Mr. A. H. Frost, Jr.
Research Contracts, Procedures,
and Reports Branch
Contract Division
U.S. Atomic Energy Commission
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tennessee 37830

Dear Mr. Frost:

We received your letter and are pleased to accept the new funds of $65,000.00 for the period August 1, 1973 through July 31, 1974, i.e. an extension of Contract No. At-(40-1)-2401.

We propose to expend these new funds as follows:

Personnel (includes fringe benefits)	$ 37,598.00
Supplies	9,359.00
Equipment	0
Travel	1,500.00
Other (indirect costs)	16,543.00
TOTAL	$ 65,000.00
University Contribution	7,749.00

Vanderbilt U. will contribute 20% of P.E. to be reflected under-the-line

You will note there have been changes in the personnel, supplies, equipment and indirect costs categories from the budget proposal submitted earlier for $75,000.00.

Thank you for your continued support for our project activity.

Sincerely yours,

A. B. Brill, M.D.
Director, Division of Nuclear Medicine & Biophysics

ABB:ce

Allan D. Bass
Associate Dean for Biomedical
Sciences
Acting Dean, Medical School

Paul Gazzerro, Jr.
Associate Vice-Chancellor
for Medical Affairs-for
Operations and Fiscal Planning

1037628

Form AEC-481
(9-72)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE: SEP 5 1973

2. AUTHORIZATION NO.: BER-74-204

3.A. TO
Robert J. Hart, Manager
Oak Ridge Operations Office

3.B. FROM
James L. Liverman, Director
Division of Biomedical
and Environmental Research

4.A. CONTRACTOR (Name, Address, Department, etc.)
Vanderbilt University
Nashville, Tennessee 37203
Department of Radiology

4.B. PRINCIPAL INVESTIGATOR(S)
A. BERTRAND BRILL

5.
☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER

6. TERM OF CONTRACT: 8-1-73 thru 7-31-74

7. CONTRACT NUMBER: AT(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)
☐ COST REIMBURSEMENT
☐ FIXED PRICE ☐ OTHER

9. PROPERTY TITLE TO VEST IN:
☐ AEC
☒ CONTRACTOR-DETERMINED TO BE IN THE PROGRAMMATIC INTEREST OF THE AEC

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE "Radioisotope Studies Utilizing a Low-Level Whole Body Counter, and Clinical Application of Activation Analysis"

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ $65,000
Estimated AEC Balance From Prior Term, if any	$ 0
Total Estimated AEC Support Cost for New Term	$ 65,000
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$ *
Estimated Project Cost, For Pertinent Budget Period	$

Budget and Reporting Classification: RX 01 03
Allotment Transfer: 06-41-91(24)

B. PLANT AND CAPITAL EQUIPMENT ..... $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

*To be determined.

15. SCOPE OF WORK

Study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

E 4014

SEP 7 1973

1037629

EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

AEC CONTRACT AT-(40-1)-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

April 30, 1973

1037630

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1037632

VANDERBILT UNIVERSITY
NASHVILLE, TENNESSEE 37232
TELEPHONE 322-7311 AREA 615
Director of Finance • Medical Center • Direct phone 322-2301

FINANCIAL STATEMENT

CONTRACT NO. AT-(40-1)-2401
Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period.	$ 43,268.
2.	Estimated total cost for remainder of period.	$ 32,409.
3.	Total actual and estimated cost chargeable to AEC for current period based on percentage of cost agreed upon as contained in A-III of Appendix "A" to Contract.	$ 64,183.
4.	Accumulated costs chargeable to AEC (include costs reported in certified statement for preceding period(s) and the costs stated in Item (3) above)	$ 242,125.
5.	Accumulated AEC Support Ceiling as stated in Article III of Contract.	$ 242,125.
6.	Total estimated AEC funds remaining under Contract (Subtract Item (4) from (5) which may be used to reduce amount of new funds required from AEC for proposed renewal period.	$ 0

Macon Somerville
Macon D. Somerville
Asst. Dir., Finance Acctg.

1037633

TO : Adressees Listed Below DATE: November 7, 1972

FROM : Ralph Elson, Director, Contract Division

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 20 to Contract AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~Lamar Medley~~	~~Contract~~	for	11-7-72	
2. ~~A. H. Frost, Jr.~~	Contract		11/8/72	
3. ~~A. E. Miller~~	~~Budget~~		11/10/72	
4. ~~W. H. Henderson~~	~~Finance~~		11/13	
5.				
6.				

RETURN TO

Alice Brown Contract Division Tel.: 3-4105

1037634

Routed by

CONTRACT DIVISION

Form OR-133 (Rev. May 1972)

ROUTE SLIP

number

	MANAGER
	Deputy Manager
	Assistant to Manager for Pub. Infor.

	CHIEF COUNSEL
	Patent Group

	ASST. MANAGER FOR OPERATIONS

	MANUFACTURING DIVISION
	Quality Assurance Branch
	Weapons Branch

	PLANNING DIVISION
	Planning Branch
	Power Branch

	RESEARCH & TECH. SUPPORT DIV.
	Classification & Tech. Services Br.
	Research & Development Branch
	Standards & Quality Assurance Branch
	Waste Management Branch
	New Brunswick Laboratory
	Puerto Rico Area Office

	SAFETY & ENVIRONMENTAL CONTROL DIV.
	Health & Nuclear Safety Branch
	Ind. Safety & Fire Protection Branch
	Reactor & Facility Safety Branch
	Waste & Pollution Control Branch

	URANIUM ENRICHMENT DIVISION
	Nuclear Materials Control Branch
	Operations Branch
	Process Improvement Branch
	Toll Enriching Branch
	Cincinnati Area Office
	Paducah Area Office
	Portsmouth Area Office

	ASST. MGR. FOR ADMINISTRATION

	BUDGET AND REPORTS DIVISION
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	Funds Control & Reports Branch

	CONTRACT DIVISION
	Negotiated Contracts Branch
	Research Contracts, Procedures, and Reports Branch
	Procurement Branch

	FINANCE DIVISION
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	Government Payroll Sect.
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	Government Personnel Branch
	Industrial Personnel Branch
	Organization & Management Branch
	Equal Opportunity Branch

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	Office Services Branch
	Records Holding Area
	Records Officer
	Supply & Maintenance Section
	Reproduction & Distr. Unit
	Stores Unit
	Mail Section
	Photographic Services
	Teletype Section
	Property Branch
	Transportation Branch

	SECURITY DIVISION
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	Physical Security Branch
	AEC Patrol

	ASST. MGR. FOR CONST. & ENGRG.

	CONSTRUCTION DIVISION
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	Special Projects Branch

	ENGINEERING DIVISION
	Design Coordination Branch
	Engineering Analysis Branch

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	Office of Manager
	Assistant Mgr. for Adm. Ser.
	Assistant Mgr. for Pro. Ser.
	Assistant Mgr. for Sci. Comm.
	Science & Tech. Branch
	Tech. Services Branch
	Assistant Mgr. for Comp. Processes & Mfg.
	Editorial Branch
	Graphics Arts Branch
	Printing Branch
	Assistant Mgr. for Doc. & Systems Dev.
	Document Mgmt. Branch
	Computer Operations Branch
	Program & Systems Dev. Branch

	RDT-OSR (ORNL)

	CONTRACT COMPLIANCE OFFICE
	(Southeastern Area)

	CONTROLLER REGIONAL AUDIT STAFF

	AECOP

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ CONCURRENCE C Emiller for

2. OFFICE OF CHIEF COUNSEL CONCURRENCE _____

USAEC Technical Information Center, Oak Ridge, Tennessee

1037635

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

October 31, 1972

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: AT-(40-1)-2401
   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 Application of Activation Analysis"

3. Type of Contract:

   [X] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: ~~$65,000~~ $54,167 per L. Medley 11-1-72

5. AEC Percentage of Est. Total Cost To Be Shown by this CA: 85%

6. Description of Other Changes To Be Covered by this CA:

   See Attachment

7. Authority:

   Form AEC-427 (CA)
   from J. R. Totter
   dated October 2, 1972

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:LM

Attachment

1037636

October 31, 1972

Attachment

REQUEST FOR CONTRACT ACTION
VANDERBILT UNIVERSITY
CONTRACT NO. AT-(40-1)-2401

6. Description of Other Changes to be Covered by this CA:

Modify Contract to provide for the performance of additional research during the period August 1, 1972 through July 31, 1973. AEC Support Ceiling will be increased from $187,958 to $242,125. Title to the following equipment shall vest in the Government: 1. Card Reader, 2. 717 Printer, 3. Printer Control, 4. Card Reader Control.

NOTE: Please note that the ending date of the period stated in Modification 19 is September 30, 1973. It was intended that the ending date be September 30, 1972.

1037637

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

1037638

(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.

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Date of Typing: October 1, 1972 Check one: XXX New; ____Renewed; ____Revised

Department: Radiology/Nuclear Medicine Principal Investigator: A.B. Brill, M.D.

Budget of: Atomic Energy Commission (AT (40-1) 2401
(Name of account, or source of funds)

Project: Radioisotope Studies Utilizing Low Level Whole Body Counter & Clinical APplications of Activation Analysis

Period Covered: 8-1-72 through 7-30-72

Item Number	DESCRIPTION: 8102-4934-018-13	Allotment Monthly	Allotment Annual
	SALARIES:		
232	Principal Investigator: A.B. Brill, M.D.,Ph.D. [redacted] Professor, Medicine & Radiology Salary support not included, proportionate sharing 25%		$ -0-
273	Co-Investigator: R.E. Johnston, Ph.D., Asst. Prof. Radiology, Salary support, Veterans Administration 50%		-0-
482	Sr. Investigator: N.C. Dyer @ $1,166.67 - 40%		7293.00
227	Sr. Investigator: R. Baglan, Ph.D., Asst. Prof. Physics, Salary support not included, proportionate sharing 10%		-0-
	Research Associates:		
340	C.O.T. Ball, Biostatistics @ $789.34, 35%		1158.00
342	J. Parker, Computer Engineer, Summer @ 5.81/hour		4609.00
481	J.J. Erickson, Radiation Physics @ $1061.00 - 40%		1225.00
341	J.E. Lagan, Electronics Eng., @$971.75 - 76%		5072.00
251	D. Patton, M.D., Assoc. Prof., Radiology, salary support not included, proportionate sharing 25%		-0-
330	R. Price, Ph.D., Radiation Dosimetry, salary support Veterans Administration 25%		-0-
350	J. Patton, Ph.D., Research Associate, salary support not included 20%		-0-
445	Secretary, part time, @ $2.45/hour		200.00
448	Secretary, C. Elam, $458.33, 100%		5500.00
	Technician, whole body counter, TBA, @$500 100%		6000.00
596	Fringe benefits, (not fixed & of salaries. Varies with employee status & option).		2800.00
595	TIAA Staff		586.00
	TOTAL SALARIES & FRINGE: 1037640		$34,443.00

Date of Typing: October 1972 Check one: XXX ____Renewed; ____Revised

Department: Radiology/Nuclear Medicine Principal Investigator: A.B. Brill, M.D.

Budget of: Atomic Energy Commission (AT (40-1) 2401
(Name of account, or source of funds)

Project: Radioisotope Studies Utilizing Low Level Whole Body Counter & Clinical Applications of Activation Analysis

Period Covered: 8-1-72 through 7-30-73

Item Number	DESCRIPTION: 8102-4934-018-13	Allotment Monthly	Allotment Annual
	SUPPLIES & MATERIALS:		
603	Animal Purchases		$ 100.00
609	Books		100.00
616	Chemicals & Glassware		300.00
617	Computer Expense - on campus		875.00
673	Laboratory Supplies - radioisotopes		
	a. Radioisotopes		2200.00
	b. Tissue sample collection & processing costs		900.00
681	Machine Service Contracts		2223.00
691	Office supplies		875.00
683	Interface Development - electronic components		3200.00
706	Equipment rental		1204.00
707	Electronic components - maintenance (repairs/equip)		1100.00
712	Subject participation		375.00
			13,452.00
	~~EQUIPMENT - typewriter replacement~~		~~300.00~~
739	PUBLICATIONS & COPYING		450.00
794	TRAVEL - domestic		
	a. domestic - scientific meetings		800,00
	b. to reactor site - sample activation		400.00
	OTHER		-0-
906	Indirect costs, 44% salaries & fringe		15,155.00
			65,000.00

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1-1275

Form AEC-481
(6-67)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
OCT 2 1972	BER-73-72A

3.A. TO	3.B. FROM
Robert J. Hart, Manager Oak Ridge Operations Office	John R. Totter, Director Division of Biomedical and Environmental Research

4.A. CONTRACTOR (Name, Address, Department, etc.)	4.B. PRINCIPAL INVESTIGATOR(S)
VANDERBILT UNIVERSITY Nashville, Tennessee	A. BERTRAND BRILL, M.D., Ph.D.

5.	6. TERM OF CONTRACT	7. CONTRACT NUMBER
☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER	10-1-72 thru 7-31-73	AT(40-1)2401

8. RECOMMENDED TYPE OF CONTRACT:	9. EQUIPMENT TITLE TO VEST IN:	10. SECURITY CLASSIFICATION:
☐ FIXED PRICE ☐ OTHER ☐ COST REIMBURSEMENT ☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)	☐ AEC ☒ CONTRACTOR	Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE RADIOISOTOPE STUDIES UTILIZING A LOW-LEVEL WHOLE BODY COUNTER, AND CLINICAL APPLICATION OF ACTIVATION ANALYSIS

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 54,167
Estimated AEC Balance From Prior Term, if any	$
	$ 54,167
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$ *
Estimated Project Cost, For Pertinent Budget Period	$

Budget and Reporting Classification: 06 03 01
Allotment Transfer: 06-31-91(24)

B. PLANT AND CAPITAL EQUIPMENT ..... $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

*To be determined

15. SCOPE OF WORK

Radiation exposure from nuclear medicine procedures.

2104

OCT 5 1972

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OFFICE OF CHIEF COUNSEL
CONTRACT FILE
REMOVAL OF PAPERS FROM
THIS FILE IS PROHIBITED

BACK UP

VANDERBILT UNIVERSITY

CONTRACT NO. DE-AS05-76ER-02401

RETURN TO CONTRACT FILES

BOOK II BEGINNING WITH MOD 13

565 R

1037643

TO : Adressees Listed Below DATE: August 28, 1972

FROM : Ralph Elson, Director, Contract Division

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 19 to Contract AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. Lamar Medley	Contract	LM	8-29-72	
2. ~~A. E. Miller~~	~~Budget~~	Ofm	8/29	
3. ~~W. H. Henderson~~	~~Finance~~		8/30	
4.				
5.				
6.				

RETURN TO

Alice Brown Contract Division Tel.: 3-4105

1037644

Routed by

CONTRACT DIVISION

Form OR-133 (Rev. March 1969)

ROUTE SLIP

Number

- MANAGER
  - Deputy Manager
  - Assistant to Manager for Pub. Infor.
- CHIEF COUNSEL
  - Patent Group
- ASST. MANAGER FOR OPERATIONS
- OPERATIONAL PLANNING & POWER DIVISION
- SAFETY DIVISION
  - Health & Nuclear Safety Br.
  - Ind. Safety & Fire Protection Br.
  - Reactor Safety Branch
- LABORATORY & UNIVERSITY DIV.
  - Research Contracts Branch
  - Reactor Contracts Br.
  - Administrative Services Br.
- PRODUCTION DIVISION
  - Operations Branch
  - Development Branch
  - Materials & Enriching Services Br.
  - Nuclear Materials Control Br.
  - Weapons Branch
- ASST. MGR. FOR CONST. & ENGRG.
- CONSTRUCTION DIVISION
  - Administrative Branch
  - General Construction Branch
  - Special Projects Branch
- ENGINEERING DIVISION
  - Design Coordination Branch
  - Power and Communications Branch
  - Reports and Control Branch
- ASST. MGR. FOR ADMINISTRATION
- BUDGET AND REPORTS DIVISION
  - Budget Analysis Branch
  - Funds Control & Reports Branch
- CONTRACT DIVISION
  - Negotiated Contracts Branch
  - Procedures, Reports & Contr. Pro. Br.
  - Procurement Branch
- FINANCE DIVISION
  - Systems & Cost Analysis Br.
  - Accounting Branch
  - Acct. Payable & Travel Sect.
  - General Ledger Section
  - Government Payroll Sect.
  - Audit Branch
  - ADP Branch
  - ADP Service Center
- ORGANIZATION & PERSONNEL DIV.
  - Government Personnel Branch
  - Industrial Personnel Branch
  - Organization & Management Branch
  - Equal Opportunity Branch
- SUPPLY DIVISION
  - Office Services Branch
  - Supply & Maintenance Section
  - Reproduction & Distr. Unit
  - Stores Unit
  - Mail Section
  - Photographic Services
  - Records Center
  - Records Officer
  - Teletype Section
  - Property Branch
  - Transportation Branch
- SECURITY DIVISION
  - Personnel Security Branch
  - Physical Security Branch
  - AEC Patrol
- CINCINNATI AREA OFFICE
- NEW BRUNSWICK AREA OFFICE
- PADUCAH AREA OFFICE
- PORTSMOUTH AREA OFFICE
- PUERTO RICO AREA OFFICE
- DIVISION OF TECHNICAL INFORMATION EXT.
  - Office of Ext. Manager
  - Ass't. Ext. Mgr. for Adm. Ser.
  - Ass't. Ext. Mgr. for Pro. Ser.
  - Ass't. Ext. Mgr. for Sci. Comm.
  - Science & Tech. Branch
  - Tech. Services Branch
  - Ass't. Ext. Mgr. for Comp. Processes & Mfg.
  - Editorial Branch
  - Graphics Arts Branch
  - Printing Branch
  - Ass't. Ext. Mgr. for Doc. & Systems Dev.
  - Document Mgmt. Branch
  - Computer Operations Br.
  - RDT-OSR (ORNL)
  - RDT-OSR (GE-Evendale)
  - RDT-OSR (BONUS)
- CONTROLLER REGIONAL AUDIT STAFF

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ CONCURRENCE A Emiller for

2. OFFICE OF CHIEF COUNSEL CONCURRENCE _____

USAEC Division of Technical Information Extension, Oak Ridge, Tennessee

1037645

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

August 14, 1972

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: AT-(40-1)-2401
   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 Application of Activation Analysis"

3. Type of Contract:

   [X] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: $10,833

5. AEC Percentage of Est. Total Cost To Be Shown by this CA: 100%

6. Description of Other Changes To Be Covered by this CA:
   Provide for the performance of additional research during the period August 1, 1972 through September 30, 1973. AEC Support Ceiling will be increased from $$177,125 to $187,958. Title to the equipment shall vest in the contractor under authority of PL 85-934.

7. Authority:

   Form AEC-481 (CA)
   fr J. R. Totter to R. J. Hart
   8-1-72

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR:IM

1037646

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:

1037647

(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.

1037648

Form AEC-481
(rev. 7)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE: AUG 1 1972	2. AUTHORIZATION NO.: BER-73-72
3.A. TO: Robert J. Hart, Manager Oak Ridge Operations Office	3.B. FROM: John R. Totter, Director Division of Biomedical and Environmental Research
4.A. CONTRACTOR (Name, Address, Department, etc.): VANDERBILT UNIVERSITY Nashville, Tennessee	4.B. PRINCIPAL INVESTIGATOR(S): A. BERTRAND BRILL, M.D.

5. ☐ NEW CONTRACT ☐ RENEWAL ☒ OTHER: 2 month extension*	6. TERM OF CONTRACT: 8-1-72 thru 9-30-73	7. CONTRACT NUMBER: AT(40-1)2401
8. RECOMMENDED TYPE OF CONTRACT: ☐ FIXED PRICE ☐ OTHER ☐ COST REIMBURSEMENT ☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)	9. EQUIPMENT TITLE TO VEST IN: ☐ AEC ☒ CONTRACTOR	10. SECURITY CLASSIFICATION: Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE: RADIOISOTOPE STUDIES UTILIZING A LOW-LEVEL WHOLE BODY COUNTER, AND CLINICAL APPLICATION OF ACTIVATION ANALYSIS

12. HEADQUARTERS TECHNICAL CONTACT: Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$10,833
Estimated AEC Balance From Prior Term, if any	$
	$10,833
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$
Estimated Project Cost, For Pertinent Budget Period	$10,833

Budget and Reporting Classification: 06 03 01

Allotment Transfer: 06-31-91(24)

B. PLANT AND CAPITAL EQUIPMENT $

Budget and Reporting Classification:

Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

*Extension necessary to allow time for outside review.

15. SCOPE OF WORK

Study of radioisotope distributing and radiation absorbed dose from medical radionuclides.

13362

AUG 3 1972

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BUDGET REVISION FOR
TWO MONTHS EXTENSION OF AEC CONTRACT
August 1 - September 30, 1972

Vanderbilt University

SALARIES		
C. O. T. Ball		438.80
J. Parker		1,830.15
N. Dyer		1,215.50
J. Erickson		270.83
C. Elam		916.67
		4,671.95
Fringe Benefits		460.00
	TOTAL =	$5,131.95
		$3,159.66
SUPPLIES		
Supply Breakdown		
Animal purchases		50.00
Books		50.00
Chemicals & Glass-ware		50.00
Lab Supplies		200.00
Machine Service Contracts		1,609.66
Office Supplies		100.00
Interface Development		500.00
Electronic Components		400.00
Subject participation		0
Communications		150.00
		$3,159.66
EQUIPMENT		0
PUBLIC. & COPYING		83.33
TRAVEL		250.00
INDIRECT COSTS	.44 X 5131.95	2,258.06
	2 mos. amount awarded =	$10,833.00

1063650

1972

University contribution:
25% of PI's time - under A-II(b)(1)

EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

AEC CONTRACT AT-(40-1)-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

April 30, 1972

1037651

C 11

MAY 1 1972

E X P E N D I T U R E S T A T E M E N T

AEC CONTRACT AT-(40-1)-2401, Modification No. 19
August 1, 1971 - July 31, 1972

		AEC		UNIVERSITY			
	% Effort	To 3/31/72	From 4/1/72	To 3/31/72	From 4/1/72	TOTAL	OTHER
A. Personnel							
Principal Investigator:							
A. B. Brill	26%-36%	-0-	-0-	-0-	-0-	-0-	--
Co-Investigator:							
R. E. Johnston	50%	-0-	-0-	-0-	-0-	-0-	VA
Sr. Investigators:							
N. C. Dyer	23%	$2,174.	$1,087			$3,261.	
R. Baglan	10%	-0-	-0-	-0-	-0-	-0-	
Research Associates:							
C. O. T. Ball	37%	$1,985.	660.	$240.	$120.	$3,005.	
J. Parker		$2,789.	544.	-0-	-0-	$3,333.	
J. Erickson	40%	859.	321.	$2,425.	$1,213.	$4,818.	
E. Lagan	76%	$3,305.	$1,525.	$2,407	$1,203	$8,440.	
D. Patton	25%	-0-	-0-	-0-	-0-	-0-	
R. Price	50%	-0-	-0-	-0-	-0-	-0-	VA
J. Patton	50%	-0-	-0-	-0-	-0-	-0-	Hertz
Y. Hsu		$1,750.	$750.			$2,500.	
E. Shipp, Sec'y.		578.	$247.			825.	
K. Burk, Sec'y.	100%	$4.954.	$1,842.			$6,796.	
W. Lutin, Technician		443.	-0-			443.	
R. Plunkett, Technician		1,470.	330.			$1,800.	
TIAA		$141.	$284.	$12.	$6.	443.	
Fringe Benefits		$906.	$555.	$282.	$141.	$1,884.	
TOTAL Salaries & Fringe:		$21,354.	$8,145.	$5,366.	$2,683.	$37,548.	
Overhead 39% Salaries & Fringe Benefits		$8,327.	$3,176.	$2,093.	$1,046.	$14,642.	
TOTAL: Salaries, Fringe, Overhead		$41,002.		$11,188.		$52,190.	

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EXPENDITURE STATEMENT CONTINUED

	AEC To 3/31/73	AEC From 4/1/72	TOTAL
B. Equipment			
a. Equipment under $500.	$120.	-0-	$120.
b. Equipment over $500.	$6,480.	-0-	$6,480.
Sub-total:	$6,600.	-0-	$6,600.
C. Materials and Supplies			
Animal Purchases	$69.	$20.	$89.
Books, Periodicals	61.	30.	91.
Chemicals $ Glassware	87.	30.	117.
Computer Expense	1,243.	280.	1,523.
Duplicating Service	748.	300.	1,048.
Lab Supplies	3,993.	250.	4,243.
Machine Service Contracts	190.	2,349.	2,539.
Miscellaneous Expense	1,663	-0-	1,663.
Office Supplies	311.	100.	411.
Postage	89.	50.	139.
Equipment Rental	73.	80.	153.
Equipment Repairs	2,575.	150.	2,725.
Subject Participation	25.	-0-	25.
Telephone	62.	61.	123.
Publication Costs	744.	150.	894.
Sub-total:	$11,933.	$3,850.	$15,783.
D. Travel			
Domestic	$428.	$772.	$1,200.
Foreign	300.	-0-	300.
Sub-total:	$728.	$772.	$1,500.

TOTAL PROJECT COSTS

AEC		UNIVERSITY	
To 3/31/72	$48,942.	To 3/1/72	$7,459.
From 4/1/72	$15,943.	From 4/1/72	3,729.
	$64,885.		$11,188.

1037653

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1037655

III. Project Abstract

The main emphasis of these studies is the development of instrumentation and analytical techniques for the quantitation of isotope metabolism. These studies involve both radioactive and stable tracers, in an attempt to minimize radiation exposure to the patient while maintaining the needed diagnostic information content.

The role of high resolution measurement systems (germanium and silicon detectors) for patient diagnosis and dosimetry studies is under investigation with radioactive and stable tracers.

The role of low resolution high energy gamma mapping systems is being evaluated using a computer controlled low level scanner. Quantitative regional kinetic analyses are conducted with this system for Fe-59 and Ca-47, and the data analyzed with a computer simulation program (SAAM-25). The prime goals of these studies are:

(1) To obtain metabolic and dosimetry data for the individual tracers and patient categories studied

(2) To demonstrate medical uses of:

(a) quantitative external mapping systems

(b) simulation analysis and modelling techniques

(c) high energy gamma emitting tracers, which have been overlooked for clinical applications in the past.

Efforts will be continued to further develop the quantitative whole body scanning system. Additional calibration factors will be obtained and re-evaluation of the present calibration methodology will be undertaken to include newer methods and data. Efforts will include expansion of computer hardware to facilitate expanded uses of the computer to increase reliability and flexibility of data acquisition, and to facilitate sharing of computer technology.

We will participate in the IAEA/WHO study to investigate distributions of trace elements in the environment and in tissues in relation to geographic patterns of mortality from ischemic heart disease. Neutron activation analysis methods developed in previous work will be used in these studies.

1037657

IV. Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the operation of the Vanderbilt Low Level Counting Facility. Dr. A. B. Brill, Principal Investigator, is the Director of the Division of Nuclear Medicine and Biophysics. The Co-Investigator, Dr. R. E. Johnston, and research associate, Dr. R. Price, receive salary support from the Veterans Administration. Dr. H. Williams, Math Dept., and Dr. R. Nash, Engineering Dept. have contributed many ideas and continue to work with us in the area of data analysis. Don Johnson, an Engineer at DuPont, Old Hickory, Tennessee, has been of great assistance to us in working with the SAAM 25 computer program. None of these personnel have been supported financially by this contract but the collaboration has strengthened our efforts and has led them to pursue research problems in our area. This will lead to the involvement of more graduate students from engineering and computer science in years to come. This, plus continuing support from the Physics Department has been of major importance in our research efforts.

The recruiting and training of basic scientists for careers in Nuclear Medicine and Medical Physics has been a major dividend from the research supported by this contract.

The staff has achieved a scientific maturity and is stronger today than ever before. 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 be even more profuse this coming year than ever before from this contract. 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 promises to accelerate our biological study output.

1037658

A. Dosimetry

1. Methodology

a. Calibration

(i) Evaluation of arithmetic mean and geometric mean of two opposed detectors

We have established calibration relationships for the radionuclides ^{131}I, ^{59}Fe and ^{47}Ca by which we relate the microcurie content of a defined region within the body to the geometric mean counts and the ratio of the two detectors. Our methodology provides quantitative measurements of radioactive content of in-vivo distributions with an accuracy of on the order of $\pm$ 10%. Independence of depth response can be improved by using the mean value of the arithmetic and geometric means of two opposed detectors (ref. 1, figure 1). It is possible that our calibration methods could be simplified and/or improved in accuracy if we use the mean of the arithmetic and geometric mean. We will incorporate the results of our re-evaluation in our calibration equations.

---

[1] Arimizu, N. and Morris, A. C., Jr., Quantitative Measurement of Radioactivity in Internal Organs by Area Scanning, J. Nuc. Med. 10: 265, 1969.

(ii) Calibration factors for specific radionuclides

We will continue our efforts to obtain biological retention data for new radiopharmaceuticals used in nuclear medicine procedures. To obtain accurate whole body retention data and absolute measurements of organ distribution data, we will determine calibration factors for ^{111}In, ^{99m}Tc and ^{137}Cs. Indium 111 DTPA and ^{99m}Tc labeled polyphosphate are clinically interesting agents and little or no dosimetry information is available. Millicurie amounts of Indium 111 DTPA

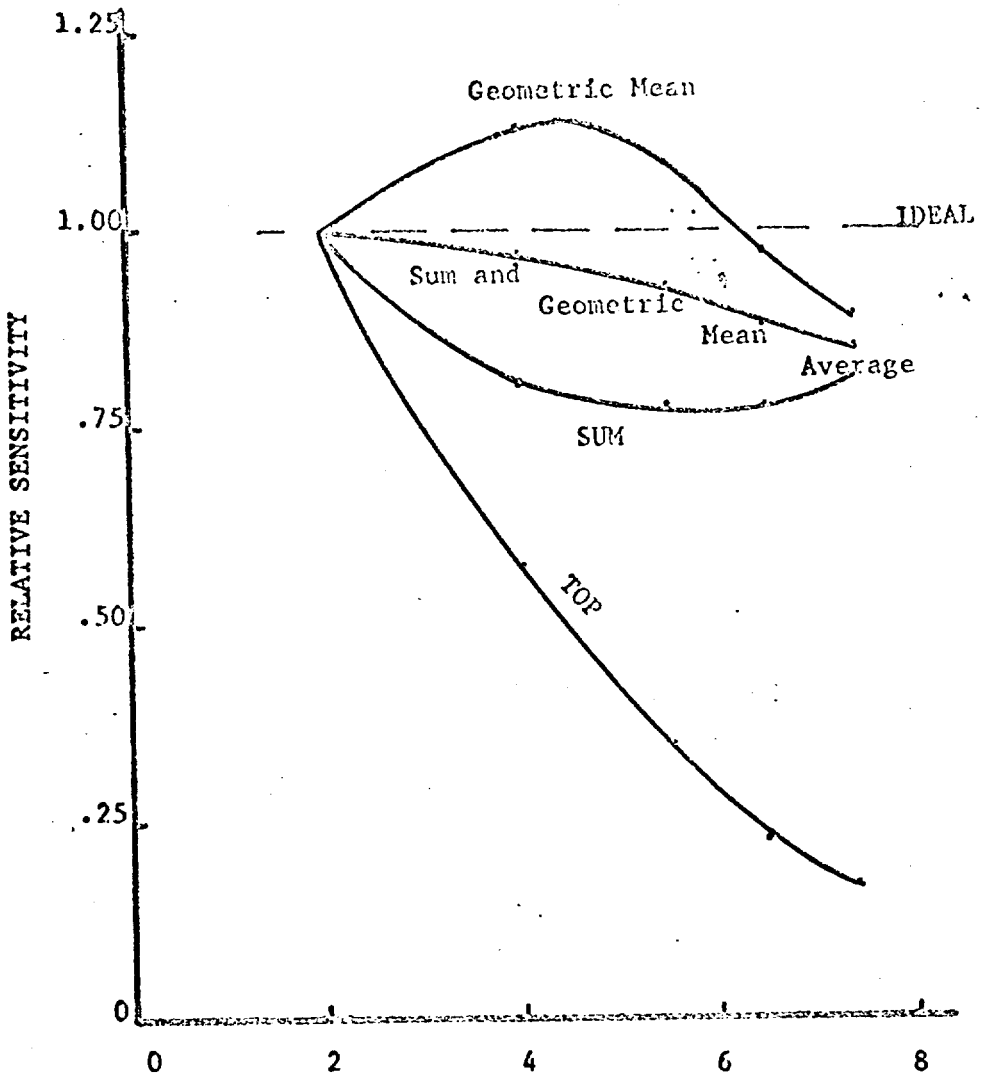


Fig. 1. Comparison of the SHTB collimator sensitivity as a function of source location for different data handling methods.

I-131 source in water phantom

1037660

and ^{99m}Tc polyphosphate are used in the clinical studies. Thus, in order to quantitatively determine the whole body retention from the time of administration over a period of many half lives requires the use of the high level whole body counter at early times and low level counter at later times. Calibration crossover factors will be determined for these radionuclides between the two whole body counters as well as between the gamma camera and whole body counter. Please refer to section A,2,c (page 18) for further discussion of the protocol for the clinical studies.

Calibration of the whole body counter for absolute measurement of ^{137}Cs body burdens will be carried out by administration of short lived ^{132}Cs to a number of volunteer subjects. This procedure was carried out for the standard chair whole body counter (AEC OEO 2401-8, 1966) and will now be repeated for the scanning bed geometry.

(iii) Correlation studies between calculated and measured radiation dose

With the increased use of internally administered radionuclides, the need has arisen to experimentally evaluate the dose predictions based upon the "standard man" model of Dr. Walter Snyder at Oak Ridge National Laboratory. This evaluation will be to see how well the "standard man" approximates an actual patient for pusposes of calculating radiation dose, and further to see what effect such variables as patient size, weight, build and physical condition have on the dose estimates.

Very small radiation detectors (LiF TLD's) are now available which can be used to measure radiation dose. To accomplish the above goals we will use a phantom which corresponds very closely to the "standard man" in size, organ shape, and composition, and place known amounts of radioactive material in

the phantom source organs. Then TLD's will be put on the target region (skin), which will give a measured value of dose to the target. The predicted dose based on the "standard man" will also be computed, and the two values of the dose compared. Since good agreement between these values is expected, this procedure will serve as a check of the TLD system being used. Also the activity in the source will be measured by scanning techniques, thus allowing a check of this aspect of experimental dosimetry data as well.

A similar study will be done on patients. Using the scanning system, the activity in the source organs in a patient will be determined. From this, the predicted dose based upon the "standard man" can be calculated. TLD's will be placed on the target region (patient's skin) and the dose measured. Then the dose measured by TLD's will be compared to that predicted from the "standard man". This will be done with several patients, thus providing quantitative evaluation of the "standard man" model and the effects of patient size, weight, physical condition, etc., on the radiation dose.

The experimental evaluation was chosen primarily because it involves a minimum of discomfort to the patients and does not require large commitments of computer time (to calculate the absorbed fractions). Surgical implantation of the TLD's in patients would allow the use of absorbed fraction data already published by Dr. Snyder, but would involve unnecessary risk to the patients. Surgical implantation of the TLD's in dogs would not be objectionable, but would necessitate the formulation of a "standard dog" model, which could not be justified. Taping the TLD's on a patient's skin seems to be a reasonable compromise between these two extremes.

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More specifically, the study will be carried out on patients receiving liver scans using ^{99m}Tc sulfur colloid and ^{75}Se-l-methionine. In both cases, the target region is a section of skin directly over the liver. This was chosen because it is expected that the dose should be roughly the same at each point in this region, so that placement of the TLD's on the patients will not be so critical as to invalidate the results of this study. Some preliminary data have been obtained to verify the suitability of the technique, and a typical variation was about 7 mrad for doses on the order of 100 mrad (range from 97 mrad to 104 mrad) for the five patients studied who had received a m C of Tc-79m sulfur colloid.

In terms of the standard man described in MIRD Pamphlet No. 5, the target region is given by: $\left(\frac{X}{19.8}\right)^2 + \left(\frac{Y}{9.8}\right)^2 \geq 1$

$$\left(\frac{X}{20}\right)^2 + \left(\frac{Y}{10}\right)^2 \leq 1$$

$$y \leq -1.168829\,x \quad \text{if } x \geq 0$$

$$y \leq 1.168829\,x \quad \text{if } x \leq 0$$

$$31 \leq Z \leq 39$$

In addition, to get an idea of the constancy of dose in this region, this region could be broken into two or three subregions having the same conditions on x and y, but with the interval of Z broken into two or three equal subintervals. The exact number of subregions (if any at all) is determined by the requirements of computer time to get reasonable statistics.

The following table gives the data on source organ and γ ray energies to be investigated by the computer program.

Isotope	Source Organ(s)	Energy of radiation (keV)
^{99m}Tc	Liver	140.5
^{75}Se	Liver, pancreas, and muscle (or total body)	10.5, 121.1, 135.9, 264.5, 279.5, 400.5

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NOTE: The target region is the same in all cases, and the activity may be assumed to be uniformly distributed within each organ.

b. (i) Software simulation analysis

The multicompartmental modelling computer program SAAM-25 has been used extensively to analyze quantitative scan data collected from the whole body counter.

SAAM-25 was made available to us by Dr. Berman and Mrs. Marjorie Weiss of the NIH. Through the cooperation of the DuPont Corporation and the help of Mr. Don Johnson, DuPont consultant engineer, we continue to use the DuPont Corporation's UNIVAC-1108 computer to process much of our data using the SAAM-25 program. In addition to having access to SAAM-25 through the DuPont facility, we have modified the program so that it can be run on the University Sigma-7 computer. Because of reduced core, the Sigma-7 version of the program has had the maximum number of data points that the program will accept reduced to 150 from the original value of 250. Because of the limitation this presents for some studies, we propose to implement the longer version of the program when the Sigma-7 expands its available core during this next year. We have also converted a version of SAAM-23 to run on the Sigma-7. SAMM-23 is smaller and considerably faster than SAAM-25 but is limited in the types of problems it can solve. Primarily because of shortened run time, we use SAAM-23 whenever applicable. SAAM-23 has the added advantage of being small enough that it can be maintained as a resident disc file. As a disc file the program can be accessed in the immediate laboratory environment through a remote terminal to the Sigma-7. We propose to couple the PDP-9 to the Sigma 7 so that the read out will return through the PDP-9 terminal allowing the use of the rapid line printer.

(ii) Hardware development

The utilization of the PDP-9 system to direct the acquisition of data and to perform data analysis has increased steadily to require time-shared use of the computer. A communications multiplexer with its associated modem and 8192 words of core storage were added to the system in the past year. A memory protection feature was also added to prevent one program from modifying storage allocated to another, and system time was improved through the implementation of a hardware priority interrupt facility.

Steps are now underway to decrease the dependence upon a plug-board logic synthesizer for data acquisition from the whole body counter. An interface directly connecting the PDP-9 system to the core of a 4096-channel pulse height analyzer has been put into routine operation and another interface is in the final stages of development which will allow the PDP-9 system to control the data acquisition from the whole body counting system in the "Low Level Counting Facility". Both interfaces will free the synthesizer from the whole body counter for other research uses and increase the reliability of data acquisition.

Image processing was facilitated by the construction of input and output interfaces for conventional 525-line video signals. A wide-band analog disk serves as a buffering medium for input and a PEP-400 electrical storage tube for output. Great flexibility is afforded in this input-output capability to receive images from and transmit them to distant locations by means of conventional cameras, monitors, and video-tape recorders.

In order to provide an interactive capability, a light pen and interface will be added to the electrical storage tube system. This system permits the storage of a 1024 x 1024 image which can be a single image, a composite of several images, or text plus images. We have used it to display 16 sequential normalized images of a dynamic function study. This can then be buffered onto video tape for long term storage

We will explore ways in which data compression for long term storage can be effected using video buffered images. This is an important practical problem and the low costof the electrical storage tube systems makes them an attractive possibility. We presented a preliminary paper on this topic at the April 21, 22 Oak Ridge meeting on the sharing of Computer Technology and the interest expressed encourages further explorations with this new display device.

A CAMAC interface system is being installed onto the PDP-9 computer. This will enable the use of nuclear instrumentation modules directly coupled to the computer. Multiple single channel analyzers can easily be used with the whole body scanner, or any other data gathering device, and data can be collected simultaneously in multiple energy regions. The use of multiple energy windows will be discussed in section C,2,b. (page 33).

The CAMAC standard should facilitate the interchange of interfaces and control programs between nuclear medicine laboratories. We have collaborated with Dr. M. Strauss (Argonne National Laboratory) in adapting the ANL-designed CAMAC controller (for the Lockheed MAC-16) for use with the PDP/9. This involved the design and construction of an interface which made the PDP/9 look like the MAC-16 so that the ANL controller could be used without any modifications. This controller was constructed using the automatic wire wrapping program written at the ANL. Whenever possible, our interfaces are being generated in a similar manner so that others can replicate these systems when they so desire with ease, and be assured that they have a workable, and documented system. (This includes the PEP display interface). In order to further this type of standardization capability a committee was appointed at the April 21, 22 Oak Ridge Computer Conference to assist in this development. The composition of these two sub-committees of the Society of Nuclear Medicine Computer Committee (A. B. Brill, Chairman) is as follows:

1037666

Hardware Standardization

Frank Clark, ORNL, Chairman

Jon Erickson, Vanderbilt

Sam Wilensky, MGH

Ross Burris, Tennecomp

Art Shufelt, Medical Data Systems

Software Standardization

Bill McClain, ORNL, Chairman

Ron Price, Vanderbilt

Joan Correll, MGH

Betty Maskewitz, ORNL (RSIC)

Earl McDow, ORAU

W. M. Flowers, Univ. of Miss.

Effort to improve the effectiveness of computers in Nuclear Medicine through standardization (where practical) and exchange of hardware and software will be emphasized in the activities with which we are actively involved.

The one item of computer equipment requested in this year's budget is an additional digital disc platter ($6000). In order to utilize the background/foreground operating system effectively, additional rapid access buffer storage area is needed for collecting data files from high data rate instruments and for acquisition control program storage. The disc system on the computer is modular and can be expanded in this fashion at low cost.

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2. Specific Studies Proposed

a. Iron Metabolism and Dosimetry in Abnormals

The purpose of this research is to study iron kinetics in selected pathological states in order to define metabolic parameters and to estimate the radiation dose for these patients. Therefore, it is of interest to determine experimentally the range of radiation dose encountered in diseased pateints as compared to normals. There is concern over the uncertainty in extrapolating radiation dose to diseased patients based upon normal patient data. To determine the absorbed radiation dose in diseased patients we will carry out these quantitative measurements in patients with various hematologic diseases. These will include red cell aplasia, hemochromatosis, paroxysmal nocturnal hemoglobinuria, as well as diverse myeloproliferative diseases in which clinical interest is evidenced.

Previous studies have allowed us to define ferrokinetic parameters in normal subjects by infusion, injection and scanning studies. Studies on abnormal subjects so far reveal that the proposed model can be used and fit to the data obtained. By studying additional patients with various diseases, we hope to test the generality of our mathematical analysis.

Previous iron kinetics studies carried out for three normal volunteers has provided us with normal ranges for the measured quantities and computer derived parameters. For each study, ten uCi of ^{59}Fe were administered I.V., plasma samples were obtained every 15 min. for the first 3 hours. Rectilinear whole-body scans and blood samples were obtained at 24 hr. intervals for 7 days then weekly out to about 150 days. A whole-body scan for a normal subject taken at 4 hours after injection of the ^{59}Fe is shown in Figure 2A.

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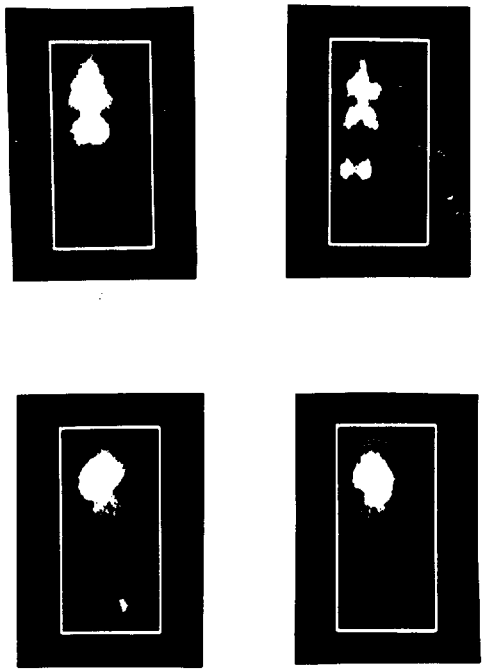


Fig. 2 Whole-body scans taken at 4 hours after administration of 10 uCi of Fe-59. (A) Normal study , J.C. , (B) sideroblastic anemia, G.G. , (C) refractory anemia, J.P. and (D) lymphoma with splenomegly, J.H.

The experimental data obtained from these measurements were analyzed using the SAAM-25 computer program. The model used for these studies is shown in figure 3A. The results of these calculations and these measurements are shown in figure 3B for the liver, spleen, marrow and total body.

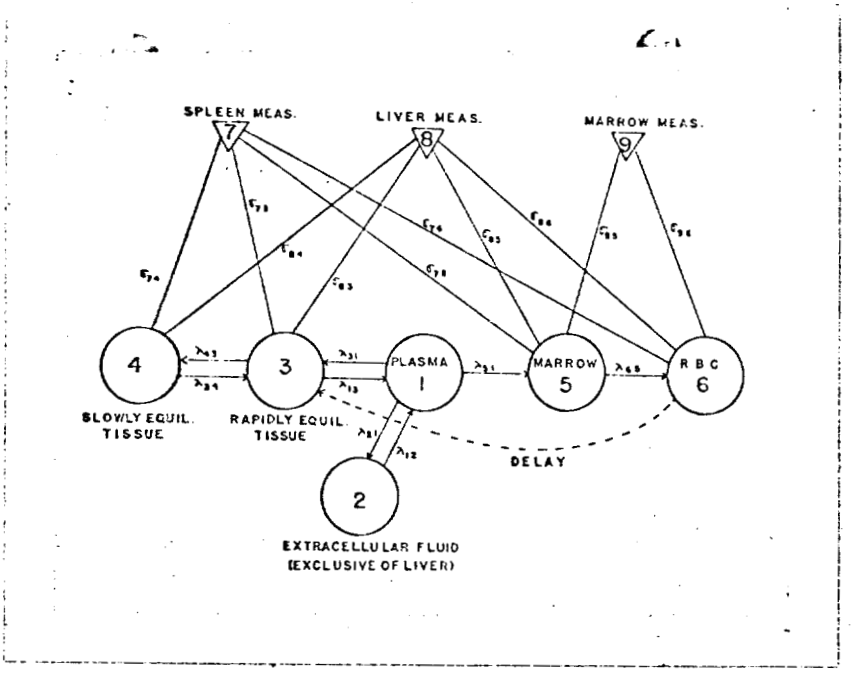
Following the protocol set up for the normal studies, we have studied four patients with various forms of anemia. Each was administered 10 uCi of ^{59}Fe i.v. Plasma samples were taken at shorter time intervals than in normals so that the more rapid plasma clearance seen in some abnormal states could be quantitated. The fraction of radioiron in the circulating blood in the liver, spleen and pelvis regions for each patient was determined from a whole-body scan for ^{51}Cr labeled red blood cells. The chromium scan is made just prior to the iron injection.

Figure 2 shows the ^{59}Fe emission images of three of these patients taken four hours after the injection of the radioiron. Figures 4A and 4B show the results from the blood, marrow, liver, and spleen measurements for patients shown in figures 2B and 2C respectively.

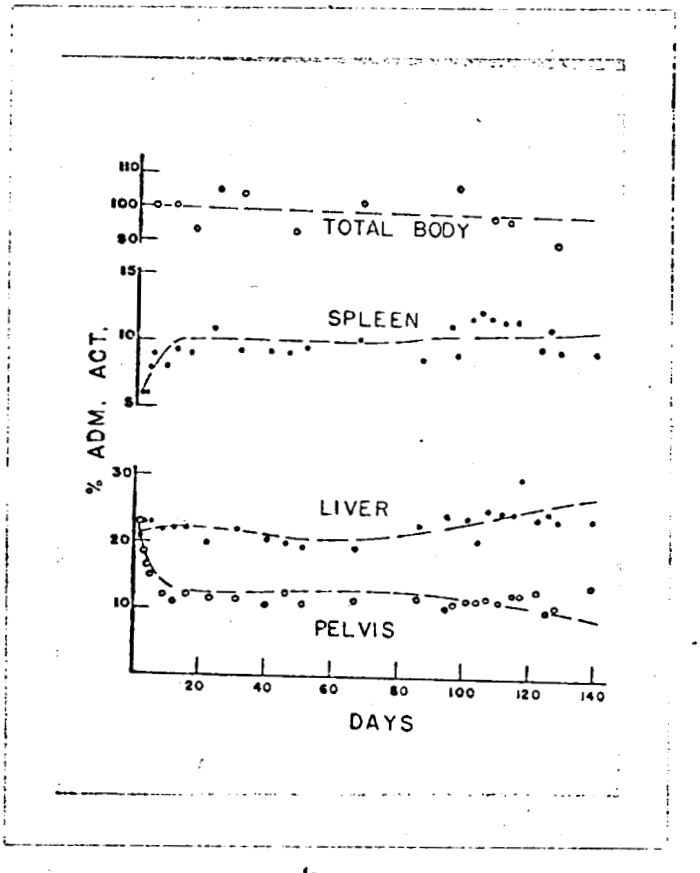
Iron is known to accumulate in the kidneys of patients with intravascular hemolysis, such as in PNH. These techniques help us to determine the quantity of iron that accumulates in the kidney and possibly to determine if the iron can be mobolized back into the circulation, or if it is always lost in the urine.

Figure 5 shows the preliminary results obtained from a patient with PNH. Since this disease is characterized by large losses of iron through the urine, we have determined urinary loss of radioiron in addition to organ content. The total body scan for ^{59}Fe (Figure 6) has revealed a most abnormal and somewhat unexpected body distribution of iron. From about twenty days after the injection of ^{59}Fe, the kidneys were found to contain approximately thirty percent of the body iron which appears to be turned over at a very slow rate.

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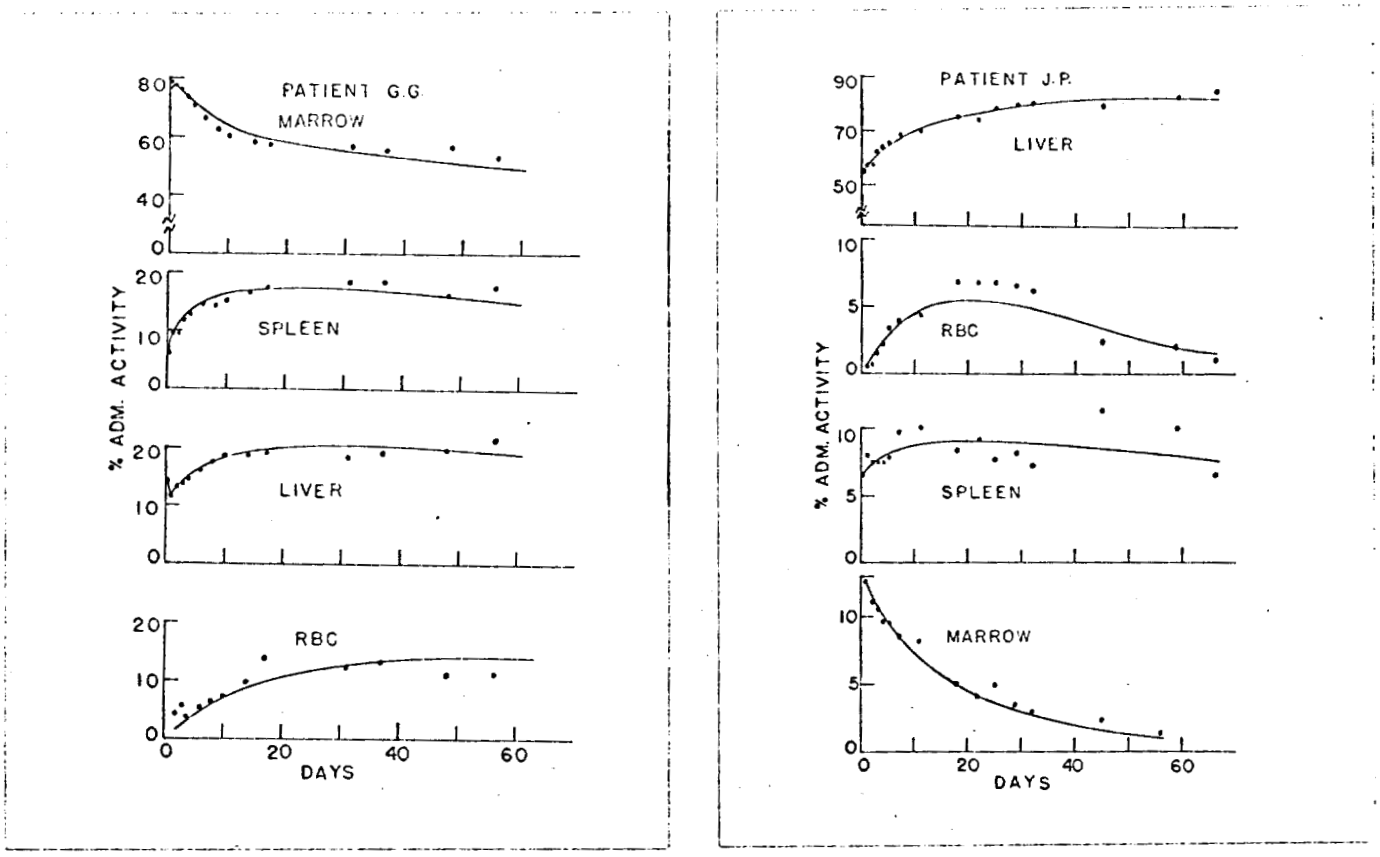
A



B

Fig. 3 (A) Proposed SAAM-25 compartmental model used for the analysis of iron kinetics data. (B) Model calculation results (line) and observed values (points) from quantitative scans of a normal subject.

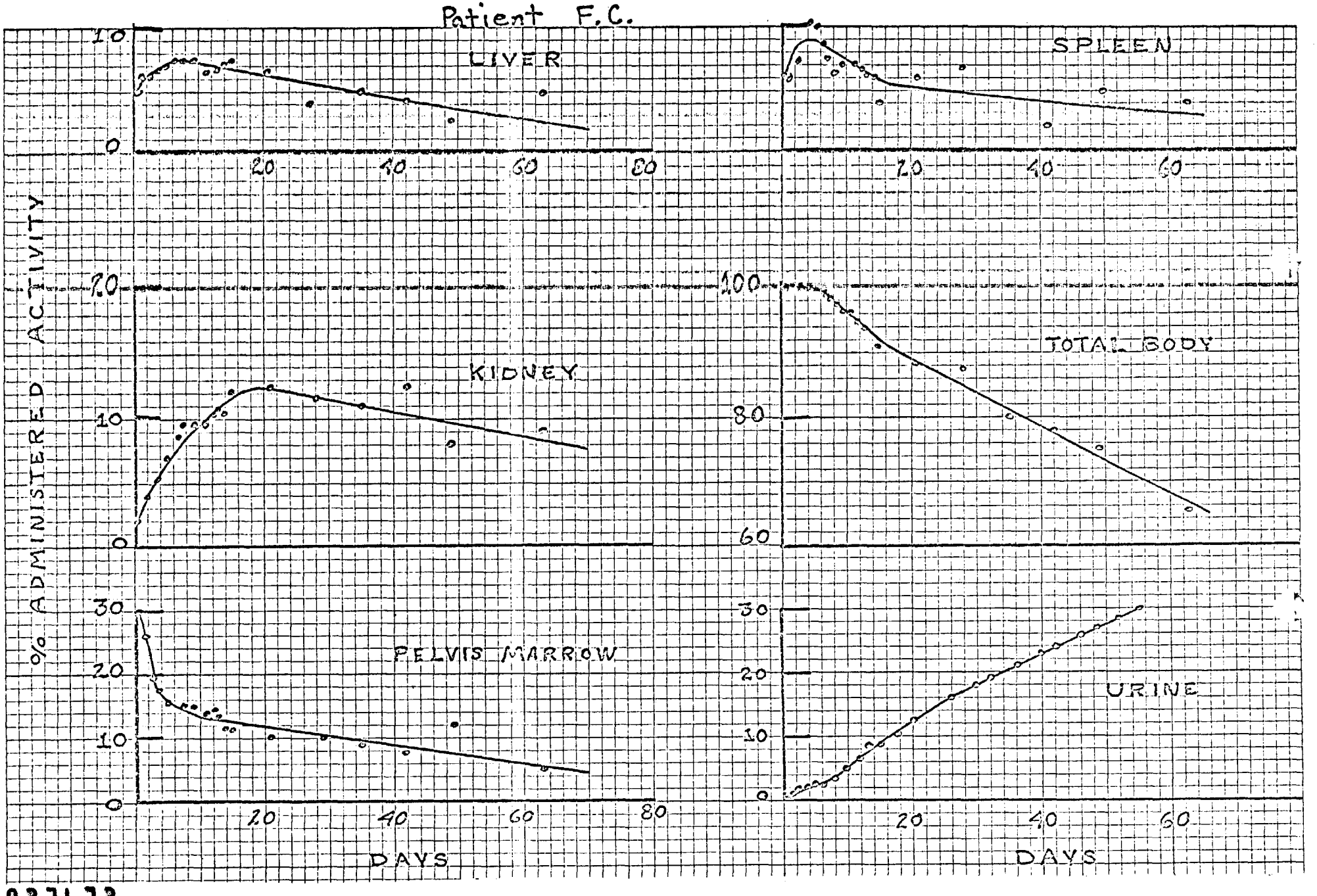
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A B

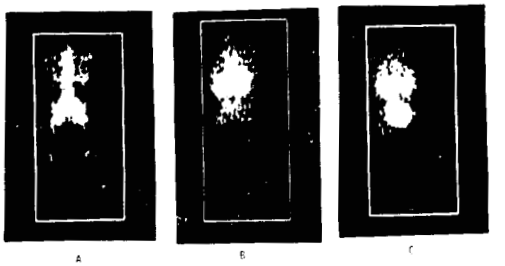
Fig. 4 (A) Model calculation results (line) and observed values (points) for sideroblastic anemia patient, G.G. and (B) refractory anemia, J.P.

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Fig. 5 Results of total body retention, organ uptake and urinary excretion of Fe-59 for PNH patient, F.C.



A B C

WHOLE BODY SCANS OF PNH PATIENT

(A) PNH patient at 4 hours after injection of $^{59}Fe(II)$ same pat... days, characterized by iron storage in kidneys, and (C) ^{131}I-... for visualization of kidneys and bladder.

Fig. 6 Whole-body scans of PNH patient.

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The SAAM-25 model for the PNH patients is currently under development. We propose to analyze this data and will attempt to study at least two other PNH patients this year.

Marrow Distribution Studies in red cell-aplasia and hypoplasia. In-vitro studies suggest that increased marrow trapping of iron might be measurable before an increase in circulating reticulocytes or red cell production. We propose to study patients undergoing immunotherapy for red cell aplasia. With the quantitative methods we have developed, we should be able to measure increased marrow activity response in the early stages of therapy.

We propose to study a group of 3-5 patients suffering from red cell aplasia and will begin development of an appropriate SAAM-25 model to explain their data.

We are continuing to calculate dose estimates from the computer derived organ retention curves for each of our studies. Table 1 shows the preliminary results for the dose to the liver, spleen, and marrow for our normal studies and two patients suffering from refractory anemia. The whole-body emission scan for ^{59}Fe for patients J.P. and G.G. are shown in Fig 2

TABLE 1

mrad/uCi ^{59}Fe Ferrous Citrate I.V.

ORGAN	LITERATURE VALUE	NORMAL	J.P.	G.G.
LIVER	150	114	440	104
SPLEEN	230	377	377*	675*
MARROW	140	61	50	258

*not corrected for enlarged spleen

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Our preliminary dose calculation for the liver assumed all radioiron sources contained with the liver contribute equally to the liver dose , whether within blood vessels or fixed within the liver cells.

The calculated dose to the bone marrow does not include dose from circulating blood activity. The spleen dose calculation for the two abnormals has assumed a normal spleen thus increasing the apparent dose. Both patients were known to have enlarged spleens.

We are continuing to refine these dose calculations taking into account more quantitatively the various contributions to the dose from surrounding sources. We will attempt to establish ranges of dose levels for the various disease states we will study.

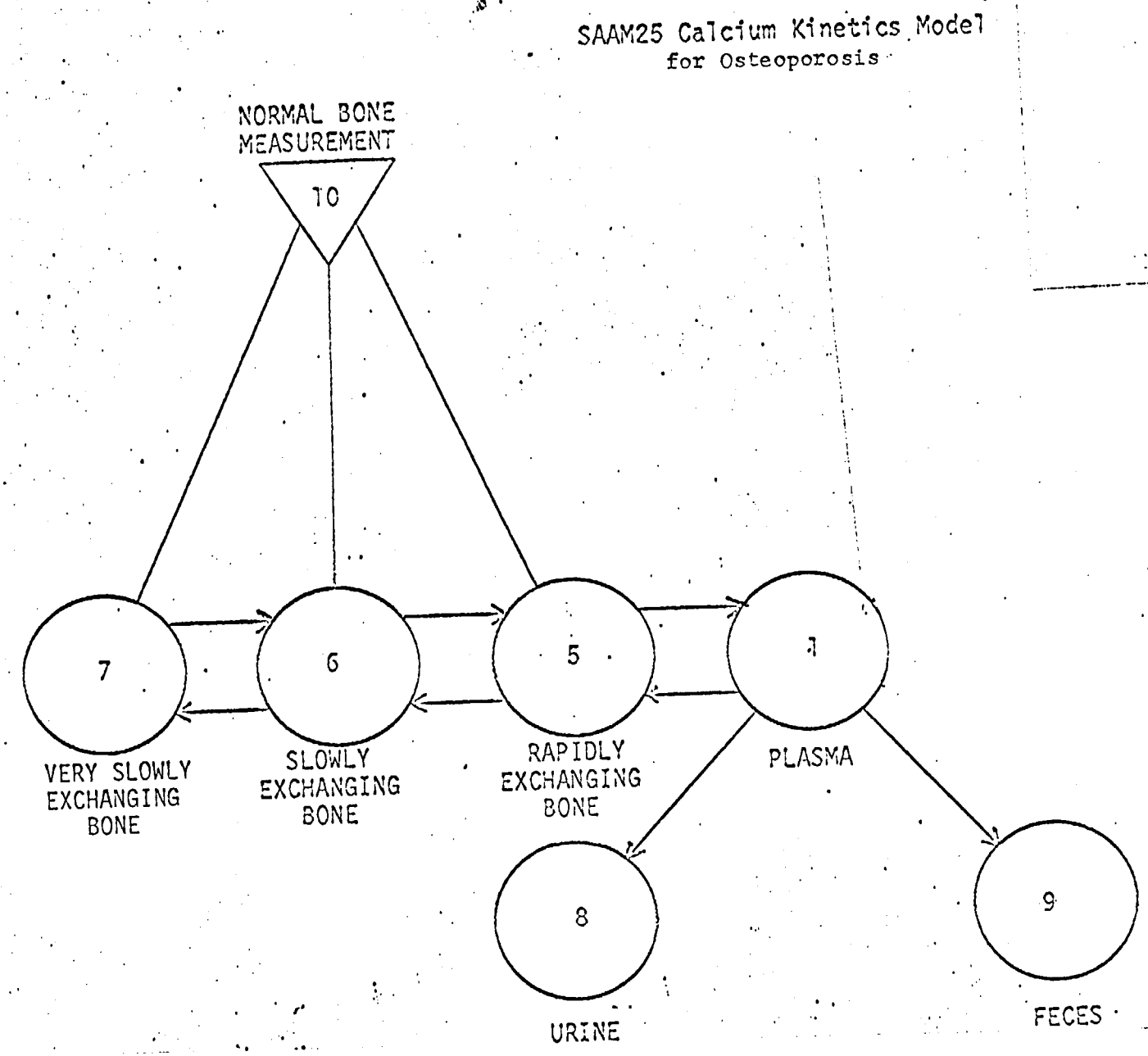
2. b. Calcium Metabolism and Dosimetry in Abnormals

Application of our quantitative methods to the study of calcium kinetics has been carried out in collaboration with Dr. Tessler and the Vanderbilt Orthopedic Surgery Department. Their primary interest is in the effects of thyrocalcitonin on calcium turnover. The quantitative measurements of Ca-47 content in selected areas as well as total body retention at different stages during treatment provide us with unique information on turnover rates and kinetics.

We have made preliminary studies of the calcium kinetics in patients suffering from osteoporosis and localized Paget's disease. These patients have been maintained on several different therapeutic regimens and are being brought back for follow up ^{47}Ca studies to determine patterns of change which can be related to therapy.

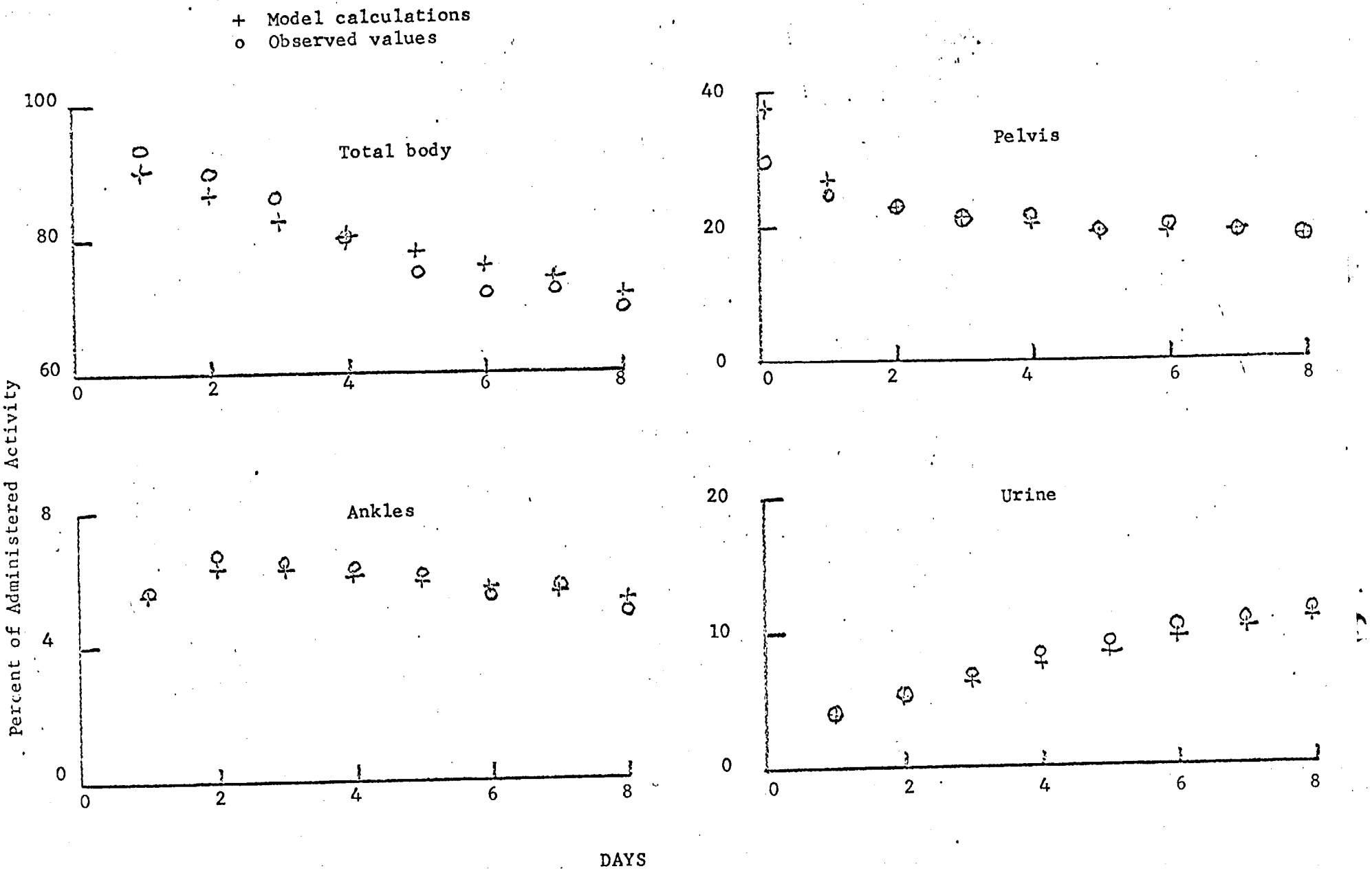
At present we are following three patients with Paget's disease and two patients with osteoporosis. We will continue to follow these patients and propose to include an additional 4 or 5 patients in our studies during the next year.

For each study, the patient is given approximately 25 uCi of ^{47}Ca, I.V. Plasma samples are taken at 30 minutes, 1,2,3,4 and 8 hours and at 24 hour intervals thereafter. A rectilinear scan is made at three hours and then daily for approximately

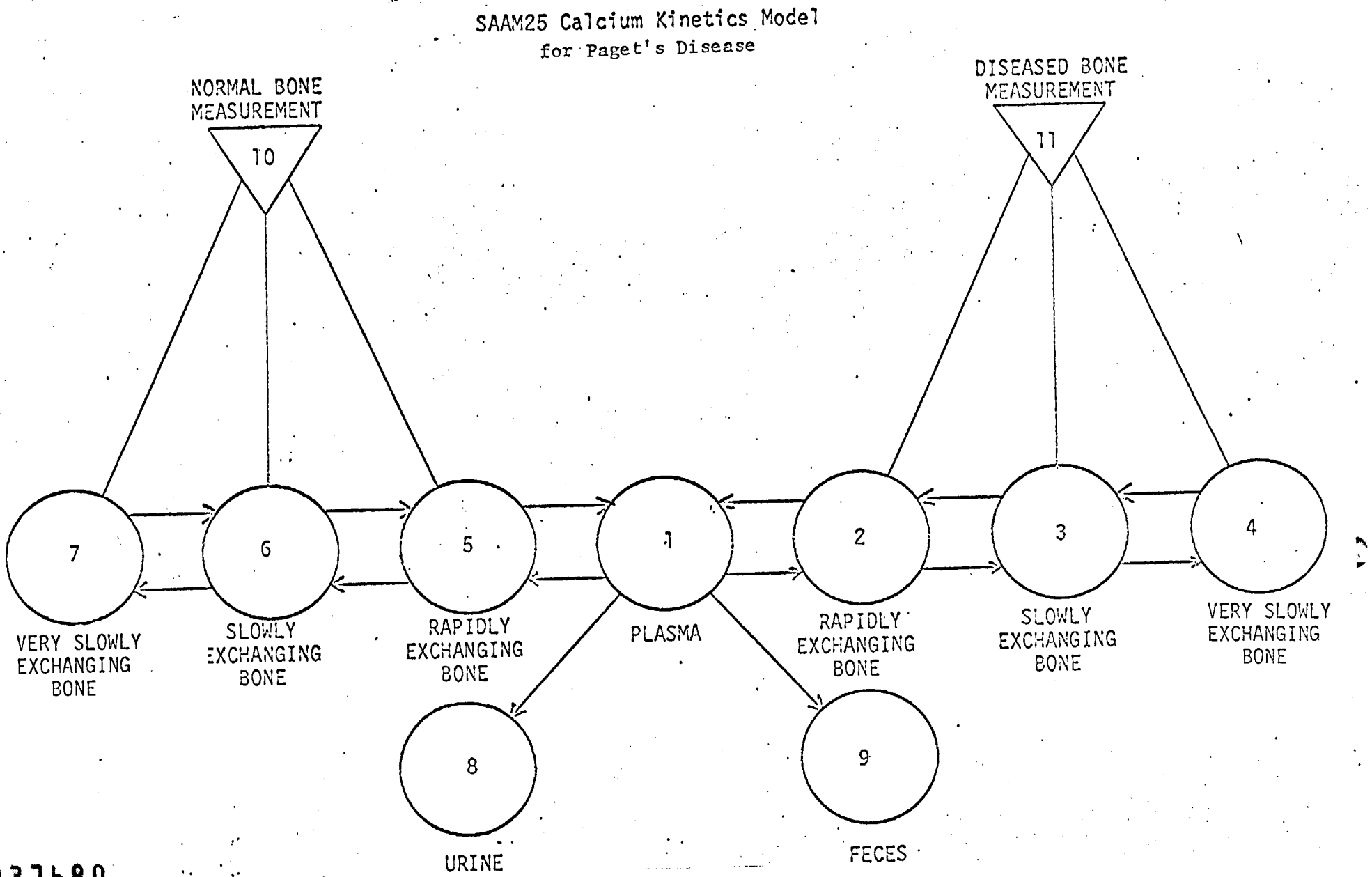


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Fig. 7 Proposed SAAM-25 calcium kinetics model for osteoporosis studies.



1037679 Fig. 8 Comparison of the observed data and corresponding SAAM-25 calculations from an osteoporosis study.



1037680

Fig. 9 SAAM-25 calcium kinetics model proposed for Paget's disease studies.



EFFECTS OF CALCITONIN THERAPY

Fig. 10 Calcium-47 whole-body scans of a Paget's disease patient, taken before and at four months of treatment with thyrocalcitonin.

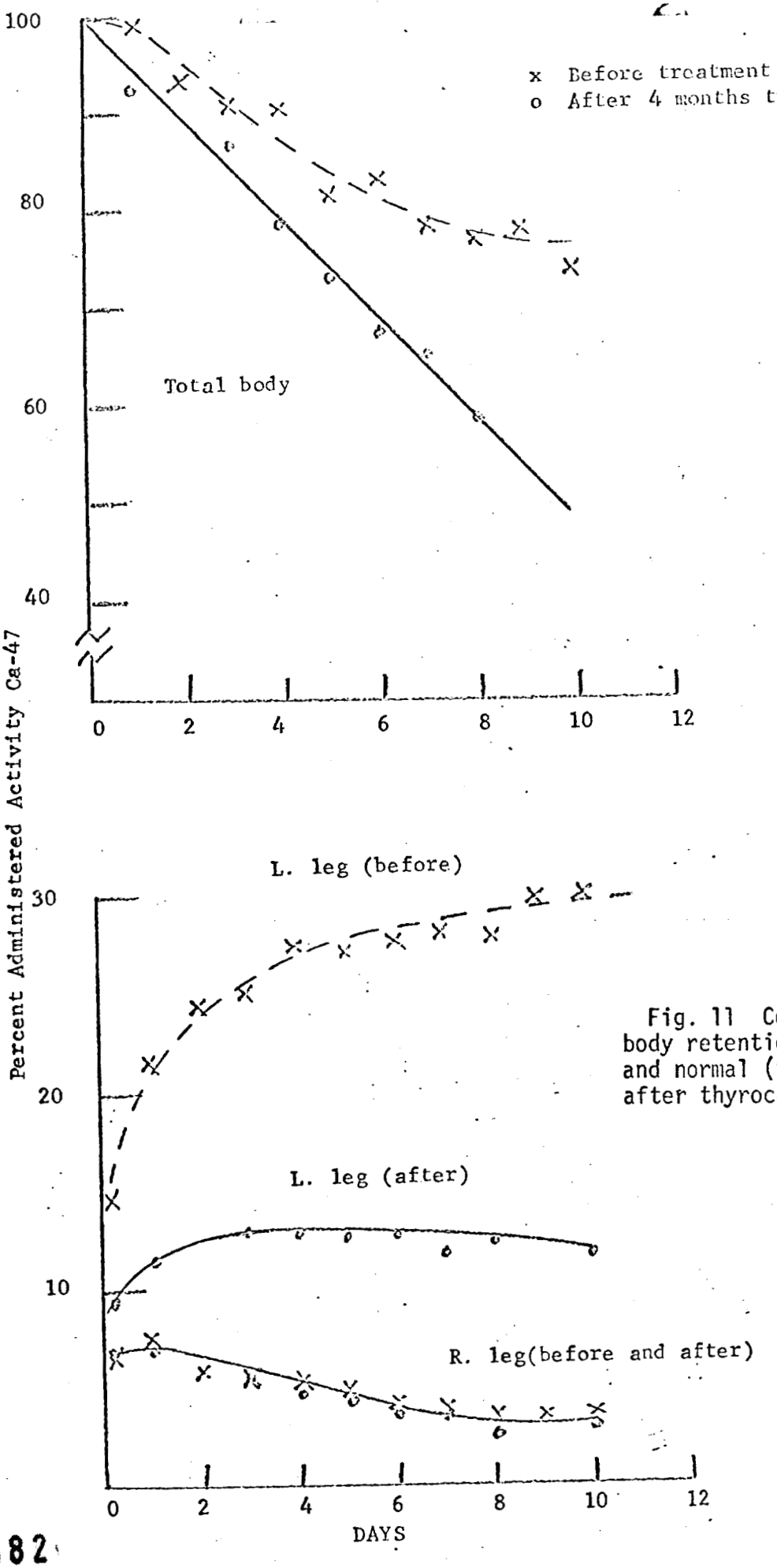


Fig. 11 Comparison of total-body retention, diseased (left) and normal (right) legs before and after thyrocalcitonin therapy.

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remained relatively unaffected, the diseased leg uptake has decreased by at least a factor of two. In addition to these results, we found that the total-body loss of ^{47}Ca showed a much accelerated rate for the study after therapy as compared to the pre therapy study. One of the prime rationale for thyrocalcitonin therapy is to retard bone resorption and the associated body loss of calcium. Our measurements show that bone accretion diminishes on therapy, and a larger fraction of the injected dose is excreted. Further in-depth analyses of these data is warranted. This analysis will not only yield information on the effects of calcitonin on calcium kinetics but will also provide calcium organ retention data that will allow us to make radiation dose estimates for ^{47}Ca in these abnormal states.

C. Bismuth-206 studies

Bismuth was first mentioned as a possible tumor-localizing agent as early as 1931. Since then studies in rat brains (1) have shown that the ratio of the bismuth activity in the tumor is 20-85 times the activity in the normal brain. If these large ratios hold true for man, bismuth may be a very valuable tumor-localizing agent. Of the several bismuth isotopes, ^{206}Bi appears to be the most favorable for scanning. It has a half-life of 6.2 days and is commercially available. It primarily emits gamma rays of energy 500-900 keV and thus requires a very well-shielded scanning detector. We have previously demonstrated that ^{206}Bi can be visualized withour low-level whole-body scanner. This was demonstrated by the successful visualization of a head phantom containing a 1/2" tumor, with a tumor/brain ratio of 10:1.

During the past year we have attempted to determine the uptake of ^{206}Bi-nitrate in spontaneous tumors in dogs. Three dogs were injected with 7uCi/kg of ^{67}Ga-citrate and 20 uCi of ^{206}Bi-nitrate obtained from the Oak Ridge National Laboratory. After 48-72 hours the dogs were sacrificed and tissue samples taken. The radiation emitted from these samples was counted with a NaI detector, and the percent uptakes per gram of ^{67}Ga and ^{206}Bi were determined. The results are described in AEC report ORO 2401-43. In

general, it appears from this preliminary study that Bismuth and Gallium are nearly equal in their capability of localizing tumors, but that the 20-85 tumor/non-tumor ratios seen in rats will probably not be observed in dogs. More studies will be obtained to definitely answer this question.

Our studies in dogs involved autopsy of animals 2 days post-injection of several tracers. As an extension of these studies, we propose to inject small amounts of Ga-67, and Bi-206, two days prior to surgery in patients with brain tumors. Whenever possible these patients will be scanned with usual doses of Tc-99m, 24 hours prior to surgery. Tissue obtained from surgery will be assayed to determine the percent of the injected dose localized in the removed tumor and to compare this to blood levels and non tumorous brain tissue (if any is present in the operative specimens). In this fashion, information on the potential utility of radiobismuth and radiogallium brain tumor localization will be obtained. In the case of Bi-206, this will be of importance not only for emission scanning, but will determine the potential utility of the bismuth fluorescence scanning systems described in section C1.(page 25).

d. Radiopharmaceuticals

(i) Rose Bengal

The dosimetry of I-131 Rose Bengal in abnormal patients has not been studied, but must be significantly different than for normal subjects. We propose to investigate the distribution of radioiodinated Rose Bengal in abnormal patients undergoing clinical procedures in our hospital.

In the proposed study, patients with known or suspected liver disease will be given ^{131}I Rose Bengal in the usual amount (300 uCi) and will be studied more intensively then in the usual diagnostic studies. Blood levels will be determined on a daily basis. In addition, daily urine and stool collections will be obtained to determine the rate of excretion of the radiopharmaceutical. The whole body counter with its spatial mapping capabilities will be used to determine the kinetics of the Rose Bengal compartments (blood, liver, gall bladder, intestine, kidneys, and possibly

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thyroid). Initially, the patients will be unselected as to the type of liver disease present. Subsequently, patients will be classified as to normal, normal liver with constipation, pure extrahepatic obstruction, pure interhepatic obstruction, mixed obstruction, and any of the above with renal disease superimposed. The classification will be made on the basis of pathological or surgical findings and will not depend on the findings of the Rose Bengal study itself. From the kinetic data, a revised estimate of radiation dose from ^{131}I Rose Bengal will be made and these will be correlated with abnormalities of the liver, colon, and kidneys. Over the past year we have not been able to procure suitable patients to participate in this study. However, efforts will again be made to select patients undergoing radioactive rose bengal clinical studies to participate in the dosimetry study.

(ii) Indium-111 DTPA

Indium 111 DTPA is a new radiopharmaceutical under consideration for use in cisternography studies. The radiopharmaceutical is injected intrathercally for the study of cerebrospinal fluid dynamics; the typical amount injected is on the order of 0.5 mCi/70kg patient. The radiation dose from In 111 cannot be extrapolated dependably from biological distribution data collected from other radiopharmaceuticals (^{99m}Tc-DTPA or ^{169}Yb DTPA). Therefore, to estimate the radiation dose to the spinal cord and other tissues, we propose to obtain quantitative measurements of the biological distribution and retention of I-111 introduced intrathecally as In-111 DTPA. The protocol includes obtaining blood samples and imaging the spinal column with the gamma camera. A lead shield with a slit 4x10 inches is placed on top of the multihole imaging collimat The camera is eletronically divided in two parts; thus, two 5 inch segments of the CSF space can be measured simultaneously. This technique is less accurate than the quantitative whole body scans, but makes feasible the opportunity to obtain large number of clinical studies and will provide relative distribution data. A smaller number of

patients will be more thoroughly studied with the whole body counters. The high level counter will be used at short times after administration for the radioactivity and the whole body scanner at later times. Correlation factors between the camera and high level counter, camera and low level counter, and two total body counters will be obtained to permit maximum utilization of available facilities.

(iii) Technetium ^{99m} Polyphosphate

Clinical bone scans are routinely done with ^{85}Sr or ^{87m}Sr. Less radiation dose is associated with flourine-18, but flourine-18 is only available to a very limited number of laboratories. Technetium-99m labeled polyphosphate appears to be a very good bone-scan agent. A number of different laboratories including Vanderbilt are investigating its use. The radiation dose to the bone and red marrow is significantly less than from radio-strontium or radio-calcium and the agent has a greatly increased photon yield. This is a major improvement in the diagnostic area of bone disease.

As part of our own research on Tc-99m polyphosphate, we will determine blood levels, whole body counts and organ distribution as a function of time after administration. We will investigate the effects of type and character of phosphate chain length, types and amounts of reducing reagents, length of reduction time and effect of trace materials in the polyphosphate on uptake in bone. Additional studies will be conducted to determine identity of metabolites of the labeled material in the body, as well as establishing quality control measures for evaluation of production of the radiopharmaceuti Estimates of the radiation dose to bone, total body and gonads will be made.

e. Dosimetry Support for NCRP

The principal investigator, A. B. Brill, is chairman of NCRP Committee 32 and the co-investigator, R.E. Johnston, is a member of this committee. Committee 32 is charged with the formulation of a report on the "Factors influencing the decision to administer radionuclides internally to man:" Those under consideration are: (1) Radiation Dose, (2) Choice of Radiopharmaceutical, (3) choice of instrumentation

and (4) efficacy of the radionuclide procedure. To date we have established an outline for the report. Over the next year we plan on directing our efforts at evaluating the biological data in the literature and calculating the radiation dose to important organs for the most used radiopharmaceuticals in Nuclear Medicine. These efforts are in cooperation with Roger Cloutier and Dr. W. Snyder at Oak Ridge National Laboratory.

f. Monitoring of ^{137}Cs Levels in Man

Cesium-137 is of continuing interest with regards to monitoring body burdens in different segments of the population. We have made preliminary measurements this past year on individuals who were measured in 1966. A comparison of ^{137}Cs levels in this group and to earlier measurements indicates a decrease in body burdens. Our measurements shown in figure 12 are compared to data reported in Health Physics for Oak Ridge Y-12 employees. Our data are in reasonable agreement. We will continue to monitor subjects including those from the earliest studies (1959) and will recalibrate the whole body counter with ^{132}Cs to achieve as accurate measurements as possible. We have made a few preliminary measurements of ^{137}Cs levels in placental tissues. Our data indicates cesium levels on the order of 50 p ci/kg. However, the estimated uncertainty is $\pm$ 140 p ci/kg. We are continuing to receive and measure tissue samples from several hospitals in the Nashville area. With access to a large number of samples, we hope to greatly improve the statistical base of our measurement.

B. Clinical Applications of Activation Analysis

1. Comparison of stable and radiotracer iron kinetics

Iron metabolism parameters during pregnancy were studied in twelve normal women for the late gestational stages from 23 to 38 weeks. Because the subjects were normal pregnant women, it was not possible to use the radioiron tracer, ^{59}Fe, so techniques for the use of the stable iron tracer, ^{58}Fe, were developed. Stable tracer studies

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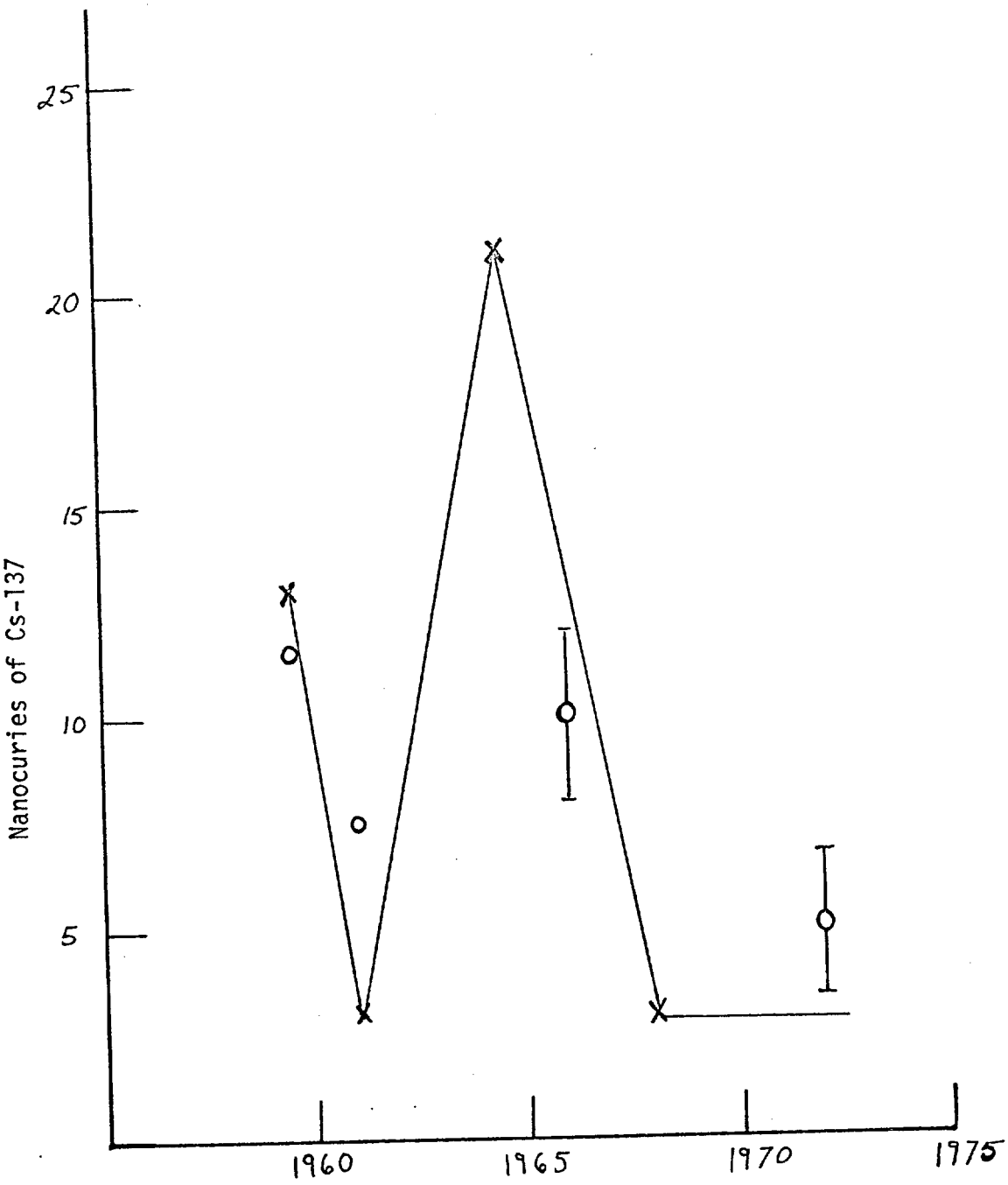


Fig. 12. Body burdens of Cs-137. Whole body counter measurements:
(X) Oak Ridge Y-12, Health Physics, 22, April 1972, p 393.
(O) Vanderbilt University.

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involve the introduction into a biological system of a highly enriched form of a naturally rare, nonradioactive isotope (^{58}Fe, 0.31% natural abundance), followed by the in-vitro quantitation of the tracer in samples from the subjects.

The subjects were given oral and intravenous iron tracer doses containing highly enriched amounts of ^{58}Fe. Fifteen days after administration, the iron tracer concentration in the red blood cells was determined. The ^{58}Fe concentration, both tracer and natural, was measured in the blood samples after neutron activation.

The measurement of the iron tracer 15 days after an intravenous administration yielded the maternal red blood cell incorporation. The iron tracer determination 15 days after an oral administration provided the maternal gastrointestinal absorption times the red blood cell incorporation. Over the gestational stages from 23 to 38 weeks the variations in maternal red blood cell incorporation and gastrointestinal absorption were found to be independent of gestational stage. Their means and standard deviations were calculated to be $65\pm12\%$ and $51\pm21\%$, respectively. With the measurement of the iron tracer in the infant's blood at birth, the transfer to the blood circulation of the infant was measured. This parameter did not appear to have any gestational age-related variations over the range investigated (23 to 38 weeks). The means and standard deviations for the transfer to the infant's blood at birth from a tracer given to the mother were orally and intravenously calculated and found to be $3.0\pm1.4\%$ and $6.6\pm3.7\%$ respectively.

We have reported the results of this investigation in detail in AEC report ORO-2401-43. In this study, however, we administered iron tracer doses of highly enriched stable ^{58}Fe for neutron activation. A possible complication of this methodology is if the quantity of administered iron (0.6 to 0.8 mg given i.v.) alters the normal iron kinetics. To evaluate this possible effect, we propose to administer ^{59}Fe to selected subjects as part of iron kinetics diagnostic studies and determine plasma clearance rates. Then in these same subjects, 2 or 3 days later, we plan to administer

an iron tracer enriched with ^{58}Fe (0.6 to 0.8 mg Fe) as in the maternal fetal study, and collect blood samples over 48 hours. These samples will then be exposed to the thermal neutron beam at the Georgia Tech. reactor and plasma clearance rates again determined. A number of subjects (8 to 10) need to be studied to determine a mean clearance rate. We hope by this protocol to determine whether iron "loading" at these dose levels causes erroneous results.

2. Tissue Levels of Trace Elements in Ischemic Heart Disease

The IAEA and WHO under the leadership of Dr. R. M. Parr has organized an international effort to investigate distributions of trace elements in the environment and in tissues, in relation to geographic patterns of mortality from ischemic heart disease. As an extension of our previous work on clinical applications of activation analysis (^{58}Fe and ^{50}Cr studies), we were invited to participate in a common protocol. This involves the collection and analysis of samples from accidental deaths (persons with no evidence of coronary artery disease) along with samples from patients with demonstrable coronary artery disease. We will analyze samples from 10 subjects by October 1972, using the Georgia Institute of Technology reactor (for long-lived induced activity) and the Oak Ridge facilities (in collaboration with Dr. William Lyons) for analysis of short-lived species. The tissues of interest include heart, liver, and kidney. The elements of primary interest include Cd, Cr, Cu, Mo, and Zn. Trace elements of secondary interest include I, Li, Ni, Pb, Se, and V along with bulk elements Ca, K, Mg, and Na. Sensitivities for determination of each of these elements are shown in table 2.

Based upon the results of these pilot studies, a final protocol will be written, which will define the exact details of methodology and sample size. The costs of these studies are included in our budget estimates. See attached preliminary Protocol.

C. Applications of Quantitative External Counting Systems

1. Evaluation of Solid State Detectors

TABLE 2

ACTIVATION ANALYSIS SENSITIVITY

(Minimum Detectable Quantity PPM)

Element	Long Half-Life	Short Half-Life
Cd	0.25	
Cr	3.5	
Cu		0.001
Mo	1.2	
Zn	1.8	
I		0.0001
Ni		0.18
Se	0.07	
V		0.0004
Ca		1.5
K		0.09
Mg		0.14
Na		0.003

Sensitivity of short half-life radionuclides is based upon a thermal neutron flux of 10^{13} n/cm^3-sec. Sensitivity of the long half-life radionuclides assumes an irradiation time of 60 hrs. at a flux of 10^{13} n/cm^3-sec. and a counting time of 5000 sec.

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a. Fluorescence scanning of the thyroid

Hoffer and his associates at the Argonne Cancer Research Hospital have conducted extensive patient studies using a Lithium-drifted silicon detector and ^{241}Am stimulating sources. They have shown the clinical utility of comparisons between the anatomical distribution of iodine and the functional anatomy based on radiotracer turnover in patients with thyroid disease. In this fluorescent mapping procedure gamma-rays from the exciting source eject electrons from the inner orbits of stable iodine atoms within the thyroid causing the production of characteristic x-ray spectra. The Kα1 x-ray of iodine has sufficient energy (28.5 keV) to escape the thyroid and be counted by a detector. The information obtained from the fluorescence technique is unique in that the normal stable iodine content is mapped with no external disturbances. Nothing is introduced into the body for this procedure.

In our laboratory we have recently constructed a fluorescent scanning apparatus similar to Hoffer's system. The exciting source is a doubly-encapsulated steel ring containing 17.2 Ci of Am-241 obtained from the Isotopes Development Group at Oak Ridge National Laboratory. The detector is a 25 mm in diameter Si(Li) detector housed in a gravity-feed Dewar obtained from Ortec, Inc. for evaluation. The detector and source configuration are shown in Fig 13.

This detector and exciting source configuration was evaluated using phantoms. Patient studies are currently underway. Adequate thyroid scans can be obtained in about fifteen minutes with this system. Dose calculations yield a value of 51 millirads to the thyroid (neglecting scatter) in comparison to a value of 65 millirads measured with thermoluminescent dosimeters.

Preliminary patient studies have shown the value of the fluorescent scan when used in conjunction with radioisotope emission scans. In Fig. 14 a fluorescent scan of a normal thyroid gland is shown along with another view after computer smoothing In Fig. 15 are shown scans of a patient suffering from thyroid cancer. The ^{99m}Tc

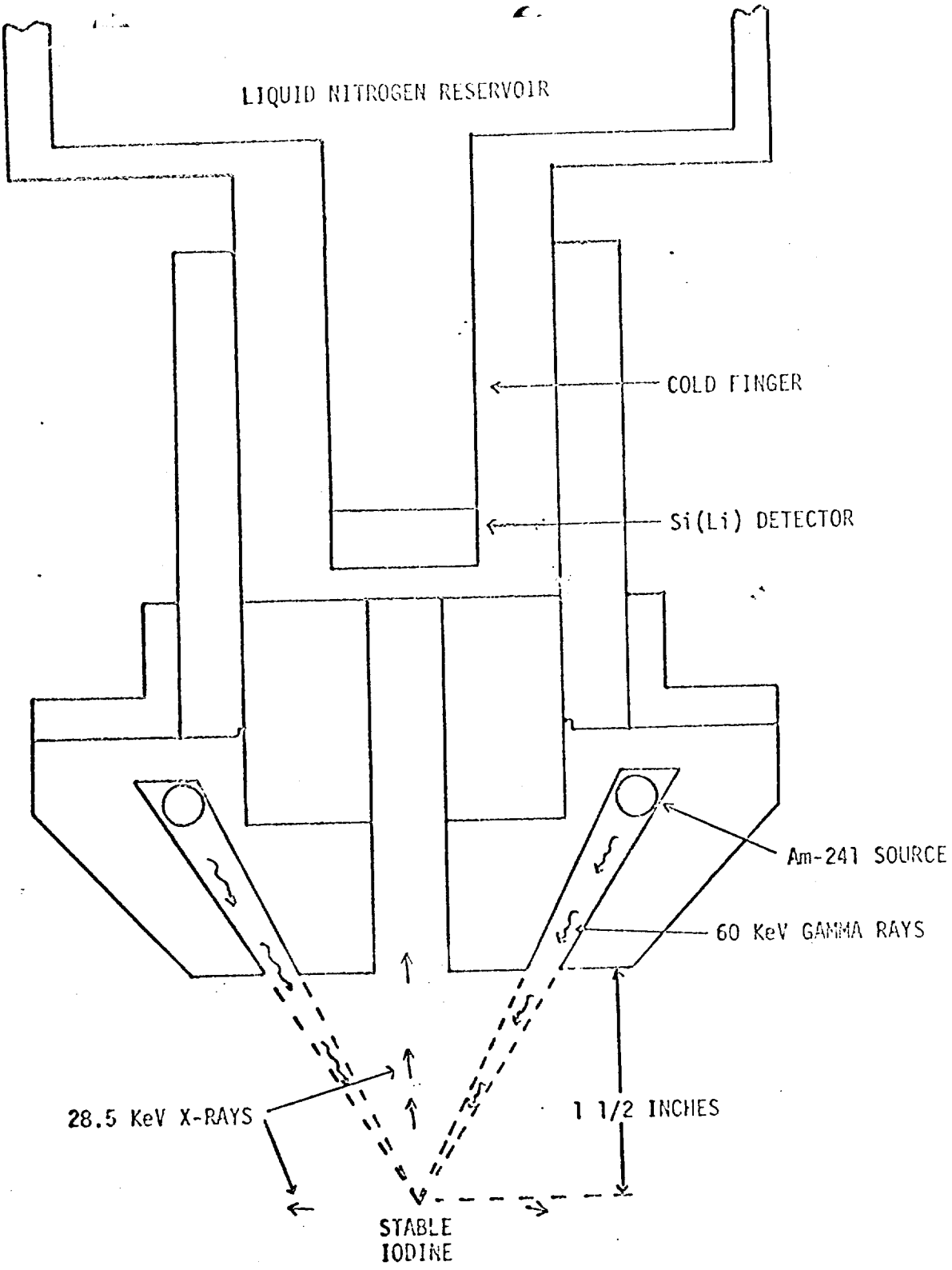


Fig. 13

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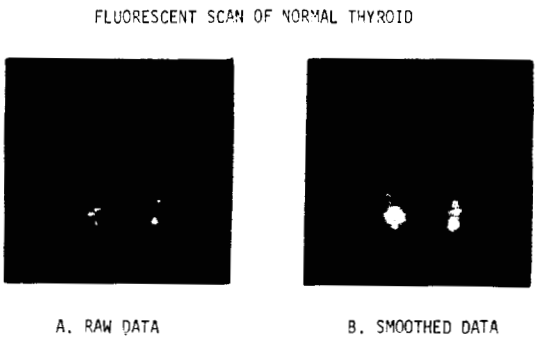


FIG. 14 FLUORESCENT SCAN OF NORMAL THYROID.

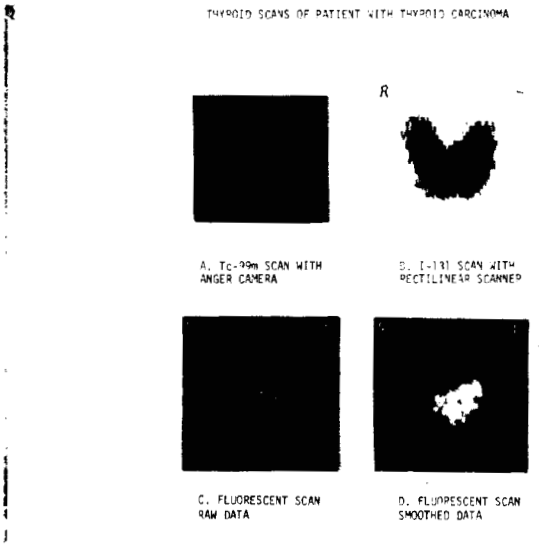


FIG. 15 THYROID SCANS OF PATIENT WITH THYROID CARCINOMA AFTER REMOVAL OF MALIGNANT NODULE IN RIGHT LOBE OF GLAND.

and ^{131}I emission scans appear normal except for a slight indentation in the right lobe. A cancerous nodule had been removed from a metastatic nodule near the right upper pole of the thyroid. A decrease in iodine content in the upper right lobe is seen on the fluorescent scan. In Fig. 16 are shown scans of a patient who had been on thyroid supression for several years. The emission scans following thyroid stimulation with TSH appeared normal although there was a questionable area in the lower right lobe. However, the fluorescent scan showed that there was virtually no iodine in the thyroid gland; an observation which could not have been made from the emission scan.

From our studies we have concluded that fluorescence thyroid scanning is a useful tool. A map of the total iodine content of the thyroid gland can be obtained in a relatively short time with low radiation exposure to the patient. We plan to continue an evaluation of this system. Information content of fluorescent scans on patients will be compared with that of ^{99m}Tc and ^{131}I in an attempt to determine the relative value of fluorescent thyroid scanning. Quantitative measurements of the iodine content of the thyroid tissues will be made. A preliminary calibration curve has been obtained from a phantom study (see figure 17).

More accurate calibration studies will be carried out with a phantom designed to simulate the anatomy of the thyroid-neck region. The results of this calibration will be applied to patient studies to determine the iodine content of their thyroid tissues.

b. Fluorescence Scanning for Brain Tumor Localization

Matthews and Molinaro have shown that transplanted brain tumors in rats take up bismuth to concentrations 20 to 85 times that of surrounding brain tissue. If these data can be applied to spontaneous tumors in humans, then bismuth would be a very powerful tumor-localizing agent. We are also studying the feasibility of imaging stable bismuth in brain tumors by means of fluorescent scanning.

Studies were conducted using NaI(Tl) detectors in a research prototype, 8-

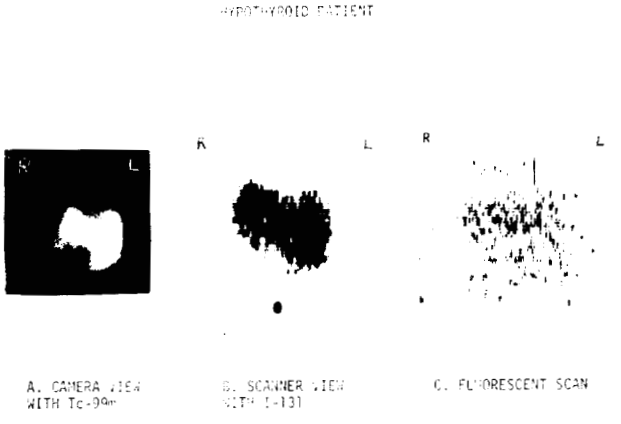


FIG. 16 THYROID SCANS OF PATIENT WHO HAD BEEN STIMULATED WITH TSH TWO DAYS PREVIOUS TO SCAN AFTER HAVING BEEN TREATED WITH SUPRESSANTS FOR SEVERAL YEARS.

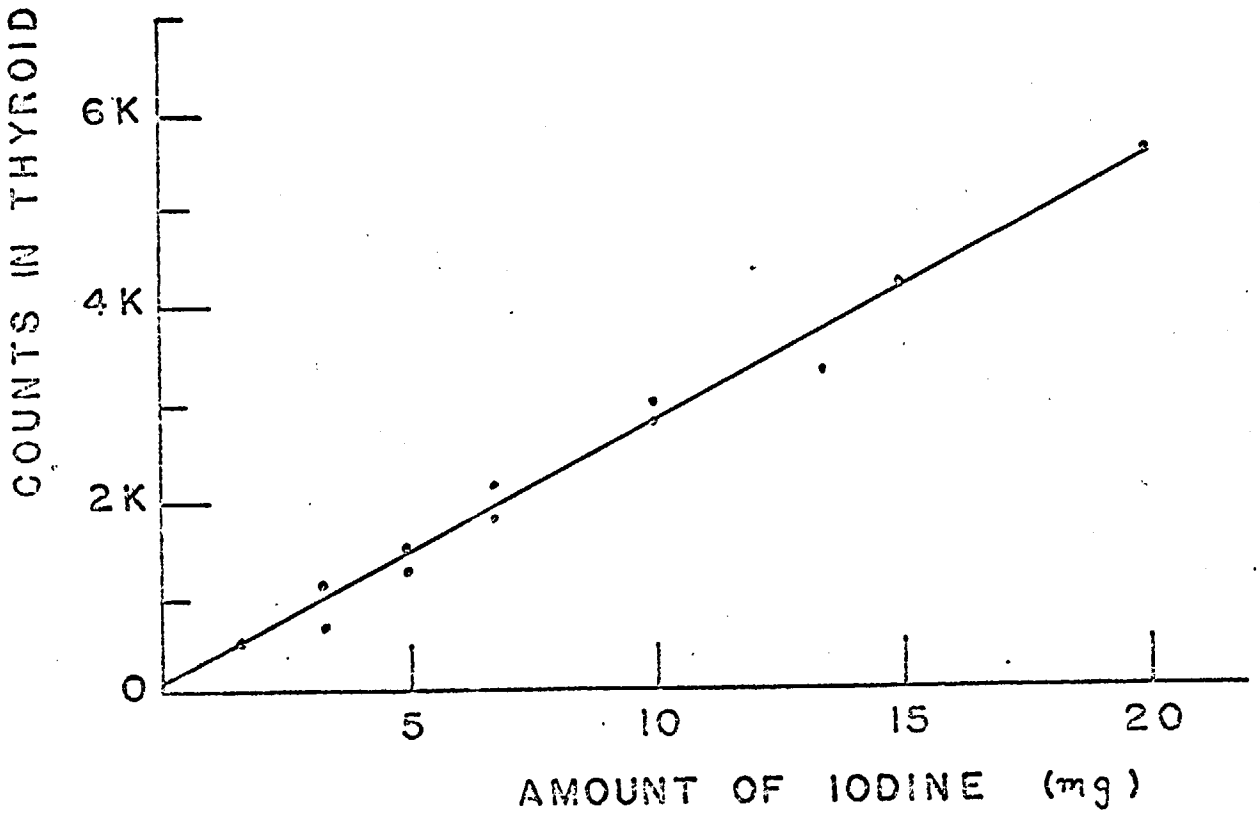


FIG 17 Relationship between fluorescence radiation counts and stable iodine content of the thyroid gland.

detector cylindrical array scanner. These studies showed that the threshold of detection for the system lies somewhere between 13 and 50 mg. of bismuth with a 200 mCi ^{99m}Tc (140 keV) exciting source and scanning time of 30 minutes. A single detector experiment was conducted which showed the minimum detectible quantity of bismuth to be 4.85 mg. This study allowed an adequate collection time to obtain excellent counting statistics.

Attempts have been made to increase the sensitivity of the system and thus reduce the minimum detectible quantity of bismuth. One approach is the use of Ge(Li) detectors to increase the contrast ratio by better discrimination against scatter counts. Two detectors were studied with this goal in mind. The first was a 25 cc. trapezoidal detector with a resolution of 1.8 keV at 122 keV. The use of this detector reduced the minimum detectible quantity by a factor of 3, but there was a loss in sensitivity by a factor of 11. The second detector studied was a high resolution Low Energy Photon Spectrometer (LEPS). This was a 16 mm. diameter planar detector with an energy resolution of 0.560 keV at 122 keV. This detector reduced the minimum detectible quantity by a factor of 6 but with a loss in sensitivity by a factor of 19 over NaI(Tl).

The sensitivity can be increased by increasing the activity contained in the exciting source. The contrast ratio can be improved by using an exciting source which emits gamma-rays of energy closer to the K-edge of bismuth to increase the fluorescent corss-section or probability of absorption. One such isotope which appears promising is ^{153}Gd (97 and 103 keV). A 3 Ci ^{153}Gd source was obtained from the Isotopes Development Group at Oak Ridge National Laboratory for evaluation. Experiments performed with this source and the LEPS Ge(Li) detector showed a reduction in the minimum detectible quantity by a factor of 8 but with a loss in sensitivity by a factor of 12 over NaI(Tl). This source had a large concentration of high energy contaminants (^{152}Eu) which made it virtually useless for fluorescent

scanning and therefore the ^{153}Gd data are highly suspect.

The data from the single detector feasibility studies are summarized in Table 3. In addition, predictions are shown for the maximum count rate and contrast ratio obtainable from a tumor for various detector and exciting source combinations. These predictions are based on the projected figures for a 10 g.tumor calculated from Matthew's and Molinaros data. The calculations involving ^{99m}Tc as an exciting source are based on an activity of 500 mCi which is readily obtainable with high purity from commercially available ^{99}Mo generators. From these calculations, it is obvious that the superior energy resolution of Ge(Li) detectors would make it possible to detect smaller lesions than with NaI(Tl). With present technology, it does not appear that bismuth fluorescent scanning is a serious competitor with emission scanning for tumor localization because of the low sensitivity and specialized equipment required. In cases where a tumor is suspect but cannot be clearly identified with radiotracers, studies might be conducted with current detectors. A small region of interest could be defined which could be scanned for longer periods of time with low resolution collimators to simple detect the presence of unusual concentrations of bismuth.

The 8-detector cylindrical array scanner is being improved by the addition of new, high resolution NaI(Tl) detectors (integral line assemblies). These detectors will have resolutions on the order of 8-9% at 122 keV compared to the resolution of the present detectors at 16-24%. These detectors should reduce the minimum detectible quantity observable with NaI(Tl) with no loss in sensitivity. The single detector studies will be repeated with these detectors and the results compared with those shown in Table 3. Also the limits of detectibility of the scanning system will be studied in a scanning situation using phantoms in an effort to optimize scanning time and exciting source strength required to obtain an adequate image. The use of 8 (or mor NaI detectors in a plane increases the system sensitivity proportionately. It is feasible to add 1 or 2 additional detector planes for simultaneous mapping and if the

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TABLE 3

COMPARISON OF DETECTION ABILITIES OF DIFFERENT DETECTOR AND EXCITING SOURCE CONFIGURATIONS

DETECTOR	EXCITING SOURCE	SENSITIVITY (SOURCE)	SENSITIVITY (NET)	MIN. DET. QUAN. (mg.)	PREDICTIONS SOURCE STRENGTH	CPS	C.R.
NaI(Tl)	^{99m}Tc	1.23×10^{-2}	4.48×10^{-3}	4.85	500 mCi	38.7	1.26
Trap. Ge(Li)	^{99m}Tc	6.37×10^{-4}	3.43×10^{-4}	1.61	500 mCi	2.01	1.78
LEPS Ge(Li)	^{99m}Tc	3.96×10^{-4}	2.35×10^{-4}	0.83	500 mCi	1.25	2.50
LEPS Ge(Li)	^{153}Gd	2.24×10^{-5}	1.79×10^{-5}	0.63	3 Ci	0.42	2.99

Sensitivity = Counts per sec. per mg. per mCi.

Predictions are for a 10 gm. tumor concentrating 6.3 mg. of Bismuth

C.R. = Contrast Ratio

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single plane studies are successful this will be considered, since such a system also will be useful for dynamic tomographic studies using radioactive tracers.

c. Dynamic Studies With Stimulated X-ray Fluorescence

It has been shown (1, 2, 3) that blood flow and blood volume measurements can be made using stimulated x-radiation. The method basically consists of collimated radiation source and a collimated detector placed at some angle such that the field of views of the two intersect at the region under study. The radiation seen by the detector is that which is scattered by the tissues out of the beam of the source into the field of view of the Ge(Li) detector. Characteristic x-rays of the tissues are too low in energy to reach the detector and high Z normal tissue constituents contribute negligible x-rays. However, if a high Z non-radioactive tracer is introduced into the blood, then as this material passes into the region viewed by the detector characteristic x-rays are generated by the radiation source and detected.

Preliminary animal studies have been reported where iodinated contrast material was injected in the internal carotid artery (ref 1) and the curves obtained correspond to those expected with radionuclide or dye-dilution techniques. Stable xenon has also been used with the advantage that it can be administered by inhalation rather than by intracarotid injection, and recirculation effects are minimized.

We plan to investigate these techniques in our laboratory during the next year. We will use a Si(Li) detector system with a collimated 17 Ci ^{241}Am source. The detector source configuration is shown in figure 13. The output signals of the Si(Li) detector will be directed to a single channel analyzer system and then through the CAMAC interface to the PDP/9 computer. The data curves will then be analyzed for blood flow and volume determinations. Field mapping studies will be performed in phantoms to determine effective site of the region of interest and the data obtained will be compared to the results of radiotracer studies.

(1) Hoffer, P.B., et.al. Fluorescence Detection: Application to the Study of Cerebral Blood Flow, J. Nuc. Med. 10, 10, 651, 1969.

d. Emission Scanning

High-resolution semiconductor detectors make it possible to obtain images of radioactive emission distributions from patients with minimum loss of contrast due to scattered radiation. Compton scattering is the principal process involved although at very low energies coherent scattering predominates. Compton scattered gamma-rays generally produce image distortion in two ways. Scattering from a hot source embedded in a scattering media results in a blooming of the apparent source size with a loss in sharpness of the edge. In the reverse situation where a cold lesion is sought within a hot field, scatter into the void region comes from a volume which is large compared to the region of interest. This poses a more serious threat to lesion detection as a result of the decrease in contrast ratio. The excellent energy resolution of the Ge(Li) detector should be useful in both instances to obtain higher quality images, but should be especially useful in the latter case.

In our laboratory we have evaluated two Ge(Li) detectors as possible emission mapping devices. The detectors were mounted on an Ohio-Nuclear rectilinear scanner for these studies. Preliminary investigations were made with a very high resolution (but physically small) detector. Our newer detector is a 53 mm diameter planar detector drifted to a depth of 7.5 mm and with an energy resolution of 3.1% at 140 keV. This detector was loaned to us by Ortec, Inc., for evaluation and has a sensitivity 14 times higher than the smaller detector. This detector was compared to a 1 1/2 x 1/2 inch NaI(Tl) detector using the same collimation (19 hole focused collimator). Sensitivity measurements made with a plane source of ^{99m}Tc showed the NaI(Tl) detector to be about 2.5 times more sensitive than the Ge(Li) detector.

Preliminary studies were made with the NaI(Tl) and Ge(Li) detectors to compare their ability to image hot sources, voids, dual isotope distributions, and isotopes with multiple photopeaks.

These will be extended to patient studies using a 3" Ge(Li) detector which we expect to receive in May or June, 1972 on loan from Ortec. Evaluations will be conducted,

both with phantoms and patients, and the results compared with those obtained previously with the smaller Ge(Li) detectors and also with a NaI(Tl) detector. This large detector should provide us with adequate sensitivity to perform patient studies with good statistics and therefore obtain a more complete comparison of the imaging abilities of Ge(Li) and NaI(Tl) detectors.

In our earlier studies we compared brain scans made with the Anger Camera to scans made with the Ge(Li) scanner. The greater detail and contrast available with the Ge(Li) detector is evident although we were statistics-limited in our scans. In Fig. 18 are shown scans of a patient with a renal cell carcinoma diagnosed 6 months previously who recently had become totally paralyzed. Thirty minutes after injection, the germanium scan was performed. The raw data from the germanium detector are shown on the left above the computer smoothed anterior scan. Two lesions are seen on the germanium scan which correspond to the two areas of increased uptake seen in the left lateral camera study performed immediately following the germanium scans. Only one of these lesions was seen in the anterior camera view and it was only clearly apparent in the bolus study.

Ge(Li) external detectors should be useful for dosimetry and metabolism studies in animals where large quantities of radioisotopes can be given to obtain a high photon flux. In quantitative studies, especially where multiple tracers are used simultaneously, the ability to record only photopeak counts is important. Also precise organ delineation is necessary. Both of these requirements are met by the Ge(Li) detectors.

An extension of our earlier multi-isotope animal tumor uptake studies is planned with the high resolution detectors. In order to evaluate methodology, rats with tumor transplants will be given multiple tracers. These animals will be scanned with our computer-controlled plotter and a fixed crystal high resolution Ge(Li) detector. Each photopeak window will be collected separately with our 8 single channel analyzer data acquisition system. Quantitative tumor turnover studies will be carried out at leas

(2) Ter-Pogossian, M.M., et.al. Chapter 17, Semiconductor Detectors in the Future of Nuclear Medicine, Ed. Hoffer, P.B., Beck, R.N., Goffschalk, A. published by Soc, Nuc. Med., 1971.
(3) Kaufman, L., Shames, D.M., Greenspan, R.H. Powell, M.R., & Perez-Mendez, V., Cardiac Output Determination by Fluorescence Excitation in the Dog. Preprint, April, 1972

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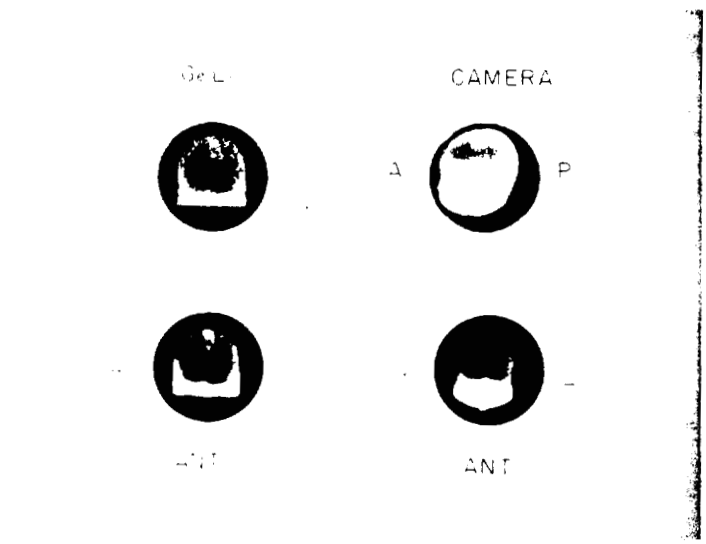


FIG. 18 COMPARISON OF Ge(Li) SCAN AND ANGER CAMERA VIEWS OF PATIENT WITH RENAL CELL CARCINOMA.

3 times daily to determine the temporal kinetics of each of the tracers in the same animal. A comparison of the tumor uptake assessed by external counting just prior to sacrifice and by autopsy sample counting will assist in calibration and validation of the analysis systems. The use of each animal as its own control permits the comparison of multiple agents in the same animal. These techniques may provide diagnostic differentiation of tumor type as well as information on the relative merits of different radiopharmaceuticals. Such a method should facilitate more rapid evaluation of new agents than is provided by the usual clinical "trial".

2. Software Development

a. Motion Correction of Liver Scans

Respiratory motion is a major factor limiting the resolution in liver scans. We have investigated correction techniques proposed by Oppenheim which assume all parts of the liver move in unison. We have found this to be inadequate for most patient studies. Our studies show that different parts of the liver have widely differing excursions throughout the respiratory cycle.

In order to correct properly for this motion, we propose to use rapid dynamic imaging where the respiratory cycle is monitored and recorded simultaneously. For this purpose we have constructed a physiological monitoring circuit which measures the thoracic impedence of the patient. This is monitored throughout the scan and is recorded in the PDP-9 computer in synchrony with the scan data.

By summing the dynamic frames corresponding to the same phase of the respiratory cycle, we will be able to minimize the effect of the respiratory motion. Suspicious regions will be identified in each image and tracked through the physiological cycle to determine whether they move in a cyclic fashion which is consistant with respiratory motion.

We propose to carry out a complete evaluation of this technique and will attempt to adapt the same procedure to the imaging of other organs.

b. Energy Spectrum Analysis to Achieve Maximum Information

Several new approaches have been proposed for maximizing the diagnostic quality of Nuclear Medicine imaging procedures while minimizing patient exposure. These, in general, attempt to use a weighted sum of all the radiation, both scattered and unscattered, emerging from a patient to form the image. (1)

1 Beck, R.N., Zimmer, L.T., Charleston, D.B., and Hoffer, P.B. Aspects of Imaging and Counting in Nuclear Medicine Using Scintillation and Semiconductor detectors. Presented at IEEE meetings, Wash. D.C., March 1972

The photons undergoing various angular scatterings have had their spatial information content degraded and are consequently assigned corresponding diminished weights. The 180 degree peak scattered photons are the exception, however. These photons though undergoing a great energy degradation have retained essentially all of their spatial information and should be assigned weights comparable to the photopeak photons. By setting multiple pulse height windows, we are able to sample the fraction of photons contributing to the various angular intervals.

We propose to determine the optimum number of pulse height windows and their corresponding weighting factors for the routine imaging procedures performed in our laboratory.

For the second approach to image enhancement utilizing scattered radiation we would like to investigate and make use of a deconvolution calculation technique which has been used previously for the analysis of spectral data.

At a particular location within a scan field the detector is presented photons with energy distribution $\phi(E)$. $\phi(E)$ has contributions from two sources

$$\phi(E) = \phi_u(E) + \phi_s(E)$$

(1) unscattered photons $\phi_u(E)$ which can be represented mathematically as a delta function of the energy $\phi_u(E) = \delta(E - E_o)$, where Eo is the unscattered photon energy and (2) scattered photons $\phi_s(E)$ which is in general a smoothly varying continuum of energies having a maximum of the photo peak energy and a minimum at the backscattered energy. This continuum can be represented as a sum of functions $f_i(E)$.

$$\phi_s(E) = \sum_{\Delta} \alpha_j f_j(E)$$

When forming an image we routinely sum pulses taken from a finite energy window. This window contains contributions from both scattered and unscattered photons. We would like to minimize the contributions from the scattered photons and form the image from those unscattered photons which have the highest spatial information content, $\phi_u(E)$. Using the observed counts in multiple pulse height windows, the energy response of the detector system for each of these regions, and the functional representation of the scatter spectrum, we can extract the unscattered contributions.

The observed counts in pulse height interval i, Di, is given by

$$\bar{D}_i = \int A_i(E)\, \phi(E)\, dE \quad , \qquad (1)$$

where Ai(E) is the energy response of the system for the pulse height interval i. This quantity will be determined from phantom measurements. Using the expansion for ϕ (E)

$$\phi(E) = \alpha_0\, \delta(E - E_0) + \sum_{j=1}^{n} \alpha_j f_j(E) \quad ,$$

where the α's represent the relative contribution of the scattered and unscattered parts of the original photon spectrum before instrument intervention. As a first approximation, we feel that we will be able to use a quadratic representation for the fj's. Putting the expanded ϕ (E) into equation (1) and performing the indicated integration, we get:

$$\bar{D}_i = \alpha_0 A_i(E_0) + \sum_{j=1}^{n} \alpha_j A_{ij}$$

$$\bar{D}_i = \sum_{j=0}^{n} \alpha_j A_{ij} \quad ,$$

where $A_{ij} = \int A_i(E) f_j(E)\, dE$

In matrix notation,

$$D = [A]\, \alpha$$

Solving for the α's

$$\alpha = [A^{-1}]\, D$$

Since we feel the image should be formed with highest fidelity from those photons which undergo no scatter, we solve for α_o in terms of the Di's and the $A^{-1}oi$

$$\alpha_o = \sum_i [A^{-1}]_{oi} D_i$$

The $(A^{-1})oi$ are derived from the energy response characteristics of the detector and the Di represent the counts from the i^{th} pulse height interval.

A complete evaluation of these image enchancement procedures will be carried out with phantom measurements. Optimum values for the number, width and corresponding weighting factors for the pulse height windows to be used will be computed. The quality of images generated by these methods will be compared with images from routine clinical Nuclear Medicine procedures.

VI. Scientific Personnel--Curriculum Vitae on file AEC

Principal Investigator:

A. B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Direction Division of
Nuclear Medicine & Biophysics and the Clinical Radioisotope Center, 25%

Co-Investigator:

R. E. Johnston, Ph.D. [redacted]
Assistant Professor, Radiology, 50%

Senior Investigator:

N. C. Dyer, Ph.D. [redacted]
Activation Analysis, 40%

Research Associates:

C. O. T. Ball, [redacted]
Biostatistics, 35%

J. J. Erickson, Ph.D. [redacted]
Radiation Physics, 40%

J. E. Lagan, Electronics Engineer
SS [redacted]

R. Price, Ph.D. [redacted]
Radiation Dosimetry 25%

J. Parker [redacted]
Computer Engineer 28%

J. A. Patton, Ph.D. [redacted]
Radiation Physics 20%

VII. Other Personnel

Technician: TBA 100%

Secretary: C. E. Elam, SS [redacted] 100%

VIII. Other Financial Assistance -- Federal or Non-University

Co-Investigator, salary support from Veterans Administration, 50% effort this research.

1 Research Associate. Salary support Veterans Administration, 25% effort on this research.

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 8,000 square feet adjacent for conference, library, clinical scanning, and instrument development and modification	100 percent
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

1037110

RENEWAL PROPOSAL
Contract At-(40-1)-2401
1 August 1972 - 31 July 1972

X. Budget Estimated Requirements	AEC	University	Total
1. Salaries & Wages Name, Title, Monthly Rate, % Effort			
Principal Investigator: A. B. Brill, M.D., Ph.D. [redacted] Professor, Medicine and Radiology Salary Support not included, proportionate sharing, 25%	-0-	---	---
Co-Investigator: R. E. Johnston, Ph.D. Asst. Professor, Radiology Salary support, Veterans Administration, 50%			
Senior Investigator: N. C. Dyer, Ph.D., @ $1,166.67, 40%	$5,600.		
Senior Investigator: R. Baglan, Ph.D., Asst. Prof. Physics, Salary support not included, proportionate sharing 10%	-0-	---	---
Research Associates:			
C.O.T. Ball, Biostatistics, @ $789.34, 35%	$2,748.	$568.	$3,316.
J. Parker, Computer Engineer, Summer, $1,000. 28%	$3,333.		
J J. Erickson, Radiation Physics @ $1,061., 40%	$1,529.	$3,566.	$5,095.
J. E. Lagan, Electronics Eng., @ $971.75, 76%-	$5,014.	$3,848.	$8,862.
D. Patton, M.D., Assoc. Prof. Radiology, Salary support not included, proportionate sharing, 25%	-0-		
R. Price, Ph.D., Radiation Dosimetry, Salary support Veterans Admin. 25%	-0-		
J. Patton, Ph.D., Research Associate, Salary support not included, 20%	-0-		
Sec'y., Part Time, Shipp, @ $2.75 per hour.	$200.		
Sec'y., C. Elam, $458.33, 100%	$5,500.		
Graduate Student, hourly, J. Jones	$3,200.		
Technician, Whole body counter, TBA, @ $500. 100%	$6,000.		

1037711

	AEC	University	Total
Fringe benefits, (not fixed & of salaries. Varies with employee status & option.)	$3,005.	-	
TIAA Staff	586.	-	
Total Salaries & Fringe:	$36,715.	$7,982.	$44,697.
2. Supplies & Materials			
Animal Purchases	$100.		
Books	$100.		
Chemicals & Glassware	$300.		
Computer Expense - on campus	$1,000.		
Laboratory Supplies			
a. Radioisotopes	$2,300.		
b. Tissue sample collection & Processing Costs	$1,000.		
Machine service contracts	$2,223.		
Office supplies	$875.		
Interface Development- Electronic Components	$3,500.		
Equipment Rental	$1,304.		
Electronic Components - Maintenance (repairs and equipment)	$1,300.		
Subject Participation	$400.		
	$14,402.	-0-	$14,402.
3. Equipment - Computer Memory Addition - DISC Memory Platter (equipment over $500.)	$6,000.	-0-	$6,000.
4. Publications and Copying	$500.	-0-	$500.
5. Travel			
a. domestic - scientific meetings	$800.	-0-	$800
b. to reactor site - sample activation	$400.	-0-	$400.
6. Other	-0-	-0-	-0-
7. Indirect Costs, 44% Salaries & Fringe:	$16,155.	-0-	$16,155.
Total Projected Costs	$74,972.	$7,982.	$82,954

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Projected Costs	AEC	UNIVERSITY	TOTAL
Percentage & Amount, Vanderbilt University	9.6%	$7,982.	
Percentage & Amounts Requested AEC	90.4%	$74,972.	

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Leon W. Cunningham
Associate Dean for Biomedical Sciences

Randolph Batson, M.D.
Vice Chancellor for Medical Affairs

NOTE: Studies described in this application, involving the investigational use of human subjects, have been reviewed and approved by this Institution's Clinical Investigation Committee.

1037713

PROPOSAL FOR RESEARCH AGREEMENT
PROPOSITION POUR UN ACCORD DE RECHERCHE

Name & Address of Institute *Nom et adresse de l'Institut*	Department where research to be performed *Département où les travaux seront exécutés*
Vanderbilt University School of Medicine Nashville, Tennessee 37232	Radiology

Proposed Title of Project
Titre du projet proposé

Activation Analysis Study of Trace Elements in Ischemic Heart Disease

Project Personnel
Personnel chargé de l'exécution du projet

	(Name) (Nom)	(Academic Degrees & University) *(Diplômes universitaires et universités qui les ont délivrés)*
Chief Scientific Investigator *Chercheur responsable du travail*	A. Bertrand Brill, M.D., Ph.D.	M.D. Univ. of Utah Ph.D. Univ. of Calif(Ber
Other Scientific Staff *Collaborateurs scientifiques*	Norman Dyer, Ph.D.	Ph.D. Vanderbilt Univ.
	Robert Baglan, Ph.D.	Ph.D. Univ. of Calif(Ber

Significance of overall problem & Long-range objectives
Importance du problème dans son ensemble et objectifs à long terme

1037714

Work plan for the coming year
Programme de travail pour l'ann[illegible]venir

During the past year, we have developed sample preparation and analysis methods for trace element determination by neutron activation of human tissues. The Pathology Dept. provides us with samples of interest for collaborative research protocols, and in July, 1972, a new faculty member joins the faculty in Pathology (cardiovascular specialist). His presence will facilitate the collection and characterization of autopsy tissue samples from accidental deaths and patients with ischemic heart disease.

We are activating samples at the Georgia Institute of Technology and count the long-lived induced radionuclides at Vanderbilt using a trapzoidal or a coaxial germanium detector and 1024 channel analyzer, or with well-shielded NaI(Tl) detectors. Spectrum stripping analysis is done in our PDP/9 computer.

Between July and October of 1972 we propose to obtain samples from 5 autopsies on patients who have had myocardial infarcts. Tissues will be obtained from the infarcted region and from a normal comparison sample taken elsewhere in the heart from five individuals approx. the same age who died of other causes, without obvious ASHD. The samples will be prepared at Vanderbilt for activation (i.e. lyophilization and encapsulation). Samples weighing between 80 and 100 milligrams of homogenized tissue will be irradiated in aluminum foil envelopes along with properly sealed standards. The samples will be sent to the Georgia Tech reactor where we are irradiating the placental and blood tissues. The samples will be irradiated for 7 days following which they will be held for a week and returned to Vanderbilt for counting the induced long-lived activities. A portion of each unirradiated sample will be sent to Oak Ridge where they will be activated and analyzed, with radiochemistry, for short-lived induced radioactivity using the ORNL facilities in accordance with working agreements(C

Brief description of facilities available
Brève description des installations disponibles

PDP/9 with 16K core, disk, magentic tape, dectape, line printer, ADC, DMA multiplexer, CRT with light pen.

Ortec 8% GeLi detector and assoc, electronics.

Northern Scientific 1024 MCA
Intertechnique 4096 MCA
Low background room for low level counting (GeLi)and/or NaI)

No radiochemistry is needed with our 1 week delay and use of GeLi detectors.

Date at which project would commence
Date à laquelle l'exécution du projet commencerait

July 1, 1972

It is understood that close contact would be maintained on matters of mutual interest and that our institute would participate in any exchange scientific information with other institutes participating in the programme in this field. We would agree to furnish at the end of the year a technic report on the work done, it being understood that this report may be in the form of a re-print, pre-print, or report normally prepared for other purpos The information so provided may be made freely available throughout the world.

Il est entendu que nous maintiendrions des contacts étroits sur toutes les questions d'intérêt mutuel et que notre institut participerait aux éch ges de renseignements scientifiques qui pourraient avoir lieu entre les instituts qui prennent part à l'exécution du programme de travaux dans ce maine. Nous accepterions de soumettre à la fin de l'année un rapport technique sur les travaux exécutés, étant entendu que ce rapport pourrait ê présenté sous la forme d'un tiré à part, d'un avant-tirage ou d'un rapport rédigé normalement à d'autres fins. Les renseignements ainsi fournis p raient être diffusés librement dans le monde entier.

G. Barnwell Bozeman 4/19/72
Chief Scientific Investigator / Chercheur principal — *Date*

Leon W. Cunningham, Ph. D., Associate
Head of Institute / Directeur de l'Institut — *Date*

0311615

Work Plan for the Coming Year (Cont'd)

with ORNL and Dr. William Lyons.

On the basis of the initial experience, a well-defined protocol will then be formulated. We will use multielement mixed standards for calibration and analysis. When NBS tissue standards become available these will be included in analysis and cross calibration studies.

1037716

TO : Addressees Listed Below Date: August 20, 1971

FROM : Ralph Elson, Director, Contract Division

SUBJECT: CONTRACTUAL DOCUMENTS 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 No. 18 to Contract No. AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~A. E. Johnston~~	~~Contract~~		8/20/71	
2. ~~A. E. Miller~~	~~Budget~~		8/23	
3. ~~C. S. Shoup~~	~~Lab. & Univ. Div.~~		8-24	
4. ~~F. O. Christie~~	~~Finance~~		8-24	
5.				
6.				
RETURN TO Jean Gann	Contract Division			Tel.: 3-4107

037717

Routed by

LABORATORY AND UNIVERSITY DIV.

Form OR-133 (Rev. March 1969)

ROUTE SLIP

File number

MANAGER
Deputy Manager
Assistant to Manager for Pub. Infor.

CHIEF COUNSEL
Patent Group

ASST. MANAGER FOR OPERATIONS

OPERATIONAL PLANNING & POWER DIVISION

SAFETY DIVISION
Health & Nuclear Safety Br.
Ind. Safety & Fire Protection Br.
Reactor Safety Branch

LABORATORY & UNIVERSITY DIV.
Research Contracts Branch
Reactor Contracts Br.
Administrative Services Br.

PRODUCTION DIVISION
Operations Branch
Development Branch
Materials & Enriching Services Br.
Nuclear Materials Control Br.
Weapons Branch

ASST. MGR. FOR CONST. & ENGRG.

CONSTRUCTION DIVISION
Administrative Branch
General Construction Branch
Special Projects Branch

ENGINEERING DIVISION
Design Coordination Branch
Power and Communications Branch
Reports and Control Branch

ASST. MGR. FOR ADMINISTRATION

BUDGET AND REPORTS DIVISION
Budget Analysis Branch
Funds Control & Reports Branch

CONTRACT DIVISION
Negotiated Contracts Branch
Procedures, Reports & Contr. Pro. Br.
Procurement Branch

FINANCE DIVISION
Systems & Cost Analysis Br.
Accounting Branch
Acct. Payable & Travel Sect.
General Ledger Section
Government Payroll Sect.
Audit Branch
ADP Branch
ADP Service Center

ORGANIZATION & PERSONNEL DIV.
Government Personnel Branch
Industrial Personnel Branch
Organization & Management Branch
Equal Opportunity Branch

SUPPLY DIVISION
Office Services Branch
Supply & Maintenance Section
Reproduction & Distr. Unit
Stores Unit
Mail Section
Photographic Services
Records Center
Records Officer
Teletype Section
Property Branch
Transportation Branch

SECURITY DIVISION
Personnel Security Branch
Physical Security Branch
AEC Patrol

CINCINNATI AREA OFFICE

NEW BRUNSWICK AREA OFFICE

PADUCAH AREA OFFICE

PORTSMOUTH AREA OFFICE

PUERTO RICO AREA OFFICE

DIVISION OF TECHNICAL INFORMATION EXT.
Office of Ext. Manager
Ass't. Ext. Mgr. for Adm. Ser.
Ass't. Ext. Mgr. for Pro. Ser.
Ass't. Ext. Mgr. for Sci. Comm.
Science & Tech. Branch
Tech. Services Branch
Ass't. Ext. Mgr. for Comp. Processes & Mfg.
Editorial Branch
Graphics Arts Branch
Printing Branch
Ass't. Ext. Mgr. for Doc. & Systems Dev.
Document Mgmt. Branch
Computer Operations Br.
RDT-OSR (ORNL)
RDT-OSR (GE-Evendale)
RDT-OSR (BONUS)

CONTROLLER REGIONAL AUDIT STAFF

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ CONCURRENCE A Emiliani for

2. ~~CONTRACT DIVISION~~ CONCURRENCE A P Johnston

3. OFFICE OF CHIEF COUNSEL CONCURRENCE _____

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USAEC Division of Technical Information Extension, Oak Ridge, Tennessee

1037718

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

AUG 12 1971

Ralph Elson, Director, Contract Division

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: AT-(40-1)-2401
   Contractor: Vanderbilt University

2. Nature of Services To Be Covered by Contract: Research

   Title: "Radioisotopes Studies Using a Low-Level Whole-Body Counter and Clinical Application of Activation Analysis"

3. Type of Contract:

   [X] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: $65,000

5. AEC Percentage of Est. Total Cost To Be Shown by this CA: 86%

6. Description of Other Changes To Be Covered by this CA:
   Modify contract to provide for the performance of additional research to be completed during the period August 1, 1971 through July 31, 1972. The AEC Support Ceiling will be increased from $112,125 to $177,125. Title to the equipment shall vest in the Contractor under authority of the AEC Act of 1954 since the Contractor's contribution is expected to equal or exceed the value of the equipment. Title to the following equipment previously acquired under the contract is to remain with the Government: Card Reader, 717 Printer, Printer Control, and Card Reader Control.

7. Authority:

Form AEC-481 (CA) frm J. R. Totter, HQ, dtd 7-19-71

Herman M. Roth, Director
Laboratory and University Division

OLE:LM

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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.

Form AEC-481
(6-67)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
JUL 19 1971	BM-72-43

3.A. TO	3.B. FROM
S. R. Sapirie, Manager Oak Ridge Operations Office	John R. Totter, Director Division of Biology and Medicine

4.A. CONTRACTOR (Name, Address, Department, etc.)	4.B. PRINCIPAL INVESTIGATOR(S)
VANDERBILT UNIVERSITY Nashville, Tennessee	A. BERTRAND BRILL

5.	6. TERM OF CONTRACT	7. CONTRACT NUMBER
☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER	8-1-71 thru 7-31-72	AT(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:	9. EQUIPMENT TITLE TO VEST IN:	10. SECURITY CLASSIFICATION:
☐ FIXED PRICE ☐ OTHER ☐ COST REIMBURSEMENT ☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)	☐ AEC ☒ CONTRACTOR	Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE "RADIOISOTOPE STUDIES UTILIZING A LOW-LEVEL WHOLE BODY COUNTER AND CLINICAL APPLICATION OF ACTIVATION ANALYSIS"

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 65,000
Estimated AEC Balance From Prior Term, if any	$
	$ 65,000
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$ *
Estimated Project Cost, For Pertinent Budget Period	$ 65,000

Budget and Reporting Classification: 06 03 01

Allotment Transfer: 06-21-91(24)

B. PLANT AND CAPITAL EQUIPMENT $

Budget and Reporting Classification:

Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

* To be determined

15. SCOPE OF WORK

Study of radioisotope distributing and radiation absorbed dose from medical radionuclides.

C 5974

JUL 20 1971

1037722

RENEWAL PROPOSAL
(Revision)
Contract AT-(40-1)-2401
1 August 1971 - 31 July 1972

X. Budget Estimated Requirements	AEC	University	Total
1. Salaries & Wages Name, Title, Monthly Rate, % Effort			
Principal Investigator: A. B. Brill, M.D., Ph.D. [redacted] Professor, Medicine and Radiology Salary Support not included, proportionate sharing, 25%	0	--	--
Co-Investigator: R. E. Johnston, Ph.D. Asst. Professor, Radiology Salary Support, Veterans Administration, 50%	0	--	--
Senior Investigator: N. C. Dyer, @1,157.67, 25%	$ 3,473	$ --	$ 3,473
R. Baglan, Asst. Professor, Physics, Salary Support not included, proportionate sharing, 10%	0	--	--
Research Associates:			
C.O.T. Ball, Biostatistics, @751.75, 35%	2,645	513	3,158
J. Parker, Computer Engineer, Summer, 1,000, 33%	3,333	--	3,333
J.J. Erickson, Radiation Physics, @1011, 52%	1,470	3,336	4,806
J.E. Lagan, Electronics Engineer, @925.50, 90%	4,830	3,666	8,496
D. Patton, M.D., Assoc. Prof., Radiology Salary Support not included, proportionate sharing, 25%	0	--	--
R. Price, Ph.D., Radiation Dosimetry, Salary Support Veterans Administration, 50%	0	--	--
Jr. Investigator, Graduate Student J. A. Patton, Hertz Foundation Fellow, 50%	0	--	--
Part-time Graduate Student, Y. Hsu, @2.00/hr.	2,500	--	2,500

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	AEC	University	Total
Secretary L. Howard, @566.33, 100%	6,796	--	6,796
Technician To be assigned, @425, 56%	2,856	--	2,856
Sub-total	$27,903	$ 7,515	$35,418
Fringe Benefits (not fixed & of salaries. Varies with employee status & option)	1,886	295	2,181
Total Salaries & Fringe	$29,789	$ 7,810	$37,599
2. Supplies & Materials			
Computer Supplies and Time	1,300		
Electronic Components			
Maintenance	1,266		
Interface development	4,000		
Maintenance Contracts	3,223		
Radioisotopes	1,500		
Stable Isotopes & Chemical Supplies	1,000		
Subject Participation	1,200		
Equipment Rental			
Current obligations	1,304		
	$14,793	--	$14,793
3. Equipment			
Computer Memory Addition	6,600	--	6,600
4. Publications and Copying	700	--	700
5. Travel	1,500	--	1,500
6. Other	--	--	--
7. Indirect Costs, 39% Salaries & Fringe; see attached document dated 1 February 1971.	11,618	3,046	14,664
Total Project Costs	$65,000	$10,856	$75,856

Percentage & Amount, Vanderbilt University. . . . 14% - $10,856

Percentage & Amounts Requested AEC. . . . . 86% - $65,000

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Leon W. Cunningham
Associate Dean for Biomedical Sciences

L. Ensign Johnson
Associate Provost

AUG 16

1037124

M-05 18

VANDERBILT UNIVERSITY

CONTRACT TRANSMITTAL FORM

(Complete in Single Copy)

Date 4/26/71

TO: Dr. W. W. Force
Vice Chancellor for Business Affairs

The contract or agreement described below and attached hereto in 1 copies has been inspected and approved for your isgnature.

Contracting Agency Atomic Energy Commission

Contract No. AT-(40-1)-2401

Effective Date 8/1/71-7/31/72

Total or Maximum Amount 74,750.

School or Division Medical School

Department or Office Radiology

Comments

Principal Investigator or Project Director

Department Head

Dean of School or Head of Division

Comptroller

Carolyn Gregory
Sponsored Research

4/30/71

James S. Worley
Associate Provost

4/30/71

Date returned to Medical School:
4/30/71

1037725

C-3557

MAY 3 1971

Revised 3/26/69

EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

AEC Contract AT-(40-1)-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 37203

April 30, 1971

1037726

EXPENDITURE STATEMENT

AEC CONTRACT AT-(40-1)-2401, Modification No 19
August 1, 1970 - July 31, 1971

		AEC		UNIVERSITY			
	% Effort	To 3/31/71	From 4/1/71	To 3/31/71	From 4/1/71	TOTAL	OTHER
A. Personnel							
Principal Investigators:							
A. B. Brill	26%-36%	4,774.	3,046.			7,820.	
Co-Investigator:							
R. E. Johnston	50%						VA
Jr. Investigators:							
Graduate Students:							
N. C. Dyer	56%-100%	5,920.	4,465.			10,385.	
J. Erickson	50%	1,871.	935.	1,964.	987.	5,757.	
J. Patton	50%	0.	0.				Hertz Foundation
Research Associates:							
C. Ball	25%-35%	1,243.	788.	299.	149.	2,479.	
J.E. Lagan	78%-98%	1,959.	1,497.	3,854.	1,426.	8,736.	
R. Price	50%						VA
R. Baglan	Summer,100%		2,222.			2,222.	
Secy.-Clerk:							
J. Sterling	100%	3,594.	2,088.			5,682.	
2 Part-time	As needed	175.	253.			428.	
Technician:							
J. Risner	50%	1,462.	998.			2,460.	
2 Part-time	Summer	760.				760.	
		21,758.	16,292.	6,117.	2,562.	46,729.	
Subtotal		38,050.		8,679.			
Fringe Benefits		1,294.	824.	337.	168.		
		2,118.		505.		2,623.	
Total Salaries & Fringe		23,052.	17,116.	6,454.	2,730.	49,352.	
		40,168.		9,184.			
Overhead 37 1/2%		15,063.		3,444.		18,507.	
TOTAL Salaries, Fringe and 37 1/2% Overhead		55,231.		12,628.		67,859.	

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EXPENDITURE STATEMENT CONTINUED:

B. Equipment						
Magmetic Tapes	26.	3,708.			3,734.	
TOTAL		3,734.			3,734.	
C. Materials and Supplies						
communications	372.			186.	558.	
Xerox		35.		666.	701.	
Other Duplication	27.			14.	41.	
Books	261.			130.	391.	
Journals	86.			43.	129.	
Data Manuscript Processing	577.			288.	865.	
Postage	239.			120.	359.	
Animal Purchase	16.			0.	16.	Institutional Cancer
Electronic Components	6,740.			1,370.	8,110.	
Misc. Laboratory Supplies	381.			0.	381.	
Computer Expense	1,068.			0.	1,068.	
Equipment Rental	569.			569.	1,138.	
Maintenance Contracts	1,246.			2,010.	3,256.	
Work Orders	128.			64.	192.	
Apparatus Shop	1,360.			0.	1,360.	
Subject Participation	500.			140.	640.	
Isotopes	680.		48.	0.	728.	Institutional Cancer
Stable Isotopes	0.			0.	0.	
Subtotal	14,250	35.	48.	5600.	19,933.	
TOTAL		14,285.		5648.	19,933.	
D. Travel	886.	614.		0.	1,500.	
		1,500.			1,500.	
TOTAL PROJECT COSTS		74,750.		18,276.	93,026.	

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III

Project Abstract

Calibration of the whole body scanner for absolute quantitative measurements will be completed for the high energy radionuclides, ^{59}Fe, ^{47}Ca, ^{85}Sr, and ^{206}Bi. Organ distribution and whole body turnover will be determined for these radionuclides in normal and diseased subjects. With the calibrated system, accurate quantitative data can be obtained for radionuclide retention in selected organs including bone marrow. The application of a simulation, analysis and modeling program (SAAM 25) and the RADOS dosimetry computer program will enable us to estimate radiation dose to tissues of interest. Analysis of new applications of solid state detectors will be continued with special emphasis on dosimetry. Dosimetry studies will be conducted with several radiopharmaceuticals of special interest, i.e. $^{206}BiNO_3$, and ^{131}I Rose Bengal. We will continue to collect data on human fetal exposures to ^{59}Fe and ^{131}I for subjects receiving therapeutic abortions.

We will define and monitor ^{137}Cs levels in a stable population of normal individuals not occupationally exposed to radiation, including a group of mothers and newborns.

Special collaborative studies will be conducted to evaluate tracer kinetics in three different patient populations--

1. ^{59}Fe metabolism in hematologic disease.
2. ^{47}Ca turnover in Paget's disease in relation to calcitonin therapy, and
3. ^{67}Ga for tumor diagnosis.

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IV

Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the operation of the Vanderbilt Low Level Counting Facility. Dr. A. B. Brill, Principal Investigator, is the Director of the Division of Nuclear Medicine and Biophysics. The Co-Investigator, Dr. R. E. Johnston, and research associate, Dr. R. Price, receive salary support from the Veterans Administration. One graduate student, Jr. Investigator, James A. Patton, is supported by a Hertz Foundation Fellowship, and Cay Flanigan is an AEC-sponsored Health Physics Fellow. Dr. L. E. Johnson continues to supervise the ferrokinetics simulation studies, in which two electrical engineering graduate students are pursuing their doctoral research. Dr. D. Patton has recently joined the clinical staff in nuclear medicine and will play an increasingly important role in the research program. Weekly meetings with faculty from the School of Engineering with whom we collaborate on ferrokinetic simulation studies, and systems analysis as applied to nuclear detection have been invaluable. Don Johnson, an Engineer at DuPont, Old Hickory, Tennessee, has been of great assistance to us in working with the RADOS and SAAM 24 computer programs. None of these personnel have been supported financially by this contract but the collaboration has strengthened our efforts and has led them to pursue research problems in our area. This will lead to the involvement of more graduate students from engineering and computer science in years to come. This, plus continuing support from the Physics Department has been of major importance in our research efforts.

The recruiting and training of basic scientists for careers in Nuclear Medicine and Medical Physics has been a major dividend from the research supported by this contract.

The staff is stronger today than ever before. 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 be even more profuse this coming year than ever before from this contract. 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 promises to accelerate our biological study output.

1037731

TO : Addressees Listed Below Date: August 20, 1971

FROM : Ralph Elson, Director, Contract Division

SUBJECT: CONTRACTUAL DOCUMENTS 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 No. 18 to Contract No. AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. A. E. Johnston	Contract		8/20/71	
2. A. E. Miller	Budget		8/23	
3. C. S. Shoup	Lab. & Univ. Div.		8-24	
4. F. O. Christie	Finance		8-24	
5.				
6.				
RETURN TO Jean Gann	Contract Division			Tel.: 3-4107

1037732

A. DOSIMETRY

1. METHODOLOGY

A. Calibration Studies

We have developed and evaluated calibration techniques for use with our whole body counter which enable us to make absolute determinations of radioactivity content of selected regions within the body. (1-2) The scanner system consists of two opposed detector assemblies moving in a controlled pattern in the horizontal plane. A schematic drawing of the total scanner is shown in Figure 1. The schematic diagram of the electronic configuration of the system is shown in Figure 2.

The particular collimators used in our initial calibrations are single-hole tapered bore collimators which have high counting efficiency but poor spatial resolution. Such collimators are useful for studies involving very low levels of activity where high spatial delineation is of secondary importance such as for ^{59}Fe whole body scans. We also successfully employed the same calibration techniques with 5" high-energy, fine-focus collimators (the latter had improved spatial resolution but 70 fold decrease in counting efficiency.)

In general, absolute measurements of radioactivity involve measuring a phantom with a known radioactivity distribution which simulates that expected in a patient. The counts collected are related to the uCi content of the phantom and thus a calibration factor can be determined. Comparison of phantom and patient measurements requires a consideration of the following variables: body thickness, source volume, source depth, and surrounding activity (body background).

To correct for variations in patient thickness we measure the attenuation of a photon beam. We do a rectilinear scan with a collimated source located underneath the subject and on the central axis on the top collimator. The transmitted counts are collected by the top detector and stored in a 64 x 64 array. Figure 3A shows an example of a whole body transmission scan. The transmission source in this case was 60 uCi of ^{85}Sr. An effective thickness is then calculated point by point for the transmission scan field using an attenuation coefficient which has been obtained from phantom studies for the given transmission source. Figure 3B shows the effective thickness image; the dot brightness is proportional to the thickness. The transmission scan also provides an anatomical outline of the subject.

The size and depth of sources within the patient usually differ from that of the calibration phantom and must be determined and correction factors obtained.

The geometric mean of the counts from the two detectors varies by only 10% for volume sources ranging from 1 to 5 inches on a side and for concentrations of activity ranging from .02 to 10 uCi/in^3. The depth of the source within the body, however, introduces a larger variation in counts, and we

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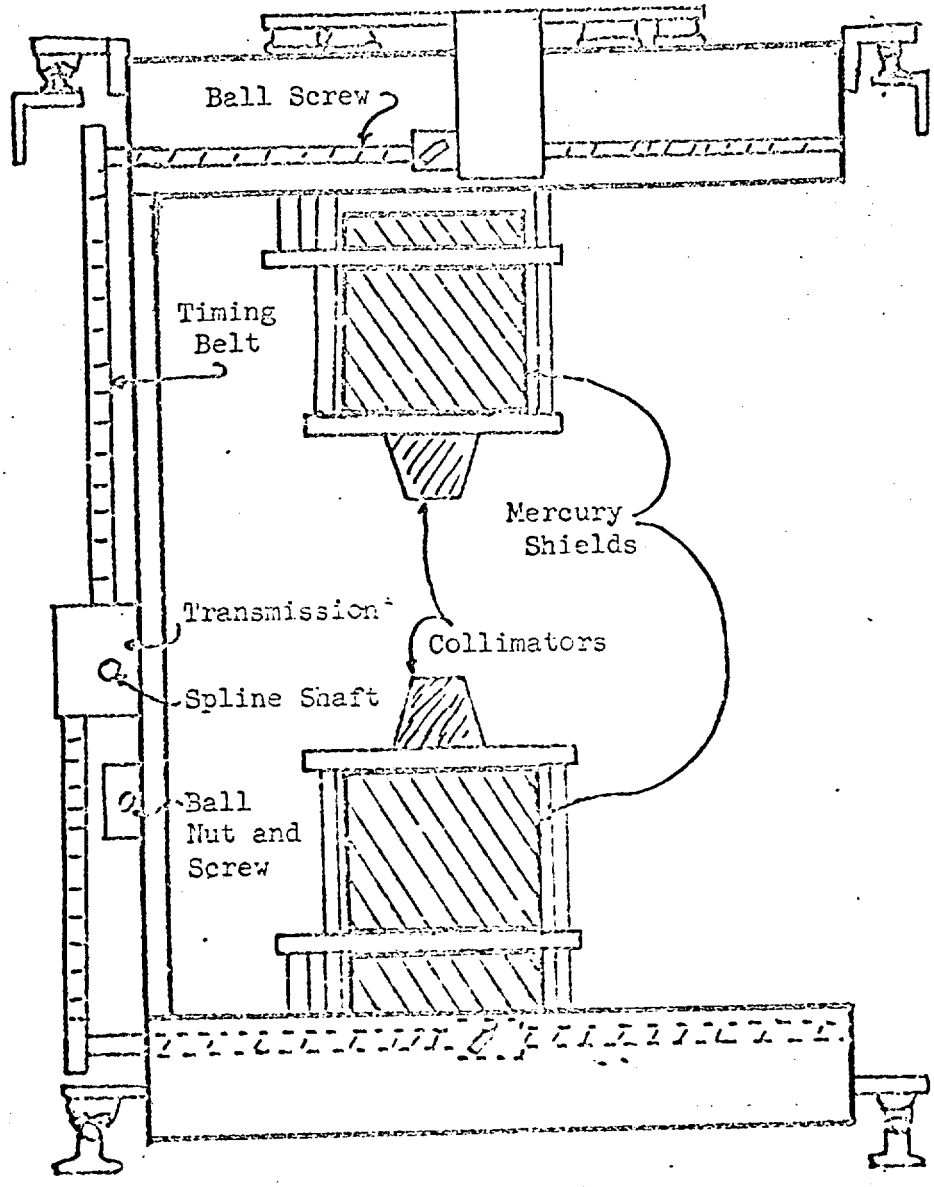


Fig. 1

Schematic drawing of the scanner C-frame assembly showing the method of mounting the C-frame and supplying driving power to the upper and lower detector assemblies.

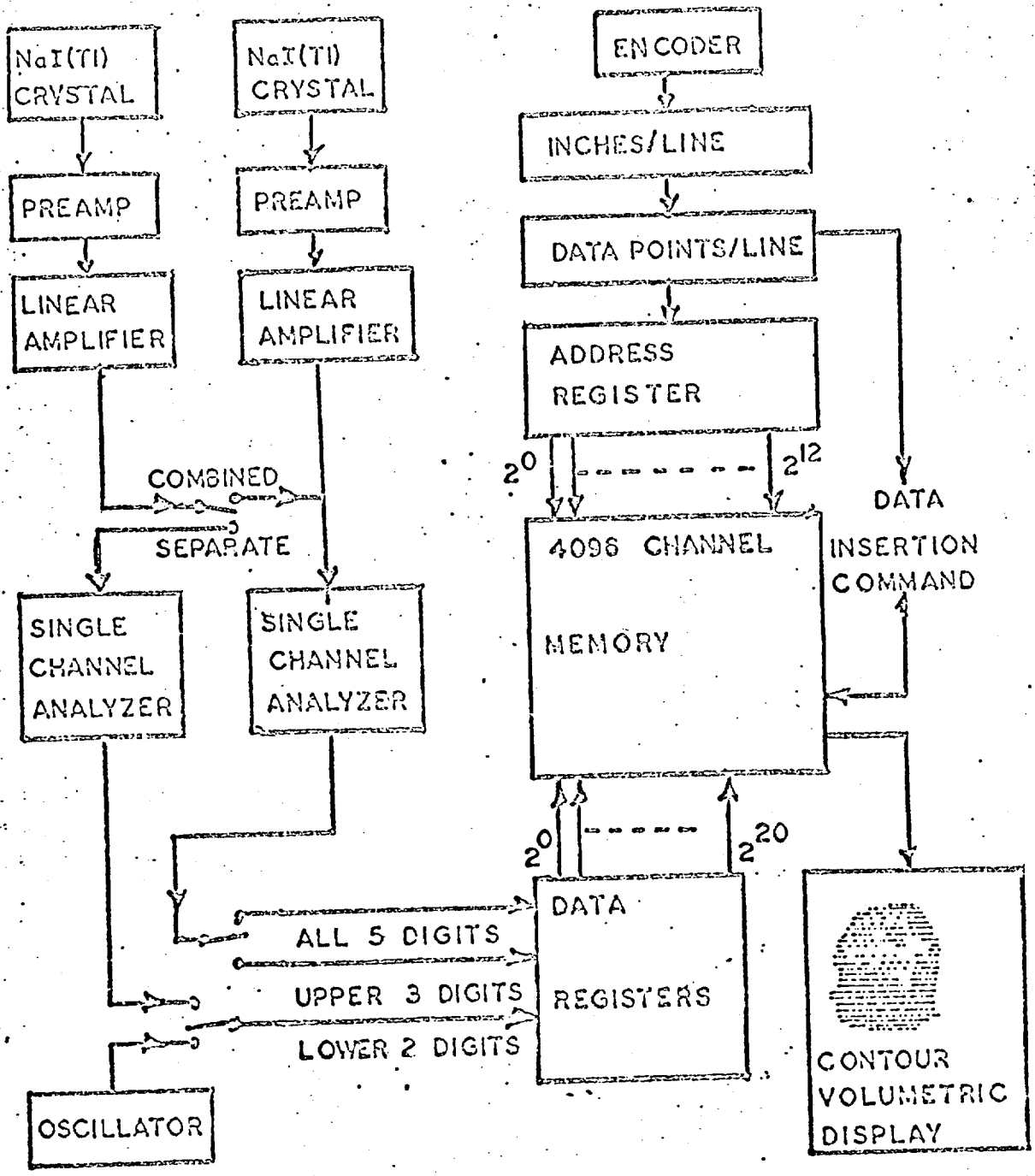


Fig. 2

Electronic system configuration for collection of a rectilinear scan with the option of simultaneously collecting either a second view or data for speed correction.

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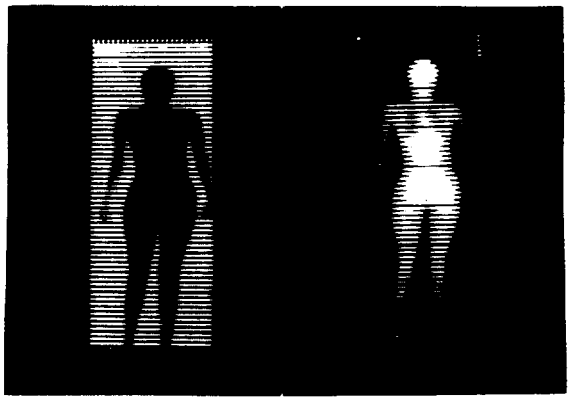


Fig. 3

have found that the ratio of counts of the two detectors can be related to the source depth. In Figure 4A, L is the depth of the source within the phantom; T is the thickness of the phantom; R is the ratio of counts from the bottom detector to the top detector; and GM is the geometric mean of the two detectors. Figure 4B shows the relationship between R, L, and T. The quantity T is measured from the transmission scan, and R is a measured value, thus L can be found from the graph. In Figure 5, the top graph shows the ratio of S_n/R as a function of L where S_n is the ratio of the geometric mean at source depth L to the geometric mean at a standard calibration depth L_s. Thus, L and R are known values and S_n can be determined. From the bottom graph, the calibration factor can be determined from the measured thickness of the subject. Thus we can determine the corrected calibration factor in terms of counts per uCi of activity.

In actual practice this procedure is carried out by computer evaluation of the following equation:

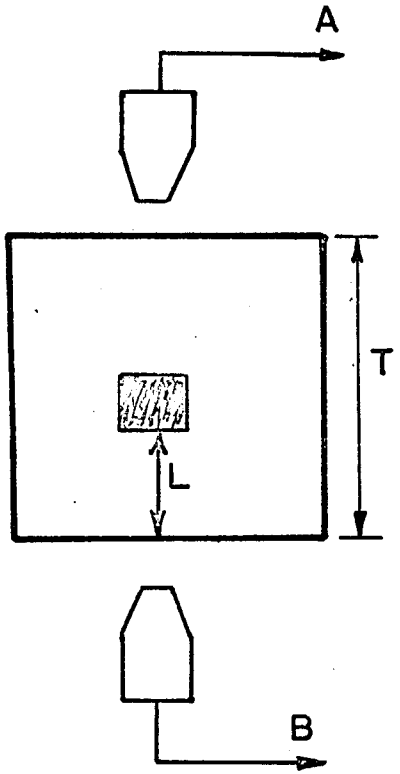
$$A(uCi) = GM\ (sample)\ \bar{e}^{\,f\,(T,R)} / R\ f\ (T)$$

The input data for this equation are the measured geometric mean of the sample scan area (GM), the ratio of bottom to top detector counts (R) and the measured effective thickness (T).

The equation, in effect, corrects the counts from the patient to correspond to the source geometry of the calibration phantom, and then relates counts to the uCi content of the source.

Our experimental check on the validity of this calibration procedure was to give two subjects 8 uCi of sodium iodide-131 for routine thyroid uptakes. The subjects were scanned at 1, 4, 24, and 48 hours after administration of the activity. Urine was collected over the time intervals between scans and the difference between the urine activity and the administered activity served as a separate measurement of whole body retention of I-131. This measurement is compared with the direct measurement in columns 1 and 2 of Table I. Thyroid uptake counts were made in the standard fashion except that the percent uptake was translated into uCi of activity. Column 4, the scan measurements agree to within ±5% whereas the thyroid measurements agree within the ranges of estimated errors i.e., 20%. In many cases counts collected from the organ of interest also include counts from overlying, underlying and adjacent sources of radioactivity. We have been exploring ways by which we can estimate the contribution from radioactivity in circulating blood included in the regions defined as the liver, spleen, red marrow, etc. The method for correction of blood activity which seems most promising is to administer ^{51}Cr labeled red blood cells to the subject prior to the major study. The subject's red blood cell volume is determined. A whole body scan is made of the subject and the fractional distribution of ^{51}Cr activity in the different regions of interest determined. With the ^{51}Cr distribution information, and levels of ^{59}Fe, for example, in the circulating blood, we can determine the amount of ^{59}Fe within the organ of

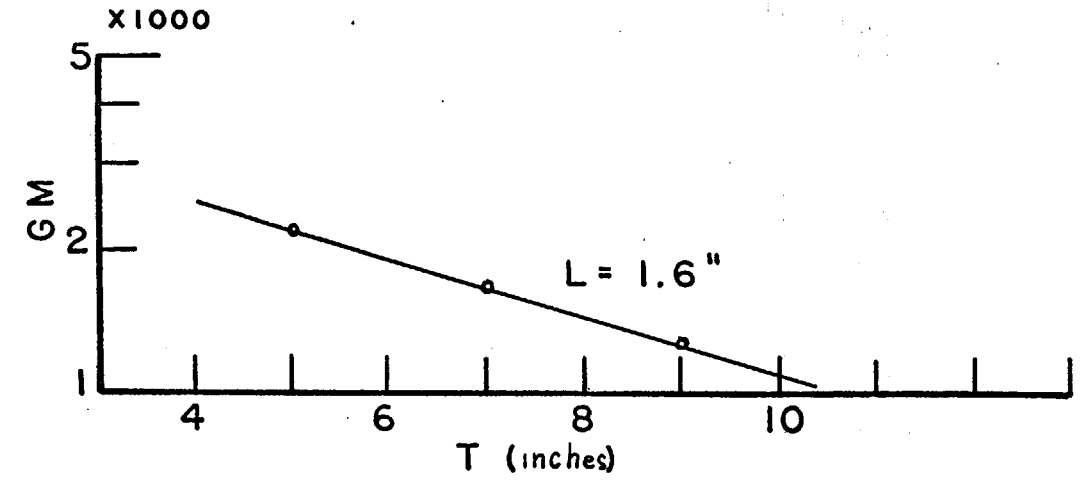
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$$R = \frac{B}{A}$$

$$GM = \sqrt{AB}$$

Fig. 4A



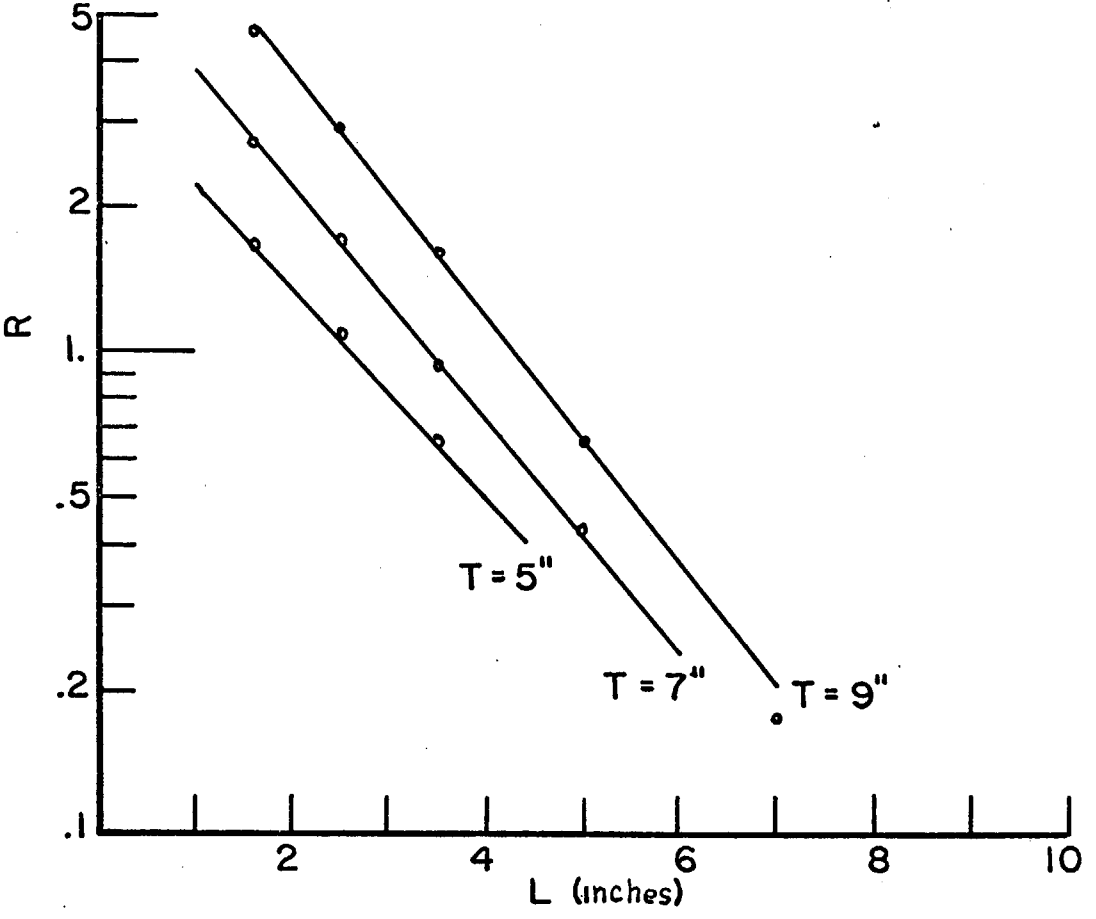
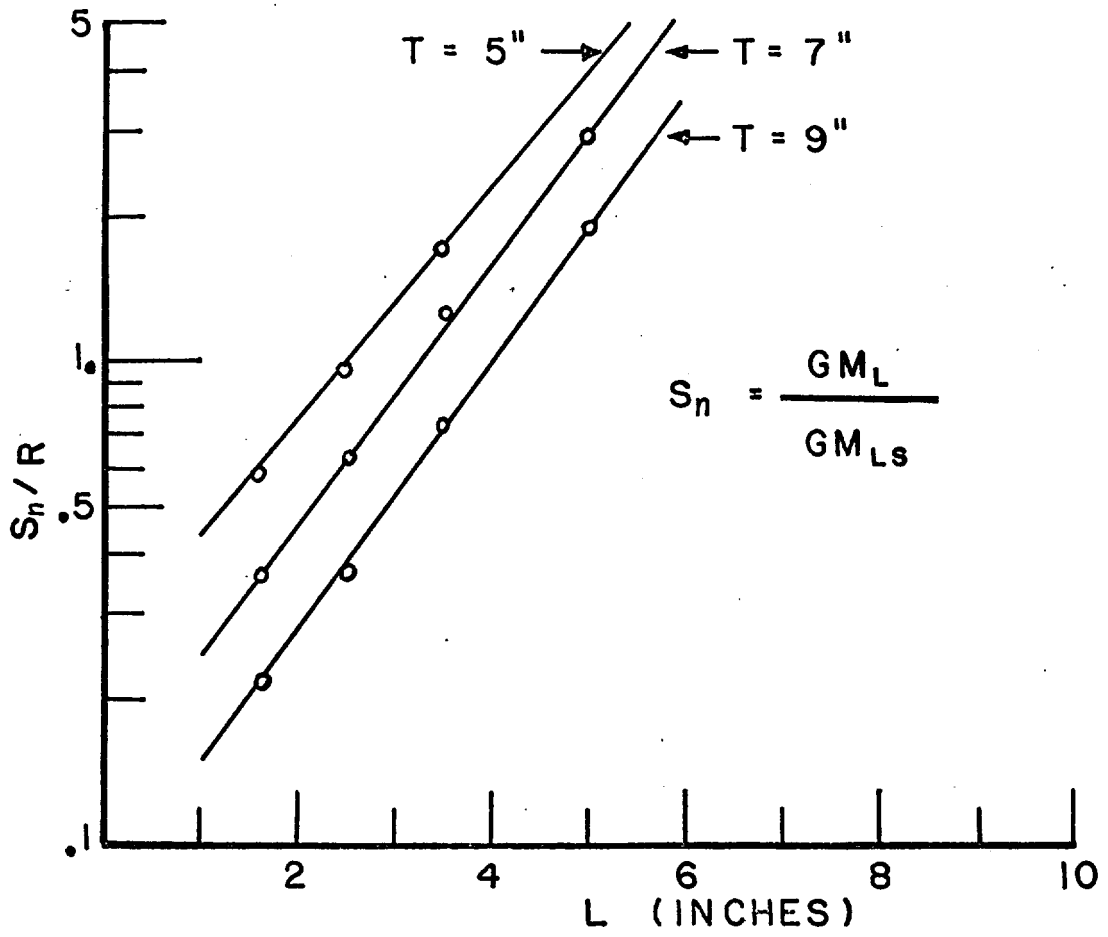


Fig. 4B

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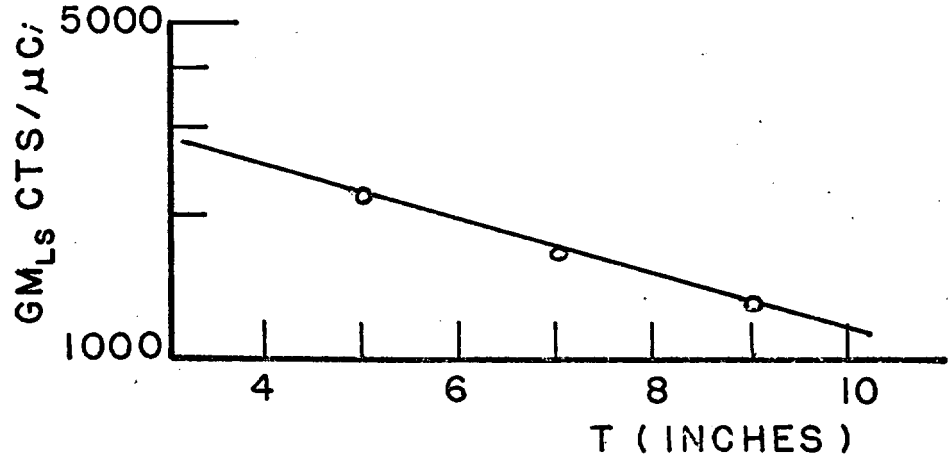


Fig. 5

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TABLE I

8 μ Ci OF ^{131}I ADMINISTERED ORALLY TO PATIENT

PATIENT	TIME HOURS	WHOLE BODY μ Ci URINE	WHOLE BODY μ Ci SCAN	THYROID μ Ci PROBE*	THYROID μ Ci SCAN
A	1	7.92	8.18	–	–
	4	6.95	6.68	0.71	1.19
	24	2.5	–	1.61	1.86
	48	2.01	2.14	1.82	1.93
B	1	7.34	7.10	–	–
	4	7.25	7.25	0.41	0.53
	24	2.54‡	2.01	0.94	1.06
	48	1.60‡	1.07	0.92	1.07

*An estimated uncertainty of ±20%.
‡Patient reported diarrhea which could account for underestimate of excreted activity.

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interest. Our preliminary work indicates this method will be very useful for correction of quantitative scan data. Ideally ^{51}Cr blood distributions studies should be obtained for each subject studied and such will be attempted. From these studies we will establish a "library" of ^{51}Cr red cell distribution data for normal subjects and for patients with different disease states.

As part of our established calibration procedure, we have used the geometric mean value of the counts obtained independently from the top and bottom detectors to minimize dependence on source depth within the body. The combined response of the opposed collimated detectors to a point source is shown in Figure 6. The geometric mean of the two detectors shown in Figure 7 clearly demonstrates an improvement in uniformity of response regardless of source depth. Arimizu (3) has shown that even better response uniformity can be obtained by using the average of the arithmetic and geometric means of counts from opposed detectors (See Figure 8). We plan on incorporating this method into our procedures for estimating radionuclide organ content.

At this time we have absolute quantitative calibration factors only for ^{131}I. We had not completed the calibration for other radionuclides of immediate interest to us (^{59}Fe, ^{47}Ca, ^{85}Sr, ^{206}Bi) because of side shield penetration of the collimators by high energy gamma rays. We have recently solved this problem by adding lead rings between the crystal and collimator (see Figure 9). The side-shield penetration was measured for 1.2 MeV gamma rays and with the rings is less than 1% of the maximum counts on the axis of the collimator field of view.

The addition of the rings changes the spatial resolution and depth response for the collimator and also reduces the detection sensitivity of the system to approximately 80% of its former value. With the additional shielding and modified collimator configuration, we now plan on carrying out a complete calibration of the system for ^{59}Fe, ^{47}Ca, ^{85}Sr, and ^{206}Bi. With the calibration factors, we will then be able to make absolute quantitative measurements of these radionuclides.

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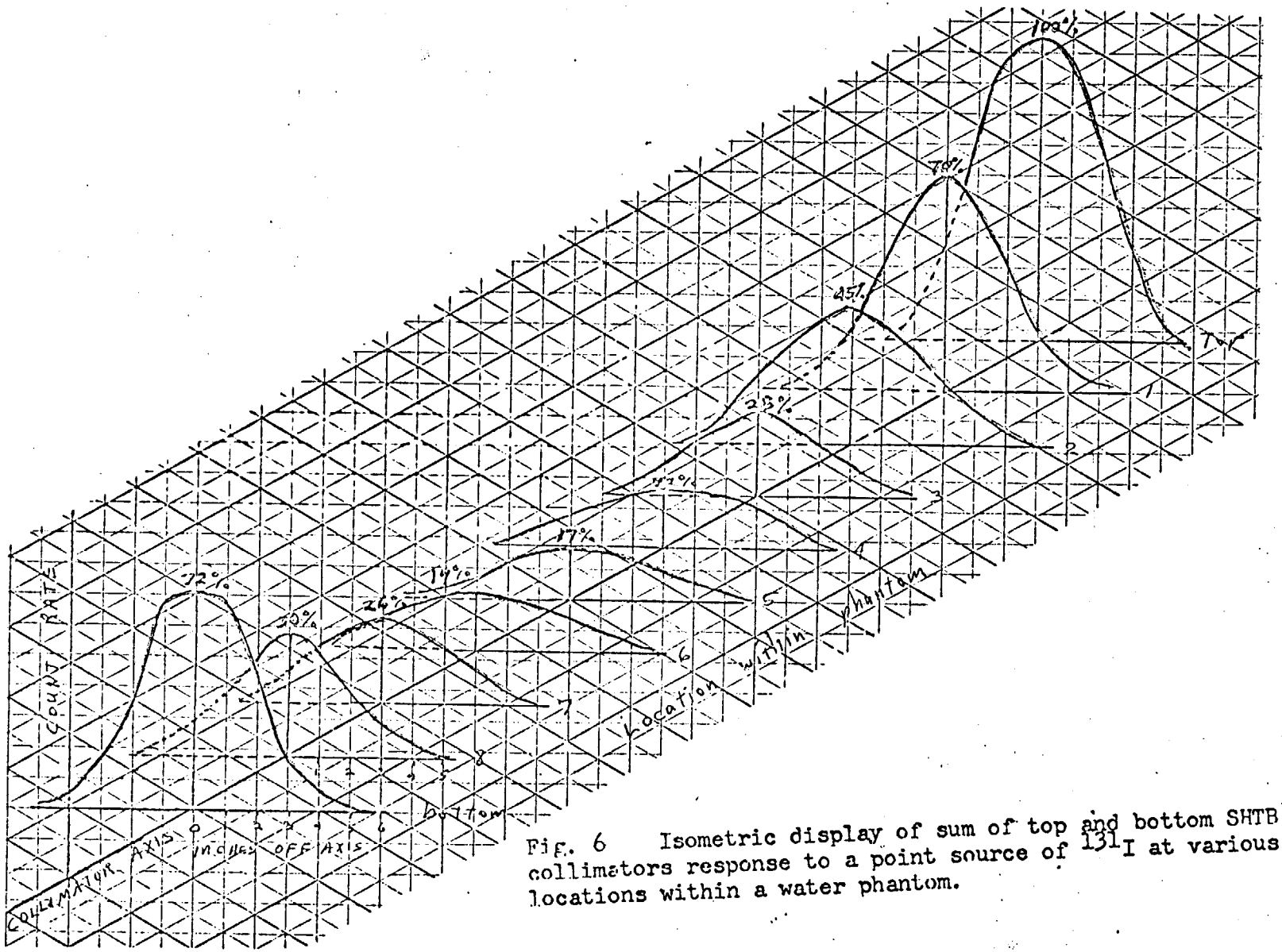


Fig. 6 Isometric display of sum of top and bottom SHTB collimators response to a point source of ^{131}I at various locations within a water phantom.

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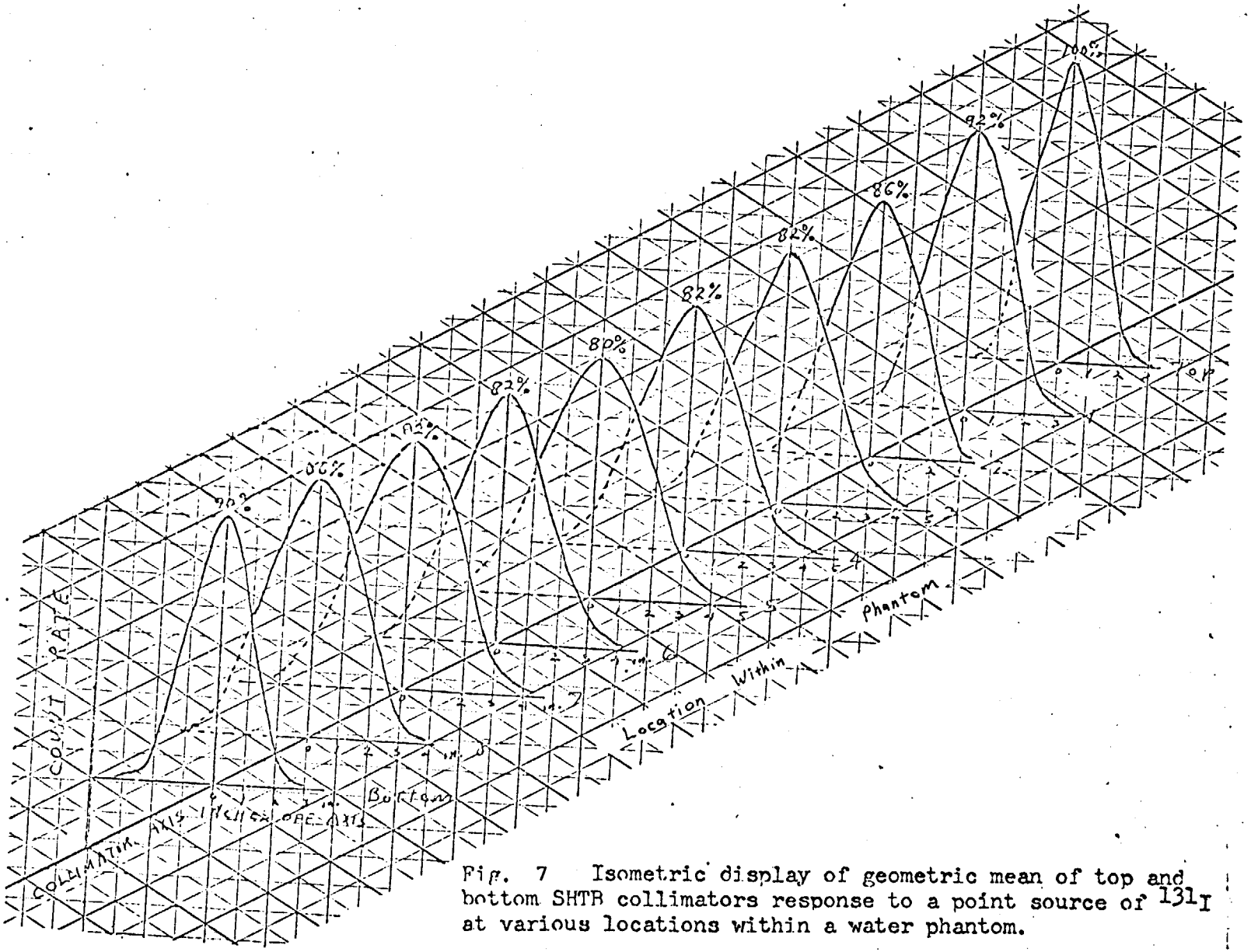


Fig. 7 Isometric display of geometric mean of top and bottom SHTB collimators response to a point source of ^{131}I at various locations within a water phantom.

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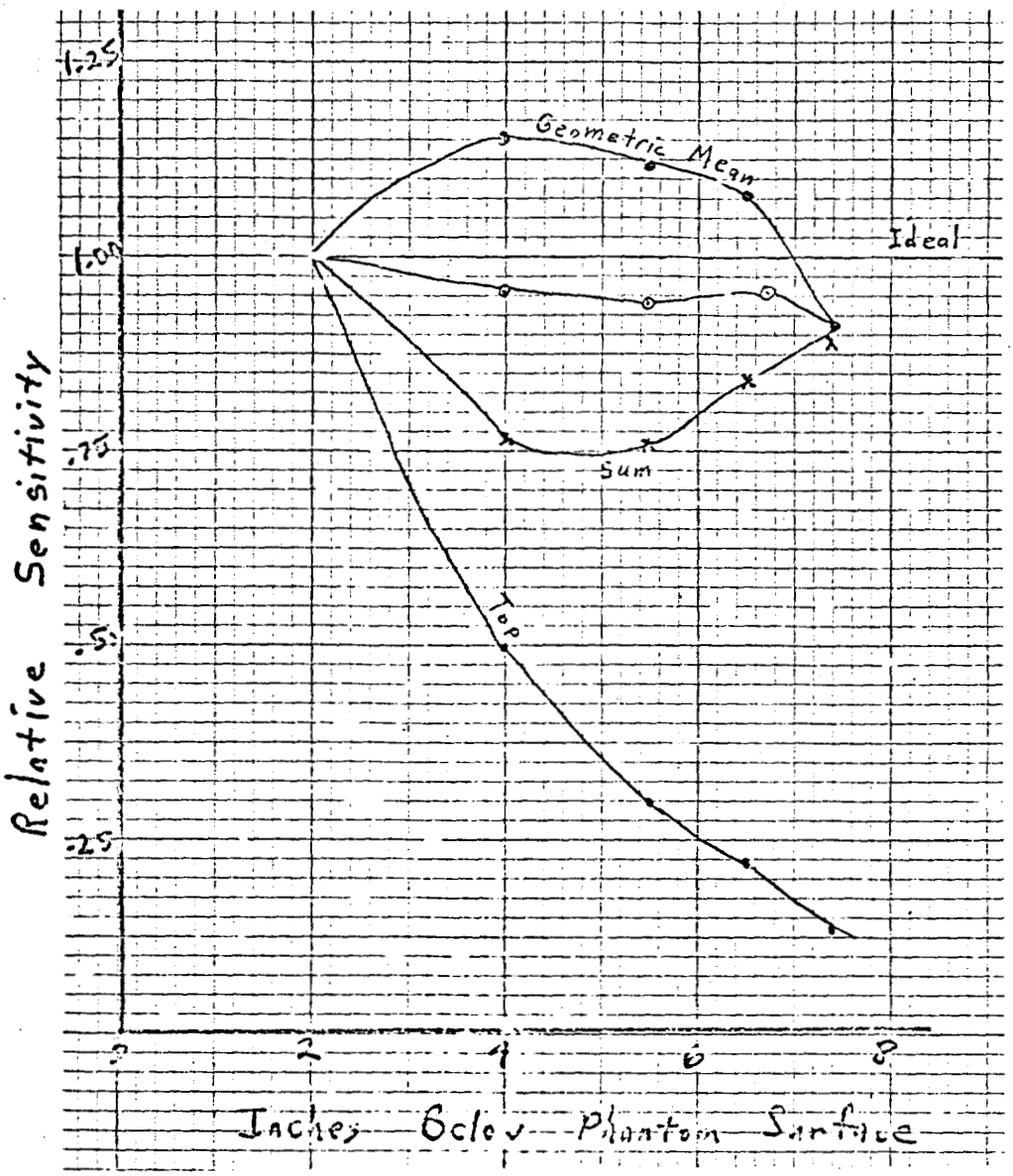


Fig. 8 . Comparison of the focussed collimator sensitivity as a function of source location for different data handling methods.

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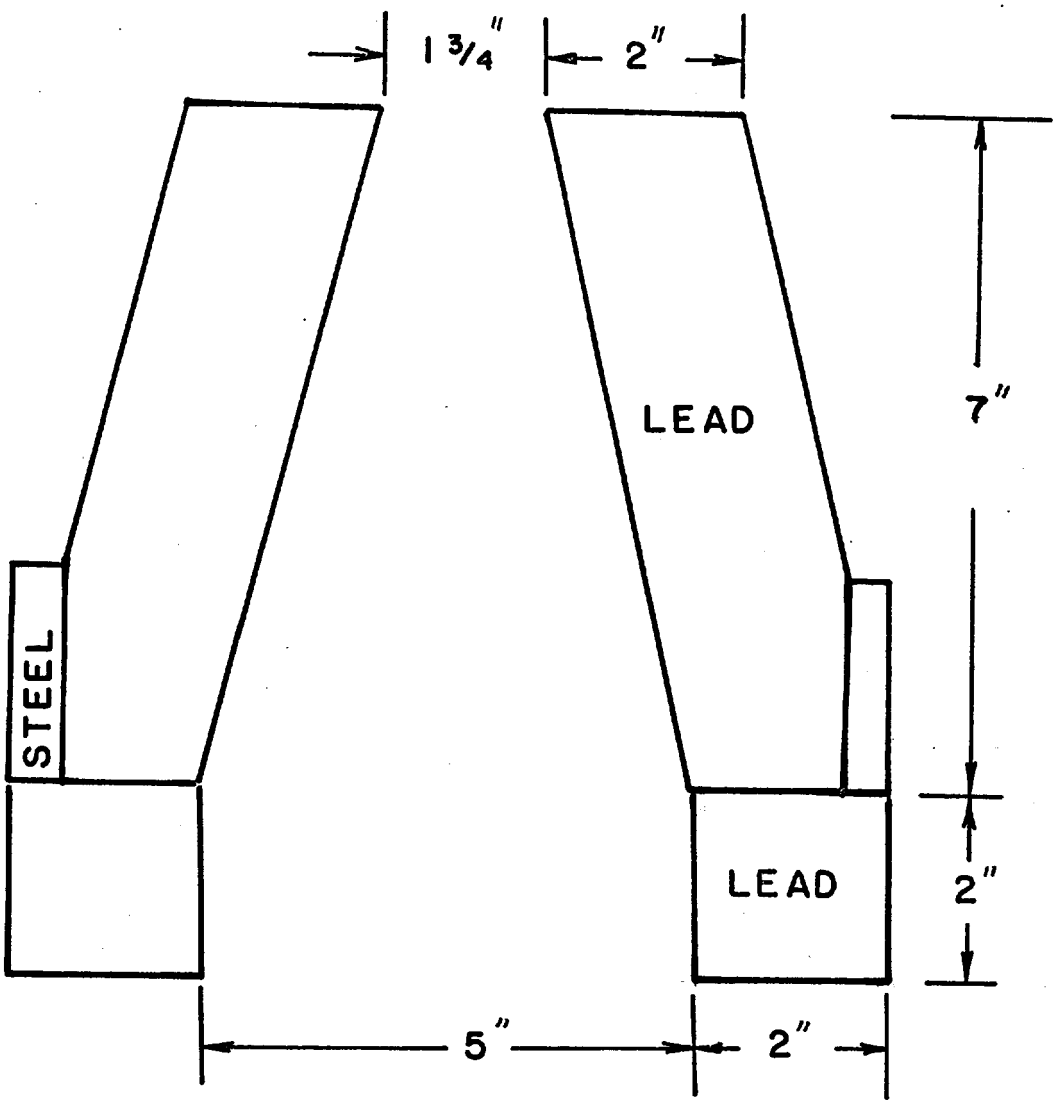


Figure 9. High Energy Collimator

A two-inch thick lead ring is added to the collimator at the crystal face to reduce high energy gamma ray penetration through the steel.

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3. Arimizu, N. and Morris A. C., Jr., Quantitative Measurement of Radioactivity in Internal Organs by Area Scanning, J. Nuc. Med. 10: 265, 1969.

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5. Dillman, L. T.; Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, MIRD suppl. 2, J. Nuc. Med., March 1969.

6. Snyder, W. S., Ford, M. R., Warner, G. G. and Fisher, H. L., Estimates of Absorbed Fraction for Monoenergetic Photon Sources Uniformly Distributed in Various Organs of A. Heterogeneous Phantom, MIRD, Suppl. 3, J. Nuc. Med., August, 1969.

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1. b. Data Analysis Methodology

A computer program (SAAM 24) developed by Dr. Berman at the NIH, Division of Computer Research and Technology, has been used in our iron metabolism and dosimetry studies. This general purpose simulation, analysis, and modeling program permits the user to formulate a model, read in experimental data for measured compartments and obtain from the computer estimates of the model parameters. The program seeks values of the model parameters which best fit the data by a least squares criterion. The user specifies initial values for the model parameters, some of which are fixed, while others are allowed to vary within defined limits. After a specified number of iterations on the parameters selected by the user, the program lists the parameter values which best fit the experimental data. The program available to us was usable only on a UNIVAC 1108 computer system to which we have had limited access from a terminal at the Old Hickory DuPont plant which is remoted to the DuPont system in Wilmington, Delaware. To more fully utilize the computer program in our research efforts, we needed to obtain increased access to the program. In collaboration with Dr. Berman and his associate Mrs. Weiss at the NIH, we have modified the most recent version of the program (SAAM 25) so that it can run on IBM, CDC, and XDS systems. In addition to program translation we have been forced to shorten the program so that it can run on smaller systems, such as our XDS, Sigma 7 at Vanderbilt. To date we have successfully run the program on the Sigma 7 in the simulation mode, and we are now using it for analysis and modeling, as well. The "debugging" problems which remain are not considered to be of major proportions and within a short time we hope to demonstrate that the modified version provides the same answers to test problems as does the 1108 version.

We are also working on additional modifications which will allow us to utilize SAAM 25 from a time-sharing terminal in our laboratory. This addition is primarily for convenience and will permit more effective testing of new models under study.

A second computer program, also developed by Dr. Berman, entitled RADOS, (Radiation Absorbed Dose) has been made operational through the DuPont computer terminal at Old Hickory, Tennessee. We have incorporated the radionuclide and absorbed fraction data from the MIRD publications (5,6) into the RADOS library. The program enables the user to obtain estimates radiation dose to various target organs for source distributions specified by the user. An example of the computer readout is shown in Figure 10. The library will be brought up to date for additional radionuclides as published by MIRD and as provided by Dr. W. Snyder at Oak Ridge National Laboratory. Due to limited availability of this program through the DuPont facility (one night per week), we will modify the program to operate on the Vanderbilt Sigma 7 computer.

Our present digital data system for collecting and handling data from the whole body counter consists of a 4096 channel analyzer interfaced through a digital logic synthesizer to the whole body counter. For data storage, we have used surplus 7-track IBM magnetic tape units. More recently we have

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ID CODE EXAMPLE

ORGAN	DOSE RATE RADS / HOUR	DOSE RADS	GAMMA RATE RADS / HOUR	GAMMA DOSE RADS	BETA RATE RADS / HOUR	BETA DOSE RADS
TIME = .000 HOURS						
TOTAL BODY	.4796-05	.0000	.4227-05	.0000	.5700-06	.0000
BLOOD	.1243-04	.0000	.1106-04	.0000	.1370-05	.0000
THYROID	.3194-05	.0000	.2259-05	.0000	.9350-06	.0000
KIDNEY	.1844-04	.0000	.1350-04	.0000	.4942-05	.0000
TESTES	.5804-05	.0000	.4839-05	.0000	.9651-06	.0000
LIVER	.2699-04	.0000	.2146-04	.0000	.5528-05	.0000
PAN	.1709-04	.0000	.1255-04	.0000	.4532-05	.0000
SPL	.1358-04	.0000	.1024-04	.0000	.3338-05	.0000
STOMACH	.5783-05	.0000	.5783-05	.0000	.0000	.0000
BLADDER	.3879-05	.0000	.3879-05	.0000	.0000	.0000
TIME = INFINITY						
TOTAL BODY	.0000	.7712-02	.0000	.6769-02	.0000	.9430-03
BLOOD	.0000	.1542-01	.0000	.1398-01	.0000	.1445-02
THYROID	.0000	.4841-02	.0000	.3743-02	.0000	.1098-02
KIDNEY	.0000	.1941-01	.0000	.1513-01	.0000	.4286-02
TESTES	.0000	.1067-01	.0000	.9296-02	.0000	.1370-02
LIVER	.0000	.2495-01	.0000	.2071-01	.0000	.4240-02
PAN	.0000	.1359-01	.0000	.1264-01	.0000	.9579-03
SPL	.0000	.1473-01	.0000	.1197-01	.0000	.2763-02
STOMACH	.0000	.8537-02	.0000	.8537-02	.0000	.0000
BLADDER	.0000	.7682-02	.0000	.7682-02	.0000	.0000

Figure 10

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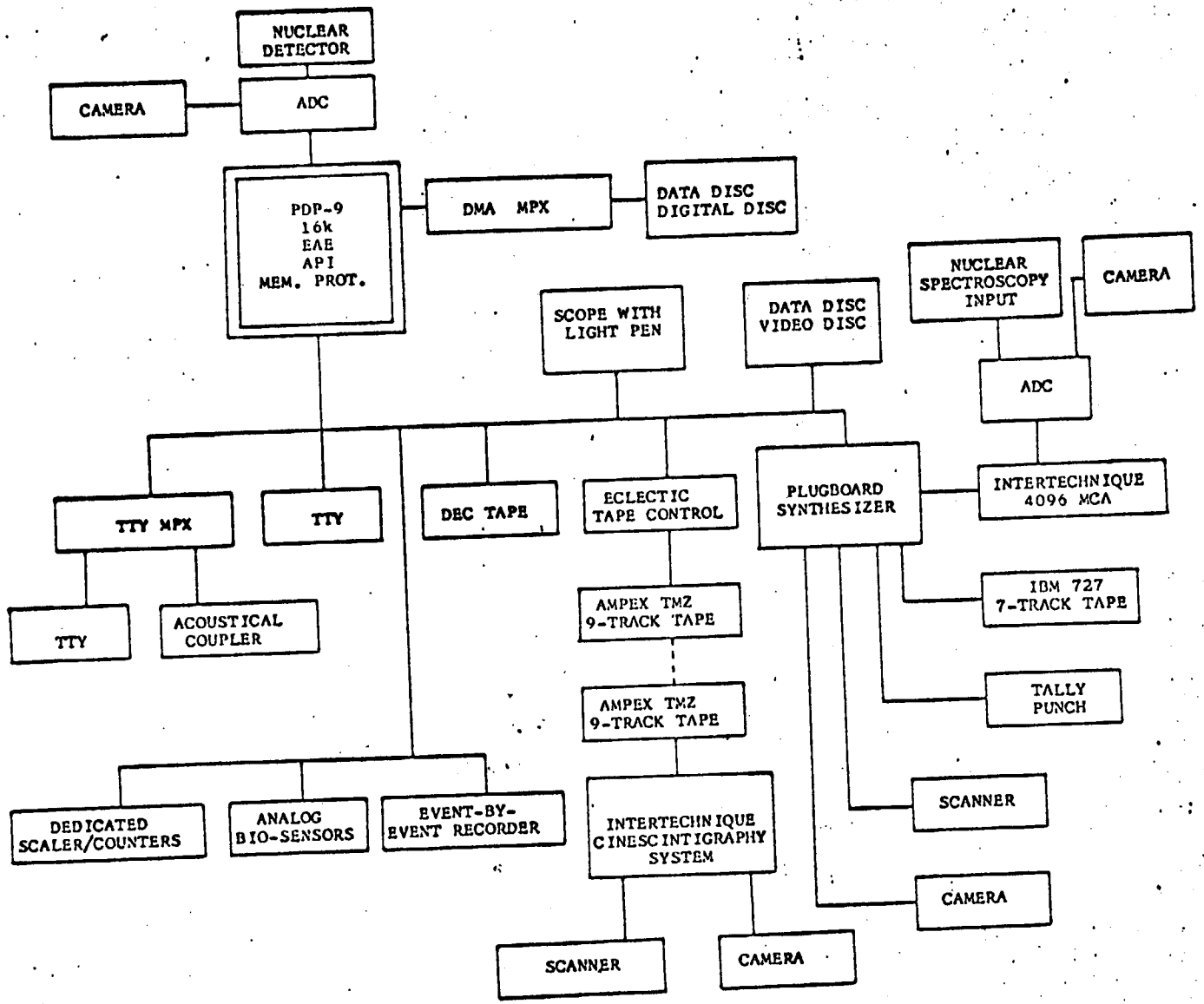


Figure 11

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interfaced the 4096 channel analyzer (MCA) to a PDP-9 computer. Data collected in the MCA are transferred to the PDP-9 and stored on DEC tape. Limitations of this present system for data handling are as follows: (1) The DEC tapes are not compatible with the tape drives on the Sigma 7 computer, (2) the collection of data through the MCA, digital logic synthesizer and PDP-9 ties up the complete system for a significant amount of time, and (3) the digital logic synthesizer has become an undependable means for transfer of data (connector problems). We arein the process of adding an industry-compatible magnetic tape unit to the PDP-9 so that quantitative image data can be stored on that unit rather than the smaller DEC tapes. This will also enable us to utilize the Sigma 7 computer facility for data analysis problems too complex for easy solution in the PDP-9. This addition will be completed within a short time and shortly thereafter we propose to replace the IBM units. The IBM tape units are obsolete tube type drives (7 track, 200 bits/inch) and can not be used with the Sigma 7 computer.

Other modifications and extensions to our total system are planned ot improve the dependability and to increase the availability of the system for data collection (more than one study at a time). The proposed total data handling system for our laboratory is shown in Figure 11. We plan to extend the PDP-9 to 16k words and add automatic priority interrupt (API). This will allow the operation of the system in background/foreground mode which will make it possible to collect and analyze data from several counting systems concurrently under computer control. This feature is becoming increasingly important since the work load of the whole body counter and gamma-ray spectroscopy studies have steadily increased and will continue to do so.

1037750

1. c. Evaluation of Solid State Detectors for Use in Nuclear Medicine

A conference held in Chicago in February, 1971, suggested some of the areas in nuclear medicine in which semiconductors will play a significant role. Two of the papers we presented summarized our early experience with lithium-drifted germanium detectors [Ge(Li)] and copies of these manuscripts are included in the Appendix of our current Progress Report. Lithium-drifted germanium and silicon detectors are very promising for in vitro sample composition studies, in vivo mapping of radionuclides (especially those with low energy or multiple emissions), and for in vivo stable tracer studies, e.g. measurement of thyroid iodine content by x-ray fluorescence. The ability to collect the emitted radiations in narrow energy bands makes it possible ti identify organ depth by differential attenuation of two different energies from the same tracer.

The high energy resolution of Ge(Li) and Si(Li) detectors when used in imaging procedures enhances the signal to noise ratio in the images obtained with low energy emitters, e.g. ^{125}I whether the nuclide is inside the body as in an emission image or external to it as in a transmission image. This permits more accurate measurement of quantitative organ retention since "cross-talk" between adjacent organs can be minimized.

1037751

1-c i Sample Composition Studies

For a number of years neutron activation analysis has been used for measuring the concentration of trace elements in biological samples. For most elements enutron activation is as sensitive as any other available technique, and in addition it has the important capability of being able to measure several elements at once. This latter point has been greatly improved upon with the use of high energy resolution solid-state detectors, i.e. Ge(Li). A simpler technique, X-ray fluorescence, also makes use of solid-state detectors, and is now receiving attention in trace element analysis. With this technique the atoms in the biological sample are excited by irradiation from an x- or γ-ray source, and the characteristic x-rays emitted by each element are detected. This technique has received renewed interest because of recent spectacular advances in the energy resolution of Si(Li) solid-state detectors at low energies. These detectors, with FWHM energy resolutions of 160ev at 6 KeV, are now capable of separating characteristic x-ray lines of adjacent elements. In general, neutron activation has higher sensitivity than the x-ray fluorescent system, but there will be some elements where the reverse is true. An important example is the highly toxic element lead, which cannot be analyzed by neutron activation. The x-ray system is much simpler than neutron activation and its use should become more widespread because of its much lower cost.

We propose to evaluate this system in terms of its sensitivity to a number of elements in a biological samples. Of special interest will be the determination of the limits of detectability. From these limits and the known concentration of the various elements in biological material, the elements for which the x-ray system will be of value will be determined.

The sensitivities will be determined by adding known amounts of a particular element to a matrix of biological material. These materials will include freeze-dried blood and freeze-dried tissue samples. The amount of element added will be reduced until its characteristic peak can no longer be detected above the background counting level. This will yield the limit of detectability. A number of elements evenly spaced across the periodic table will be measured in this way. Two separate x-ray fluorescent sources will be used. The first is an x-ray tube which emits a continuous distribution of x-ray energies, and thus excites a number of elements. The second will be an Am^{241} source whose 60 KeV x-rays are allowed to strike a target material which has been chosen to emit characteristic x-rays of the appropriate energy to excite a selected element of interest. The second irradiating source will have a higher sensitivity but the first will be useful in surveying samples bacause of its ability to give information on many elements at once.

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1-C. ii. Fluoresence Scanning of the Thyroid

Hoffer and his associates at the Argonne Cancer Research Hospital have conducted extensive patient studies using a lithium-drifted silicon detector and ^{241}Am stimulating sources. They have shown the importance of comparisons between the anatomical distribution of iodine and the functional anatomy based on radiotracer turnover in patients with thyroid disease.

We are obtaining a 10-15 Ci annular source of ^{241}Am which will be used with a 2" diameter lithium-drifted silicon detector loaned to us by ORTEC. We plan to evaluate this system in patients with thyroid disease coming through our clinic. We will collect digital data and will analyze the relation between thyroid iodine content and thyroid function test results in normal and diseased patients. We will compare the images obtained from subsequent doses of ^{125}I in these patients (using separate windows on the 28 and 35 Kev radiations) with images obtained from the same patient given $^{99}Tc^{m}$ mapped with the BNL 5" technetium collimator and using the same display system. These studies will be conducted in our clinic and will not involve a major effort on the part of the research staff.

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1. c. iii. Fluorescence Scanning for Brain tumor Localization

Matthews and Molinaro have shown that transplanted brain tumors in rats take up bismuth to concentrations 20 to 85 times that of surrounding brain tissue. If these data can be applied to spontaneous tumors in humans, then bismuth would be a very powerful tumor-localizing agent.

We are exploring the feasibility of bismuth fluorescence scanning using both NaI(Tl) and Ge(Li) detectors. The NaI measurements are being done using a research prototype, 8-detector cylindrical array scanner. This system is shown in Figure 12 with the exciting source suspended from the driving point of the system. The detectors are aimed so that their field of view intersect at a point directly below the exciting source. The height of the collimated exciting source is adjusted so that its focal point is common to this intersection. The exciting source is driven in a rectilinear raster, and the detectors rotate about their axes so as to always be aimed at the focal point of the exciting source. Digital data are collected in a 64 x 64 array in a 4096 channel analyzer corresponding to an 8 x 8 inch area.

A single detector arrangement is shown in Figure 13. Using $^{99}Tc^{m}$ as the exciting source, the 77 Kev x-rays are emitted by a bismuth source and counted by the detector. Cadmium focusing collimators were constructed because NaI detectors cannot resolve the 75 Kev lead x-rays from the 77 Kev bismuth x-rays. Figure 14 shows plots of the count rates from a vial containing 13 mg. of bismuth and a vial of water for different strength exciting sources.

Tomographic fluorescence scans were made with 1/2 inch vials of bismuth in a water phantom. A 15 Kev window was set symmetrically about the 77 Kev photopeak. Each scan was made with a 200 mCi exciting source and required 30 minutes. The data were collected in a 64 x 64 data array and photographs were made from a computer-generated display. The threshold of detection of this system lies somewhere between 13 and 50 mg. of bismuth with a 200 mCi exciting source and scanning time of 30 minutes.

Two means of approaching the problem of increasing the sensitivity of the system are being explored. One possibility is the use of Ge(Li) detectors to increase the contrast ratio by better discrimination against scatter counts. Figure 15 shows a plot of net counts from a 13 mg. source of bismuth versus exciting source strength using a Ge(Li) detector with $^{99}Tc^{m}$ as the exciting source in the same geometrical arrangement as shown earlier for NaI. A comparison of the two figures shows that the net bismuth-to-scatter ratio has been increased by a factor of 2.5 but with a loss in net bismuth counts by a factor of 10 for this particular Ge(Li) detector which was not ideally suited for counting 77 Kev x-rays.

Another procedure would be to increase the activity contained in the exciting source. $^{99}Tc^{m}$ is not an ideal radionuclide for use as an irradiation source because of its 6 hour half life. A 3 curie ^{153}Gd source recently was obtained from the Isotopes Development Group at Oak Ridge National Laboratory for evaluation. Spectra collected with the Ge(Li) detector from a vial of bismuth and a vial of water when irradiated at 90° by the exciting source are

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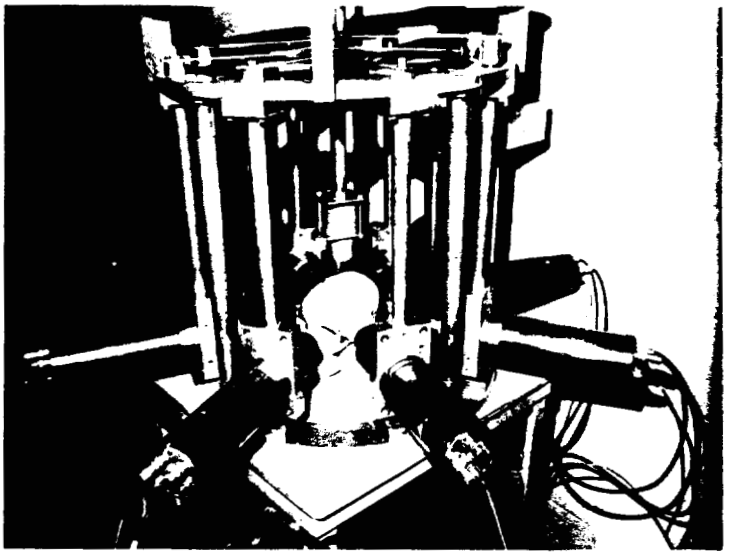


Fig. 12

BISMUTH FLUORESCENCE STUDY

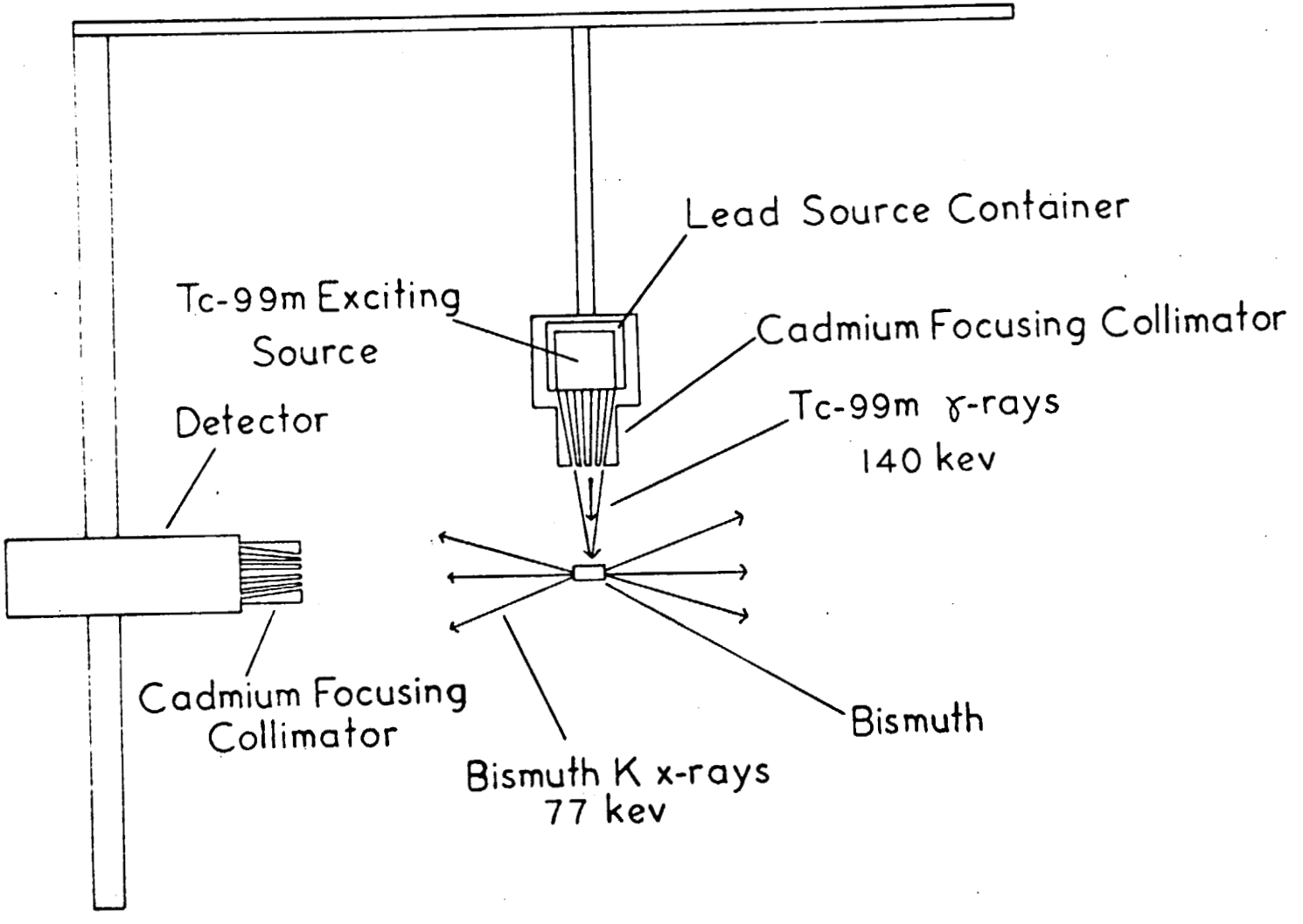


Fig. 13

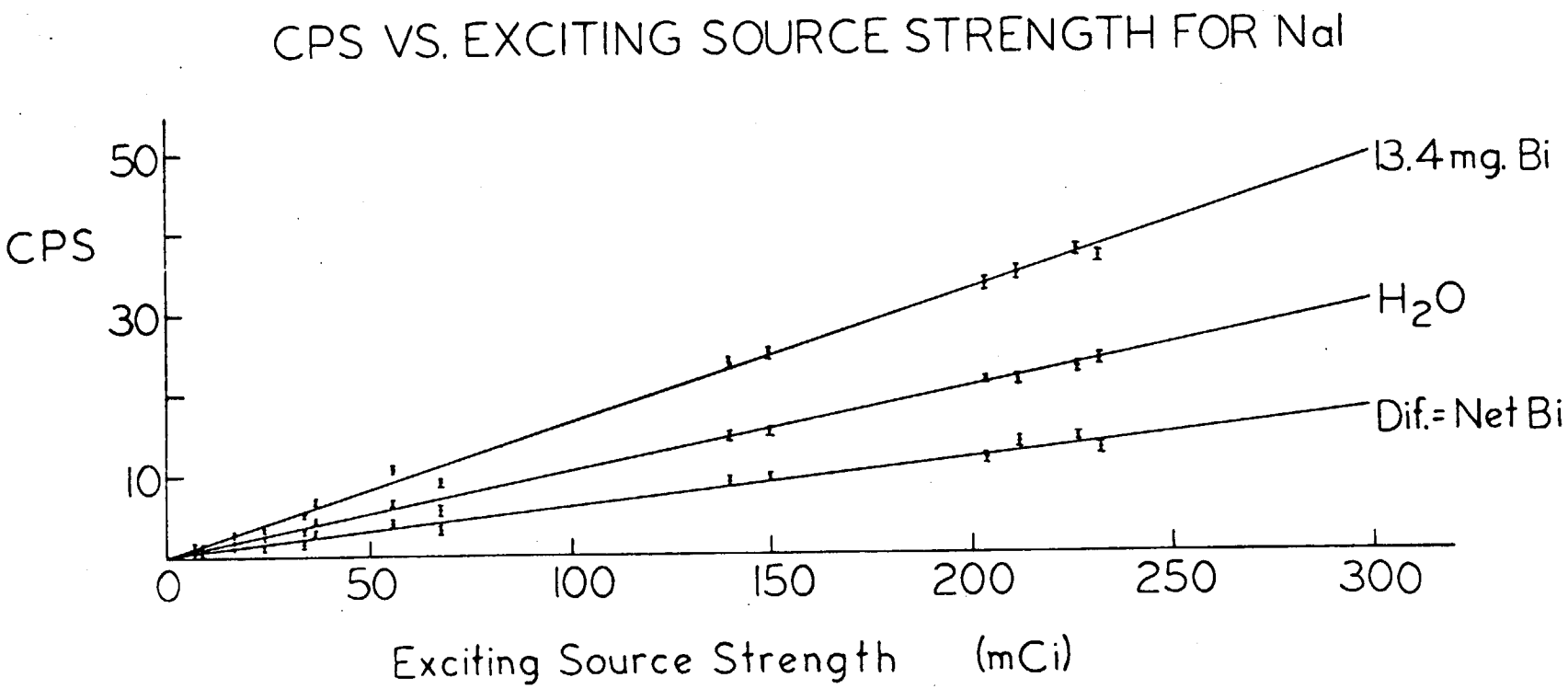


Fig. 14

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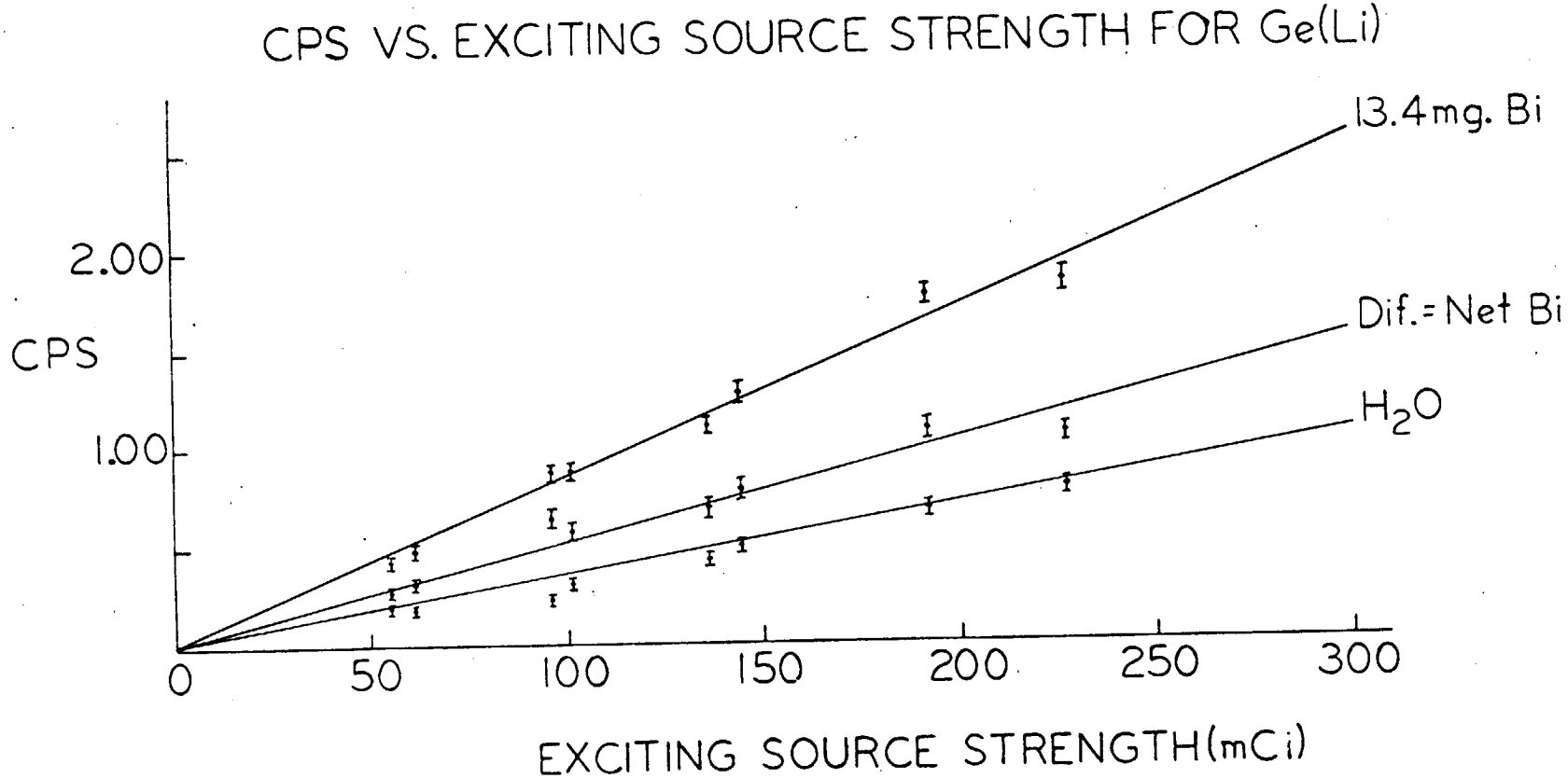

CPS VS. EXCITING SOURCE STRENGTH FOR Ge(Li)
13.4mg. Bi
Dif.= Net Bi
H_2O
2.00
1.00
CPS
0
50
100
150
200
250
300
EXCITING SOURCE STRENGTH(mCi)

Fig. 15

shown in Figure 16. The $K\alpha_1$ and $K\alpha_2$ x-ray peak of lead are visible to the left of the 90° scatter peaks from the 97 and 103 gamma-rays from ^{153}Gd. A net count rate of 4.7 counts per second was measured from the vial containing 13 mg. of bismuth with a ratio of bismuth counts to scatter counts of only 0.54. This is an increase in sensitivity by a factor of 5 better than obtained with $^{99}Tc^{m}$. The bismuth-to-scatter ratio was considerably lower than we expected which is probably due to the presence of high energy gamma-emitting impurities in the exciting source which raise the scatter background considerably.

A 50 mg. vial of bismuth was placed in a 5-inch cube of paraffin, and a scan was simulated by moving the phantom through the intersection of the focal points of the collimated ^{153}Gd source and the Ge(Li) detector. Using scatter subtraction techniques, a net count rate of 5.3 counts per second was obtained.

Measurements of radiation doses to patients from different stimulating sources used in fluorescence mapping studies are needed. Since one of the advantages of stable tracer mapping by fluorescence scanning is that no radioactive material is actually given to the patient, it is extremely important to compare the dose rates from these procedures with those received from radioactive tracer imaging techniques. Calculations of dose rates will be made for the various isotopes being used as exciting sources in the scanning configurations described. Those include ^{241}Am, ^{153}Gd, and $^{99}Tc^{m}$. Actual measurements will also be made using LiF thermoluminescent detectors which will be inserted in phantoms and taped to patients in the areas being scanned.

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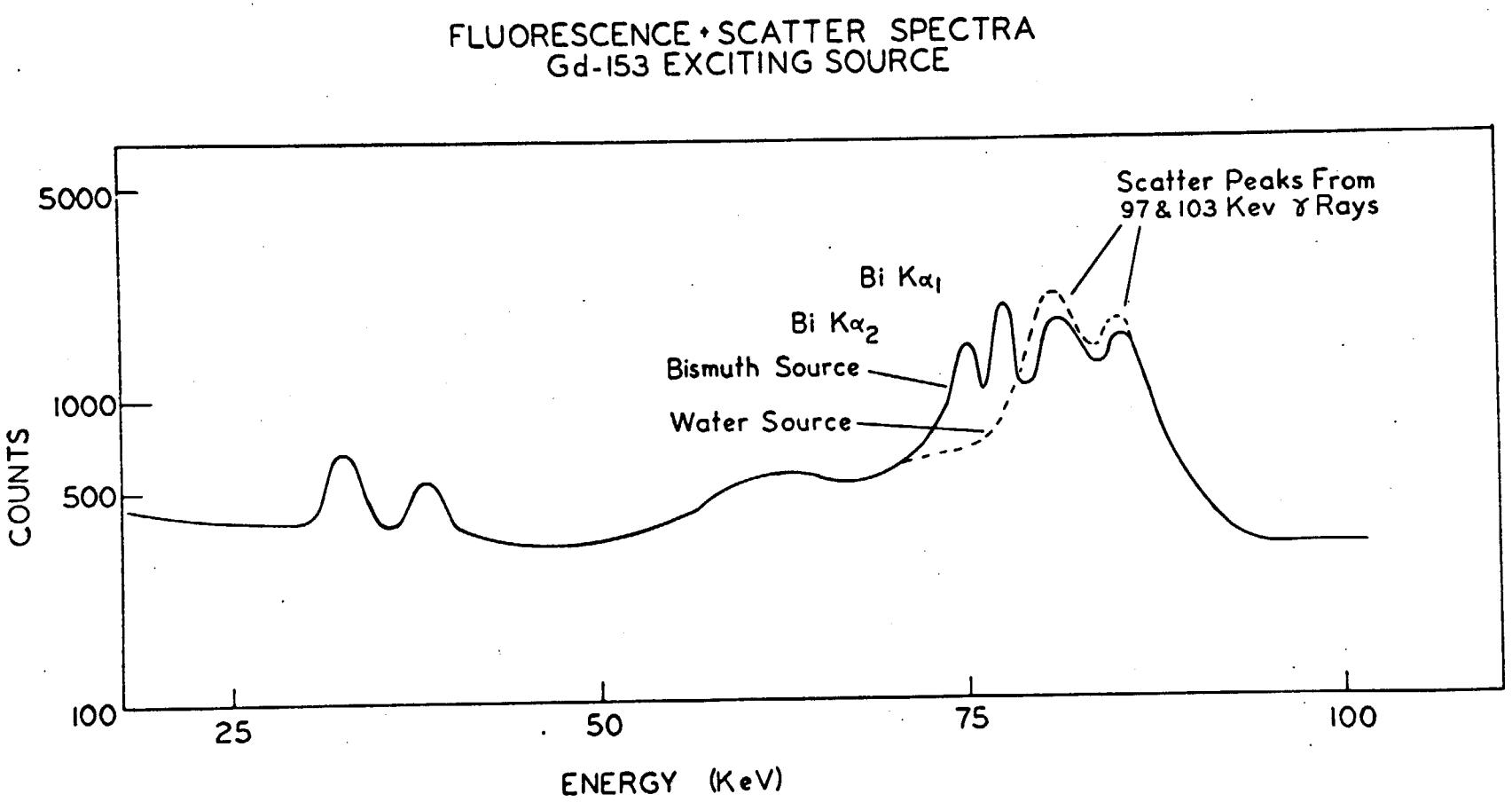


Fig. 16

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1. c. iv. Emission Scanning

Adequate sensitivity is a prime requisite for detection of small level changes in diagnostic studies. Good spatial and energy resolution is needed for accurate determinations of size and shape of emitting regions. Preliminary studies made by the Argonne Cancer Research Hospital group have shown that some tumors can be defined with Ge(Li) scans which could not be identified clearly with NaI(Tl) detectors (Hoffer, et.al., J. Nuc. Med. 12, 25-27, 1971). A major difficulty with the use of Ge(Li) has been the small size of the detectors available and hence their low sensitivity. In order to make large planar detectors, 5-7 mm. drift depth, one encounters large capacitances and diminished resolution is attainable. On the basis of our studies (Brill, et.al., Appendix 4 of the Progress Report), we feel that resolutions of the order of 2-5 Kev will be acceptable if 3" diameter Ge(Li) detectors can be obtained. We plan to evaluate a 53 mm. planar germanium detector (8 mm. drift depth, 3.5 Kev resolution at 122 Kev) in patient studies and plan to present preliminary results of these studies at the June, 1971, Society of Nuclear Medicine meeting. Within the next three months we expect to receive and embark upon a clinical test of a 65 mm. Ge(Li) detector. In these studies, we will compare the results of $^{99}Tc^{m}$ brain scans in patients with border-line detectable lesions and with thyroid imaging in patients found to be anomalies in the ^{125}I or ^{127}I scans described in a preceding section.

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1. c. v. Evaluation of Different Systems for Transmission Studies with Emphasis on Radiation Dosimetry

Transmission scanning as a diagnostic tool shows interesting possibilities for future use. In this procedure, a collimated beam from a radioactive source is passed through a patient and unattenuated photons are collected by a collimated detector. Attenuation is proportional to the density of material through which it is passing, and quantitative assessment of bone mineral content can be derived. (Cameron, et.al., Proceedings of Bone Measurement Conference, USAEC CONF-700515). Low energy isotopes such as ^{125}I, ^{241}Am, and ^{153}Gd have been used successfully for bone mineral determinations. Higher energy isotopes such as $^{99}Tc^{m}$, ^{131}I, and ^{85}Sr have been used to obtain anatomical information necessary with certain emission scanning procedures, particularly for dosimetry measurement. For example, organ location and relative thickness measurements are made in our laboratory by means of transmission scanning as a necessary part of our quantitation procedures with the whole body counter.

The detector of choice in these procedures is usually NaI(Tl). Ge(Li) semiconductor detectors have very good energy resolution and permit more discrimination against scatter than is possible with NaI(Tl) detectors. A comparison of NaI and Ge(Li) transmission scans made with ^{125}I are shown in Figure 17. These scans were made of the hand of an x-ray phantom used for instructional purposes. The same collimator was used with both detectors. Figure 18 shows a scan made of the trunk of the phantom using $^{99}Tc^{m}$ with the Ge(Li) detector, showing the air (foam) soft tissue interfaces with great clarity.

With the increased use of transmission scanning as a diagnostic procedure, the need arises for measurement of radiation doses to the patient from these procedures. We plan to evaluate radiation exposures in two ways. First, calculations will be made of the dose received from the various isotopes used on the basis of mrads/mCi/hr. Then using TLDs actual measurements will be made of the dose from the transmission sources. This will be done with phantoms by inserting the dosimeters into the phantom and with patients by taping dosimeters to the patients in the areas to be scanned.

This information is of interest since the technique is coming into common use. One of the advantages of transmission scanning is that no radioactive material is actually given to the patient. The only radiation dose received is that due to exposure from the transmission source. Since high activity sources (for example, 5-15 Ci of ^{241}Am) are being used in clinical studies, a careful evaluation of the doses appears warranted.

A source of particular interest to us is ^{153}Gd. We have used this material for fluorescence and transmission scanning with success. The availability of two photons (99 Kev γ and 40 Kev Eu x-ray) make it possible to do quantitative bone mineral measurements with this agent. The Isotopes Development Group at Oak Ridge National Laboratory has made available a 3 Ci source for evaluation. This source has too much high energy gamma ray contamination for clinical studies, and a new source is under development

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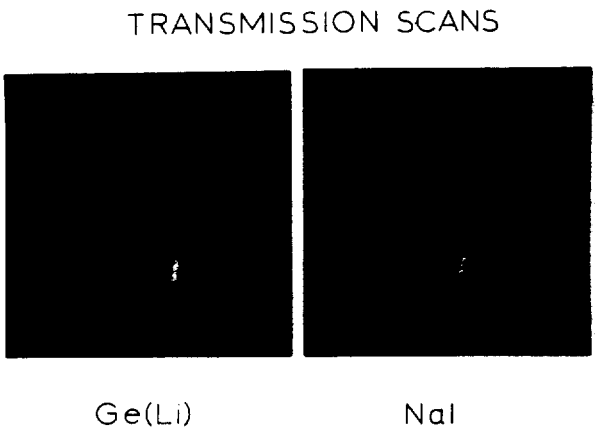


Fig. 17

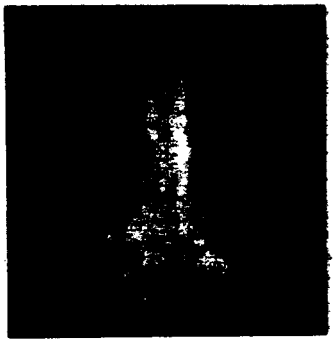


Fig. 18

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for these investigations. The determination of bone mineral content will be carried out sequentially in patients with Paget's disease in a study described in section B2.

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2. SPECIFIC STUDIES PROPOSED

a. Iron Dosimetry in Normal and Diseased Patients

We have developed a method for quantitating radioisotope distributions in patients and applied it to the measurement of the radioiron content in the liver, red bone marrow and spleen. These studies involve the use of a whole-body rectilinear scanner and a digital data acquisition and display system we have built for these purposes.

Three normal subjects were administered 10 μCi of ^{59}Fe, I.V. Plasma samples were obtained every 15 min. for the first 3 hours. Rectilinear whole-body scans and blood samples were obtained at 24-hour intervals for 7 days then weekly out to about 150 days.

Simultaneous anterior and posterior whole body scans are collected in digital form from two opposed detectors and stored in a 4096 memory. The system has been calibrated so that the μCi content of any selected region can be determined. The regions of interest are selected from the scan image displayed on an oscilloscope. Figure 19 is the picture of an ^{59}Fe emission scan of a typical normal subject at 48 hours post injection. The emission scan has had a transmission scan overlaid to aid in the identification of anatomical regions.

The fraction of the radioiron in the circulating blood in the liver, spleen, and pelvis regions is determined by scanning a patient given ^{51}Cr labeled red blood cells. We find that 26% of the blood radioactivity is included in the liver region, 6% in the spleen region, and 10% in the pelvis region. These factors combined with measured blood activity allow us to correct for the circulating blood activity included in the liver, spleen and pelvis regions. A correction was also made for the red marrow space included in the liver and spleen regions. The pelvis region was selected as representative of the red marrow space.

The experimental data obtained from these measurements are analyzed mathematically using Berman's digital simulation and analysis program, SAAM 25. The time rate of change of activity in the liver, spleen, and red marrow are derived from direct measurements rather than inferentially from analysis of plasma iron disappearance and red cell incorporation data as ordinarily done in ferrokinetic studies.

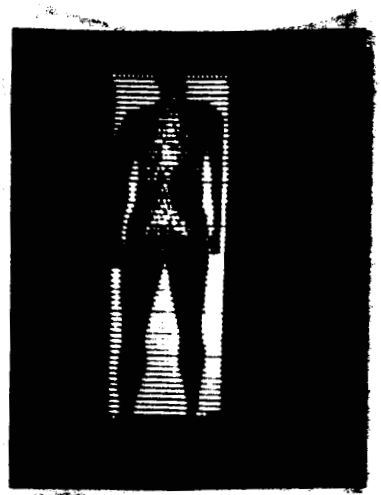
Figure 20 is a diagram of the compartmental model we have employed in the study of normal subjects. Figure 21 shows the preliminary results of the RBC, liver, and red marrow compartment measurements and the corresponding model fits to the data. Figure 22 displays how the program is able to separate the net retention curves for the organs of interest from the primary measurements. The time retention curve for each organ allows us to calculate the radiation dose to the organ of interest resulting both from self radiation and radiations from surrounding organs.

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Following essentially the same protocol as for the normal studies, we have recently begun the study of several patients with abnormal iron distribution. Figure 23 is a scan of a leukemic patient with abnormal iron uptake in the liver and spleen with marrow extension to the knees. The model is currently being extended to accomodate diseased states so that dose estimates for each disease group can be tabulated. A scan for ^{51}Cr labeled red blood cells is made just prior to the injection of ^{59}Fe in each of the abnormal studies. The ^{51}Cr scan is particularly important in abnormals because the correction for circulating blood background is large in most cases and the size of the blood pools varies widely among diseased patients.

Calculations of radiation dose to blood, marrow, liver, and spleen will be made using SAAM 25, and RADOS for normals (3) and for 15-20 patients with leukemia, aplastic anemia, splenomegaly of diverse etiology, and various hemolytic anemias. In addition to external counting of ^{59}Fe, multiple blood samples will be taken to define the plasma iron clearance and RBC inroporation as inferred from classical ferrokinetics studies. The results of these studies will be compared to those obtained by the external probe studies. Digital simulation of the iron metabolism data will be pursued in conjunction with Dr. L. E. Johnson, of the Electrical Engineering Department and his graduate studentswith whom we have conducted joint efforts for many years.

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^{59}Fe scan of a normal subject with transmission scan overlaid.

Fig. 19

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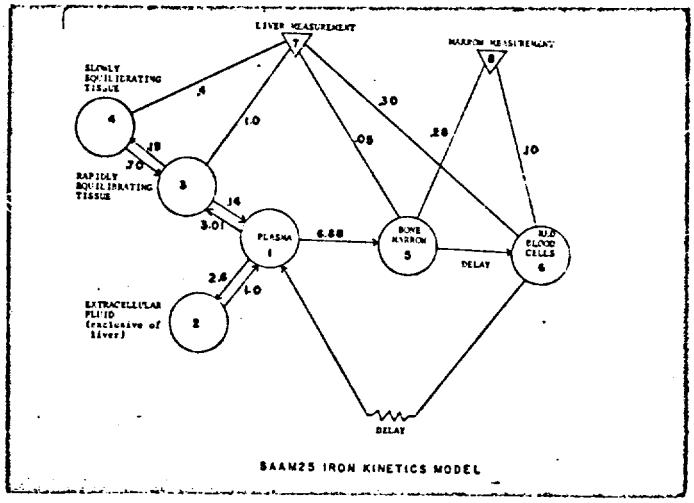


Fig. 20

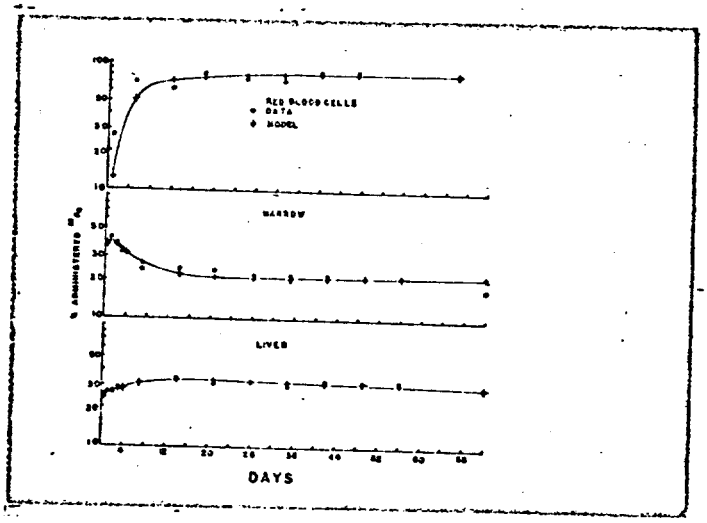


Fig. 21

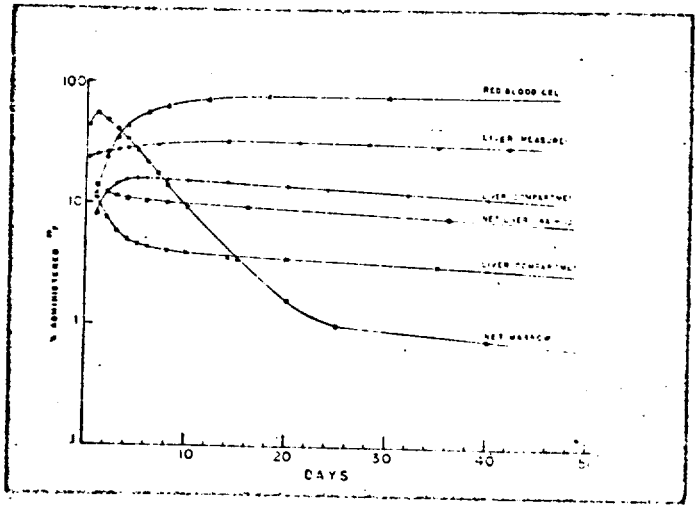
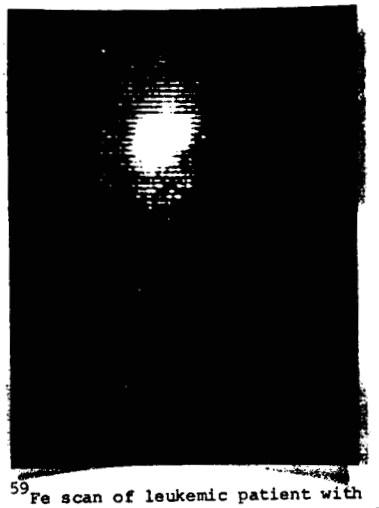


Fig. 22

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^{59}Fe scan of leukemic patient with increased uptake in liver, knees and ankles.

Fig. 23

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2. b. Bismuth-206 Studies

Bismuth was first mentioned as a possible tumor-localizing agent as early as 1931. Since then it has been shown that the ratio of activity in a brain tumor to the activity in the brain is higher for bismuth than any other tracer material. Studies on rats (1) show the tumor/brain ratio to be 20-85 as compared with ratios of ~10 for most brain scanning agents. These numbers indicate that based on isotope uptake data alone, bismuth would be an excellent tumor-localizing agent. In addition to localizing tumors, bismuth may assist in differntiating tumor type on the basis of bismuth uptake pattern. Characteristics accumulation and storage times have been found (2) for several varieties of tumors. Of the several bismuth isotopes, ^{206}Bi appears to be the most favorable for scanning. It has a half-life of 6.2 days and is commercially avilable. It emits characteristic γ-rays of energy 500-1900 Kev (predominantly 800-900 Kev), and requires a very well-shielded scanning detector. We have demonstrated that ^{206}Bi can be visualized clearly with our low-level whole-body scanner. This was demonstrated by the successful visualization of a head phantom containing a 1/2" tumor, with the tumor/brain ratio fixed at 10:1. (As mentioned above, this ratio is probably closer to 50:1.)

As part of the evaluation of bismuth as a clinically useful agent, careful whole body dosimetry data must be collected. Bismuth is known (2,3) to accumulate in the kidneys and to a lesser extent in the liver. These data, however, are based on studies with rats. We have performed one bismuth study in a patient (brain and whole body scan) and confirmed that most of the bismuth activity goes to the kidney region. This patient had a known hemangioendothelioma which was not visualized with $^{99}Tc^{m}$ or ^{206}Bi.

We are proposing to do additional bismuth studies on humans. These will be done in patients in whom tumors have been diagnosed and $^{99}Tc^{m}$ scans are normal. These patients will be injected with 200 μCi of Bismuth Nitrate and after 2-3 days brain scans will be done. In addition, whole body scan will be taken on each of the first three days after injection, and thereafter several measurements will be made out to several weeks. The whole body counter will be calibrated for ^{206}Bi and the biological distribution of bismuth will be determined. From these data and the known physical decay properties of ^{206}Bi, radiation dose estimates will be made using RADOS (4).

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3. Eridani, S., Balzarini, M., Taglioretti, D., Romussi, M., and Valentini, R., Brit. J. Radiol. 37, 331-4, April, 1969.
4. RADOS--Radiation dosimetry program developed by Mones Berman, NIH.

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2. c. Dosimetry of ^{131}I Rose Bengal

The dosimetry of ^{131}I Rose Bengal has been worked out to an acceptable degree of accuracy using the normal patient as a model. In this mode, Rose Bengal is taken from the bloodstream by the polygonal cells of the liver and is excreted in the bile (unconjugated) to the intestine, from which it is not reabsorbed. In the normal adult, estimated doses to the liver range between 1.0 and 3.4 mrads/μCi of injected ^{131}I Rose Bengal (1-5). For the abnormal patient, however, the dosimetry model must be different, and the resulting radiation levels may well be significantly higher. The patient with early extrahepatic obstruction will concentrate the Rose Bengal in the liver, where it will stay for a prolonged time; in this case the critical target organ may be the liver or the gall bladder and the absorbed dose may be several times higher than in normals. The patient with intrahepatic obstruction, or long-standing extrahepatic obstruction, will excrete the isotope largely through the kidneys. Since there is evidence that absorbed doses of only a few tens of rads may cause measurable changes in renal function, it becomes important to determine the radiation dose to the kidneys in the abnormal patient. Furthermore, the constipated patient, without liver disease, may retain the isotope in his colon for an excessively long time and will sustain a greater radiation dose than usual.

In the proposed study, patient with known or suspected liver disease will receive ^{131}I Rose Bengal in the usual amount (300 μCi) and will undergo the usual diagnostic studies. Blood levels will be determined on a daily basis. In addition, daily urine and stool collections will be made to determine the rate of excretion of the radiopharmaceutical. The whole body counter with its spatial distribution capabilities will be used to determine the kinetics of the Rose Bengal compartments (blood, liver, gall baldder, intestine, kidneys, and possibly thyroid). Initially, the patients will be unselected as to the type of liver disease present, so as to gather a larger group of heterogeneous problems that would be possible if the study was restricted to volunteers. Subsequently, patients will be classified as to normal, normal liver with constipation, pure extrahepatic obstruction, pure intrahepatic obstruction, mixed obstruction, and any of the above with renal disease superimposed. The classificaton will be made on the basis of pathological or surgical findings and will not depend on the findings of the Rose Bengal study itself. From the kinetic data, a revised estimate of radiation dose from ^{131}I Rose Bengal will be described in terms of specific abnormalities of the liver, colon, and kidneys.

References

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2. d. Whole Body Turn-over of Radiopharmaceuticals in Man

The development of new radiotracers for use in nuclear medicine is rapid and many laboratories are participating in this process. Few laboratories are equipped with whole body counters, and those that have them are usually not in clinical facilities. The utility of high-level whole body counters as developed by the Medical Division at Oak Ridge Associated Universities and in use in our laboratory has been publicized but still relatively few institutions use these devices for clinical whole body counting. In part, this is due to the physical separation between these facilities and the patient area, and in part due to the difficulty in implementing special measuring systems in clinical laboratories.

In a recent visit to our laboratory, Harold Glass suggested that he and his associates are using an Angera camera to obtain whole body turn-over data. The uncollimated detector is aimed at the patient, and scaler counts from the energy region of interest are collected. The detector is raised and lowered continuously during counting to collect photons with approximately equal efficiency from different regions in the patient placed in front of the detector.

In studies with Rose Bengal ^{131}I, we will obtain estimates of whole body retention from the low level body counter (collimated), high level whole body counter, and from the Anger camera. Comparisons of these means of measurement of biological turn=over will be obtained from these and other new studies that are introduced into our clinic during this coming year. If the Anger camera method provide to be simple and accurate, this could be a significant factor in increasing the number of laboratories collecting radiopharmaceutical metabolism data.

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2. e. Dosimetry Support for NCRP

Scientific Committee 32 of the National Council on Radiation Protection and Measurements is charged with formulating a report concerned with the use of radiopharmaceuticals in diagnostic nuclear medicine. In particular the committee is expected to give attention to factors influencing medical decisions in radionuclide studies including such factors as choice of radiopharmaceutical, choice of detection system, medical need for information sought, radiation hazard level for different age groups and the balance between benefits and risks. Dr. Brill, principal investigator of this research proposal, is Chairman of Committee 32 and Dr. Johnston, co-investigator, serves on the Committee. As part of our participation in this committee effort, we will contribute data from our own dosimetry research as well as participate in the assemblage of the report. As we proceed, we will be able to identify the important problem areas to which we can direct our future research efforts in order to make the most effective contribution.

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3. Maternal-Fetal Transfer of Radionuclides

a. Review of Hahn Data

In the late 1940's, Hahn and co-workers conducted a study on iron metabolism in human pregnancy (1). Over eight-hundred women who had been admitted to the Obstetrics Out Patient Clinic of Vanderbilt University Hospital were studied. Radioactive ^{59}Fe plus stable iron carrier (from 2 to 120 mg.) were given orally to the subjects. At about two weeks after oral ingestion, blood samples were obtained from the subject and quantitated for the iron tracer contained in the red blood cells of the maternal circulation. They estimated the subject's blood volume and determined the percent uptake of the orally administered iron. (The percent uptake was the product of the fractional efficiency of maternal gastro-intestinal absorption and the incorporation into red blood cells).

Hahn and co-workers demonstrated striking variations in the percent uptake with amount of elemental iron fed. The more elemental iron fed along with the ^{59}Fe tracer, the lower the percent uptake observed. In the range of 1.8 to 9.0 mg. of elemental iron given, they have data on percentage uptake with gestational stage from less than 10 weeks to term. This amount of elemental iron given is comparable to the normal daily dietary intake levels.

We have measured iron metabolism parameters using the stable tracer, ^{58}Fe, in normal pregnant subjects and the radioactive tracer, ^{59}Fe, for subjects undergoing therapeutic abortions (2,3). The stable tracer studies were conducted in such a manner that the percent incorporation into maternal red blood cells and the percent uptake were both measured. The stable tracer studies were done over the gestational stages from 25 through 38 weeks. The oral doses varied from 4 to 7 mg. of elemental iron. Our measurement of the percent uptake agreed very well with the data of Hahn and co-workers. For the radioactive ^{59}Fe tracer studies, we measured only the percent incorporation following I.V. injections over the gestational stages from 9 to 20 weeks.

The data of Hahn and co-workers provide a great deal of information on the metabolism of iron in pregnancy. The results were presented as percent uptake and at that time they could not separate red blood cell incorporation and gastro-intestinal absorption. With the new data we have collected, we propose to change the presentation of the data of Hahn and co-workers. separating the percentage uptake into absorption and percent utilization as a function of pregnancy stage. The data on iron incorporation into maternal red blood cells which we have determined in pregnant women (gestational stages from 9 to 38 weeks) provide the basis for the re-evaluation of the Hahn data.

In the early 1940's, Pommerenke and co-workers at the University of Rochester reported on iron transport to and distribution within the human fetus following ^{59}Fe ingestion by the mother prior to a therapeutic abortion (4). For correlation of these data with our findings in therapeutic abortions, we need to know the total red blood cell mass in both the mother and fetus. Pommerenke, et.al., fed the iron tracer orally and our data

are from an I.V. injection. Pommerenke presents the maternal activity in terms of the amount of radioiron per 100 ml. of maternal blood at delivery. With information on maternal weight and height, we will be able to estimate the maternal RBC mass. Also, for the fetus, Pommerenke and co-workers present the fetal RBC data per 100 ml. For proper correlation with our iron data, fetal weights are needed to estimate the fetal RBC mass. We have written the group at the University of Rochester in order to obtain this information and will combine our data and their data on the transport and distribution of radioiron for the human fetus. This summary will assist investigators interested in iron metabolism and will augment the number of subjects that are used in our estimates of absorbed radiation dose to fetal organs from ^{59}Fe in pregnancy.

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3. b. ^{131}I and ^{59}Fe Transport in Human Pregnancy

The tranfer of ^{131}I and ^{59}Fe from the mother to the fetus and the distribution of these transferred radionuclides within the fetus have been studied in twelve women who received therapeutic abortions at Vanderbilt University Hospital. The purpose of these studies is to determine the transport and distribution parameters in order to obtain better estimates of radiation dose to the fetus when a pregnant woman is given diagnostic doses of ^{131}I and ^{59}Fe. The gestational ages of the fetuses have varied from nine to twenty-two weeks.

From the transfer and distribution data obtained, absorbed dose calculations have been made for the total fetus and fetal organs with high radioisotope concentrations. Table II presents the results of these absorbed dose calculations. For ^{131}I, the fetal absorbed dose increases from about 0.8 rad/mCi for the 9 week fetus to 2.99 rad/mCi for the 22 week fetus. For the fetal thyroid, the absorbed dose from ^{131}I increases from about 1000 rad/mCi for the 13-14 week fetus to about 6000 rad/mCi for the 22-week fetus. Over the gestational age range from 9 to 22 weeks, the fetal absorbed dose from ^{59}Fe varies from 28.6 to 39.4 rad/mCi with only a slight hint of increasing dose with increasing age. The fetal liver absorbed dose from ^{59}Fe varies from 237 to 429 rad/mCi with no definite relationship to gestational age while the fetal spleen absorbed dose appears to increase from 60 rad/mCi for the 13-week fetus to 186 rad/mCi at 22 weeks. The absorbed radiation doses are quoted for activity given to the mother, orally for ^{131}I and intravenously for ^{59}Fe. The data on ^{131}I uptake in the fetal thyroid are consistent with the results of previous studies.

In addition, we have conducted preliminary studies in pregnant sheep in which blocking agents, i.e. L-Thyroxine and Lugol's solution have been introduced. The protocol for the sheep studies involved the administration of an ^{125}I tracer dose on day one which serves as a reference for thyroid uptake. At day two a blocking procedure is initiated. TableIIIpresents the blocking procedures which we have used on the eight sheep studied to date. After completion of the blockade procedure, an ^{131}I tracer dose is given. All materials are given intravenously to the ewe. The ewe and fetus(es) are sacrificed one or more days after the ^{131}I tracer dose and the thyroids obtained. The amounts of ^{125}I and ^{131}I within the maternal and fetal thyroids are determined as a percent of the injected doses. The radioactive counting was done with a NaI(Tl) well-crystal detector and two channel analyser system. The counting results were processed for the separate activities using a program written for the PDP-9 computer.

To date, we have preliminary data on eight sheep. The results of these preliminary studies show that Lugol's solution is the more effective blocking agent. The effect of Lugol's is proportional to the amount administered and equally effective for both the ewe and lamb. The results on the three sheep in which thyroxine was administered indicate that this agent is not effective for thyroid blocking in low doses given for short times. The preliminary studies in sheep have been useful in identifying and solving methodologic problems. The next step will be to obtain information on the relative effectiveness of blockage of I transport in humans.

During the past year, we have had fewer therapeutic abortions in whom we could carry out these studies due to several factors, one of which has been the increased frequency of early abortions in which hysterotomy is not performed. In the next year, we should be able to perform 3-10 studies in which we will evaluate the effect of Lubol's solution on transfer of a small ^{131}I tracer dose to the

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fetus. The data collected to date will be used as the reference against which to assess degree of blockade. This information is needed to determine the expected diminution in radiation dose to the fetal thyroid from ^{131}I ingested by the mother that can be effected by the use of blocking agents. This is of potential importance in circumstances where planned or accidental exposures to ^{131}I occur in pregnancy.

The data on ^{59}Fe distribution during pregnancy provide a solid basis for dose estimation. Studies on transport at longer times following IV injection are needed to determine the fraction of transport that occurs in the 18 hour interval used in the studies to date. We are attempting to start our studies in patients scheduled for therapeutic abortions earlier to obtain these data and in particular are interested in patients who are 15 or more weeks of gestational age. We have alerted our colleagues in Obstetrics and Gynecology to the types of patients upon which we need data and should obtain the missing data in the coming year.

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TABLE II

ABSORBED DOSE TO FETUS AND SPECIFIC

FETAL ORGANS FROM MATERNALLY ADMINISTERED ^{131}I and ^{59}Fe

Subject	Gestational Age (wk)	^{131}I		^{59}Fe		
		Fetal Dose (Rad/mCi)	Fetal Thyroid Dose (Rad/mCi)	Fetal Dose (Rad/mCi)	Fetal Liver Dose (Rad/mCi)	Fetal Spleen Dose (Rad/mCi)
M1	9	0.794	*	33.6	417.	*
A1	11	0.874	*	35.8	334.	*
C1	11	+	*	28.6	237.	*
M2	13	1.10	743.	38.1	427.	60.0
S1	14	1.16	1270.	35.1	392.	89.8
S2	14	1.37	*	38.0	429.	121.
P1	14.5	1.25	2380.	38.3	381.	145.
R1	15	1.05	1450.	37.8	326.	115.
F1	15	1.50	1820.	36.4	380.	132.
D1	16	1.89	4350.	35.9	259.	81.5
O1	20	2.35	4400.	37.5	329.	141.
H1	22	2.99	5920.	39.4	330.	186.

*: Organ not dissectable.

+: ^{131}I Data not available on this fetus

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TABLE III

BLOCKADE PROCEDURE FOR SHEEP THYROID STUDY

Sheep I.D.	Type of Blocking Solution	Amount of Blocking Injection	How Blocking Solution Given
131-71	None	----	Sheep had to be sacrificed before blocking.
804-71	Lugol's	0.60 g	One I.V. injection
909-71	Lugol's	0.61 g	One I.V. injection
904-71	Lugol's	1.03 g	Two I.V. injections - 4 hours apart.
122-71	Lugol's	3.16 g	24 hour I.V. infusion
69-71	Synthroid	40µg	One I.V. injection
183-71	Synthroid	46µg	One I.V. Injection
975-71	Synthroid	789µg	Four I.V. injections - 24 hours apart

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4. Monitoring of Cs-137 Levels in Man

Laboratories in different parts of the world are measuring levels of Cs-137 in normal individuals using whole body counting techniques. In 1960, our laboratory made Cs-137 measurements on 514 Nashville residents. Results of the survey of Cs-137 levels in this stratified random sample revealed wide differences between individuals in the population and suggested that inferences regarding population exposure required measurements on representative population samples. (Meneeley, G. R. etal. Cesium-137 Burdens in a Defined Sample, in Radioactivity in Man, Second Symposium. C. C. Thomas, 1965). No systematic follow-up of measurements on this population has been made in the ensuing years. In this time interval many changes have occurred. These include changes in:

1. Vanderbilt whole body counter design
2. Sample population age, and accessibility, and
3. Levels and accumulations of Cs-137.

On the basis of known rates of injection of Cs-137 into the biosphere, and measured body burdens, lower levels of Cs-137 were predicted than are currently measured in man. (Personal Communication C. Richmond, April, 1971). The extent to which this reflects unusual population samples that are being measured or true discrepancies is uncertain. In an attempt to obtain data on this point and to bridge the hiatus between measurements made in 1960 and present body burdens in this region of the country, we propose to make repeat measurements on a sample of the group studied earlier. During the interim years, we have sequential measurements on several staff members and these will be useful in correcting for systematic changes in the counter. In addition, they will provide data of interest regarding the changes experienced in this region in the missing time interval.

In addition, we propose to measure whole body cesium content in two other population samples:

1. Vanderbilt University Medical Center employees. We propose to select a sample ($30 < N < 60$) from long term employees at the Medical Center similar in age/sex/race to the 1960 study group. This will simplify the problem of patient contacting and will minimize sample attrition. Measurements in the whole body counter will be made twice a year.
2. A sample of pregnant women whose babies are delivered at Vanderbilt will be selected (~ 4/mos.). We will attempt to measure Cs-137 in the mother (post partum), and the baby in the whole body counter. In addition measurements will be made with a lithium drifted germanium detector on lyophilized placental tissue, if quantifiable levels are present.

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B. APPLICATIONS OF QUANTITATIVE EXTERNAL COUNTING SYSTEMS

1. Evaluation of Iron Metabolism in Hematologic Disease.

In addition to dosimetry studies of ^{59}Fe described in earlier sections, we plan to study the kinetics of ^{59}Fe in patients with hematologic diseases. With the whole body counter we have been able to measure the turn over of ^{59}Fe by external counting and to estimate the kinetics of turnover in liver, spleen, and bone marrow. In collaboration with staff of the Hematology Division of the Department of Medicine we plan to study iron kinetics in patients with hemolytic anemias, aplastic states, myelosclerosis, leukemia and patients with splenomegaly of known and unknown origin. The study will include the following measurements:

1. Red cell survival, Cr^{51} blood volume and serial scans.
2. Iron kinetics based on blood sampling:
   a. Plasma iron clearance
   b. Plasma iron transport rate
   c. Red cell unilization of Fe^{59}
3. Quantitative scanning in the whole body counter for regional iron kinetics evaluations. The rationale for the Cr^{51} scans is twofold: (1) to determine the fraction of the blood volume in regions of interest i.e. liver, spleen and marrow, and (2) for splenic sequestration studies. The iron whole body scan will identify unusual sites of bone marrow function as as areas of decreased function. The pattern and kinetics of accumulation of Fe^{59} in marrow, liver, spleen, will be followed to determine whether they can be of diagnostic value or whether they allow therapeutic conclusions (for example: indication for splenectomy).

An outline of the protocol for patients with hemolytic and non hemolytic disorders is shown in Tables IV and V .

The data will be analyzed using SAAM 25. We will attempt to fit the data using the model proposed by Winchell which we are using for the ^{59}Fe dosimetry analyses. The analyses will be performed in collaboration with Dr.Ensign Johnson of the Electrical Engineering Department of Vanderbilt, as well as faculty of the Hematology Division (Robert Hartman, L. Clifford McKee, and Renate Peytremann).

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Table IV

Hemolytic Anemias

Day	Procedure	Blood Sample for Cr^{51} (10 cc anti-coag.)	Blood Sample for Fe^{59} (5 cc anti-coag.)	Blood Sample for Stable Fe 10 cc	Whole Body Scan
1	Cr^{51} blood volume Cr^{51} scan Diurnal pattern of serum Fe	60 min.		6 a.m., 2 p.m., 10 p.m.	1 hr. after Cr^{51} inj.
2	Fe^{59} injection		0,10, 20, 30, 45 60, 90 min. 2, 4, 8 hrs.	10 cc before Fe^{59} injection 60 & 120 min. later	Fe^{59} / Cr^{51} 4 hrs. after Fe^{59} injection
3-9			5 cc a day		Fe^{59} / Cr^{51} once a day
10-16			5 cc every other day		once every other day - Fe^{59}
>16 Once weekly			5 cc		once weekly Fe^{59}

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Table V

Hematologic Disorders Other Than

Hemolytic Anemias

Day	Procedure	Blood Sample for Cr^{51} (10 cc anti-coagulated)	Blood sample for Fe^{59} (5cc anti-coagulated)	Blood sample for Stable Fe (10 cc)	Whole Body Scan
1	Cr^{51} blood volume Cr^{51} scan Diurnal pattern of Serum Fe	60 min. after Cr^{51} tagged red cell injection etc.		6 a.m., 2 p.m., 10 p.m.	1 hr. after Cr^{51} injecti
2	Fe^{59} injection		0, 20, 40, 60, 90, 120 min. 4, 8 hrs. after Fe^{59} injection	Before Fe^{59} injection (60 & 120 min.)	Fe^{59} / Cr^{51} 4 hrs. after Fe^{59} injectic
3 - 9			5 cc a day		Fe^{59} / Cr^{51} once a day
10 to 16			5 cc every other day		Fe^{59} once every other day
>16 Weekly during study duration			5 cc		Fe^{59} Scan

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B. 2. Calcium Kinetics in Paget's Disease

Using our unique quantitative mapping system, we are studying calcium kinetics in a group of 10 patients with localized Paget's disease to assess the effect of calcitonin therapy on calcium turnover in normal and diseased bones. These studies are being carried out in colloboration with the Endocrinology Division of the Department of Medicine and the Orthopedic Surgery Department at Vanderbilt University Hospital. The quantitative scanning procedure allows us to make in-vivo measurements of the radiocalcium turnover in selected bones as well as total-body kinetics, before, duirng and after prolonged administration of calcitonin. Quantitative measurements of bone kinetics ordinarily have been made based on analysis of the blood disappearance curve since bone samples are difficult to obtain. Figure24 is a picture of a ^{47}Ca emission scan in a 68-year-old female with localized Paget's disease in the right leg which clearly reveals the increased localization of ^{47}Ca in the affected region.

The patients are administered approximately 35 μCi of ^{47}Ca, I.V. Plasma samples are obtained each hour for the first four hours post injection and then daily thereafter. Urine and stool collections are made daily in addition to a daily whole-body rectilinear scan out to day 7 to 10. To date we have studied calcium kinetics in 3 patients before calcitonin. The protocol for these studies includes pretreatment base line kinetics,a repeat study after patients have been on calcitonin for several months, and again two weeks after withdrawal. Careful control of dietary calcium is assured as these patients are in the Clinical Research Center.

Although the hormone effect is complex, useful information can be obtained using compartmental analysis techniques to calculate steady state compartment sizes, transfer rates between compartments and their fractional turnover rates. We have employed Berman's digital compartmental analysis program, SAAM 25, for initial analyses. Too little data are available at this time to establish a model with confidence.

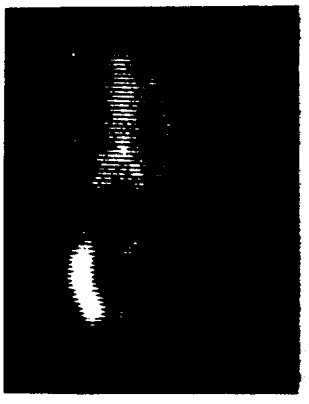
The preliminary model, as we have defined it, is shown in Figure 25. Data on compartments 1, 3 and 4 are derived from sample collections. Data on the bone compartments are obtained from the rectilinear whole-body scans. The overall system is normalized by the whole-body retention data obtained from the scan.

Figure 26shows the drastically increased plasma clearance rate for calcium in a Paget's patient as compared to a normal subject.

The data presented in Figure27 is from a 65 year old male who had localized Paget's disease affecting the upper left leg. The uptake curve for the left leg as compared to the corresponding region from the apparently normal right leg shows at least a three-fold increased uptake.

The effectiveness of the hormone treatment will be analyzed in terms of changes in the transfer rates and possibly in terms of changes in compartment sizes.

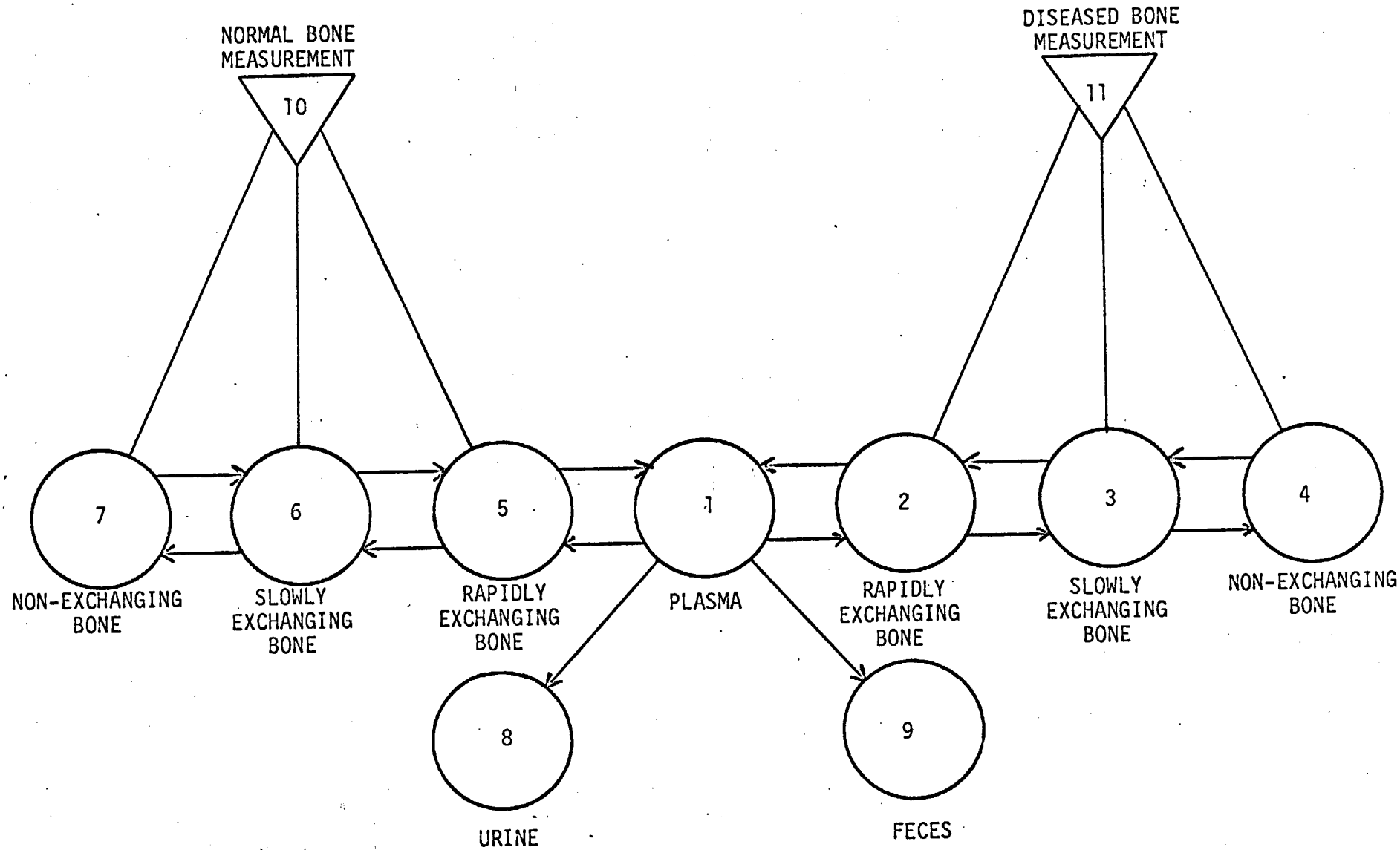
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^{47}Ca scan of a patient
with localized Paget's disease in lower right leg

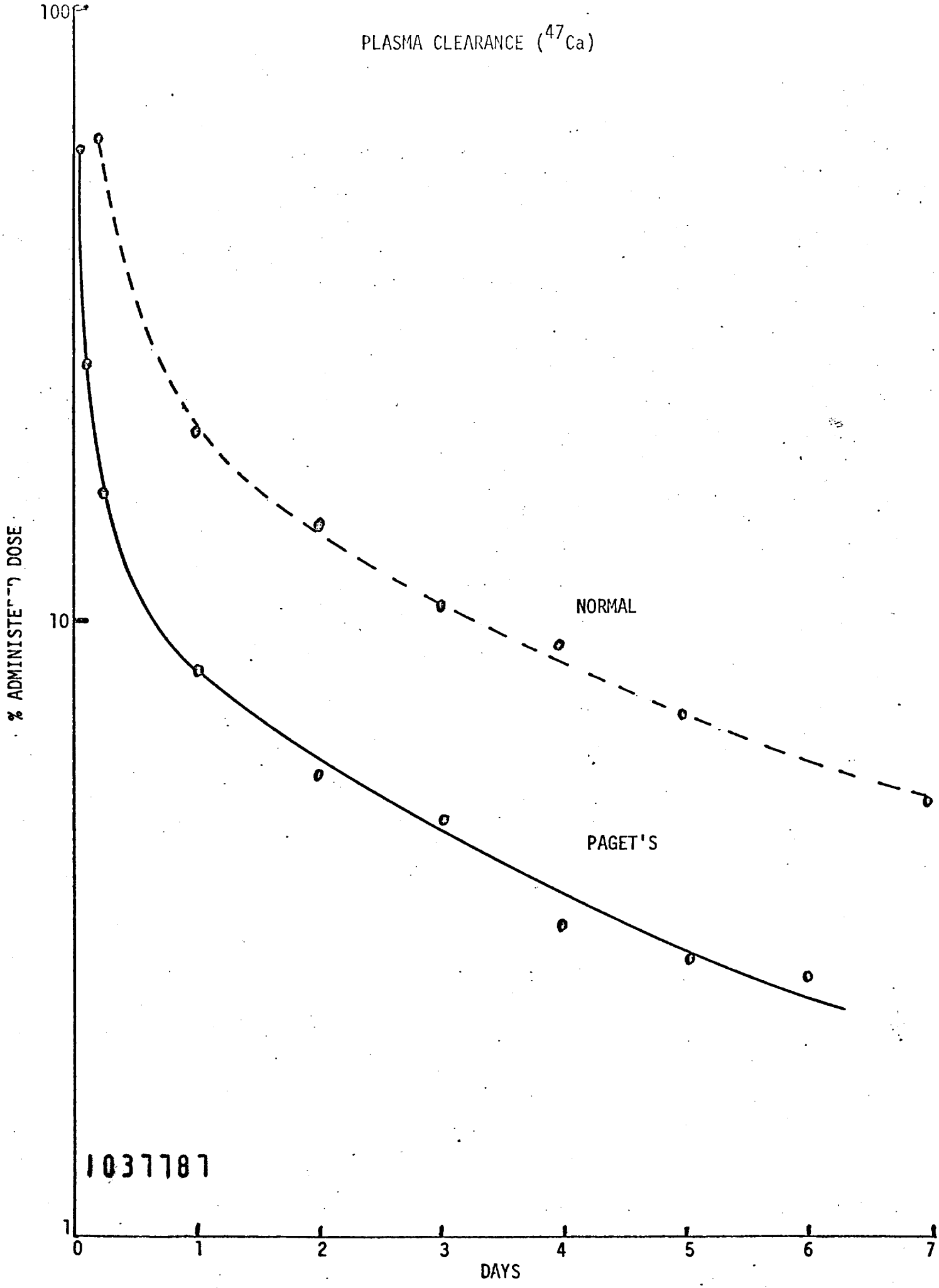
Fig. 24

SAAM25 Calcium Kinetics Model



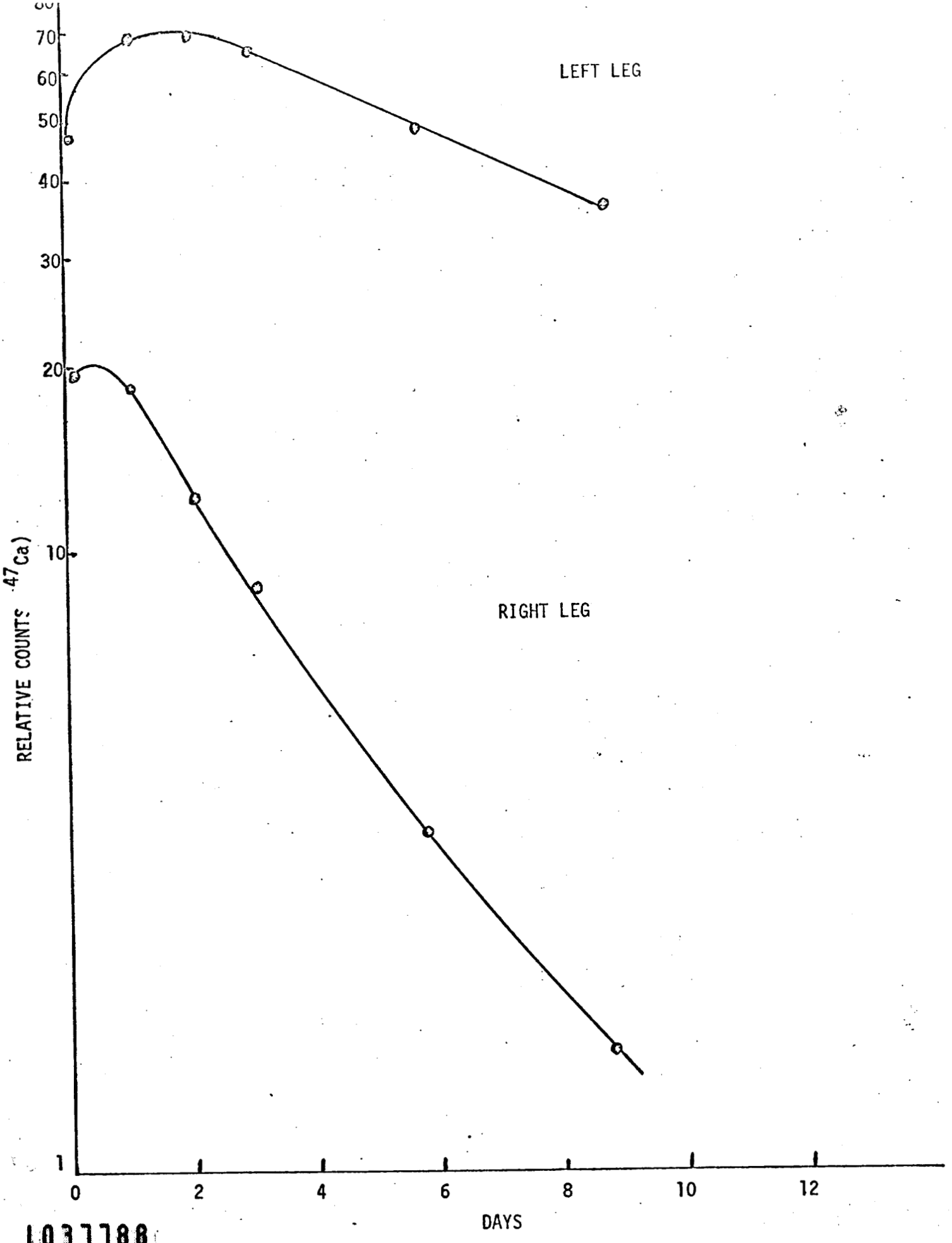
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Fig. 25



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Fig. 26



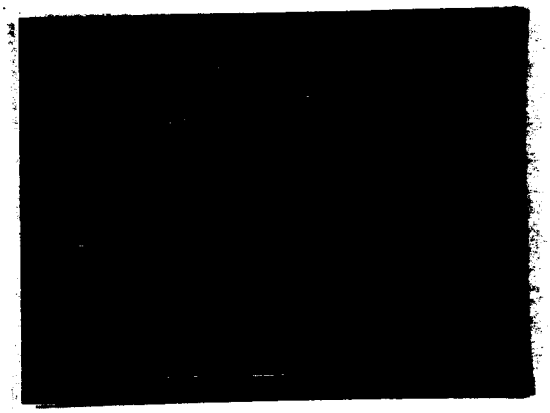
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Fig. 27

B. 3. Gallium Localization and Metabolism in Malignant Lymphoma and Lung Cancer

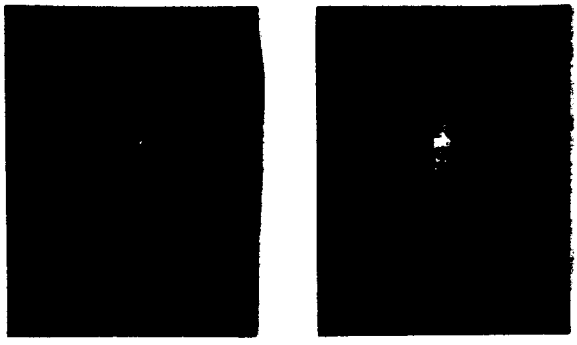
The Nuclear Medicine and Biophysics Division at Vanderbilt University is one of the groups participating in the ORAU-sponsored cooperative group to study tumor-localizing radioindicators. This study is described in detail in a memorandum to Dr. John Totter from Dr. Ralph Kniseley, dated December 15, 1970, a copy of which is attached. The costs of radiopharmaceutical preparation and distribution, and the costs of central review and analysis of the data will be covered by a contract for the headquarters operation. The costs of conducting and reporting the studies, collecting samples, and carrying our the protocol must be covered by the participating laboratories. Funds provided by this contract will be used to cover our costs for participating in the study. Our whole body scanning systems will provide quantitative data from scans, and in addition Anger camera views will be taken over suspicious and abnormal regions. With the scanner studies we will collect data using six separate single channel analyzers, set to collect the three major gamma ray transitions from each of two opposed detectors. The ^{67}Ga spectrum obtained from our scanner (upper probe) is shown in Figure 28 in the upper curve. The lower curve shows the output of the three separate single channel analyzers (coincidence gated spectrum) set to accpet the 93, 185 and 296 KeV photon energies from Ga^{67}. The equipment for these studies is available at present, and no additional cost will be incurred besides personnel time. To date we have conducted extensive animal studies with Ge^{67} but have studied only one patient. This was a young woman with known Hodgkin's disease in whom right inguinal adenopathy developed one year following radiotherapy to the neck. The patient was given 5 mCi and was scanned 48 hours thereafter. The image obtained with Picker medium energy high resolution collimators is shown in Figure 29 . Although the image obtained was sub-optimal (15 min. scan time with 90 counts in the maximum cell) increased uptake was seen in the right inguinal region. Count rate was limited since this was the first patient we studied and unfortunately it took longer to set up the procedure than expected and the patient could not be further detained. We plan to study at least 12 patinets in the first year of the study, which should begin on or before July 1, 1971, and we will follow the common protocol agreed upon.

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^{67}Ga Windows

Fig. 28



Whole body scan image of a patient administered 5 mCi of ^{67}Ga at 48 hrs. An abnormal uptake can be seen in the patient's right pelvic region. The picture on the right is a minified image.

Fig. 29

VI. Scientific Personnel--Curriculum Vitae on file AEC

Principal Investigator:
A. B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Director, Division of Nuclear Medicine & Biophysics and the Clinical Radioisotope Center, 25%

Co-Investigator:
R. E. Johnston, Ph.D., [redacted]
Assistant Professor, Radiology, 50%

Senior Investigator:
N. C. Dyer, Ph.D. Candidate, [redacted]
Activation Analysis, 25%

R. Baglan, Asst. Prof., Physics
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Research Associates:
C. O. T. Ball, [redacted]
Biostatistics, 35%

J. Parker, Computer Engineer
[redacted], 33%

J.J. Erickson, Ph.D. Candidate,
[redacted] Radiation Physics, 50%

J.E. Lagan, Electronics Engineer,
[redacted] 90%

L. C. McKee, Jr., M.D., [redacted]
Assistant Prof. of Medicine, 5%

E.V. Staab, M.D., [redacted]
Assistant Prof. of Radiology, 25%

D. Patton, M.D., [redacted]
Associate Prof. of Radiology, 25%

R. Price, Ph.D., [redacted]
Radiation Dosimetry, 50%

Jr. Investigator--Graduate Student:
J. A. Patton, Ph.D. Candidate, [redacted]
Hertz Foundation Fellow, 50%

VII. Other Personnel

Technician: J.A. Risner, [redacted] 56%

Secretary: J.E. Sterling, [redacted] 100%

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VANDERBILT UNIVERSITY

CURRICULUM VITAE

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4. Place of Birth: [redacted]

5. Date of Birth: [redacted]

6. Marital Status: [redacted]

7. Children: [redacted]

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University of Kentucky, Lexington, Ky., B. S., 1965.

9. Graduate work: University of California, Berkeley, Calif.,
Ph.D., 1970.

10. Professional experience:

Summer, 1965--Research Assistant, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Summer, 1966-67--Research Assistant, Lawrence Radiation Laboratory, Livermore, California.

January, 1968-September, 1970--Junior Physicist, Lawrence Radiation Laboratory, Livermore, California.

September, 1970-present--Assistant Professor of Physics; Research area--Medical Physics.

11. Society Membership--American Physical Society

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1. Energy Levels of Zirconium Isotopes, J. Inorg. Nucl. Chem. 31, 9 (1969).

2. Detection of Nonresonant Neutron Capture in Pb^{207} via the Threshold Photoneutron Cross Section for Pb^{208}, Phys. Rev. Letters 23, 796 (1969).

3. Threshold Photoneutron Cross Section for Mg^{25} and Isobaric Analogs of Na^{25}, Phys. Rev. Letters 24, 319 (1970).

4. A New Detector for keV Neutrons, to be published in Nucl. Instr. and Methods.

5. keV Fission Cross Section of U^{235} Measured with High Resolution, UCRL-72472, Lawrence Radiation Laboratory, Livermore, Calif. (1970).

6. M1 Giant Resonance in Pb^{208} from Threshold Photoneutron Measurements, Phys. Rev. Letters 25, 1302 (1970).

7. Threshold Photoneutron Cross Sections for $Pb^{206,207,208}$, $Fe^{56,57}$, $Cr^{52,53}$, $Mg^{24,25,26}$, and F^{19}, Physical Rev. C., 1971.

8. Ground-State Gamma-Ray Width of the "Doorway" State in Pb^{207} from Threshold Photoneutron Cross-Section Measurements, to be published in Physical Review.

9. Design and Evaluation of a Scanning-Bed Whole-Body Counter for Use in Clinical Studies, submitted to Health Physics Journal.

10. An Evaluation of Lithium-Drifted Germanium Detectors for Use in Radioisotope Scanning and Activation Analysis Studies, to be published by Journal of Nuclear Medicine, Proceedings of the Symposium on the Role of Semiconductor Detectors in the Future of Nuclear Medicine, February 12 and 13, 1971, Chicago, Illinois.

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Name: Judson F[loyd] Park Birthdate: [redacted]

Address: [redacted] Telephone: [redacted]
Soc. Sec. No.: [redacted]

Family: [redacted]

Education:

School	Major Field	Dates Attended	Degree
Univ. of Illinois, Urbana, Ill.	Physics	9/56 -- 6/60	BS
Franklin & Marshall Col., Lancaster, Pa.	Physics	9/63 -- 9/67	MS (thesis incomplete)
Lancaster Theological Sem., Lancaster, Pa.	New Testament	9/67 -- 6/70	MDiv, Magna cum Laude

Previous Employment:

Employer	Job Title	Dates Employed	Final Wages
H. G. Bancroft, Lancaster, Pa.	Salesman	6/56 -- 8/56	15% comm.
Physics Dept., Univ. of Ill., Urbana, Ill.	Lab Technician	1/57 -- 6/59	1.40 /hr.
RCA, Lancaster, Pa.	Eng. Technician	6/59 -- 9/59	2.10 /hr.
Physics Dept., Univ. of Ill., Urbana, Ill.	Lab Technicisn	1/60 -- 6/60	1.45 /hr.
RCA, Lancaster, Pa.	Engineer: Admnstrtr Tech. Data Syst.	6/60 -- 9/67	12,500 /yr.
Christ Un. Meth. Church, Lancaster, Pa.	Associate Pastor	1/68 -- 6/70	1560 /yr.
RCA, Lancaster, Pa.	Engineer	6/68 -- 9/68	231 /wk.
RCA, Lancaster, Pa.	Engineer	6/69 -- 8/69	240 /wk.
RCA, Lancaster, Pa.	Engineer	3/70 -- 8/70	250 /wk.

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Summary of Experience:

At Bancroft my responsibilities were two: to contact established office supplies customers and to canvass for new accounts, relieving regular salesmen during the summer. While at Illinois, I worked part-time during the school year and full-time one summer with a research group in solid-state physics; more significant tasks were the construction of a glass vacuum system of 10^{-8} torr ultimate pressure and the design and construction of an evaporator (3×10^{-7} torr) and of special electronics. The first summer job with RCA was in the display storage tube advanced development group, for whom I first applied a digital computer [IBM-650] to the design of the collimator portion of such tubes and also developed a semi-digital technique to solve electron optics problems (making use of a lumped-constant analog and a calculator) which remained cost-competitive until the third generation digital computers.

The bulk of my time at RCA was divided into two periods: prior to 6/63 I was an engineer working with electro-optical components; subsequently I held a staff position reporting to the manager of data processing for the plant. In the former job some of the more notable accomplishments were the design of the first fiber-optics cathode-ray tube produced by a manufacturing facility of RCA and the use of large computers [IBM-7094] to solve electron optical problems arising in the design of classified devices for Ft. Belvoir. In the latter assignment I was responsible for all engineering use of computers within the plant with respect to training, the establishing of standards, purchase of outside time, and technical assistance on both software problems and hardware problems, such as selecting mini-computers or designing data acquisition systems (including stochastic simulation).

After entering seminary, I served as part-time associate pastor of a 700-member congregation, working primarily with youth yet also assisting with all aspects of the pastoral ministry. I returned to RCA each of the intervening summers, working with a group which has implemented the multi-processing use of a rather complete PDP-9 to manufacture and test photomultiplier tubes. Virtually all of the software and the digital logic in the interface is my design, since the programmers and technicians have generally implemented the algorithms, circuits, and operating systems laid out during the summers.

Present Objectives:

I entered Vanderbilt Graduate school 9/70 to pursue a PhD in New Testament with a minor area in Systems and Information Sciences, which ought to take three or four years. I am interested in a limited amount of part-time work during the school year and urgently looking for a position each summer. I feel I can make a real contribution to almost any computer-oriented technical group and would expect a salary consistent with that contribution.

CURRICULUM VITAE
Dennis D. Patton

EDUCATION:

Lowell High School, San Francisco; Diploma and California Scholarship Federation, 1948.

University of California, Berkeley; A.B. (Physics), 1953.

University of Heidelberg, Germany; German Language Certificate, 1951.

UCLA School of Medicine, Los Angeles, California; M.D., 1959.

EMPLOYMENT:

University of California, Berkeley:
University of California General Library, Berkeley, 1948-1950, 1951-1952.

University of California Radiation Laboratory, Berkeley:
Research in Medical Physics as graduate student under Joseph G. Hamilton, M.D.; studied metabolism of fission products in rats, metabolism of astatine, and use of astatine in clinical application, 1953-1954.

University of California, Berkeley:
Taught Physics 126 and 126L (Tracer Techniques in Medicine and Biology), lectures and laboratory, 1953 and 1954; faculty title of Associate in Medical Physics.

University of California, Los Angeles, Department of Radiology:
Senior Laboratory Technician, 1955-1957, (summers and part-time during medical school). Participated in studies of radiation-induced renal hypertension in rats and in measurement of cardiac output by dye-dilution curves.

Atomic Research Laboratory, Culver City, California:
Laboratory Director, 1958.

Planning Research Corporation, Los Angeles, California:
Biomedical Group; Associate, 1958-1960; Manager, 1960-1965. In charge of group of M.D.'s whose work involved the planning and evaluation of medical-research programs, including public health and epidemiology, bioastronautics, medical electronics, radiation safety, experimental design, and other analytical work. A summary of the actual projects completed by the Biomedical Group is presented in the attached sheet, "Brief Summary of PRC's Corporate Biomedical Experience."

Wadsworth VA Hospital, Los Angeles, California:
Intern, 1959-1960.

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EMPLOYMENT: (continued)

University of California, Los Angeles, Department of Medicine:
Assistant Research Neurologist, 1964-1965. Worked with William H. Oldendorf, M.D. in research on the use of isotopes to measure cranial blood flow, on modifications of cerebral angiography, and on improvements in brain scanning techniques.

Wadsworth VA Hospital, Los Angeles, California:
Clinical Neurologist, 1964-1965 (in conjunction with the above projects).

General Practitioner, Santa Monica, California (limited practice): 1961-1965; Santa Monica Hospital staff privileges.

University of California, California College of Medicine, Los Angeles, California:
Fellow in Radiology, 1954.

University of California, California College of Medicine, Los Angeles, California:
Teaching Fellow, 1966; duties included design and presentation of basic logic, mathematics, and statistics courses to medical students.

Los Angeles County General Hospital, Unit II, Los Angeles, California:
Resident in Radiology 1965-1968.

Fellow in Radiology, Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D.C., July-October 1967. Sponsored by the Radiological Society of North America.

Orange County Medical Center, Orange, California:
Head, Division of Nuclear Medicine, 1968-December, 1970.

University of California, California College of Medicine, Irvine, California:
Assistant Professor, Department of Radiological Sciences, 1968-December, 1970.

Vanderbilt University School of Medicine, Nashville, Tennessee;
Associate Professor of Radiology, December, 1970 - present.

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Brief Summary of Projects Completed at Planning Research Corporation

(These projects included participation by the Biomedical Group, but were not primarily the Group's responsibility; primarily biomedical projects are presented in a separate listing).

Acting as Group Manager, Dr. Patton:

Developed damage models for use in the formulation of a probabilistic methodology for the safety analyses of nuclear reactors.

Determined safety factors in a nuclear engine test facility.

Analyzed short-term and long-term effects of contamination of food and water supply by fission products.

Conducted civil defense studies involving the results of nuclear attack on Los Angeles, with special regard to medical facilities.

Conducted systems-oriented studies of the effects of biological and chemical agents on military and civilian organizations.

Developed an original model for evaluation of incapacitation, in terms of qualitative and quantitative residual functions.

Participated in studies involving the application of electronics and computer technology to biomedical research and data engineering.

Investigated the roles of operations research and systems analysis in medicine, with forecasts of potential markets for "hardware" and "software".

Participated in studies involving the interpretation of telemetered and recorded bioastronautics data.

Investigated the nature and relative information content of in-flight physiological monitoring systems, and the information obtainable from astronauts and X-15 pilots.

Conducted a study of the physiological information derivable from various types of ballistocardiograms, and the potential use of this measurement in astronaut monitoring.

Participated in studies involving defense against ballistic and guided missiles, predetonation of enemy missiles in flight (including effects on exposed personnel), early-warning radar systems, and anti-radar systems.

Participated in a study of electro-optical factors in relation to a satellite reconnaissance system (ARS).

Analyzed ARS coverage as a function of satellite characteristics.

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Brief Summary of Projects Completed at Planning Research Corporation

(continued)

Developed an improved system of parameters for photo interpreters.

Prepared a mathematical model of the USSR rail transportation system for reconnaissance purposes, devising an original and simplifying algebra.

Prepared a study of the proposed University of California, San Diego School of Medicine, and its role in the medical community, in the educational community, and in the complex of medical schools in the Western States.

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AFFILIATIONS:

American Medical Association
California Medical Association
Los Angeles County Medical Association
New York Academy of Sciences
*Institute of Electrical and Electronic Engineers, Professional Group on Medical Electronics
Aerospace Medical Association
*Los Angeles County Radiological Society (Associate Member, Resident)
*American College of Radiology (Associate Member, Resident)
*Society of Nuclear Medicine
*San Francisco Zoological Society

*Current Affiliations

AWARDS:

First Prize, Los Angeles Radiological Society, Residents' Essay Contest, 1965. Essay entitled "Liver Scanning with Technetium 99m Colloid."

First Prize, Los Angeles Radiological Society, Residents' Essay Contest, 1966. Essay entitled "Current Concepts in the Use of Technetium 99m in Tracer Studies of the Gastrointestinal Tract."

First Prize, Los Angeles Radiological Society, Residents' Essay Contest, 1967. Essay entitled "The Seven Faces of Barium."

(This prize had never been won twice by the same resident. The fact that it was won three consecutive years by the same resident was mentioned in the President's Report to the Regents of the University of California, July 14, 1967).

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PERSONAL:

Born in [redacted]

Married [redacted]

Present Home Address: [redacted]

HOBBIES:

Music: Second Bassoon, Atlanta Symphony Orchestra, 1946-1947.
First Bassoon, University of California Symphony Orchestra, 1948-1954, including one formal concert of solo bassoon music, 1953.
First Bassoon, Santa Monica Symphony Orchestra, 1956-1961.
First Bassoon, Los Angeles Doctors Symphony Orchestra, 1961-1967, including several formal concerts at Los Angeles Philharmonic and Los Angeles Music Center.

Other Hobbies: Skiing, camping, oil painting, California history, and furniture and cabinet making.

COMMUNITY ACTIVITIES:

Sponsored High School Hi-Y Group in West Los Angeles, 1955-1958.

Active in Santa Monica YMCA 1960-1964; active member of the Y's Men, the YMCA sponsoring organization; attended several community leadership conferences.

Organized, formed, and maintained a highly successful Boy Scout Troup for handicapped boys (Troop 228), West Los Angeles, 1957-1965, which gained national recognition in Scouting. This troop was under the sponsorship of the Brentwood Optimist Club. An explorer post and cub pack were formed in 1963 and 1964, under the same framework.

Certificate of Achievement for Outstanding Volunteer Service, Washington Boulevard School for Handicapped, 1963.

Elected to Top Man Conference, Santa Monica, 1961 (conference of twenty most outstanding community leaders).

Active member, Brentwood Optimist Club, 1957 to 1965. Member, Board of Directors, Optimist Home for Boys, 1960-1964.

Sponsor and "foster parent", Music Educators National Conference, Santa Monica, California, 1961.

Lay instructor in Sunday School, Santa Monica First Methodist Church, 1962-1965, instructing at the high school level. Took formal, church-sponsored course in leadership, education, and training, the highest lay level of instruction of its type.

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COMMUNITY ACTIVITIES: (continued)

Sponsor, Wesley College Age Fellowship, Santa Monica First Methodist Church, 1964 (co-sponsor with wife).

Organized a group of physicians and psychologists giving discussions on facts of life to children and parents, Santa Monica YMCA, 1961-1965; received service award for this project.

Consultant to Santa Monica and Los Angeles YMCA on Big Bear Health Center, a 200 bed infirmary to be built in the Big Bear Recreation Area, serving camps in that region. Pierre Claeyssens, architect.

Consultant to Moody Institute of Science, West Los Angeles, 1958-1963 (producers of religiously oriented science films). Contributed to the film "City of the Bees", participating in studies of physical and physiological optics relating to navigation of bees using polarized light.

OTHER SCIENTIFIC AND PROFESSIONAL ACTIVITIES:

Organized, designed, and taught a course in basic logic, mathematics, and statistics to freshman medical students at the California College of Medicine, 1965 (as Teaching Fellow), 1966 and 1967.

Advised summer fellows in Radiology, 1966 and 1967. The summer fellows were second year medical students engaged in research activities, one in colon scanning and the other in pancreas scanning.

Participated in medical educational television program, "Respiratory Distress in the Newborn", broadcast on closed circuit television, channel 28 (KCET), 1966. This program was jointly sponsored by the Departments of Pediatrics and Radiological Sciences, California College of Medicine.

Organized and sponsored meetings between students and members of the faculty, in which ideas and discussions could be exchanged, often concerning planning of the new Irvine Medical School (California College of Medicine).

Research projects in progress include clinical evaluation of colon scanning; studies of safety of placental scanning using technetium 99m; the metabolism of technetium in the fetus; a new technique of scanning the pancreas; preparation of a scan teaching file for use in the California College of Medicine, and for submission to the Armed Forces Institute of Pathology; studies of data processing applicable to information derived in isotope studies; and studies in physical and physiological optics relative to radioisotope scan imaging.

1037801

NATIONAL AND INTERNATIONAL MEETINGS ATTENDED:

1. 15th Annual Conference on Engineering in Medicine and Biology (IRE/IEEE AIEE, ISA). Chicago, Illinois, November 1962 (discussant by invitation).

2. 34th Annual Meeting of the Aerospace Medical Association, Los Angeles, California, April 1963.

3. 5th International Congress on Medical Electronics, Liege, Belgium, July 1963.

4. 35th Annual Meeting of the Aerospace Medical Association, Bal Harbour, Florida, May 1964.

5. UCLA Symposium on Neuroradiology, Los Angeles, California, February 1965.

6. UCLA Symposium on Radioisotope Organ Scanning, Los Angeles, California, April 1965.

7. XIth International Congress of Radiology, Rome, Italy, September 1965 (by invitation of American delegate).

8. 14th Annual Meeting of the Association of University Radiologists, Little Rock, Arkansas, May 1964 (presented paper).

9. Conference on Computers in Radiology, University of Missouri, Columbia, Missouri, April 1967.

10. Symposium on Pediatric Radiology, UCLA, Los Angeles, California, April 1967.

11. Symposium on Biomedical Engineering, San Diego, California, June 1966 (presented paper).

12. 52nd Annual Meeting of the Radiological Society of North American, Chicago, Illinois (presented exhibit).

13. 14th Annual Meeting of the Society of Nuclear Medicine, Seattle, Washington, June 1967 (presented exhibits).

14. Symposium on Clinical Applications of Nuclear Medicine, presented by the Lahey Clinic, Boston, Massachusetts, September 1967.

15. UCLA Symposium on Neuroradiology, Los Angeles, California, November 1967.

16. 96th Annual Meeting of the California Medical Association, Los Angeles, California, April 1967 (presented paper).

17. 68th Annual Meeting, American Roentgen Ray Society, Washington, D.C., September 1967.

18. Society of Nuclear Medicine, St. Louis, Missouri, June 27-30, 1968.

19. Society of Nuclear Medicine, New Orleans, Louisiana, Presented paper entitled "Desk Top Computers in Nuclear Medicine", June 1969.

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SPECIAL COURSES ATTENDED:

1. Refresher Course in Radiology, University of California, San Francisco, March 1966.

2. IBM Course: "Computing for Medical Doctors", Los Angeles, California, May 1966.

3. Mammography (NIH-sponsored course), University of California, San Francisco, September 1966.

4. Refresher Course in Radiology, University of California, San Francisco, March 1967.

5. Fellowship in Radiology, Armed Forces Institute of Pathology, Washington, D.C., July through October 1967.

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CURRICULUM VITAE

1. Name: Price, Ronald Rhoads

2. Department: Department of Radioisotope Research

3. Present title: Research Associate, Radioisotope Research, Veterans Administration Hospital, Nashville, Tennessee.

4. Place of Birth: [redacted]

5. Date of Birth; [redacted]

6. Marital Status: [redacted]

7. Children: [redacted]

8. Undergraduate Work: B. S. in Physics, 1964, Western Kentucky University, Bowling Green, Kentucky.

9. Graduate work: Ph.D. (1971) in Physics, Vanderbilt University, Nashville, Tennessee.

10. Society Memberships: Health Physics Society
American Physical Society
Sigma Pi Sigma

11. Professional Experience:

1970-present: Research Associate, Department of Radioisotope Research, Veterans Administration Hospital, Nashville, Tennessee.

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VIII. Other Financial Assistance--Federal or Non-University

Co-Investigator, salary support from Veterans Administration, 50% effort this research.
2 Research Associates. Salary support Veterans Administration, 1 at 50% effort and 1 at 33% efort on this research.
1 Research Associate. Salary support Hertz Foundation Fellowship, 50% effort on this research.

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low=level counting facility with some 18,000 square feet adjacent for conference, library, clinical scanning, and instrument development and modification	100 percent
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 and journals
Medical Illustrations	Drawings, slides, photographs for presentations and publications

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RENEWAL PROPOSAL
Contract AT-(40-1)-2401
1 August 1971 - 31 July 1972

X. Budget Estimated Requirements	AEC	University	Total
1. Salaries & Wages Name, Title, Monthly Rate, % Effort			
Principal Investigator: A. B. Brill, M.D., Ph.D. [redacted] Professor, Medicine and Radiology Salary Support not included, proportionate sharing, 25%	0	---	---
Co-Investigator: R.E. Johnston, Ph.D. Asst. Professor, Radiology Salary support, Veterans Administration, 50%	0	---	---
Senior Investigator: N. C. Dyer, @1,157.67, 25%	3,473.	---	3,473.
R. Baglan, Asst. Prof., Physics Salary support University not considered proportionate costs, 25%	3,333.	---	3,333.
Research Associates: C.O.T. Ball, Biostatistics, @789, 35%	2,271.	1,044.	3,315.
J. Parker, Computer Engineer, Summer, 1,000, 33%	3,333.	---	3,333.
J.J. Erickson, Radiation Physics, @1011, 52%	2,471.	3,864.	6,335.
J.E. Lagan, Electronics Engineer, @961.58, 90%	5,264.	5,077.	10,341.
D. Patton, M.D., Assoc. Prof., Radiology, salary support, University not included, proportionate sharing, 25%	0	---	---
R. Price, Ph.D., Radiation Dosimetry, salary support Veterans Administration, 50%	0	---	---
Jr. Investigator, Graduate Student J.A. Patton, Hertz Foundation Fellow, 50%	0	---	---
Part-Time Medical and Graduate Students 4 @ $1500.	6,000.	---	6,000.

(continued)

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	AEC	University	Total
Secretary			
J.E. Sterling, @432. 100%	5,179.	---	5,179.
Technician			
J. Risner, @425, 56%	2,842.	---	2,842.
Sub-total	34,166.	9,985.	44,151.
Fringe Benefits (not fixed & of salaries. Varies with employee status & option)	1,318.	514.	1,832.
Total Salaries & Fringe	35,484.	10,499.	45,983.
2. Supplies & Materials			
Computer Supplies and Time	2,000.		
Electronic Components			
Maintenance	2,000.		
Interface development	4,000.		
Maintenance Contracts	3,223.		
Radioisotopes	1,500.		
Stable Isotopes and Chemical Supplies	1,000.		
Subject Participation	1,200.		
Equipment Rental			
Current obligations	1,304.		
Proposed computer memory addition	7,000.		
	23,227.		23,227.
3. Equipment	0		0.
4. Publications and Copying	700.		700.
5. Travel	1,500.		1,500.
6. Other	---		
7. Indirect Costs, 39% Salaries & Fringe; see attached document dated 1 February 71.	13,839.	4,094.	17,933.
Total Project Costs	74,750.	14,593.	89,343.

Percentage & Amount, Vanderbilt University--------- 16% 14,593.

Percentage & Amounts Requested AEC---------- 84% 74,750.

XI. AUTHENTICATION

A. Bertrand Brill, M.D.
Principal Investigator

Leon W. Cunningham
Associate Dean for Biomedical Sciences

James S. Worley
Associate Provost

NOTE: Studies described in this application, involving the investigational use of human subjects, have been reviewed and approved by this Institution's Clinical Investigation Committee.

1037807

TO: Division of Biology and Medicine, U. S. Atomic Energy Commission (John R. Totter, Director), and the National Cancer Institute (Paul Carbone, Chief, Medicine Branch)

SUBJECT: Joint Support for a Clinical Project to Study Gallium-67 in 1) Lymphoma, and 2) Lung Cancer

FROM: Ralph M. Kniseley, M.D., Secretary
Cooperative Group to Study Localization of Radiopharmaceuticals (CGSR)
Sponsored by Oak Ridge Associated Universities (ORAU)

DATE: December 15, 1970

SUMMARY: Recently staff members of the Medical Division of Oak Ridge Associated Universities found that gallium-67 has a noteworthy concentration in many but not all human malignant tumors. They have also demonstrated this phenomenon in animal tumor models and are working to elucidate the mechanism of uptake. Several laboratories in the United States and abroad have confirmed these observations. The isotope is being developed by the Isotopes Development Center of the Oak Ridge National Laboratory. Important questions must be answered about the best use of this agent and its clinical efficacy in all human tumors, a task not feasible for one group of investigators in one institution. In this initial protocol the Cooperative Group to Study Localization of Radic- indicators (CGSR) in a joint effort with the staff members of the Clinical Center (NCI) seeks to determine the usefulness of gallium-67 in a) Hodgkin's disease and other lymphomas, and b) in lung cancer. The immediate objective is limited to answering questions about the value of this agent as an additional diagnostic aid for staging (a prerequisite for planning optimal therapy), for determining the effectiveness of treatment, and, later on, for assessing the need for further treatment. This protocol is chosen because, in the one instance, renewed hope to cure Hodgkin's disease has recently emerged through results of vigorous radiotherapy and chemotherapy protocols; a higher cure rate is possible by better methods of assessing the extent of the disease. In cancer of the lung, we see the continuing inexorable rise in incidence, coupled with low cure rates and low operability rates because of late detection; here gallium scanning may offer a method of detection.

The CGSR and the NCI clinical groups will attempt to answer several specific questions. Gallium-67 will be distributed in radiopharmaceutical form by the Medical Division at a level of 100 millicuries/wk among participants. The data will provide part of a scientific base essential before we could recommend marketing the agent as a radiopharmaceutical under a New Drug Application (NDA) in compliance with FDA regulations (Section 505 (b) Federal Food, Drug, and Cosmetic Act, Title 21 of the U.S. Code). If this important phase of the work is to proceed, we will require the support of the Division of Isotopes Development.

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BUDGET

The proposal requests support for the radionuclide from the Division of Isotopes Development of the U. S. Atomic Energy Commission. (It seeks from NCI, funds for converting gallium-67 to a radiopharmaceutical, distributing to participating institutions, data collecting, and analysis.) Through this project we hope to determine the clinical efficacy in two important kinds of cancer. The data will form part of the base leading to a New Drug Application (NDA) under Section 505 (b) of the Federal Food, Drug, and Cosmetic Act.

1. Support from Division of Isotope Development, USAEC.

^{67}Ga, 100 millicuries/wk @ $8.00/millicurie	$ 41,600
(Price to be determined by Atomic Energy Commission and ORNL's Isotopes Development Center.)	

2. Support from the National Cancer Institute.

Packaging and Shipping Costs	$ 4,000
Testing and Handling Costs	2,600
Secretarial Expense (part time)	3,500
Data Processing	6,000
Travel to Work Meetings by Participants	2,500
Construction, Distribution of Phantoms for Instrument Calibration	500
Consultant Services of Biostatistician	800
Direct Costs	$ 19,900
Indirect Costs (35.72%)	7,100
Total NCI Costs	$ 27,000

3. Support by Participants.

Each institution contributes scanning and technician time and supplies data on cases included in study. Estimated conservatively $50.00 per scan study.	$ 50,000

I. Introduction and Background.

A. Previous Clinical Work.

Staff members at the Medical Division of Oak Ridge Associated Universities discovered that gallium-67, in carrier-free state, given as citrate, localized strikingly in a variety of malignant human tumors; the hope for a general tumor-scanning agent was renewed. At the present state of our knowledge we know that it localizes in many types of cancers, but, for as yet unexplained reasons, not all types. The phenomenon has been confirmed in a number of laboratories in this country and abroad. This nuclide has been tested in more than 100 patients with at least 20 different diseases, and the best results are found in patients with reticulum cell sarcoma and lymphoblastoma with intermediate results in Hodgkin's disease and cancer of the lung. All of four squamous cell carcinomas of the lung gave positive results. Sometimes only bone metastases are detected, though usually it is not possible to tell from the scan alone if the gallium is in a tumor or in the reactive surrounding bone. In some patients, with both osseous and soft tissue metastases, the activity can be discerned in both.

After intravenous injection, gallium is bound quickly to plasma proteins, especially transferrin, and is removed from the blood by tissue uptake and excretion; about 5% remains in the blood at 40 hr and about 2% still circulates at 5 days. Urinary excretion during the 6 days after administration totals 20 to 30%, with about half of this occurring in the first 24 hr. Fecal excretion averages 10%, leaving a whole-body retention of 65%. The portion of the nuclide taken up in normal and neoplastic tissue is firmly bound, apparently in lysosome-like structures. Autopsies on four patients who received gallium 6 to 17 days before death contributed some information on tissue concentrations; there is wide variability in these patients with much retained in the liver, spleen, bone marrow, kidneys, and bones. The average tissue concentration in the four patients were spleen 11%/kilo; bone marrow 5%/kilo; liver 4%/kilo; kidney cortex 4%/kilo; bone 2%/kilo. In nine patients with surgical excision or biopsy of tumors, after test doses with gallium, tumor concentrations as high as 60% of the administered dose per kilo have been observed and with tumor to blood ratios as high as 100:1. In autoradiograms, the activity is distributed nonhomogeneously in tumor with lower uptakes in areas of fibrosis or necrosis. In at least some malignant lesions, the uptakes revert from positive to equivocal or negative after irradiation or chemotherapy. The Medical Division continues to collect data on tissue distribution and turnover.

These findings have renewed the hope for tumor-localizing radioindicators, a primary concern of the scanning aspect of nuclear medicine. Success in the past has been largely with specific organs (especially the brain), thyroid with functioning thyroid tissue, and osseous lesions where sites of rapid turnover of bone salts enhance the uptake of bone-seeking elements, such as fluorine, strontium, or gallium. Lesions in the liver, in contrast, are visualized as "cold spots" after radioisotopes localizing in the organ

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are given (radioactive colloids, rose bengal). Limited success with clinical tumor-scanning agents has been reported by several investigators using sodium selenite, selenomethionine, chlormerodrin, indium-111, radioiodinated antifibrinogen, and technetium-99m. At this point, gallium-67 offers the most promise for extended clinical trials.

B. Animal Work.

The recent clinical finding that intravenously administered gallium-67 localizes in a variety of cancers in man has prompted an intensive investigation of this agent in experimental animals. Variable but distinct preferential uptake in nonosseous tumor tissue has been observed in 13 different types of tumor-bearing rats, mice, and hamsters; the highest was uptake in a hepatoma where the concentration in the tumor was approximately 10 times that in the liver, bone, and spleen. (Liver, bone, and spleen have the highest gallium uptakes of any normal tissues.) The concentration in this tumor was approximately 100 times that in muscle and blood. In comparing gallium-67 with other agents we find it to be superior to iodinated serum albumin, chlormerodrin (mercury), selenomethionine (selenium), indium, and bismuth in both its absolute affinity for tumor tissue as well as the ratios to normal tissues. Other workers have investigated those agents, labeled with appropriate radionuclides, as tumor indicators.

Our animal studies have mainly dealt with conditions that might lead to maximum localization of gallium in tumors. Factors have included: distribution with time; effects of size of the tumor, type and amount of chelating agent, amount of stable gallium given with the gallium-67, sex and age of the animal; and the influence of substances known to change the tissue distribution of gallium in normal animals. The uptake in tumor is complete by 24 hr and remains essentially constant for many days thereafter; small tumors reach higher concentrations than do large ones, possibly because of a better blood supply and because of less competing tumor tissue. The amount of solubilizing agent (citrate) in the dose appears to have little effect on the deposition. Strong chelates decrease the gallium in tumors and increase the excretion,but the ratios with normal tissues remain approximately the same, indicating that an ionic form is involved in the initial process. Stable gallium greatly decreased the localization of gallium-67 in tumor tissue as it also does in soft tissues (kidney excepted), explaining why little soft-tissue tumor localization occurred in previous clinical trials of gallium-72 where stable gallium was also given.

Of particular interest has been the discovery that the element scandium, a close neighbor to gallium in the periodic chart, in small amounts (0.5 mg/kg) causes gallium-67 to rapidly clear from normal tissues other than bone and kidney while producing no decrease in the retention in tumor. This leads to early (2 to 4 hr) elevated concentration ratios of tumor to nontumor tissue and may provide the basis for the use of the shorter-lived radionuclides of gallium (^{68}Ga, $T_{1/2}$ = 68 min; ^{66}Ga, $T_{1/2}$ = 9.5 hr)

in both diagnosis and possible therapy. A study of the toxicity of scandium is now in progress.

The mechanism(s) involved in the localization in tumor and nontumor tissue is not yet understood; in tumor-bearing animals deposition occurs mainly in living cells rather than in dying or necrotic tissue. Electron microscopic autoradiography and separating parts of cells with the zonal ultracentrifuge (in collaboration with the Molecular Anatomy Program at the Oak Ridge National Laboratory) indicate that the majority of the gallium-67 in tumor and nontumor cells is associated with submicroscopic particles that are similar in structure to lysosomes. Dialysis and ultrafiltration of soluble extracts of homogenized tumor tissue indicate that the gallium is bound to a large-sized molecule. Since gallium is known to bind to plasma proteins, it is possible that this molecule is a kind of protein, perhaps one of the hydrolytic enzymes present in lysosomes. The different effects produced by scandium on tumor and nontumor tissue suggest that the molecule(s) may be different from that present in nontumor tissue.

C. Radiation Dosimetry.

With these figures, one assumes the worst possible conditions; i.e., no excretion and 100% localization in the skeleton for the first figure and 100% uniform distribution with no excretion for the second. The radiation exposure resulting from the ^{67}Ga is calculated to be less than 2.1 rads/mCi to the skeleton and less than 0.4 rads/mCi to the whole body: that from ^{66}Ga will not exceed 0.05 rads/mCi to bone, and 0.007 rads/mCI to the whole body. Animal data and earlier human data obtained with other isotopes of gallium indicate at least 40% excretion within the first half-life and no more than 50% localization in the skeleton. More precise human data for this preparation is unavailable but is being obtained from the patients under study at ORAU.

D. References.

R. L. Hayes, et al. Bone scanning with gallium-68: A carrier effect. J Nucl Med 6: 605-610, 1965.

C. L. Edwards and R. L. Hayes. Tumor scanning with ^{67}Ga citrate. J Nucl Med 10: 103-105, 1969.

R. E. Hartman and R. L. Hayes. The binding of gallium by blood serum. J Pharmacol Exp Therap 168: 193-198, 1969.

R. M. Kniseley, et al. Bone-marrow and skeletal scanning. Radiologic Clinics of North America 7: 265-280, 1969.

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R. L. Hayes. Radioisotopes of gallium. IN Radioactive Pharmaceuticals, G. A. Andrews, R. M. Kniseley, and H. N. Wagner, Jr., Eds. AEC Symposium Series No. 6, CONF-651111, 1966, pp. 603-618.

T. Higasi, S. Suzuki, and A. Murata. Diagnosis of malignant tumor with ^{67}Ga-citrate. Jap Med J 2388: 37-40, 1970 (in Japanese).

T. Higasi, et al. Diagnosis of malignant tumor with ^{67}Ga-citrate (1st Report). Jap J Nucl Med 6: 217-226, 1969 (in Japanese).

E. Preparation of the Radionuclide.

Gallium-67 is produced by the Oak Ridge National Laboratory by proton bombardment of 99.99% pure zinc. After bombardment the center section ($\sim$6.5) of the tube target is cut free and dissolved in 75 ml of 10 M HCl ($\sim$7 M HCl after solution). Following filtration to remove any traces of oil, any ferric iron present is reduced to the ferrous state by adding 20% titanous chloride dropwise until the blue color of the titanous ion is maintained on standing for 10 minutes. The gallium activity is then extracted with peroxide-free isopropyl ether (peroxide removed by filtration through alumina). After 3 washes with 7 M HCl the gallium activity is back-extracted with 0.2 M HCl. This extract is then evaporated to dryness and the product taken up in 0.05 M HCl.

All of the radioactivity determinations are performed by the method described by Heath (Scintillation Spectrometry, 2nd ed., Vol. 1, USAEC Report IDO-16880-1, Idaho Operations Office, August 1964) using a 9.3-cm source distance from a calibrated 3 x 3-in. NaI(Tl) crystal detector coupled with a multichannel analyzer.

The ^{67}Ga is assayed using the 0.296 MeV photon (22 photons per 100 nuclear transformations). The contribution to the peak area from the 0.511 MeV annihilation photons of ^{66}Ga is subtracted using a ^{22}Na (β) source. The ^{66}Ga is assayed using the 0.511 MeV annihilation photon (114 photons per 100 nuclear transformations).

Purity of the gallium product is ascertained by examining the gamma spectrum using a Ge (Li) detector coupled to a multichannel analyzer. Spot tests are made for stable iron and zinc to insure that their levels are below 5μg/ml and 20 μg/ml respectively.

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II. Objectives and Specific Aims.

1. Lymphomas

To determine the percent of positive scans after administering ^{67}Ga to known cases of these disorders, the place of ^{67}Ga as an adjunct in staging (determine the extent of the disease), and the efficacy of ^{67}Ga as an indicator of response to therapy or need for additional therapy.

2. Lung Cancer

To determine the percent of positive scans with ^{67}Ga in the several kinds of carcinoma primary in the lung, whether ^{67}Ga is of value as an aid in planning therapy, to detect recurrence and metastases in patients under therapy, especially to demonstrate the need for further treatment, and to determine whether benign solitary lung lesions, suspected to be carcinoma, will concentrate gallium.

III. Materials and Methods.

A. Preparation of the Pharmaceutical

After separation and purification of the gallium-67 (II E.) sufficient sodium citrate (from commerical pharmaceutical sources is added to provide 0.1 to 0.5 mg of citrate per kilogram of body weight when the preparation is administered at a ^{67}Ga dose level of 35 microcuries per kilogram. The solution is made 1% (based on final volume) with respect to benzyl alcohol and the pH adjusted to 7.0 ± 0.2 using a pH meter and combination electrode. Sufficient sterile 0.9% saline is added to achieve the desired final volume. The solution is then micro-filtered through a sterile 0.22 micron filter into precapped and sterilized multi-entry vials. The filled vials will then be transferred immediately to the Medical Division and steam sterilized (15 minutes at 121° C). One vial will be tested for pyrogenicity and sterility. As a backup check, spot tests for iron and zinc will be repeated. ORAU Radiation Safety Office will confirm the ORNL assay, and the radionuclide purity of the preparation. They will then attach suitable labels, package the vials, and arrange for shipment to individual investigators.

B. Instrument Calibration (to be prepared by D. Ross and P. R. Bell)

All participants will use the P. R. Bell - D. Ross gallium phantom. These devices will be constructed in the Y-12 shop under the direction of the ORNL Medical Instrumentation group. The phantom design provides a rigorous test of the resolving capacity of the scanning system.

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Its essential features include a polyethylene reservoir that contains water as a scattering medium, and three movable compartments for solutions of gallium-67 that will allow one to say whether the system can see a small source placed close to a larger source of the same concentration per milliliter; the sources span a 1:1000 range of activity.

C. Lymphoma

1. Patient Selection.

New patients will be included if they have microscopic evidence of reticulum sarcoma or Hodgkin's disease and have had no previous treatment. Lymphocytic lymphosarcoma will not be included.

2. Initial Examination.

The initial examination will include the procedures necessary for staging the tumor along the guidelines recommended in the Rye Conference Proceedings and those described in Appendix A and B attached. A ^{67}Ga scan will also be done as part of the initial evaluation. It should be done prior to liver biopsy, either open or percutaneous, before laparotomy or scans with ^{85}Sr and ^{198}Au. It can be done after ^{99m}Tc colloid liver scan if the former is needed.

A separate group of patients would be those already in apparent remission from an earlier intensive course of therapy who could be scanned for occult disease.

3. Treatment.

The patients will be placed in treatment protocols offered at the individual institution, depending upon the stage of their disease.

4. Reevaluation.

A ^{67}Ga scan will be done within 4 weeks of the completion of radiation therapy for patients with Stage I, II, or III A disease. If residual disease is indicated by the scan, tissue confirmation will be obtained where possible and further therapy administered as indicated by the circumstances. Those patients with Stage III B or IV disease also will be scanned with ^{67}Ga 4 weeks after the completion of the initial combination therapy. If the scan indicates residual disease, this will be confirmed microscopically, and, if possible, other appropriate therapy given, e.g., local irradiation.

Patients in complete remission (no evidence of disease by ^{67}Ga scan or other criteria) will be scanned at 6 months, then yearly.

5. Reporting

The results of the initial evaluation will be reported in terms of the stage of the disease as judged by the scan alone, all other criteria alone, and both the scan and other criteria. Where differences occur, the location and evidence for tumor at each site will be recorded. A standard reporting form will be used by all participants. It will incorporate features of the anatomic grid used in the NIH "Solid Tumor Measurement Form" (NIH 442-3).

Data Collection.

Classification of Scans
Positive Scans (Pos). Those that show a statistically valid and clinically discernible focus of activity in an abnormal site.

Negative Scans (Neg). A normal scan from the standpoint of tumor, i.e., no abnormal foci of activity.

Uncertain Scans (Un). One in which it is uncertain whether the activity seen in a particular location is significantly different from normal. A 90-day follow-up should be made on all patients with equivocal scans in an effort to reclassify the scans retrospectively.

Evidence for Neoplasm.
The evidence for neoplasm at any anatomic site will be correlated with the interpretation for the scan to derive the classification of the scans. Evidence for neoplasm will be classified as:
Proven (Pr). A histologically proven tumor at the site in question, proven either by biopsy or at autopsy; Class V exfoliative cytology.

Apparent (App). A tumor for which there is substantial evidence but lacking histologic proof; e.g., X-ray evidence, palpable masses, tumors visualized at surgery or detected by other standard scanning procedures, such as brain scan, etc.

Suspected (Sus). Lesions lacking clear localizing evidence but suspected because of symptoms or biochemical abnormalities. Examples of this type are an enlarged liver with elevated alkaline phosphatase in a patient with a history of carcinoma of the colon; persistent pain in the hip of a patient with multiple myeloma.

Negative (Neg). This designation should be reserved for anatomic sites for which there is no evidence for neoplasm or definite evidence for the absence of tumor such as with a careful necropsy.

By integrating the three interpretations of the scans and four classes of evidence for tumor we have a possibility of 12 classifications for scans:

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		Evidence for Tumor			
		Proven	Apparent	Suspected	Negative
Scan	Positive	Pos - Pr	Pos - App	Pos - Sus	Pos - Neg
	Uncertain	Un - Pr	Un - App	Un - Sus	Un - Neg
	Negative	Neg - Pr	Neg - App	Neg - Sus	Neg - Neg

A standard data sheet will be completed for each study (dose) indicating the anatomic site, interpretation of the scan, apparent size of the lesion on the scan, classification and description of the evidence for neoplasm at each site.

The data sheets will be collected centrally and the data recorded for computer analysis.

Whenever available, quantitative tissue concentration data will be collected. The ratio of tumor concentration to that in blood, muscle, or other normal tissues will be correlated with scan findings.

6. Number of Patients.

Approximately 150 patients with Hodgkin's disease or reticulum cell sarcoma could be studied assuming an average of 3 to 5 doses for each subject. To minimize waste of the agent, distribution will be made to participants on the basis of suitable patients available for accession into the study. A sequential procedure will be established during the collection of data for statistical clues to permit termination of any sub-group. This "stopping rule" will protect us from continued collection of data in fruitless, false-negative groupings of patients.

Abnormal localization of gallium will be reported in follow-up scans, along with other evidence for recurring or residual tumor at each site in question.

Some patients will have a negative scan on the initial examination. These should be retained in the protocol and re-scanned at the appropriate times despite the tumor's failure to concentrate gallium initially. Whenever a ^{67}Ga scan indicates residual or recurrent tumor, this should be confirmed by histopathology.

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D. Lung Cancer

1. Patient Selection and Treatment Plan

Patients will be selected on the basis of clinical suspicion of lung cancer (radiologic evidence; symptomatology) who are candidates for surgical exploration. Also included will be patients with microscopic evidence of primary lung cancer (cytology, biopsy) who may be inoperable.

2. Initial Evaluation and Reevaluation

A ^{67}Ga scan will be done as part of the initial evaluation and at two-month intervals during and at least six months after treatment.

3. Reporting.

The scans will be reported individually for evidence of tumor localization and with other evidence at each site in question. All participants will adhere to a standard report form, and scans classified according to the schema in the previous section.

4. Number of Cases

With the amounts of radioactivity available, approximately 125 to 150 patients with lung cancer could be evaluated, if an average of four scan doses could be given each patient. Distribution would be carefully allocated among participants to insure minimum waste of the agent based on suitable subjects who could be accessioned into the study.

IV. Beginning Dates and Length of Study

We propose to initiate the program with a target date of February 1, 1971 or soon thereafter, depending on completion of arrangements with the various concerned parties.

The initial phase is aimed at a one-year period. Not all data on accessioned cases will be obtained during this time, and we expect that the results of our running analyses may oblige us to modify the protocol.

One of the first steps will be instrument standardization using the Bell-Ross gallium phantom. It has been suggested that early in the study, after an initial trial period, a work meeting should be arranged to hammer out any differences in individual approaches to the interpretation of scans and recording of data. These activities in themselves will require some time and to some extent delay full-scale operation of the project.

V. The Medical Division of Oak Ridge Associated Universities operates a biomedical program supported under a long-term operating contract with the U. S. Atomic Energy Commission. The AEC facilities, insofar as they may be required for work under this proposal, may be used only as the AEC may approve.

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APPENDIX A
(from NCI)

The Clinical Evaluation of Patients with Advanced Hodgkin's Disease

Initial examination of the patient might indicate the exact stage of the disease, however, the majority of patients require extensive radiographic and possibly surgical exploration to obtain the necessary information. The importance of staging in the treatment of the disease has been emphasized by many workers especially in the use of radiotherapy since the elimination of the disease from lymph node areas can be expected with supravoltage radiotherapy. The presence of disease in extranodal sites contributes to the failure of curative nodal radiotherapy, therefore, the search for cryptic involvement of parenchymal organs is warranted, lest extensive marrow-depressing doses of radiation limit the ability of such patients to receive chemotherapy. The success of combination chemotherapy in some patients with extensive disease especially when adequate dosage can be administered, has added importance to the stage process.

One of the most important features of the disease is the presence of systemic symptoms. These are primarily (1) pruritus, (2) night seats, (3) fever. Record should be made of other symptoms such as weight loss, fatigability, malaise, and anorexia. Anemia can occur, but it is uncertain as to its gravity. Patients possessing these symptoms are designated "B." Those without symptoms are designated "A."

The second aspect of staging refers to the anatomic extent of disease.

Stage I	--	single node bearing area involved
Stage II	--	two adjacent node areas
Stage III	--	disease above and below the diaphragm
Stage IV	--	extranodal involvement such as bone, liver, lung, marrow and skin

The third aspect of the staging process refers to the histology of the tumor according to the Lukes-Butler classification. The histologic features of the disease which merit emphasis include:

(a) extent of lymphocytosis in the node
(b) presence of fibrotic bands forming nodules -- so called nodular sclerosis
(c) anaplastic nature of the malignant reticulum cells

The radiographic studies are outlined in the protocol ST-7. Once the appropriate studies have been performed, each case is discussed formally at a Lymphoma Staging Conference which is attended by physicians, radiotherapists, pathologists, diagnostic radiologists and on occasion nuclear medicine, surgery and clinical pathology. Some patients have to be subjected to surgical exploration of suspicious thoracic lesions or isolated lymph nodes which have a lymphomatous pattern on lymphangiography.

The role of liver involvement in the natural history of the disease has been enigmatic. Therefore, patients with III B disease and abnormal liver studies receive percutaneous biopsy. The return from such a procedure has been disappointing in the past and at present peritoneoscopy has been employed as an alternative to open liver biopsy. The value of the latter is indeterminate at the present time.

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APPENDIX B
(from NCI)

LYMPHOMA STAGING CHECK LIST

I. H and P including standard chest X ray — check clinically involved areas.

Cervical
Supraclavicular
Mediastinum
Infraclavicular
Epitrochlear
Axillary
Ilio-inguinal
Femoral
Popliteal
Spleen
Fever
Night sweats
Pruritis
Weight loss greater than 10%

II. X-ray studies
Chest
IVC with IVP
Lymphangiogram
Whole chest tomograms
Metastatic series

III. Isotope studies
Liver scan with ^{99m}Tc if liver function is abnormal or patient has hepatomegaly. (Bone scan ^{85}Sr. If performed, after ^{67}Ga scan only. Note the ^{67}Ga scan could serve for bone scanning in lieu of ^{85}Sr.)

NAME: AGE:
SEX:

IV. Bone-marrow biopsy

Lymphoma Staging Check List

V. Liver chemistries
Alkaline phosphatase
SGOT
LDH
Thymol turbidity
BSP
Total bilirubin
Prothrombin time

VI. Liver biopsy - percutaneous
All patients with hepatomegaly (should have scan first)
All patients with any abnormality of alkaline phosphatase, BSP, thymol turbidity or SGOT

VII. Liver biopsy - open
All patients with two function abnormality and negative percutaneous biopsy, unless clinically contra-indicated.

VIII. Final stage

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APPENDIX C

Draft
10/5/70
Exec. Comm.

CONSTITUTION AND BYLAWS FOR THE COOPERATIVE GROUP TO STUDY LOCALIZATION OF RADIOPHARMACEUTICALS

I. Name and Purpose

The Cooperative Group to Study Localization of Radiopharmaceuticals, hereinafter called the "Group," is an organization of specialists in nuclear medicine organized under the auspices of Oak Ridge Associated Universities (ORAU) for the purpose of carrying out cooperative efforts for the evaluation of various radiopharmaceuticals. At its inception, the primary interest is in those agents that localize in neoplasms with the objective of improving the diagnosis and treatment of cancer.

II. Membership

1. Membership lies with the Investigator at the designated institution. In the event of moves, the Investigator, from his new institution, and his successor each may apply for membership. The Membership of the Group shall consist initially of the following Investigators and participating institutions:

Richard S. Benua	Memorial-Sloan Kettering
F. J. Bonte	Southwestern Medical School
Charles M. Boyd	University of Arkansas
A. B. Brill	Vanderbilt University
Frank DeLand	University of Florida
C. Lowell Edwards	Oak Ridge Associated Universities
Ben I. Friedman	University of Tennessee
Robert H. Greenlaw	Marshfield Clinic
John K. McBain	University of Louisville
David Preston	University of Kentucky
Joseph V. Schlosser	Charity Hospital - Tulane University
Alton R. Sharpe, Jr.	Virginia Commonwealth University
Carl W. Smith	University of Oklahoma
Charles D. Teates	University of Virginia
Morton B. Weinstein	University of Miami
Robert A. Wilkinson	Duke University
Joseph B. Workman	University of Maryland

2. Additional investigators who are experienced in radiopharmaceutical research and whose institutions have adequate facilities and wish to participate in the work of the Group, may be admitted to membership in the Group on application to the Secretary, subsequently on recommendation of the Executive Committee, and then by a majority vote of the membership.

3. Membership in the Group may be terminated by resignation, or upon recommendation of the Executive Committee confirmed by a majority vote of the membership at its next regular meeting.

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4. In addition to the Member, each institution may be represented by an Associate Member designated by the Member and elected by the Group on recommendation of the Executive Committee.

5. The Executive Committee may elect other individuals who have a specific interest in the work of this Group as Collaborators.

III. Officers and Executive Committee

Elected officers shall be a Chairman and a Vice-Chairman. Subject to the approval of the Executive Committee, ORAU shall appoint a Secretary. ORAU will provide the Secretariat for the Group. The Executive Committee shall consist of the above mentioned officers and 4 members elected at large. The members at large shall be from different institutions. The term of service on the Executive Committee shall be three years without restriction of reelection.

IV. Election of Officers and Members of the Executive Committee

Prior to the expiration of any term of office or vacancy of any office, a Nominating Committee consisting of three members shall be appointed by the Chairman with the approval of the Executive Committee. Members of the Executive Committee shall not be eligible for service on the Nominating Committee. The Nominating Committee shall compile a list of one or more members who are qualified for each position and have signified willingness to serve in that capacity if elected by the Group.

The nomination(s) will be mailed to all members of the Group at least three weeks prior to the meeting at which elections are scheduled. Nominations may be made from the floor at time of election. Election of members of the Executive Committee shall be by secret ballot at the time of election or submitted in advance as an absentee ballot. The absentee ballot will be by double envelop method with the outer envelope identifying the member.

The candidate receiving a majority of the votes cast by each voting member shall be declared elected. If no nominee receives a majority on the first ballot, there shall be a run-off election between the two nominees receiving the most votes. A majority shall be deemed sufficient to elect the officers.

V. Duties and Powers of Officers

1. The CHAIRMAN shall be the chief executive officer of the Group. He shall call and preside at meetings of the Group and Executive Committee, and shall represent the Group at meetings affecting the business or interests of the Group. He shall report to the Executive Committee and to the Group whatever appropriate information shall come to him as executive officer. He may establish ad hoc committees or appoint individuals for specific purposes and delegate proper authority to such committees or individuals.

2. The VICE-CHAIRMAN shall act as Chairman whenever requested to do so by the Chairman of the Group and whenever the Chairman is unable to act as such.

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The Vice-Chairman will assist the Chairman in carrying out the duties of the Chairmanship.

3. The SECRETARY shall be responsible for keeping a written record of all meetings of the Group and the Executive Committee for timely distribution to all Group members. He shall prepare required reports of progress of the Group. He shall be responsible for coordinating the work of the Group. Personnel and facilities of ORAU will be available as necessary to provide a Secretariat for the Group.

VI. Duties and Powers of the Executive Committee

1. The Executive Committee shall have the authority to act for the Group on all matters except those reserved to the Chairman. The Executive Committee shall consider and recommend new policies or changes in existing policies of the Group. It shall consider and make recommendations concerning new clinical protocols and ancillary studies although final approval is reserved for action of the Group membership. It shall assist the Chairman in preparation of necessary reports and in the evaluation of manuscripts derived from Group efforts. It may recommend termination of memberships, project chairmanships, and committee assignments. The Executive Committee shall have the responsibility to investigate prospective new members and institutions who have submitted applications for membership and shall make recommendations to the membership. It may serve as a grievance committee and act upon complaints from members.

2. The Executive Committee shall act upon and approve all applications to be submitted by ORAU to government agencies or foundations for grants or contracts to be made with ORAU in support of the work of the Group. ORAU will make disbursements from such funds in accordance with policies established by the Executive Committee. ORAU will make regular financial reports to the Executive Committee on the status and use of all funds it has received in support of the work of the Group.

3. The Executive Committee is responsible to the Group for all of its deliberations and actions at each meeting of the Group. Actions by the Executive Committee may be censured or overridden by a two-thirds majority of all members eligible to vote at any duly called meeting of the Group.

VII. Voting

On all matters concerning Group administration or research activities, each Member and Associate Member present at the meeting is entitled to one vote. Guests and Collaborators shall not vote. A simple majority of votes cast is required for approval of all matters, unless otherwise specified in this Constitution and Bylaws.

The Group Chairman may designate the applicable voting procedure for any issue under consideration by the membership except for election of Officers and members of the Executive Committee.

VIII. Meetings

The Group will meet semi-annually or more frequently at a place and date designated by the Chairman.

IX. Operating Policies

1. Policies will be delineated in the body of each protocol, including publications policy, principal investigator, participating collaborators, and relevant matters.

2. Members are free to decline from participating in any specific protocol.

3. Data generated within the protocol will be published as a Group communication. Separate publications by individual investigators utilizing data derived from the studies will require approval of the Executive Committee.

4. The Group will require assurance to protect the rights of individuals as research subjects.

X. Amendments

Any member may propose an amendment to this Constitution and Bylaws by submitting the amendment in writing to the Secretary. The Secretary will circulate the proposed amendment of the membership at least 3 weeks prior to the next meeting. A majority of votes cast, including absentee ballots, is necessary to adopt the amendment.

1037822

Participants in Lymphoma and Lung Cancer Protocol

INSTITUTION	PARTICIPANTS
NIH Clinical Center NCI Baltimore Cancer Research Center	Dr. Gerald Johnston, Dr. Paul Carbone Dr. M. D. Walker
NCI-WVAH Medical Oncology Section	Dr. B. J. Sauerbrunn, Dr. Oleg Selawry
Charity Hospital - Tulane University	Dr. Joseph V. Schlosser, Associate Director, Therapeutic Radiology
Duke University School of Medicine	Dr. Robert A. Wilkinson, Jr. Assistant Professor of Radiology Division of Nuclear Medicine
Marshfield Clinic	Dr. Robert H. Greenlaw Chief of Nuclear Medicine
University of Arkansas School of Medicine	Dr. Charles M. Boyd, Associate Director Nuclear Medicine Division
University of Florida College of Medicine	Dr. Frank Deland Chief of Nuclear Medicine
University of Kentucky College of Medicine	Dr. David F. Preston, Assistant Professor Radiology and Nuclear Medicine
University of Louisville School of Medicine	Dr. John K. McBain, Director Nuclear Medicine
University of Maryland School of Medicine	Dr. Joseph B. Workman Associate Professor of Medicine Director of Nuclear Medicine
University of Miami School of Medicine	Dr. Morton B. Weinstein, Assistant Professor Radiology and Medicine
University of Oklahoma School of Medicine	Dr. Carl W. Smith, Director Section of Nuclear Medicine
University of Tennessee College of Medicine	Dr. Ben I. Friedman, Head Section of Nuclear Medicine
University of Virginia School of Medicine	Dr. Charles D. Teates Assistant Professor of Radiology
Vanderbilt University School of Medicine	Dr. A. B. Brill, Director Division of Nuclear Medicine
Virginia Commonwealth University (Medical College of Virginia)	Dr. Alton R. Sharpe, Jr., Chairman Division of Nuclear Medicine
Oak Ridge Associated Universities Medical Division	Dr. C. Lowell Edwards, Chief Clinical Research

1037823

TO : STAFF REVIEWERS LIS D BELOW DATE: Sept. 18, 1970

FROM : Ralph Elson, Director, Contract Division

SUBJECT: CONTRACT (OR SUBCONTRACT) ACTION FOR STAFF REVIEW

The contract (or subcontract) action briefly described below with supporting documents are submitted herewith for your staff review ~~under the alternate review procedures authorized by ORPI 9-51.403.2.~~ Upon completion of your review, check your recommendation for either approval or disapproval, initial in the space provided, attach any comments you may have, and forward to next in turn. On prime contract actions, also place your initials in the space provided on the attached file copy of the contract document. Expeditious handling of your review will be appreciated.

DESCRIPTION OF ACTION FOR REVIEW:

Modification No. 17 to Contract No. AT-(40-1)-2401 with Vanderbilt University

NAME OF REVIEWER	DIVISION	RECOMMEND (✓) APPROVAL	RECOMMEND (✓) DISAPPROVAL	INITIALS	DATE
~~D. E. Miller~~	~~Contract~~	✓		DEM	9/18
~~A. E. Miller~~	~~Budget~~	✓		AEM	9/21
~~C. S. Shoup~~	~~Lab. & Univ.~~	✓		CSS	9/22
~~W. H. Henderson~~	~~Finance~~				9/23

RETURN TO Alice Brown Contract Division Tel.: 3-4107

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Routed by

LABORATORY AND UNIVERSITY DIV.

Form OR-133 (Rev. Oct. 1968)

ROUTE SLIP

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- [ ] Deputy Manager
- [ ] Assistant to Manager for Pub. Infor.
- [ ]

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- [ ] Patent Group

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- [ ] SAFETY DIVISION
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- [ ] Government Payroll Sect.
- [ ] Audit Branch
- [ ]

- [ ] ORGANIZATION & PERSONNEL DIV.
- [ ] Government Personnel Branch
- [ ] Industrial Personnel Branch
- [ ] Organization & Management Branch
- [ ] Equal Opportunity Branch

- [ ] SUPPLY DIVISION
- [ ] Office Services Branch
- [ ] Supply & Maintenance Section
- [ ] Reproduction & Distr. Unit
- [ ] Stores Unit
- [ ] Mail Section
- [ ] Photographic Services
- [ ] Records Center
- [ ] Records Officer
- [ ] Teletype Section
- [ ] Property Branch
- [ ] Transportation Branch
- [ ]

- [ ] SECURITY DIVISION
- [ ] Personnel Security Branch
- [ ] Physical Security Branch
- [ ] AEC Patrol
- [ ]

- [ ] CINCINNATI AREA OFFICE
- [ ]
- [ ]

- [ ] NEW BRUNSWICK AREA OFFICE

- [ ] PADUCAH AREA OFFICE

- [ ] PORTSMOUTH AREA OFFICE

- [ ] PUERTO RICO AREA OFFICE

- [ ] DIVISION OF TECHNICAL INFORMATION EXT.
- [ ] Office of Ext. Manager
- [ ] Ass't. Ext. Mgr. for Adm. Ser.
- [ ] Ass't. Ext. Mgr. for Pro. Ser.
- [ ] Ass't. Ext. Mgr. for Sci. Comm.
- [ ] Science & Tech. Branch
- [ ] Tech. Services Branch
- [ ] Ass't. Ext. Mgr. for Comp. Processes & Mfg.
- [ ] Editorial Branch
- [ ] Graphics Arts Branch
- [ ] Printing Branch
- [ ] Ass't. Ext. Mgr. for Doc. & Systems Dev.
- [ ] Document Mgmt. Branch
- [ ] Computer Operations Br.
- [ ]
- [ ]
- [ ]
- [ ]
- [ ]
- [ ] RDT-OSR (ORNL)
- [ ]
- [ ] RDT-OSR (GE-Evendale)
- [ ]
- [ ] RDT-OSR (BONUS)

- [ ] CONTROLLER REGIONAL AUDIT STAFF

- [ ]
- [ ]
- [ ]
- [ ]

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ CONCURRENCE *A Gmelich for*
2. CONTRACT DIVISION ~~CONCURRENCE~~ *A E Johnston*
3. ASSISTANT GENERAL COUNSEL ACTION

USAEC Division of Technical Information Extension, Oak Ridge, Tennessee

3329

1037825

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

AUG 18 1970

Ralph Elson, Director Contract Division

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: AT-(40-1)-2401
   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 APPLICATION OF ACTIVATION ANALYSIS

3. Type of Contract:

   [X] Support Agreement [[Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by this CA: $74,750.00

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: 86%

6. Description of Other Changes To Be Covered by This CA:

   Modify contract to provide for the performance of additional research to be completed during the period 8-1-70 - 7-31-71. Increase the AEC support ceiling from $37,375 to $112,125. Title to equipment shall vest in the contractor under authority of the AEC Act of 1954. Title to the following government furnished items of equipment will remain with the Government: Card reader, 717 printer, printer control, card reader control.

7. Authority:
   Form AEC-481 (CA) fr J. R. Totter dated July 23, 1970.

Herman M. Roth
Herman M. Roth, Director
Laboratory and University Divisior

OLE:LM

5117

103782b

Form AEC-481
(6-67)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
JUL 23 1970 John R. Totter	BM-71-34

3.A. TO S. R. Sapirie, Manager
Oak Ridge Operations Office

3.B. FROM John R. Totter, Director
Division of Biology & Medicine

4.A. CONTRACTOR *(Name, Address, Department, etc.)*
VANDERBILT UNIVERSITY
Nashville, Tennessee

4.B. PRINCIPAL INVESTIGATOR(S)
A. BERTRAND BRILL

5. ☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER

6. TERM OF CONTRACT 8-1-70 thru 7-31-71

7. CONTRACT NUMBER (40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☐ FIXED PRICE ☐ OTHER
☐ COST REIMBURSEMENT
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)

9. EQUIPMENT TITLE TO VEST IN:
☐ AEC
☒ CONTRACTOR

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE RADIOISOTOPE STUDIES UTILIZING A LOW-LEVEL WHOLE BODY COUNTER AND CLINICAL APPLICATION OF ACTIVATION ANALYSIS

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen Wweyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 74,750
Estimated AEC Balance From Prior Term, if any	$
	$ 74,750
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$ *
Estimated Project Cost, For Pertinent Budget Period	$

Budget and Reporting Classification: 06-03-01

Allotment Transfer: 06-11-91(24)

B. PLANT AND CAPITAL EQUIPMENT ..... $

Budget and Reporting Classification:

Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

*To be determined.

15. SCOPE OF WORK

1. Measurement of radiation absorbed dose due to medical use of radionuclides.
2. Use of stable isotopes in metabolic studies.

B 6211

1037827

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

1037828

(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.

TO : Addressees Listed Below DATE: April 3, 1970

FROM : Ralph Elson, Director, Contract Division

SUBJECT: CONTRACTUAL DOCUMENTS 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 16 to Contract AT-(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. A. E. Johnston	~~Contract~~		4/3/70	
2. A. E. Miller	Budget		4-3	
3. ~~E. S. Shoup~~	~~Lab. & Univ.~~		4-6	
4. W. H. Henderson	Finance		4/8	
5.				
6.				
RETURN TO: Alice Brown	Contract Division			Tel.: 3-4107

1037830

Routed by:

LABORATORY AND UNIVERSITY DIV.

Form OR-133 (Rev. Oct. 1968)

ROUTE SLIP

File numbe.

	MANAGER
	Deputy Manager
	Assistant to Manager for Pub. Infor.

	CHIEF COUNSEL
	Patent Group

	ASST. MANAGER FOR OPERATIONS

	OPERATIONAL PLANNING & POWER DIVISION

	SAFETY DIVISION
	Health & Nuclear Safety Br.
	Ind. Safety & Fire Protection Br.
	Reactor Safety Branch

	LABORATORY & UNIVERSITY DIV.
	Research Contracts Branch
	Reactor Contracts Br.
	Administrative Services Br.

	PRODUCTION DIVISION
	Operations Branch
	Development Branch
	Materials & Enriching Services Br.
	Nuclear Materials Control Br.
	Weapons Branch

	ASST. MGR. FOR CONST. & ENGRG.

	CONSTRUCTION DIVISION
	Administrative Branch
	General Construction Branch
	Special Projects Branch

	ENGINEERING DIVISION
	Design Coordination Branch
	Power and Communications Branch
	Reports and Control Branch

	ASST. MGR. FOR ADMINISTRATION

	BUDGET AND REPORTS DIVISION
	Budget Analysis Branch
	Funds Control & Reports Branch

	CONTRACT DIVISION

	FINANCE DIVISION
	Systems & Cost Analysis Br.
	Accounting Branch
	Acct. Payable & Travel Sect.
	ADP Service Center
	General Ledger Section
	Government Payroll Sect.
	Audit Branch

	ORGANIZATION & PERSONNEL DIV.
	Government Personnel Branch
	Industrial Personnel Branch
	Organization & Management Branch
	Equal Opportunity Branch

	SUPPLY DIVISION
	Office Services Branch
	Supply & Maintenance Section
	Reproduction & Distr. Unit
	Stores Unit
	Mail Section
	Photographic Services
	Records Center
	Records Officer
	Teletype Section
	Property Branch
	Transportation Branch

	SECURITY DIVISION
	Personnel Security Branch
	Physical Security Branch
	AEC Patrol

	CINCINNATI AREA OFFICE

	NEW BRUNSWICK AREA OFFICE

	PADUCAH AREA OFFICE

	PORTSMOUTH AREA OFFICE

	PUERTO RICO AREA OFFICE

	DIVISION OF TECHNICAL INFORMATION EXT.
	Office of Ext. Manager
	Ass't. Ext. Mgr. for Adm. Ser.
	Ass't. Ext. Mgr. for Pro. Ser.
	Ass't. Ext. Mgr. for Sci. Comm.
	Science & Tech. Branch
	Tech. Services Branch
	Ass't. Ext. Mgr. for Comp. Processes & Mfg.
	Editorial Branch
	Graphics Arts Branch
	Printing Branch
	Ass't. Ext. Mgr. for Doc. & Systems Dev.
	Document Mgmt. Branch
	Computer Operations Br.
	RDT-OSR (ORNL)
	RDT-OSR (GE-Evendale)
	RDT-OSR (BONUS)

	CONTROLLER REGIONAL AUDIT STAFF

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. ~~BUDGET AND REPORTS DIVISION~~ ~~CONCURRENCE~~ [signature]

2. ~~CONTRACT DIVISION~~ ~~CONCURRENCE~~ [signature]

3. ASSISTANT GENERAL COUNSEL ACTION

1144

1037831

USAEC Division of Technical Information Extension, Oak Ridge, Tennessee

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P.O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

MAR 24 1970

Ralph Elson, Director, Contract Division

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:

   [XX] Modification of Contract
   Number: AT-(40-1)-2401
   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 APPLICATION OF ACTIVATION ANALYSIS

3. Type of Contract:

   [XX] Support Agreement [ ] Cost Type [ ] Other

4. Amount of AEC Funds To Be Obligated by This CA: $37,375

5. AEC Percentage of Est. Total Cost To Be Shown by This CA: 86%

6. Description of Other Changes To Be Covered by This CA:

   See Attachment "A"

7. Authority:

   Form AEC-481 (CA) fr J. R. Totter dtd 2-6-70.

   Herman M. Roth
   Herman M. Roth, Director
   Laboratory and University Division

OLE: LM

4999

1037832

VANDERBILT UNIVERSITY CONTRACT NO. AT-(40-1)-2401

ATTACHMENT "A"

Modify contract to provide for the performance of additional research to be completed during the period February 1, 1970 through July 31, 1970. The AEC support ceiling for theextended period is $37,375.

Title to equipment shall vest in the contractor under authority of the AEC Act of 1954 since the contractor's contribution is expected to equal or exceed the value of the equipment.

Also provide for vesting title to the following items of equipment in the contractor:

Eight Crystals NAI (Tl), 1-1/2" x 1/2
Eight Photomultiplier Tubes

Title to the following government furnished items of equipment will remain with the Government:

Card Reader
717 Printer
Printer Control
Card Reader Control

1037833

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.

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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.

1037837

Form AEC-481
(6-67)

AECPR 9-4.51

U. S. ATOMIC ENERGY COMMISSION

CONTRACT AUTHORIZATION

1. DATE	2. AUTHORIZATION NO.
FEB 6 1970	BM-70-357A

3.A. TO
S. R. Sapirie, Manager
Oak Ridge Operations Office

3.B. FROM
John R. Totter, Director
Division of Biology and Medicine

4.A. CONTRACTOR *(Name, Address, Department, etc.)*
VANDERBILT UNIVERSITY
Nashville, Tennessee

4.B. PRINCIPAL INVESTIGATOR(S)
A. BERTRAND BRILL

5. 6 mo. extension
☐ NEW CONTRACT ☐ RENEWAL ☒ OTHER

6. TERM OF CONTRACT
2-1-70 thru 7-31-70

7. CONTRACT NUMBER
AT(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☐ FIXED PRICE ☐ OTHER
☐ COST REIMBURSEMENT
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)

9. EQUIPMENT TITLE TO VEST IN:
☐ AEC
☒ CONTRACTOR

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by AEC Manual Appendix 3401.

11. PROJECT TITLE "RADIOISOTOPE STUDIES UTILIZING A LOW-LEVEL WHOLE BODY COUNTER AND CLINICAL APPLICATION OF ACTIVATION ANALYSIS"

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New AEC Funds	$ 37,375
Estimated AEC Balance From Prior Term, if any	$
	$ 37,375
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$
Estimated Project Cost, For Pertinent Budget Period	$ 37,375

Budget and Reporting Classification: 06 10
Allotment Transfer: 06 01 91 (24)

B. PLANT AND CAPITAL EQUIPMENT ..... $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:

The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the AEC funds shall be used to confer a fellowship.

Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.

If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

This C/A cancels and supersedes BM-70-357 dated 2/2/70.

15. SCOPE OF WORK

1. Measurement of radiation absorbed dose due to medical use of radionuclides.
2. Use of stable isotopes in metabolic studies.

B 1036

FEB 9 1970

1037838

STANDARD FORM 122
OCTOBER 1963
PRESCRIBED BY
GSA REG. 1-111-303.05
122-103

TRANSFER ORDER
EXCESS PERSONAL PROPERTY

1. ORDER NO. 70444

2. DATE 2-18-70

3. TO: GENERAL SERVICES ADMINISTRATION
UTILIZATION AND DISPOSAL SERVICE
PERSONAL PROPERTY DIVISION

4. ORDERING AGENCY (Full name and address)
U. S. Atomic Energy Commission
Oak Ridge Operations Office
Post Office Box E
Oak Ridge, Tennessee 37830

5. HOLDING AGENCY (Name and address)
U. S. Atomic Energy Commission
Savannah River Operations Office
Aiken, South Carolina

6. SHIP TO (Consignee and destination)
U. S. Atomic Energy Commission
c/o Vanderbilt University
Nashville, Tennessee

7. LOCATION OF PROPERTY
Vanderbilt University
Nashville, Tennessee

8. SHIPPING INSTRUCTIONS
Transfer in Place.

9. ORDERING AGENCY APPROVAL
SIGNATURE R. M. McGlasson
DATE 2-18-70
TITLE Supply Officer

10. APPROPRIATION SYMBOL AND TITLE

11. ALLOTMENT

12. GOVERNMENT B/L NO.

13. PROPERTY ORDERED

GSA AND HOLDING AGENCY NOS. (a)	ITEM NO. (b)	DESCRIPTION (Include noun name, FSC Group and Class, Condition Code and, if available, Federal Stock Number) (c)	UNIT (d)	QUANTITY (e)	ACQUISITION COST UNIT (f)	ACQUISITION COST TOTAL (g)
		The following property presently on loan from duPont to Vanderbilt is to be permanently transferred per phone R. M. McGlasson, OR to Hugh Gasque, SR.				
	1.	Crystals NAI (Tl), 1-1/2" x 1/2".	Ea.	8	$40.00	$320.00
	2.	Photomultiplier Tube.	Ea.	8	59.83	478.64
		TOTAL				$798.64

For Use on Contract AT-(40-1)-2401

Packing and loading charges incurred by other Government Agencies (or their Agents) not exceeding 5% of acquisition cost, will be paid by: NOT APPL.

14. GSA APPROVAL — SIGNATURE — TITLE — DATE

FOR GSA USE ONLY — AGENCY AND LOCATION: AGENCY — STATE — FSC — CONDITION — SOURCE CODE

CC: General Ledger Section
Lab & Univ. Div. (6)

☆ U. S. GOVERNMENT PRINTING OFFICE: 1964-710-071

1037839

REVISED BUDGET
U. S. ATOMIC ENERGY COMMISSION CONTRACT # AT-(40-1)-2401
in response to telegram C. S. Shoup 2/11/70
$37,375 new AEC funds through July 31, 1970

	AEC	University	Total
1. Salaries & Wages Name, Title, Monthly rate, % Effort			
Principal Investigator: A. B. Brill, M.D., Ph.D., [redacted] Assoc. Professor, Medicine & Radiology @2,017--2,118, 25%	3,027		3,027
Co-Investigator: R. E. Johnston, Ph.D., Asst. Professor Radiology, salary support Veterans Administration, 50%			
Senior Investigator--Activation Analysis: N. C. Dyer, @1,050--1,102, 54-56%	3,453		3,453
Research Associates:			
C.O.T. Ball, Biostatistics @716-752, 35-23%	1,424		1,424
H.A. Davies, Ph.D., Nuclear Medicine Post-doctorate fellow, salary support not included, proportionate sharing, 25%			
J.J. Erickson, Radiation Physics, @917-962, 42-50%	222	2,300	2,522
J.E. Lagan, Electronics Engineer, @797-874, 20-25%	200	1,000	1,200
L.C. McKee, M.D., Asst. Prof., Medicine, Salary support not included, proportionate sharing, 5%			
E.V. Staab, M.D., Asst. Prof., Radiology Salary support not included, proportionate sharing, 25%			
E.G. Stant, Ph.D., Radiobiology, @919-965, 19%		1,058	1,058

037840

	AEC	University	Total
Junior Investigators, Graduate Students: J.A. Patton, Hertz Foundation Fellow, 50% J. Watts, @630, February, 100%	630		630
Secretary--J.E. Sterling, 2.45-2.59/hr., 100%	2,591		2,591
Secretary--Special Services, @2.25/hr.	200		200
Radioisotope Operations Technician, R. Bowen @2.28/hr., 100%	2,371		2,371
Undergraduate student--part time	108		108
TOTAL SALARIES	14,226	4,358	18,584
Fringe benefits (not fixed % of salaries Varies with employee status & option) assigned personnel	1,144	224	1,368
TOTAL SALARIES & FRINGE	15,370	4,582	19,952
2. Supplies & Materials			
Computer supplies & time	3,000		3,000
Electronic components	2,500		2,500
Maintenance contracts, equipment rental	1,891		1,891
Radioisotopes	1,500		1,500
Stable Isotopes & Chemicals	2,000		2,000
Subject Participation	500		500
TOTAL	11,391		11,391
3. Equipment Co-axial Ge(Li) detector--3 kev resolution & 5% efficiency to replace ^{60}Co (exchange price--to replace current lower sensitivity detector as described Renewal Application)	4,000		4,000
4. Publications & Copying	100		100
5. Travel to Reactor for Activation & analysis of short-lived materials & to meetings for exchange of scientific information	750		750
6. Other	NONE		NONE
7. Indirect Costs = 37.5% salaries & fringe assigned personnel DCAA '65-66 provisional rate.	5,764	1,718	7,482.
TOTAL PROJECT COSTS	37,375	6,300	43,675

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Percentage & Amount	Vanderbilt University	14.4%	6,300
" & "	AEC	85.6%	37,375

AUTHENTICATION

A. Bertrand Brill, M. D.
Principal Investigator

Leon W. Cunningham
Associate Dean for Biomedical Sciences

William W. Force
Vice-Chancellor for Business Affairs

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EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

AEC Contract AT-(40-1)-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 37203

October 31, 1969

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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

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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.

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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:

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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;

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(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.

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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.

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)
RESEARCH AND DEVELOPMENT DIVISION

VANDERBILT UNIVERSITY

BY: William W. Force
William W. Force
TITLE: Vice-Chancellor for Business Affairs

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

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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

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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.

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(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.

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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.

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(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).

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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).

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(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

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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

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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.

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(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.

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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).

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(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

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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

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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

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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

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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.

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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:

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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;

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(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.

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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.

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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

HERMAN M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R R Purdy

Dr. R. R. Purdy

TITLE: Vice-Chancellor

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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

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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

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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.

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(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.

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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.

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(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).

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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).

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(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

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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

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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.

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(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.

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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).

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(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

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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

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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

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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

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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.

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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:

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a. Employees of the Contractor engaging in employment by activities

[redacted]

(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.

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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"

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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

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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. Furay

Dr. R. R. Furay

TITLE: Vice-Chancellor

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.

(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.

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

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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

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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.

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(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.

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(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,

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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.

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(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

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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

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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.

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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.

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(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.

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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.

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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.

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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.

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(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

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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.

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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

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elects to terminate performance the provisions of this contract respecting termination for the convenience of the Government shall apply.

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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:

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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;

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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.

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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.

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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.

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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 M. ROTH
DIRECTOR
RESEARCH AND DEVELOPMENT DIVISION
(Contracting Officer)

VANDERBILT UNIVERSITY

BY: R. R. Purdy

TITLE: R. R. PURDY
VICE CHANCELLOR

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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.

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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

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"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.

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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.

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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.

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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).

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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.

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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

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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.

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

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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.

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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.

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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.

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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.

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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".

"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

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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

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(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

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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.

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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:

(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.

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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

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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

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.

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

R. T. Lagemann

Senior Investigator

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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

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(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

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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.

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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.

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.

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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.

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.

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)."

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."

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: Lloyd W. Rittenhouse

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	

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(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 20th 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."

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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."

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.

"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: _____

A. A. Johnston

Acting Director, Contract Division, OROO

(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

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

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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:

1037044

"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

HERMAN M. ROTH
DIRECTOR
RESEARCH 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.

Geo. R. Hamed
Senior Investigator

Robert T. Lagemann
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

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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

1037047

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).

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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

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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,

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:

VANDERBILT UNIVERSITY

BY: Frank L. Humphreys

TITLE: Vice Chancellor

(Address)

(Address)

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.

George R. Mitchell
Senior Investigator

R. T. Lagemann
Senior Investigator

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**

1037054

*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.

1037055

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.

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.

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.

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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.

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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.

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(R)

OFFICE OF CHIEF COUNSEL
CONTRACT FILE
REMOVAL OF PAPERS FROM
THIS FILE IS PROHIBITED

BACK UP

VANDERBILT UNIVERSITY

CONTRACT NO. DE-AS05-76ER-02401

RETURN TO CONTRACT FILES

BOOK IV BEGINNING WITH MOD 27

1037066

17/8

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. E. 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 Files
1 Copy - Contract Administrator
1 Copy - Budget
1 Copy - Finance
1 Copy - Patents Group
2 Copies - HQS Program Office

1037067

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

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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

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(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 .

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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".

1037071

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

1037072

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V. Scientific Scope

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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

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d. Sharing of Computer Programs in Nuclear Medicine

e. ORIS-11 Evaluation

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Appendix I - Pho/Con Interface

Appendix II - Deconvolution Information Flow Software System

Appendix III - Software System for Quantitative Scanner

1037074

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.

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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

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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.

1037077

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.

1037078

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,

1037079

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.

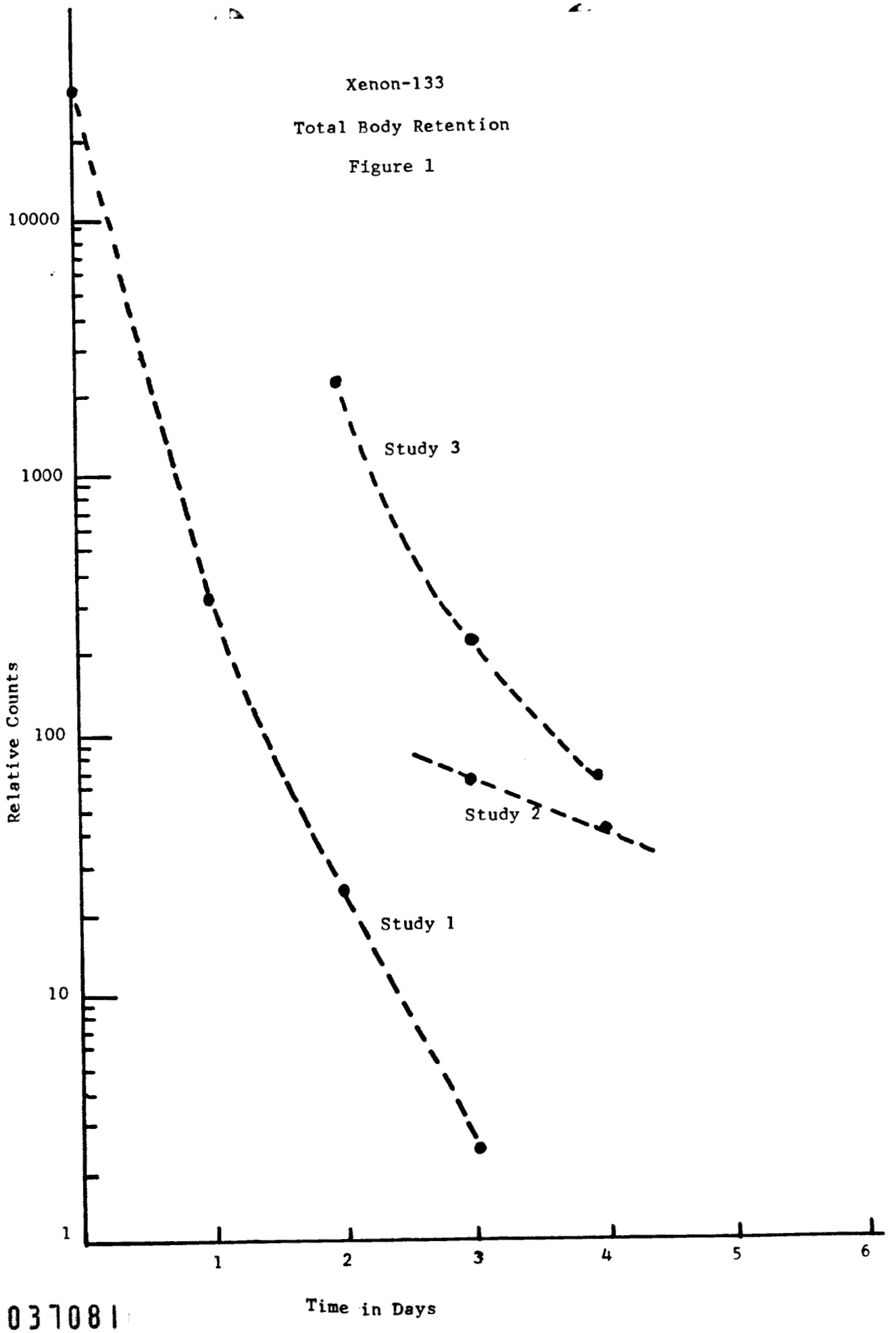
The total-body scanner system that will be configured about the position sensitive proportional detectors on loan from Oak Ridge National Laboratory (see Section B.1.d.) will be evaluated for possible use in this project.

1037080

Xenon-133

Total Body Retention

Figure 1



1037081

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

1037082

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.

1037083

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

1037084

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. Bill, Vanderbilt: He indicated reduction should be made in "other direct costs."

Ogilvie

11-24-78

1037085

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. Galde ✓
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 F Buchanan
SIGNATURE

11/21/78
DATE

1037086

m 028

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

☐ GRANT ☒ CONTRACT ☐ FELLOW ☐ OTHER

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☒ ORIGINAL ☐ FOLLOWUP ☐ REVISION

☐ 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.

1037081

AUGUST 1978

U. S. DEPARTMENT OF ENERGY

PROCURE /FINANCIAL ASSISTANCE REQUEST - HORIZATION

. TO Hart, R. J., Mgr
Oak Ridge Operations Office, Oak Ridge, TN 37830

. FROM INITIATING OFFICE Human Health Studies Programs, OHER:EVA
Room E-201 Washington, D. C. 20545

. INITIAL: [X] UPDATE: [ ] 4. PROCUREMENT: [X] FINANCIAL ASSISTANCE: [ ]

. PR NUMBER: 05-79EV02401-001 6. PR CORRECTION LETTER: _ 7. RELATED PR NUMBER: _____

CTION IDENTIFICATION

. 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: U7801613 10. PROJECT NO: 6105 11. CFDA NO: _____

2. PRODUCT OR SERVICE:* A10 13. SUPPORT SERVICES: YES [ ] NO [X] 14. CONSULTANT AWARD: YES [ ] NO [X]

5. CONTROLLED DELIVERABLE:* C6N 16. REPORT/DRAWING REQ: YES [X] NO [ ] IF YES, ATTACH DETAILS Per SRSA

7. CLASSIFICATION OF MATERIALS/WORK: U U — UNCLASSIFIED C — CONFIDENTIAL S — SECRET T — TOP SECRET

8. GOVERNMENT PROPERTY: N F — FURNISHED P — PURCHASED N — NOT INVOLVED IF CODE F OR P, ATTACH DETAILS.

WARD PLANNING

9. AWARD AS ORDER UNDER BIN: _____

0. 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.

3. IF MULTI-YEAR AWARD, INDICATE NUMBER OF YEARS: _ 24. TYPE SOLICITATION INSTRUMENT: * UP

5. 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).

6. SOURCE SELECTION PROCEDURE: 4 1 — A-E 2 — SEB 3 — OTHER 4 — NONE

7. FOR A-E, SHOW ESTIMATED CONSTRUCTION COST IN DOLLARS: N/A

WARDEE

IF COMPETITIVE, HAS LIST OF SOURCES BEEN ATTACHED? YES [ ] NO [X] IF NON-COMPETITIVE, COMPLETE 28 - 31.

8. NAME: Vanderbilt University 29. ADDRESS: Nashville, TN 37232

0. DIVISION: Nuclear Medicine

1. GOCO/LAB: C A — GOCO/LAB B — GOCO/NON-LAB C — NON-GOCO/LAB D — NOT APPLICABLE

INANCIAL

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.

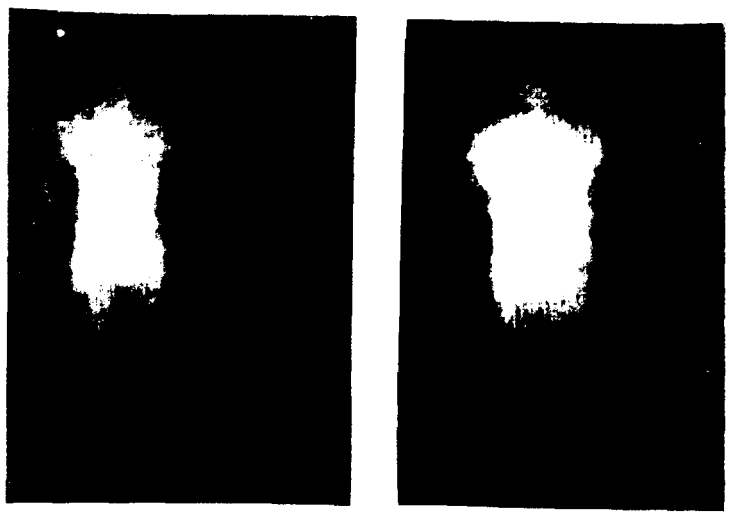
54. SIGNATURE: D D Mayhew

55. DATE: 10 (MONTH) 28 (DAY) 78 (YEAR)

NOV 3 1978

* SEE BACK OF FORM FOR CODES

1037088



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.

1037090

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:

1037091

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.

1037092

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

1037093

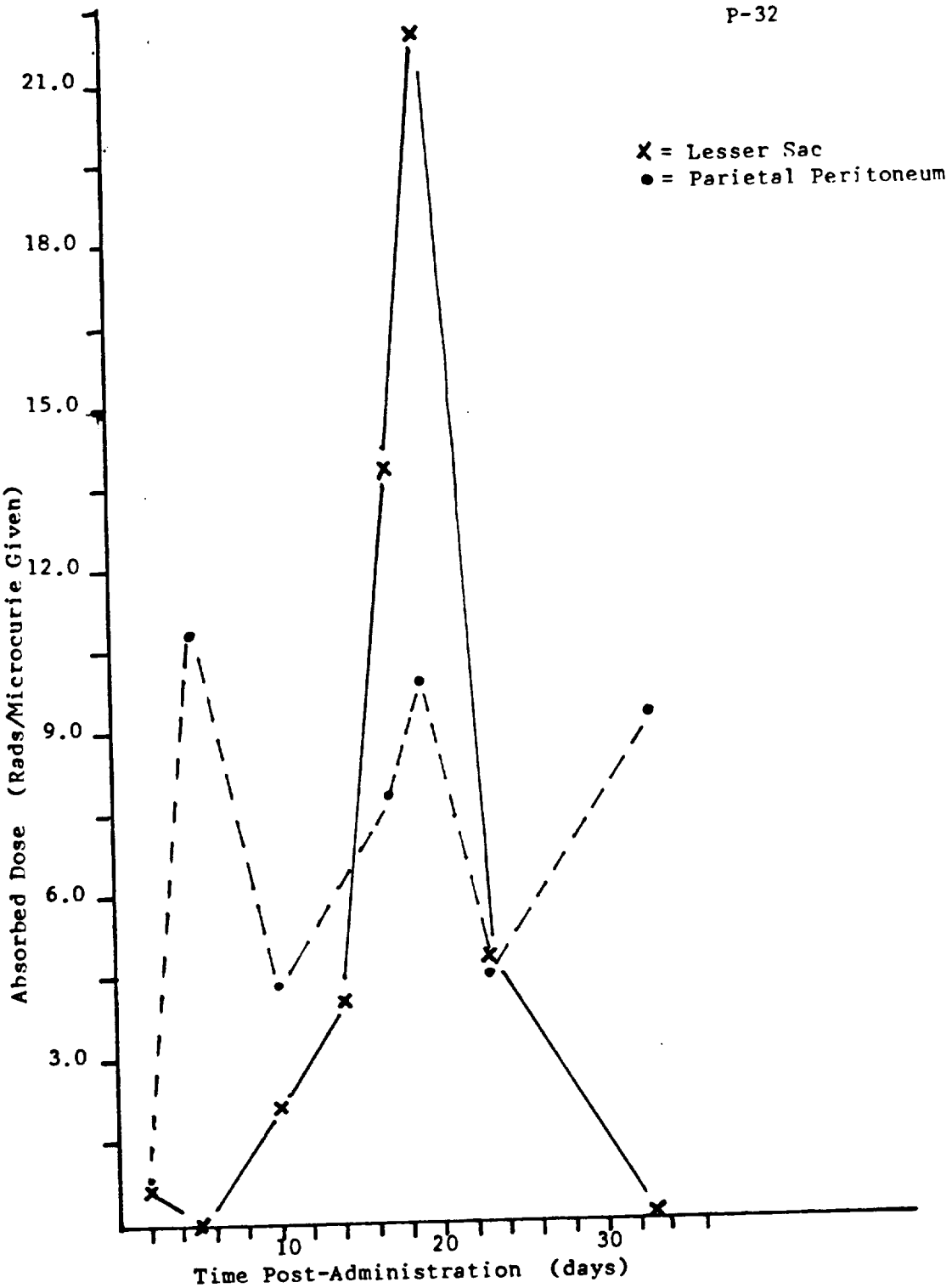


FIGURE 1

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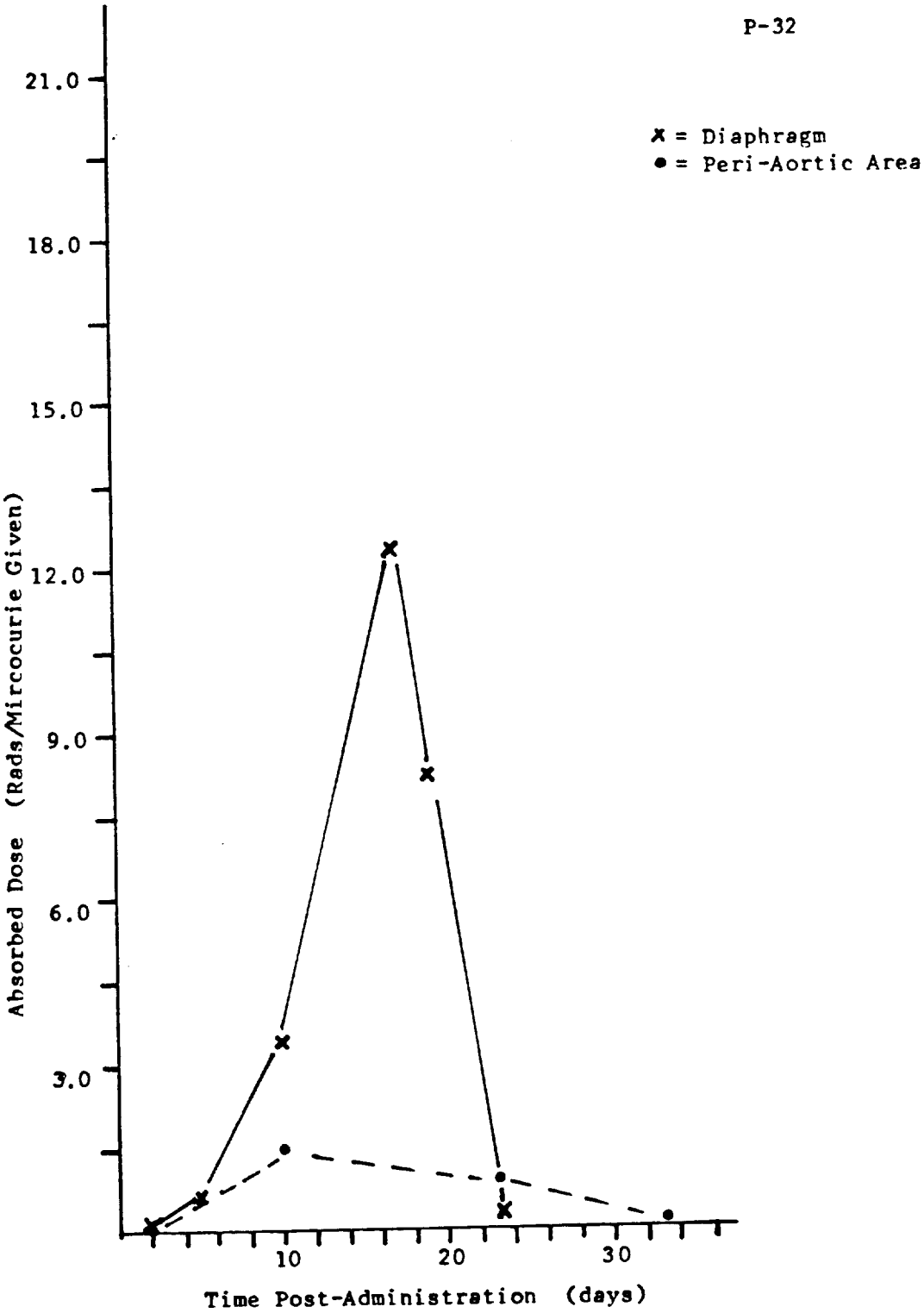


FIGURE 2

1037095

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

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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.

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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

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TABLE 2

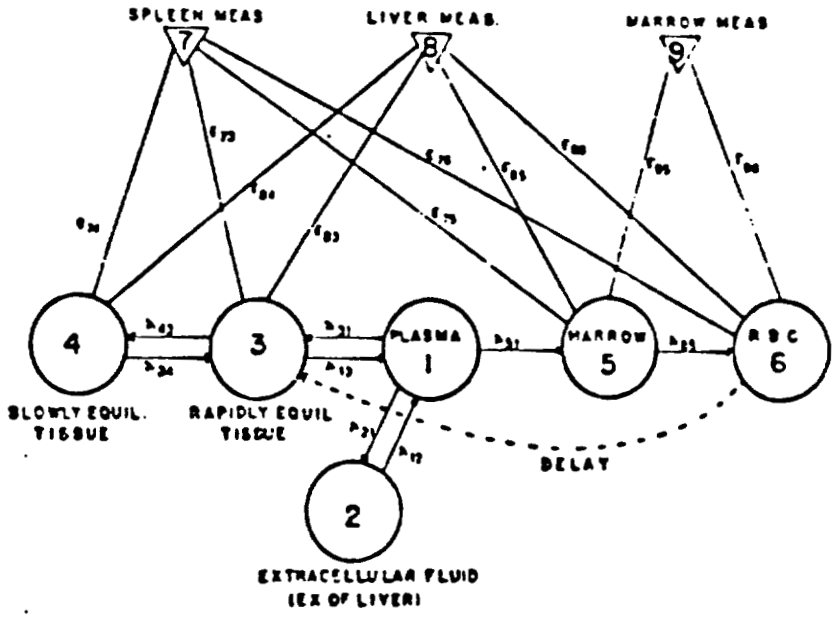
Nuclear Data

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

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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

1037100

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

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TABLE 4

Fe-59 Dosimetry

Intercompartmental Rate Constants (fraction/day)

λ_1 λ_2

	Disease	Plasma to Marrow	Marrow to RBC	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

1037102

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.

1037103

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

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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.

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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.

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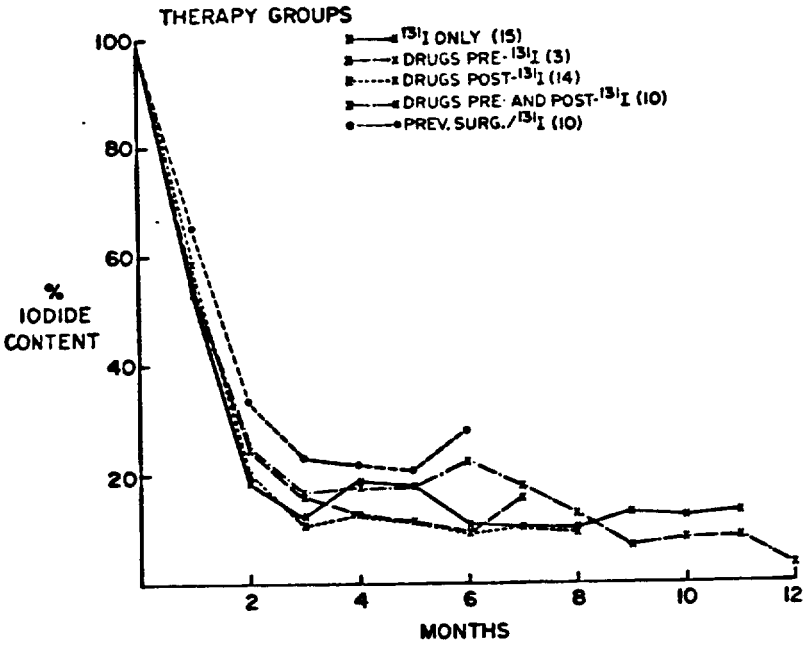


FIGURE 1

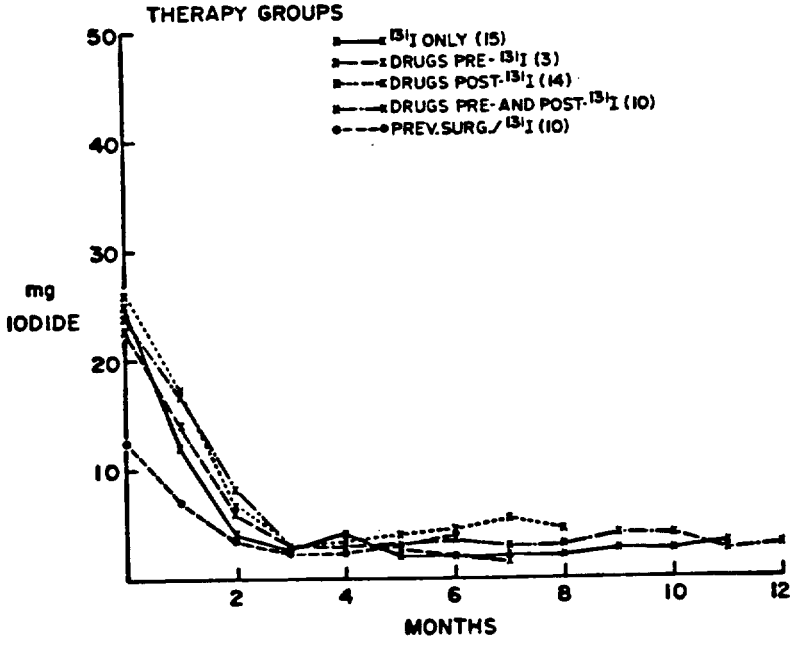


FIGURE 2

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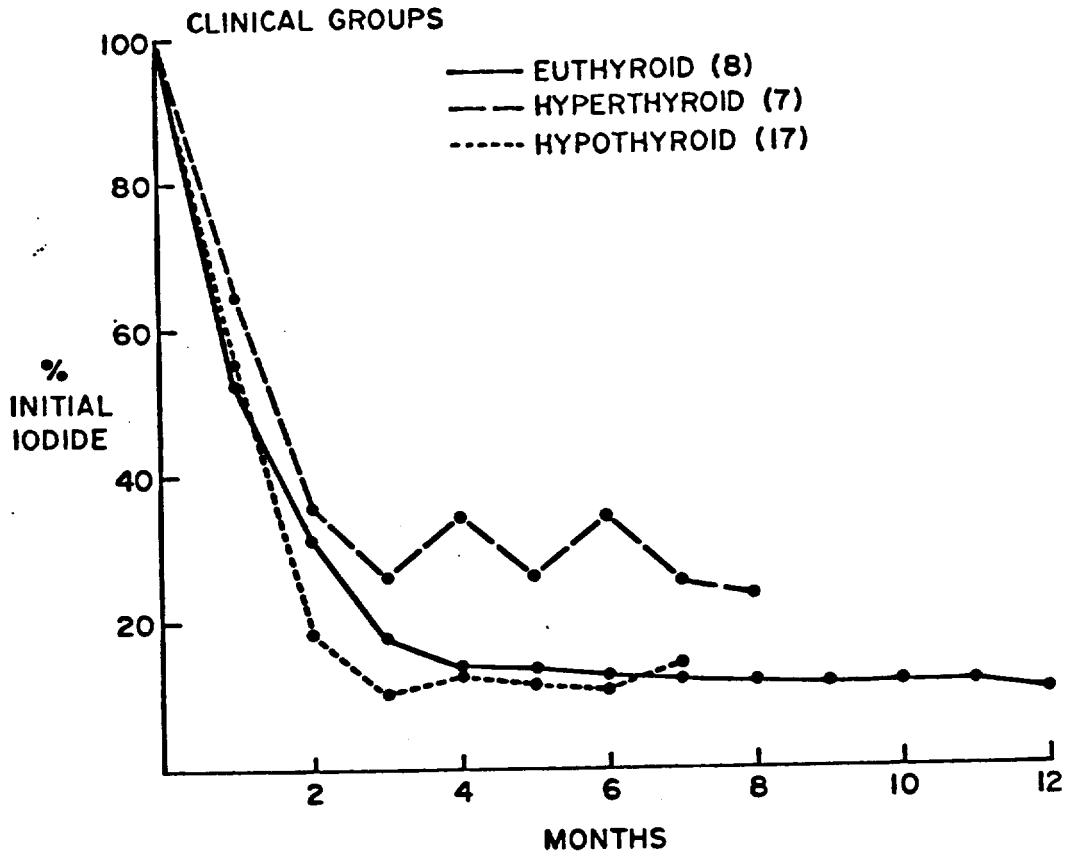
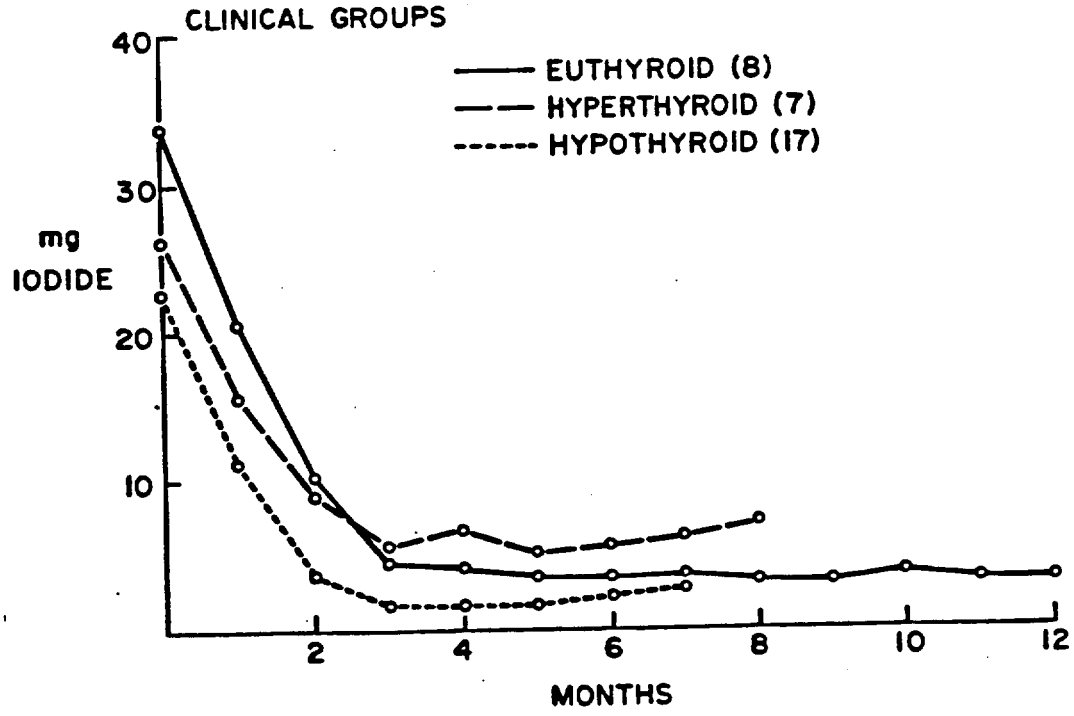


FIGURE 3



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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

1037109

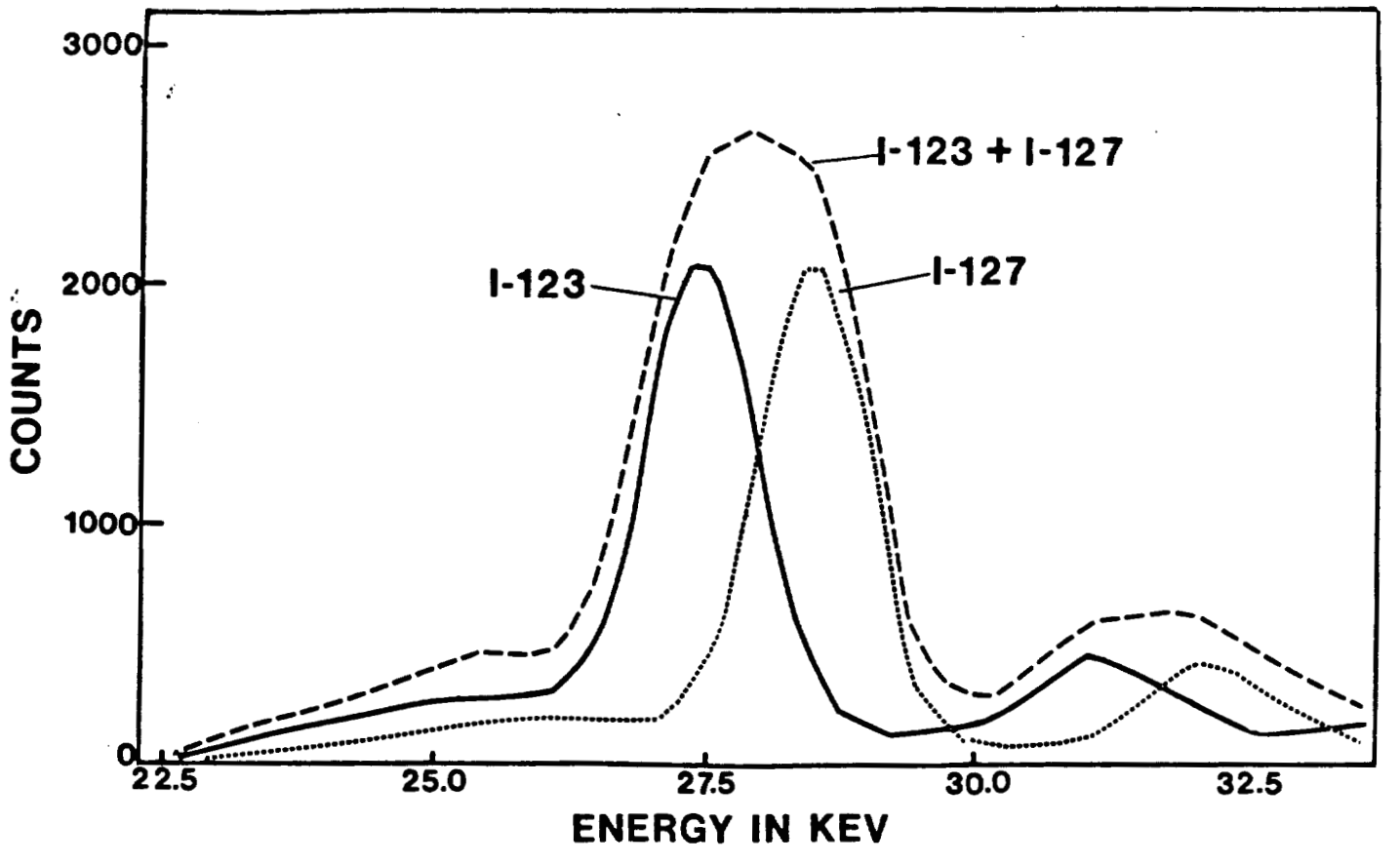


Figure 5 Energy spectrum from an I-123 source and a fluorescent energy spectrum from stable iodine (I-127) and a combined energy spectrum collected with the lithium-drifted silicon detector x-ray fluorescence system currently utilized for iodine content determinations of the thyroid.

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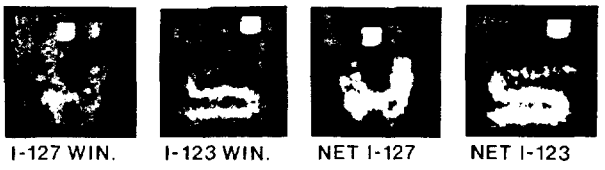


Figure 6 Simultaneous scans of a thyroid phantom containing stable iodine (I-127) and radioactive iodine (I-123) and the distributions separated by computer techniques (Net I-127 and Net I-123).

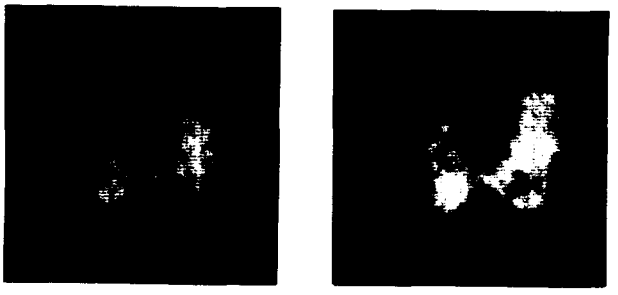


Figure 7 Separated distributions obtained by scanning a thyroid phantom containing 20 mg. of I-127 and 60 micro-Curies of I-123.

1037111

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.

1037112

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.

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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:

$$Tj(f_x f_y) = \sum_{i} 0_i\,(fxfy) \cdot H_{ij}(fxfy)$$

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 (0_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.

1037114

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.

1037115

TABLE I

POINT SOURCE DATA FOR HIGH PURITY GERMANIUM DETECTOR ARRAY.
NORMALIZED MAXIMUM COUNT VALUES FOR EACH DETECTOR IN EACH PLANE.

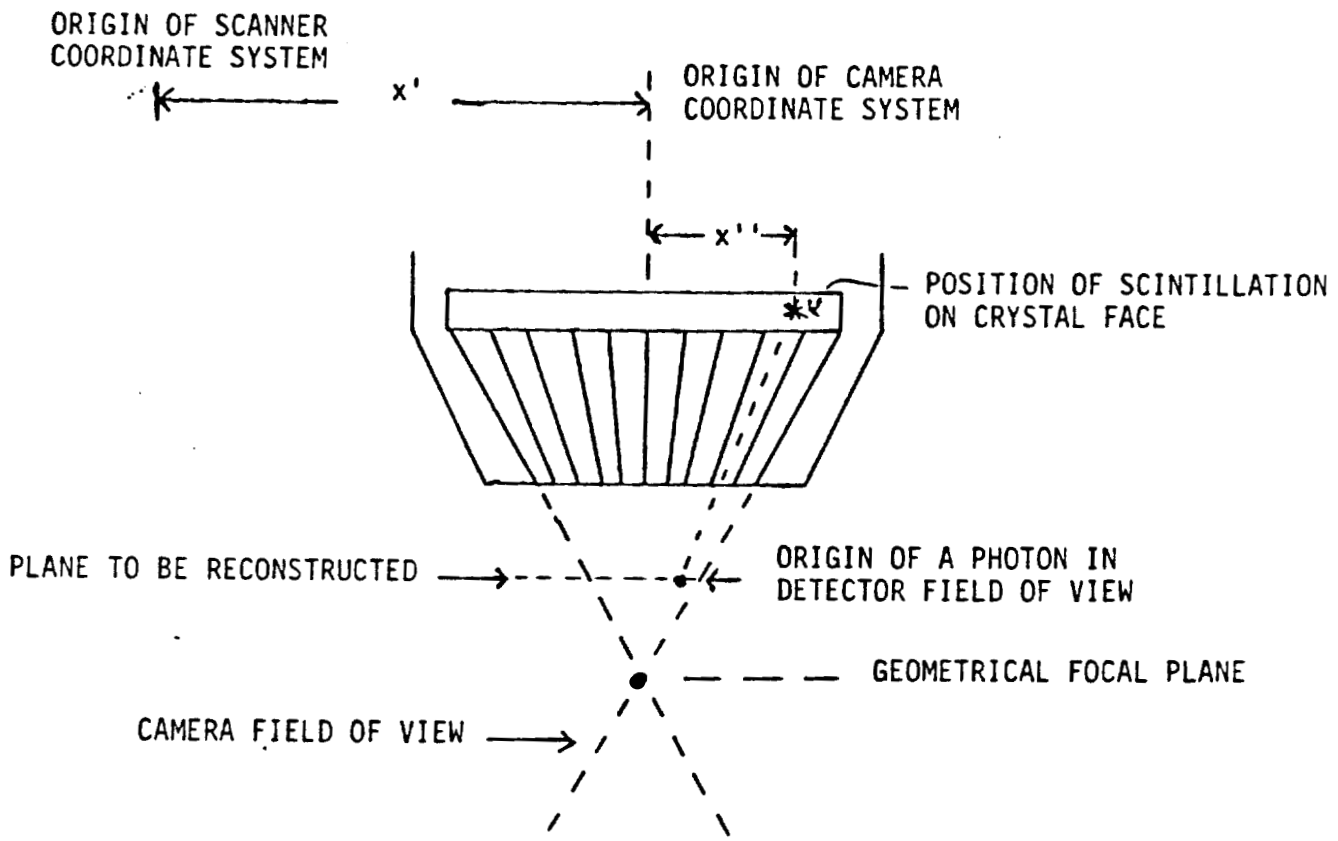
PLANE/DETECTOR	1	2	3	4	5	6	7	8	9
1	0.918	0.968	0.886	0.958	1.436	0.941	0.747	1.255	0.897
2	1.045	1.195	0.731	1.159	1.273	0.736	0.659	1.205	0.998
3	1.178	1.036	0.749	1.227	1.229	0.754	0.732	1.213	0.972
4	0.795	1.293	0.697	1.287	1.230	0.808	0.744	1.329	0.817
5	0.953	0.897	0.857	1.392	1.023	0.862	0.873	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

1037116



$X = x' + kx''$

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.

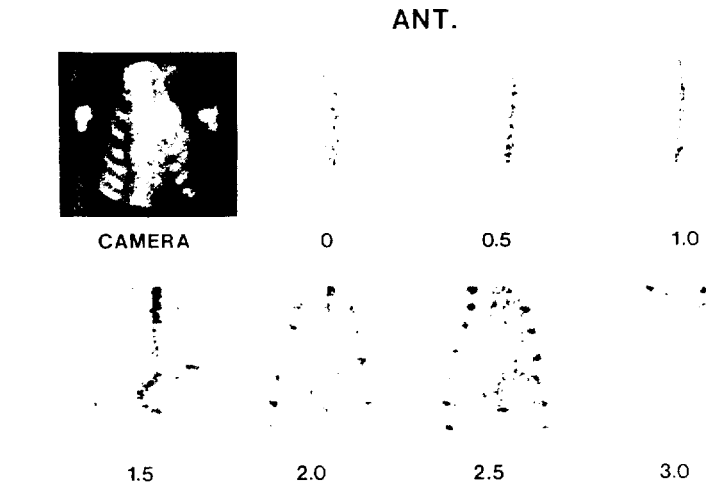
k = constant determined by distance and direction of reconstructed plane from geometrical focal plane.

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

$Y = y' + ky''$

FIGURE 1

1037117



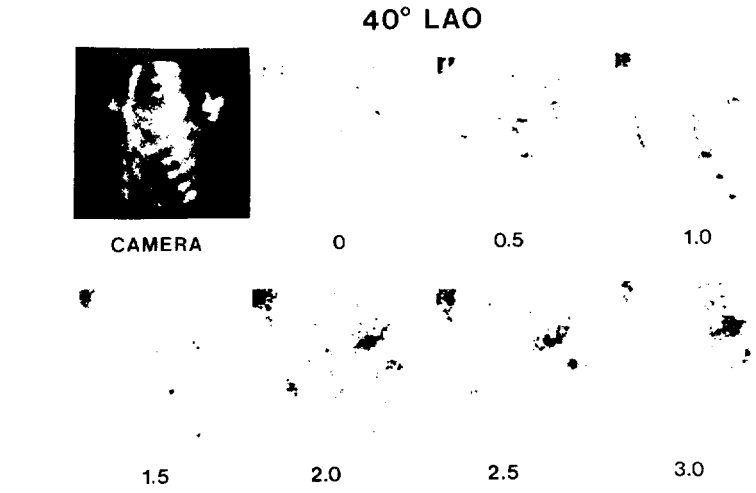


Figure 2 Anterior and 40 degree LAO views of a dog with a surgically induced infarction imaged with Tc-99m pyrophosphate using the scintillation camera and the high purity germanium array in the tomographic mode. The distances are in inches from the anterior surface of the dog. Note the planer separation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

1037118

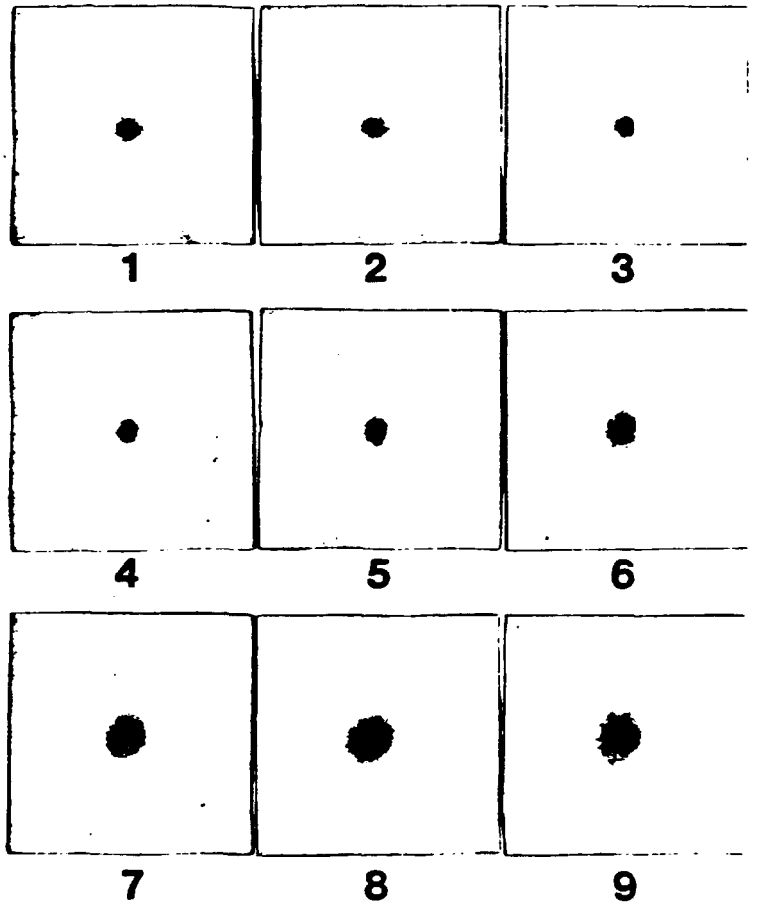


Figure 3 Point source response with Tc-99m (140 keV) for the high purity germanium array at 0.75 inch increments from 1.50 inches above the focal plane to 4.50 inches below the focal plane. Each image is a 64 x 64 array corresponding to a 6 x 6 inch scan field.

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.

1037120

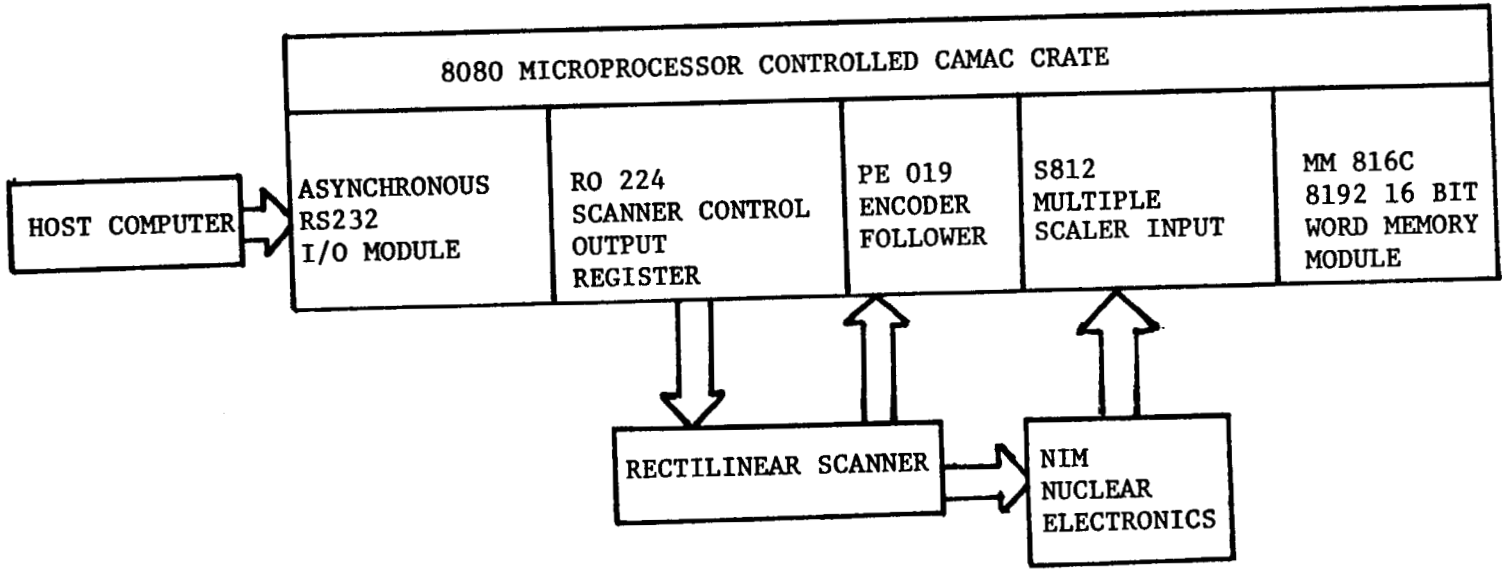


Figure 1: System diagram of microprocessor controlled scanner.

1037121

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.

1037122

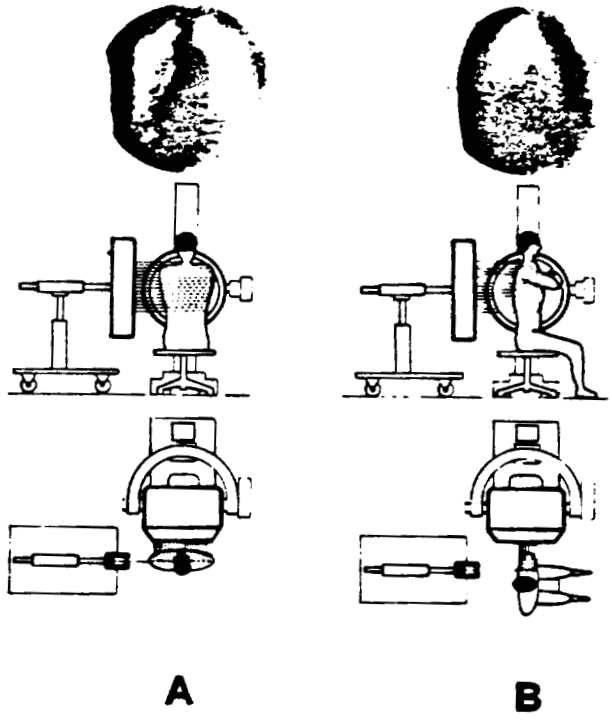


Figure 1 Schematic representation of external gamma source and gamma camera positioned for frontal chest tomogram(A) and sagittal tomogram(B). (From Pistolesi, et.al. Chest Tomography by Gamma Camera and External Gamma Source: Concise Communication, Journal of Nuclear Medicine, 19:94-97,1978.)

1037123

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).

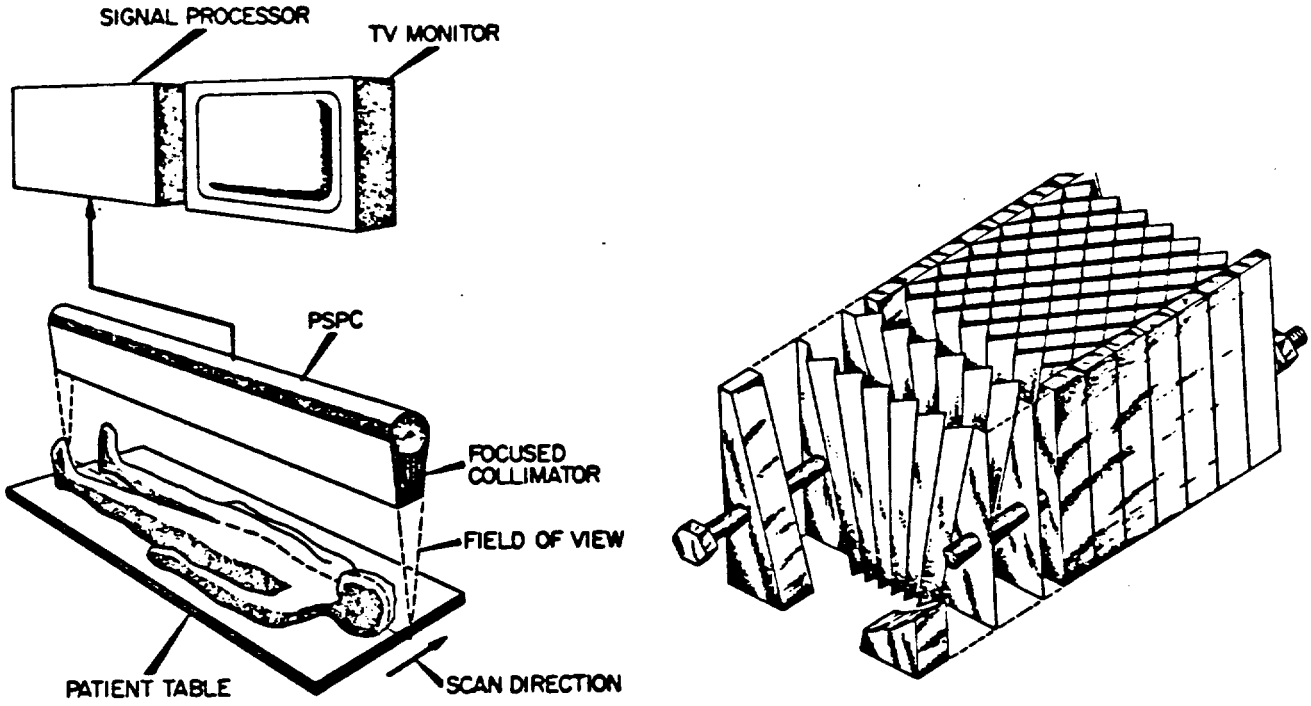
The initial system that we will configure will utilize two 60cm xenon filled PSPC's pressurized to 6 atmospheres and mounted in a dual opposed geometry on the Ohio-Nuclear scanner. The detectors will be mounted at right angles to the long axis fo the body with the mechanical motion of the scanner being 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.

1037124

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.

1037125



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).

1037126

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.

1037127

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.

1037128

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.

1037129

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 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.

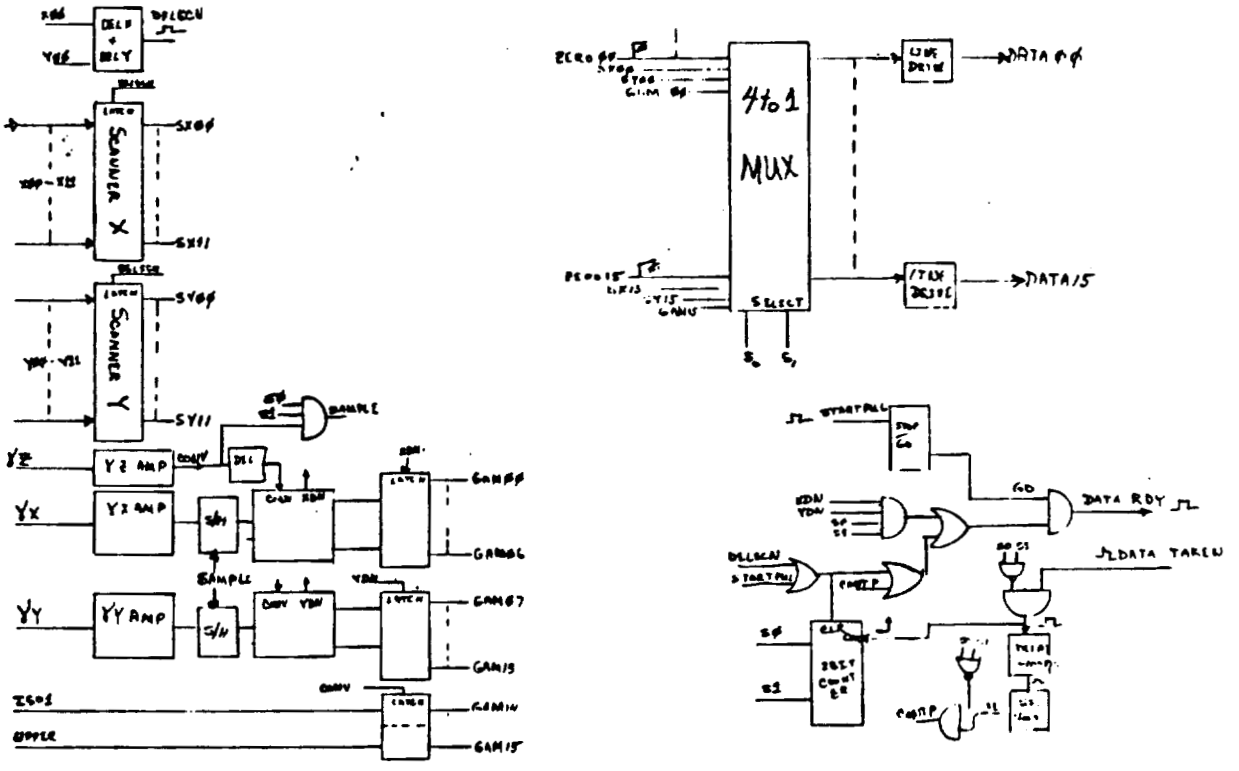
This method of data storage will result in a list of data which will be very amenable to reconstruction of tomographic images. The 3 word block with the leading flag word can be used for other information such as elapsed time for decay correction by use of a different flag word. This is possible since 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).

1037131

Figure 1

Computer Interface for Searle Pho/Con Scanner



1037132

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.

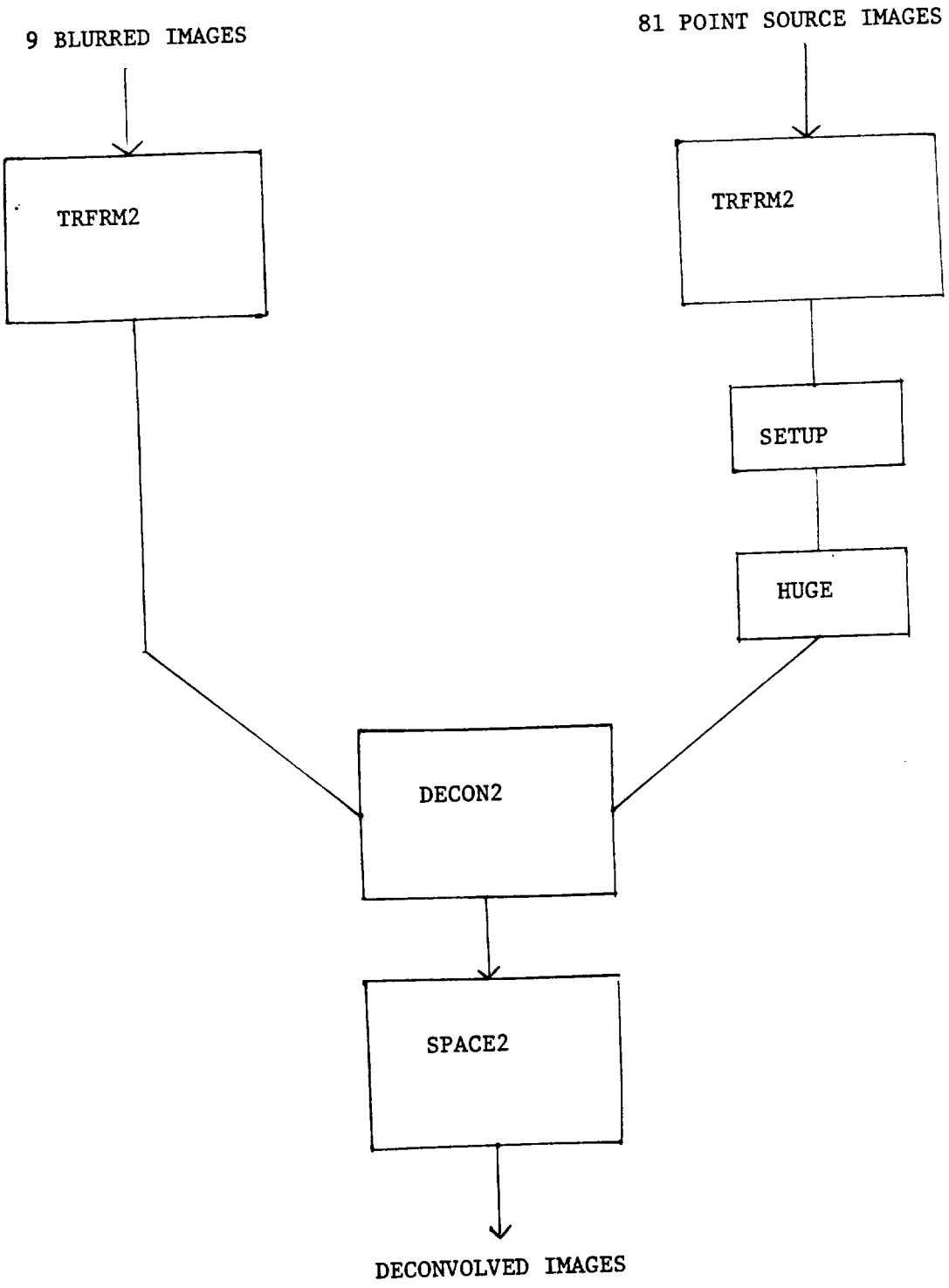
5. HUGE forms a single file containing all point source information which represents the system response and is used for each deconvolution.

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.

1037133

DECONVOLUTION INFORMATION FLOW



1037134

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=1,64,4
        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)
D       DO 1200 I=1,N
D       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,D
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
D150    WRITE(7,1100) (D(I),I=1,18)
1100    FORMAT(1X,3(6G13.6/))
D       DO 1300 I=1,N
D       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
D       WRITE(7,560)
550     FORMAT(' END FACTOR')
560     FORMAT(' END FACTOR, SMALL NO.')
        RETURN
        END
$
```

1037135

```
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(66)
        DIMENSION N(2), DI(9,66,4)
        DATA N(1),N(2)/64,64/
2       NDIM=2
        WRITE(7,5)
5       FORMAT(1X 'WRITE FILE: ',$)
        CALL ASSIGN(2,'DK1:',-1)
        CALL ASSIGN (3,'DK1:XYZ.DAT',0,'SCR')
        DO 100 IARY=1,9
        WRITE(7,7)IARY
7       FORMAT(1X 'READ FILE #',I1,'  ',$)
        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 #',I1,' FINISHED.')
100     CONTINUE
        ENDFILE 3
        DO 120 J=1,64,4
        REWIND 3
        NUM=(J-1)*66
        DO 110 I=1,9
        NN=NUM
        READ(3)DATA
        DO 110 M=1,4
        DO 110 K=1,66
        NN=NN+1
110     DI(I,K,M)=DATA(NN)
120     WRITE(2)DI
        CALL CLOSE(2)
        CALL CLOSE (3)
        STOP
        END
```

```
TTZ\Z\I=SETUP.FOR
C       SETUP
C       PROM REFORMATS H DATA FROM TRFRM2
C
        DIMENSION C(9,66,4),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
$
```

```
TTI=SPACE2.FOR
C       SPACE2
C       CONVERTS FROM FREQ. TO SPACE
C       THIS PROGRAM CAN ONLY BE USED
C       WITH DECON2
        DIMENSION NX(2),E(9,66)
        COMMON DATA(4224),IC(64),DC(66),NN(4096)
        DATA NX(1),NX(2)/64,64/
        WRITE(7,2)
2       FORMAT(1X' ENTER INPUT FILE ',$)
        CALL ASSIGN(1,'DK1:',-1,'RDO')
C       DO LOOP OVER 9 IMAGES
100     DO 1 M=1,9
        WRITE(7,5)M
5       FORMAT(1X,'WRITE FILE #',I1,' ?',$)
        CALL ASSIGN (2,'DK1:',-1)
        NC=0
        DO 3 L=1,64
        READ(1)E
        DO 3 N=1,66
        NC=NC+1
        DATA(NC)=E(M,N)
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
        MM=0
        DO 40 J=1,4096
        MM=MM+1
C       IC(MM)=(DATA(J)/100.)
D       IC(MM)=((DATA(J)-AMN)/R)*100
        IF(MM.NE.64) GO TO 40
        MM=0
        WRITE(2)IC
40      CONTINUE
50      CONTINUE
        CALL CLOSE(2)
        REWIND 1
1       CONTINUE
        STOP
        END
$
```

```
TTI=HUGE.FOR
C       HUGE
C       PROM 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 ',$)
        CALL ASSIGN(1,'DK1:',-1)
        DEFINE FILE 1(2112,324,U,KR)
        I1=0
        DO 50 I=11,19
        I1=I1+1
        WRITE(7,20)I1
20      FORMAT(' ENTER READ FILE FOR LEVEL',I2,1X,$)
        CALL ASSIGN(I,'DK1:',-1,'RDO')
50      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
D       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
$
```

1037136

```
      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=IP0*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,IP0
        DO 40 I5=I1,IP5,IP3
        J0=I5
        J1=J0+IP2
        TEMPR=DATA(J1)
        TEMPI=DATA(J1+1)
        DATA(J1)=DATA(J0)-TEMPR
        DATA(J1+1)=DATA(J0+1)-TEMPI
        DATA(J0)=DATA(J0)+TEMPR
   40   DATA(J0+1)=DATA(J0+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-IP0
        DO 120 I1=I2,I1MAX,IP0
        DO 120 I5=I1,IP5,IP3
        J0=I5
        J1=J0+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   T0R=DATA(J0)+DATA(J1)
        T0I=DATA(J0+1)+DATA(J1+1)
        T1R=DATA(J0)-DATA(J1)
        T1I=DATA(J0+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(J0)=T0R+T2R
        DATA(J0+1)=T0I+T2I
        DATA(J2)=T0R-T2R
        DATA(J2+1)=T0I-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*TEMPR-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)
            IP0=2
        IP1=IP0*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-IP0
        DO 20 I1=I4,I1MAX,IP0
        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)
        TWOPI=6.283185307*FLOAT(ISIGN)
D       WRITE(7,349)
349     FORMAT( ' ENTER FIXRL ' )
        IP0=2
        IP1=IP0*(N/2)
        IP2=IP1*NREM
        IF(IFORM)10,60,60
   10   J1=IP1+1
        DATA(2)=DATA(J1)
        J1=J1+IP0
        I2MIN=IP1+1
        DO 50 I2=I2MIN,IP2,IP1
        DATA(I2)=DATA(J1)
        J1=J1+IP0
        IF(N-2)40,40,20
   20   I1MIN=I2+IP0
        I1MAX=I2+IP1-IP0
        DO 30 I1=I1MIN,I1MAX,IP0
        DATA(I1)=DATA(J1)
        DATA(I1+1)=DATA(J1+1)
   30   J1=J1+IP0
   40   DATA(I2+1)=DATA(J1)
   50   J1=J1+IP0
   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=IP0+1
        I1MAX=IP0*(N/4)+1
        DO 160 I1=I1MIN,I1MAX,IP0
        DO 150 I2=I1,IP2,IP1
        I2CNJ=N+IP0-2*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=IP0*(N/2+1)*NREM+1
        GO TO 220
  190   DATA(J1)=DATA(I1)
        DATA(J1+1)=DATA(I1+1)
        I1=I1-IP0
        J1=J1-IP0
  200   IF(I2-I1)190,210,210
  210   DATA(J1)=DATA(I1)
        DATA(J1+1)=0.
  220   I2=I2-IP1
        J1=J1-IP0
        DATA(J1)=DATA(I2+1)
        DATA(J1+1)=0.
        I1=I1-IP0
        J1=J1-IP0
        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
```

1037137

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

1037138

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

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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	------	------

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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

1037141

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).

1037142

"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, M.D., Ph.D.

Date: 1-28-78

1037143

```
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)
```

10374

```
70      FORMAT(1X 'T  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)/X
540   IG(J,I)=XG
C
C     SET-UP FOR DISPLAY OF ONE LINE OF DATA
C
550   IF(INP.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(INP.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

*
```

Routed by: Contract Division

FORM OR-133 (Rev. March 1975)

ROUTE SLIP

F ... er

	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 WHB

2. OFFICE OF CHIEF COUNSEL CONCURRENCE [illegible] 1-12-78

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

1037149

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	[illegible]	1-16	
3. H. S. Oster, Jr.	Finance	[illegible]	1/17	
4. W. L. Buchanan	Budget	WLB	1/19/78	
5.				
6.				
RETURN TO Alice Brown, Contract Division, Room 109				

1037150

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

1037151

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

1037152

(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

(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 .

1037153

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".

1037154

UNITED STATES DEPARTMENT OF ENERGY

PROCUREMENT COMMITMENT/OBLIGATION RECORD

1. TO: Certifying Official	2. FROM: Procurement Office	3. Control 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 TC/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		

1037155

FORM ERDA-799
(3-76)
ERDA-PR 9-16

U.S. Department of Energy

~~U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION~~

SP

PROCUREMENT REQUEST

*Please Type

(See Instructions on Reverse of Last Sheet)

1. TO: Procurement Office	2. From	3. Procurement Request Number
R. J. Hart, Mgr., OR Vanderbilt Univ. Nashville, TN 37232 Dr. A. Bertrand Brill, P.I.	Activity Title: EV Division: BER Project: HHSP	P. 05-78:0116

4.	5. Priority Rating (Ref. FPR 1-1.311)	6. Desired Award Date	7. Security Classification (ERDAM APP. 3401)
☐ Contract ☐ Grant ☒ Special Research Support Agreement (SRSA) ☐ Other ☐ Modification of EY-76-S-05-2401 Contract Number TO/PA ☐ Change Order ☐ Supplemental Agreement	Routine	11 01 77	☒ 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*)	19. Certifying Official (*Typed name, title, location, telephone number, date*)
DEC 13 ... Donald W. Cole, BER/HHSP x33268 (Name) Donald W Cole 11-4-77 (Signature)	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. EY 82-91(OR) (Signature)
18. Authorizing Program Official (*Typed name, title, location, telephone number, date*) James L. Liverman, ASEV (Signature)	

1037156

PROCUREMENT OFFICE

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

1037157

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 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).

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	TELEPHONE NUMBER
John Hash, Ph.D. Assoc. Dean, Biomedical Sciences	615)322-2281
SIGNATURE OF INSTITUTIONAL OFFICIAL	DATE
John H Hash	7/29/77

HEW-596 (Rev. 4-75)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY.

0037158

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)*

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GPO : 1975 O - 574-849

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

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

1037161

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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.

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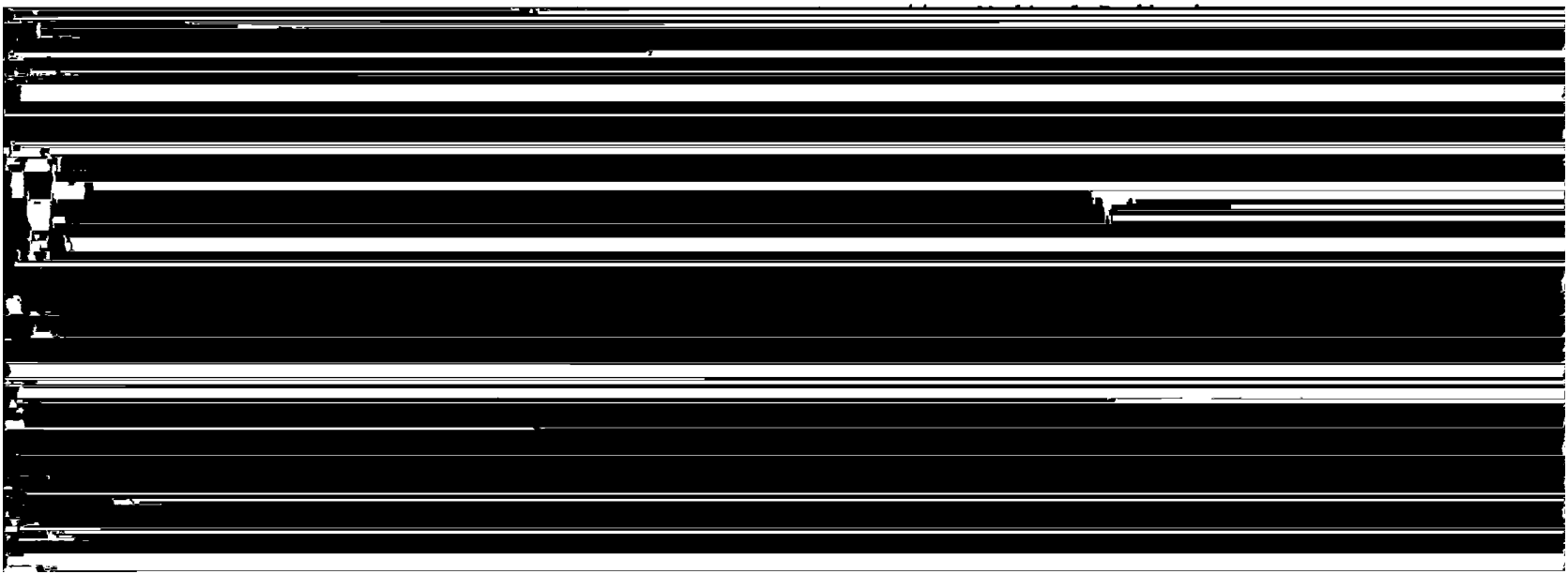
The loan of a "Pho/Con" longitudinal tomographic scanner from the Searle Corporation will prove to be a boon to our ongoing iodocholesterol/adrenal dosimetry project. The Pho/Con is the instrument of choice providing the optimum in speed and sensitivity for quantitating isolated distributions of radiopharmaceuticals 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 instrumentation 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



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.

1037165

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, Prinicipal 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 Enviromental Engineering Group have collaborated with us in the design and conduct of experiments involving the use of radioactive and stable tracers for ecological studies. Dr. J. Parker (acting Chairman of the Systems and Information Science Department) and C. Bradshaw, Director of Vanderbilt University Computer Center, and their staffs have contributed significantly to our work. None of the personnel in other departments is being supported financially be 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.

1037166

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.

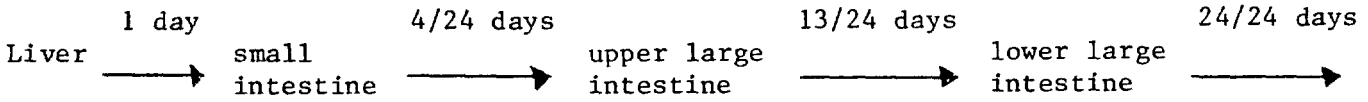
Radiation absorbed dose estimates have been completed on the 19IC compound. Preliminary dose calculations have also been made for the 6NC compound. It should be pointed out that the 6NC results are preliminary and are based on a limited number of measurements. More data will be forthcoming during the 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.

L91160

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.

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 .

1037169

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

1037170

Table 1 Ctd.

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

1037171

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

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Table 5

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

Organ	$\overline{Dp}$	$\overline{Dnp}$	$\overline{D}$ 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

1037173

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

1037174

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

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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	$\tilde{A}$ $\frac{\mu Ci \cdot hour}{\mu Ci}$
Total Body	10.9
Liver	33.0
Thyroid	2.8
Adrenal	---

Table 6

Dose Summary

($\bar{D}$ rad/mCi)

6NC

Organ	$\bar{D}p$	$\bar{D}np$	$\bar{D}$ 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

$\bar{D}$ (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	---

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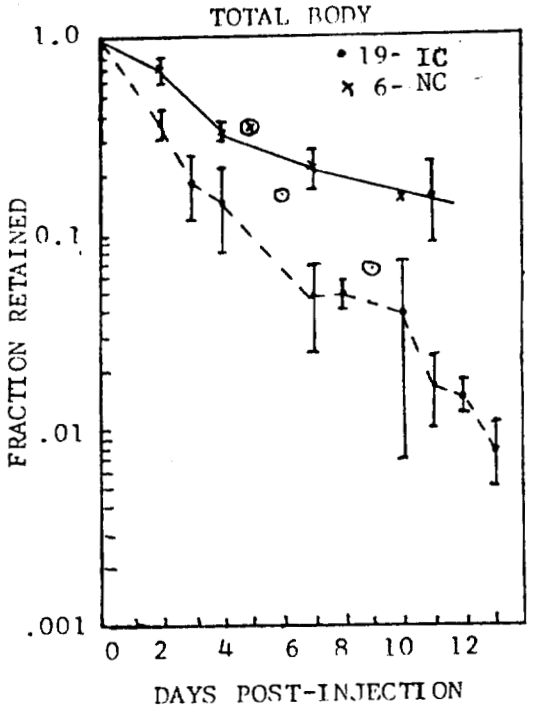


FIGURE 1

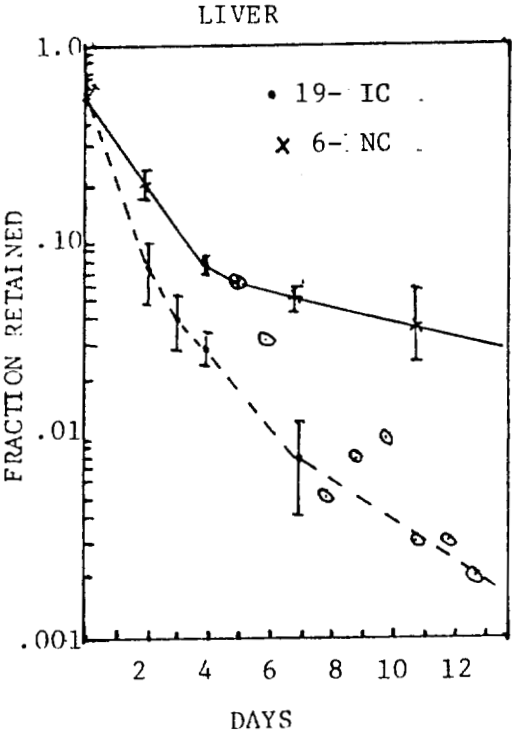


FIGURE 2

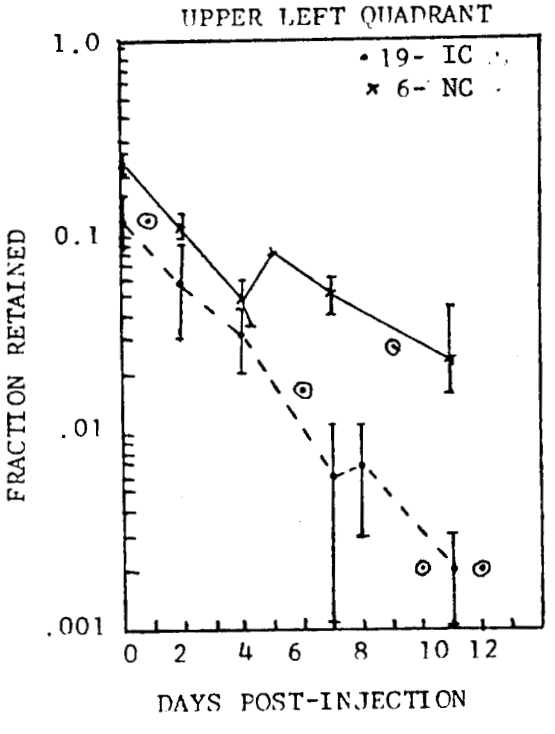


FIGURE 3

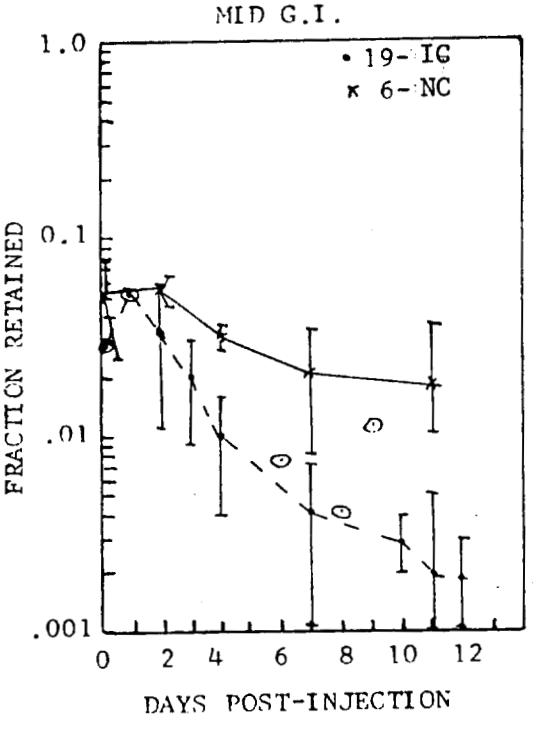


FIGURE 4

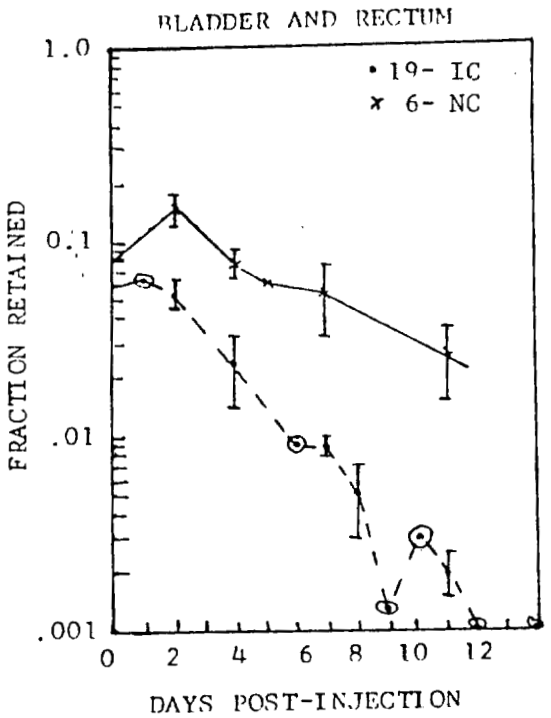


FIGURE 5

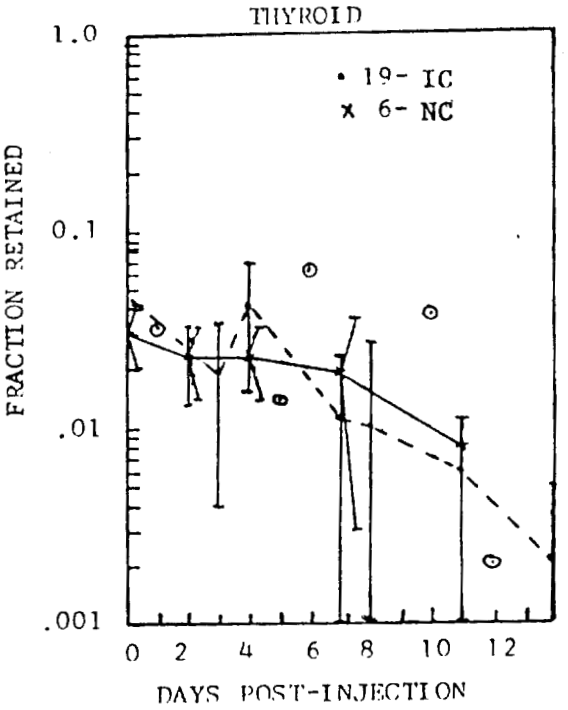


FIGURE 6

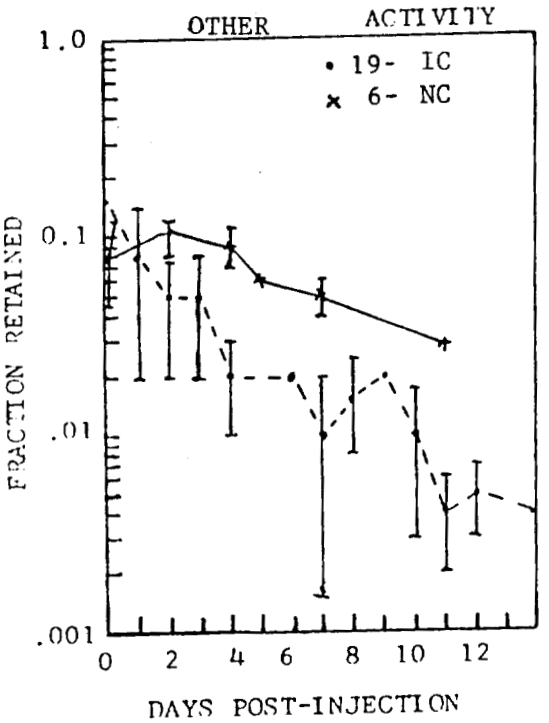
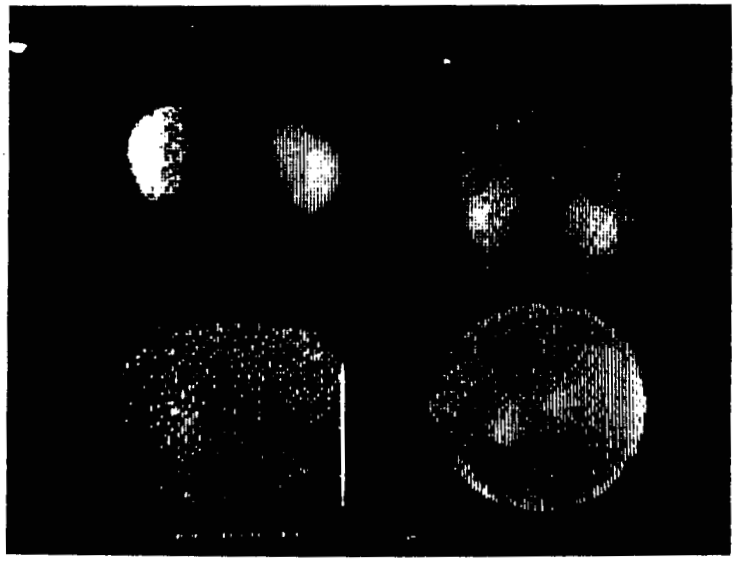


FIGURE 7

DAY 7

19 IC 6 NC

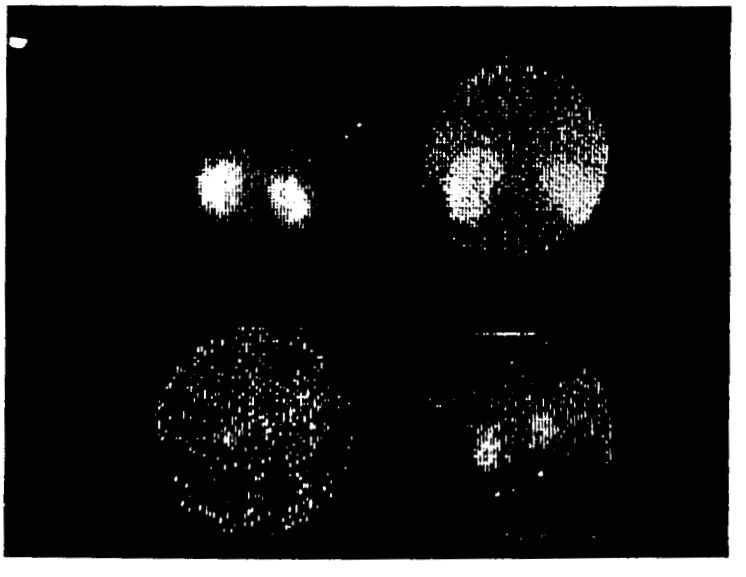


KIDNEY
Tc-DMSA

ADRENAL

DAY 11

19 IC 6 NC



KIDNEY

ADRENAL

FIGURE 8

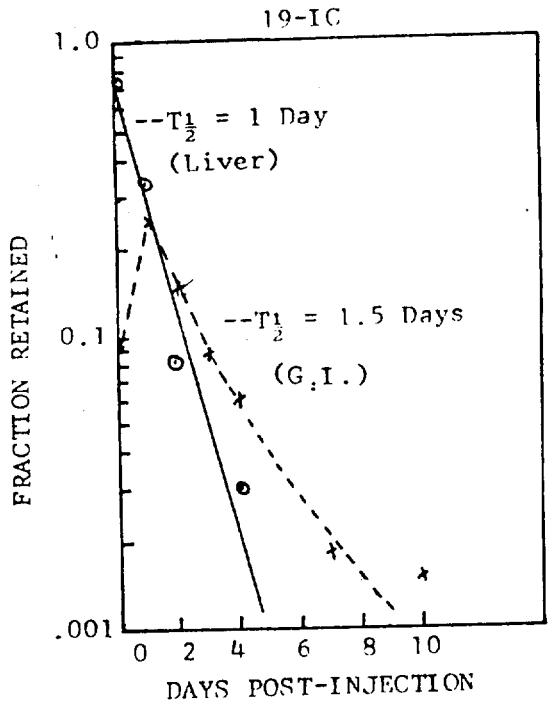


FIGURE 9

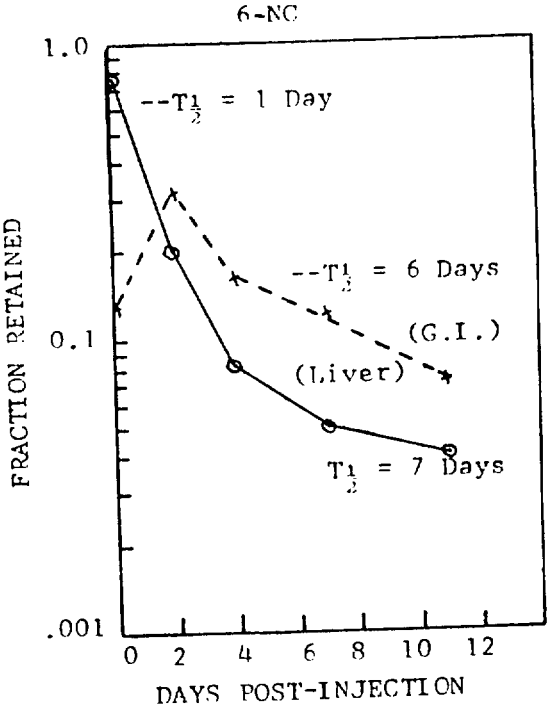


FIGURE 10

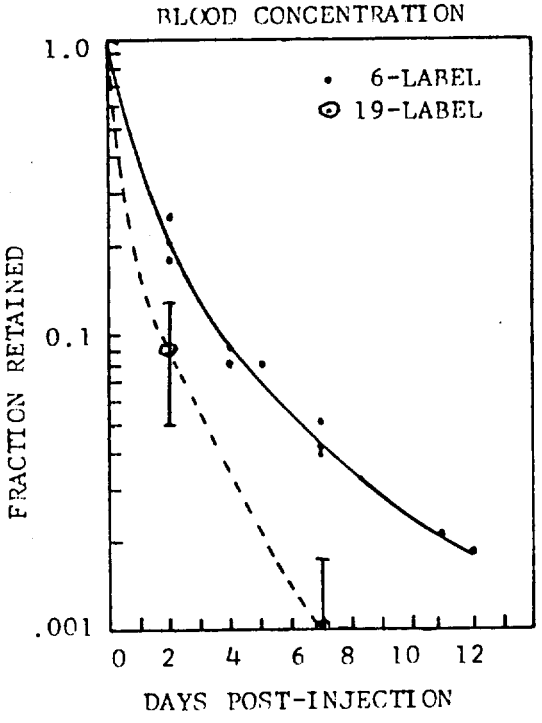


FIGURE 11

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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

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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

1037183

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 ∞).

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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.

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

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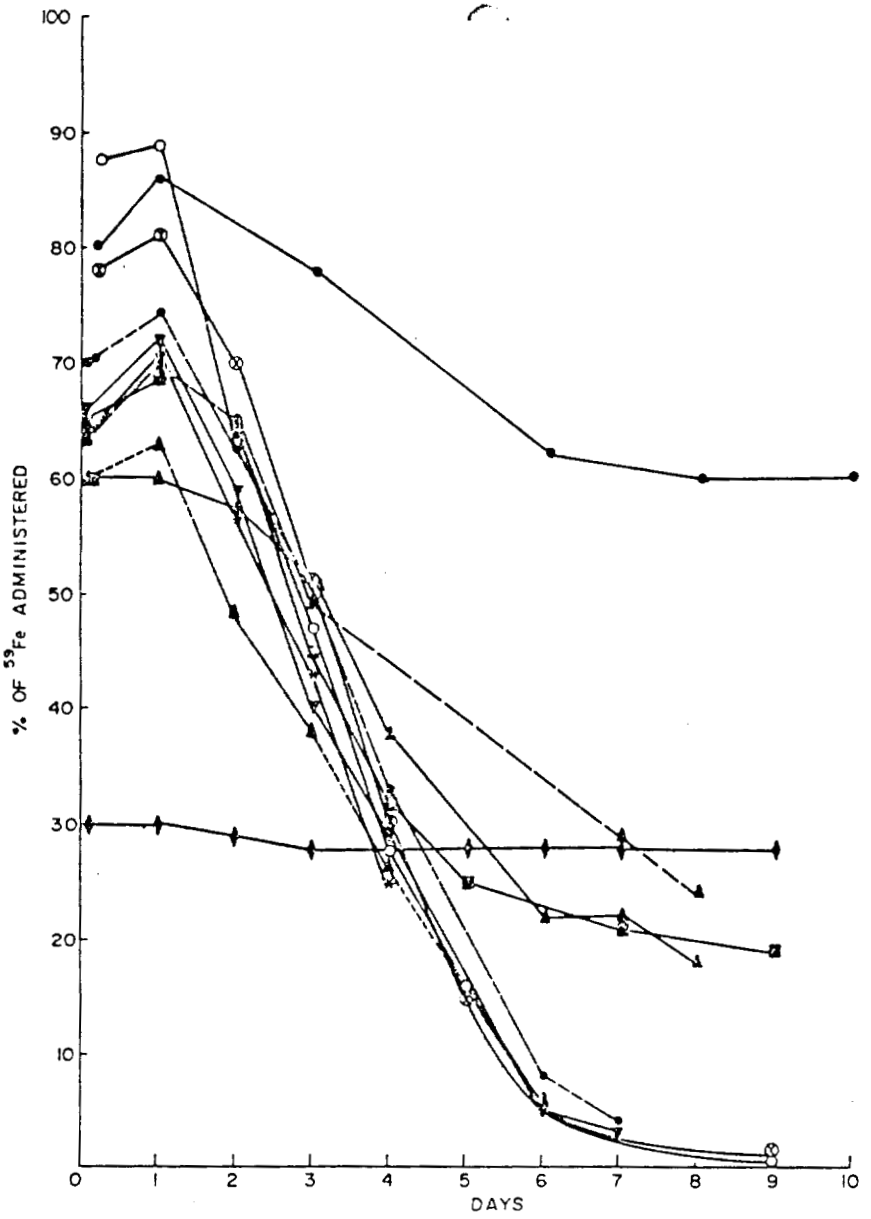


Figure 1. Marrow radioiron transit time curves. Normal volunteers o - - o and o——o. Patient number 6 with PRCA ◊—— ◊. Patients with PRCA in remission: number 1, Oct., 74 △——△, June, 75 △- - -△, and Nov., 76 △——△, number 2, Nov., 73 o——o and Aug., 76 o- - -o; number 3, □—— □; number 4, ▽——▽; number 5, *——*.

PRCA = pure red cell aplasia

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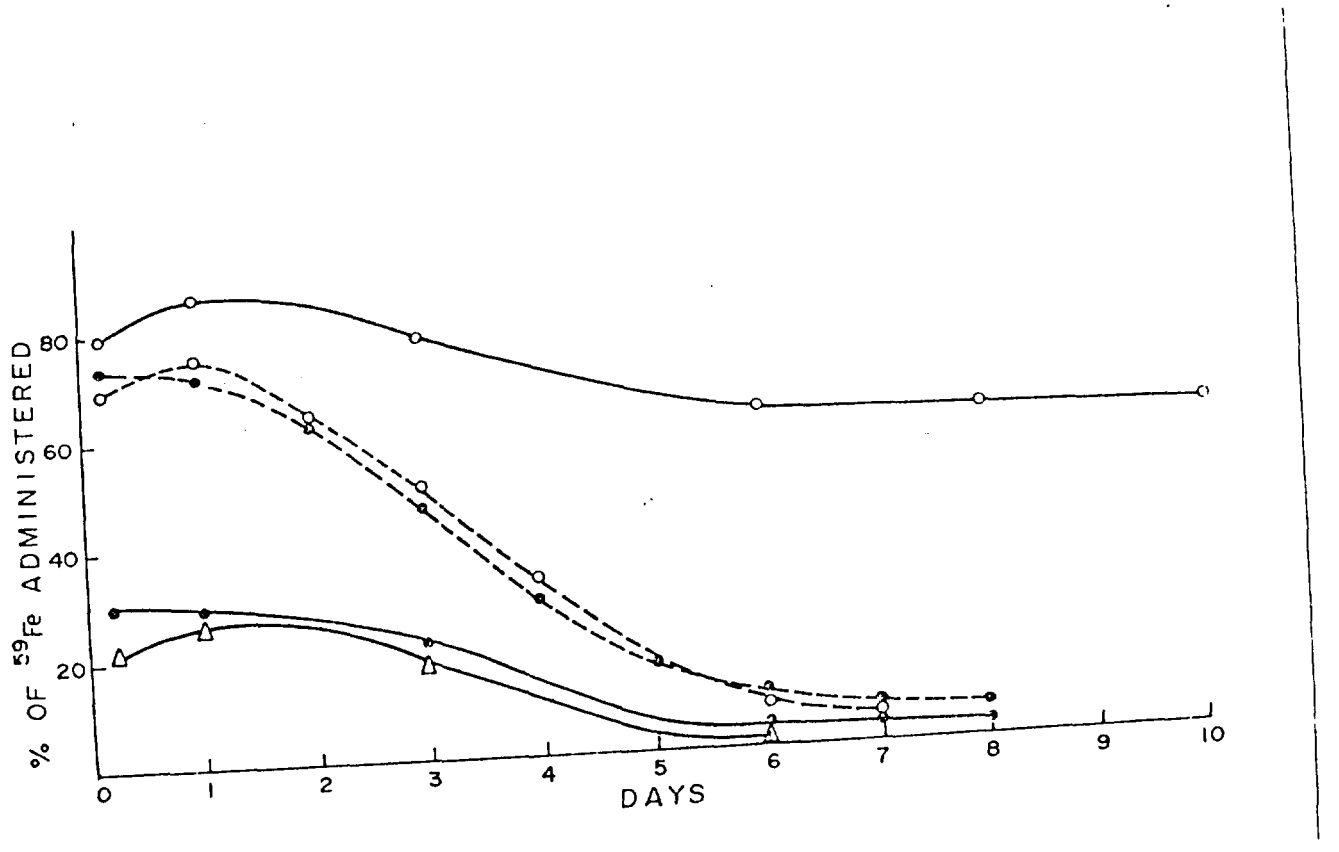


Figure 2. Comparison of marrow transit time curves for patient number 2 determined by two methods. Transit time curves derived by direct measurement of radioiron activity in the pelvis are compared with curves calculated from circulatory levels of radioiron in the plasma and red cells (14). Measurements 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).

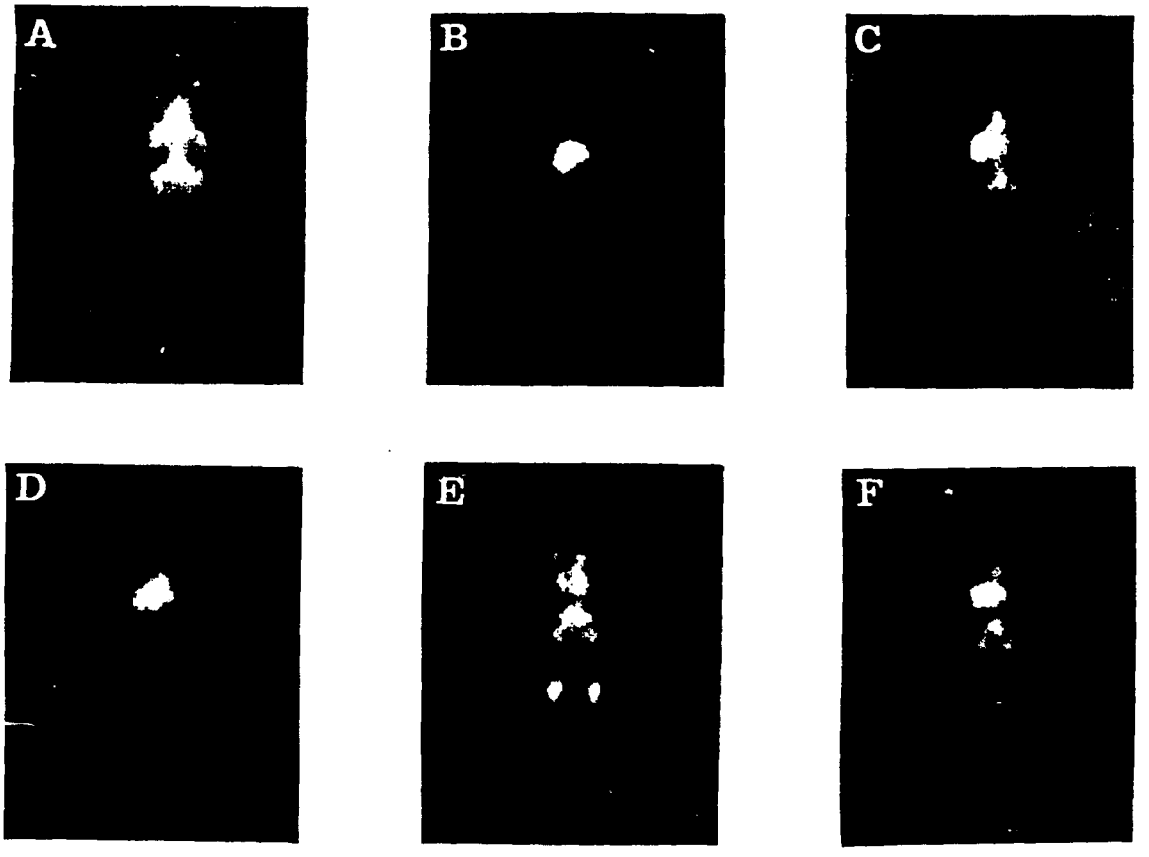


Figure 3. Surface organ scanning (A) Normal volunteer. (B) Patient number 6 with PRCA. (C,D,E,F) Patients with PRCA in remission showing (C) normal marrow distribution of ^{59}Fe in patient number 3, (D) moderate extension of bone marrow into lower extremities in patient number 5, (E) marked extension 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

1037189

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 mem bers 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.

1037190

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.

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PATIENTS WITH INITIAL IODINE CONTENT LESS THAN 15.5 MG.

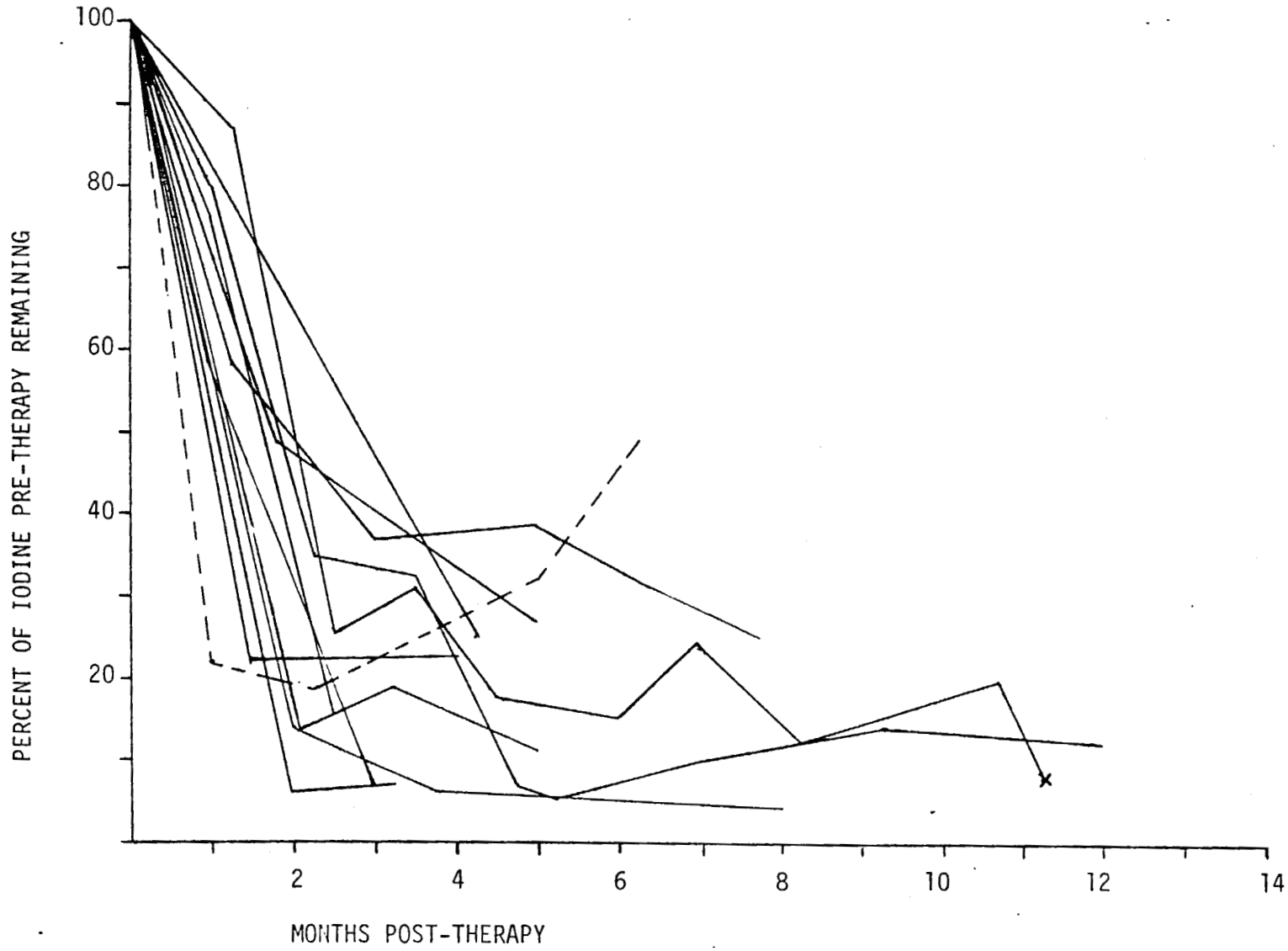


Figure 1

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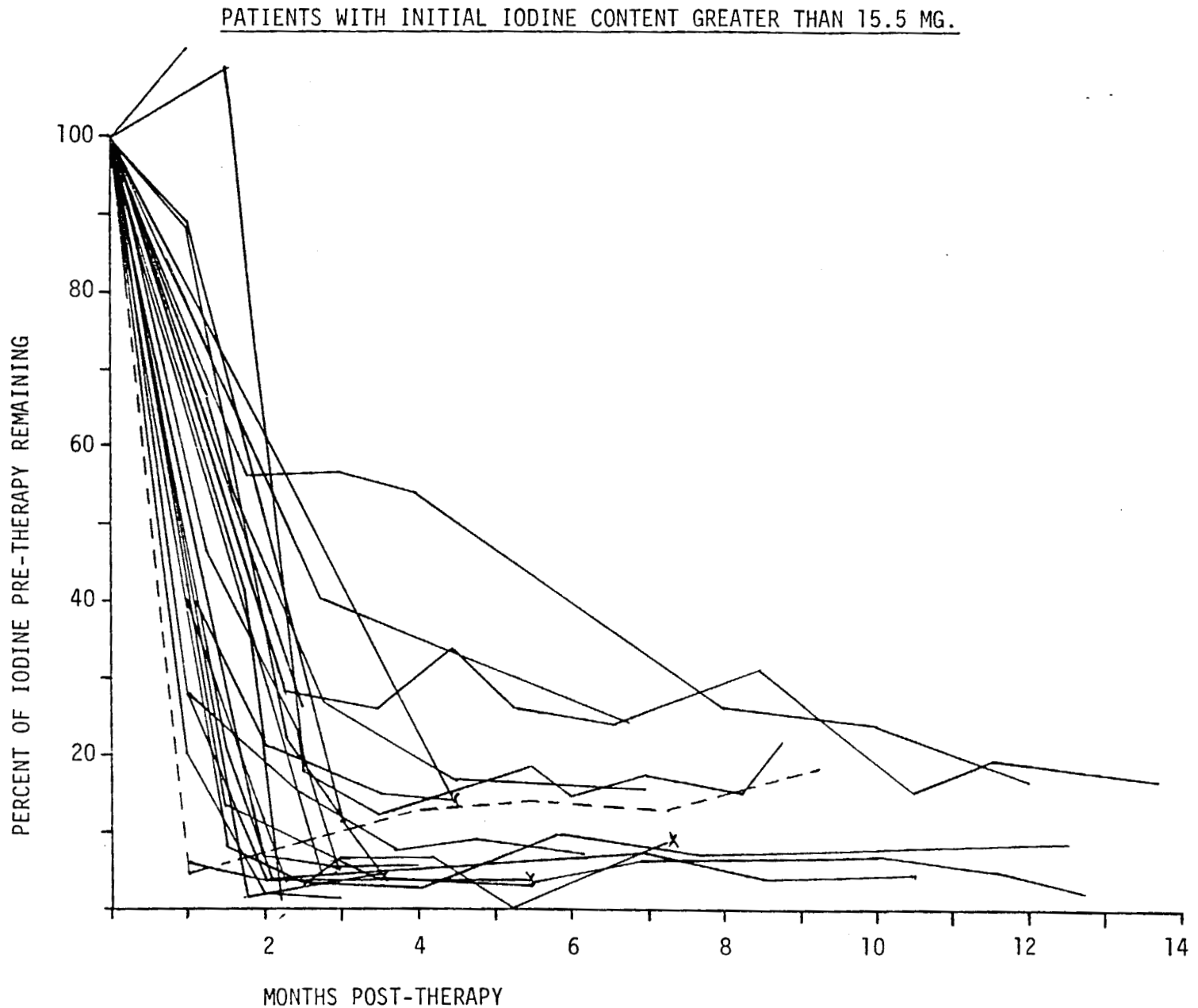


Figure 2

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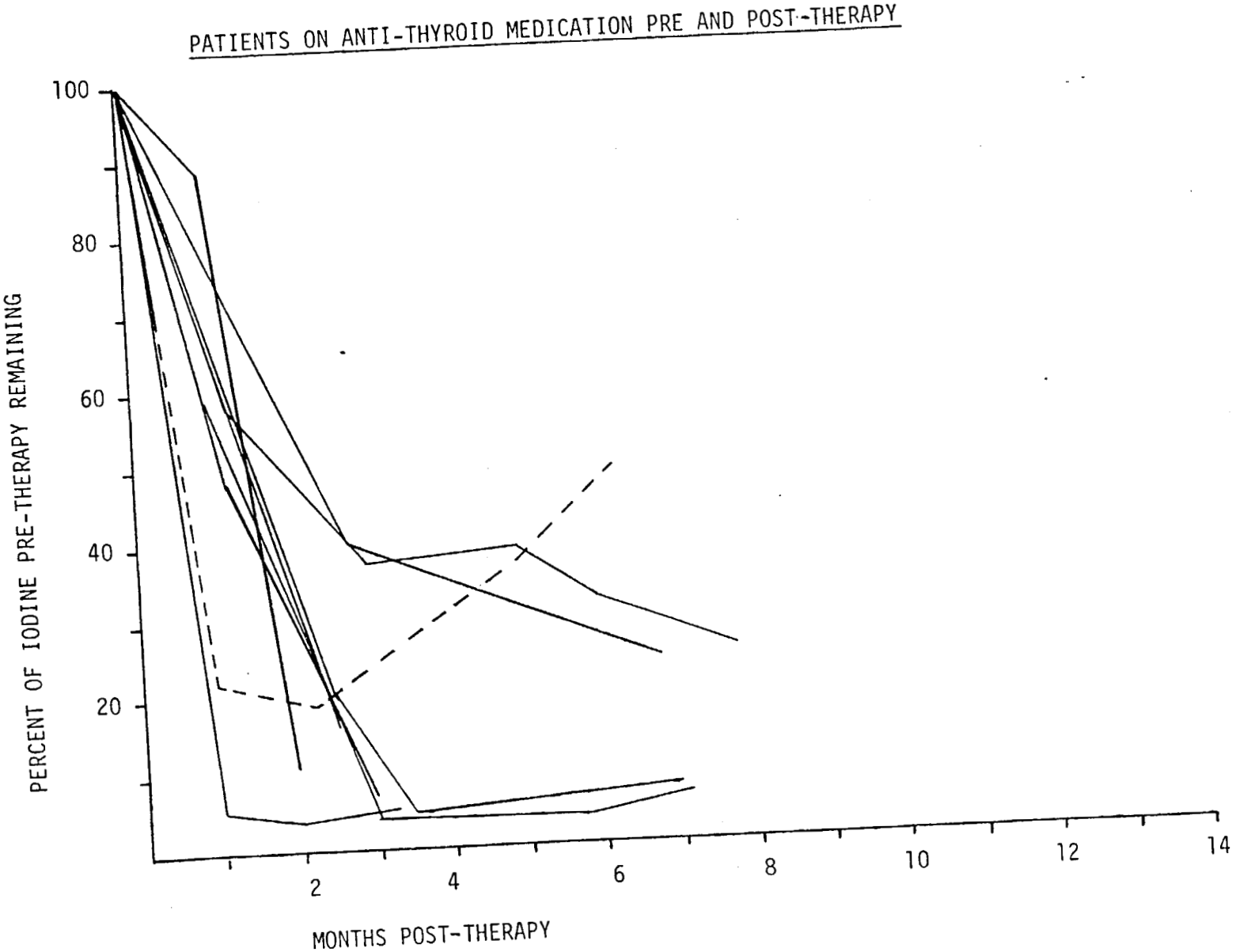

PATIENTS ON ANTI-THYROID MEDICATION PRE AND POST-THERAPY
100
80
60
40
20
PERCENT OF IODINE PRE-THERAPY REMAINING
2
4
6
8
10
12
14
MONTHS POST-THERAPY

Figure 3

PATIENTS ON NO ANTI-THYROID MEDICATION PRE AND POST-THERAPY

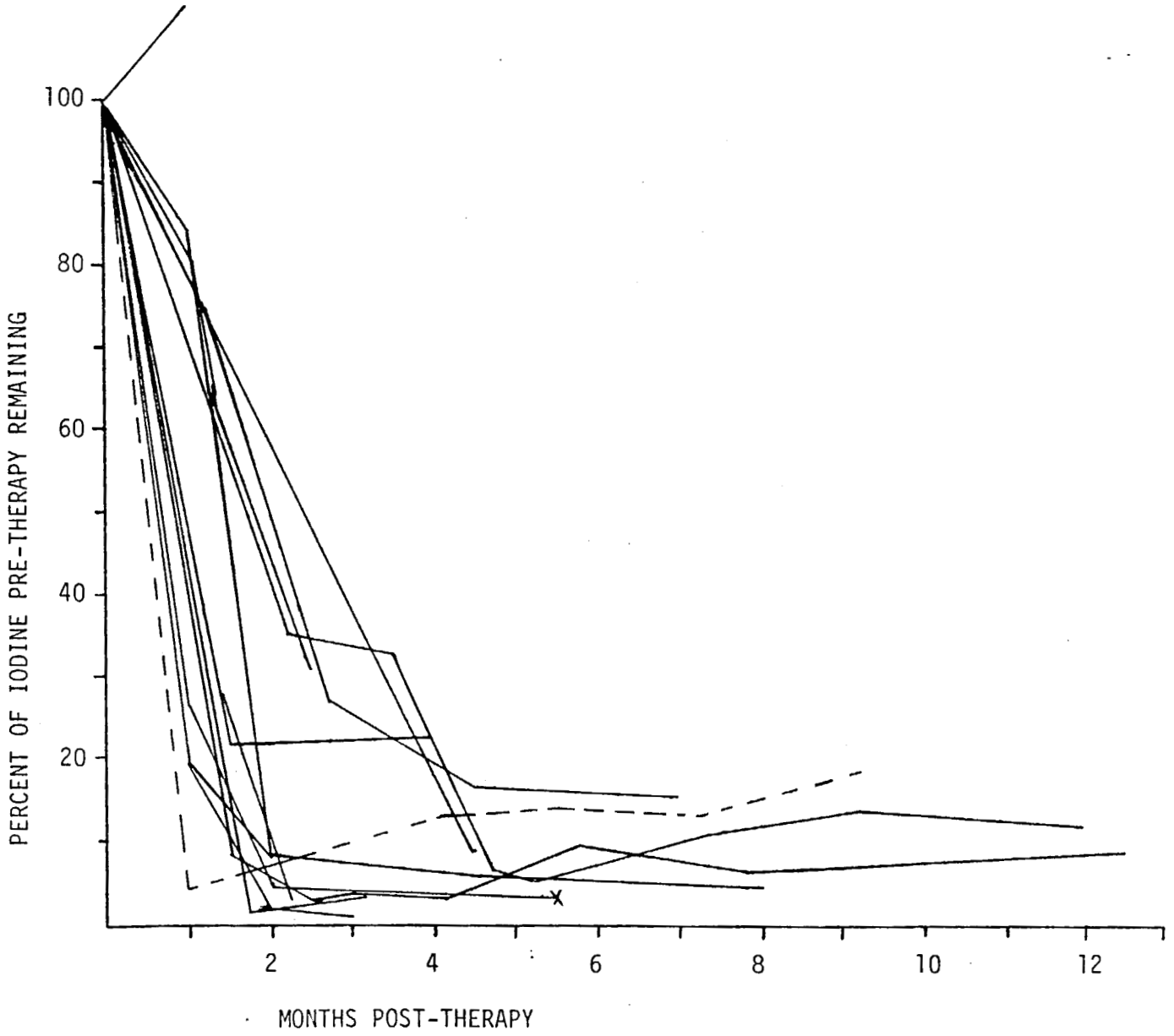


Figure 4

1037196

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.

1037197

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.

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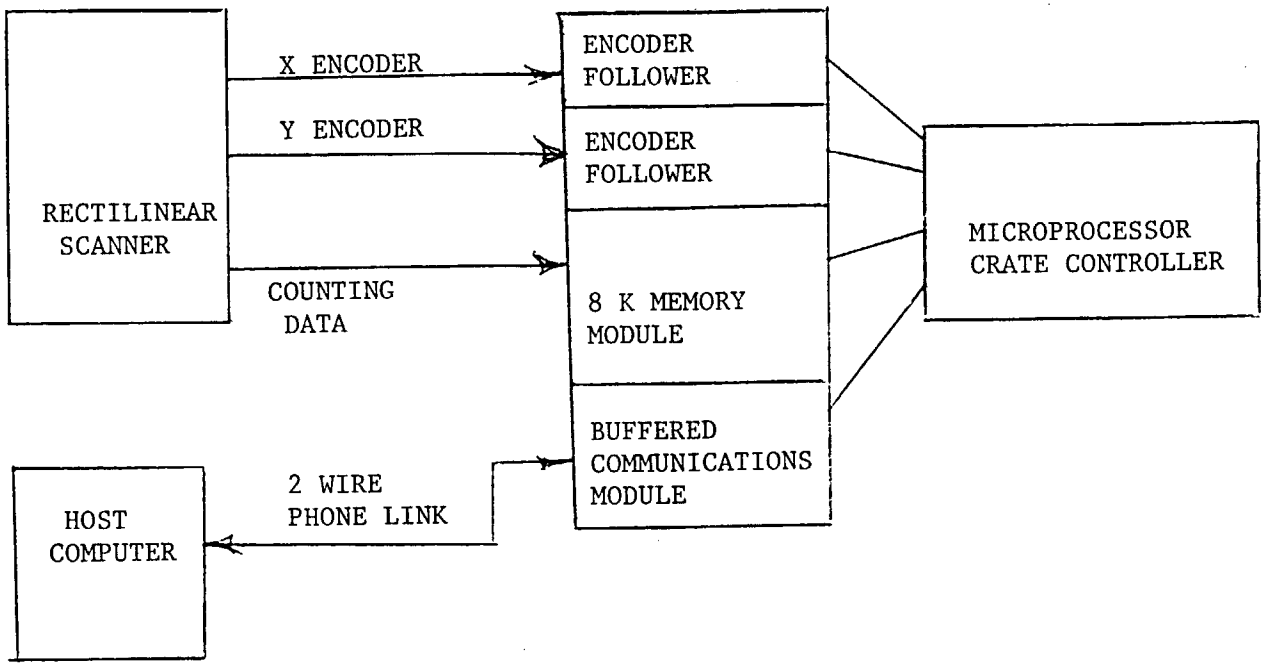


Figure 1. Proposed autonomous CAMAC crate based system for gathering data from a rectilinear scanner with subsequent transmittal to a host computer over a standard telephone line.

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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.,

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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.

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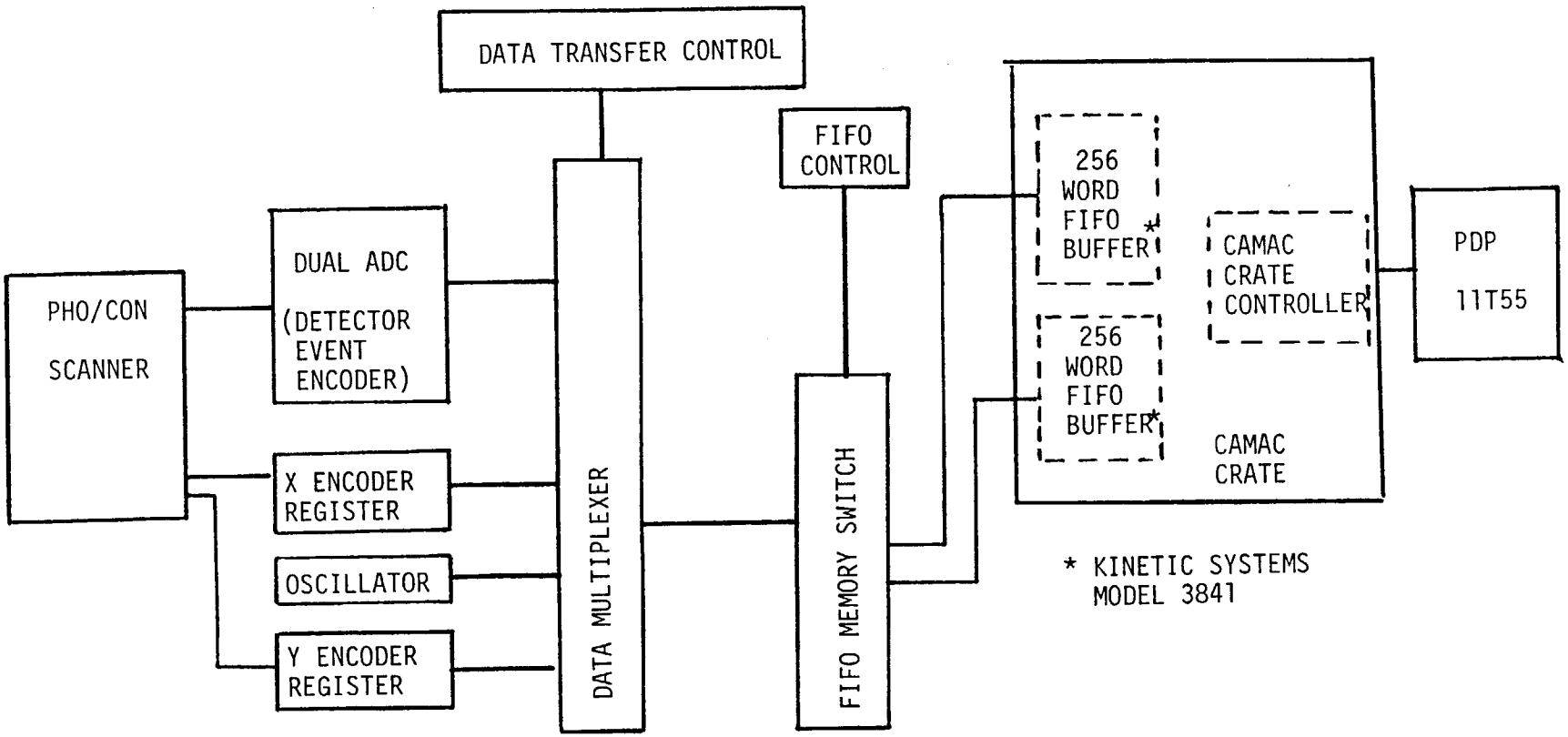


Figure 2. Proposed computer interface for collection of data from a Searle PHO/CON tomographic scanner.

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2. Software

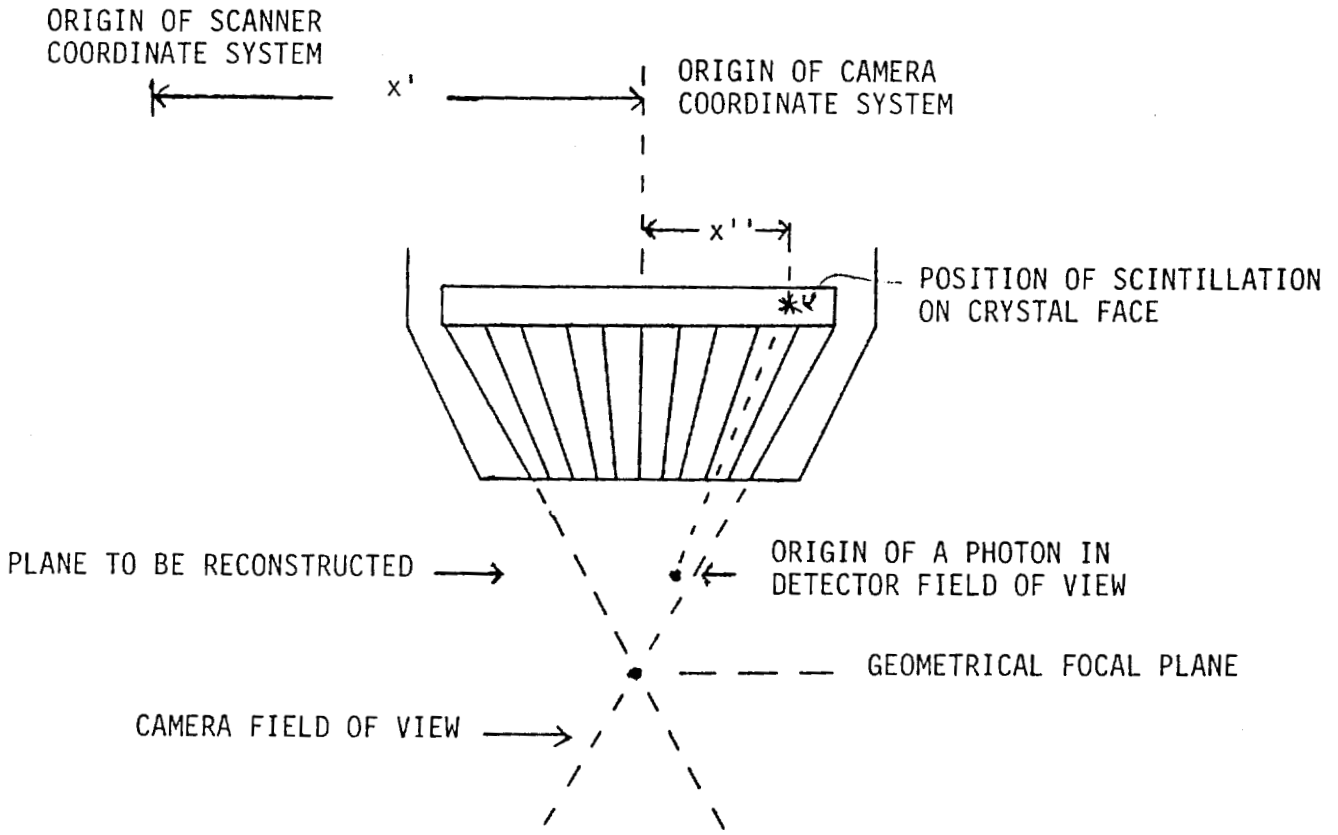
B. 2. a. Acquisition/Reconstruction/Display of Tomographic Data

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 ANAC 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.

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$X = x' + kx''$

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.

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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.

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

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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.

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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

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in obtaining its submission ot BCTIC and in its subsequent testing prior to distribution.

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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

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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

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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.-	---	---

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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.

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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.

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"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

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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

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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

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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.

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 x 10^9/l with a normal differential; the platelets were 160 x 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 x 10^9/l; the reticulocyte count was 1.5%; the platelets were 180 x 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 x 10^9/l with a normal differential; the platelets were 240 x 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.

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.

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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, *——*.

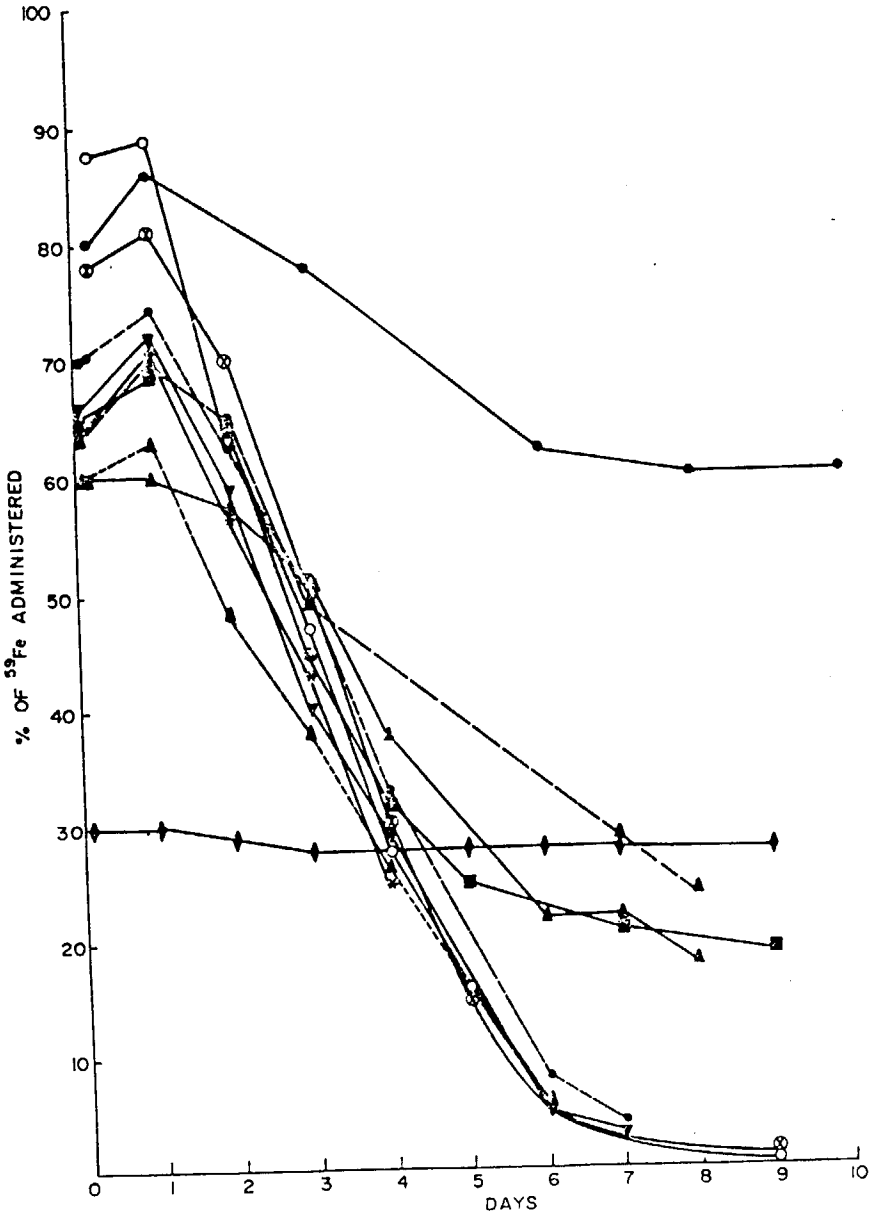

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% OF ^{59}Fe ADMINISTERED
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DAYS

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).

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Fig - C

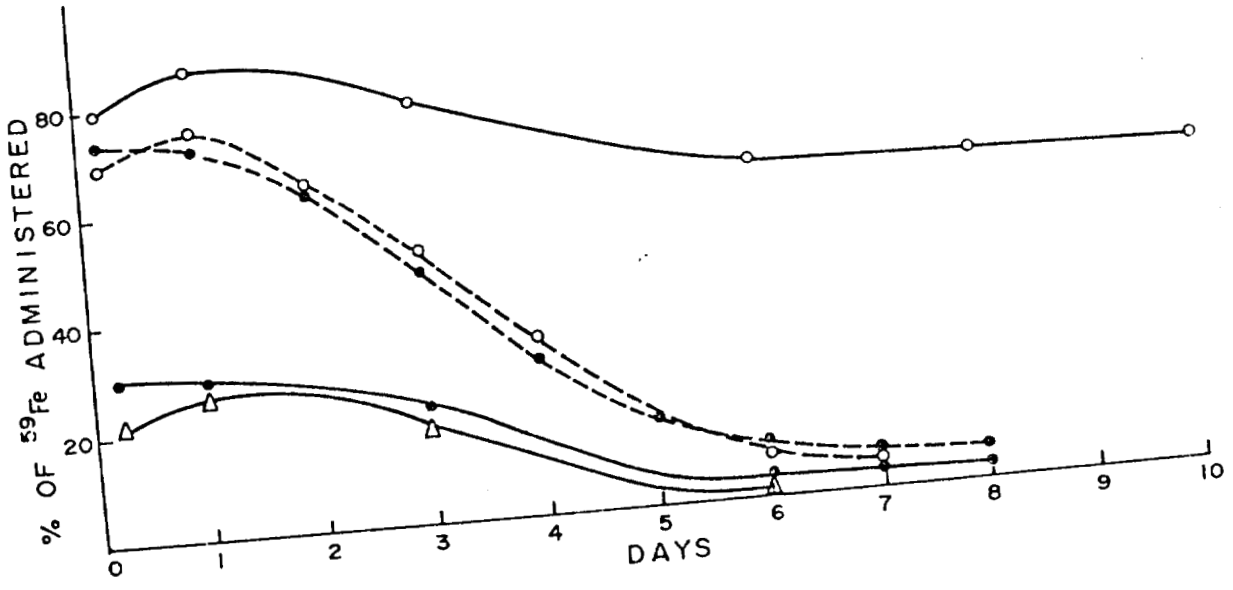
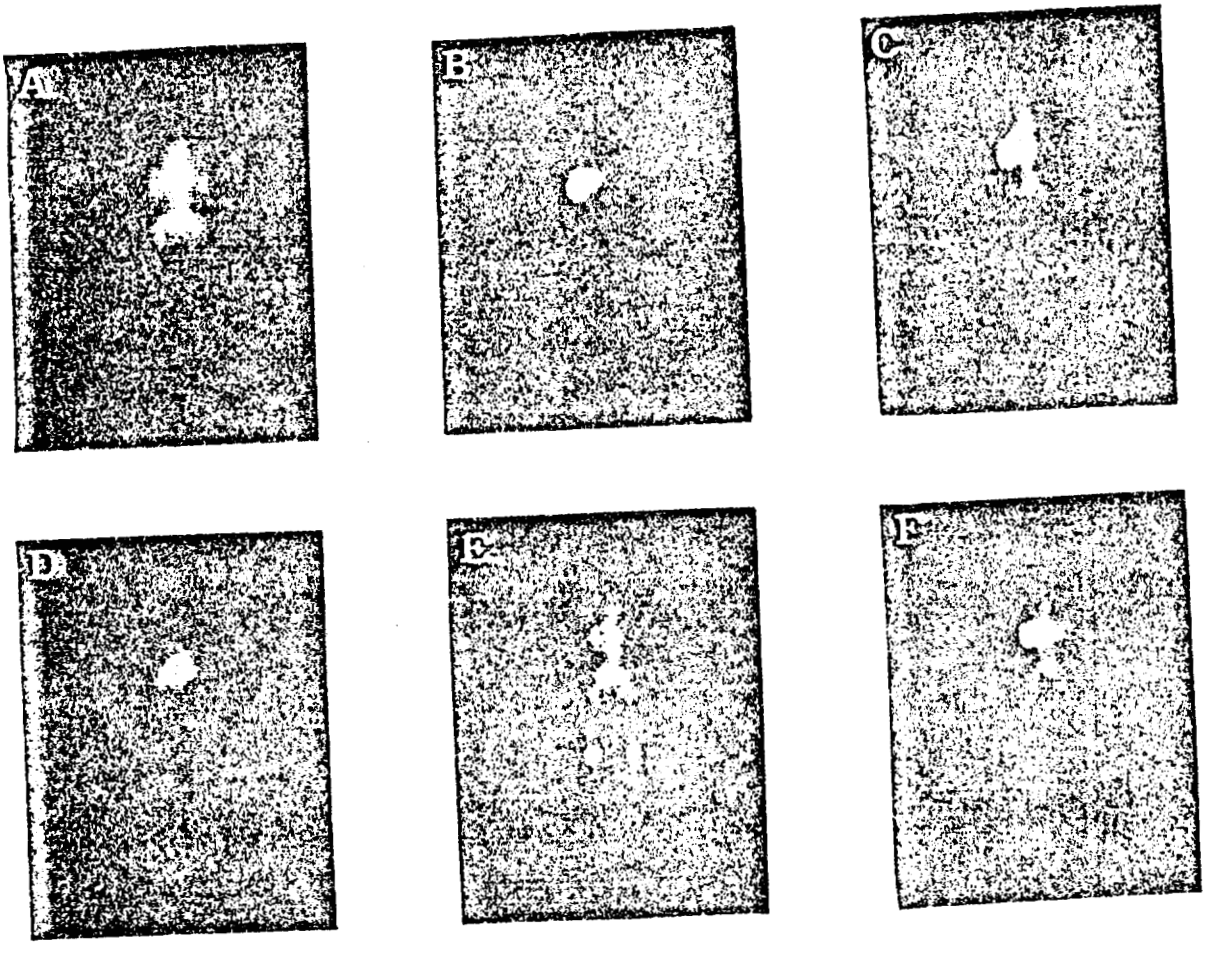


Figure 3. Surface organ scanning (A) Normal volunteer. (B) Patient number 6 with PRCA. (C,D,E,F) Patients with PRCA in remission showing (C) normal marrow distribution of ^{59}Fe in patient number 3, (D) moderate extension of bone marrow into lower extremities in patient number 5, (E) marked extension 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.

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 partcularly useful for dosimetry purposes because the computer program (SAAM),(8) can directly provide the cumulated activities, Ã 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.

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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

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:

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 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.

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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.

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

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TABLE II

Fe-59 Dosimetry

Intercompartmental Rate Constants (fraction/day)

λ_1 λ_2

	Disease	Plasma to Marrow	Marrow to RBC	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

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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."

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	54
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	

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Table V

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.

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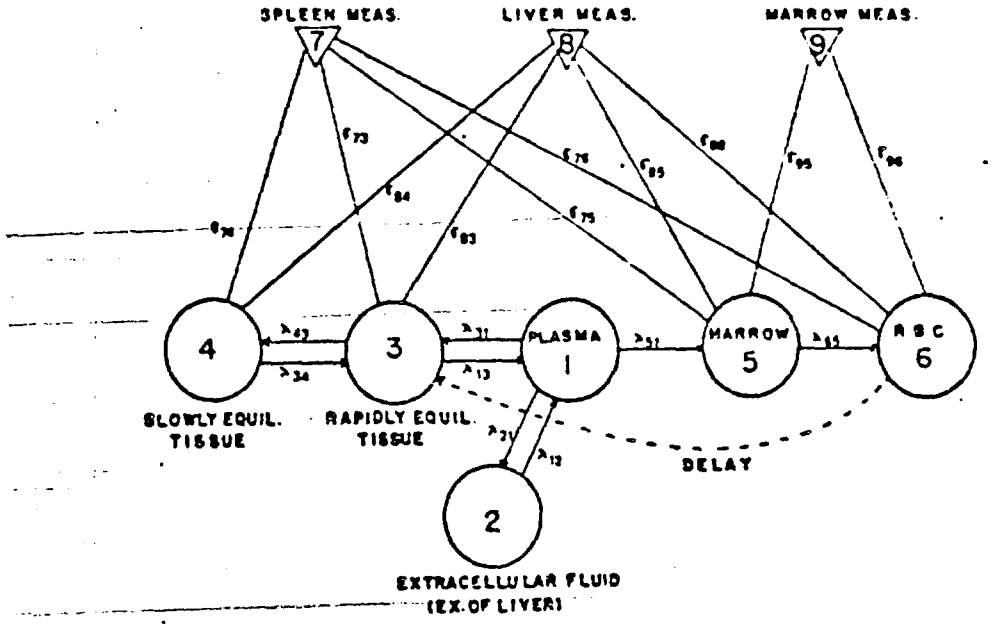
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Appendix I

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)

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

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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•/	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	•/	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•8	•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

SOURCE / TARGET	RED 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	16.0	1.6	19.7

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

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

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

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

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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•8	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

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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

$\Omega_{ij}(d_j, z)$ = 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

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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

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

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:

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

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):

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

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

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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

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

$A'/A >$ 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

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(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

$$T_j = a \exp\left[-\mu(d_j \mp t_j/2 - z_{1,j})\right] \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)} \tag{11a}$$

$$B_j = b \exp\left[-\mu(t_j/2 + z_{1,j})\right] \frac{\sinh(\mu t_j/2)}{(\mu t_j/2)}, \tag{11b}$$

and (6) becomes

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

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

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

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

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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

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):

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

By expanding the exponential in a power series, one has

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

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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).

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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

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

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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.

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Appendix IV a.

Draft - Section 5. NCRP-55 (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

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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.

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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

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 inrregularly-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,

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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 overlaving the liver. On humans, this slab was simulated with an array of LiF TLD's of the same thickness. Again reasonable agreement

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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

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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

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

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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

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

Edward Purich
Lederle Labs
Pearl River, New York 10965

1037281

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(R)

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CONTRACT NO. DE-AS05-76ER02401

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BOOK III BEGINNING WITH MOD 20

1037282

TO : Addressees Listed Below DATE: December 27, 1976

FROM : F. O. Christie, Director, Contract Division, ORO

SUBJECT: CONTRACTUAL DOCUMENT(S) FOR REVIEW, COMMENTS AND INITIALING

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Modification A026 to Contract EY-76-S-05-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~W. L. Bowser~~	~~Contract~~	WLB	12/27	
2. ~~A. H. Frost, Jr.~~	~~Contract~~	AHF	12/28	
3. H. S. Oster, Jr.	Finance	HSO	12/29	
4. ~~W. L. Buchanan~~	Budget	WLB	1/5/77	RDS.
5.				
6.	23279			
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Alice Brown	Contract Division - Room 109			

1037283

TO : Addressees Listed Below DATE: September 20, 1976

FROM : F. O. Christie, Director, Contract Division, ORO

SUBJECT: CONTRACTUAL DOCUMENT(S) FOR REVIEW, COMMENTS AND INITIALING

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Modification 25 to Contract E(40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~W. L. Bowser~~	~~Contract~~	WLB	9-20	
2. A. H. Frost, Jr.	Contract			
3. ~~H. S.~~ Oster, Jr.	~~Finance~~	EJC	9/22/76	
4. ~~W. L.~~ Buchanan	~~Budget~~	WLB	9/23/76	
5.				
6.	19362			
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Alice Brown	Contract Division			Room 1011

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Routed by Research Contracts, Procedures and Reports & Contract Division

FORM OR-133 (Rev. December 1975) number

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	Deputy Manager
	Assistant to Manager for Pub. Infor.

	CHIEF COUNSEL
	Patent Group

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	Research Contracts, Procedures,
	and Reports Branch
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	(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 WHB

2. OFFICE OF CHIEF COUNSEL CONCURRENCE DMS 12/15/76

1031285

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

November 24, 1976

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-A026
   Contractor: Vanderbilt University

2. Nature of Services To Be Covered by Contract: Research

   Title: "Radioisotope Studies-Clinical Application of Activation Analysis"

3. Type of Contract:
   (X) Support Agreement ( ) Cost Type ( ) Other

4. Amount of ERDA Funds To Be Obligated by this CA: $74,419

5. ERDA Percentage of Est. Total Cost To Be shown by this CA: 100%

6. Description or Other Changes To Be Covered by this CA:
   Modify contract to provide for $74,419 in additional funds. Increase support ceiling from $469,699 to $544,118. Appendix "A" is revised accordingly. There are no other changes to the contract.

7. Authority:
   PR# E05-77-0022
   from J. L. Liverman, AES, HQ
   dtd 11-3-76

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACK: WLB

AMERICAN REVOLUTION BICENTENNIAL 1776-1976

1037286

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

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(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.

1037288

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".

1037289

U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
PROCUREMENT COMMITMENT/OBLIGATION RECORD

1. TO: Certifying Official	2. FROM: Procurement Office	3. Control Number
BUDGET DIVISION	CONTRACT DIVISION	CD-38
		4. Date Negotiated
5. Allotment Symbol	6. Signature of Contracting Officer and Title	7. Telephone Number
06 70 91 (24)	A. H. Frost, Jr.	3-4105

8. Contract Number and TO/PA	9. Modification No.	10. Funding Period
EY-76-S-05-2401	A-26	

11. Name of Contractor	12. Type of Contract
VANDERBILT UNIVERSITY	SRSA

13. Procurement Request Number	14. Budget and Reporting Classification	15. Object Class	16. Amount Of This Action
E05-77-0022	RT-01	04	$74,415
21439			
12-8-76			
17. Total			

Receipt of original Procurement Request noted.

18. Signature	19. Telephone Number	20. Date
[signature]		11/12/76

21. Remarks

22. Negotiating Complete and Funds Reserved on:		23. Signed Contract Received and Effectively Obligated by Budget on:	
Date	Initials	Date	Initials
12/1	[initials]		

FORM ERDA 799
(3-76)
ERDA-PR 9-16

U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

PROCUREMENT REQUEST

Please Type (See Instructions on Reverse of Last Sheet)

1. TO: Procurement Office	2. From	3. Procurement Request Number
R. J. Hart, Mgr., OR -- Vanderbilt University Dr. A. Brill, P.I.	Activity Title: AES Division: BER Project: P&T	E-05-77-0022

4.	5. Priority Rating (Ref. FPR 1-1.311)	6. Desired Award Date	7. Security Classification (ERDAM APP. 3401)
☐ Contract ☐ Grant ☒ Special Research Support Agreement (SRSA) ☐ Other ☐ Modification of E=(40-1)-2401 Contract Number TO/PA ☐ Change Order ☐ Supplemental Agreement	Routine	11/01/76	☒ Unclass. ☐ Secret ☐ Conf. ☐ Top Secret

8. SERVICES, ARTICLES, MODIFICATIONS OR OTHER ACTION REQUIRED

TITLE Radioisotope Studies - Clinical Appl. of Activation 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 adsorbed dose from medical radionuclides. TERM: 11/01/76-10/31/77 - 12 months. Subject to availability of FY 1977 appropriations.		

e. TOTAL ESTIMATED AMOUNT OF THIS ACTION $

9. Competitive Procurement / Non-Competitive Procurement	10. Is Source Evaluation Board Required?	11. Procurement Request Resulting From Unsolicited Proposal
☐ Competitive ☒ Non-Competitive If competitive, attach technical evaluation plan. If non-competitive, attach justification. Ref.: FPR 1-3.101(d) & ERDA-PR 9-55.2	☐ YES ☒ NO Ref.: ERDA Source Evaluation and Selection Handbook	If yes, attach copy of proposal and determination Ref.: ERDA-PR 9-4.52 and 9-4.51 ☒ YES ☐ NO BER-00-636 UNSOLICITED PROPOSAL NUMBER

12. Cost Sharing Contract	13. Government Furnished Equipment and Facilities Required? Property title to vest in contract	14. Recommended Source(s)
☐ YES ☒ NO If yes, attach details of cost sharing. Ref.: ERDA-PR 9-4.56	If yes, attach details of requirements. ☐ YES ☐ NO	Attach name(s) and address(es) of source(s).

15. Report and Drawings Requirements	16. Budget Activity Program, Subprogram, and Activity (ERDAM Appendix 1101, Part II)
If yes, attach details of requirements. ☐ YES ☒ NO	RT 01 04 $ 74,419. Amount of Funds Authorized

17. Requestor (Typed name, title, location, telephone number, date)	19. Certifying Official (Typed name, title, location, telephone number, date)
Walter H. Weyzen, PTP/BER x35355 (Name) W H Weyzen 9-16-76 (Signature)	NOV [illegible] (Date) *I hereby certify that funds in the amount here stated are available for such purposes under Allotment* 4230 06-70-01(24) NOV 05 1976 H. G. Fish, Dir:OPC/AES x33541 (Signature)

18. Authorizing Program Official (Typed name, title, location, telephone number, date)

James L. Liverman, AAES 11/1/76
(Signature)

1037291

PROCUREMENT OFFICE

VANDERBILT UNIVERSITY

NASHVILLE, TENNESSEE 37232 TELEPHONE 322-7311 AREA 615

Division of Nuclear Medicine & Biophysics • School of Medicine • Direct phone 322-2394

November 17, 1976

A.H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division
U.S. ERDA
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tennessee 37830

Re: EY-76-S-05-2401

Dear Mr. Frost:

The expenditure of funds for the period November 1, 1976 through October 31, 1977 will be as follows:

$33,038.	Personnel
20,484.	Indirect Costs @ 62%
14,997.	Supplies
4,400.	Equipment
1,500.	Travel - domestic
$74,419.	

Thank you again for your continued support for our project.

Sincerely,

A.B. Brill, M.D.
Chief Division of Nuclear Medicine

ABB/bjc

John H. Hash, Ph.D.
Associate Dean for
Biomedical Sciences

Paul D. Gazzerro, Jr.,
Associate Vice-Chancellor
for Medical Affairs Operations
and Fiscal Planning

NOV 22 1976

22032

1037292

VANDERBILT UNIVERSITY

NASHVILLE, TENNESSEE 37232 TELEPHONE (615) 322-7311

Director of Finance • Medical Center • Direct phone 322-6684

FINANCIAL STATEMENT

CONTRACT NO. AT-(40-1)-2401

Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period.	$ 35,137.00
2.	Estimated total cost for remainder of period.	$ 51,777.00
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	$ 81,873.00
4.	Accumulated costs chargeable to ERDA (include costs reported in certified statement for preceding period(s) and the costs stated in Item (3) above.)	$ 451,094.00
5.	Accumulated ERDA Support Ceiling as stated in Article 111 of contract.	$ 451,094.00
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

Dr. A. Bertrand Brill

1037293

Expenditure Statement and Renewal Proposal

ERDA Contract E-(40-1)-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

April 30, 1976

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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 work to improve on the methods to diminish errors. The major problem that we face involves the integration of our interests and capabilities with those of the 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 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 the dosimetry of I-131 hippuran. In these studies, we will investigate dose variations resulting from kinetic changes to disease variations due to non-standard organ sizes, and inhomogeneous radioisotope distributions. A new study will be carried out in cooperation with the Division of Endocrinology with a new iodocholesterol adrenal scanning agent to compare the dosimetry 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 will investigate 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 used in an effort to formulate sensitivity functions.

We are completing the development of a 9-detector mosaic intrinsic germanium system. The system was designed and built in collaboration with the Lawrence Berkeley Radiation Laboratory under NIH sponsorship for high resolution tumor scanning. The system was delivered in December 1975. Evaluation experiments on resolution and sensitivity have been most encouraging. The system interface to a PDP-11 computer acquisition system is currently being updated in order to allow more rapid data collection and image generation. The system will be used to determine the dosimetry of myocardial scanning agents in animal models, as well as in man.

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

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insuring the general acceptance and survival of this important internationally accepted interfacing standard. We are continuing to extend our system to acquire data from additional diagnostic instruments. For this purpose, we are collaborating with the Fermi National Accelerator Laboratory and the Los Alamos Scientific Laboratory. From FNAL we recently borrowed an autonomous crate controller which utilizes an Intel 8080 micropressor. This controller has the potential of acquiring and storing data from numerous clinical devices without the aid of a larger computer thus, cutting down the overhead on more general purpose systems. We are dedicated to assessing the utility of such systems in the nuclear medicine laboratory, and plan to organize a conference in conjunction with the IEEE Meeting in New Orleans (October 1976) to acquaint scientists in nuclear medicine with this technology.

During the past year, the Radiology Department has been greatly strengthened by the arrival of Dr. A. Everette James, Jr. as Department Chairman. In addition, he has recruited outstanding clinicians and scientists to Vanderbilt. Many of the new faculty members added in the last year have distinguished themselves in nuclear medicine. These include Dr. James, himself, plus Henry Pendergrass (from Massachusetts General Hospital - diagnostic radiology plus nuclear medicine), Juan Touya (from UCLA and Montevideo - nuclear medicine), Barry Grove (Walter Reed and Johns Hopkins - nuclear medicine), Gopal Rao (Johns Hopkins - radiological physics and imaging systems). New space will be available shortly which will decompress our research and clinical areas. This will enhance our facilities capabilities significantly. The only remaining need that if met would improve our output, is a faster means of doing quantitative whole body scans. A multicrystal array scanner such as built by Anger, or a commercial analog, as built by Cleon, is being sought for work on this contract.

The staff has achieved a scientific maturity and is a stable group of 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.

We are attempting to disseminate information on our dosimetry work as broadly as possible. Results of studies to date are being presented at ORAU (April Dosimetry Meeing) and University of Michigan (May Isotope Source Meeting).

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. Erickson	BCTIC - Directory Task Group
Dr. Brill	BCTIC - Advisory Committee
	Chairman, NCRP Committee 32 - Administered Radioactivity
	Member, NAS Subcommittee on Radioactivity in Drinking Water

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Dr. Brill (con't)

Chairman, ANSI Committee 44 - Medical Radiation Devices
Chairman, IEEE Committee on Nuclear Medical Scientists
Member, LASL Committee on Instrumentation and Radiopharmaceuticals
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.

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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 Nuclear Medicine and Biophysics. 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. Dr. P. Krolac and staff of the Information Science Program and C. Bradshaw, Director of the Vanderbilt University Computer Center, and his staff have contributed significantly to our work. None of the personnel in other departments have been 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.

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V. Scientific Scope

A. Specific Dosimetry Projects

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

We have just reported that for Tc-99m uniformly distributed in the liver, the standard man model gives dose estimates that compare favorably with dose measurements made on living patients (usually within 30%; but discrepancies up to a factor of two were observed). The target region in that research was a LiF area on the skin of the patient/model over the center of the liver. A thorough investigation of the applicability of the model for patient dose calculation is clearly desirable, and while the research just done gives important results and demonstrates the validity of the methods it now remains to apply it systematically in one of more areas. Patients are of widely different sizes, shapes, and medical conditions, which factors affect dosimetry results. A means of assessing the dose correlates of geometric differences is needed, especially for commonly-occuring source distributions.

One way to do this is by ultrasonic scanning, particularly for organs in the abdomen. From a series of ultrasonic scans of several patients, one can compare the geometric relationsips between major organs (liver, spleen, kidneys) of patients and the model. Further, this can be done quantitatively, rather than qualitatively, using techniques developed in our previous study to evaluate the accuracy of liver activity estimates. An important consideration in relating detector count rate to source activity is the geometric relationship between body thickness and source organ thickness. If this relationship meets a certain condition, the Schwarz Inequality[1,2] becomes an equality, and the relation between source activity and detector count rate is relatively simple. If not, the relationship is more complex. The condition itself combines the effects of geometry with photon attenuation. Since attenuation can be found easily by scanning the desired radionuclides in phantoms, and geometry can be found from the ultrasound data, a more thorough evaluation of the effects of patient size and shape can be made as a function of photon energy, and can be quantitatively compared to the model.

These investigations will be carried out in patients receiving Tc-sulfur colloid and I-131 rose bengal liver scans. The frequency of rose bengal studies in our laboratory is quite low and it may consequently be difficult to obtain adequate dosimetric data. Studies will be obtained whenever possible. Ultrasonic organ volume technique used for tnese studies will also be used for the liver and spleen volume estimate in the Fe-59 citrate studies.

2. Iron-59 Citrate Dosimetry in Abnormals

We have collected quantitative information on the metabolic fate of Fe-59 administered intravenously for many years in a number of abnormal subjects. During the past year we have carried out detailed kinetic studies on an additional 10 patients. These studies have been in cooperation with Dr. Sandford Krantz of the Department of Hematology, each of which has lasted an average of 12-14 days. Measurements have consisted of daily quantitative whole-body scans, plasma disappearance measurements and daily red blood cell incorporation measurements.

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 an injected tracer with these pools. In order to adequately characterize the storage pools of the liver and spleen 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 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 estimate of absolute circulating iron levels. Our approach, as described in previous reports, has been to develop techniques for making quantitative external measurements of the peripheral iron storage pools and to combine these data with the measurements of the circulating iron pools in a normalized 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.

The MIRD Committee in the United States has created a task group to gather dosimetric information on 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 as a MIRD pamphlet.

In order to conform to earlier MIRD publications, we have sought to derive analytical expressions for the time activity curves of the various organs and model compartments utilizing the iteratively derived least square "best" fit values for the intercompartmental flow rates of the model. (Table I shows the results of these calculations for a group of abnormal subjects having a variety of erythropoietic diseases).

As described in our current Progress Report, we have derived analytical activity functions, utilizing the intercompartmental flow rates for the circulating red blood cell and red marrow compartments. These functions were used to determine the cumulative activity ($\tilde{A}$) for each subject studied to date. For the storage compartments (liver and spleen) each individual study was integrated numerically using the SAAM computer program. During the coming year, we propose to develop similar analytical expressions for the storage compartments.

Using the cumulative activities determined as described above, we have carried out dose estimates to the liver, spleen, red marrow, gonads, blood and total body. A summary of 16 abnormal studies are shown in Table II alongwith literature values from a publication of the Free University of Berlin in 1973. The most striking feature of these data are the extreme ranges of the dose estimates. In particular, we point out the dose estimates to the spleen. In one pathological case (lymphoma of the spleen), we estimated a dose of approximately 13 rem, which is ~10 times higher than normally expected.

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. Table III is a summary of our results to date.

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 might be significant and will be investigated. Liver and spleen volume estimates will be made using ultrasonic scans, whenever possible. Estimates of the regional marrow volume will be made using the projected area from the Fe-59 scans along with standard tables of red marrow distributions. Substantially increased dose estimates resulting from diminished marrow volume will be investigated.

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 component from the storage component using external marrow measurement, 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 (erthyropoietic) pool, and thus, that we can use the In-111 distribution to measure the storage pools of the marrow relative to the spleen and liver. These ratios will then be used to estimate the relative storage content 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.

1037302

TABLE I

Fe-59 Dosimetry (VU Data)

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

1037303

TABLE II

Summary of Fe-59 Citrate Dosimetry
in Abnormals
(mrem/μCi)

	Liver	Spleen	Red Marrow	Gonads	Blood*	Total Body
Vanderbilt	77-425	169-1296	8-191	2-28	1-53	11- 35
Berlin (1973)	100	130	-	27	22	22

* non-penetrating dose only

1037304

Table III

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 Aplasia	114 - 335	169 - 310	14 - 32	2 - 25	1 - 37	15 - 25
Intestinal Bleeding	126	172	52	24	50	25
Normal	77	175	41	23	53	25

1037305

3. Renal Dosimetry
   a. I-131 Hippuran

In our clinic, we do large numbers of renal function studies in a wide variety of patients. Routine procedures include I-131 labelled hippuran studies in patients with two kidneys (bilateral renograms) and transplant studies. Tc-99m labelled DTPA is used frequently in bilateral studies (including bolus studies), and pertechnetate bolus studies are used frequently to examine renal blood flow. Parameters of interest include renal clearance (GFR and ERPF), as well as the distribution of transit times of the flow of pertechnetate through the kidneys.

Our method of measuring renal clearance uses the output of a probe placed over the heart in conjunction with the assay of blood samples. The clearance is then given by the ratio of the injected activity to the integrated plasma concentration. In an effort to improve the amount of information that can be derived from these data, a three-compartment model of plasma, extracellular fluid (EF), and kidney, with flow allowed from plasma to EF, plasma to kidney, and EF to plasma has been analytically solved using first order dynamics. From the probe and blood sample data, one can determine the activity in each compartment as a function of time, as well as all three flow constants. In addition, since clearance is equal to the product of the plasma to kidney flow constant and the plasma volume, one can deduce this last parameter as well. Data from these studies is also useful for dosimetry purposes. Systems developed for dual camera data acquisition, described in section A.1a1 of our current progress report will be used for these studies.

This analysis has been done for several patients, and revealed a difficulty - namely, the calculated plasma volume has been far too large (≃8 liter; ≃1.5 liters expected). Thus, the three compartment model is inadequate, although the cause of the problem is unclear. We suspect it may be related to difficulty of interpretation of the bolus phase of uptake, and propose to study this matter in more detail. Resolution of this problem would then permit the computations of realistic compartmental volumes and intercompartments flow rates, which will be of use both diagnostically and dosimetrically.

We also plan to study the distribution of transit times of activity through the kidney in more detail, with an attempt to separate cortical and medullary components, as described in the next project.

Pertechnetate bolus studies of renal blood flow are being done with transplant kidney patients in an effort to assess the patency of vascular channels, particularly whenever little function is observed with hippuran. The basic method is one of deconvolution of known input and output activity distributions, giving one a distribution of transit times. Since a tendency toward long transit times is suggestive of rejection, it is of interest to evaluate the usefulness of this technique for this purpose, as well as for dose calculations.

1037306

To further assess renal transplant dosimetry, we plan to examine the question of genetic dose for these patients. This will require the use of absorbed fraction data not yet available; i.e. the location of a typical kidney (close to the bladder) is not the same as the source location of normal kidneys in the standard man model, and genetic dose will depend strongly upon appropriate source/target geometry for correct absorbed fractions. We plan to determine these absorbed fractions by either our own calculations, or in collaboration with the Health Physics Division at Oak Ridge National Laboratory. Genetic dose due to bladder activity will also be assessed, but the absorbed fractions here should be approximately correct.

1037307

b. Separation of Cortical and Medullary Activity Distributions

Estimates of the average radiation dose to the kidneys may not be an adequate parameter for an assessment of tissue dose to cortical and medullary tissues from diagnostic radioisotopic procedures in abnormal subjects. The assumption of a homogeneous distribution of radioactivity in the kidney is not rigorously correct even for normal renal kinetics; however, due to the short time constants of the normal system no significant dose increase may be realized for agents which are not retained in the kidney. The same is not the case for abnormals. Depending upon the tracer and the disease state, grossly inhomogeneous distributions of the radioisotopes may result with greatly lengthened time constants. All of these factors lead potentially to significantly increased doses to identifiable subregions of the kidney.

We propose to carry out experiments designed to study the distribution of transit times through the kidney with an attempt to separate the cortical and medullary components. From simultaneous injections of Tl-201 (which localizes in the renal medulla) and Tc-99m DMSA (which localizes in the cortex) the relative "mass" of functional cortical and medullary tissue may be estimated for each point in the renal image. The regional "mass" ratios may then be used with the I-131 hippuran renogram to estimate the net time-activity curves for the total kidney, cortex and medulla. By selecting a very peripheral region of the kidney from the I-131 hippuran renogram, we can derive an estimate of the shape of the time-activity curve of the cortex, assuming that all cortical tissues in the kidney have the same transit-time curve this curve can be used along with the "mass" ratio to decompose the total transit-time curve from the I-131 hippuran study into normalized cortical and medullary curves. Activity curves derived in this manner will be used to make dose estimates to the cortex and medulla. These investigations will be carried out in a prepared dog model for validation.

4. 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 were 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 our total body measurements are shown in Figure 1. The data from the normals and abnormals were fit to a two exponential form:

$$A(t) = a_1 e^{\frac{-0.693}{T1} t} + a_2 e^{\frac{-0.693}{T2} t}$$

The results of these analyses (Table I) indicate no significant differences between normals and abnormals however, both show a significant (12-17%) component having a biological half-time of infinity. Due to the combination of the unfavorable decay properties of I-131 and the long biological half-time of the compound, significant doses are delivered to the blood, gonads and total body.

As shown in Table II, we have estimated total body doses of the order of 1 rad, ovary doses ≈2.2 rads and a blood dose of 1.5 rads per study (assuming 1 mCi administered).

Since that time it has become apparent that the material obtained from the Phoenix Laboratories was contaminated with varying amounts of a second iodocholestral compound, namely the 6 nor methyl derivative (6NC). These two compounds have now been separated, and Searle is planning to distribute the 19IC, while the Phoenix Lab is preparing to distribute 6NC for adrenal visualization studies. It is uncertain at present which compound will have the major advantages in terms of adrenal uptake and retention, target to background ratios and dose considerations in man. We are preparing to embark upon a study to evaluate these factors. During the next year, we propose to carry out studies in approximately 15 patients in cooperation with the Division of Endocrinology at Vanderbilt. Professors Grant Liddle and John Hollifield of that department are following a large number of patients suffering from various adrenal disorders and plan to admit approximately 30 patients during the coming year in whom adrenal functional evaluation will be sought. We plan to collaborate with them in the evaluation of these patients using the 19IC compound for which we have a current IND, and with the 6NC compound as soon as our approval is received.

1037309

TABLE I

Total Body
Biological Retention
of 131-I 19-Iodocholesterol

	Normal	Abnormal
a_1	82.8±14.4	88.4 ± 3.3
T_1	2.19±0.38 days	2.29±0.08 days
a_2	17.2±3.0	11.6±0.4
λ_2	0.00±0.07 1/days	0.00±0.03 1/days
	($T_2 = \infty$)	($T_2 = \infty$)

TABLE II

rads/mCi from I-131 19-iodocholesterol

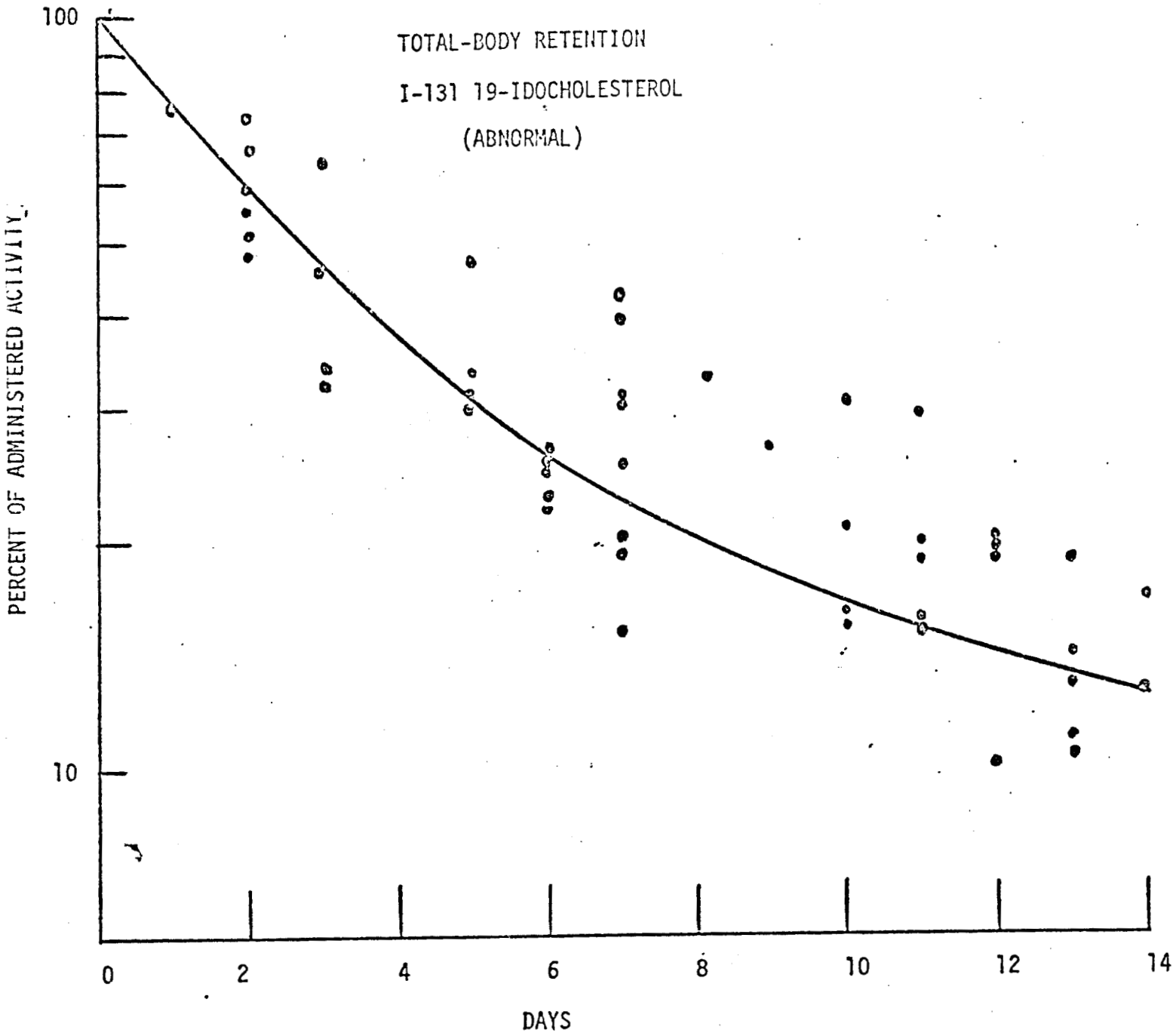
Administered I.V.

Vanderbilt	Beierwaltes* rads/mCi		
.84 - .95	Total body	-	.94
-	Adrenals	-	30.
.44 - .45	Testes	-	2.01
2.17 - 2.33	Ovaries	-	2.88
-	Liver	-	1.38
1.54	Blood	-	-

*Journal of Nuclear Medicine, 16:249, 1975

1037310

Figure 1

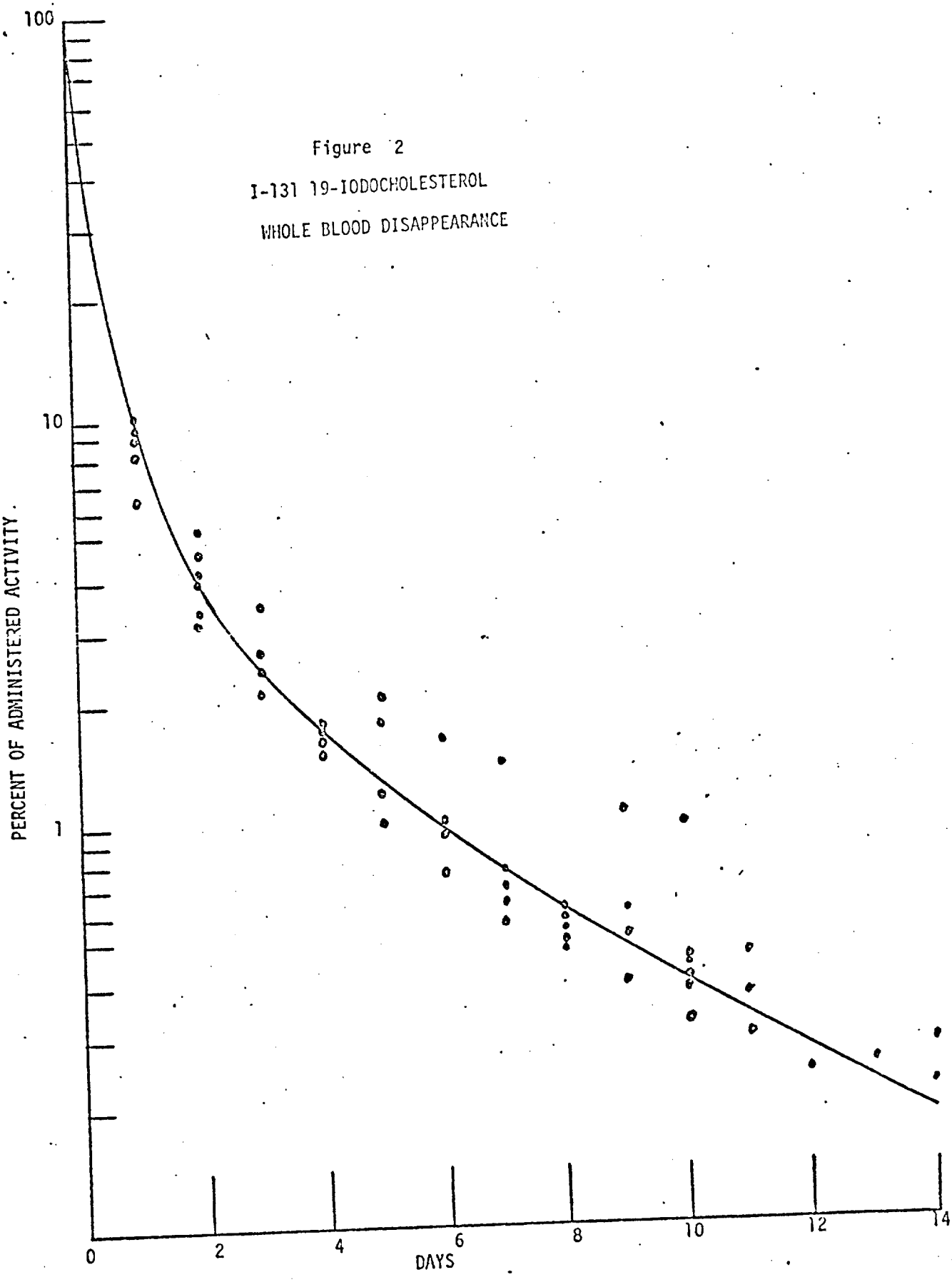


1037311

Figure 2

I-131 19-IODOCHOLESTEROL

WHOLE BLOOD DISAPPEARANCE



1037312

5. Dosimetry Related to Photon Attenuation Measurements of Body Composition

In conjunction with our use of transmission scanning to determine body composition we intend to do dosimetric measurements to insure that our predicted dose estimates are correct. In the past few months we have modified our bone mineral measuring equipment to allow us to quantitate bone mineral content in the lower thoracic and lumbar spine, as well as in the arm.

These measurements involve more radiation sensitive portions of the body than the arm. Our initial calculation as well as measurements on phantoms indicate that the surface doses are < 10 mrad for spine or whole body scans. Using thermoluminescent dosimeters (TLDs) we intend to measure entrance and exist doses in patients of different sizes.

We also plan to initiate multiphoton absorption studies utilizing Gd-153, Am-241 and I-125. Using this technique we hope to determine the amount of calcium and phosphorous separately in small bones in the hand. This method will demand very accurate and precise transmission measurements. Therefore, we expect the radiation dose associated with this procedure to be about 1 or 2 orders or magnitude greater than our other transmission scanning measurements. Because of this, we are tentatively planning on doing these measurements on fingers. Even so, we feel that accurate dose measurements of radiation dose will be necessary. We expect to use TLD's to measure the dose to fingers and compare to the calculations to be made.

1037313

6. 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.

Physicians differ greatly in their ability to estimate thyroid gland size by palpation. It is generally agreed that estimates can be off by as much as 100%, although some persons who have devoted significant efforts to improve their skills are usually within 20% of the true weight, as revealed by analysis of correlations with surgical specimen weights. The use of gland size estimates from outlines of scan defined margins is an imprecise predictor, but does correlate strongly with gland size. The use of x-ray fluorescence provides analogous measurements of gland dimensions based on iodine content distribution, which also correlates very well with gland size (Figures 1 and 2). In addition, given a known iodine content per unit mass of thyroid tissue one can predict thyroid weight with great accuracy in patients with Graves' Disease since the measurement of iodine content has high precision. Needle biopsies, however, in Graves' Disease are rarely performed and hence this is not a practical answer to the mass estimation problem at this time. The remaining technique which works, in principle, but is not used routinely involves the use of ultrasound, to determine thyroid volume. By multiple passes over the thyroid, cross-section maps can be established from which estimates of thyroid volume and inferentially mass can be established. We propose to use this technique in patients going to surgery for thyroid resections and on fresh cadavers prior to autopsy and to evaluate the accuracy of this method in the coming year.

To evaluate thyroid sensitivity, we need to measure a parameter

In some patients we attempt to overtreat them recognizing that hypothyroidism will supervene. We will attempt to relate predictors of hypothyroidism to the observed outcome in these patients with the sensitivity response function (thyroglobulin leakage, and rate of change of iodine content in the gland) and dosimetry (iodine kinetics and ultrasound measurements).

1037315

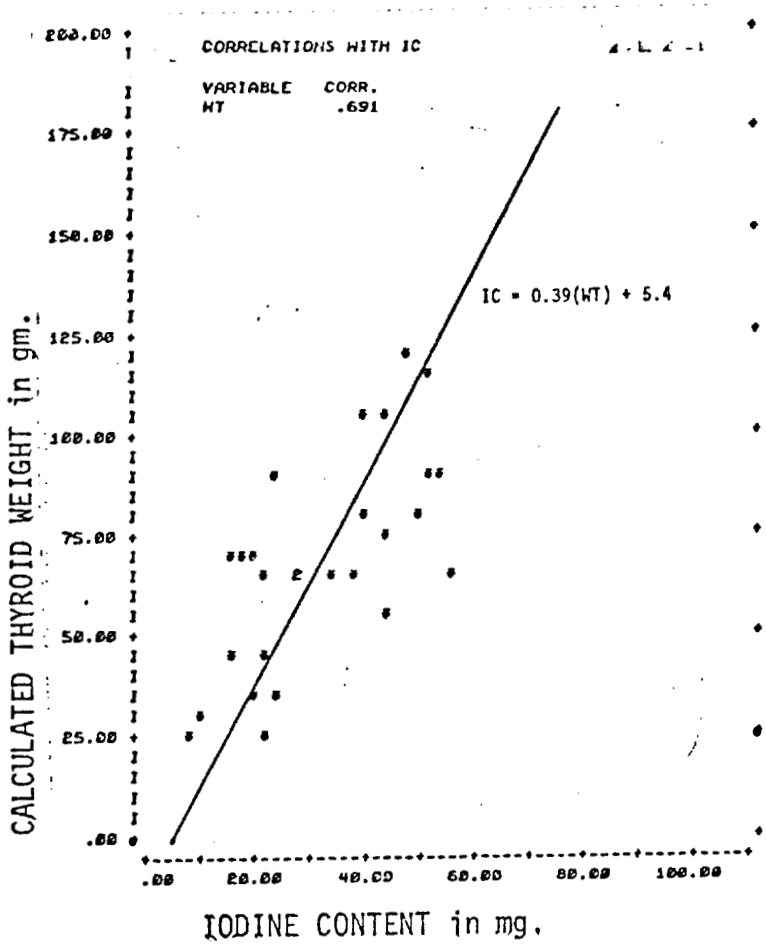


Fig. 1 Plot of estimated thyroid weight vs. iodine content. Values for both variables were obtained from quantitative fluorescent scans of the thyroid.

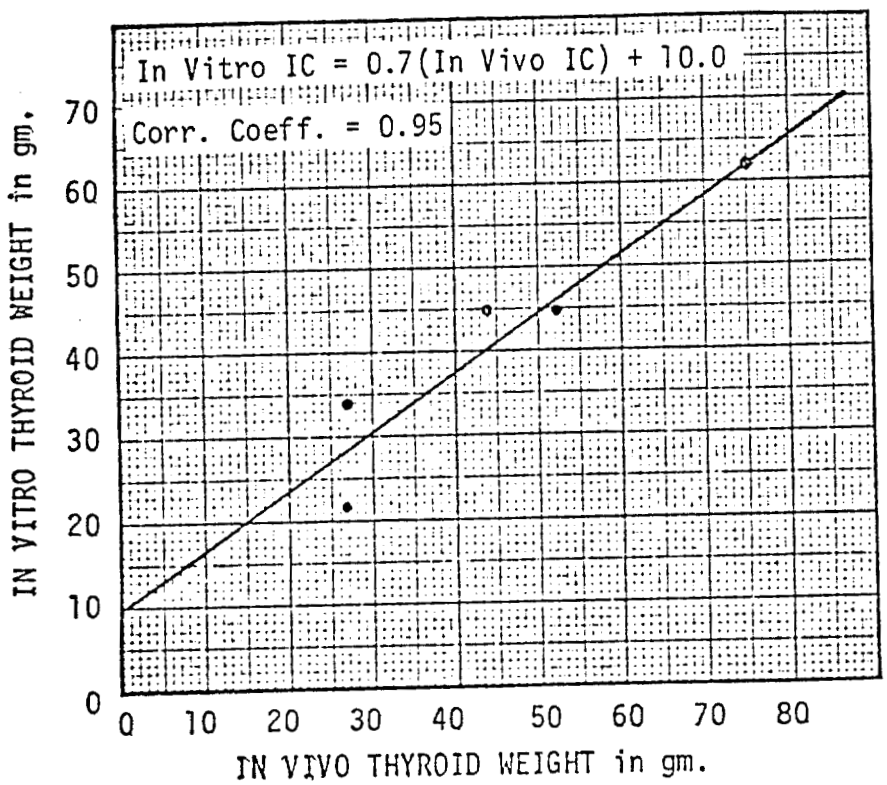


Fig. 2 Plot of in vitro weight as determined post-surgery vs. in vivo weight of the thyroid as determined from quantitative fluorescent scans.

1037316

7. Dosimetry of Myocardial Scanning Agents

Much work is currently being done at Vanderbilt and other laboratories to develop techniques for imaging and delineating areas of myocardial ischemia in patients suspected of suffering from heart disease. The two most common isotopes currently being used are Tc-99m pyrophosphate(Tc PYP) which accumulates in damaged heart muscle and potassium analogs such as Tl, Rb or Cs isotopes which accumulate in normal heart muscle. Simultaneous mapping of the two distributions,(one hot and the other cold), may offer more information than single isotope studies and we plan to explore this possibility in dogs with experimentally induced infarcts. We also plan to obtain dosimetry data from rat studies conducted simultaneously with suitable isotopes of these elements using the germanium system*. Tracers used will be TcPYP, Tl-201, Rb-81, and Cs-131. These radionuclides are selected due to energy and half-life considerations. This system has the spatial resolution necessary to perform these studies in small animals as can be seen from the comparative studies shown in Figure 1. A thyroid phantom containing Tl-201 was imaged utilizing the 70 keV peak with the germanium system*and with two different types of Anger scintillation cameras. From the images it is observed that the spatial resolution of the system is comparable to that of our highest resolution scintillation camera, the Ohio-Nuclear mobile camera, at this energy.

The germanium system also has the energy resolution necessary to perform these simultaneously as shown in Figure 2. A phantom was constructed simulating the heart with two vials representing regions of infarction. The volume was filled with Tl-201 (70 keV), one vial with water, and the other with Tc-99m (140 keV). The Tc-99m activity was 50% of the Tl-201 activity. Both systems imaged the Tc-99m distribution satisfactorily. However, the Tl-201 images show that a void can be imaged clearly with the camera only in the absence of Tc-99m in the void whereas the germanium system images both voids quite well. NaI(Tl) detectors do not have the energy resolution necessary to differentiate adequately between scattered Tc-99m photons, lead x-rays at 75 keV produced in the collimator, and primary Tl-201 photons at 70 keV. Thus the germanium system should be very useful in the simultaneous mapping of multiple distributions such as used in this study. We will attempt to document this presumed fact in our studies.

In addition to Tl-201, Cs-131 and Rb-81 (potassium analogs) will be studied. Rats will be injected with the 3 radionuclides and simultaneous images of the 3 distributions will be obtained at multiple times during the first day and at 1 day intervals for 7 days post-injection. Urine and fecal collection will be attempted throughout the time course of the study and blood samples will be taken at selected intervals. From the quantitative scans, organ uptake values will be obtained and radiation dose calculations performed on the basis of these data.

* intrinsic germanium mosaic array

103717

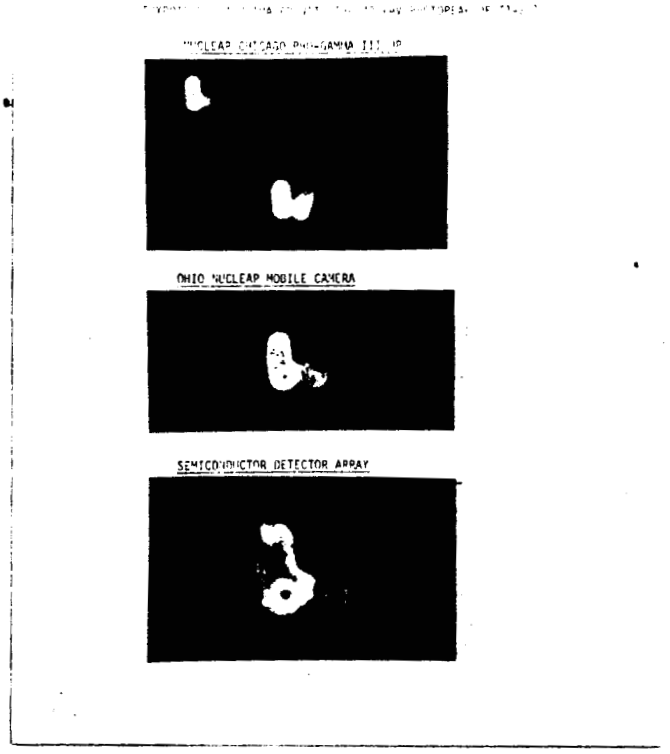


Fig. 1 Photograph of scans of the Picker thyroid phantom imaged with two scintillation cameras and the intrinsic germanium system. The phantom contained Tl-201 and SCA windows were set on the 70 keV peak.

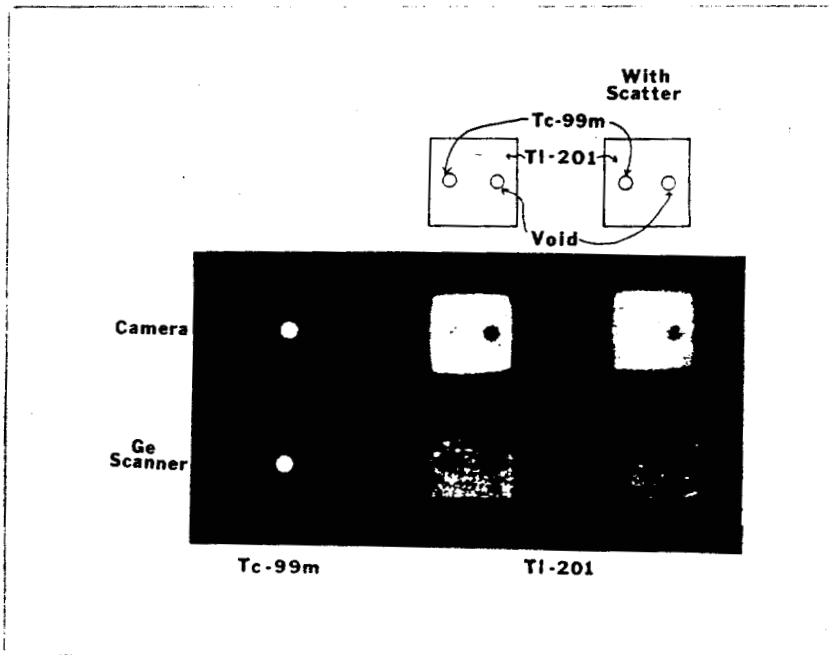


Fig. 2 Photograph of images obtained with the Ohio Nuclear mobile camera and the intrinsic germanium system of a dual isotope distribution of Tc-99m and Tl-201.

1037318

B. Supporting Systems
1. Hardware Development
a. CAMAC Autonomous Crate Controller

Figure 1 illustrates the autonomous CAMAC crate controller system which we presently have on loan from the Fermi National Accelerator Laboratory. We are presently evaluating this system and gaining experience in the programming and use of Intel 8080 microprocessor driven crate controller. At this time the only connection between this CAMAC crate and other computational equipment is the RS-232 CAMAC module indicated in the diagram.

All programming commands and data must pass through this module. The 1200 bit/second rate of this module will pose a significant impediment in all but the simplest data gathering situations. Also, this method of data transfer requires the active intervention of the software in the central computer to transfer the data from its RS-232 port to memory. This would represent an increase in the software overhead of the main computer which would obviate one of the prime advantages of the autonomous crate controller.

For this reason, during the coming year, we plan to complete the design and implementation of a direct memory access port for our PDP-9's. This will allow the transferring of data into and out of the PDP-9 at up to 1 million words/second without software intervention. This device will be used in conjunction with the autonmous crate controller as shown in Figure 2 . In order to fully utilize these transfer capabilities over potentially long distances, the data will be transmitted over a single pair of wires at high speed--(up to 96,000 bytes/sec) in bit serial, byte synchronous mode. The PDP-9 data port will be designed to accept this data format and produce the 18 bit parallel data word required for that computer. In addition, this data port will be designed to be compatible with the CAMAC input and output registers now in use in our laboratory. This will provide us with a high speed parallel I/O port for the PDP-9 as well as the required serial link to the autonomous CAMAC crate. This portion of the system should be complete by the end of July.

In order to fully utilize a high speed data link, the fast input module interfaced to the PDP-9 DMA port (as just described) is needed, plus a similar module at the distal CAMAC crate end of the link. We plan to implement this distal portion of the data link in two steps. At the present time the engineers at FNAL are in the final stages (completion estimated for June 1976) of constructing a high speed data transmission CAMAC module which we plan to borrow as the first step in bringing up our transmission path. This module will be capable of transmitting data at 96,000 bytes/second as required for our design but it has 2 serious disadvantages which prevent its use as the final form of the CAMAC data port. When operating this module uses the CAMAC dataway to obtain data from the Intel 8080 memory thus preventing its use in other CAMAC control and data collection functions during this time period. Also the data transmission module must be supplied data from the 8080 memory by program transfer in the 8080 CPU thus tying up the controller during transmission. Working with the engineers at FNAL we have started to design and plan to construct a CAMAC module which will have the same data transmission capabilities

as the one presently in use but which will utilize a direct memory access path into the Intel 8080 memory. This module is scheduled for completion by October 1976 and will complete the equipment for the autonomous CAMAC data acquisition system.

Dr. Brill is responsible for organizing a special 1 day meeting on interfacing devices to computers in conjunction with the October 1976 meeting of the IEEE in New Orleans. The results of these systems development will be presented along with examples drawn from our work. These will include data collection from scanners, cameras, probes, and mosaic arrays.

1037320

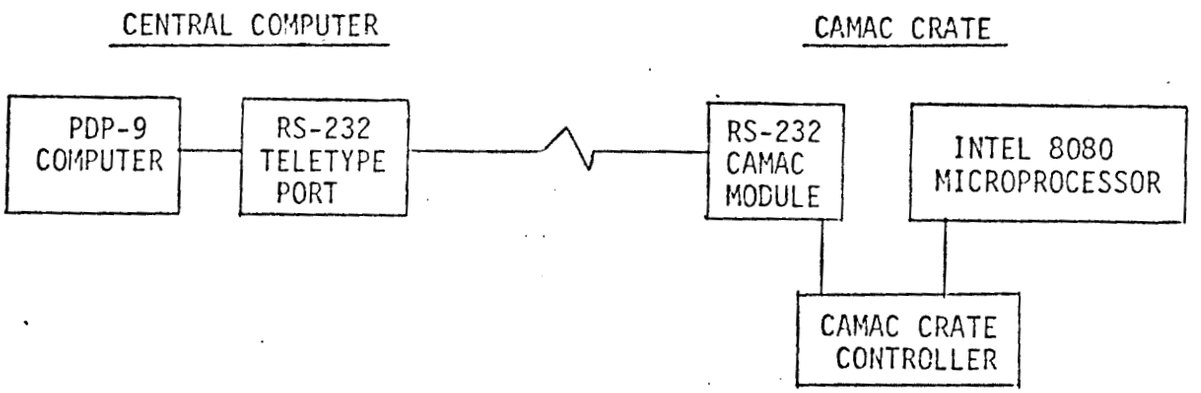


Figure 1. Block diagram of the autonomous CAMAC crate controller system based on the Intel 8080 microprocessor.

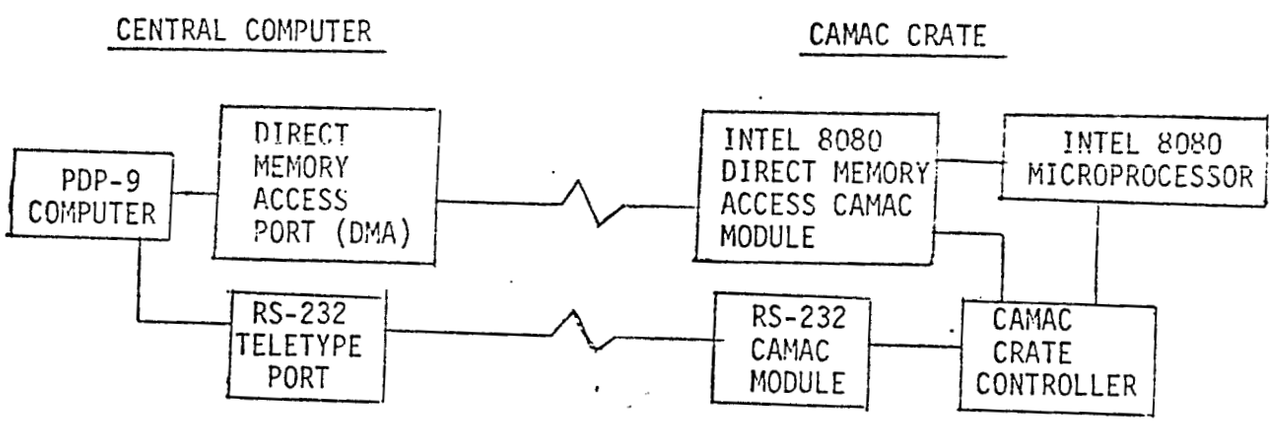


Figure 2. Block diagram of the autonomous CAMAC crate controller showing the high speed, bit serial data link between the DMA of the PDP-9 and the DMA of the Intel 8080 microprocessor

1037321

b. Intrinsic Germanium Detector Array

The use of solid state or semiconductor detectors makes it possible to map very accurately isotope distributions (good spatial resolution) and permits the simultaneous mapping of multiple isotope distributions (good energy resolution). These two characteristics of semiconductor detectors make them very attractive for use in obtaining internal dosimetry data for radioisotopes. However, low sensitivity due to small size has limited the usefulness of these detectors. To solve this problem, Goulding and Pehl designed and fabricated a mosaic detector system at the Lawrence Berkeley Radiation Laboratory under funding by a one year grant from NIH (April 1974-1975). This system arrived at Vanderbilt in November 1975 and preliminary evaluations and monitoring of the system have been performed.

The intrinsic or high purity (HP) germanium (Ge) detector array shown in Figure 1 consists of 9 detectors each 35 mm in diameter, 10 mm thick, and arranged in a 3 x 3 matrix with 50 mm between centers. The 9 detectors are cooled by a common liquid nitrogen reservoir. The electronics associated with the system include two single channel analyzers (SCA) for each detector coupled to the linear amplifiers. All nine detectors are powered by a common high voltage supply with a voltage divider network employed to maintain each detector at its optimum operating voltage. Energy resolution and relative sensitivity measurements made with a point source of Tc-99m at 1 meter from the front surface of the detectors show that the detectors and electronics are very closely matched and the energy resolutions are excellent (1.06 - 1.18 keV at 140 keV).

For routine frontal plane scanning 19 hole focussed collimators with a geometric resolution of .56 cms and a focal length of 8.25 cms have been designed and constructed. These collimators have excellent resolution and relatively uniform response from 2 to 13 cms from the face of the collimator.

The detector electronics have been interfaced to a PDP/11 minicomputer via CAMAC for data acquisition. The system is designed to remain stationary during an imaging procedure with the object to be imaged being moved in an x-y raster. Two modes of operation are available with the instrument.

For phantom and small animal studies the collimated system is suspended over a precision stepping motor-controlled x-y drive system. This scanning system is also interfaced to the PDP/11 computer via CAMAC as shown in the block diagram in Figure 2. The x-y scanner is moved in a rectilinear raster under computer control and data are collected from each of the 18 single channel analyzers (2 for each detector, i.e. 2 photopeaks) simultaneously. Interpretive language programs have been written such that by moving the object to be scanned in a 50 x 50 mm raster (50 mm is the distance between detector centers) and collecting 21 x 21 (medium spatial resolution (2.4 mm/point)) or 42 x 42 (high resolution (1.2 mm/point)) data points from each detector a 64 x 64 or 128 x 128 array can be constructed corresponding to a 150 x 150 mm scan field. The detectors and electronics are very closely matched in efficiency and performance making it possible to normalize between detectors by counting a plane source of activity with each detector and thereby obtaining correction factors. A 64 x 64

10313322

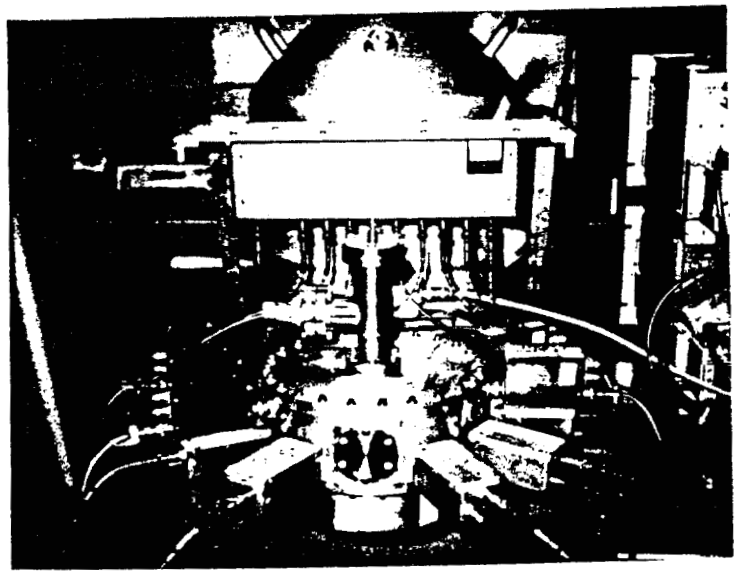


Fig. 1 Photograph of nine detector intrinsic germanium system.

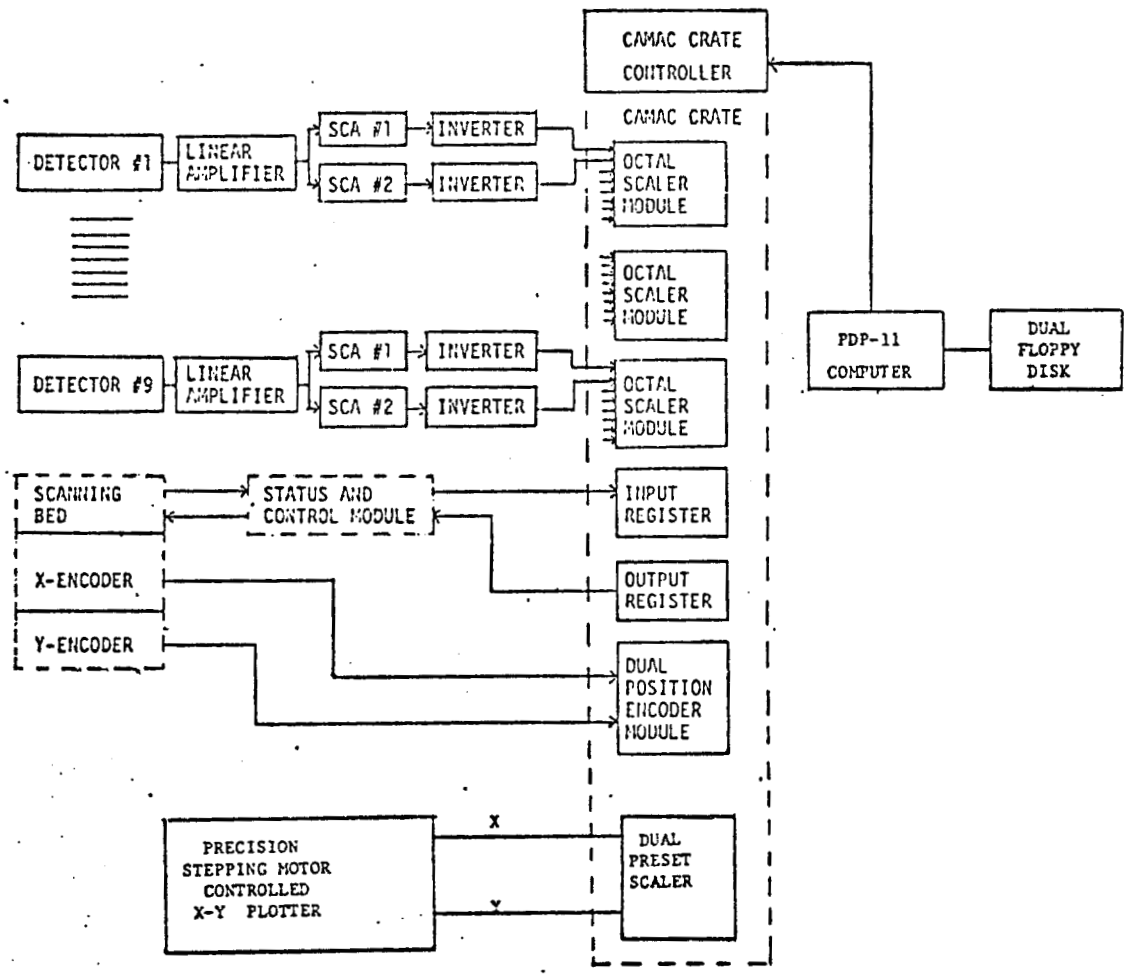


Fig. 2 Block diagram of data acquisition system for intrinsic germanium detector array.

1037323

data point scan of a 125 x 125 mm line phantom of Tc-99m is shown in Figure 3 to demonstrate this data collection technique.

For large animals and patients the computer is interfaced to our scanning bed (dashed lines in Figure 2) which can be moved in an x-y raster under computer control. This interfacing was accomplished initially on our PDP/9 computer via CAMAC and the same system is being duplicated for use with the PDP/11. The system will operate in the same fashion as for the stepping motor-controlled system described above. In scanning areas larger than 150 x 150 mm, the scanning bed is being programmed such that multiple scan fields will be mapped and the resulting data will be rearranged in the computer to produce a single image corresponding to the total scan field. A C-frame support arrangement has been designed and constructed (Figure 4) so that the detector array will be suspended over the scanning bed with the only possible movement being in the vertical direction for positioning. The detector system will then be self-contained with the electronics mounted at the back of the C-frame. Only minor details remain to be completed before this support system is operational.

The work remaining to be done on the scanning bed configuration involves completion of the status and control module interface and the development of machine language programs for efficient data collection. Preliminary studies were conducted using inefficient interpretive language programs. These were adequate for initial test purposes but are very inefficient in time utilization for routine studies, and need to be recoded as soon as possible. This will be accomplished before the end of the summer.

We also plan to complete work on a set of collimators to collect tomographic information with the system. These collimators will have a uniform resolution over a long distance and will be aimed in different directions so that their fields of view intersect at a point which is directly below the central detector. If we define the plane mapped by this common view point as the focal plane of the system, then we can obtain a good representation of the radioisotope distribution in this focal plane by simply summing the data collected from all detectors. However, images of planes lying above and below the focal plane can also be obtained by maintaining the data separately and recombining, after suitable translations of the data into new coordinate systems. These translations are a special case of the general theory for longitudinal section image construction by computer described by Anger for data collected from his multiplane tomographic scanner. After fabrication of the tomographic collimators is complete, programs will be developed for construction of images of transverse sections and the applicability of this system for this purpose will be explored.

10371324

The system as currently used has the ability of selecting two energy windows per detector. However it may become necessary to select a larger number of windows and this may be accomplished by use of an ADC and signal routing information derived from a relatively wide window SCA. A diagram showing the ADC system to be used with 9 detectors is shown in Figure 5A. The dotted lines indicate additional electronics that we borrowed to test the system concept. A wide window is set to include the region of the spectrum to be analyzed by each detector. This is a routing and gating pulse to start digitization in the ADC. Analog inverters are needed between the linear amplifiers and the ADC inputs

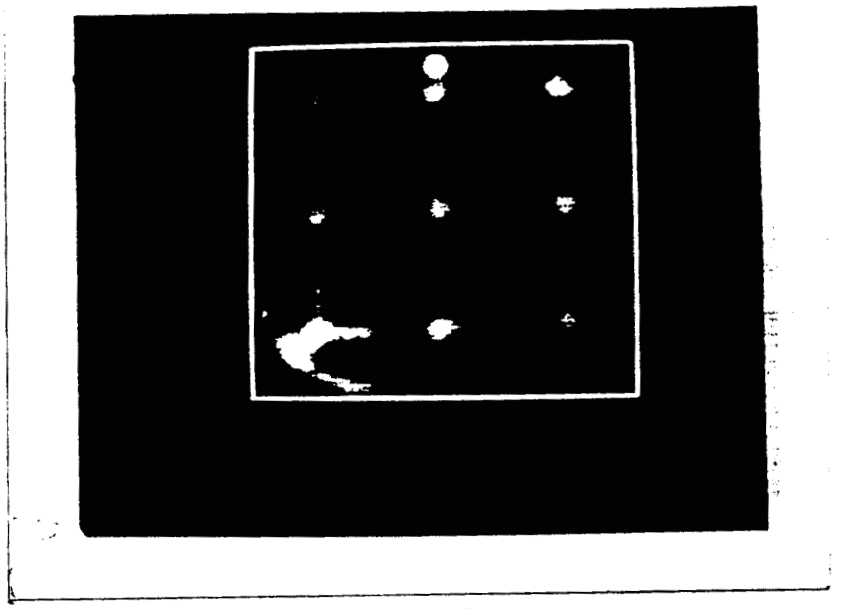


Fig. 3 Photograph of scan of line phantom imaged with intrinsic germanium system. White frame corresponds to a 150 x 150 mm. area.

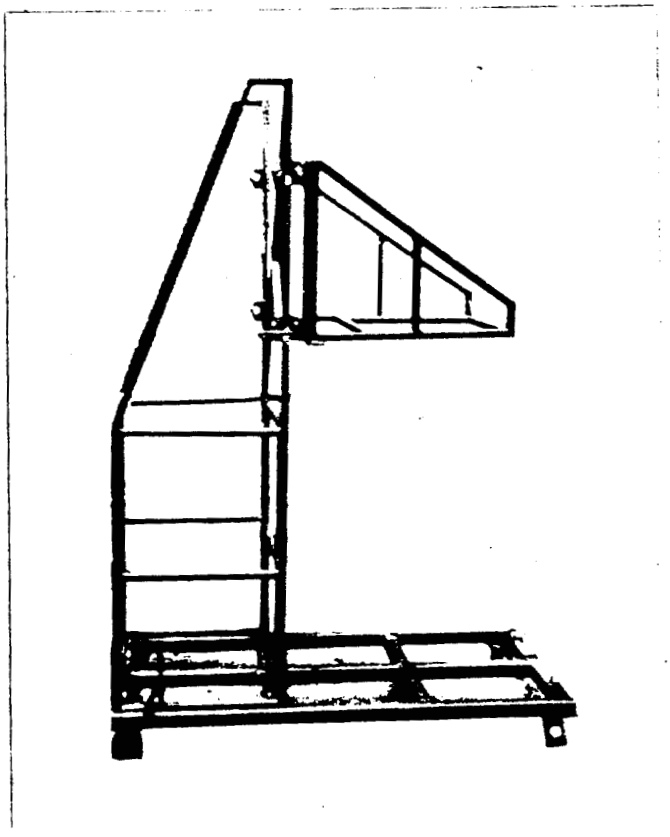
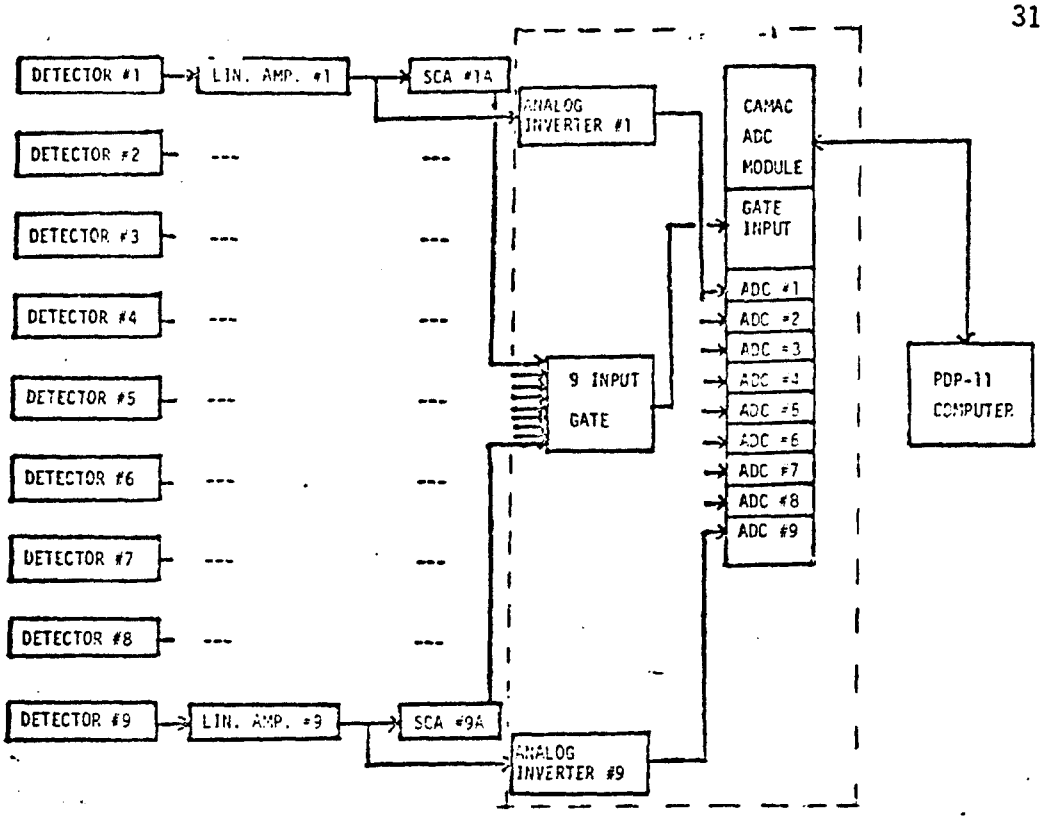
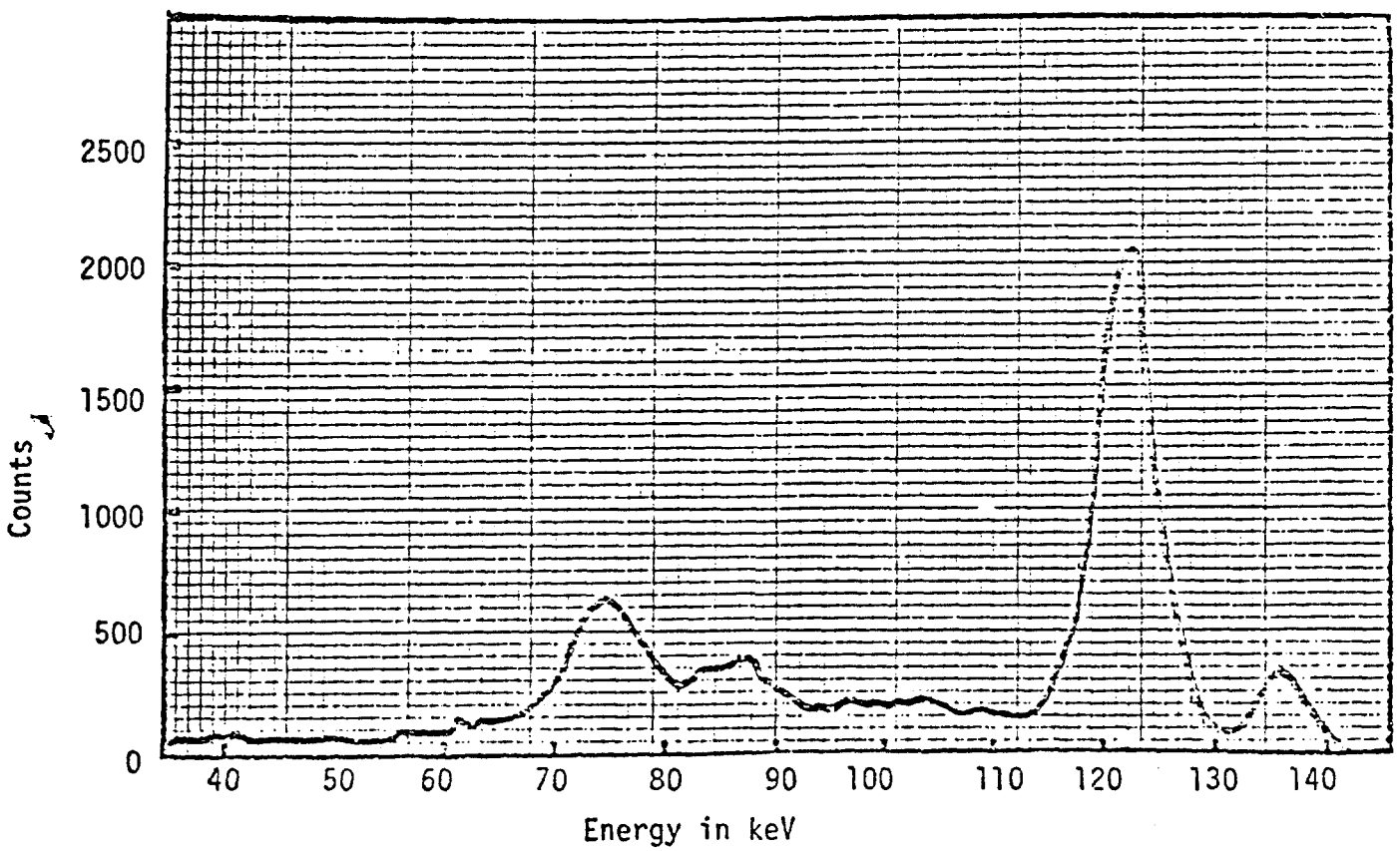


Fig. 4 Photograph of detector mounting system for use with the scanning bed in imaging large animals and patients.

1037325



5A. Block diagram of multiple ADCs in CAMAC for simultaneous collection of multiple energy peaks from multiple detectors.



5B. Energy spectrum collected from a Co-57 source with a single coarse resolution germanium detector to demonstrate capability of system shown at top. SCA window was set to include energy range from 35 to 145 keV.

10313261

because the germanium electronics produce positive signals while the CAMAC ADCs require negative inputs. Timing required by the ADCs is such that the gate signal must bracket in time the analog signal to be digitized. The system would function in the following manner. When an event is detected by one of the detectors and falls into the region of the spectrum to be analyzed, a gate pulse is sent to the ADC to start digitization. After 12.5 micrc-seconds an 8 bit digitized value is available for reading by the computer. A flag is set by the ADC module indicating the particular ADC that has the value to be read. Since the data rates from the individual detectors are not extremely high, the probability of chance coincidences will be small. If this becomes a problem, the SCA pulses can be used to determine the detector from which the event came by means of a CAMAC interrupt register module. An experimental evaluation was performed with a single Ge(Li) detector with relatively poor resolution, not one of the 9 detectors in the intrinsic array, and a LRS 12 input peak sensing ADC CAMAC module obtained on loan to study the feasibility of this concept. Figure 5B shows an energy spectrum obtained from a Co-57 source and clearly demonstrates the capability of this system. The SCA window was set to include the entire spectrum of energies from 35 to 145 keV.

We plan to acquire this multiple ADC module, construct the necessary timing and inverting electronics, and thus add the capability of collecting multiple isotope distributions (i.e. more than two) to our data collection system.

1037327

2. Software Development
   a. 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 computer users will be published by July 1976. 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 software, hardware and clinical contacts at the various institutions. We will continue to submit appropriate software packages to BCTIC for distribution to interested institutions. 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 in obtaining its submission to BCTIC and in its subsequent testing prior to distribution.

1037328

b. Simulation and Modelling

We are continuing to develop and test new kinetic models in an effort to understand better the total body and organ retention of medically administered radioactive materials. Solutions to these models have been sought generally through the use of Berman's SAAM 25 computer program. Our efforts are being 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 iron, I-131 hippuran, 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 preceding sections dealing with the specific material.

As a member of the MIRD task group to gather data on Fe-59 dosimetry, we are using the Vanderbilt SAAM-25 iron kinetics model to describe the kinetics of normal and abnormal subjects studied at Vanderbilt and at the University of California. Data from the two laboratories are being merged and the resulting dosimetry information will be published as a MIRD pamphlet.

1037329

VI. Scientific Personnel - Curriculum Vitae on file ERDA

Principal Investigator:

A.B. Brill, M.D., Ph.D. [redacted]
Professor of Medicine & Radiology, Director, Division of Nuclear Medicine & Biophysics and the Clinical Radioisotope Center

Co-Investigators:

R.R. Price, Ph.D. [redacted]
Assistant Professor, Radiology

Research Associates:

J.J. Erickson, Ph.D. [redacted]
Assistant Professor, Radiology

J.A. Patton, Ph.D. [redacted]
Assistant Professor, Radiology

J.F. Parker, M.S. [redacted]
Computer Engineer

J.E. Lagan, [redacted]
Electronics Engineer

VII. Other Personnel

Graduate Students:

J. Jones, [redacted]
K. Larsen, [redacted]

Secretary:

Deborah Ruff, [redacted] 100%

VIII. Other Financial Assistance - None

IX. Premises, Facilities, Equipment and Materials to be Furnished by Contractor

Institutional Facilities Available	Level of Effort
Low-level counting facility with some 8,000 square feet adjacent for conference, library clinical scanning, and instrument development and modification	100 percent
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

1037331

RENEWAL PROPOSAL

ERDA E-(40-1)-2401 August 1, 1976 through July 31, 1977

X. Budget Estimated Requirements	ERDA	University	TOTAL
1. Salaries and Wages Name, title monthly rate, % effort			
A.B. Brill, M.D., Ph.D. [redacted] Professor Medicine & Radiology, 16%	-0-	9000.	9000.
Co-Principal Investigator R.R. Price, Ph.D. Ass't Professor Radiology @ $1833/mo, 32%	7038.	---	7038.
Research Associates:			
J. Erickson, Ph.D. Ass't Professor Radiology @ $1470/mo, 20%	3528.	---	3528.
J.A. Patton, Ph.D. Ass't Professor Radiology @ $1582/mo, 28%	5316.	---	5316.
J.F. Parker, M.S. Computer Engineer	1000.	---	1000.
J.E. Lagan Electronics Engineer @ $1332/mo, 10%	1600.	---	1600.
Graduate Student (1)	1844.	---	1844.
Secretary, D. Ruff 100%	7190.	---	7190.
Research Technician, J. Ford, 51%	2589.	---	2589.
Research Technician, TBA, 100%	5678.	---	5678.
Fringe Benefits (not fixed % of salaries. Varies with employee status and option)	4483.	1163.	5646.
TOTAL SALARIES & FRINGE BENEFITS	40,266.	10,163.	50,429.
INDIRECT COSTS (55% S & W)	22,146.	---	---

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2. SUPPLIES AND MATERIALS

Books, Periodicals, Journals	$1200.
Computer Supplies (line printer paper, magnetic tapes)	1000.
Lab Supplies, Isotopes	1000.
Maintenance Service (computer only)	1000.
Office supplies/duplicating	1200.
Electronic Components & Replacement Parts	9000.

3. EQUIPMENT

CAMAC ADC LRS	2400.
Module for autonomous crate controller	2000.

4. Publications Costs	600.
5. Travel - domestic	1500.

TOTAL FUNDS REQUESTED ERDA	$ 83,312.
VANDERBILT UNIVERSITY CONTRIBUTION	$ 10,163.
	$ 93,475.

1037333

Projected Costs

Percentage & Amount, Vanderbilt University	$ 10,163.	11%
Percentage & Amount, Requested ERDA	$ 83,312.	89%

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.

1037334

"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: April 30, 1976

1037335

Routed by ... Research Contracts, ...cedure... and Reports Branch

ORM OR-133 (Rev. December 1975) ... number

ROUTE SLIP

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	Deputy Manager
	Assistant to Manager for Pub. Infor.

	CHIEF COUNSEL
	Patent Group

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	Research Contracts, Procedures, and Reports Branch
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	Weapons Branch

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	REACTOR DIVISION

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	Ind. Safety & Fire Protection Br.
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	Environmental Prot. Br.

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	DEVELOPMENT DIVISION

	PLANNING DIVISION
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	Engineering Analysis Branch

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	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)

Please Expedite

REQUEST FOR CONTRACT ACTION - HEADQUARTERS DESIGNATED RESEARCH CONTRACT

1. BUDGET AND REPORTS DIVISION CONCURRENCE WHB 9/15/76

2. OFFICE OF CHIEF COUNSEL CONCURRENCE

5425

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

1037336

UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830
AREA CODE 615
TELEPHONE 483-8611

September 14, 1976

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: E-(40-1)-2401
   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 ERDA Funds To Be Obligated by this CA: $18,605

5. ERDA 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 provide for the performance of additional research during the period August 1, 1976 through October 31, 1977. ERDA Support Ceiling will be increased from $451,094 to $469,699. Title to equipment, if any, shall vest in the Contractor under the authority of P. L. 85-934.

7. Authority:
   Form ERDA-799, PR #E-05-76 0498
   dtd 8-4-76 from J. L. Liverman, AES,
   BER, HQ

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

CR:WLB

1037337

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

1037338

(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.

1037339

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.

1037340

VANDERBILT UNIVERSITY

NASHVILLE, TENNESSEE 37232 TELEPHONE (615) 322-7311

Division of Nuclear Medicine & Biophysics • School of Medicine • Direct phone 322-2394

August 27, 1976

Lamar Medley
Laboratory and University Division
U.S. Energy Research and Development
Administration
Oak Ridge Operations P.O. Box E
Oak Ridge, Tennessee 37830

Re: E-(40-1) 2401

Dear Dr. Medley:

The expenditure of funds for the period August 1, 1976 through October 31, 1976 will be as follows:

$15,755.00*	Personnel { 9,725 = S+W; 6,030 = Indirect cost
$ 300.00	Supplies
$ 800.00	Travel - domestic
$ 1,750.00	Electronic Components
$18,605.00	

Thank you for your continued support for our project.

Sincerely,

A.B. Brill, M.D.
Chief Division of Nuclear Medicine

ABB/bjc

John H. Hash, Ph.D.
Associate Dean for
Biomedical Sciences

Paul Gazzerro, Jr.
Assoc Vice Chancellor for
Med Affairs Operations &
Fiscal Planning

*Includes 62% indirect costs.

25% of P.I.'s time @ no cost to Contract.

18593

1037341

SEP 02 1976

FORM ERDA-799
(3-76)
ERDA-PR 9-16

U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

PROCUREMENT REQUEST

• *Please Type* *(See Instructions on Reverse of Last Sheet)*

1. TO: Procurement Office	2. From	3. Procurement Request Number
R. J. Hart, Mgr., OR --- Vanderbilt University Dr. A. Brill, PI	Activity Title: AES Division: BER Project: P&T	E-05-76 0498

4.	5. Priority Rating (Ref. FPR 1-1.311)	6. Desired Award Date	7. Security Classification (ERDAM APP. 3401)
☐ Contract ☐ Grant ☒ Special Research Support Agreement (SRSA) ☐ Other ☐ Modification of E-(40-1)-2401 Contract Number TO/PA ☐ Change Order ☐ Supplemental Agreement	Routine	08/01/76	☒ Unclass. ☐ Secret ☐ Conf. ☐ Top Secret

8. SERVICES, ARTICLES, MODIFICATIONS OR OTHER ACTION REQUIRED

TITLE Radioisotope Studies - Clinical Appl. of Activation 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 & radiation adsorbed dose from medical radionuclides. -- TERM: 08/01/76-10/31/77. This renewal has been approved for 15 mos. Funds for 3 mos. are hereby provided. Funds for remaining period will be provided when funds become available in FY 77.		
	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 BER-00-0636 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? Property title vested in Contractor ☐ YES ☒ NO If yes, attach details of requirements.	14. Recommended Source(s) Attach name(s) and address(es) of source(s).
15. Report and Drawings Requirements ☐ YES ☒ NO If yes, attach details of requirements.	16. Budget Activity Program, Subprogram, and Activity (ERDAM Appendix 1101, Part II) RT 01 03 $ 18,605. Amount of Funds Authorized	

17. Requestor (*Typed name, title, location, telephone number, date*)

Walter H. Weyzen, PTP/BER Ex. 35355
(Name)

Walter H. Weyzen 7/21/76
(Signature)

18. Authorizing Program Official (*Typed name, title, location, telephone number, date*)

James L. Liverman, AAES X 35171 8/2
(Signature)

19. Certifying Official (*Typed name, title, location, telephone number, date*)

AUG 4 1976
(Date)

I hereby certify that funds in the amount here stated are available for such purposes under Allotment.

No. 06-60-91(24)

H. G. Fish, Dir., OPC X-33541
(Signature)

PROCUREMENT OFFICE

AUG 09 1976

1037342

17605

TO : Addressees Listed Below DATE: March 31, 1976

FROM : F. O. Christie, Director, Contract Division, ORO

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. Expenditious handling of this matter will be appreciated.

Modification 24 to Contract E 40-1)-2401 with Vanderbilt University

Addressee	Division	Init.	Date	Remarks
1. ~~Lamar Medley~~	Contract		3/31/76	
2. A. H. Frost, Jr.	~~Contract~~		3/31	
3. W. L. Buchanan	~~Budget~~		4/2/76	
4. H. S. ~~Oster, Jr.~~	Finance		4/5/76	
5.				
6.				
RETURN TO:	~~3083~~			
Alice Brown	Contract Division			Tel.: 3-4105

1037343

Routed by: ~~Research Contracts, Procedu. and Reports Branch Contract Division~~

FORM OR-133 (Rev. March 1975)

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File num

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	Deputy Manager
	Assistant to Manager for Pub. Infor.

X	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.
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	MATERIALS MANAGEMENT DIV.
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	Classification & Tech. Services Br.
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	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 _____

~~2. OFFICE OF CHIEF COUNSEL~~ ~~CONCURRENCE~~ J. Johnson

1011

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

1037344

UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

February 24, 1976

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: E-(40-1)-2401
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 ERDA Funds To Be Obligated by this CA: $57,031

5. ERDA Percentage of Est. Total Cost To Be Shown by this CA: 94.2%

6. Description of Other Changes To Be Covered by this CA:

Modify contract to provide for the performance of additional research during the period November 1, 1975 through July 31, 1976. ERDA Support Ceiling will be increased from $394,063 to $451,094. Title to equipment, if any, shall vest in the Contractor under authority of PL-93-438.

7. Authority:

Form ERDA-481-(CA) from J.L. Liverman, DBER, HQ dated Nov. 18, 1975.

A. H. Frost, Jr., Chief
Research Contracts, Procedures
and Reports Branch
Contract Division

ACR: LM

1037345

APPENDIX "A"

(REVISED)

CONTRACTOR: Vanderbilt University
CONTRACT NO.: E-(40-1)-2401

For the contract period: August 1, 1975 through July 31, 1976

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 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: $42,818

(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

1037346

(3) Travel: $1,500

Domestic--------$1,500
Foreign---------$ 0

(4) Other direct costs: $15,867

(5) Indirect costs (based on a predetermined rate of 44 % of salaries and wages): $18,840

(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 $ 79,025 ; ERDA will pay 94.2 % 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 ERDA Support Cost for the contract period stated in this Appendix "A" is $ 74,419 .

1037347

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:	$74,419

The new funds being added in A-III (b) constitute the basis for advance payments provided under Article B-X.

1037348

Medicine & Biophysics • School of Medicine • Direct phone 322-2394

February 13, 1976

Lamar Medley
Laboratory and University Division
U.S. Energy Research and Development
Administration
Oak Ridge Operations P.O. Box E
Oak Ridge, Tennessee 37830

Dear Dr. Medley:

The expenditure of funds for the period of August 1, 1975 through July 31, 1976 is as follows:

$ 39,638.	Personnel	42,818
15,867.	Supplies	15,867
1,500.	Travel	1,500
17,414.	Indirect Costs	18,840 (44% of S+W)
$ 74,419.		79,025 = Total
4,606.	University Contribution	

Thank you for your continued support for our project and again I apologize for the delay in getting this information to you.

Per tele-con with Dr. [illegible]

Sincerely,

A.B. Brill, M.D.
Chief, Division of Nuclear Medicine

ABB/bjc

Lloyd H. Ramsey
Associate Dean of Biomedical Sciences

Paul Gazzerro, Jr.
Associate Vice Chancellor
for Medical Affairs for
Operations and Fiscal Planning

FEB 20 1976
11928

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FORM ERDA-461
(7/75)
ERDA-PR 9-4

U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

CONTRACT AUTHORIZATION

1. DATE NOV 18 1975

2. AUTHORIZATION NO. BER: 76-266

3.A. TO
Robert J. Hart, Manager
Oak Ridge Operations Office

3.B. FROM
James L. Liverman, Director
Division of Biomedical and Environmental Research

4.A. CONTRACTOR (Name, Address, Department, etc.)
Department of Radiology
Vanderbilt University
Nashville, Tennessee 37232

4.B. PRINCIPAL INVESTIGATOR(S)
Dr. A. Bertrand Brill

5. ☐ NEW CONTRACT ☒ RENEWAL ☐ OTHER

6. TERM OF CONTRACT: 11/1/75 - 7/31/76

7. CONTRACT NUMBER: E-(40-1)-2401

8. RECOMMENDED TYPE OF CONTRACT:
☒ SPECIAL RESEARCH SUPPORT AGREEMENT (SRSA)
☐ COST REIMBURSEMENT
☐ FIXED PRICE ☐ OTHER

9. PROPERTY TITLE TO VEST IN:
☐ ERDA
☒ CONTRACTOR-DETERMINED TO BE IN THE PROGRAMMATIC INTEREST OF THE ERDA

10. SECURITY CLASSIFICATION:
Work to be performed is under category I as defined by ERDA Manual Appendix 3401.

11. PROJECT TITLE: Radioisotope Studies Utilizing a Low-Level Whole Body Counter and Clinical Applications of Activation Analysis

12. HEADQUARTERS TECHNICAL CONTACT
Walter H. Weyzen

13. FINANCING

A. OPERATING EXPENSES

New ERDA Funds	$ 57,031.
Estimated ERDA Balance From Prior Term, if any	$
Total Estimated ERDA Support Cost for New Term	$ 57,031.
Estimated Contractor Contribution, On Proportionate Sharing Basis, if any	$
Estimated Project Cost, For Pertinent Budget Period	$ 57,031.

Budget and Reporting Classification: ~~RT 03 01~~ RT 003 Dpt
Allotment Transfer: 06-60-91(24)

B. PLANT AND CAPITAL EQUIPMENT ..... $
Budget and Reporting Classification:
Allotment Transfer:

14. SPECIAL PROVISIONS AND INSTRUCTIONS:
The technical aspects of the proposed work have been reviewed and are approved. A need currently exists for the results of the research or other work that is to be undertaken. None of the ERDA funds shall be used to confer a fellowship.
Please keep us informed as to any problems encountered in your negotiations, as well as the date of execution of this contract and the amount of funds obligated. If the budget as negotiated differs substantially from that in the proposal, please forward a copy of the revised budget to Headquarters.
If not already submitted, a 200-word summary of the proposed work should be forwarded by the contractor as soon as possible after negotiation of the contract.

15. SCOPE OF WORK: Study of radioisotope distribution and radiation absorbed dose from medical radionuclides.

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EXPENDITURE STATEMENT AND RENEWAL PROPOSAL

ERDA CONTRACT AT-(40-1)-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

April 30, 1975

2869

MAY 1 1975

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OMB No. 68-R1143

IFICATION NUMBER (If known)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PROTECTION OF HUMAN SUBJECTS CERTIFICATION

- [XX] Contract
- [ ] Grant
- [ ] Fellowship
- [ ] New
- [X] Renewal
- [ ] Continuation

STATEMENT OF POLICY: Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the DHEW is the responsibility of the institution which receives or is accountable to the 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 the Department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an appropriate institutional committee. (References "Institutional Guide to DHEW Policy on the Protection of Human Subjects.")

1. TITLE OF PROPOSAL

Radioisotopes Studies Utilizing Low Level Whole Body Counter & Clinical Application of Activation Analysis

2. PROJECT DIRECTOR/PROGRAM DIRECTOR/FELLOW	3. INSTITUTIONAL COMPONENT OR DEPARTMENT
A. B. Brill, M.D., Ph.D. POSITION TITLE	Radiology

4. CHECK ONE OF THE FOLLOWING STATEMENTS AS APPLICABLE:

- [ ] A. This application does not propose any activities that would involve human beings who might be considered subjects, human material, or personal data from primary or secondary sources.
- [ ] B. This is to CERTIFY that this application which does propose activities involving human subjects has been reviewed and approved by our institutional committee on the date of _____ in accordance with the DHEW policy and the institutional assurance on file with the DHEW. (The review date should be recent; certification is invalid if review date would precede award date by more than one year.)
- [X] C. This is to CERTIFY that this application which proposes to involve human subjects is pending review on the date of May 22, 1975 in accordance with the DHEW policy and the institutional assurance on file with the DHEW. If the committee does not review and approve the proposal by or on the date certified, the agency office requesting this certification will be notified immediately by telephone, telegraph, or mail. (Review date should precede requested or planned date of award by at least one month whenever possible.)
- [ ] D. This application proposes to involve human subjects. This institution does not now have an active assurance on file with the DHEW. I understand that information on the assurance procedure will be received should the application become eligible for an award.

5. SIGNATURE OF INSTITUTIONAL OFFICIAL AUTHORIZED TO SIGN PROPOSALS	DATE
Paul Gazzerro	April 30, 1975
6. TITLE Paul Gazzerro, Jr., Assoc. Vice-Chancellor, Med. Affairs, Operations & Fiscal Planning	TELEPHONE NO. (Code, No., Extension) (615) 322-2145

7. NAME AND ADDRESS OF INSTITUTION (Street, City, State, zip code)
Vanderbilt University
Nashville, TN 37232

NOTE TO AGENCY: This form should NOT be included with application forms that have provision for human subject certification. It may be used to request certification, or correction of certification.

HEW 596 (Formerly NIH 1611)
6-72

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO THE AGENCY REQUESTING ITS COMPLETION

1037352

SIE-78a

PUBLICATION BY AEC AUTHORIZED ☐

NOTICE OF RESEARCH PROJECT
SCIENCE INFORMATION EXCHAN
SMITHSONIAN INSTITUTION

U.S. ATOMIC ENERGY COMMISSION

SIE NO.

AEC CONTRACT NO.

SUPPORTING DIV. OR OFFICE:

NAME & ADDRESS OF CONTRACTOR OR INSTITUTION: (State the division, department, or professional school, medical, graduate or other, with which this project should be identified.)

Vanderbilt University
Department of Radiology, Division of Nuclear Medicine
21st Avenue South
Nashville, Tennessee 37232

TITLE OF PROJECT:

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

NAMES, DEPARTMENT, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS AND OTHER PROFESSIONAL SCIENTIFIC PERSONNEL: (not including graduate students) engaged on the project, and fraction of man-year devoted to the project by each person.

A.B. Brill, M.D., Ph.D. - Radiology - Professor - Principal Investigator
R.R. Price, Ph.D. - Radiology - Assistant Professor - Co-Principal Investigator
J.J. Erickson, Ph.D. - Radiology - Assistant Professor - Research Associate
J.A. Patton, Ph.D. - Radiology - Assistant Professor - Research Associate
J.F. Parker, M.S. - Radiology - Research Associate
J.E. Lagan - Radiology - Research Associate
J. Wagner, Ph.D. - Physics- Assistant Professor - Research Associate

NO. OF GRADUATE STUDENTS ON PROJECT: 2 NO. OF GRADUATE STUDENT MAN-YEARS: 2

SUMMARY OF PROPOSED WORK: (200-300 words, omit Confidential Data). Summaries are exchanged with government and private agencies supporting research, are supplied to investigaters upon request, and may be published in AEC documents. Make summaries substantive, giving initially and for each annual revision the following: OBJECTIVE; SCIENTIFIC BACKGROUND FOR STUDY; PROPOSED PROCEDURE; TEST OBJECTS AND AGENTS.

The main emphasis of these studies is the development of instrumentation and analytical techniques for the acquisition and analysis of isotope tracer kinetic data, emphasizing dosimetry. Tracer turnover studies involve both radioactive and stable tracers. We continue to explore ways of using neutrons for activation analysis in an attempt to minimize radiation exposure to the patient while obtaining needed diagnostic information.

We are attempting to validate assumptions in dosimetry calculations. We are collecting quantitative data on diagnostic tracers administered to patients and analyzing these results with currently accepted methods. Berman's computer programs for simulation and modelling (SAAM 25) and dosimetry calculations (RADOS) are used in these studies, in addition to Monte Carlo programs being run at ORNL.

Dosimetry and clinical studies will be carried out on patients using new, approved radiopharmaceuticals where dosimetry data are lacking. These will include Tc-99m pyrophosphates as a new bone scanning agent and new radiolabelled compounds used in lung scanning. Extensive data files on Ca-47 kinetics and the kinetics of I-131 administered in therapy quantities will be analyzed using compartmental modelling analysis to provide dosimetric information.

RESULTS TO DATE: We have developed instrumentation and analytical techniques for radiation dosimetry and trace kinetic studies which allow measurements on both normal and abnormal subjects. Data obtained on Fe-59 and I-131 hippuran revealed rad/mC dose estimates in normals which agreed with previous estimates. Absorbed doses in abnormals deviate greatly from normals and are being extended. Dose estimates from new lung scanning agents are presented. Detailed presentations of results are published or in press.

	PROGRAM CATEGORY NO.
BUDGET	
PRIMARY	
SECONDARY	

A. B. Brill
Signature of Principal Investigator

DATE: April 30, 1975

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INVESTIGATOR – DO NOT USE THIS SPACE

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. AT-(40-1)-2401

Dr. A. Bertrand Brill

1.	Total actual project cost to date for the current period.	$ 51,785.70
2.	Estimated total cost for remainder of period.	$ 27,398.90
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.	$ 71,662.06 ~~79,184.60~~
4.	Accumulated costs chargeable to ERDA (include costs reported in certified statement for preceding period(s) and the costs stated in Item (3) above).	$ 376,675.00
5.	Accumulated ERDA Support Ceiling as stated in Article III of Contract.	376,675.00 $
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

Macon D. Somerville
Assistant Director, Finance Accounting

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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 used in nuclear medicine. The systems we have developed are well suited to this task, but nonetheless, we continue to work to improve on the methods to diminish errors. The major problem that we face involves the integration of our interests and capabilities with those of the patients and their physicians. We stand by ready to adjust our personnel and facility schedules so that we are able to answer patients' problems as they arise and from careful sequential studies arrive at information that is needed for patient diagnosis and management and at the same time provide the needed data for dosimetry and metabolic kinetics studies.

We continue to work on methods to reduce patient exposures to the minimum needed to answer specific diagnostic problems. In this search, we have developed stable tracer techniques utilizing remote radiation sources and on-site counting and analysis facilities including high resolution solid state detectors and interactive computer systems. In cooperation with the Oak Ridge National Laboratory we are developing techniques to measure deuterium-labelled compounds using the $D(\gamma,n)H$ reaction. This work should result in a convenient and routine method for measuring the non-radioactive tracer of the biologically important element - hydrogen. Continuing efforts will be devoted to specific projects in which we have a long history of interest. These include iron metabolism in various disease states, calcium metabolism in abnormals, iodine metabolism and dosimetry in I-131 therapy patients, monitoring of Cs-137 levels and the dosimetry associated with diagnostic uses of new radiopharmaceuticals, in particular, lung and bone scanning agents.

We are completing the development of a 9-detector mosaic intrinsic germanium system in collaboration with Lawrence Berkeley Radiation Laboratory under NIH sponsorship for high resolution tumor scanning. The system will be delivered in May 1975 and will be evaluated for this purpose and other applications by our staff, and dosimetry associated with new nuclides used in these applications will be performed. The utility of solid state detectors requires increased sensitivity, and we are hopeful that the results of AEC-sponsored work on intrinsic germanium detector technology will prove to be useful in nuclear medicine.

The staff has achieved a scientific maturity and is a stable group of 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 promises to accelerate our biological study output.

We are continuing to explore the potential of CAMAC for hardware and software standardization for nuclear medicine data acquisition and display systems. The

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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 are continuing to extend our system to acquire data from additional diagnostic instruments. 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.

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IV. Scientific Background

Earlier proposals and project reports have documented the scientific background of this research project. No other federal agencies support the operation of the Vanderbilt Low Level Counting Facility. Dr. A.B. Brill, Principal Investigator, is the Research Director within the division. operation of the Vanderbilt Low Level Counting Facility. Dr. A. B. Brill, Principal Investigator, is the Director of the Division of Nuclear Medicine and Biophysics. Dr. R. Price is the Research Director within the division. Dr. J. Wagner, Physics Department has contributed many ideas and assistance in the direction of graduate student thesis research. 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. Dr. W. Rowan and staff of the Information Science Program and C. Bradshaw, Director of the Vanderbilt University Computer Center, and his staff have contributed significantly to our work. DuPont employees at the Old Hickory, Tennessee, and Wilmington, Delaware, plants have been of great assistance to us in working with Berman's SAAM 25 and RADOS computer programs. None of the personnel in other departments have been 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 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.

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V. Scientific Scope
A. Dosimetry and Tracer Kinetics
1. Methodology
a. Hardware Development
1. Whole-body Scanning Bed

The dosimetry of Tc-99m labelled pyrophosphate is becoming a significant area of interest in clinical nuclear medicine. This bone scanning agent is gaining in popularity because of its excellent imaging qualities. However, the radiation dosimetry of this pharmaceutical is not well understood because of its relative newness but must be considered important because of its widespread use. We propose to investigate this area of dosimetry in our laboratory. Because the pharmaceutical is widely distributed in the body combined with the fact that in many cases patients with bone involvement are in extreme discomfort, we propose to utilize a scanning bed-imaging system for this study. We have designed and are implementing a computer controlled scanning bed-scintillation camera data collection system. The scanning bed allows the effective field of view of the scintillation camera to be increased to that required for a total body image. The system we have designed is shown in Figurel and is based on a CAMAC module crate interfaced to our PDP/9. The system consists of two primary subsystems, i.e., the bed control system and the image data acquisition system. The bed control system consisting of the encoder follower, output register and in-house designed interface module allows the bed to be controlled by the computer and moved with a positional accuracy of 0.01 in. The scanning area of the bed is 75 inches by 30 inches with a maximum scanning speed of 18 inches per minute. The image data acquisition subsystem consisting of the input register and dual ADC allows image data to be collected from the camera with digital resolution of 256 x 256.

Figure 2 shows the anterior and posterior views of a Tc-99m pyrophosphate whole body scan acquired with this system. Each view consists of 3 scan lines separated by 8 inches. Each of the 65 inch scan lines required approximately 5 minutes to collect for a total of 15 minutes per view. The image reconstruction and photo generation also required approximately 10 minutes per view. Thus a total time of 50 minutes is required for this study. This is compared to the 1½ to 2½ hours required for a comparable study performed with the rectilinear whole body scanner. These images each contain about 300 K counts and are comparable in information content to those obtained from the scanners. The images shown here are in a 128 x 500 digital array. It is possible to rebuild subregions of the image with higher digital resolution thus providing a "close up" view of any region of interest. The images may also be manipulated by a software package we developed to provide contouring, smoothing and foreground-background erase. It should be noted that the computer controls the scanning process and thus allows one to scan any smaller region than the entire body if one wishes and consequently not spend time imaging body regions not of interest to the current study.

This data collection system was designed with a capability of collecting dual isotope images. This capability has not been fully implemented at present but will allow us to collect images from more than one isotope or from multiple peaks of the same isotope. One further aspect which must be

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developed in order that we can perform accurate dosimetry studies is a speed correction method. This is required because the bed speed is not a constant at all times and variations which would not be significant in routine clinical imaging can be of importance in quantitative studies. The scanning bed will allow us to obtain data on the distribution of the Tc-labelled pyrophosphate (and related compounds used in our clinic) in a large number of patient studies. In this instance the scanning bed has several advantages over the dual probe whole body scanner. These are:

1. decreased scanning time
2. the response of the camera is more depth independent than the focused collimators of the scanner
3. finer digital detail is available

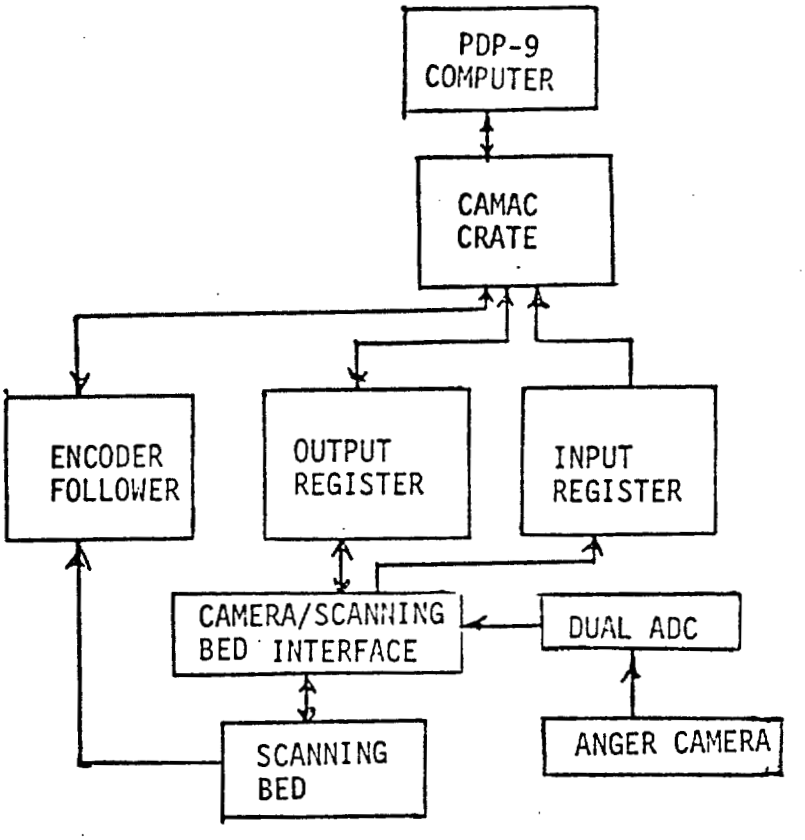
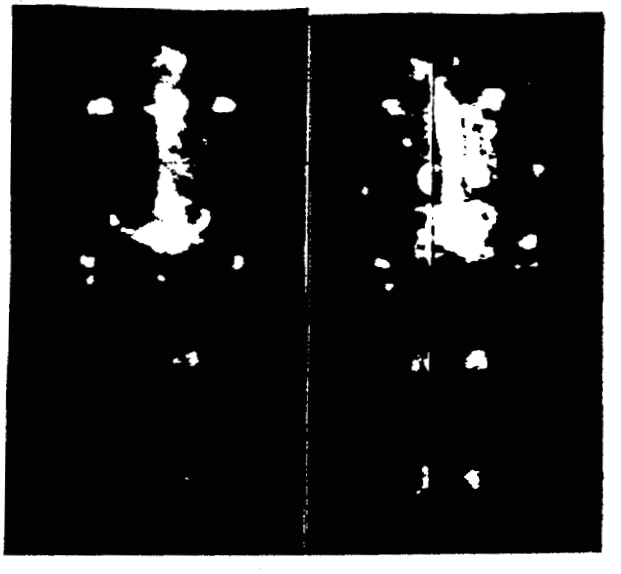


Figure 1 Block diagram of Scanning Bed Data Acquisition System.



ANTERIOR POSTERIOR

Figure 2 Whole Body Scans of Patient collected with Scanning Bed.

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2. Multi-energy Aperature Camera

In our 1974 proposal we described plans to collect image data required for multi-energy aperture image correction techniques from the scintillation camera through the CAMAC data acquisition system. This work has been delayed due to problems arising in the development of the computer - CAMAC - Anger camera interface. Now that these problems have been solved we plan to implement the multiple energy aperture camera system in the coming year. We propose to collect data for these studies by combining the electronics we designed and constructed for use with a scanning bed/imaging system with a single channel analyzer and a third ADC. The data will be collected in the following manner: the undiscriminated energy signal from the scintillation camera will be fed into an SCA whose window will be adjusted to bracket the potential energy range of interest. The output of this SCA will then be used to cause analog to digital conversion of the X, Y, and Z signals from the camera. These three digitized values will then be transferred through CAMAC input registers to the PDP-9 to be stored in list mode on disk. A block diagram of the system parts of which are now operational in Figure 1.

The extra SCA is required in this instance because the energy window width of the camera's SCA is limited to 35% of the center photopeak energy, and this is not sufficient to bracket the wider contemplated window widths, for example, using Ga-67.

The multi-energy camera system will be very useful in our dosimetry studies in studies involving isotopes with multiple photopeaks and also in studies where it is necessary to correct for blood background. An example of the latter is the bone scanning techniques employed with Tc-99m labelled compounds such as pyrophosphate. In these studies the relative uptake in bone seems to be a measure of relative osteoblastic activity and is increased in primary and metastatic cancer in bone and in a variety of bone disorders. However, only part of the injected radioisotope is taken up by bone; a significant fraction circulates in blood and is slowly excreted by the kidneys. This produces a significant blood background that causes difficulties in reading the scans and in determining actual bone uptake for dosimetry studies. These problems can be reduced by labelling the blood with a suitable agent such as In-113m (transferrin) at the same time as the bone scanning agent is administered. Images of the bone and blood distributions may then be collected at the same time from specific regions of interest on the total body (with the scanning bed system) and the net bone distribution obtained by point-by-point subtraction. An example of this technique is shown in Figure 2 using images collected at different times. One can observe the increase in detail of the femoral heads in the corrected image.

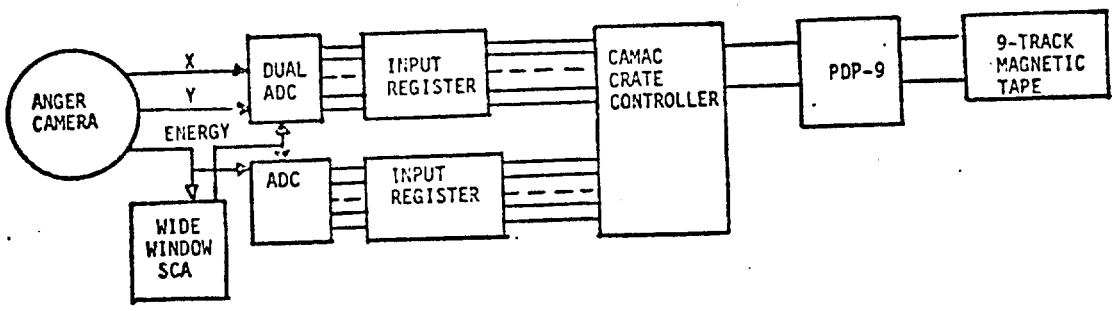


Figure 1. Block diagram of the data acquisition system for use with the multiple energy aperature camera.

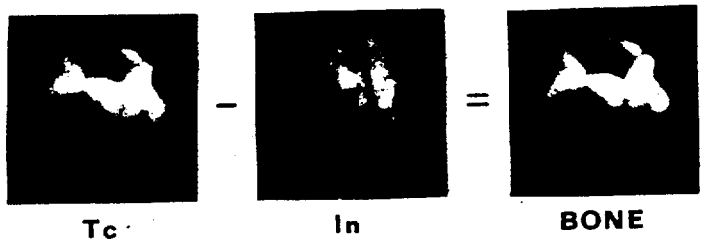


Figure 2. Dual Isotope Subtraction Technique

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3. Intrinsic Germanium Detector Array

In determining internal dosimetry data from radioisotopes, it is important to know the distributions of the isotopes as accurately as possible. However, the present imaging systems in common use cannot adequately discriminate against scattered radiation due to relatively poor energy resolution and therefore the images obtained are not exact representations of the actual distributions. The use of high resolution solid state detectors permits the rejection of scattered radiation which degrades images, and introduces sources of error in quantitative studies especially when low energy isotopes are used. Until recently these detection systems have been limited in sensitivity and adequate clinical trials have not been performed. We have designed and fabricated a mosaic detector system in conjunction with Goulding and Pehl at Lawrence Berkeley Radiation Laboratory under funding by a one year grant from NIH which expires in April 1975. This detector will be delivered in May for evaluation.

The intrinsic or high purity (HP) germanium (Ge) detector array will consist of 9 detectors each 35mm in diameter arranged in a 3 x 3 matrix with 50mm between centers. The 9 detectors will be cooled by a common liquid nitrogen reservoir. The electronics associated with the system include two single channel analyzers (SCA) coupled to the linear amplifier attached to each detector. A larger number of energy windows may be selected from each detector by use of an ADC and signal routing information from a relatively wide window SCA. A block diagram showing the standard data collection process is shown in Figure 1. The detector array will be mounted above our scanning bed and fixed so as to permit vertical movement only. In a scanning situation the detector system will remain stationary and the patient will be moved in a rectilinear raster while lying on the scanning bed. This bed is motor driven with two degrees of freedom under control by a PDP/9 computer. Status and control functions are handled by the input and output registers in the CAMAC crate. Position information is obtained by a dual position encoder module connected to a position encoder mounted on each axis. Events from radioactive decay of isotopes within the subject that are observed by the detectors and selected by the SCA's will be recorded in octal scaler modules and transferred to the computer at pre-determined intervals corresponding to the selected data cell size. Data will be maintained separately from each SCA either on disk or DEC tape until the scan is completed. Frontal plane as well as longitudinal and transverse section images will then be constructed through selected regions of interest.

High resolution focussed collimators in front of each element in the planar array of detectors, when pointed normal to the detectors should provide high resolution, well-defined images with minimal degradation due to scattered radiation. However, tomographic information is also available with this system. The inherent ability to collect data from which tomographic sections may be constructed is due to a second type of collimator array that will be incorporated into the system. High resolution collimators will be used which have relatively uniform resolutions over a long distance. (This is possible because of the small diameter of each detector.) The collimators will be aimed such that their fields of view intersect at a point which is directly below the central detector. If we define the plane mapped by this common view point as the focal plane of the system, then we can obtain a good representation of the radioisotope distribution in this focal plane by simply summing the data collected from all detectors. However, images of planes lying above and below the focal plane can also be obtained by maintaining the data separately and recombining, after suitable translations of the data into new coordinate systems have been performed. These translations are a special case of the general theory for longitudinal section image construction by computer described by Anger for data collected from his multiplane tomographic scanner.

It is also possible to construct transverse section images from these data. This can be done by constructing many longitudinal sections with very small distances between planes. Transverse sections can then be constructed by selecting corresponding lines from each of the longitudinal sections. For display purposes the data arrays representing transverse sections may be enlarged by linear interpolation between adjacent lines.

The interface for the detection system has been completed. Work on the system in the coming year will involve the design and fabrication of frontal plane and tomographic collimator arryas, the development of computer algorithyms for data collection and construction of images of frontal planes as well as transverse and longitudinal section planes.

This system should be useful in imaging all body organs but should be especially useful in the liver where it is extremely difficult to image voids which are signs of diminished liver function as well as in pancreas and kidney scanning. The excellent spatial and superior energy resolution should permit us to reduce the minimum detectible lesion size (1-2 cm minimum at present). The system should also be extremely useful in our dosimetry work because of its ability to map multiple tracers simultaneously in 3 dimensional space and should add significantly to the accuracy of the dosimetry studies proposed in section 2 of this proposal.

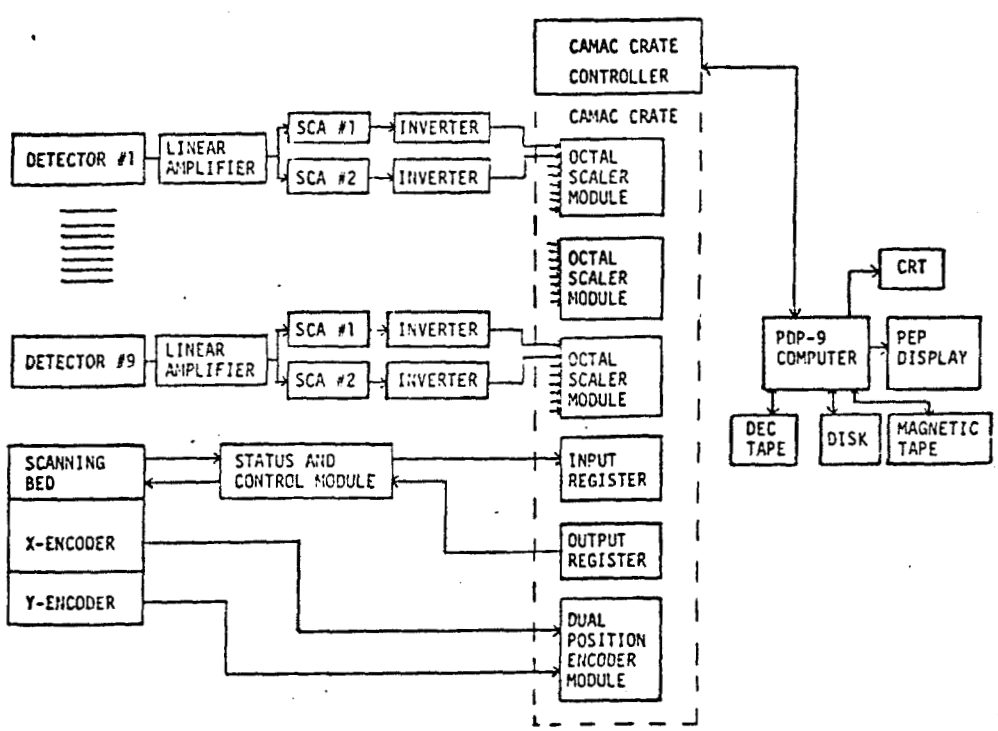


FIG. 1, BLOCK DIAGRAM OF DATA COLLECTION FROM INTRINSIC GERMANIUM DETECTOR ARRAY.

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4. CAMAC: Design of Autonomous Crate Controller

Experience with the CAMAC instrumentation system continues to demonstrate to us that such standardization and modularity benefit medical systems by enabling them to become operational sooner and to be both more reliable and more easily repaired than those containing special purpose electronics. CAMAC is supported by a crate which conforms to AEC specification TID-25875. This crate is connected to one of the PDP-9 computers by means of a dedicated controller adapted from an Argonne National Laboratories design.

Funds were requested but not granted last year to bring this system into conformity with AEC specification TIC-25876. The reasons for this request remain with us:

1. In developing new diagnostic techniques, such as scanning bed tomography, multiple energy camera studies, it becomes necessary to test new devices and concepts without jeopardizing operational systems.
2. Higher data rates are rapidly saturating the capacity of our home-made crate controller
3. The need to share results with other medical users of CAMAC, such as the Meson production facility at Los Alamos, suggests a level of standardization which is independent of the computer used. The addition of a second PDP-9 computer has provided its own pressure for a parallel CAMAC system, both for back-up and through-put.

In the absence of funds, CAMAC components were borrowed from the experimental inventory at Fermi National Accelerator Laboratories (FNAL) to test specific concepts related to the design of an autonomous crate controller. We remain in contact with the several national laboratories using CAMAC and are participating in the review of a FNAL-designed autonomous crate controller. This instrument is comparable in price but promises to be higher in performance that a full-blown TID-25876 branch highway CAMAC system. Test results are anticipated by the end of June.

Based upon the results of these test data, we will make a decision as to the continued development of CAMAC in our system. If the design of the autonomous crate controller proves to be inadequate, funds will be sought to add a second crate and to bring our facility into conformity with AEC standard TID-25876. Specifically, this means the addition of a branch highway driver as a peripheral device on the PDP-9, the acquisition of a second powered crate, the acquisition of standard "type A-1" crate controllers, and the necessary connectors and terminators.

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5. Integrated Anger Camera-Stationary Scintillation Probe

We are currently investigating the utility of data collected from the same subject simultaneously, by an Anger Camera and stationary probes. This technique will be used to collect data in studies where the Anger Camera alone yields inadequate data for analysis. These include liver, lung, and renal function studies where the field of view of the camera is inadequate to capture all of the pertinent regions of interest. Data presented in the section on I-131 Hippuran dosimetry demonstrates the potential utility of the collection system. In these studies, the camera is capable of monitoring the kidneys but frequently the bladder is not visualized. Typically, the camera provides marginal data on the blood pool clearance. The addition of a two probe system would yield data on all of these regions of interest simultaneously. In our present configuration the camera data are collected off-line in an Intertechnique cine-scintigraphy system while the probe data are collected directly into the PDP-9 via CAMAC modules.

A block diagram of the integrated camera/probe data acquisition system is shown in Figure 1. Figure 2 shows an example of the data obtained from the integrated system from a patient receiving an I-131 renogram at 10 days post-transplantations.

During the coming year we propose to use this system to collect all of the data for the I-131 hippuran dosimetry project described in section A. 2. c. The additional data (blood pool and bladder) provided by the stationary probes will make it possible to obtain unique solutions to the compartmental modelling calculations. This system will also be employed to acquire data from studies of cardiac function, where the stationary probers will be used to monitor the lung and systemic circulation.

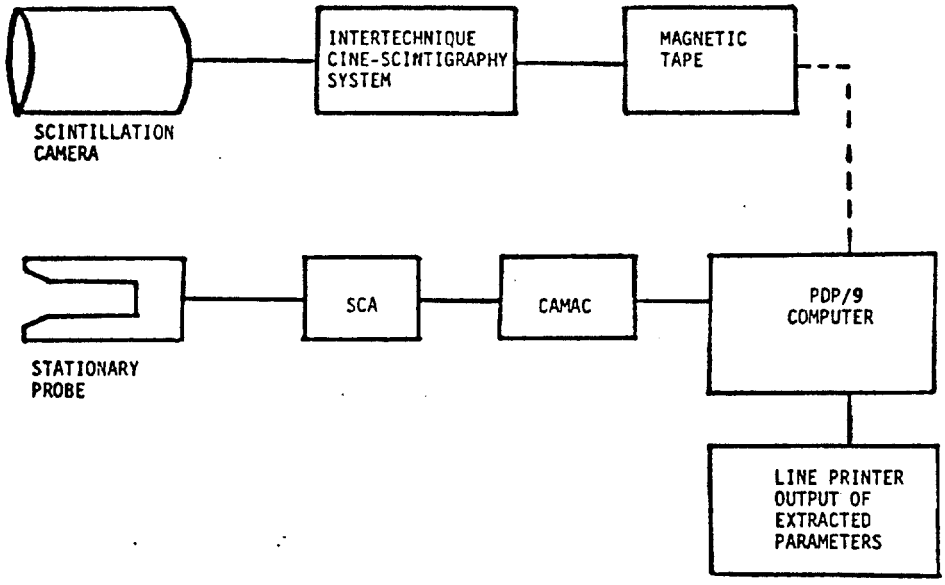


Figure 1. Schematic of Combined Scintillation Camera Stationary Probe Data Collection System

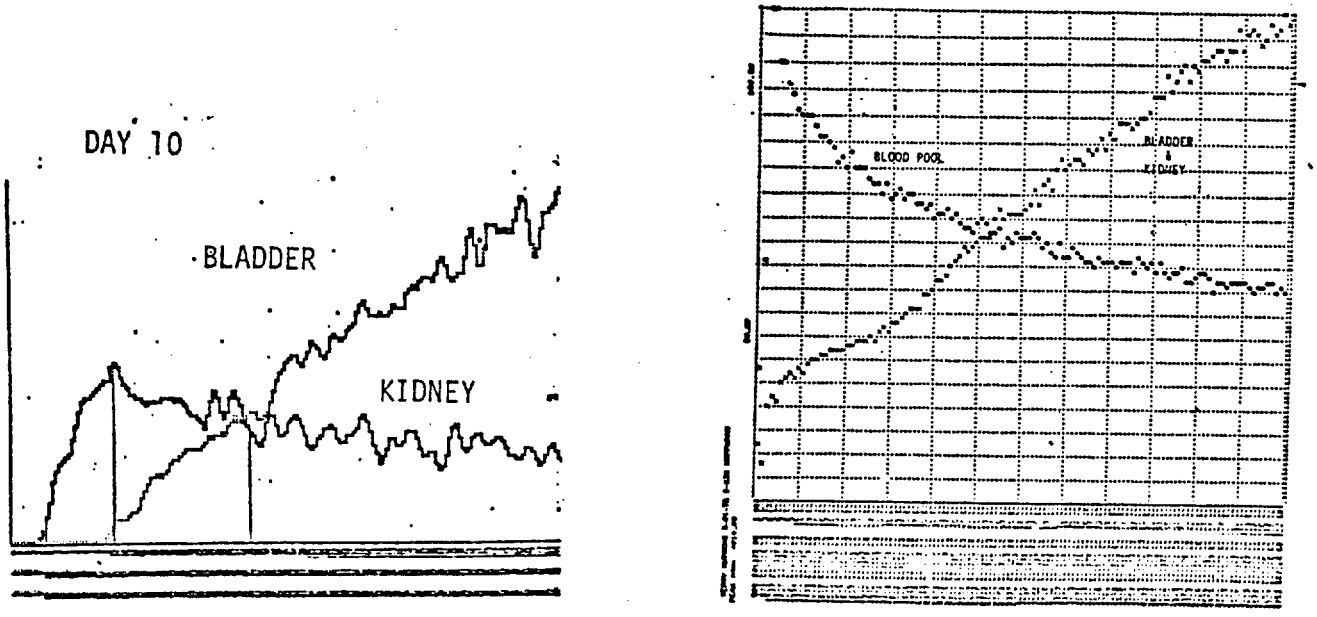


Figure 2. Combined Camera/Probe Renogram Study

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6. Video Line Buffer Display System

Although medical isotope images are collected, processed, and analyzed with digital computers, human interaction is often required to monitor data collection or processing, as well as to interpret the final images. A wide variety of computer displays are available, and although each has its advantages, very few are suitable for producing high quality, high resolution, multiple gray scale images such as would be required for organ delineation for dosimetry studies, and region of interest definition for calculating dimensions of anatomical structures.

At present, we have several devices which are suitable for output of gray-scale images from the PDP-9 computer. An oscilloscope display with a polaroid camera attached is much the same as that of the oscilloscope/polaroid camera combinations commonly used on scintillation cameras. Because the image must be written one dot at a time and integrated onto the film, the process is slow. Exposures must be determined by trial and error. The oscilloscope is useful for producing small images for archiving in patient records, but is virtually useless as a monitor in image processing and enhancement tasks.

A PEP-400 silicon storage tube was interfaced to the PDP-9 several years ago. With this device, we expected to be able to produce computer-generated displays of 500 x 500 resolution and ten or twelve viewable gray scales with a standard video monitor. In practice, only 250 x 250 arrays of dots can be generated and the regularity of the placement of the dots is degraded by spurious noise in the x-y deflection circuitry. Despite these problems, this system is useful for producing rough images, line graphs, and even text but is inadequate for quantitative organ measurements.

Because of the problems noted in our present implementation of the silicon storage tube and the further degradation of picture quality which occurs when an image is transferred to the video disc, we have been exploring the possibility of interfacing the video disc directly to the PDP-9 computer. The very qualities which make the video format attractive for high quality computer displays make direct interfacing difficult. To produce a real-time video frame of 500 x 500 resolution and 64 shades of grey, would require converting 1.5 million bits into analog form in 1/30 second, or 45×10^6 bits per second. Only a very large computer would have such speed. There is no need to construct complete video frames in 1/30 second, however, if an image can be written onto a video buffer at a rate compatible with the capabilities of a small computer. The video disc could serve as a buffer in this application.

To implement these concepts, a video line buffer (VLB) has been designed. The funds to purchase the required electronics were provided by an internal University sponsored research program. During the coming year the VLB will be constructed and interfaced to the PDP/9 computer and evaluated for its utility using the images from the Tc-99m lung scanning agent dosimetry project and from the Tc-99m sulfur colloid liver dosimetry study, in particular.

The VLB is designed around a fast (10 MHz) bipolar random access memory board with a 512 word by 8 bit configuration. This memory can be loaded with data asynchronously by the computer, and dumped through a DAC onto the video disc when a full line of data has been accumulated. Timing signals from the disc ensure that the disc is properly positioned to write the data in the physical location corresponding to the desired video line. In the worst possible case, the interface would have to wait for one revolution of the disc before writing a line, so that a 500 x 500 array would be written in about 17 seconds. By optimizing the order in which lines are written, the time required could be cut to less than 9 seconds. For many applications, a smaller array would suffice, with a corresponding increase in writing speed.

The structure of the interface is such that most of the data can be loaded into the VLB with a single I/O instruction. The lower ten bits are used for data, while the upper six bits are used to increment the x- or y- address to zero, and one bit initiates the dumping of the memory to the video disc. Other separate I/O commands are used to enable the interrupt flag, initialize the interface, and erase the VLB. The buffer address register may be loaded by the computer so that, for example, data could be written on the right side of the screen. The y-register can also be loaded directly, so that lines can be written in any order. The Video Line Buffer is in the final stages of design and most of the critical components are on order.

Another possible application of the VLB is a three-dimensional display. Since the video lines can be written individually, it should be possible to construct an image for one eye in one video field and the other eye in the other field. By viewing this composite image through

b. Software Development

1. Simulation and Modelling

We are continuing to develop and test new kinetic models in an effort to understand better the total body and organ retention of medically administered radioactive materials. Solutions to these models have been sought generally through the use of Berman's SAAM 25 computer program. Our efforts are being 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 iron, calcium, I-131 hippiran, pyrophosphate and iodine kinetics in addition to a number of new radiopharmaceuticals. The details of these models and model calculations will be discussed in the following sections dealing with the specific material.

As a member of the MIRD task group to gather data on Fe-59 dosimetry, we are investigating the utility of the Vanderbilt SAAM-25 iron kinetics model to describe the kinetics of normal and abnormal subjects studied at Vanderbilt and at the University of California. Data from the two laboratories will be merged and the resulting dosimetry information will be published as a MIRD phamphlet.

During the past year Dr. Brill has served as a consultant to the Department of Nuclear Medicine operated by the National Atomic Commission in Buenos Aires, Argentina. As a result of this communication we are proposing to collaborate with The Center to analyze extensive compiled data on calcium and iodine kinetics. Buenos Aires lacks the necessary computational facilities to carry out their analyses. In addition to these existing data, new data are being collected at the rate of 25-30 new studies per year. The difficulty associated with obtaining such data is very great thus making this data base very valuable. When these data are merged with data collected in our institution they should provide extensive and accurate dosimetric information.

The calcium (Ca-47) data are collected over time periods extending up to 4 times the physical half-life of the radio calcium. In addition to blood, urine and feces measurements, total body and regional scintillation counter data are available. The analysis will be carried out using the SAAM-25 calcium kinetics models shown in Figures 1 and 2. The Buenos Aires data include measurements before and after drug therapies.

Buenos Aires is also collecting complete kinetic data on all I-131 administered in therapy quantities. Approximately 30 new patients are treated per year. These data will be analyzed using a non-linear dose dependent model described in section A. 2. f.

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SAAM 25 Ca 'ODEL 'OSTEOPOROSI'

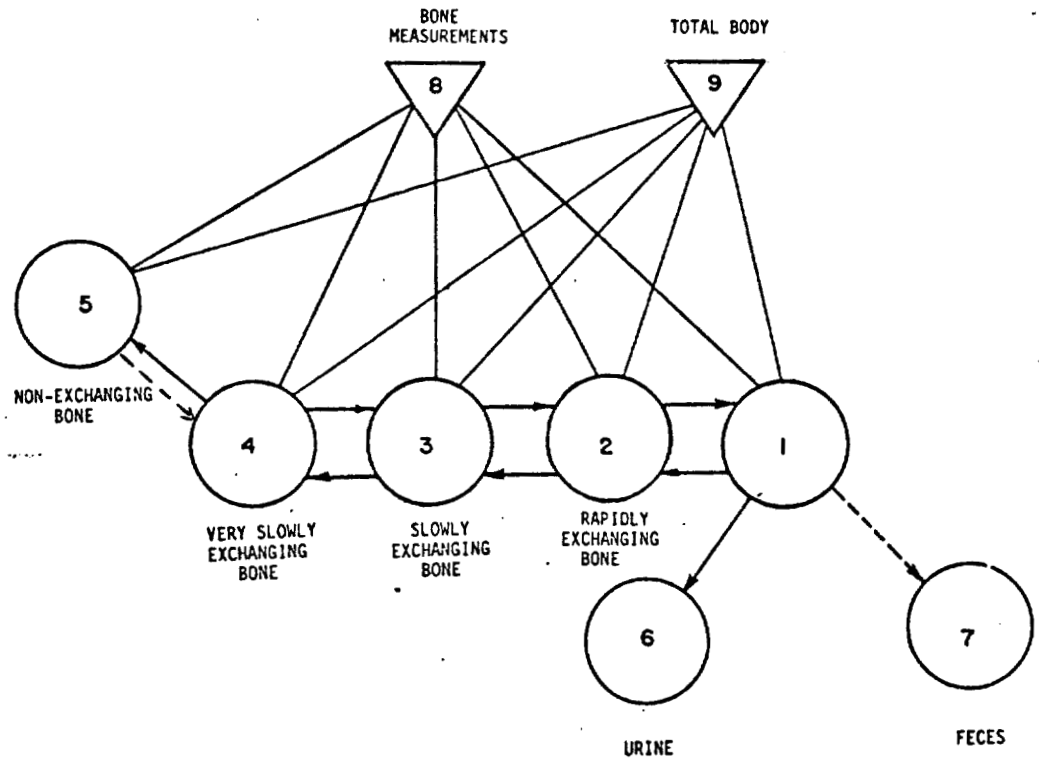


Figure 1: Compartmental Model for Normal and Osteoporotic Calcium Kinetics

SAAM 25 Ca MODEL 'PAGET'S DISEASE'

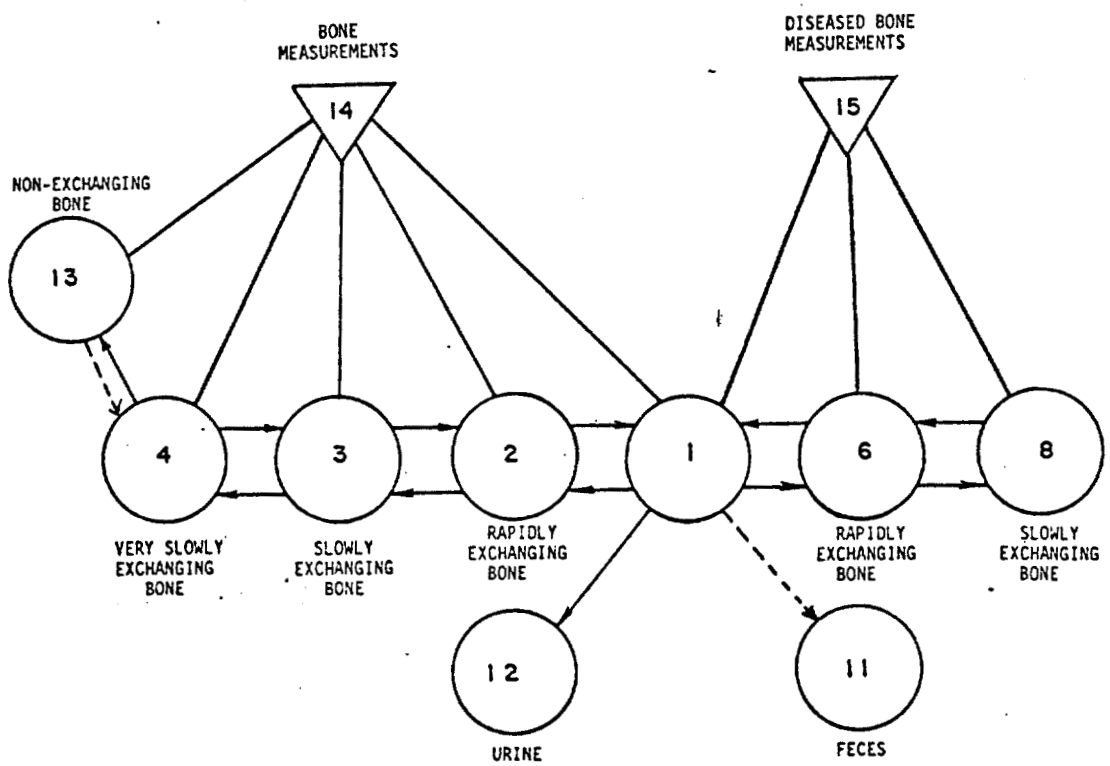


Figure 2: Compartmental Model for Calcium Kinetics in Paget's Disease

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2. Multi-instrument Executive for Data Collection and Display

The executive for operating multiple instruments concurrently and asynchronously received routine use and was also extended in capability. This is important to our research since, for instance, routine use of the low level counting facility with the computer, places a relatively low average data rate burden upon the PDP-9 computer yet requires rapid response from the computer to control the position of the scanner without introducing positional skew due to dead time. Similar situations occur with other devices, whether the data acquisition and display instruments are interfaced through the AEC standard CAMAC system or through dedicated pre-CAMAC hardware.

Presently running under the "Background-Foreground Monitor" (supplied by Digital Equipment Corporation), this substantial program (the executive is over 4500 lines of source code, much of this in "macro instruction") permits the simultaneous utilization of the following devices:

1. The low level whole body counting facility in a rectilinear scanning mode.
2. The electrical storage tube video buffer for local and remote graphic and image display.
3. A multichannel analyzer in a frame mode of image acquisition.
4. Via CAMAC:
   a. Position encoders for two independent and autonomous rectilinear scanners.
   b. Event sensors from remote locations, such as QRS-complex discriminator or beginning-of-procedure indications from the Cardiac Catheterization Facility.
   c. Multiple scaler/counter units which capture physiological information from the patient under study.
5. Transfers of cinescintigraphy system to:
   a. Industry standard magnetic tape (available on one PDP-9).
   b. Proprietary DEC tape which is available on both PDP-9s.
   c. Directly to the second PDP-9.

The PDP-9 system upon which the executive was first made operational was expanded to include 3 million words of head-per-track disk. Suitable modifications were made in executive so that this high-speed medium is now the primary data collection buffer, with the slower DEC tapes serving to record the data without the pressure of real-time acquisition.

The executive program is very modular in architecture so as to facilitate new requirements. Extensive use is made of the CAMAC macro instructions to enhance the initial programming task, to guard against obsolescence, and to promote the sharing of technology. It is anticipated that additional data acquisition and display capabilities can be added readily. Documentation of the executive is complete and reports on these systems will be presented annually to the Oak Ridge Symposia on the Sharing of Computer Technology in Nuclear Medicine.

During the coming year it is planned to extend the executive program to include the following:

1. Scanning Anger-type camera (via CAMAC).

2. Multiple-probe tomography system (via CAMAC).
3. Multiplexed ADC for use with slowly varying inputs, such as physiological data (via CAMAC).

As the computer requirements increase, it is expected that it will become necessary to devise an overlay structure to allow the software to be brought into the memory of the PDP-9 from disc storage only when required. This revision should not require major rewriting of the subroutines because of the modular nature of the executive and the capabilities of the operating system. Similarly, no problems are anticipated with the executive in the conversion from a basic CAMAC system with a dedicated controller in accordance with AEC standard TID-25876, since most of the changes will be accomodated by redefining the CAMAC macro instruction expansions.

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3. The Sharing of Computer Programs in Nuclear Medicine

During the past year we have received and distributed numerous computer programs for the quantitation and analysis of radioisotopic spectral and image data. We have continued to work with Dr. Berman and Mrs. Weiss to help distribute the NIH Simulation and Modelling Program package (SAAM) to users with 32-bit computers. During the past year we have supplied copies to two medical centers (University of Wisconsin-Milwaukee and the Orange County Medical Center-California). We will continue to help introduce new users to the capabilities of the SAAM programs for the analyses of kinetic data and the calculation of radiation absorbed doses.

Recently we have received a program called CAMIRD (Computer Assisted Medical Internal Radiation Dosimetry) from the Cincinnati General Hospital. CAMIRD computes absorbed doses to specified organs in a standard man from internally administered radionuclides according to the MIRD schema. We are in the process of implementing this program on our Sigma-7 computer to aid us in our continuing dosimetry calculations.

As part of our continuing effort to promote the sharing of computer progrmas in nuclear medicine, we co-sponsored the Fifth Annual Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicne. The symposium was held January 15-17, 1975 in Salt Lake City, Utah and resulted in the formation of a number of task groups assigned to investigate significant problems in the analysis of radioisotopic data and to propose standard protocols for data acquisition and analysis. During the coming year we again propose to co-sponsor along with the Radiation Shielding Information Center at the Oak Ridge National Laboratory the Sixth Symposium on the Sharing of Computer Programs. This conference will in part be used to introduce prospective users to SAAM and will help current users to utilize SAAM to its highest potential.

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c. Correlation Studies between Calculated and TLD Measurements of Radiation Dose-applied to Tc-99m Sulfur Colloid Liver Scanning

The purpose of this project is to make an evaluation of the standard man model using patient data, which requires careful evaluation of the techniques used to measure the dose and the activity in patients. The patient data obtained so far indicates that the calculated dose (based upon activity measurements and the standard man model) is larger than the measured dose (using TLD's) by about a factor of two. This error may not be due just to inadequacy of the standard man madel, however, because various checks on the accuracy of our measurement techniques have yielded inconsistent results. These are

1. TLD measurements at ORNL on a physical phantom closely approximating the mathematical phantom also show the calculated dose to be larger than the measured dose, but by only 50% rather than a factor of two. This discrepancy could be due to some error in the TLD readings, error in the computer calculations, or inconsistency between our activity measurements and those used at ORNL.
2. The cube problem, reported to be in error last year, has now given results in agreement with those from a Tc-99m "point" source. Since we made all the activity measurements for this, our activity measurements and TLD readings are evidently self-consistent.
3. A comparison of TLD sensitivity to Cs-137 gamma rays to that for Tc-99m gamma rays shows a difference of about 30%, which should not be the case. This implies either some error concerning the TLD's themselves, or error in the activity determination of Tc-99m and/or the Cs-137 source. The latter has been checked using ionization chambers, and is felt to be correct.

In trying to find the cause of conflicts, one must know the uncertainty of each measurement. If these do not account for the observed differences, then systematic effects must be present. The doses were measured with LiF TLD's, and the random error was evaluated as shown below.

Our investigation began with the observation that whenever a large group of TLD's (>~50) was read out, the last few would read lower than the first few by 10-20%. This was true regardless of the order in which they were read, so this decrease was not due to the TLD's themselves. Then a group of ten TLD's was annealed, exposed to Cs-137 γ-rays, and read out, with this cycle repeated twice more. The results are shown in Table 1.

Table 1

	True Exposure	Exposure from Average of TLD Readings
First Readout	580.0 mR	580.8 mR (calibration exposure)
Second Readout	33 mR	31 mR
Third Readout	33 mR	29 mR

Just as interesting as the steady drop of the TLD-inferred exposures was the fact the standard deviation of the TLD readings was 3 mR for both the second and third readouts, suggesting that the problem was not due to the low light levels resulting from 33 mR exposures. The suspected cause was the silver heating pan of the reader, since visual inspection showed it to be dirty. This was first checked by thoroughly cleaning the pan, and then inspecting it during personnel badge readout by the Radiation Safety Office. After the first TLD was read, a faint imprint of exactly the same size and shape of a TLD could be

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seen on the pan. The next few TLD's were placed over this imprint, which became steadily whiter. By the time all the personnel badges were read (~200), almost all of the pan was covered with this white material. Evidently, each TLD was chemically reacting with the silver pan, producing a substance (probably AgF) which reflected less light than the shiny silver. Since some of the detected light would be reflected off the pan, this increasing dirtiness would tend to lower TLD readings as more of them were read.

Before discussing the correction for this, first consider the chain of relationships involved which comprise the relationship between a TLD readout and the TLD dose. One has the TLD dose $\longrightarrow$ light emitted by the TLD $\longrightarrow$ light detected by the PM tube $\longrightarrow$ total charge delivered by the PM tube (the number obtained from the readout process). In order to have good reproducibility, one clearly must be able to correct for changes that may occure along this chain. The first part depends upon the inherent properties of each TLD as a phosphor, as well as its optical clarity, cleanliness, and the type of heating cycle used. The next part depends upon the pan reflectivity and the geometry of the pan, TLD, and PM tube setup, while the last part depends upon the PM tube gain and the performance of the other electronics of the reader. With our reader (model TLR-5, Eberline Instrument Company), an internal light source is used to easily check and correct for variations in this last part, so the correction method is primarily intended to check the other parts of the chain.

To do this, one simply reads out a "standard" TLD between each TLD of the desired set. For the calibration readout, one first reads the first "standard" TLD, then the first TLD being calibrated, then the second "standard" TLD, then the second one being calibrated, and so on until all the TLD's of the set have been read, followed by the last "standard" TLD. To determine a dose with these calibrated TLD's, the same readout process is used, with the same TLD's being read in exactly the same order as before. Comparison of corresponding "standard" readings would give correction factors for differences in the chain of relationships, and interpolation of these correction factors would give estimates for correcting the reading of each calibrated TLD.

In order for this method to be effective, changes in the chain must occur in a smooth, continuous fashion. However, the buildup of dirt on the TLD's and brief fluctuations in line voltage might not meet this condition, so special care was taken to keep the TLD's as clean as practical, and if opaque spots were noted on a TLD, it was always placed with the same side down against the pan. The line voltage was also monitored, and observed to fluctuate unpredictably between 110 v. and 120 v., which was enough to affect the heating components of the reader and its cooling fan. Since this might also affect the charge-collection and counting electronics, a variable power transformer was used to keep the reader voltage between 119 v. and 120 v. This seemed to be significant, because before the transformer was used, the reader would sometimes cut off prematurely (about once every 100 readings). Since the transformer has been used, no premature cutoffs have occurred (about 300 readings to date).

To test this method, as well as to check for the effects of the TLD's becoming dirty, a group of five TLD's was exposed and read repeatedly (and pre-annealed for 1 hour at 400° C each time). The pan was cleaned for the calibration readouts, and the results of the succeeding readouts are shown in Table 2. The first, third, and fifth TLD's were used as the "standard" TLD's, while the second and fourth were the ones tested for reproducibility. The table entries are the

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percent error of the TLD-determined dose from the actual dose.

Table 2. Percent Errors from Calibration Exposure

	Corrected Readings			Uncorrected Readings		
Trial #	TLD #2	TLD #4	Dose (mrad)	TLD #2	TLD #4	Cleaned Pan?
1	+ .46	+ .28	430	- 3.5	- 3.7	No
2	+ .58	- .91	488	- 1.4	- 3.0	No
3	+ .39	+ 2.8	32	+ 2.4	+ 4.8	No
4	- 1.2	+ 5.5	523	+ .8	+ 7.5	No
5	- .33	+ 2.7	412	+ 4.7	+ 7.7	Yes
6	- 2.2	+ .08	463	+ 2.8	+ 5.1	No
7	- 2.3	+ 1.5	522	+ .7	+ 4.5	Yes
8	- .69	+ .28	355	+ 2.3	+ 3.3	No
9	.00	+ 1.1	507	+ 5.0	+ 6.1	Yes
10	- .74	+ 4.0	35	+ 2.3	+ 7.0	No
Average	.89	1.9		2.6	5.3	

On the whole, the corrected readings were less in error, and the largest errors in the corrected readings tended to occur when the pan was not cleaned. Trials 1-4 show that the error gets worse as the pan gets dirtier, particularly for TLD #4. However, note was made of the dirtiness of each TLD each time. TLD #2 was relatively clear, while TLD #4 was not. The dirt spot(s) on TLD #4 varied in size and color (black $\longleftrightarrow$ white) from trial to trial, probably because of the effects of the 400°C anneal. This is probably why it had a larger average error, whether corrected or not. The size of the dose does not appear to make much difference, although more trials in the 30 mrad range will be done to check this. For the last three trials, the TLD's were rinsed in acetone before annealing, which seemed to improve the accuracy of TLD #2's corrected readings. Inspection of the uncorrected results shows a striking effect - for the first two trials, they read low, as expected, but thereafter, read high. It may be that some silver-containing contamination from the pan also has thermoluminescent properties, and that this contamination is partly absorbed into a TLD during anneal, creating the high response after a few trials. In any event, this effect would occur with all TLD's read, so that a correction based upon the "standard" TLD's would tend to take this into account. The uncertainty of the dose measurements then, was taken to be about ±2%, which does not account for the differences seen with patient data.

The next consideration is the accuracy of the estimate of the patient activity. The mathematical reasoning of this is shown in Appendix I, but the steps followed are outlined below.

1. Sum each detector counts over the desired organ image, without regard to various source and phantom thicknesses. If there is more than one source organ in the scan field, only those organs which are resolved can be treated separately. Organs not resolved must be processed as a single source. Naturally, one must subtract background counts from these sums.

2. Using the transmission scan data, compute the average patient thickness (d) from

$$e^{-\mu \frac{d}{2}} = \frac{1}{m} \sum_{j}^{m} e^{-\mu \frac{d_j}{2}}$$

where the d_j are the various patient thicknesses, and m is the number of cells comprising the source. From a knowledge of the number of data points in the image and the size of the collimator field of view, d can be found accurately even if m is not exactly known. Notice that d will be somewhat less than the arithmetic mean of the d_j values; this is important and is discussed in Appendix I.

3. Using the ultrasonic data, evaluate the expression

$$E = \sum_j^m \sinh(\mu t_j/2) \Big/ \sum_j^m (\mu t_j/2),$$

where t_j are the various source thicknessess and μ is determined from the exponential attenuation of the calibration data. Here, since only ratios of sums are needed, this should be accurate.

4. Calculate the estimate of the source activity from

$$A = (C_T C_B)^{1/2} / [GM(d) \cdot E],$$

where
C_T = the sum of the top detector counts
C_B = the sum of the bottom detector counts
E = the expression from step 3
GM(d) = the geometric mean of the calibration functions for each detector. This is assumed to be independent of point source depth, although it does depend upon the phantom thickness (see Appendix I).

5. The activity estimate just found will be, at worst, an upper limit to the true source activity, provided that all the terms in the above equation are accurately known. There are three checks which can be run to assure that this upper limit is only negligibly different from the true activity.
   a. Check the approximations using the method described in Appendix I with the infinite series.
   b. Since the Tc-99m sulfur colloid should be fixed in the liver and spleen, check to see that the activity computed for each organ decays with a six hour half-life (this will not uncover systematic errors).
   c. Extrapolate the activity estimates back to the time of injection. If the value obtained is somewhat less than the amount withdrawn from the sulfur colloid vial for the patient injection (this number, rather than the amount injected, is recorded for inventory purposes), then the activity estimate is probably correct. If not, or if they are equal, the activity estimate is probably in error.

For the patient studies, all three of these checks on the activity determination were made and appeared to be adequate. The rate of activity decay implied a half-life of slightly less than six hours (>5.9 hours), the test on the infinite series implied an error of about 1%, and the activity extrapolated back to injection time was about 2.5 mCi. The activity withdrawn from the sulfur colloid vial was 3.0 mCi in each case; the difference of 0.5 mCi may well have been left in the syringe after injection (specific activity of colloid was approximately 10 mCi/ml.

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Based upon these results, we do not feel that random error is enough to account for the patient differences in this case, either. Apparently, there is a systematic effect somewhere, with either the TLD-measured dose or measured activity being figured incorrectly, or perhaps the standard man formalism does not apply any better than this to patients. The measurements on the physical phantom at ORNL allow a direct check on the former possibilities, and as mentioned earlier, show a discrepancy of about the same order as the patient data. Thus, we need to resolve this discrepancy before the patient results can be used to evaluate the standard man model. We plan to do this in the following way:

1. Do a cross-check of the activity of a Tc-99m source between our laboratory and ORNL. This would check the discrepancy observed with the phantom exposures at ORNL, and we expect to have this done shortly (the arrangements are being made now).
2. Check the TLD's in detail for electron equilibrium under various geometries and exposure conditions. This, too, is being done at the moment and should be finished shortly.
3. Obtain more patient data, to be sure that the differences seen thus far are real. This is our main priority, since this study is one of the first to check the standard man model using patients.
4. Make a check of the limitations of the activity determination method (in patients) using a very heterogenous phantom (simulating soft tissue, air, and bone in an irregular geometry).
5. Make additional investigations, if necessary, based upon the outcomes of the above ones. When satisfactory results have been obtained, we will then be able to report a carefully checked experimental evaluation of the standard man model using patient data.

d. Positron Time-of-Flight Imaging System - feasibility study

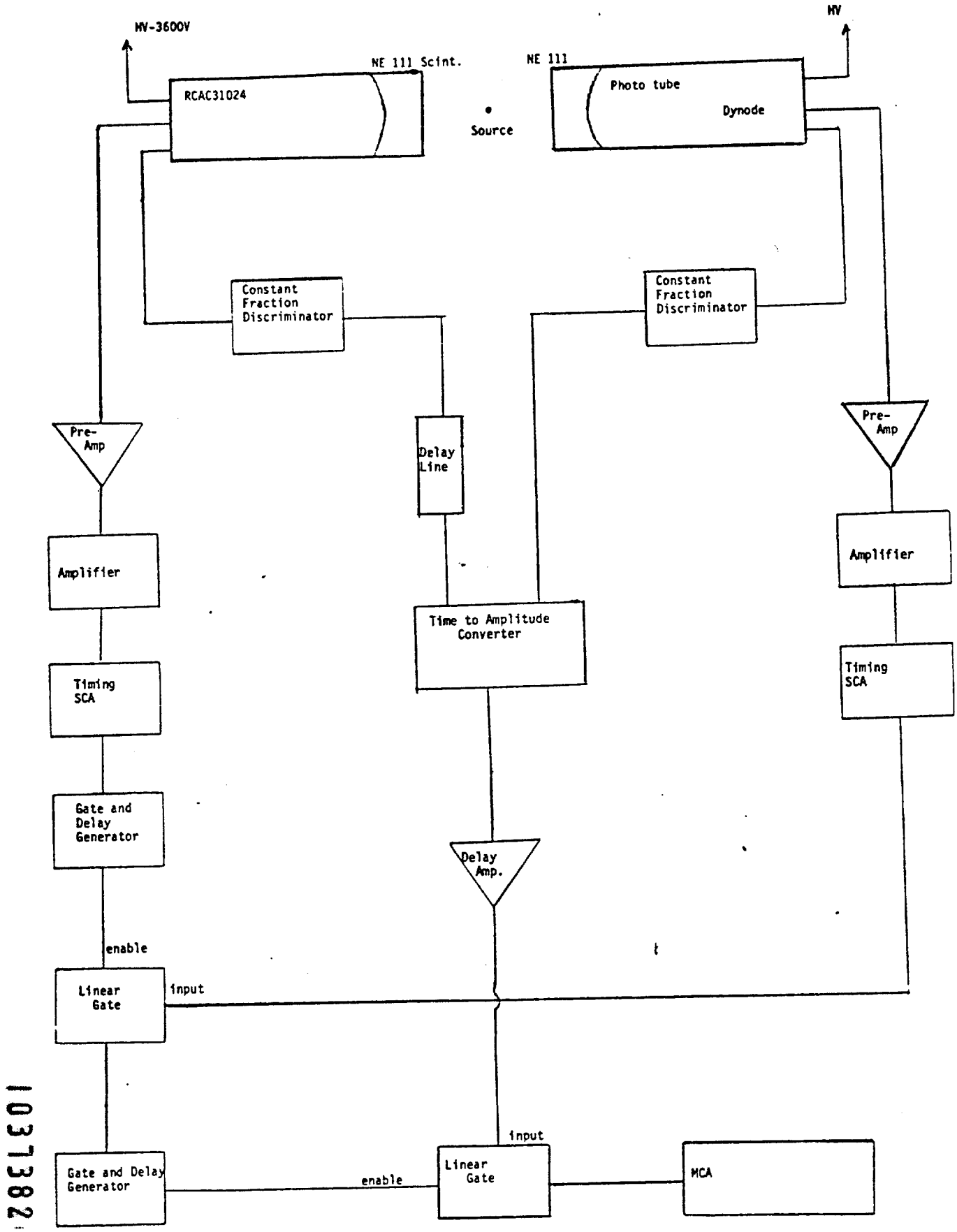
We have undertaken, in co-operation with the Nuclear Physics Group of Vanderbilt a feasibility study to determine if the current state-of-the-art radiation detection systems make time-of-flight positron imaging a clinical possibility. When a positron annihilates with an electron they produce 2 annihilation quanta of approximately 0.511 MeV which by the Principle of the Conservation of Momentum must go in directions at an angle of 180° with respect to one another. Therefore using 2 detectors and coincidence techniques one can determine the line along which the annihilation occurred uniquely. This property has allowed Brownell and several other groups to develop rather complicated positron imaging systems.

If the annihilation does not occur equidistant from the 2 detectors, then the photons will have slightly different arrival times. Light travels in air 30 cm in 10^{-9} sec (1 nano sec). Therefore, if ones detection system is capable of resolving time differentials of a few tenths of a nano second the spacial resolutions will be adequate to do medical imaging of the positron distribution. This technique is referred to as time-of-flight positron imaging.

We have performed a preliminary experiment to determine how accurately we could determine the positron distribution for various source configurations using differential time-of-flight techniques. The experimental set-up is schematically shown in Figure 1*. The incoming quanta are converted to scintillation photons in the plastic (NE 111) scintillator and then converted to an electrical pulse by the Photomultiplier tube. The constant fraction device then relates the pulse to a time measurement and the two times from the two parallel systems are then compared and converted to a voltage in the TAC. This can be displayed on a multichannel analyzer. Each channel then corresponds to a given time differential between the arrival of the two quanta at the detection system. Signals are also taken off the last dynode after amplification and put through a pulse height analyzer. By this energy discriminating one can control the size of accepted pulses seen by a constant fraction device which may then more accurately resolve the timing of the event. One then observes a timing spectrum on the MCA whose position corresponds to the position of the source and of width determined by the time broadening caused by the different components of the detection system. We feel that the equipment we have gathered for this preliminary experiment was true state-of-the-art equipment although we also feel that due to the preliminary nature of what has been done thus far, we should be able to improve our timing spectrum (timing resolution) somewhat.

In order to assess the medical utility of this system, we propose to carry out a number of realistic phantom studies simulating, in particular, lesions of the brain. If the phantom studies prove encouraging, experiments will be carried out in animals with experimentally created lesions.

*The photomultiplier tubes are on loan from RCA; much of the electronics is the property of the Vanderbilt Nuclear Physics Group and the Oak Rige UNISOR Group.



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Figure 1. Block Diagram of Positron Time-of-Flight Imaging System

2. Specific Projects

a. Dosimetry of New Tc-99m Labelled Lung Scanning Agent in Abnormals

Results from a pilot study on patients receiving Tc-99m macro-aggregated albumin and albumin microspheres for lung scans indicated that the biological retention of this material in the lung was much longer than previously had been believed. Since this test is a widely used clinical procedure, we feel that it is of significant importance that the biological turnover and body distribution of these materials be determined so that realistic radiation absorbed dose estimates may be made.

During the last year we carried out studies on 12 normal volunteers. Each volunteer was administered 500 μCi (one-quarter of the recommended dose) of the Tc-99m labelled compounds. Whole body scans and blood samples were taken at 1, 3, 6, and 24 hours post injection. From these data the radiation dose to the total body, lungs and gonads were calculated. During the next year we propose to continue these studies to include a group of approximately 12 abnormal subjects following the same protocol as was used for normal subjects.

Figures 1 and 2 show the averaged biological retention data from the normal studies. Figure 1 is for the group administered the commercially prepared macro-aggregated albumin. The total body and lung retention data are described by the following equations:

Total Body: $A(t) = 100\, e^{-\frac{0.693\,t}{52.1}}$ $(r = -0.97)$

Lungs: $L(t) = 43.8\, e^{-\frac{0.693t}{4.64}} + 0.50$ $(r = -0.96)$

Figure 2 is the data from the group administered the labelled albumin microspheres. The macroaggregate data for both the total-body and lung data show behavior similar to the microsphere date:

Total Body: $A(t) = 100\, e^{-\frac{0.693t}{48.1}}$ $(r = -0.92)$

Lungs: $L(t) = 52.5\, e^{-\frac{0.693t}{3.27}} + 0.40$ $(r = -0.90)$

The data shown graphically in Figures 1 and 2 are shown in tabular form in Tables 1 and 2. The errors were calculated based on the spread in the observations. Our preliminary dosimetry calculations assumed the radioactive source to be uniformly distributed in the lungs obeying the biological retention equations shown above. For the activity not residing in the lungs, we have assumed it to be uniformly distributed in the total body and obeying the following equation:

$TB(A) = A(t) - L(t)$,

where A(t) is the equation describing the total body activity (including lungs) and L(t) is the lung activity. The cumulative activity A(t) for the total body and lungs for both radiopharmaceuticals are shown in Table 3. Table 4 shows the resulting dose equivalent mCi/day. Tables 5 and 6 show the results of the dose estimates to the total body, lungs, ovaries, and testes assuming radiation sources in the lungs and total body.

The described representation of the radioactivity not found in the lungs is obviously not correct. As can be seen from figures 1 and 2, the liver and spleen appear to sequester the radioactive material and contain amounts which are significantly higher than the rest of the body. The behavior of the curves suggest that the liver and spleen take up the radioactive material as it is released from the lungs.

Upper limits on the dose to the liver and spleen were calculated and presented in the progress report; however, we propose to improve these estimates by employing compartmental modelling analysis to describe the complicated kinetics of these materials in the liver and spleen. The initial model will be a five compartment model with the circulating blood pool being the central compartment housing one way communications from the lungs, and to the liver, spleen and excretion compartments. The model calculations should prove important to the description of the normal kinetics but should prove to be most significant for the abnormal studies. New dosimetry tables will be generated from the model results and will include contributions from source distributions in the liver and spleen.

Study time for the abnormals will be kept to a minimum through the use of the scanning bed. The resulting images will be viewed on the proposed Video Line Buffer Display and compared with their corresponding radiographic films of the chest to aid in the delineation of the lung fields. In particular this comparison will aid in the separation of the lung and liver fields so that the radioactive content of each field may be more accurately determined.

LUNG SCANNING AGENTS
MACROAGGREGATED ALBUMIN

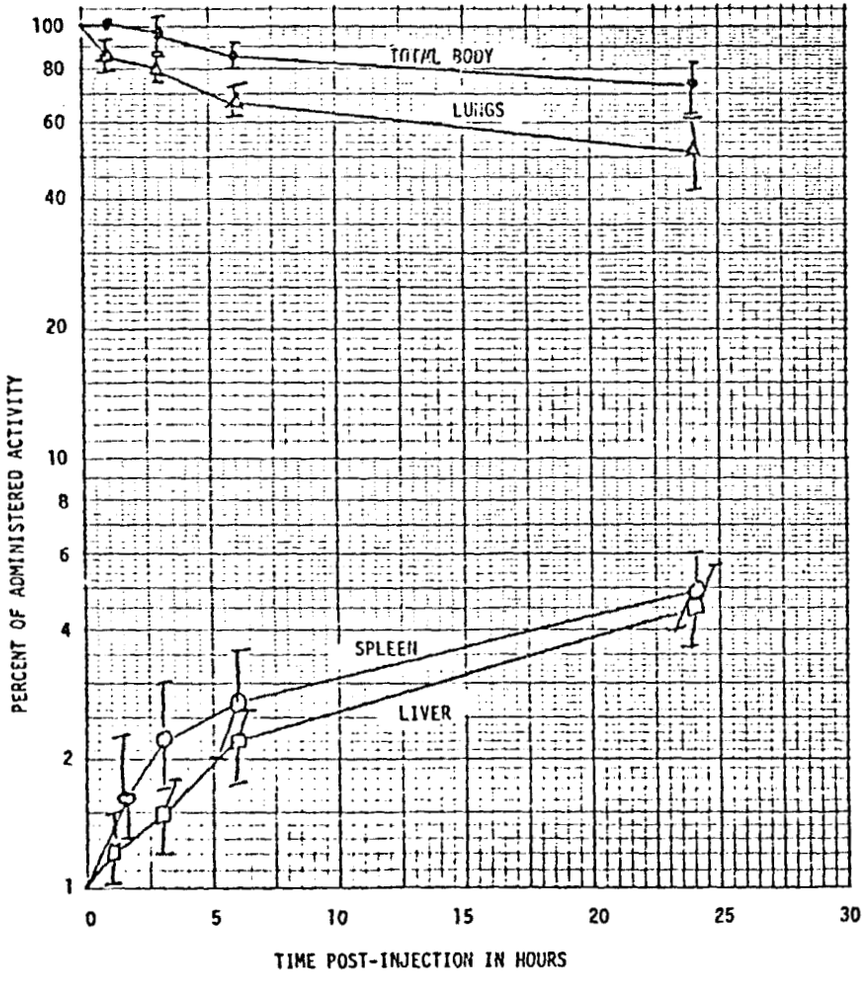


FIGURE 1

LUNG SCANNING AGENTS
ALBUMIN MICROSPHERES

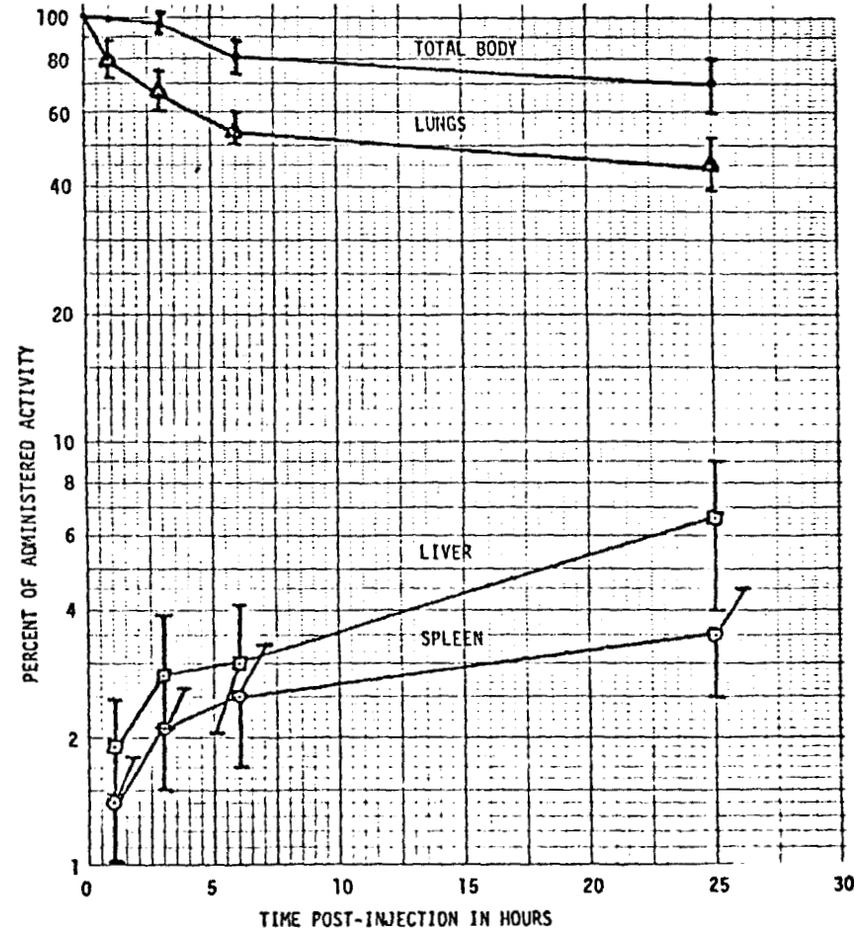


FIGURE 2

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Table 1

MACROAGGREGATED ALBUMIN (GROUP MEAN)

Time (hours)	Total Body	Lungs	Liver	Spleen	Blood
.25					2.3 ± 0.6
1	100	86.5 ± 1.8	1.1 ± 0.2	1.6 ± 0.7	5.5 ± 2.6
3	98.1 ± .9	79.6 ± 1.8	1.5 ± 0.2	2.2 ± 0.7	5.2 ± 0.9
6	87.1 ± 2.4	67.5 ± 1.4	2.2 ± 1.4	2.8 ± 0.8	6.5 ± 1.6
24	73.0 ± 14.8	52.3 ± 12.2	4.5 ± 1.2	4.8 ± 1.0	3.2 ± 1.7

Table 2

ALBUMIN MICROSPHERES (GROUP MEAN)

Time (hours)	Total Body	Lungs	Liver	Spleen	Blood
.25					2.3 ± 0.6
1	100	82.3 ± 4.6	1.9 ± 0.4	1.6 ± 0.7	5.5 ± 2.6
3	98.1 ± 0.9	68.5 ± 4.5	2.8 ± 1.0	2.2 ± 0.7	5.2 ± 0.9
6	81.4 ± 6.0	54.7 ± 3.7	3.0 ± 1.0	2.8 ± 0.8	6.5 ± 1.6
24	70.4 ± 12.0	45.1 ± 6.5	6.8 ± 2.9	4.8 ± 1.0	3.2 ± 1.7

Table 3

Cumulative Activity

$$\frac{\text{mCi Days}}{\text{Administered Dose in mCi}}$$

	Total Body	Lungs
Tc-99m Albumin Macroaggregate	0.074	0.248
Tc-99m Albumin Microspheres	0.177	0.169

Table 4

$$\frac{\text{m rem}}{\text{mCi day}}$$

Tc-99m

Source / Target	Total Body	Lungs
Total Body	46.9	48.5
Lungs	47.0	1260.0
Ovaries	57.2	22.7
Testes	39.8	.019

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Table 5

$$\frac{\text{m rem}}{\text{mCi Administered}}$$

Tc-99m Albumin Macroaggregate

Target \ Source	Total Body	Lungs
Total Body	3.47	12.03
Lungs	3.48	312.48
Ovaries	4.23	5.63
Testes	2.95	.0047

Table 6

$$\frac{\text{m rem}}{\text{mCi Administered}}$$

Tc-99m Albumin Microspheres

Target \ Source	Total Body	Lungs
Total Body	8.30	8.20
Lungs	8.32	212.94
Ovaries	10.12	3.84
Testes	7.04	.0032

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b. Fe-59 Dosimetry - Abnormals

Recognizing the need for dosimetry data for abnormal subjects, we at Vanderbilt are using our fund of abnormal patients combined with clinical and research instrumentation designed to collect quantitative information to obtain organ retention data by external counting. These studies are very difficult to conduct, especially in very ill patients; however, these data are badly needed and significant effort is devoted to these studies.

The MIRD Committee in the United States is collecting data from laboratories doing dosimetry studies and analyzing the new data along with well-documented literature data. In the past we have supplied the MIRD Committee with extensive data on a number of radiopharmaceuticals and are continuing our relationship. Currently we are a member (R. Price) of the task group charged to collect data on Fe-59 and I-131 iodocholesterol. Data collected at Vanderbilt will be merged with data from the University of California (Donner Laboratory) to create a single data base. The current plan of the task group is to use the Vanderbilt SAAM-25 iron kinetics model for the calculation of the cumulative organ activity for the compiled data.

The Vanderbilt SAAM-25 model was presented in last years' report. The flow rates and the derived dose estimates for normals and a number of selected abnormals were also presented. A more complete report of the kinetic model parameters are presented in an IAEA publication which is included as an appended document to the progress report. In cooperation with Dr. Krantz in the Department of Hematology we are continuing to study a variety of patients with various hematologic diseases. We propose to continue these measurements during the next year in order that a more complete sampling of the radiation dose distribution may be obtained. Dose estimates for abnormals have shown large variations from the normal values. We anticiapte kinetic studies on 10-15 patients with long term measurements on 4-5 during the coming year.

In our calculations we have included the source organs and target organs shown in Table 1. We have taken the blood source distribution to be identical to the total body. In order to calculate the blood self-dose we have ignored the effects of penetrating radiation and assumed the primary dose contribution to be from nonpenetrating radiation. In those studies where measurements were made for periods $\leq$ 45 days, the organ effective half-life was taken to be equal to the physical half-life.

Table 2 is a summary of our results for a group of abnormals and our average normal. The table is subdivided so that the fractional dose to each target organ from each source organ may be found. The total target dose resulting from all sources is also recorded.

Table 3 contains the list of the working diagnosis of the patients presented in Table 2. In addition the range of these dose estimates are compared to the 1973 report from the Free University of Berlin.

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Table 1

Dose Equivalent/Microcurie-day
(rem/μCi-day)

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}

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Table 2

Radiation Dose in mrad per μCi of

Fe-59 Ferrous Citrate Administered I.V.

SOURCE	TARGET	A(F)	B(F)	C(F)	D(M)	E(M)	F(M)	G(M)	H(F)	I(F)	J(M)	K(M)
Liver	Liver	211.0	106.0	158.0	158.0	132.0	158.0	317.0	370.0	106.0	422.0	53.0
Spleen	"	0.8	1.0	0.6	1.0	0.8	1.0	0.8	0.8	3.0	1.0	0.6
Marrow	"	0.4	0.4	1.0	0.1	0.6	0.9	0.0	0.1	8.0	0.1	1.0
Blood	"	7.0	8.0	22.0	2.0	11.0	17.0	0.6	1.0	6.0	3.0	22.0
Total		219.2	115.4	181.6	161.1	144.4	176.9	318.4	371.9	123.0	426.1	76.6
Liver	Spleen	6.0	3.0	4.0	4.0	3.0	4.0	8.0	10.0	3.0	11.0	1.0
Spleen	"	225.0	299.0	150.0	263.0	225.0	374.0	225.0	225.0	750.0	299.0	150.0
Marrow	"	0.4	0.4	1.0	0.1	0.6	0.9	0.0	0.1	8.0	0.1	1.0
Blood	"	7.0	8.0	21.0	2.0	11.0	16.0	0.5	1.0	5.0	3.0	21.0
Total		238.4	310.4	176.0	269.1	239.6	394.9	233.5	236.1	766.0	313.1	173.0
Liver	Red Marrow	5.0	3.0	4.0	4.0	3.0	4.0	8.0	9.0	3.0	10.0	1.0
Spleen	" "	0.8	1.0	0.6	1.0	0.8	1.0	0.8	0.8	3.0	1.0	0.6
Marrow	" "	9.0	10.0	27.0	3.0	14.0	21.0	0.7	2.0	184.0	3.0	27.0
Blood	" "	6.0	8.0	20.0	2.0	10.0	15.0	0.5	1.0	5.0	3.0	20.0
Total		20.8	22.0	51.6	10.0	27.8	41.0	10.0	12.8	195.0	17.0	48.6
Liver	Total Body	11.0	5.0	8.0	8.0	7.0	8.0	16.0	19.0	5.0	21.0	3.0
Spleen	" "	2.0	2.0	1.0	2.0	2.0	3.0	2.0	2.0	5.0	2.0	1.0
Marrow	" "	0.7	0.9	2.0	0.2	1.0	2.0	0.1	0.1	15.0	0.3	2.0
Blood	" "	6.0	4.0	19.0	2.0	10.0	14.0	0.5	1.0	5.0	2.0	19.0
Total		19.7	14.9	30.0	12.2	20.0	27.0	18.6	22.1	30.0	25.3	25.0
Liver	Gonads	4.5	2.2	3.4	0.8	0.7	0.8	1.7	7.9	2.2	2.3	0.3
Spleen	"	0.4	0.6	0.3	0.1	0.1	0.2	0.1	0.4	1.5	0.1	0.1
Marrow	"	1.1	1.3	3.4	0.0	0.2	0.3	0.0	0.2	22.6	0.1	0.4
Blood	"	6.5	7.8	20.7	2.7	10.7	16.1	0.5	1.3	5.2	2.7	21.5
Total		12.5	11.9	27.8	3.1	11.7	17.4	2.3	9.8	31.5	5.2	22.1
Blood*	Blood	16.4	19.7	52.6	5.2	26.3	39.4	1.3	3.3	13.1	6.6	52.6

*non-penetrating dose only

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Table 3

Patient	Diagnosis
A	Pure red cell aplasia
B	Red cell aplasia (in remission)
C	Red cell aplasia (in remission)
D	Suspected red cell aplasia
E	Suspected red cell aplasia
F	Suspected red cell aplasia
G	Suspected red cell aplasia
H	Refractory anemia
I	Refractory anemia-marrow storage disease
J	Refractory anemia-liver storage disease
K	Normal

Summary (mrad/μCi)

	Liver	Spleen	Red Marrow	Gonads	Blood	Total Body
Vanderbilt	77-426	173-395	10-195	2-32	1-53	12-30
Berlin (1973)	100	130	-	27	22	22

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All of the dose estimates presented in Table 2 were calculated based upon the standard man model. The presumption that these abnormal patients had normal sized organs is an obvious over simplification. During the coming year we propose to utilize the proposed video line buffer display coupled with overlays of radiographic images whenever available to make accurate organ size estimates. Ultrasonic data will also be employed when possible to help define liver and spleen dimensions. Accurate organ size estimates will result in more accurate dose estimate.

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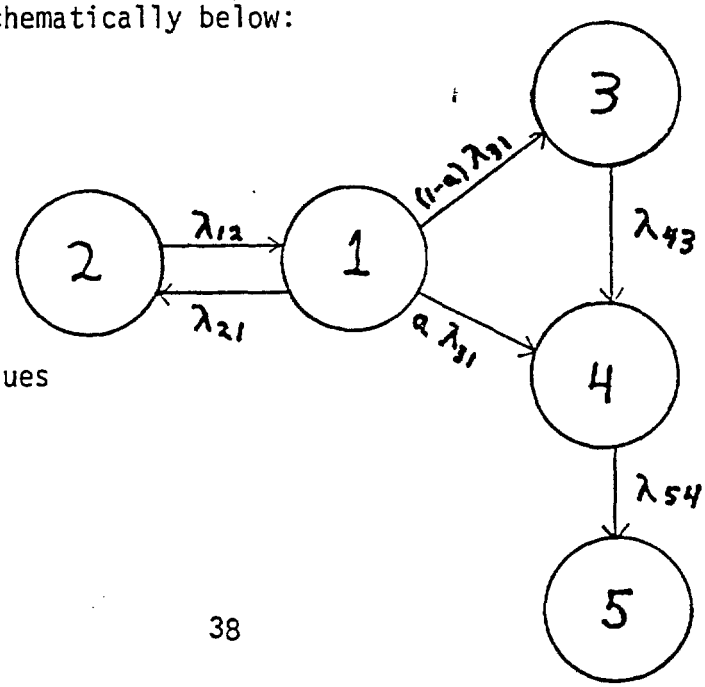
c. Dosimetry of I-131 Hippuran in Bi-lateral and Transplant Renograms

The I-131 hippuran renogram has been an established clinical test used to assess renal function. Due to the facts that this procedure is frequently used to assess degenerative changes by means of sequential measurements and the known unfavorably dosimetric properties of I-131, we feel that the detailed dosimetry associated with these studies must be determined. As a continuation of work already started we propose to carry out these investigations in patients referred to the Division of Nuclear Medicine for routine renal function tests. We propose to carry out studies in patients with two kidneys (bi-lateral) as well as patients with a transplanted kidney. We expect to be able to acquire at least 50 subjects in each of these categories so that we may relate the absorbed dose to function impairing kidney disease as well as renal obstruction. Simulations carried out during the past year indicate that the average dose to the whole kidney in the absence of excretion function would be approximately 45 rads. The fact that the isotope is not uniformly distributed in the kidney (the isotope in fact pools in the collecting apparatus) has led us to estimate that doses as high as 600 rads to some cell groups may result from these studies. In order to investigate these asymmetric distributions we will attempt to carry out a regional assessment of the activity within the kidney from the cumulative scintillation camera images and from the pre-study residual scan images.

The transplant patient presents a particularly interesting problem in that renal function may vary dramatically from essentially no function to normal within a matter of a few weeks. At Vanderbilt Medical Center there is a very active transplant program with an average of 4-6 in-patients under constant study and observation at any time. As a part of the post operative procedures, the transplant patients have I-131 hippuran renograms performed every other day until the acute rejection period is passed and then less frequently for an extended period on an outpatients basis.

In order to carry out these studies we are employing a mathematical model to fit the data from the patient studies and to simulate the hippuran kinetics for both normal and abnormal functions.

The model we have chosen was adapted from the model suggested by Lindmo, et. al. and is shown schematically below:



1: Plasma
2: Extra vascular tissues
3: Tubular parenchym
4: Tubular lumen
5: Bladder

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Patient data were collected by means of an Anger Camera placed anteriorly over the kidneys and bladder. In addition, a stationary probe is placed over the heart to monitor the blood pool activity. A second probe is needed if placed over the bladder catheter when one is present in order that the total bladder activity may be measured.

Using the flow parameters shown in Table 1 for normal renal function, the values of the renal uptake ($\lambda 31 + \lambda 41$) and excretion ($\lambda 54$) rates are slowly varied and the resulting renograms were generated.

Two such simulated renograms are shown in Figure 1. The upper curve is for the extreme case where the kidney retained a normal extraction or uptake while the excretion capability was completely lost. The lower curve displays a normal function. The radiation dose derived from these two simulations is shown in Table 2.

In the clinical environment the transplant patient is studied every other day until normal or a clinically adequate function is reached. A set of typical transplant renograms covering a two weeks period is shown in Figure 2. For each patient flow parameters are computed and the radiation dose is calculated from the 30 minute renogram data plus the measured residual activity prior to each successive study. Figure 3 shows the comparison of the computer model calculations to the observed data shown in Figure 2 at Day 10. As part of the model calculations, the computer utilized data for the blood pool clearance of the I-131 hippuran as monitored by a probe positioned over the heart. These data are shown in Figure 4.

Data from each patient will be summarized as a function of time post transplantation and the average radiation dose to the kidney will be calculated. A typical plot of kidney dose versus time after transplantation is shown in Figure 5. The upper curve corresponds to a case where the kidney responded very slowly and consequently resulted in continued large kidney doses finally converging to the normal radiation dose of approximately 60-80 mrads. The lower curve was obtained from a patient who responded rather quickly and approached normal function within 12-14 days. Difficulty arose in estimating the excretion parameter which corresponded to washout half-times from 2-8 hours. For these studies the 30 minute renogram was inadequate to determine a non-zero washout rate while the rates were in fact fast enough to bring the residual to $\leq 1\%$ of the injected dose when measured at the 48 hour renogram. For these cases we have estimated the mean dose to be: 1.0 ± 0.6 rads. In order to remedy this problem we will institute additional residual images which will be taken at 4-8 hours and at 24 hours post injection.

The range of radiation doses to the kidney during the first 1-3 days in the preliminary studies usually ranged from 1-8 rads. After this time, dose estimates ranged from 0.1 or about normal to presumably the maximum possible dose for those kidneys which fail to function. In addition to the kidney dose, dose estimates to the gonads, bladder and total body will also be made.

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