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20b. Publications

Fiscal Year 1986

Crook, J., Washburn, L., Sun, T., Byrd, B., Brill, A., Kubota, K., Bennett, G., Zanzi, I., and Yeh, S.
D- and L-enantiomers of ^{11}C-valine in the evaluation of pancreatic adenocarcinoma.
Dig. Dis. Sci. 30:968, 1985.

Washburn, L.C. and Carlton, J.E.
A modified Limulus lysate technique for routine pyrogen testing of gallium-68 EDTA.
33rd Annual Meeting, Society of Nuclear Medicine, Washington, D.C. (submitted).

20c. Purpose

The purpose of this task is to apply nuclear imaging techniques to the testing of radiopharmaceuticals for diagnostic and physiologic studies in patients with gastrointestinal, respiratory tract and cardiovascular diseases. This program focuses largely on two areas in nuclear medicine, (1) Positron Emission Tomography (PET) with positron-emitting radiopharmaceuticals, and (2) computer applications in image analysis. During the past decade emphasis was placed on diagnostic and research applications of ^{11}C-labeled amino acids for the study of neoplastic diseases, particularly of the brain and pancreas. More recently, the area of interest has been expanded to include the cardiovascular system as well as vascular abnormalities of the central nervous system. Cyclotron-independent radionuclides such as ^{68}Ga, ^{64}Cu, and ^{18}F are being investigated for potential applications in research and diagnostic PET imaging. This route is being utilized and emphasized as a means of replacing clinical research which had previously utilized ^{11}C produced by the Brookhaven National Laboratory (BNL) cyclotron. New radiopharmaceuticals showing potential in preclinical investigations are tested in humans through Phase I and II pharmacological and clinical efficacy studies. In conjunction with the Phase I and II studies, improvement in computer applications and the development of software programs for PET imaging for quantitative non-invasive studies of organ or tissue (tumor) function are carried out.

The long range objectives of this task are (1) to refocus and expand the positron tomography program and make it less dependent on the availability of a local cyclotron through the development of radiopharmaceuticals labeled with reactor-produced or generator-produced positron emitters, (2) to apply newly identified positron-emitting radiopharmaceuticals for the study and diagnosis of neoplasms and diseases of the pancreas, lung, brain, and cardiovascular system, and (3) to further develop PET as a research and clinical tool through improving computer applications for image analysis and quantitation of PET data. The goal of this basic research is the development of new diagnostic procedures for use in nuclear medicine.

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20f. Technical Progress

Progress FY-85 and FY-86

This project includes Phase I and Phase II testing of positron-emitting radiopharmaceuticals using PET technology. In the past this project has relied heavily on the ORNL 86-inch cyclotron which is no longer available for our use. Thus, continuation of the ^{11}C-labeled amino acid/positron tomography clinical investigations in patients with pancreatic cancer was carried out through collaborative arrangements with the Nuclear Medicine Department of Brookhaven National Laboratory (BNL). Patients were referred for this project from the Sloan Kettering Cancer Research Center, New York, NY and the Northshore Hospital on Long Island, NY to determine if there was a predilection of the pancreas and/or pancreatic tumor for either the D- or the L-enantiomeric form of ^{11}C-labeled valine or tryptophan. The intravenous injection dose ranged from 2.5 to 10.0 mCi. Scanning was performed utilizing the now defunct PETT III instrument. Results of that investigation revealed a marked diminution of uptake of the D-isomer of ^{11}C-labeled valine by the liver. Of the two patients who received both D- and L-valine, the percent of the D-isomer localized in the tumor was less than the uptake of the L-isomer in one patient and equal in another. Of the four patients studied with D-valine only, it appeared that there was a lower percentage of the injected dose present in the tumor than in the remainder of the pancreas. ^{11}C-Labeled D-tryptophan was administered to a patient for the first time during this period, which is to our knowledge the first clinical study anywhere with this agent.

A study utilizing ^{68}Ga-EDTA in PET brain scanning in patients with small vessel atherosclerosis was initiated. A total of 6 patients have been studied. All the patients had well-documented dementia of either the Alzheimer's variety or subcortical infarcts. The results of the PET imaging were interpreted in conjunction with CT scans and magnetic resonance imaging studies where available. Although the number of patients so far is small, there appears to be areas of white matter pathology mutual to all three imaging modalities employed. Preliminary discussions were held with Dr. Votaw of the Quillen-Dishner School of Medicine, Johnson City, TN regarding the collaborative investigation of copper-64 citrate as a tumor-imaging agent in Hodgkin's disease.

The Preclinical Radiopharmaceutical Development group has explored alternative synthetic processes which include the incorporation and substitution of fluorine-18 as a positron emitter in place of carbon-11 for compounds that have displayed specificity for tumor localization and as indicators of both acute and chronic diseases such as those arising from exposure to substances injurious to the pulmonary parenchyma and endothelium. Therefore, we are actively involved with the Tandem van de Graaff accelerator group and the Nuclear Medicine Technology section at ORNL to produce ^{18}F. Several pilot experiments have taken place in the Tandem van de Graaff accelerator employing an ^{18}O-enriched water target which have resulted in the production of small amounts of ^{18}F.

Region-of-interest methodology for both brain and thorax imaging have been vastly improved through rewriting of the original computer program and adapting an NIH program for the calculation of attentuation correction factors for these two anatomical regions.

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20f. Technical Progess (continued)

We assisted J. Neiler of ORBIT, Inc. in the successful completion of his Small Business Innovative Research Program, Phase I, proposal to DOE for the further development of a mini-cyclotron that would be housed at ORAU M&HSD and ultimately be capable of producing on-site clinically useful quantities of positron emitters.

Planned Progress FY-86 and FY-87

Arrangements have been made with the Nuclear Medicine Department of Brookhaven National Laboratory to continue clinical investigations in patients with cancer of the pancreas. Patient referral for this project has been assured by the Sloan Kettering Cancer Research Center and the Northshore Hospital on Long Island. The studies will focus mainly on determining the imaging superiority of one amino acid over the other, as well as one isomer over the other. Also, we will have an opportunity to assess the utility of a multi-wire proportional chamber in imaging tumors of the pancreas.

Collaborative efforts with the University of Tennessee Memorial Research Center and Hospital and St. Mary's Medical Center have been established to continue a study of small vessel atherosclerosis using ^{68}Ga in patients suffering from either a cerebrovascular accident or multi-infarct dementia. These studies are viewed as a prelude to a more ambitious investigation of Alzheimer's disease and underlying existent modification of the blood-brain-barrier due to the disease.

A clinical investigative protocol utilizing the positron emitter, ^{64}Cu, to evaluate lymphomas, especially Hodgkins disease, will be initiated. In addition to evaluating its ability to provide enhanced images of lymphomas, we will have an opportunity to explore the kinetics of copper uptake and clearance and how therapy effects these two parameters.

Plans are to file an amendment to the present IND for copper-64 citrate to allow for its use in non-tumor applications such as cardiomegaly and aortic aneurysms. Concurrently with this, a pilot protocol will be developed to begin clinical studies of individuals with cardiomegaly secondary to diverse etiologies, e.g., infections, hypertension, etc.

Planned Progress FY-88

The collaborative arrangement with BNL for the study of the D- and L-isomers of valine and tryptophan in patients with pancreatic adenocarcinoma will be concluded. The final studies of D- vs L-tryptophan uptake in pancreatic carcinoma and how it relates to the effects of treatment will be determined. The prognostic value of the uptake studies should be answered.

The usefulness of ^{64}Cu in cardiovascular disease and soft tissue tumors as well as hepatic disease will remain under investigation. Whether or not the ORNL Tandem van de Graaff accelerator can routinely produce sufficient quantities of ^{18}F for PET imaging studies will be resolved. Gallium-68 investigations in patients with diverse forms of disease of the central nervous system will still be under active investigation. Consideration will be given to initiating clinical trials of ^{90}Y- or ^{255}Fm-labeled monoclonal antibodies in patients with colorectal carcinoma and/or melanoma.

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20h. Relationship to Other Projects

The Clinical Nuclear Medicine Program is very closely linked with the Preclinical Radiopharmaceutical Development group of the M&HSD, especially since both of these programs are heavily focused on developing and testing new radiopharmaceuticals. The existing relationship to the Nuclear Medicine group at the Oak Ridge National Laboratory will be intensified because of our need for fluorine-18 and copper-64, as well as possibly other radionuclides. An interdisciplinary task force within the M&HSD combines efforts in radiopharmaceutical development, biochemistry, pharmacology, and nuclear medicine for the purpose of developing diagnostic nuclear medicine procedures for lung disease. A collaborative relationship has been established between the M&HSD's nuclear medicine programs and the Nuclear Medicine Department at the Brookhaven National Laboratory. This latter arrangement is supported in terms of patient selection and referral by the Sloan Kettering Cancer Research Center and the Long Island Northshore Hospital. On a regional basis we maintain a collaborative relationship with The University of Tennessee Memorial Research Center and Hospital, Knoxville; in particular, with clinical groups in neurology (Dr. John Doughterty) and radiology (Dr. Karl Hubner). All of these relationships are essential to this program.

20k. Capital Equipment FY 1987

PDP 11/44 Computer $ 20.0

The success of the Clinical Nuclear Medicine program depends on the development of new software and programs. At present we are experiencing difficulties due to the storage capabilities of the existing system, down time, and costs to maintain it in an operating mode.

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201. Foreign Travel

III World Conference on Clinical Pharmacology and Therapeutics, July 27 - August 1, 1986, Stockholm, Sweden. $2500.00

European Nuclear Medicine Congress, September 2-5, 1986, Goslar, FRG. $2500.00

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20c. Purpose

This task is combined into service-oriented and research activities for the specific purpose to improve the medical care of persons injured in radiation accidents. To meet these objectives, a multi-disciplinary staff trained in medical management of radiation accidents is responsible for handling radiological emergencies in a specially equipped facility and to train others in radiation accident management. Keeping a professional staff in a state of readiness to assist in the management of radiological emergencies and radiation injury of DOE nuclear workers in Oak Ridge as well as outside Oak Ridge assures optimal management of individual cases and provides a back-up medical team for on-site emergencies. Teaching and training in the area of radiation accident management contributes to the overall improvement of the quality of both national and institutional medical emergency and occupational medical service systems.

Research activities within this task include: (1) basic research regarding the mechanism damage induced by radiation and the use of cytogenetic techniques as a biological indicator of dose in suspected radiation overexposures; (2) attempts to improve the diagnosis and assessment of severe local radiation injury by such pharmacologic means as prostaglandins and other anti-inflammatory vascular protective drugs; (3) continued national management for DOE of the FDA-IND clinical trials of calcium and zinc DTPA chelation therapy for internally deposited actinides, evaluation of new developments in chelation therapy involving either improved protocols for the existing agents or research on improved chelators; when indicated, submission of the appropriate IND amendments or new IND's to FDA through DOE; and management of the DTPA Registry, a computer-assisted collection of case histories of DTPA-treated individuals, to assist in the determination of the safety and efficacy of DTPA drugs and to facilitate long-term medical follow-up of these persons; and (4) a continuing study of past and present radiation accidents and their medical consequences. The US Radiation Accident Registry, a centralized medical data base of past radiation accidents, provides a ready source of information on the radiobiology of man, the efficacy of treatment protocols, and supports epidemiologic studies of selected populations. Consultation during compensation proceedings where it is alleged that radiation exposures were causally related to the subsequent manifestation of disease provides forensic support in both the medical and health physics aspects of accident investigation.

Provide for nonrecoverable medical expenses of qualifying former patients of the Medical and Health Sciences Division's inpatient program.

20f. Technical Progress

Progress in FY85 and FY86

Assistance and Consultation by REAC/TS

The REAC/TS emergency response program and team continues to provide assistance to the private nuclear power industry and fuel reprocessing facilities in the event of radiation accidents involving personnel injury. These commitments are documented by letter agreements

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between the requesting party and the U.S. DOE Oak Ridge Operations. At present, 42 such letter agreements are in effect with REAC/TS response capabilities to meet these commitments routinely tested through participation in on-site accident drills, telephone consultation, testing of emergency communications networks, and call-out drills simulating reception of radiation accident victims.

During FY85-86, REAC/TS updated its analytical capabilities for gamma spectrometry through the addition of a new multichannel analyzer to be used with the ultra low background level counting chamber. This new system is now fully installed, calibrated, and ready for emergency management of radiation accidents.

In FY85-86, REAC/TS, with the approval of DOE and the State Department, continued to assist the World Health Organization through designation as the "WHO Radiation Emergency Consultation Center" with responsibilities to North America, Mexico, Central and South America, and the Islands of the Caribbean. The REAC/TS WHO collaboration system continued to provide assistance to the Mexican government regarding the Ciudad Juarez cobalt-60 accident. Recent efforts have concentrated on follow-up of persons involved in this accident to determine the relative lifespanof lymphocytes bearing radiation-induced chromosome aberrations in selected persons having received the highest exposures. In addition, two new accident victims have been identified with suspected high-level exposure and cytogenetic dosimetric estimates accomplished. REAC/TS will continue to work with the Mexican government through the WHO designation with advise and on-site consultation as needed regarding the establishment of medical follow-up protocols in the exposed Mexican population.

In FY85, REAC/TS assisted the FEMA Emergency Management Institute in two major efforts at FEMA's national emergency training center, Emmittsburg, MD. In the first effort, REAC/TS participated in the National Workshop on Hazardous Materials Emergency Training with activities focused on the role of the federal government in providing hazardous materials training in the areas of planning, preparedness, response, and recovery, the need for a coordinated effort in providing such training and the relationship of federal training to that training provided by state and local governments in the private sector. In this effort, hazardous materials included both radioactive and nonradioactive hazmat. The result of the workshop was a better appreciation and understanding of the respective roles and responsibilities of federal agencies involved in hazardous materials training, the development of criteria for a national curriculum of hazardous materials training, and improved interaction between and among federal, state, and local agencies. The role that REAC/TS emergency response and training plays in this effort was discussed. Secondly, REAC/TS participated in an evaluation and recommendation for updating of a program of study consisting of five radiological courses currently field deployed by FEMA. Two of these courses were written under terms of an interagency agreement between DOE and FEMA with REAC/TS providing all components of the training package. This curriculum advisory committee meeting made appropriate recommendations for change in each of the five courses under review. To better coordinate federal radiological training activities, FEMA requested input to these reviews by the Federal Radiological Preparedness Coordinating Committee Training and Exercises Subcommittee member agencies.

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In FY85/86, REAC/TS staff responded to 62 requests for assistance involving a maximum of 92 persons (an unspecified number of persons were involved in five of these situations); this is a 6.5% increase over the number of requests for assistance received during the same period in FY84/85. Of these, 61 requests were from within the US; six requests concerned radiation exposures to nine persons that met the DOE/NRC radiation accident dose criteria; another request concerned a serious radiation-related accident at Kerr McGee's Sequoyah Nuclear Facility, Gore, OK involving approximately 110 persons, but the injuries, including one fatality were chemically (UF_6 gas), not radiation induced. Nine employees of the Goodyear Atomic Corporation's Gaseous Diffusion Plant in Piketon, Ohio, were referred to REAC/TS for whole body and lung counts because of their concern about having been occupationally exposed to uranium and thorium. The counts were conducted at the Whole Body Counting Facility at Oak Ridge National Laboratory; no radioactivity in excess of the normal range was detected in any of the individuals counted. Cytogenetic analysis was conducted on cultured peripheral lymphocytes of 11 persons suspected of being overexposed to radiation to estimate any radiation dose they had actually received.

The REAC/TS Registries

In FY85/86, a total of 96 radiation-related events involving more than 185 persons was recorded in the central REAC/TS Registry; REAC/TS provided consultative assistance in 61 of the events recorded.. Thirty-two events met the criteria for inclusion in specific registries and were assigned as follows:

(1) U.S. Radiation Accident Registry: 19 accidents involving more than a total of 25 persons, were recorded in FY85/86. REAC/TS was consulted in 7 of the 12 accidents that actually occurred during this period; these concerned five instances of high dose local exposures for ^{192}Ir industrial radiography sources (4 accidents, 4 persons) and from a fluroscope in a food preparation plant (1 accident, 4 persons); 1 plutonium contaminated wound (1 person); and 1 uncontrolled release of UF_6 that involved approximately 110 persons, 20 of them seriously, and resulted in one non-radiation induced fatality. Five additional accidents were the result of the misadministration of radiation or radioactive materials (^{131}I) for diagnostic and therapeutic purposes; these accidents came to REAC/TS attention via NRC reports. The remaining seven accidents occurred prior to the current reporting period and were recorded retrospectively; these included therapeutic overdoses from ^{60}Co radiotherapy devices (3 accidents, 3 persons), an X-ray source (1 accident, 1 person), and an unrecovered radium implant (1 accident, 1 person); a diagnostic overdose of ^{131}I (1 accident, 1 person); and a whole body exposure greater than 25 rems to one person from an accelerator unit.

Follow-up continued of survivors of previously recorded radiation accidents. Five of the six living survivors of the 1958 accident at the Oak Ridge Y-12 plant were examined at REAC/TS in FY85 and the findings were reported to their personal physicians; only one of these individuals is still employed at Y-12, three have retired, and one is employed elsewhere. Illnesses prevented the sixth Y-12 survivor and the survivor of the 1971 UT-CARL accident from being examined at REAC/TS this year, they are in the continuing care of their personal physicians. Follow-up cytogenetic analyses were conducted on samples of peripheral lymphocytes obtained from the five survivors who were examined and from eight other survivors of earlier accidents including the 1984 accident in Juarez, Mexico.

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(2) Foreign Registry: Eight accidents occurring outside the US and involving a total of 18 persons were recorded in this registry in FY85/86. Of these, six accidents occurred in France prior to FY85 and resulted in high dose local radiation-induced injuries that were treated surgically. One other previously unrecorded accident occurred in England in 1961 and resulted in the local overexposure of the skin of 11 patients receiving X-ray treatments for chronic eczema. A serious high dose local exposure accident occurred in Brazil in FY85; one person developed radiation induced burns of the hand following contact with an 88.6 Ci ^{192}Ir industrial radiography source; this case was presented to REAC/TS course participants in FY86 by the physician in charge of the case. Unreported confidential clinical information on the victims and survivors of the 1984 accident in Morocco was provided to REAC/TS staff in FY86. Registry data on high dose radiation exposure accidents was reviewed in a paper entitled "Historical Update of Past and Recent Skin Damage Radiation Accidents" that was presented at the workshop on Radiation Damage to Skin: Fundamental and Practical Aspects in October 1985 in Paris, France.

(3) DOE $\geq$5 Rem Study Registry: REAC/TS received no reports of $\geq$5 rem/year exposures among DOE workers in FY85/86. The registry currently includes 3,145 present and former employees at 40 DOE/DOE contractor plants nationwide. In FY85/86, efforts have focused on the selection and follow-up of matched comparison subjects who were employed at the same plant at the time a member of the $\geq$5 rem/year cohort received $\geq$5 rems. Three comparison subjects are being selected for each worker with 5 rems/year. These individuals will comprise the internal comparison population for the morbidity follow-up study and the updated mortality study. Employment histories and annual radiation monitoring data are being retrieved from the plants for individuals selected as comparison subjects. The computer system developed for the search, contact, and follow-up of the 5 rem cohort and the comparison population was tested in FY85 in a pilot study that involved study participants identified at Oak Ridge. Improvements based on the pilot study experience have been made to the system and procedures in preparation for the follow-up of study participants identified at plants outside Oak Ridge.

(4) DTPA Registry: During the June 1, 1984-May 31, 1985 FDA reporting period, 42 physicians were authorized as co-investigators on the FDA's IND with DOE for the administration of both Ca and Zn DTPA. In this project, five co-investigators reported treating a total of 29 persons with DTPA because of real or suspected actinide contamination; the remaining 37 co-investigators stated they had administered no DTPA. Two of 29 persons treated, received Ca-DTPA only; of these 16 persons, including 2 who were continuing therapy begun previously for a plutonium contamination incident in April 1984, each received a single dose, the 4 others each received 2 doses. Five of 6 persons treated with Zn only received multiple doses up to a maximum of 18, as continuing therapy for americum-241 contamination acquired in FY83; the sixth person received a single dose of Zn-DTPA. In addition, three persons received multiple doses of both Ca- and Zn-DTPA for separate contamination incidents. Ca-DTPA (35 x 1 gm doses) and Zn-DTPA (161 x 1 gm doses) were administered by direct IV (Push) injection, IV infusion in normal saline, aerosol inhalation, and wound irrigation. No toxic nor other untoward effects were reported to have occurred in any of the persons treated. This usage of DTPA was reported to the FDA. Follow-up of persons previously treated with Ca- and Zn-DTPA was on-going via the Social Security Administration (mortality), attending physicians, or direct contact with treated persons.

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Training Medical and Paramedical Personnel

In FY 85-86, 12 formal radiation accident management training courses were held including 4 courses entitled "Medical Planning and Care in Radiation Accidents" designed for occupational health physicians and nurses, 6 courses entitled "Handling of Radiation Accidents by Emergency Personnel" designed for emergency physicians and 2 courses entitled "Health Physics in Radiation Accidents" designed for the health/medical physicist. A total of 209 persons were trained at REAC/TS in FY85-86 including 89 MDs, 66 RNs, 1 EMT/Paramedic, 38 health physicists and 15 others. A total of 1,511 persons have been trained since June of 1976 in REAC/TS radiation accident management training courses. A cadre of over 1,000 physicians and nurses geographically distributed throughout the United States represents a medical resource base in the event of radiation accidents involving personnel injury. REAC/TS courses continue to be recognized for CME credit by the American College of Emergency Physicians, the American Medical Association, and the American Board of Health Physics. REAC/TS also participated in the FY85 Health Physics Summer School, assisted the U.S. Public Health Service in training a national public health service response team for hazardous materials accidents and otherwise participated in seminars and training outside the Oak Ridge area. In addition, over 5,000 persons were reached through a variety of lectures, post-graduate courses, exhibits, demonstrations at professional meetings, and through the use of the REAC/TS informational exhibit.

In FY85, REAC/TS, with the assistance of ORAU Office of Information Services, developed a questionnaire for evaluating the use and implementation of radiation accident management techniques set forth in two training packages entitled "Pre-hospital Management of Radiation Accidents" and "Hospital Emergency Department Management of Radiation Accidents". The user survey was designed to determine total number of individuals trained, professional affiliation and background, paid or volunteer emergency medical responder, rural or urban setting, and the experience in radiation accident management since using these materials for training. Results of the questionnaire will be published in FY86 and used to update radiation accident management training materials as needed as well as for review by the FRPCC T&E Subcommittee with application to any future subcommittee training endeavors.

In FY85-86, REAC/TS continued to publish its quarterly newsletter with approximately 15,000 copies mailed annually and another 1,000 distributed in conjunction with the REAC/TS informational exhibit. Through the newsletter, REAC/TS continues to inform its readers concerning information on newly discovered radiation accidents, emerging methodologies and treatment protocols, innovations in training, emergency response, and contributed materials reflecting course participant activities. The REAC/TS medical and emergency response staff have also received training on continuing education through drills and exercises as well as participation in off-site training activities.

Biological Dose Estimation

During FY 85-86 cytogenetic dosimetry estimates or follow-up evaluations were provided for 24 persons referred to REAC/TS because of suspected recent or previous radiation overexposures. Relevant information on the lifespan of T-lymphocytes was obtained from our follow-up studies in five persons having estimated whole-body exposures ranging from 25 to < 200 rad gamma radiation in the Mexican ^{60}Co Accident. When first studied in February 1984,

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the frequencies of metaphases bearing rings or dicentrics varied from 5 to 108 per 500 lymphocyte metaphases in preparations from these individuals. Twenty-two months later the frequency was reduced by an average of 71.4% (range 61-93.5%). Our findings in these five persons having protracted whole-body exposures are in good agreement with earlier estimates of lymphocyte lifespan based on evaluations of persistent aberrations in ankylosing spondylitis patients who received fractionated partial-body exposures to X-radiation.

Blood samples were also obtained from two additional Juarez residents on whom earlier cytogenetic studies had not been conducted. Evaluations in a 50-year-old woman and a 16 year-old adolescent who lived on Aldama Street, and who were at risk for exposure from the radioactive pick-up truck, demonstrated persistent unstable aberrations in 1.8 and 1.0% of their metaphases. Assuming that only one-fourth of their irradiated T-lymphocyte population has survived for 22 months, these dicentric frequencies estimate that these two persons received minimum doses of approximately 100 and 70 rad, respectively, in 1984.

In radiation accidents that potentially involve large numbers of persons (such as occurred in Juarez) it may not be feasible to promptly initiate and harvest cultures from all persons suspected of overexposure. Recently completed experimental studies have demonstrated that blood samples from such individuals may be preserved by freezing without compromising the accurate assessment of radiation-induced chromosome aberrations in lymphocyte cultures initiated at later dates. To quantify the effects of cryopreservation on baseline and radiation-induced chromosome aberrations, human lymphocytes were exposed in vitro to varying doses of ^{60}Co radiation and cultured either immediately or after one week's storage at -70°C. A slight depression in cellular proliferation and a significant increase in chromatid breakages were observed in cultures initiated from frozen lymphocytes. However, in preparations from both frozen and nonfrozen lymphocytes, the dose response relationships for radiation-induced dicentrics gave a best fit to the linear-quadratic dose response model with no significant differences in aberration frequencies between the two sets of cultures. This finding provides evidence that lymphocytes bearing radiation-induced chromosome aberrations are not at selective risk for cell death as a result of cryopreservation.

The Cytogenetics Program has continued participation as a U. S. Representative in an IAEA-sponsored International Cooperative Program on the Routine Use of Chromosome Aberration Analysis in Occupationally Exposed Radiation Workers. In a recent collaborative study, investigators at the National Radiological Protection Board in Great Britain exposed human blood to various doses of X or gamma radiation under conditions designed to mimic acute whole-body or partial-body exposures. Replicate irradiated blood samples were shipped by air to cytogenetics laboratories in 10 countries for the analysis of radiation-induced chromosome aberrations. Preliminary results and interlaboratory comparisons of data were presented and discussed at an IAEA Meeting which was held at the University of Kyoto, Japan in November, 1985. Detailed statistical evaluations are currently in progress at the NRPB.

During last year, data collection was also completed in an interlaboratory study of the cytogenetic effectiveness of low energy (0.2 MeV) fission spectrum neutrons. Earlier, an assembly at Los Alamos of a Hiroshima Bomb replica, as a reactor, was used to expose human lymphocytes to varying doses of fission neutrons. Evaluations of slides for radiation-induced chromosome aberration frequencies were jointly conducted by cytogeneticists at Lawrence Livermore Laboratory, ORAU, and the RERF in Hiroshima. Preliminary statistical

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evaluations demonstrated that the Hiroshima-type neutrons are similar to ordinary fission spectrum neutrons in their cytogenetic effectiveness, inducing about one dicentric/cell/ Gy. Data from this collaborative study may aid dosimetry evaluations now under way in the A-Bomb Survivors.

In collaboration with scientists at the Radiation Epidemiology Branch of NCI, basic research studies aimed at determining the applicability of cytogenetic systems for dose estimation in persons having radiation exposure many years previously have continued. We have now completed detailed cytogenetic evaluations in approximately 500 control and irradiated persons selected from various cohorts having medical exposures 20-40 years ago. Relative to findings in nonirradiated controls, a small but statistically significant increase in the frequency of metaphases bearing stable radiation-induced chromosome aberrations was observed in persons who previously received 400-1200 rad localized radiation to the tonsil. In lymphocyte cultures from 98 cervical cancer patients who received average marrow doses of 750 rad, the numbers of metaphases with symmetrical and asymmetrical chromosome-type aberrations ranged from 0 to 12%. In spite of considerable variability in findings among women who received similar doses, preliminary statistical evaluations demonstrated that the mean frequencies of metaphases bearing radiation-induced aberrations varies as a linear function of total marrow dose for about 20 years after radiotherapy for cervical cancer. During this year we completed cytogenetic evaluations of approximately 30,000 lymphocyte

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and validate the increased sensitivity of the assay obtained by sampling at later times. Since late sampling necessitates the use of bromodeoxyuridine to avoid scoring second division metaphases, we have also compared aberration levels in mice with and without bromodeoxyuridine implants to establish whether this chemical has an effect on aberration rates.

An unusual pair of related chemicals was examined in some detail for their aberration-inducing potential. Tests with 4-chloro-o-phenylene diamine had earlier identified it as a suspected clastogen. Further evaluations during the past year have shown it to be a rather unique chemical in that it causes no detectable damage in the majority of marrow cells but in up to 3% of the cells, depending on dose, causes extensive structural rearrangement of the chromosomes. The very closely related compound 4-nitro-o-phenylene diamine did not have this effect when simutaneously tested. It is uncertain at this time whether this all-or-none type effect of the 4-chloro compound is due to a small population of cells with highly sensitive chromosomes or to differential penetration of the compound into select cells.

Health Physics

In FY85, REAC/TS expanded its emergency response team with the addition of a facility health physicist. This individual has assumed the responsibilities for health physics team leadership as well as calibration and maintenance of all related emergency response equipment for radiological assessment. In addition, assistance with physical dosimetry, estimation of body burdens of internally deposited radionuclides and internal dose calculation were provided to health physicists, physicians, nurses, and other emergency medical personnel.

DTPA Chelation Therapy

Management of the Ca-DTPA and Zn-DTPA IND's for DOE involved: (a) performing periodic analyses on randomly selected ampules of both chelator drugs to ascertain their continued suitability for clinical use (purity, sterility, pyrogenicity, and proper DTPA concentration); (b) surveying on an annual basis the authorized physician co-investigators on the IND's for Ca-DTPA and Zn-DTPA to determine their clinical experience with these drugs (usage, clinical efficacy, side-effects, and replenishment requirements); (c) submitting annual reports for both chelator drugs to FDA as required by the IND's; (d) educating those industrial physicians in facilities having potential radiation accidents involving actinides about the availability and use of chelating drugs; and (e) establishing those physicians with a potential need for DTPA drugs as co-investigators on the IND's and supplying them with these drugs from the existing stockpiles at ORAU.

During the most recent FDA reporting period, June 1984 through May 1985, 42 physicians (39 in the U.S. and one each in Canada, England, and Spain) were authorized as co-investigators on the IND's for both Ca-DTPA and Zn-DTPA. In this period, five co-investigators in the U.S. reported treating a total of 29 persons with DTPA because of real or suspected actinide contamination; the remaining 37 co-investigators stated they had administered no DTPA. Twenty of the 29 persons treated received Ca-DTPA only; of these, 16 persons, including two who were continuing therapy begun previously for a plutonium contamination incident in April

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1984, each received a single dose, and the four others each received two doses. Five of six persons treated with Zn-DTPA only received multiple doses up to a maximum of 18 as continuing therapy for americium-241 contamination acquired in FY 83; the sixth person received a single dose of Zn-DTPA. In addition, three persons received multiple doses of both Ca-DTPA and Zn-DTPA for separate contamination incidents. Ca-DTPA (35 one-gram doses) and Zn-DTPA (161 one-gram doses) were administered by direct intravenous (push) injection, intravenous infusion in normal saline, aerosol inhalation, and wound irrigation. No toxic or other untoward effects were reported to have occurred in any of the persons treated. This usage of DTPA in FY 84/85 was reported to the FDA.

Medical follow-up of persons previously treated with Ca-DTPA or Zn-DTPA was carried out on a continuing basis by means of Social Security Administration records (mortality), reports from attending physicians, or direct contact with treated persons using an OMB-approved comprehensive telephone interview questionnaire.

In an effort to better educate nuclear employees who work with actinides about the indications, efficacy, and safety of DTPA chelation therapy and to alleviate fears and misconceptions, a DTPA fact sheet written in nontechnical language was prepared. Site personnel directors at the three Oak Ridge plants determined in what areas a potential for actinide exposure existed (only in certain areas at Oak Ridge National Laboratory) and the employees who worked in those areas. Informational meetings were held during each of the three shifts for those workers with a potential for internal actinide contamination requiring DTPA therapy. The DTPA fact sheet was made available to these workers at the meetings.

Previous studies showed that Ca-DTPA encapsulated in liposomes, either of the multilamellar vesicle (MLV) type or of the newer large unilamellar vesicle (LUV) type, produced better decorporation of colloidal ^{169}Yb, a model contaminant, from rats than was obtained with the free chelating agent. However, the LUV-encapsulated Ca-DTPA, because of its much greater entrapment capacity (and consequent reduction in the quantity of lipid required for encapsulation of a fixed dosage of chelator) and its smaller, more uniform size distribution, did not cause the spleen weight increase always observed with MLV-encapsulated Ca-DTPA. We investigated the use of both dicetylphosphate and stearylamine, which produce net negative charges and net positive charges, respectively, as a component of LUV-type liposomes. The ability of such modifications to improve the performance of liposome-encapsulated Ca-DTPA was studied. Neither the efficiency of Ca-DTPA encapsulation nor the storage stability seemed to be affected by the charge on the liposomal particle. Its effect on the decorporation efficacy was studied in detail by treating 40 male Fischer rats intravenously with colloidal ^{169}Yb. After 24 hr the rats were divided into eight groups: one group each received LUV-encapsulated Ca-DTPA bearing neutral, positive, or negative charges; one group each received "empty" liposomes bearing neutral, positive, or negative charges; one group received free Ca-DTPA; and one control group received no injection. Decorporation of ^{169}Yb was monitored using a small-animal whole body counter. No significant difference in decorporation efficacy was found to be caused by the charge on the liposomal particle. As was observed previously, each of the groups receiving liposome-encapsulated Ca-DTPA, regardless of the charge on the particles, removed more ^{169}Yb than the free chelator, which in turn removed significantly more than was observed in the control group. The groups receiving "empty" liposomes, regardless of the charge, were

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statistically indistinguishable from the control animals. Unlike our previous experiment, each of the three groups receiving liposome-encapsulated Ca-DTPA produced a small but significant increase in the spleen weight (expressed as a percentage of the total animal weight). However, based on our earlier work, we know that the rat is much more susceptible to splenic enlargement than other species, and, therefore, this finding is probably not of major concern.

Former Patient Care

During FY85 we processed twenty actions on six patients who are eligible for coverage under the AEC directive of October 1984 for assistance to former inpatients of the cancer clinic. A survey in February 1986 identified fourteen surviving patients. During the first three months of FY86 we have processed seven actions on five patients.

Planned progress FY86-87

Assistance and Consultation by REAC/TS

The REAC/TS facility and staff will continue to be available to handle or otherwise assist in treating radiation accident patients. Relationships with emergency response staff of nuclear facilities will be maintained with continuation of letter agreements, training of medical, paramedical, and health physics personnel, and REAC/TS participation in drills and exercises. REAC/TS will continue to integrate its activities with those of the DOE/DOD Accident Response Group (ARG) as well as participate more closely in nuclear weapons accident management training courses. REAC/TS will continue its close liaison with the Federal Emergency Management Agency and continue to meet its obligations to the World Health Organization.

The REAC/TS Registries

The registries will be maintained in accordance with the programmatic needs of the Medical and Health Sciences Division and other routine users. The annual status of the radiation accident registries and updated bibliography will be published as a technical report.

Registry data on acute clinical effects observed among radiation accident victims who received whole body doses of $\geq$50 rems, will be reported for publication and to the UNSCEAR committee on the acute effects of radiation. The U.S. experience of the use of DTPA in the chelation of transuranics will be reported at a meeting of radiation protection physicians in Germany; this report subsequently will be submitted for publication in the U.S.

Survivors of the 1958 and 1971 Oak Ridge radiation accidents will be invited to REAC/TS for routine follow-up interviews and examinations. A report on the current status of these and other radiation accident survivors will be prepared for publication.

Active follow up of $\geq$5 rem study participants and of persons previously treated with DTPA will be completed for workers at Rocky Flats, Mound Laboratories, Argonne, and Brookhaven National Laboratories, Savannah River, Bettis, REECo and Holmes and Narver, and Hanford as resources allow. Vital status of the 5 rem study population and their matched comparisons

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will be updated through the Social Security Administration. Selection of internal comparison subjects for workers with ≥5 rem/year at remaining sites, will be completed. Retrieval of work history and annual radiation monitoring data for individual study participants will proceed as resources allow. Compilation of the ≥5 rem per year career exposure roster will proceed as the data are available.

DOE/DOE contractor employees reported to have received ≥5 rem per year in calendar years 1985 and 1986, and persons treated with DTPA between June 1985 and May 1986 and between June 1986 and May 1987 will be added to the registries' data base for inclusion on future studies.

Training Medical and Paramedical Personnel

During the remainder of FY86, a total of 8 training courses will be held with a projected enrollment of 158 participants. All training courses for the remainder of FY86 are currently or projected to be fully subscribed.

In FY86, REAC/TS will continue to participate in selected off-site radiation accident management courses with emphasis directed to the American Occupational Medical Association, Nuclear Industry Physician's Association, the Federal Emergency Management Agency, and various state and local medical associations.

In FY87, REAC/TS will sponsor the Second International Conference on the Medical Basis for Radiation Accident Preparedness. As in the previous conference, held in 1979, the Second International Conference will pull together all leading experts in the field of medical management of radiation accidents for purposes of updating radiation accident history, the follow-up of accident survivors and a review of current state-of-the-art medical/health physics procedures for managing the radiation accident victim.

Biological Dose Estimation

Microscopic analysis of radiation-induced micronuclei in cultured lymphocytes has been proposed as a simpler and statistically more precise method for quantifying radiation exposure levels than the more time-consuming aberration analysis. The primary disadvantage of this system is that micronuclei can only be observed in interphase nuclei that have completed one cell division after radiation exposure. In asynchronously dividing cell populations (such as mitogen-stimulated T-lymphocytes) the accurate enumeration of micronuclei is highly dependent upon being able to determine the proportion of responding cells that have divided once, twice or more times during the in vitro culture period. Last year, a method which allows selective analysis of micronuclei frequencies in exclusively second division interphase nuclei was published. The experimental protocol employs addition of the chemical, cytochalasin B, to proliferating lymphocyte cultures as a method for chemically blocking cytokinesis. Micronuclei are subsequently scored in binucleate interphase cells. Should this method prove to be reproducible and accurate, it could potentially increase the sensitivity and reliability of the micronucleus assay system. As a part of our continued participation in the IAEA-sponsored Program on cytogenetic dosimetry, our laboratory, in collaboration with cytogeneticists from five other countries, is undertaking basic research studies aimed at defining variables that may affect the induction

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or expression of micronuclei in cytochalasin B blocked cells. During next year, we will conduct studies to determine the kinetics of lymphocyte proliferation in the presence of cytochalasin, the dose-response relationships for X-ray-induced micronuclei in single, bi- and multinucleated lymphocytes, and the variability in response between different blood donors.

In studies conducted last year, we determined that human lymphocytes exposed in vitro to radiation doses of up to 400 rad could be successfully cultured after being stored at -70°C for periods of several days. Our studies further demonstrated that accurate estimates of radiation-induced chromosome aberrations could be made in lymphocytes which had been cultured after cryopreservation. Presently, numerous types of human cells, including early zygotes, are preserved in the frozen state for periods ranging from several months to several years. Unless properly shielded, such cryopreserved material is at risk for accumulating low doses of radiation due to background exposures. During next year, we intend to employ human lymphocytes as a system for assessing the potential cytogenetic detriment of radiation exposure during cryopreservation. Successful freezing of human lymphocytes depends upon suspending cells in a medium containing either DMSO or glycerol to inhibit formation of large ice crystals. Since DMSO is known to have a radioprotective effect in terms of cell killing, preliminary studies will be conducted to determine the dose response relationship for chromosome aberration induction in human lymphocytes exposed to radiation in medium with and without this oxygen-radical scavenging chemical. Lymphocytes preserved in DMSO and frozen at -70°C will then be exposed to varying radiation doses while in the frozen state, and subsequently cultured for evaluation of all classes of radiation-induced chromosome aberrations.

During FY 86-87 the REAC/TS Cytogenetics Group will continue studies aimed at defining the long-term cytogenetic sequelae of partial-body radiation exposures. Detailed cytogenetic analyses of persistent radiation-induced chromosome aberrations are currently in progress in 200 selected adults who received localized radiotherapy for enlarged thymus glands in infancy. In addition, serial blood samples have also been collected from cervical cancer patients before, during and six months after they completed radiation treatment, as well as from selected women who were irradiated two, five, 10 and 15 years earlier. When data collections are completed on these patient populations, cytogenetic findings in the TB, thymus, tonsil and cervical cancer cohorts will be compared to assess the consequences of partial body exposure, fractionation of dose, and the effects of age and sex on the recovery of lymphocytes bearing aberrations many years after exposure.

In studies completed last year we observed pronounced depression in mitotic activity in human lymphocytes treated during the G_2 stage of the cell cycle with the protein crosslinking agent, methyl acetimidate (MAI). In our preliminary evaluations of slide material, we observed several types of aberrant mitotic configurations suggestive of anomalous formation of the spindle apparatus. A possible explanation for the MAI-induced inhibition in lymphocyte proliferation is that this compound may act at the molecular level by crosslinking lysine residues in microtubles, thereby preventing chromosome migration and completion of cytokinesis. To further define the detrimental action of this crosslinking agent at the cellular level, we plan to employ cell-cycle stage specific treatments with MAI in conjunction with specialized conventional and fluorescent staining techniques for

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visualizing alterations in the spindle apparatus. In addition to providing relevant information on the possible cytogenetic sequela of human exposure to imidates, these studies may also provide basic information related to the mechanisms involved in the production of tubulin and formation of the spindle apparatus in mitotic lymphocytes.

In parallel experiments, in vivo assays of MAI in the bone marrow system will be utilized to determine which of the unusual chemical effects resulting from in vitro exposure also occur following in vivo administration of a chemical. The potential of such agents for inducing genotoxic effects will also be assessed by simultaneous measurement of their chromosome aberration and SCE inducing potential under in vivo conditions.

Investigations will continue into the induction of chromosome aberrations and sister chromatid exchanges in the bone marrow of mice following the administration of various chemicals. Emphasis will be placed on the comparison of pairs of related chemicals wherein one member is accepted as noncarcinogenic while the other is known or suspected to be a carcinogen. Such data are expected to give further insight into the possible relationship the most realistic evaluation of the genotoxicity of a chemical, it is also time-consuming and expensive. Most of the chemicals being tested have also been evaluated in one or more in vitro assay systems. Comparisons of our results with those from in vitro test systems will provide a means for critically evaluating the effectiveness of the in vitro assays and will give a good indication of whether or not these faster and cheaper assays adequately measure the in vivo potency of chemicals. The simultaneous SCE and chromosome aberration data being gathered on a variety of chemicals will also furnish a basis for evaluating the relative sensitivity of the SCE and chromosome aberration assays and will provide some insight into the mechanisms underlying SCE induction.

DTPA Chelation Therapy

Management of the Ca-DTPA and Zn-DTPA IND's will continue, with the same general responsibilities as indicated for FY 85/86. Annual usage of DTPA by co-investigators will be reported to the FDA as required under the DOE IND's. This information will also be added to the data base of the DTPA Registry.

Long-term follow-up of persons previously treated with DTPA will continue. The U.S. clinical experience with DTPA drugs will be summarized for presentation to physicians involved in radiation protection programs and for subsequent publication.

We will investigate with representatives from DOE and FDA the feasibility and desirability of obtaining NDA status for Ca-DTPA and/or Zn-DTPA. Because the need for chelation therapy is so infrequent and the usage of DTPA is very low in volume compared to most drugs, the pharmaceutical industry has shown little interest in agents for actinide decorporation. However, the recently passed Orphan Drug Act (Pub. Law 97-414 as amended) may provide an avenue for obtaining NDA status for DTPA drugs. We will interact with FDA officials to compile information about the requirements for NDA status under this legislation and the potential benefits of such status. This information will be submitted to DOE to allow an appropriate decision to be made with regard to filing an NDA application.

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This program will continue to monitor and evaluate up-to-date developments in chelation therapy involving improved protocols and carrier forms for Ca-DTPA and Zn-DTPA as well as research on new chelators. In some cases, reports of new developments will be tested experimentally in animals. When clinical testing of these new developments is indicated, the appropriate IND amendments or new IND applications will be submitted through DOE to FDA.

The potential of Ca-DTPA encapsulated in LUV-type neutral liposomes will be investigated further by determining the best protocol for removal of ^{169}Yb from rats. We will determine the most favorable time after exposure for administering the chelating agent. The possibility that using a combination of free and liposome-encapsulated chelators may be more effective than either agent by itself will be investigated. If this is the case, the optimal sequence for the two types of chelating agents will be determined. These experiments should allow us to select the best overall treatment technique, using liposomal and/or free DTPA, for removal of ^{169}Yb from rats.

Planned Progress in FY88

Assistance and Consultation by REAC/TS

REAC/TS will continue to provide routine 24-hour per day service through assistance by consultation or direct involvement. Efforts will be directed to continue development of medical protocols for handling the exposed/contaminated radiation accident victim.

The REAC/TS Registries

The Registries will be maintained to meet programmatic needs of investigators in the Medical and Health Sciences Division and other routine users. Analyses will be completed of mortality and morbidity among DOE/DOE contractor workers using workers selected from the same sites for comparison. Data for civilian nuclear shipyard workers will be included in these analyses as they become available from the Johns Hopkins epidemiology group. Compilation of the DOE $\geq$5 rem career exposure roster will be completed for selected facilities as resources allow in preparation for a study of mortality among persons with $\geq$5 rem per year compared with that among persons with total career exposures of $\geq$5 rems.

Training Medical and Paramedical Personnel

In FY88, REAC/TS will continue its training program and it is projected that a total of 10 formal training courses will be offered including three courses for occupational physicians and nurses, two for health physicists, and five for hospital emergency department personnel. REAC/TS will continue to publish its quarterly newsletter and participate in off-site training activities as requested by both health physics and medical associations at the local, state, and national levels.

Biological Dose Estimation

During FY 88 the REAC/TS Cytogenetics Group will continue dosimetry and follow-up evaluations in selected persons having recent or previous radiaiton exposures.

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Depending upon the outcome of preliminary experiments conducted in FY 86 and 87, we will continue basic studies to define the dose-response relationships for micronuclei induction in human lymphocytes exposed in vitro to radiations of differing LET. Should the method prove to be a sensitive indicator of exposure to doses of less than 50 rad, we will undertake additional studies with low LET radiation to determine the effects of dose fractionation and protraction on micronucleus induction. As a final evaluation of the assessment of the cytochalasin B technique, we plan to expose marmosets to chronic low doses of low LET radiation to determine the in vivo sensitivity of the method.

We also plan to continue our studies with cryopreserved lymphocytes to include evaluations of the effects of dose fractionation and protraction on the induction of DNA lesions that lead to chromosome aberration formation in lymphocytes exposed in the frozen state. It is anticipated that enzymatically dependent repair systems would be inoperative in cryopreserved lymphocytes, and that DNA damage induced by chronic radiation exposure would simply be accumulated in the cells in the frozen state. Thus the formation of two-break chromosome aberrations as a result of misrepair of DNA damage should not occur until the cryopreserved cells have been rehydrated and thawed. To test this hypothesis, split dose experiments will be undertaken to determine whether fractionation effects can be observed in cryopreserved lymphocytes. Data from these studies will not only provide information regarding aberration production in frozen cells, but will also serve as a system for evaluating mechanisms involved in the formation of two-break aberrations in lymphocytes.

Preliminary data have indicated that when bromodeoxyuridine is present at the time of treatment with a chemical it may act synergistically with some chemicals. Further investigations will be conducted to determine if such a problem exists in our assay system to the extent that it contraindicates the present practice of using bromodeoxyuridine to insure that only first division metaphases are scored. The micronucleus assay offers certain advantages over other cytogenetic methods for genotoxicity measurements. The relative merits of the three common cytogenetic assays will be evaluated by including simutaneous micronucleus assays of chemicals being tested for SCE and aberration induction.

Health Physics

The health physics component of the REAC/TS emergency response team will continue to support REAC/TS commitments in radiation emergency assistance and in training efforts. Efforts will be made to enhance the capabilities for predicting radiation dose following internal contamination.

DPTA Chelation Therapy

Management of the Ca-DTPA and Zn-DTPA IND's will continue, along with the evaluation of new developments in chelation therapy, to determine the importance of further preclinical or clinical investigation.

The use of DTPA reported by co-investigators in FY 87 will be reported to the FDA and added to the DTPA Registry data base for evaluation. Long-term medical follow-up of DTPA-treated individuals will continue.

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The efficiency of localized versus systemic administration of lipophilic chelating agents in removing ^{169}Yb from contaminated lungs and wounds will be assessed. The results with lipophilic chelating agents will be evaluated to assess the potential value of clinical trials and any additional preclinical work which may be required in support of an IND. When indicated, an IND will be submitted to FDA through DOE.

20h. Relationship to Other Projects

Within ORAU, REAC/TS has close collaborative relationships with the (a) Radiation Safety Office, (b) the Preclinical and Clinical Radiopharmaceutical Development Groups, (c) the Center for Epidemiology Research, (d) the Manpower Education, Research, and Training Division's Professional Training Programs, (e) the Internal Dosimetry Center, and (f) the Biochemistry Group.

Outside relationships in the Oak Ridge area exist between REAC/TS and (a) the staff of the Methodist Medical Center of Oak Ridge; (b) the Medical Departments of the DOE-Oak Ridge nuclear facilities (X-10, K-25, and Y-12); (c) the Health and Safety Research Divisions of ORNL; (d) private physicians of the Oak Ridge Medical Community; and (e) a number of outside consultants serving as faculty members of the REAC/TS training programs.

In addition, REAC/TS has established relationships for teaching, consultation, and expert testimony with the AFRRI, the VA hospital system, FEMA, WHO, PAHO, and the U.S. Department of Justice.

The DTPA chelation therapy program is managed by REAC/TS, because of its involvement in the medical management of radiation accidents and training. Other staff members of ORAU 's MHSD (preclinical radio-pharmaceutical development, biological chemistry, and epidemiology) and consultants contribute to this task: S. Garrett, M.D., Oak Ridge National Laboratory; G. Poda, M.D., Savannah River Laboratory; G. Voelz, M.D., Los Alamos Scientific Laboratory; B. Breitenstein, M.D., Hanford Enviormental Health Foundation; E. Saenger, M.D., University of Cincinnati; N. Wald, M.D., University of Pittsburgh; N. Cohen, New York University; and C. Mays, University of Utah.

FIELD TASK PROPOSAL/AGREEMENT
DETAIL ATTACHMENTS

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201. Capital Equipment	FY 87	FY 88
Zeiss IBAS 2000 Image Analysis System to upgrade existing equipment	106.8	
The Zeiss IBAS 2000 Image Analysis System is required to upgrade and modernize existing chromosome analysis capabilities. The instrument automatically scans slides, locates metaphases, records coordinates, and provides preliminary karyotypic analysis. These functions reduce time required for scoring of preparations by about 75% and, therefore, greatly increase volume of work that can be generated by Research Associate Staff.		
Two Linear Transducer Digital Readouts for microscopes	5.0	

Foreign Travel	FY 87	FY 88
Toronto, Canada IAEA-sponsored working group meeting on use of chromosome aberration analysis in biological dosimetry - REAC/TS Cytogenetics experience will be presented	1.5	
Edinburgh, Scotland Participation in the Eighth International Congress of Radiation Research	2.5	

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U.S. DEPARTMENT OF ENERGY

FIELD TASK PROPOSAL/AGREEMENT

1. WORK PACKAGE NUMBER	2. TASK NO.	3. REV. NO	4. PROJECT NO.	5. DATE PREPARED	6. CONTRACTOR NUMBER
		0		Feb. 28, 1986	1758.00

7. TASK TITLE	8. WORK PACKAGE TITLE
Nutrition, Radiation, and Cancer	

9. BUDGET AND REPORTING CODE	10. TASK TERM Begin:	End:	11. CONTRACTOR NAME	12. CODE (See instructions)
HA 02 02 01	10-1-86	Continuing	Oak Ridge Associated Universities	ORH

13. CONTRACTOR TASK MANAGER (Name: Last, First, MI) (FTS No.)	14. PRINCIPAL INVESTIGATORS (Name: Last, First, MI)
Whittle, Charles E. 626-3171	Totter, John 626-3345

15. WORK LOCATION (See instructions): Name of facility, City, State, Zip Code	16. Is this task included in the Institutional Plan?	17. Does this task include any management services efforts?
Oak Ridge Associated Universities Energy Building, Badger Avenue Oak Ridge, Tennessee 37831-0117	☒ YES ☐ NO	☐ YES ☒ NO

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

The Institute for Energy Analysis of Oak Ridge Associated Universities has been examining potential relationships between ionizing radiation and age-specific cancer incidence. Results to date indicate that low-level whole-body ionizing radiation exposure alters the hormonal system to reduce appetite and the resulting reduction of food intake prolongs the life of different individuals to different degrees. The age-specific incidence of cancer in a population is somewhat reduced by this mechanism.

During FY 1986 the Institute is investigating this relationship to develop the hypothesis and its relationship to other causes of senescent death. The approach is to search the literature; review the available data in the specialized fields of nutrition and caloric intake, radiation effects, and natural selection; and attempt to identify causal relationships between observed sets of data. We are consulting closely and holding discussions with other scientists whose special laboratory research comprises specific segments of the overall physiology that would be involved in these concepts.

During FY 1987 and FY 1988 the Institute will continue examining the potential relationships between age-specific cancer incidence in light of new data and collaborate with other institutions doing laboratory research which may illuminate the hypothesis we are developing.

19. CONTRACTOR TASK MANAGER

(Signature) (Date)

20. DETAIL ATTACHMENTS: (See instructions)

☐ a. Facility Requirements	☐ d. Background	☐ g. Future accomplishments	☐ j. Explanation of milestones
☐ b. Publications	☐ e. Approach	☐ h. Relationships to other projects	☐ k. ZBB Detail
☐ c. Impacts	☐ f. Technical progress	☐ i. Environmental assessment	☐ l. Other (Specify):

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