PNL-9055 DEL 701610

Battelle
Pacific Northwest Laboratories
P.O. Box 999
Richland, Washington U.S.A. 99352
Telephone (509) 375-2461
Telex 15-2874

October 25, 1984

P. K. Clark
Energy Programs Division
Richland Operations Office
U. S. Department of Energy
216 Federal Building
Richland, Washington 99352

Dear Paula:

The enclosed is a copy of the material on human experimentation solicited by OHER staff for transmission to Representative Ottinger, which I picked up during a recent visit to DOE Headquarters. Much of our input is included in modified form. I understand that there may be some network coverage of this issue soon with Jim Kane, Dr. Trivelpiece's deputy, interviewed.

Sincerely,

Sid

Sidney Marks, M.D.
Associate Manager
Environment, Health and
Safety Research Program

SM:gm

Enclosure

xc mailed to
P.K. Clark 12/13/85

bcc: WJ Bair
RP Marshall
BL Matthews
file/lb

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*See Previous Concurrences

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Honorable Richard L. Ottinger
Chairman, Subcommittee on Energy
Conservation and Power
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your letter requesting certain information about projects involving human test subjects and radiation that have been funded by the Department of Energy and its predecessor agencies.

An enclosed memorandum outlines the approach that was taken to assemble the pertinent information and lists in chronological order the Government officials responsible for the studies.

Also enclosed are summaries of the projects, grouped by topic.

We trust that this information will be useful to you in your investigation. We continue to search for additional information and will forward such information if it covers projects not reported by this letter.

Sincerely,

DONALD PAUL HODEL

13 Enclosures

cc:
Honorable Carlos J. Moorhead
Ranking Minority Member

bcc: ES (4)
CP-1 (2)
ER-1
ER-2
ER-60
ER-622
ER-70 (2)
ER-71
MA-1
MA-3

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ER-73

INFORMATION: Response to Request from Honorable Richard L. Ottinger

The Secretary

This memorandum and the attached summary fact sheets have been prepared in response to Mr. Ottinger's letter, requesting certain information about projects involving human test subjects and radiation that have been funded by the Department of Energy and its predecessor agencies.

Medical radiation research has been conducted for many years for a variety of reasons. In some projects, such as the production and use of plutonium during the war years, there was an urgent need to obtain radiobiological data on certain radionuclides for the purpose of establishing safety criteria for protection of individuals in the workplace. In other research, it was clear that the use of radiation provided considerable improvement in the treatment of certain human diseases, such as cancer. In addition, there was also a need for basic knowledge about the biological effects produced to determine whether repair of biological damage occurred, and to ascertain the treatments necessary to promote recovery of the individuals who had been exposed. Thus, depending upon the magnitude of the problem, there were instances in which humans were exposed to radiation for the purpose of determining the relationship between biological effects and radiation dose, to determine the metabolism, deposition, and elimination of radioactive substances of interest which had been inhaled or ingested by the individual, or to demonstrate the effectiveness of radiation in the treatment of cancer or other diseases.

Prior to the time that formal guidelines were promulgated, there was a general practice to inform participants in human volunteer studies with respect to the purpose of the experiment and the potential hazards involved. In clinical studies related to the use of radiation or radioactivity for medical treatment purposes, such information was provided as a matter of routine. In addition, no proposed treatment protocol by an individual physician could be used without approval of all the clinical staff. In November 1966, the Advisory Committee for Biology and Medicine recommended to the AEC that formal procedures be established in AEC laboratories to ensure that ethical practices then extant were followed with respect to use of human volunteers for research purposes.

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In December of 1966, Dr. Charles L. Dunham, then Director of the Division of Biology and Medicine, directed the program directors of the laboratories to consider current laboratory practices and revise their procedures, if necessary, to comply with the code of ethics which the Surgeon General had instituted.

Subsequently, in 1970, Dr. John R. Totter notified the laboratories that the AEC had officially adopted the National Institute of Health procedures which were described in the booklet entitled "Protection of the Individual as a Research Subject." At an early time, therefore, the AEC and its laboratories were cognizant of and sensitive to the need for implementation of procedures to ensure a responsive code of ethics in their research programs.

The information that is summarized on the attached fact sheets was obtained from several sources. The more recent projects are documented in files at DOE Headquarters in Germantown, Maryland. For others, it was necessary to request our field offices to obtain fact sheets from current or previous contractors. In some instances, the information has been obtained from summary reports or from data published in the open literature. Pertinent information is recorded in the proceedings of two previous congressional investigations: (1) Hon. Chet Holifield (Chairman), Applications of Radio-isotopes and Radiation in the Life Sciences, Hearings before the Subcommittee on Research, Development and Radiation of the Joint Committee on Atomic Energy, March 27-30, 1961, and (2) Hon. Albert Gore, Jr. (Chairman), Oversight - Human Total Body Irradiation (TBI) Program at Oak Ridge, Hearing before the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology, September 23, 1981.

The information currently available is necessarily incomplete, in part because of the length of time that has elapsed since the beginning of these studies. Many of the original records are currently unavailable because they have been lost or destroyed. However, although it is possible that some additional studies will still be found, it seems unlikely that any significant project has been omitted.

The reports have been grouped into the following categories:

1. Metabolism and Biological Effects of Plutonium, Polonium, Thorium, Uranium, Radium and Lead-212
2. Testicular Irradiation
3. Whole-body Irradiation for Treatment of Leukemia and Lymphoma
4. Teletherapy with Particle Beams
5. Other Teletherapy Studies
6. Treatment of Polycythemia
7. Hematological Effects
8. Neutron Capture Therapy
9. Other Radiation Therapy
10. Biological Effects of Iodine-131
11. Other Biological Effects Studies
12. Metabolic and Physiological Studies

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The responsible government officials for these studies are listed below in chronological order:

Period	Name	Agency	Division or Office	Title
42-45	Stafford L. Warren, M.D.*	MED		
45-47	Robert S. Stone, M.D.*	MED		
47-52	Shields Warren, M.D.*	AEC	DBM	Director
52-54	John C. Bugher, M.D.*	AEC	DBM	Director
54-67	Charles L. Dunham, M.D.*	AEC	DBM	Director
67-72	John R. Totter, M.D.	AEC	DBM	Director
72-77	James L. Liverman, Ph.D.	AEC/ERDA	DBER	Director
77-81	William W. Burr, M.D.	DOE	DBER/OHER	ActDir/Director
81-date	Charles W. Edington, Ph.D.	DOE	OHER	ActDir/ActAssoc Director/Assoc Director

*deceased

Abbreviations:

MED - Manhattan Engineer District (1942-1945)
AEC - Atomic Energy Commission (1945-1975)
ERDA - Energy Research & Development Administration (1975-1977)
DOE - Department of Energy (1977-date)
DBM - Division of Biology & Medicine (1945-1974)
DBER - Division of Biomedical & Environmental Research (1975-1981)
OHER - Office of Health and Environmental Research (1981-date)

We trust that this information will be useful to Mr. Ottinger in his investigation. We continue to search for additional information and will forward such information if it covers projects not reported by this memorandum.

Alvin W. Trivelpiece
Director, Office of
Energy Research

12 Attachments

ER-73:JSRobertson:lw:353-5355:9-6-84

bcc: ES (40) ER-622
CP (2) ER-70 (2)
ER-1 ER-71
ER-2 MA-1
ER-60 MA-3
ER-61

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We trust that this information will be useful to you in your investigation. We continue to search for additional information and will forward such information if it covers projects not reported by this letter.

Sincerely,

DONALD PAUL HODEL

cc: Honorable Carlos J. Moorhead
Ranking Minority Member

MA-3

8/ /84

12 Enclosures

bcc: ES (4)
ER-1
ER-2
ER-60
ER-61
ER-622
ER-70 (2)
ER-71

Prepared by:JSRobertson/cm:353-5355
8/17/84

ES84-007251

MA-3
MA-1

MA-1

8/ /84

CONCURRENCES

RTG SYMBOL	INITIALS/SIG.	DATE
ER-71	JSRobertson	8/17/84
ER-71	JWThiessen	8/17/84
ER-70	CWEdington	8/17/84
ER-61	IAdler	8/ /84
ER-60	RYoung	8/ /84
ER-2	JKane	8/ /84
ER-1	ATrivelpi	8/ /84
CP-30		8/ /84
CP-1		8/ /84

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	LTR: X	MEMO:	REPORT: OTHER:
TO: Donald P. Hodel (Energy Research)	ORIG: X	CC:	OTHER:
	CLASSIFICATION/CONTROL MARKINGS: Uncl		
REG. NO:	DUE DATE: 6/20/84	FILE CODE:	DATE ANSWERED: BY:

DESCRIPTION *(Must Be Unclassified)*

Requesting a list of each human experimentation project involving human test subjects and radiation that has been funded by the Atomic Energy Commission, the Energy Research and Development Adm., and/or DOE.

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Edington-action	6/11/84	[illegible] 6/1	[illegible]
Thiessen	6/13		
R. Young-info	6/11/84		
ZLU	6/12/84		

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OFFICE OF THE EXECUTIVE SECRETARY

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M: OTTINGER, RICHARD L CHR NY D
SUBCOMMITTEE ON ENERGY
CONSERVATION AND POWER

J: ENERGY INFORMATION
CONGRESSIONAL REQUESTS
HUMAN EXPERIMENTATION PROJECT

REMARKS: THIS IS A HIGH PRIORITY ITEM.
DUE DATE MUST BE MET. MA-293
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MA-293

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NINETY-NINTH CONGRESS

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U.S. HOUSE OF REPRESENTATIVES
SUBCOMMITTEE ON ENERGY CONSERVATION AND POWER
OF THE
COMMITTEE ON ENERGY AND COMMERCE
WASHINGTON, D.C. 20515

June 7, 1984

Honorable Donald P. Hodel
Secretary
Department of Energy
Forrestal Building
Washington, D.C. 20585

Dear Mr. Secretary:

As you know, the Subcommittee is investigating the health and safety policies of the Department of Energy. Your assistance is requested for this effort. Please prepare a list of each human experimentation project involving human test subjects and radiation that has been funded by the Atomic Energy Commission, the Energy Research and Development Administration and/or DOE.

The list should include, for each project:

1. the project name, the facility (ies) at which it was conducted, and the dates during which it was conducted;

2. the medical manager of the project, as well as the contracting officer within AEC, ERDA, and DOE who was responsible for monitoring the project;

3. a brief description of the tests, what was done to the participants, including the objectives of the experiments, both therapeutic and experimental;

4. the policy and specific methods for follow-up and long-term tracking of the participants in these projects. Please note if no follow-up review or long-term tracking was conducted.

84 530

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In addition to the human experimentation projects which the AEC, ERDA, and/or DOE commissioned, please specify each project that these agencies provided support for or conducted jointly with other agencies such as NASA, the Defense Atomic Support Agency, and the Defense Nuclear Agency of the Department of Defense.

Your cooperation is appreciated. Please provide your response by June 25, 1984. If there are any questions regarding this request, please contact Jeanine Hull, Subcommittee counsel, at 226-2424.

Sincerely,

Richard Ottinger

Richard L. Ottinger
Chairman

SUMMARY FACTSHEET HUMAN EXPERIMENTATION SFS1.001

Project Category: Metabolism and Biological Effects of Plutonium, Polonium, Radium, Thorium, Uranium and Lead-212

Funding Source(s): MED
AEC (one patient)

Institution(s): University of Rochester, University of California, University of Chicago, Clinton Laboratories (Oak Ridge)

Principal Investigator: Robert S. Stone

Objective(s) of Project: To determine the excretion rate of plutonium in man in order to provide the information necessary for setting safety criteria for the several thousand MED workers handling plutonium.

Short Description: During the period 4-10-45 to 7-18-47 a total of 18 patients with an estimated life expectancy (because of existing disease) of less than 10 years were injected with on the average 0.3 microcurie of plutonium-239 or -238 (range: 0.05 to 6 microcurie) at: MED Hospital, Oak Ridge, TN (1 patient); Strong Med. Hosp., Rochester, NY (11); Billings Hosp., U. of Chicago, IL (3); Univ. Hosp. UCSF, San Francisco, CA (3).

The patients included 13 males and 5 females. By race there were 15 whites and 3 blacks. The ages of 13 were 45-65 years, 4 were 18-45 and one was 4 years old. Body excretions were collected and measured for plutonium content for several weeks after injection. These data have been analyzed many times in efforts to find the best mathematical parameters.

Follow-up Data: Six of the patients died in less than 1 year, three in 1 to 3 years, three in 8 to 14 years, and four after 20 years. One is still living (Oct. 1983) and the status of one is unknown. None of the deaths was related to plutonium exposure and there is no evidence to suggest that plutonium injection influenced the course of the diseases. The bodies of four of the deceased patients have been studied for residual plutonium content. With the excretion data these studies provide a basis for estimating plutonium body burdens from plutonium urinary excretion rates.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS1.002

Project Category: Metabolism and Biological Effects of Plutonium, Polonium, Radium, Thorium, Uranium and Lead-212

Funding Source(s): AEC

Institution(s): Massachusetts Institute of Technology

Principal Investigator(s): Robley Evans

Objective(s) of Project: To determine the relative uptake via the gut of radium and thorium. This information was considered to be necessary in the interpretation of the toxicity data of radium dial painters.

Short Description: During the period 1961-1965, tracer doses of the short-lived nuclides radium-224 and thorium-234 were given by mouth to 20 volunteers (ages 63 to 83 years), and the relative absorptions measured. Metabolic studies, conducted over a period of 21 days for Ra and 4 months for Th, included measurements of blood, urine, feces and breath samples, and on the whole body and the upper 20% of the body with the GI tract shielded.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS1.003

Project Category: Metabolism and Biological Effects of Plutonium, Polonium, Radium, Thorium, Uranium and Lead-212

Funding Source(s): MED/AEC

Institution(s): Univ. of Rochester (Polonium, Lead 212)
Los Alamos Scientific Laboratory (Uranium)
Massachusetts General Hospital (Uranium)
Oak Ridge National Laboratory (Uranium)

Principal Investigator(s): N. E. Silberstein (Polonium)
J. B. Hursa (Lead-212)
W. H. Sweet (Uranium)

Objective(s) of Project: Data on the distribution and metabolism of these substances in the body was needed for evaluation of the health hazards of exposure to these and related substances.

Short Description: In 1947 at Rochester, four human subjects were injected intravenously with 0.17 to 0.3 microcurie of polonium per kg body weight, and a fifth subject was given polonium orally. Fecal and urinary excretion rates were measured.

In Boston, Hexavalent uranium was given to 12 terminal brain tumor patients. Blood, urine and feces samples were obtained. Tissue samples were obtained at biopsy and autopsy and were studied at Oak Ridge (Oct. 1953-Oct. 1959).

In 1965 at Los Alamos the mean transit times for microspheres labeled with uranium-235 through the gastrointestinal tract was studied in 57 normal adults. Particle sizes were about 100 to a few hundred micrometers diameter. The mean transit times were 34.5 ±16.6 hours.

In 1967 at Rochester, lead-212 was administered by mouth to three human subjects. Gastrointestinal absorptions of 1.3, 8.1 and 16.0% were found. Excretion rates were compared with those for two subjects who received lead-212 intravenously. The uptake and retention of lead in red blood cells was studied.

Follow-up Data: All of the brain tumor patients died of their disease within less than one and one-half years after entering the study. No follow-up was obtained in the other studies.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS2.001

Project Category: Effects of Radiation on the Human Testes

Funding Source(s): AEC/ERDA

Institution(s): Pacific Northwest Research Foundation, Seattle, WA

Principal Investigator(s): Carl C. Heller (succeeded by Mavis Rowley Feb. 27, 1973)

Objective(s) of Project: To obtain data on the effects of ionizing radiation on testicular cytochemistry and function in man

Short Description: During the period August 22, 1963 to May 6, 1971, 67 volunteers at the Oregon State Prison were subjected to testicular irradiation by 140 kvp X-rays. Radiation doses ranged from 8 to 600 R in single acute exposures except that six were irradiated a second time, one a third time, and one was given weekly irradiations of 5 R per week for eleven weeks. Studies included serial testicular biopsies, sperm counts, and urinary or plasma steroid and hormone evaluations.

Follow-up Data: Complete recovery as shown by a return to pre-irradiated sperm concentrations and germinal cell numbers was found to be within 9-18 months for doses of 100 rad and below, 30 months for doses of 200 and 300 rad and 5 or more years for doses of 400 and 600 rad.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS2.002

Project Category: Effects of Radiation on the Human Testes

Funding Source(s): AEC/ERDA

Institution(s): University of Washington

Principal Investigator(s): C. Alvin Paulsen

Objective(s) of Project: 1) To relate radiation dosage to changes in gonadal function, 2) to utilize the radiation gonadal changes as means for studying pituitary-testis interrelationships, 3) to explore therapeutic and medical protective measures with respect to gonadal irradiation, 4) to explore our current concepts concerning radiation dosage expressed in physical terms and their relation to biologic effects.

Short Description: During the period June 1, 1963 to February 1, 1973, 64 volunteers at the Washington State Prison were irradiated by 250 kvp X-rays. After appropriate baseline studies were performed, subjects received from 7.5 R to 400 R x-ray irradiation or sham irradiation to the testis only. Testicular biopsies were performed prior to and up to 6 years post-irradiation to assess changes in the germinal epithelium. Seminal fluid specimens were obtained at two-week intervals throughout the study and were analyzed for morphologic changes and changes in total number of sperm. Urine specimens were obtained monthly for evaluation of hormonal changes. Later, when the techniques were available, serum LH was measured by radioimmunoassay. Studies of ultrastructure changes in testis tissue were performed using electron microscopy. Subjects were followed until hormonal values returned to normal levels and until sperm counts returned to normal ranges. Vasectomies were performed prior to discharge from the study to eliminate the possibility of defective offspring. Only individuals desiring vasectomy were accepted for the study; but in several instances the volunteers changed their mind and did not desire a vasectomy at the conclusion of the study. Subjects were informed in detail regarding the study and signed consent forms were obtained from subjects and from spouses if subjects were married. Subjects were prison inmates only, thus eliminating the possibility of conception during the study.

Follow-up Data: Recovery of cell morphology and function were found after a maximum of 501 days. It was concluded that man is very sensitive in regard to temporary sterility, but is very resistant to complete sterility.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS3.001

Project Category: Whole Body Irradiation

Funding Source(s): AEC (92%) NASA (8%)

Institution(s): Oak Ridge Institute of Nuclear Studies (ORINS)
Oak Ridge Associated Universities (ORAU)

Principal Investigator(s): Gould A. Andrews
Clarence C. Lushbaugh
R. M. Kniseley

Objective(s) of Project: 1) To explore the possibilities for treatment of chronic leukemia, lymphoma and polycythemia with radiation; 2) To obtain radiobiological data.

Short Description: In 1957 ORAU began a program designed for treatment of cancer patients and for assessment of the health effects of total body radiation. In 1964, NASA began to provide additional funds to include measuring the biological effects of low radiation doses and low dose rate exposures. Nearly 200 patients were treated with 50 or 100 R in a Cs-137 whole body irradiation facility. A few patients with acute leukemia were given doses of 300 R or more. Detailed and systematic studies were made of blood cells, bone marrow, clinical effects and selected laboratory tests. In some of the patients with high doses, the effects of autogenous and homologous bone marrow grafts were studied.

Follow-up Data: Measurements were continued for at least 6 weeks for each patient. The studies were not designed to analyze the late effects.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS4.001

Project Category: Teletherapy with Particle Beams

Funding Source(s): AEC

Institution(s): (1), (2) Univ. of California, Berkeley
(3) Univ. of California, San Francisco

Principal Investigator(s): (1) J. H. Lawrence, C. A. Tobias
(2) John A. Linfoot
(3) J. R. Castro

Objective(s) of Project: To determine possible beneficial effects in various neoplastic and metabolic diseases

Short Description: (1) In the period 1953-1959 the pituitary glands of patients with advanced metastatic mammary carcinoma or other endocrine related diseases were irradiated with beams from the 184 inch cyclotron at first with the 340 meV proton beam, later with the 900 meV alpha particle beam. Doses of 24,000 to 30,000 rad to the pituitary were given.

(2) Heavy particle irradiation was used (1968) for the irradiation of the pituitary in acromegaly, Cushing's disease, and chromophobe adenomas of the pituitary and in metabolic disease such as diabetic retinopathy, metastatic breast and prostatic carcinoma where these are sensitive to hormonal control through the pituitary or the endocrine end organs of the pituitary. Heavy particle irradiation was used for direct tumor irradiation at other sites in the body where the tumor boundaries can be adequately delineated.

(3) Since 1975, 94 patients with localized unresectable carcinoma of the pancreas have been irradiated using helium and heavier particles.

Follow-up Data: (1) By April 1959, 103 patients had been treated. Clinical and laboratory studies were conducted every 4-8 weeks on survivors. Twenty-nine of the 82 with metastatic carcinoma were living in 1959, the longest being 4 years post irradiation.

(2) Four hundred and twenty six patients have had heavy particle therapy. In the series of 66 patients with acromegaly, 90% have had a complete amelioration of their disease process establishing heavy particle irradiation to the pituitary as being the optimal form of treatment at the present time. Highly successful results have also been achieved in patients with Cushing's disease and in 10 patients with chromophobe adenomas. The results in diabetic retinopathy are promising, but require longer follow-up for definitive evaluation.

SFS4.001 (con't)

(3) Many patients proved to have occult liver metastases manifested within 9 months post treatment. In addition, local and regional control of the primary neoplasm (approx. 20%) has been difficult to obtain even with doses of 6000 rad in 7 1/2 weeks. Gastric and biliary obstruction have required surgical bypass procedures since irradiation has not been successful in relieving obstructive symptoms. Evidence of gastrointestinal injury has been present in postradiation therapy in approximately 10% of patients.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS4.002

Project Category: Teletherapy with Particle Beams

Funding Source(s): DOE

Institution(s): Lawrence Berkeley Laboratory

Principal Investigator(s): Jacob I. Fabrikant

Objective(s) of Project: To establish stereotactic heavy-ion Bragg peak radiosurgery for brain disorders, including intracranial arteriovenous malformations.

Short Description: Initial observations in 55 patients treated to date (1980-1984) indicate that the clinical objectives of a decrease in (1) frequency of hemorrhages, (2) in neurological deficiencies, (3) subjective complaints incuding headaches, or (4) in frequency of seizures are being achieved.

Follow-up Data: There have been no neurological complications of radiation damage to the normal brain tissue; thus far, no evidence of brain injury or progressive or fixed neurological deficiencies have occurred as a result of the stereotactic radiosurgical procedure.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS4.003

Project Category: Teletherapy with Particle Beams

Funding Source(s): AEC/ERDA/DOE, NCI

Institution(s): Los Alamos National Laboratory

Principal Investigator(s): M. Kligerman
S. Bush
R. D. Moseley
J. Bradbury

Objective(s) of Project: To conduct the necessary physical, biological, and clinical studies to evaluate the efficacy, potential benefit, and role of pions in the management of some types and stages of solid tumors.

Short Description: This program was a joint effort between the University of New Mexico and the Los Alamos National Laboratory utilizing negative pions produced by the 800 MeV LAMPF accelerator. The program involved beam development, radiobiology studies, new dosimetry and patient positioning techniques, and the evaluation of different total dose/fractionation schemes. During the program 234 patients were treated with tumor sites including prostate, head and neck, rectum and colon, cervix, brain, pancreas, and bladder. The studies began October 1974 and were terminated in late 1981.

Follow-up Data: One hundred and ninety-six patients have been followed for a minimum of 18 months. Crude survival data range from 11% for unresectable pancreatic carcinoma to 82% for stages C and D1 adenocarcinoma of the prostate indicate that this modality did not demonstrate advantages over more traditional radiotherapy and was therefore discontinued.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS4.004

Project Category: Neutron Therapy Facility

Funding Source(s): Funded by NCI in a DOE-owned facility

Institution(s): Fermi National Accelerator Laboratory

Principal Investigator(s): L. Cohen
F. R. Hendrickson

Objective(s) of Project: The scientific objective is to determine the effectiveness of neutron beam irradiation as compared to standard photon irradiation for the management of certain malignant tumors.

Short Description: Patients are identified as being eligible for inclusion in the clinical trials based on the type, extent and location of their cancer. Suitable candidates have tumors that are thought to be resistant to standard therapies. Informed consent is obtained. These clinical trials are conducted under the auspices of the Institutional Review Board. National cooperative trials are carried out in coordination with the Radiation Therapy Oncology Group (funded by the National Cancer Institute). Some patients are treated with neutron beam irradiation only. Others receive a combination of neutron beam irradiation and one or more standard modalities such as photon irradiation, surgery and chemotherapy. The program began in July 1975 and is continuing.

Follow-up Data: Approximately 1400 patients have been referred to this facility. Prior to treatment, patients must agree to comply with long term follow-up requirements. Physical examinations, laboratory tests and radiographic investigations are conducted regularly. If a patient does not keep his scheduled appointments, every effort is made to contact him. Fewer than 1% of the patients treated at this facility are considered currently lost to follow-up.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS5.001

Project Category: Other Teletherapy

Funding Source(s): AEC

Institution(s): (1) University of California, San Francisco
(2) University of Arkansas
(3) (4) Argonne Cancer Research Hospital
(5) Univ. of Michigan
(6) Oak Ridge Inst. of Nuclear Studies
(7) CEER, Puerto Rico

Principal Investigator(s): (1) R. S. Stone
(2) H. J. Barnhard
(3) M. L. Griem
(4) James W. J. Carpenter
(5) I. Lampe
(6) F. V. Comas
(7) V. Marcial

Objective(s) of Project: Development and Evaluation of Teletherapy Methods

Short Description: (1) During the years 1956 to 1958, 67 patients were irradiated with 70 MeV x-rays from the synchrotron. Doses were 5250 R in 5 weeks or 6000 R in 6 weeks. Patients with bronchogenic carcinoma, tumors of the oral cavity and carcinomas of the cervix were treated.

Follow-up Data: In August 1958, of the 67 patients treated, 25 had died within 2 years of starting treatment. A subsequent report indicates that as of June 1962, 310 patients had been treated but survial data is not given.

(2) A cobalt-60 teletherapy unit was used to treat 227 patients with various types of neoplasms (Progress report dated July 1956).

(3) From 1972 to 1979, Hodgkin's disease and other lymphomas were treated by a combination of laparotomy to improve staging and diagnosis, and carefully planned radiation to indicated organs of involvement. A number of malignancies were treated with ultra high dose rate electrons to study the effects of this radiation. Chromium-51 radioactive permanent implants were also evaluated. Head and neck malignancies were subjected to combined treatment schedules, including drug pre-treatment and split-course radiation. The sensitizing qualities of hydroxyurea and cytosine arabinoside were tested on a hair follicle indicating system before being tested on animal tumors and patients.

0008710

SFS5.001 (con't)

(4) From 1963 to 1965 joint study was being carried out in conjunction with the Ear, Nose, and Throat Clinic in an attempt to evaluate the effects of pre- and post-operative radiation treatment of various malignancies using the Van de Graaff x-ray generator, the rotational cobalt-60 machine, and the linear accelerator electron beam. All patients were seen in the ENT Clinic and randomized for treatment schedules. It was believed that some lung malignanies were made operable by irradiation.

Follow-up Data: One patient having an inoperable gastric malignancy treated with a combination of colchicine and radiation was still alive and gave no evidence of the disease after 2 years.

(5) During the period 1952-1966, cobalt-60 and cesium-137 teletherapy units were used in a comparative clinical evaluation in the radiation treatment of malignant disease. Modification of a theratron-B to permit clinical employment of a cesium-137 source was achieved and the radiation from this isotope was applied clinically to evaluate the potential role of this radiation in clinical radiotherapy in comparison with cobalt-60 radiation and past and current experience with orthovoltage radiation.

(6) In 1966, to determine the effects of cobalt-60 teletherapy on certain kinds of cancer two patients were given 500 R to spleen and liver. One patient showed no hematologic changes when the liver was irradiated, but a profound fall in circulating white blood cells occurred after irradiation of the spleen. The other patient responded to liver irradiation in a way undistinguishable from the changes occurring after spleen irradiation; in both instances the peripheral white count went from about 100,000 to 20,000 with a fast return to pretreatment levels.

(7) During the period 1964-1967 in a study of the optimal tumor dose in radiation therapy of cancer of the esophagus, half of the cases treated received cobalt teletherapy doses of 5000 roentgens in four weeks and the other half received doses of 6000 roentgens in six weeks. Disappearance of dysphagia and twelve months survival were compared in each group.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS5.002

Project Category: Treatment of Cancer with Supervoltage Machines

Funding Source(s): AEC

Institution(s): Argonne Cancer Research Hospital

Principal Investigator(s): M. L. Griem
J. W. J. Carpenter
L. H. Lanzl
L. S. Skaggs

Objective(s) of Project: To use new high-energy research machines to apply x-rays and gamma-rays to cancer patients

Short Description: Starting in 1954, with the ACRH 2-MeV Van de Graaff x-ray generator, a treatment field of sufficient size was made available so that patients with certain lymphomas could be treated from the neck to below the waist at one time, including all affected lymph nodes. This resulted in shorter overall treatment times and lowering of total radiation doses.

The cobalt-60 rotational therapy machine, with its small, high-specific-activity source and uranium shield, was designed and built at ACRH. Patients with advanced carcinoma of the uterus and cervix and other malignancies who were treated with this cobalt machine, sometimes in combination with other modalities such as the Van de Graaf, radium implants, surgery, or drugs, had favorable survival and cure rates.

Studies were also carried out on use of a variety of radiation-sensitizing agents, in an effort to achieve cures with lower doses of radiation.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS5.003

Project Category: Therapy with High-Energy Electrons

Funding Source(s): AEC

Institution(s): Argonne Cancer Research Hospital

Principal Investigator(s): M. L. Griem
J. W. J. Carpenter
L. S. Skaggs
L. H. Lanzl

Objective(s) of Project: To use high-energy electrons from a scanning-beam linear accelerator in tumor treatment, alone and with other treatment modalities

Short Description: Starting in 1959, ACRH scientists developed a unique instrument for electron-beam therapy combining a linear accelerator of the Standord type with a beam-scanning device. This unit was constructed for investigation of the clinical advantages of electron-beam therapy. The linear accelerator and pencil beam scanning system were used in the treatment of different forms of cancer beginning in 1959. The malignant growths treated included head and neck cancer, chest tumors, mycosis fungoides, skin cancer, carcinoma of the urinary bladder, and others. By 1969, more than 500 patients had been irradiated with the electron beam, and a remarkable feature was the lack of a skin reaction in the patients.

Follow-up Data: The linear accelerator was used successfully for treatment of patients with mycosis fungoides. The high doses of electrons to the skin which became possible with this unit led to eradication of these difficult lesions, and in 1970, Dr. Griem reported very few recurrences up to 5 years after treatment in combination with Van de Graaff x-rays.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS6.001

Project Category: Control of Polycythemia by Marrow Inhibition

Funding Source(s): Univ. of California, AEC (after 1945)

Institution(s): Univ. of California Radiation Laboratory

Principal Investigator(s): J. H. Lawrence

Objective(s) of Project: Treatment of Polycythemia Vera

Short Description: In 1938 two patients with polycythemia vera were treated with P-32. Over the next 10 years, 119 patients were treated. The patients ranged in age from 19 to 75 years. Of these, 56.5% were male and 43.5% female. Typical doses were 2 to 6 mCi of P-32. The patients usually received multiple doses over a period of several years.

Follow-up Data: At the time of a summary report in 1949 there had been 24 deaths. The causes of death were arteriosclerosis (5), leukemia (5), neoplasm (3), coronary occlusion (3), cardiac failure (2), portal thrombosis (1), and unknown (2). The high incidence of leukemia as a complication of polycythemia is well known. The incidence in this series was not significantly different from untreated series.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS7.001

Project Category: Hematological Effects

Funding Source(s): MED
AEC

Institution(s): 1) Univ. of Cal. Radiation Lab (AEC)
2) Memorial Hospital, New York (MED)
3) Metallurgical Lab, Manhattan Project (MED)
4) ORAU (AEC)
5) University of Cincinnati (AEC)

Principal Investigator(s): 1) B. V. A. Low-Beer; P. M. Aggeler
2) L. F. Craver
3) J. J. Nickson
4) G. A. Andrews
5) E. L. Saenger

Objective(s) of Project: To determine changes in the blood-forming organs and the peripheral blood as an index of exposure to total-body irradiation.

Short Description and Follow-up: 1) From 1943 to 1950, a total of 32 patients were treated with X-rays generated by 100, 200, and 1000 kv. Individual exposures varied from 5 to 50 R measured on the body surface at each treatment. The total accumulated doses varied from 100 to 390 R total-body dose as measured on the skin. The calculated tissue dose in the central plane of the body varied from approximately 60 to 264 R. The total elapsed time from the first to the last treatment varied between 5 and 92 days. The 32 patients treated in this manner were followed hematologically for periods as long as possible after treatment. The longest period of observation for any member of the group is six and one-half years, the average for the group as a whole is approximately four years.

2) From 1942 to 1944, patients were exposed using 180-185 kv x-rays to a total dose of 300 R at dose rates of 10, 15 or 20 R/day. Patients selected with untreatable metastatic cancer but able to tolerate procedure. Six patients received the planned 300 R. Two started but didn't finish. Three patients followed longer than 6 months. No deterioration of blood count or general health was attributable to radiation.

SFS7.001 (con't)

3) Eight persons with incurable neoplasms were given single exposure doses of 27, 60, and 120 R in the period 1943 to 1944. Three patients with chronic diseases were given fractionated whole-body irradiation of 100, 300 and 500 R. Three volunteers were given fractionated irradiation totaling 21 R. No-blood alterations were noted in the 21 R volunteer group. In the others, the predominant effect was lymphocyte depression.

4) Three groups of patients were treated in the period 1965 to 1966

1) chronic hematologic disorders
2) neoplasm
3) acute leukemia in relapse

Eleven patients with acute or subacute leukemia were treated with 200 to 900 R of total body irradiation. Of these, 5 showed incomplete suppression of the leukemia process, 5 showed apparent complete or nearly complete suppression, and 2 had early deaths (one patient was treated twice).

5) In the period 1961 to 1962, patients with metastatic or incurable neoplasms who had not received previous radio- or chemotherapy were given whole-body gamma radiation in doses varying from 85-336 R. Clinical and hematologic parameters were followed for 6-8 weeks subsequently.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS8.001

Project Category: Neutron Capture Therapy

Funding Source(s): AEC

Institution(s): Brookhaven National Laboratory

Principal Investigator(s): L. E. Farr
J. S. Robertson
R. Sweet
G. Brownell

Objective(s) of Project: Brain tumor therapy

Short Description: Neutron capture therapy uses the localization of boron in tumors and the reaction of boron with neutrons to achieve localized radiation of brain tumors. Over a period of two years beginning February 15, 1951, 10 patients with proved glioblastoma were treated by neutron capture therapy at the graphite research reactor. The longest survival was 186 days.

A second series of 9 patients were treated with higher neutron doses. One patient survived 18 months.

In 1959, a series using the Medical Research Reactor was started. Fifteeen patients were treated. Survival times were in the same range as for the previous series.

Follow-up Data: Whole brain sections were obtained in at least 16 of the patients and studied for tissue reactions to radiation. With the boron compounds then in use it was not possible to achieve adequate tumor control without unacceptable damage to normal tissues and the project was discontinued.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS9.001

Project Category: Other Radiation Therapy

Funding Source(s): MED
AEC

Institution(s): 1) Argonne Cancer Research Hospital and Univ. of Chicago (AEC)
2) Brookhaven National Laboratory (AEC)
3) Lawrence Berkeley Laboratory (MED/AEC)
4) Oak Ridge Associated Univ. (AEC)
5) Piedmont Hospital, Atlanta (AEC)

Principal Investigator(s): 1) R. D. Moseley, W. M. S. Ironside, P. V. Harper
2) J. S. Robertson
3) N. I. Berlin, J. L. Born, L. Dobson, J. G. Hamilton, L. Hollander, J. H. Lawrence, B. V. A. Low-Beer, M. Pollycove, D. J. Rosenthal, H. H. Stauffer, R. C. Steinkamp, S. Winchell
4) C. C. Lushbaugh
5) E. D. Grady

Objective(s) of Project: To develop treatments for certain medical disorders with radioisotopes that can be selectively localized in tissues to be irradiated.

Short Description: During the period 1939-1974, several research projects were undertaken to improve therapy of cancer and other diseases by methods using radioisotopes. Radioisotopes (such as iodine-131, gallium-72, gold-198 and others) were given to patients under rigidly controlled conditions to determine whether their treatment could be improved by absorption (or localization) of the radioactivity directly in the cancer. Palladium-109 was administered by direct infiltration to three patients to study tissue and tumor response. Small 1-millicurie yttrium-90 pellets were implanted for treatment of certain cancers, notably metastatic breast and prostate carcinoma. In addition, yttrium-90 oxide particulate radioisotopes was established as an agent suitable for localizing radiation in an area by injecting the artery supplying that area. Thirty-five of 51 patients with advanced and otherwise uncontrollable cancer benefited from intravascular administration.

SFS9.001 (con't)

Agents labeled with phosphorus-32 were used to treat a variety of hemotological and medical disorders. Strontium-90 was used in the treatment of bone metastases.

Follow-up Data: Initial follow-up visits were as frequent as required (weekly, monthly, etc.). Subsequent follow-ups were usually on an annual basis. Follow-up visits include routine physical examinations and interval histories, and appropriate supporting clinical laboratory studies and diagnostic studies.

At time of death, complete information was sought to determine cause of death. When available, the postmortem findings were reviewed.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS9.002

Project Category: Other Radiation Therapy

Funding Source(s): AEC

Institution(s): Center for Energy and Environmental Research, Puerto Rico

Principal Investigator(s): V. Marcial

Objective(s) of Project: To determine optimum fractionation of irradiation for cancer, to evaluate a split-dose technique for radiotherapy of cancer, and to determine the effectiveness of radiation therapy for the regional lymph nodes areas as an adjuvant to surgery for carcinoma of the breast.

Short Description: In the period 1964 to 1970, various fractionation regimes were studied (1 vs 5 per week and 3 vs 5 per week) to observe tumor effect, survival, and normal tissue reactions. Studies were conducted to compare the results obtained by the usual uninterrupted radiation treatment with a similar dose given in two separate two-week periods with a rest interval of two to three weeks halfway in the treatment (split-dose). Finally, post-operative irradiation of lymph node areas was studied to improve prognosis in patients with breast cancer treated with radical mastectomy.

Follow-up Data: Results for fractionation of irradiation showed that the curability and complication rates were identical at 3 years in a group of 260 patients.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS10.001

Project Category: Biological Effects of Iodine-131

Funding Source(s): AEC/ERDA

Institution(s): 1) Case Western Reserve Univ. (AEC/ERDA)
2) Univ. of Puerto Rico (AEC)
3) Sloan-Kettering Institute for Cancer Research (AEC)

Principal Investigator(s): 1) B. M. Dobyns
2) V. Marcial
3) R. W. Rawson

Objective(s) of Project: To determine the physiological and morphological effects of iodine-131 radiation on the thyroid of humans

Short Description and Follow-up Data:

1) During a 25 year period, 7/1/51 to 9/30/76, over 500 patients with hyperthyroidism were studied in great detail. During the first few days after treatment the observations essentially reflected unaltered function of the thyroid, but with the passage of time, the observations reflected the effects of radiation. The changing patterns of iodinated compounds in the blood, alterations in rate of return of the radioactivity to the thyroid, and the subsequent testing of the functional capacity of the gland permit an analysis of the effects of radiation.

2) During the period 1952 to 1958, radioiodine was used for therapy of hyperthyroidism and metastatic thyroid cancer. Therapeutic doses gave 2,000 to 100,000 rad to the thyroid. Whole body doses up to 20 rad. One patient with pulmonary metastases given 18 mCi I-131 received 40 to 80 rad whole body. This patient was doing well six years later.

3) In the 1948-1956 period, 22 patients were treated with therapeutic doses of I-131 to destroy thyroid tissue. Doses ranged from 95 to 329 mCi. In 1960, of 55 patients, 26 were known to be dead. Others being followed.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS11.001

Project Category: Other Biological Effects

Funding Source(s): MED

Institution(s): 1a) Clinton Laboratory
1b) New York University
1c) Oak Ridge National Laboratory
2) Harvard Medical School
3) Lawrence Radiation Laboratory
Oak Ridge Associated Universities
4) Oak Ridge National Laboratory
General Electric Company

Principal Investigator(s): 1a) J. E. Wirth and J. R. Raper
1b) Unknown
1c) M. Nikson
2) F. D. Moore
3) J. H. Lawrence
H. Vodapick
4) E. C. Anderson, E. Pinson, V. Lote & C. W. Delong
5) C. W. Delong

Objective(s) of Project:
1) To determine the biological effects of irradiation to the skin
2) To study transplantation of tissues and whole organs
3) To evaluate the effects of internal irradiation from P-32, Y-90, Sr-90, and I-131 when therapeutically used in certain diseases, and the evaluation of the hematological response obtained from their use
4) To determine the distribution of tritium in the human body resulting from surface contamination, inhalation and ingestion

Short Description and Follow-up Data:
1a) Shielded disks of 1-inch diameter containing P-32 were used. Exposures were made by setting the source directly on the skin. Two groups of ten healthy volunteers each were exposed to doses of 140 to 1180 rep. The dose required to produce a visible reaction in 80% of the people was found to be between 170 and 200 rep. For an erythema the dose was determined to be 635 to 813 rep. (Report dated 1946.)

1b) Experiments carried out on living human skin in situ demonstrated that the iontophoresis of weak solutions of thorium X will increase its biological effects as judged by erythema and pigmentation, and cause greater penetration as shown by autoradiography. (Report dated 1955.)

SFS11.001 (con't)

1c) Fifteen subjects were exposed on their left fourth finger to 200-600 R of 130kv x-rays in a single exposure. Microscopic observations were made before and after treatment. (Report dated 1947.)

2) During the period 1960 to 1963, one patient (in this report) received 250 R total body x-ray irradiation to suppress the immune reaction to a kidney transplant. Seven other patients received doses of 350 or 450 R. The treatment apparently was not successful but survival time wasn't stated.

3) During the period 1938 to 1963, internal irradiations using P-32, Y-90 and I-131 were continued and their clinical therapeutic and irradiation effects studied in patients with polycythemia, chronic leukemias, multiple myeloma, lymphogranuloses and thyroid disorders, including thyroid carcinoma. The patients receiving internal irradiation over the past 25 years have been closely followed. A high percentage post-mortem examinations have been obtained on the deceased patients.

4a) In 1950, six subjects received a few millicuries of tritium by inhalation of isotopically labeled hydrogen gas. Tritium concentration in urine was monitored for 15 subsequent days.

4b) In 1952, subjects inspired HTO saturated oxygen for 4 to 5 minutes. The HTO retained in the body during the exposure was obtained by subtracting the HTO expired from the HTO inspired.

4c) Also in 1952, measured amounts of tritium as HTO were ingested by male subjects. Venous blood and urine were monitored for tritium activity for 2-1/2 to 5 hours subsequently.

4d) The lower arm of subjects was exposed for variable lengths of time to various activities of HTO as water vapor and the HTO in water. Tritium activity in urine was monitored. (1952.)

4e) Air saturated with tritium oxide was circulated for one hour over a 9.8 cm^2 area of a male subject's forearm. Absorption was estimated from the tritium activity in urine passed several hours following exposure. (1952.)

5) In 1951, fourteen human subjects were exposed over a small area ($\sim$10 cm^2) on the forearm or abdomen to a water-vapor atmosphere labeled with tritium oxide (HTO). A single human subject was similarly exposed over his total skin area while breathing uncontaminated air. Absorption of tritium oxide was estimated by measurement of tritium oxide subsequently excreted in the subject's urine. The data from these experiments indicated a 4-fold greater absorption rate than that measured earlier in rats. These studies established the importance of the skin as a route of entry for tritium oxide and led to reductions in the allowable concentration of tritium oxide in air.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS12.001

Project Category: Metabolic and Physiological Studies

Funding Source(s): AEC/ERDA/DOE

Institution(s) and Principal Investigator:

Argonne Cancer Research Hospital
1. P. M. Ejarque
2. L. D. Jacobson
3. G. V. LeRoy
4. P. V. Harper

Argonne National Laboratory
5. R. E. Rowland

Los Alamos Scientific Laboratory
6. C. C. Lushbaugh

Pacific Northwest Laboratory
7. T. M. Beasley
8. H. E. Palmer

Sloan-Kettering Inst. for Cancer Research
9. J. S. Laughlin

Univ. California, Berkeley
10. M. Pollycove

Univ. California, Los Angeles
11. J. F. Ross
12. G. V. Taplin

Univ. Minnesota
13. M. B. Becaner

Univ. Pisa (Italy)
14. G. Monasterio

Univ. Washington
15. W. B. Nelp

Objective(s) of Project: Tracer studies using various radionuclides

Short Description: During the period 1950-1980 many tracer studies were conducted on human subjects for the purposes of studying the physiology and metabolism of labeled substances. Usually only a few subjects are involved in each study. No late effects are expected and in general, there has not been a systematic follow-up. Brief description of the studies are:

(1) Progesterone-4 labeled with carbon-14 was used to study progesterone metabolism in two patients. Doses were 5.27 and 37.81 uCi. A third patient who was 10 weeks pregnant was given 28.3 uCi. A therapeutic abortion 6 days later because of severe sickle cell anemia was performed. Activity in maternal and fetal tissues studied. Storage of the hormone in the fat compartments were found. (1958.)

0008724

SFS12.001 (con't)

(2) 450 uCi of DL-glutamic acid-1-C14 were injected in a patient to investigate whether synthesis of Bence-Jones protein is related to that of myeloma globulin. Urinary and expiratory CO-2 were measured. (1958.)

(3) Metabolism of glucose studied with C-14, by CO-2 in expired air samples. (1958.)

(4) Sequential studies were made of the body potassium content of man in various cardiac disease states, in aldosteronism, and in hypertension with suspected hyperaldosteronism. A special study was made of the relationship between plasma potassium shifts and total-body content of potassium in man in various disease states. They are also measuring the effect of magnesium deficiency on levels of sodium, potassium, magnesium, and calcium in plasma, cerebrospinal fluid, brain and skeletal muscle. (1968.)

(5) Retention curve data with Ca-45, Sr-85, and radium were obtained. (1959.)

(6) An arm counter was used to measure activity in blood to determine the clearance of ^{131}I - Rose Bengal in the liver. The curve has two exponential components, interpreted as reflecting hepatic uptake and excretion rates. (1960.)

(7, 8 and 15) (1965.) A study was conducted to measure the long-term retention and localization of technetium in humans following both oral and intravenous administration and to derive mathematical models for excretion, which are very useful in determining the radiation dose to humans from technetium isotopes in the body. They are important from both medical and occupational standpoints.

^{95m}Tc and ^{96}Tc were administered to 8 subjects by physicians at the University of Washington Hospital in Seattle. The subjects were hospitalized at the University of Washington Clinical Research Center for the first week. Whole body counting and excreta measurements were made for 60 days. The University of Washington obtained and reimbursed the subjects for their services. The participation by PNL personnel was limited to providing the equipment, making the whole body counting and excreta measurements and analyzing the data. The PNL participation was funded by AEC but not the University of Washington participation.

(8) A study was conducted to determine the uptake, retention, distribution and excretion of promethium in humans following both oral and intravenous administration and to study the effectiveness of DTPA in removing promethium from the body. These concentrations were relevant to possible exposure of plant personnel. (1967.)

$^{143}PmCl_3$ was administered to 14 volunteers by physicians of the Hanford Environmental Health Foundation (HEHF). Whole body counting and excreta measurements were made by PNL for one year following administration of the ^{143}Pm. Six of the volunteers were also injected with DTPA at various intervals before and after the administration of the ^{143}Pm. Both the HEHF and PNL contributions to the study were funded by AEC.

(9) (1977-1982.)

(9a) To extend the knowledge of tumor metabolism and to define the localization and improve the diagnosis of cancer in animal models and man, studies have been in progress over the seven year period (1977-1984).
The specific aims are as follows: (1) To synthesize from different radiolabeled precursors a large variety of: (a) N-13 and C-11 labeled amino acids using enzymatic procedures. (b) C-11 radiolabeled carboxylic acids. (c) 1-(C-(c) 1-(C-11)-2-deoxy-D-glucose. (2) To employ the synthesized compounds for quantitative assessment of regional perfusion, transport, and metabolism to improve treatment of cancer, cancer diagnosis and the monitoring of treatment response.

(9b) To investigate the alteration in metabolic patterns related to cancer, methionine, technetium-99m and iodine-131 were used. These were used in various compounds for the study of their metabolism in bone, parathyroid tissue, liver, lung, pancreas and brain. Research was directed towards basic metabolic patterns and their alteration by malignant processes and by therapy, and also towards the development of useful diagnostic tests for early malignancy.

(10) Various hematological studies included: (1959.)
a) in 35 patients iron kinetics with Fe-59 and cell volume with P-32
b) survival of red cells, white cells and platelets with P-32 diisopropylfluoro-phosphonate.
c) intermediary metabolism of glucose and uric acid with C-14 glucose and C-14 uric acid.
d) heart function with I-131 albumin.
e) Co-60 vitamin B-12 absorption.

(11) The metabolic turnover of zinc-65 was studied, using a total body counter. (1966.)

(12) a) I-131 Hippuran was compared with other renogram agents and found to have the higher renal excretion efficiency.
b) I-131 cholegrafin was used in 35 patients to measure plasma volume as a substitute for human serum albumin.
c) I-131 Rose Bengal was used to study hepatic blood flow compared with the colloidal gold-198 disappearance rate.
d) Sr-85 was used as a tracer for calcium metabolism. This is safer than Sr-90 and more available than Ca-47. (1959.)

(13) A radioisotope technique for measuring regional blood flow was utilized to measure the effect of ionizing radiation on the bowel in experimental animals. In humans the effect of ionizing radiation on the colon was studied in women receiving radiation therapy for carcinoma of the cervix. They were studied before radiation, immediately after radiation and 6-12 weeks after radiation when healing had occurred. In addition, other diseases of the colon such as ulcerative colitis and diverticulitis were investigated to find out if there were detectable disturbances in regional circulation. (1963-1968.)

(14) To evaluate the mechanisms controlling pulmonary circulation, studies were carried out in normal and pathologic subjects, in basal conditions and under various stimulations. The data confirmed the relationships previously found between pulmonary blood volume, stroke volume and total blood volume and provided new material for an integrated evaluation of mechanisms controlling the pulmonary circulation. (1960-1965.)

(15) See item (7).

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS12.002

Project Category: Metabolic and Physiological Studies

Funding Source(s): AEC

Institution(s): INEL

Principal Investigator(s): C. A. Hawley

Objective(s) of Project: To obtain quantitative information on the kinetics of radioiodine transport from the point of release to the atmosphere through the entire air-vegetation-cow-milk sequence in the human food chain.

Short Description: The preliminary experiment was conducted during May and June of 1963. The experiment was conducted near the southern boundary of the INEL (formerly the NRTS). Approximately one curie of Iodine-131 was released atmospherically, and deposited on pasture area downwind from the release point. Six dairy cows were placed on the contaminated pasture and seven human volunteers consumed portions of the resulting contaminated milk over an 18-day period.

During September 1964, approximately the same quantity and chemical form of Iodine-131 was atmospherically released to an area designated the Experimental Dairy Farm located on the INEL (approximately seven miles northeast of the Idaho Chemical Processing Plant). Three human volunteers were on the test area during the time of cloud passage and were later subjected to inhalation thyroid dose measurements.

During November 1965, the 1964 experiment was repeated using similar quantities and forms of Iodine-131 in the same area. Seven volunteers were seated in the test area next to high volume air samplers to correlate inhalation uptake with the amounts of iodine present in the air.

Follow-up Data: Due to the relatively short half-life of Iodine-131 (eight days) and the low thyroid doses received by the human volunteers (ingestion dose, range 230 to 630 mrad; inhalation dose, range 6.1 to 15 mrad) no follow-up data acquisition was considered necessary.

SUMMARY FACTSHEET HUMAN EXPERIMENTATION - SFS12.003

Project Category: Metabolic and Physiological Studies

Funding Source(s): AEC

Institution(s): INEL

Principal Investigator(s): C. W. Still

Objective(s) of Project: The determination of the metabolic fate of radionuclides ingested or inhaled by humans in good health, and calibration of both static and rotational scanning instruments for the direct in-vivo measurement at internally deposited radionuclides.

Short Description: Eight human volunteers were involved with the human studies endeavor, which consisted of thirteen individual experiments conducted during the period May 1965 to January 1972. All of the eight persons involved were employed by the ID-AEC, and all were associated with the Analytical Chemistry Branch of the Health and Safety Division. Four of the experiments involved inhalation of Argon-41 (a noble gas with a half life of 1.8 hours) and nine experiments resulted in the volunteers swallowing insoluble polyethylene capsules containing microcurie amounts of radioactivity.

Follow-up Data: The short half life of Argon-41 and its small residence time in the body resulted in very small radiation doses to the volunteers. The insoluble capsules required about 24 hours to pass through the body and produced very small doses due to the quantities of radioisotopes involved. As a consequence, no follow-up data acquisition was considered necessary.

12/20/85

HUMAN SUBJECT STUDIES

STUDY	FUNDING SOURCE	CONTRACT NO.	NAME OR TITLE	LEAD CONTRACTOR(S)	PNL, G.E. OR HEHF ROLE	START AND FINISH DATE IF KNOWN	PURPOSE AND APPROACH	SUBJECTS (NUMBER, AFFILIATION)	FOLLOW-UP
Tritium Absorption	AEC	W-31-109-Eng-52	N.K.	G.E.	G.E. responsible for all aspects	1951; only available information	Limited areas on forearm or abdomen of skin of human volunteers exposed to water vapor labeled with tritium through intact skin for radiation protection purpose. One subject exposed over whole body.	15 G.E. employee volunteers	None because of small rad dose to subjects
Radioiron Studies (two studies)	AEC	AT (45-1) -218	N.K.	U.W.	G.E. role was development of counting equipment for radiation	About 1952 start; about 1958 finish	Fe-55 and Fe-59 injected into normal volunteers and diseased patients and counted with equipment to quantitate and classify red cell production physiologically for clinical purposes.	About 20 normal volunteers; about 60-80 anemic patients	None
Prisoner Study	AEC	AT (45-1) -225 Task #6	The study of Irradiation Effects in the Human Testis, Including Histologic, Chromosomal and Hormonal Aspects	U.W.	GE and PNL role to check calibration equipment for exposure and to provide semen analysis for for sperm counts, morphology, etc.	August 1963 to December 1970	The purpose was to study testicular effects as a function of dose for radiation protection purposes. Approach was to expose volunteer inmates to various exposure levels of x-ray and study effects in terms of pathologic changes in biopsy specimens, sperm counts and morphology in semen specimens, etc.	Number not known at this time; subjects volunteer inmates of Walla Walla penitentiary.	N.K.

N.K. - not known

0008130

HUMAN SUBJECT STUDIES - continued

STUDY	FUNDING SOURCE	CONTRACT NO.	NAME OR TITLE	LEAD CONTRACTOR(S)	PNL, G.E. OR HEHF ROLE	START AND FINISH DATE IF KNOWN	PURPOSE AND APPROACH	SUBJECTS (NUMBER, AFFILIATION)	FOLLOW-UP
Heller Prisoner Study	AEC	AT (45-1) 1780	The Effect of Ionizing Radiation on the Male Reproductive System.	Pacific Northwest Research Foundation	No GE, PNL or HEHF involvement.	Started in August 1963. finished in May 1971	The purpose was to determine nature of cellular damage produced in the germinal epithelium of the testis, effects on sperm production and morphology, and recovery at different levels of radiation exposure. Approach was to irradiate testis with an x-ray source at different levels and study semen and tissue biopsy specimens.	Sixty-seven prisoner volunteers in the State of Oregon.	Follow-up continued until Dr. Heller suffered severe illness in 1972. Subsequent efforts to follow subjects were unsuccessful.
^{51}Cr Study	AEC	AT (45-1)-344	N.K.	UW	No GE involvement	Started about 1952. Completed about 1958.	The purpose was to study red cell viability in human subjects to evaluate blood preservatives. ^{51}Cr-tagged red cells were injected into normal volunteers in quantities equal to those used in blood volume determinations. Led to use of adenine as blood preservative.	About 50 normal volunteers at UW	N.K.

HUMAN SUBJECT STUDIES - continued

STUDY	FUNDING SOURCE	CONTRACT NO.	NAME OR TITLE	LEAD CONTRACTOR(S)	PNL, G.E. OR HEHF ROLE	START AND FINISH DATE IF KNOWN	PURPOSE AND APPROACH	SUBJECTS (NUMBER, AFFILIATION)	FOLLOW-UP
^{49}Ca Estimate of Body Calcium	AEC and Public Health Service	AT (45-1) 2046 and AM-09096	N.K.	U.W.	PNL performed earlier animal and cadaver studies and developed equipment for human study. Did not actively participate in human study.	Initiated in late 1960s. Ongoing clinical use.	The purpose was to develop a means of measuring total body neutron activation analysis in order to estimate calcium loss from bone in metabolic diseases. The approach was to develop a whole body counter appropriate to measurement of ^{49}Ca induced in the body by neutron activation.	Metabolic disease patients at UW. Procedure has been continued and is still in use.	Usual clinical follow-up
^{37}Ar Estimate of Body Calcium	NASA and AEC	NAS9-13019 and AT (45-1) 2225	N.K.	U.W.	PNL performed earlier animal studies and developed equipment for human studies. Did not participate in human study.	Start date unknown. Finish date about 1975.	The purpose was to develop a means of measuring total body calcium in vivo by the use of neutron activation analysis in order to estimate calcium loss from bone in metabolic diseases. The approach was to measure ^{37}Ar in the breath. The ^{37}Ar is produced by a reaction of neutrons with ^{40}Ca.	Sixteen of the above ^{49}Ca patients had breath tested for ^{37}Ar.	Usual clinical follow-up

HUMAN SUBJECT STUDIES - continued

STUDY	FUNDING SOURCE	CONTRACT NO.	NAME OR TITLE	LEAD CONTRACTOR(S)	PNL, G.E. OR HEHF ROLE	START AND FINISH DATE IF KNOWN	PURPOSE AND APPROACH	SUBJECTS (NUMBER, AFFILIATION)	FOLLOW-UP
P-32 Study	AEC	W-31-109-ENG-52	N.K.	GE	GE designed study, developed instrumentation and did measurements.	Started Dec. 1963. Completed Feb. 1964.	Purpose was to calibrate equipment for counting ^{32}P in order to estimate body burdens of people eating Columbia River fish. The approach involved counting beta emission from the head in patients and volunteers who were injected with known quantities of ^{32}P.	Three U of Oregon blood disease patients; two normal GE volunteers at Swedish Hospital in Seattle.	Follow-up for several weeks.
Technetium Study	AEC	AT (45-1) 1830	N.K.	PNL and UW	Volunteers were studied at UW and administered ^{95m}Tc and ^{96}Tc by UW physicians. PNL provided equipment, made whole body and excreta measurements and analyzed data.	Start July 1965. Finished September 1965.	Purpose was to study long-term retention and localization of Tc in humans after oral and intravenous administration and derive models for excretion. Relevant to medical and occupational needs. Approach to do body counts and measurements on excreta after both routes of administration.	Eight normal volunteers (unaffiliated).	Continued for 60 days.
Promethium Study	AEC	AT (45-1) 1830 DE-AC06-76RL 01837	N.K.	PNL and HEHF	HEHF physicians administered Pm and DTPA when used. PNL conducted all measurements and data analysis.	September 1967 start. Lasted one year.	Purpose was to study uptake retention, distribution and and excretion of promethium in the human and effectiveness of DTPA in its decorporation for radiation protection. Approach was to administer Pm orally and intravenously and do whole body counts and excreta measurements. Some were treated with DTPA.	Fourteen normal volunteers (local unaffiliated)	Follow-up for one year.

Department of Energy
Richland Operations Office
P.O. Box 550
Richland, Washington 99352

Dr. James S. Robertson, Director
Human Health and Assessments
Division, ER-73, HQ

CONGRESSIONAL INQUIRY INTO FOLLOW-UP STUDIES ON HUMAN RADIATION EXPERIMENTATION

In response to Charles DeLisi's memorandum of October 30, 1986, to Michael J. Lawrence, enclosed is the Richland Operations Office (RL) assessment of feasibility of obtaining follow-up information on studies funded through RL.

If we can be of any further assistance, please feel free to call me on FTS 444-7770 or Paula K. Clark of my staff on FTS 444-6681.

J. J. Sutey, Director
Site and Laboratory Management Division

SMD:PKC

Enclosure:
RL Assessment

0008134

bcc: SMD Off. file
SMD Rdg file
AMF Rdg file
PK Clark, SMD

Record Note: Response based on input from PNL and HEHF. Due to limited time for response, offsite principal investigators were not contacted. PNL provided information on prisoner studies

6-9363

SMD	SMD	PRO	OCC	COM	SMD
CLARK:MMW	JONES	LARSON	PRIDE	WHEELESS	SUTEY
11/4/86					

FEASIBILITY OF FOLLOW-UP OF HUMAN SUBJECTS

For studies funded through RL, a preliminary assessment was made of the feasibility of identifying, locating, and performing medical follow-up. The study category and project number were taken from the subcommittee staff report. To the extent possible in the time allowed, the following considerations were addressed:

1. Identifying Subjects

   Are the subjects identified in study records?

   What actions are necessary to locate and access such records? Where study records are no longer in existence, can the subjects be identified by recollection of investigators?

   Are there confidentiality agreements between investigator and investigating institutions and the subjects? Do such agreements present a potential barrier to identification or location?

   Information on individual studies is provided below. Further work would be required to identify and characterize any confidentiality agreements.

2. Locating subjects

   Are the whereabouts of the subjects known?

   What methods for locating the subjects might be employed?

   The location of very few subjects is currently known. Use of the services of companies that track subjects in epidemiology studies as a principal, ongoing company activity is the most effective means of locating former subjects when identified. In most cases, a properly identified individual can be located in this manner. Names of such companies can be provided.

3. Medical follow-up

   Ascertainment of disease history after locating subjects can be accomplished by the use of standard epidemiologic techniques, such as mailing individuals questionnaires to be completed (with follow-up if necessary) or conducting interviews with former subjects. Verification of the accuracy of medical information provided in this manner may be more difficult.

The relationship of estimated dose incurred as a result of the study to current annual occupational limits is addressed in some cases.

<u>Studies Conducted by Onsite Contractors</u>

Regarding the feasibility of follow-up for subjects in studies involving administration of tritium, ^{32}P, ^{143}Pm and of ^{95m}Tc and ^{96}Tc, the principal

uncertainty relates to the identification of the subjects. Locating human subjects many years after the studies can be accomplished in some of these cases by contacting currently active former associates of the subjects.

The following pertains to the four relevant studies:

Tritium Study (11.001, Number 112)

With regard to identification of subjects, about four subjects can be identified readily. For the remaining ten subjects, the General Electric Company can be queried as to the availability of their research notebooks for 1952 for the Hanford Biology Laboratory. If available, the relevant notebooks could be checked to see whether the names of subjects were recorded at the time. An alternative would be to contact the principal investigator for the study, who is no longer employed at Hanford, to learn whether he recalls or has records concerning the identity of subjects.

Regarding the need for such follow-up, the single total body exposure resulted in an intake of about 3.3 mCi of tritium. The ICRP-recommended annual limit on intake (ALI) for tritium is 3×10^9 Bq, or about 81 mCi. The subject's exposure, therefore, amounted to about 4 percent of an annual limit. The dose incurred was probably only about 0.1 rem because of large intake of water by the subject to speed excretion of the tritium (2 percent of the annual dose limit for workers). The other subjects had only limited skin exposure on the forearm or abdomen, which would have caused only a small fraction of the dose incurred in the case of the total body exposure.

Phosphorus-32 Study (12.001, Number 111)

The study involved three groups of individuals, consisting, respectively, of three patients at the University of Oregon Medical School, two Hanford volunteers who were injected and studied for calibration purposes at the Swedish Hospital in Seattle, Washington, and five volunteers who ate whitefish from the Columbia River.

The three medical school patients have been identified. It would be necessary to access the medical school records to obtain further information. However, the need for follow-up of the patients is questionable because the radionuclide was administered for medical therapy.

The two volunteers administered ^{32}P at the Swedish Hospital are identified. The radiation doses to the volunteers injected for calibration purposes were 0.025 rem to the bone, 0.009 rem to the liver, and 0.005 rem to the whole body. The respective annual exposure limits are 30 rem to bone, 15 rem to liver, and 5 rem to the whole body.

Two of the five volunteers who ate the whitefish have been identified, and there is a strong possibility that the others can be identified as well.

The amounts of ^{32}P in the subjects one day after eating the whitefish were 70, 110, 89, 72, and 93 nCi for an average of 87 nCi, which would give a total radiation dose of .005 rem to the bone, .002 rem to the liver, and

.001 rem to the total body.

Promethium Study (12.001, Number 110)

All subjects can be identified for the promethium project.

Estimated doses were 0.036 rem to the liver, 0.008 rem to bone, and 0.005 rem to the whole body in the case of injection of the promethium-143. In the case of ingestion, the dose to the upper large intestine was 0.038 rem and to the lower large intestine 0.077 rem. The annual occupational dose limits are 30 rem to bone, 15 rem to liver and intestine, and 5 rem to the whole body.

Technetium Study (12.001, Number 109)

The identity of the subjects will be available only if contained in University of Washington records. That source remains to be explored. The isotopes have relatively short half lives (4.3 days for ^{96}Tc and 60 days for ^{95m}Tc) and are rapidly eliminated from the body. The Maximum Permissable Body Burden (MPBB) is not applicable to acute ingested or injected doses; thus, it is inappropriate to compare administered quantities of radionuclides with MPBB. It is more appropriate to compare the total dose received with the annual occupational dose limit. The whole-body doses to the subjects were estimated to be about 0.145 rem in comparison to the annual occupational limit of 5 rem.

Testicular Irradiation (2.002 - Nos. 2 and 189)

The feasibility of any follow-up studies of the Oregon and Washington state penitentiary inmate volunteers who participated in testicular irradiation studies is diminished by the difficulty of locating a large number of the inmates. The studies were actually conducted by the Pacific Northwest Research Foundation of Seattle and by the University of Washington Medical School, and the deliverables required by AEC were the technical reports produced as a result of the studies. These reports did not include names. In November of 1984, RL was requested by Dr. Charles Edington to provide the names and current addresses of these subjects to OHER if they could be obtained.

No. 189

RL has no record of the names of the inmate volunteers at the Washington State Penitentiary. The principal investigator of the Washington study was unwilling to provide the names to RL in 1984. His position was that to do so would be unethical unless he received a formal written request from the person originally requiring the information (at that time the Congressional inquiry was from Rep. Ottinger). He did agree to consult with the state attorney general about a proper response if Dr. Edington would send a formal request. RL has no knowledge of whether the information was provided.

No. 2

RL does have access to records which allowed us to identify the Oregon inmate subjects. When RL asked the Oregon State Corrections Department to provide the last known addresses of these people, the request was refused because the Department was unwilling to violate official state confidentiality policy. The State agreed to tell RL only which individuals were still in the state prison system and to provide the date of release of those who were not. This information was forwarded to Dr. Edington with a memorandum dated November 19, 1984.

The following information with regard to follow-up and confidentiality is from DOE-EV-02405-3:

> Page 2 - "To insure complete protection (confidentiality of identity) of all subjects as required by federal human experimentation policies, all data has been re-coded, so no reference can be found which will in any manner identify any of the volunteers."
>
> Appendix B, Page 10 - From the consent form used: "I consent to the publication of the results of the project with the understanding that I shall not be personally identified." "I have been advised that I may withdraw my consent at any time."

(sent by electronic mail) Heller project

375-2461

August 20, 1984

TO: J. Robertson DOE1217

FROM: Sidney Marks, M.D.

SUBJECT: Congressional Response

Mavis Rowley has just informed me that the prisoners at the Oregon State Penitentiary in Salem were followed with regular examinations from the start of the study in 1963 until Dr. Carl Heller suffered a stroke early in 1973. The follow-up examinations were performed on inmates who remained in prison and on any discharged prisoners who were willing to return for the examinations. An assiduous effort was made to obtain such follow-up examinations on all subjects.

Subsequent to Dr. Heller's stroke, an effort was made to continue the follow-up program, but the prison authorities refused to enter into an arrangement with any other physicians, even if associated with the same organization. At that point, they apparently indicated that examinations by the prison physicians would suffice in following the health of the prisoners. They also had no interest in further examinations from a scientific standpoint.

Please call if you have any questions.

SM:gm
..SEND
.SEND

J.ROBERTSON -- Sent

¶OFF
Off

Keep this or send to storage.

0008739

Telecopy to Dr. C. W. Edington, DOE, GTN

Pacific Northwest Research Foundation
1102 Columbia Street
Seattle WA 98104

July 19, 1984

Dr. Sidney Marks
Battelle, Pacific Northwest laboratory
P. O. Box 999
Richland, WA 99352

Dear Dr. Marks:

Attached is a brief response to the request made by R. D. Larson in his letter of July 3, 1984.

Sincerely,

Mavis Rowley

MR:rs
Attachment

Page 1

TELEC O DR. C. W. EDINGTON, USDOE-GTN

0008740

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

The Effect of Ionizing Radiation on the Male Reproductive System.

Date Started: 1963
Date Terminated: 1972

Identification:
Principal Investigator(s): Carl G. Heller, M.D., Ph.D. (deceased)

Responsible Government Official(s):

Objective(s) of test:

SEE ATTACHED FOR NARRATIVE

Short description:

Follow-up data:

References:

Attachment(s):

0008741

ELECOPY TO

Objective(s) of test:

1) To determine the exact nature of the cytological defect produced in the development of the germinal epithelium and to relate the extent of the defect to dosage and time;

2) To find the minimal dosage that would affect the germinal epithelium;

3) To determine the time of recovery from any given dosage;

4) To determine whether the higher dosages given would lead to permanent damage of spermatogenic cells;

5) To determine the simultaneous effects of any dosage upon the Leydig cell cytology.

6) To determine the influence of any given dosage upon other parameters such as excretion of total gonadotropic hormone (FSH), lutenizing hormone (LH), estrogens and androgens;

7) To determine the influence of any given dosage upon plasma levels of FSH, LH and testosterone; and

8) To complete a statistical analysis of the results obtained.

Short Description:

In 1963 Dr. Heller initiated a project to determine the effects of graded doses of ionizing radiation upon the human male reproductive system. Actual irradiations were begun in August of 1963 using volunteers. Between 1963 and May of 1971 a total of 67 individuals received acute irradiation in varying doses.

During 1963, 1965 and 1967, ad hoc advisory/review committees were assembled by the Atomic Energy Commission to give overview and direction to this program.

Follow-up data:

After Dr. Heller's acute health failure in December of 1972, several proposals for longterm subject follow-up were presented.

Considerable discussion was held with various agencies about how contact with the volunteers could be maintained in order to allow a life time follow-up. No mechanism was found to allow or implement a long term contact.

BEST COPY AVAILABLE

References:

There have been numerous publications on this project and its findings beginning in 1963 and extending through 1974. The attached bibliography refers to many of them.

0008742

BIBLIOGRAPHY

1. C. G. Heller, G. V. Heller, and M. J. Rowley, Human spermatogenesis: An estimate of the duration of each cell association and of each cell type. III International Congress of Endrocrinology, June 30 - July 5, 1968, Mexico City, Excerpta Med. Found. Int. Congr. Ser. 184, 1012-1018 (1969).

2. C. G. Heller, F. Teshima and M. J. Rowley, Duration of transport of spermatozoa through the human male ductular system. Fert. Steril. 21, 390-396 (1970).

3. M. J. Rowley and C. G. Heller, Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant. Z. Zellforsch. 115, 461-172 (1971).

4. C. G. Heller, P. Wootton, M. J. Rowley, M. F. Lalli, and D. R. Brusca, Action of radiation upon human spermatogenesis. Excerpta Med. Found. Int. Congr. Ser. 112, 408-410 (1966).

5. E. F. Oakberg, Mammalian gametogenesis and species comparisons in radiation response of the gonads. In Effects of Radiation on Meiotic Systems, pp. 3-15. Int. Atomic Energy Agency, Austria, 1968.

6. M. J. Rowley, J. D. Berlin, and C. G. Heller, The ultrastructure of four types of human spermatogonia. Z. Zellforsch, 112, 139-157 (1971).

7. C. G. Heller, M. F. Lalli, J. E. Pearson, and D. R. Leach, A method for the quantification of Leydig cells in man. J. Reprod. Fert., 25, 177-184 (1971).

8. D. R. Brusca, J. M. Kastella, and C. G. Heller, Urinary testosterone excretion as an index of testicular secretion. In Proc. US Endrocinol. Soc., Chicago (F. G. Hofman and N. P. Christy, Eds.) p. 142. J. P. Lipincott, Philadelphia, Pennsylvania, 1966.

9. M. J. Rowley, D. R. Leach, G. A. Warner and C. G. Heller, Effect of graded doses of ionizing radiation on the human testis. Radiat. Res. 59, 665-678 (1974).

TELECOPY TO C. W. EDINGTON, USDOE-GTN

0008743

Complete copy

elle
hwest Laboratories
shington U.S.A. 99352
09) 375-2461

July 25, 1984

Mrs. Paula K. Clark
Administrator
PNL Programs Division
Richland Operations Office
Department of Energy
PO Box 550
Richland, WA 99352

Dear Paula:

I have enclosed PNL fact sheets relative to human experimentation conducted at the Hanford site in accordance with our earlier conversations. The fact sheet and cover letter for Dr. Heller's study as submitted by Mavis Rowley are enclosed.

I discussed with Dr. Finch of the University of Washington yesterday his submitted fact sheets concerning two studies conducted at the University in the 1950s. The additional information acquired during that conversation has been incorporated into the fact sheets, which are enclosed with the cover letter from Dr. Finch. In the first paragraph in his cover letter, Dr. Finch refers to two studies on iron absorption. However, he did not submit fact sheets for the two studies nor do the enclosed articles to which he refers cite any involvement of human subjects. He also has no recollection of using human subjects in the studies. They, therefore, fall outside the scope of this inquiry.

Dr. Paulsen will be unavailable to provide a fact sheet on his study until early in August. In the meantime, he communicated with me by telephone that he had made an effort to arrange for follow-up of the prisoner subjects but that both the subjects and the cognizant authorities felt that the subjects might be compromised by a follow-up procedure. Therefore, he was unable to develop and carry out a follow-up plan.

The enclosures comprise all materials collected to date. I will forward additional fact sheets as they are received.

Sincerely,

Sid

Sidney Marks, M.D.
Associate Manager
Environment, Health and
Safety Research Program

SM:lm

Enclosures

cc: W. J. Bair wo/enclosures
J. J. Fuquay wo/enclosures
R. P. Marshall wo/enclosures
W. R. Wiley wo/enclosures

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project involved study of absorption of tritium oxide through skin.

Date Started: 1951
Date Terminated: 1951

Identification: Unknown
Principal Investigator(s): Chester W. DeLong, Biology Laboratory, General Electric Company, Richland, WA
Responsible Government Official(s):

Objective(s) of test: To determine the rate of absorption of tritium oxide through the intact skin of man.

Short description: Fourteen human subjects were exposed over a small area ($\sim$ 10 cm^2) on the forearm or abdomen to a water-vapor atmosphere labeled with tritium oxide (HTO). A single human subject was similarly exposed over his total skin area while breathing uncontaminated air. Absorption of tritium oxide was estimated by measurement of tritium oxide subsequently excreted in the subjects' urine. The data from these experiments indicated a 4-fold greater absorption rate than that measured earlier in rats. These studies established the importance of the skin as a route of entry for tritium oxide and led to reductions in the allowable concentration of tritium oxide in air.

Follow-up data: No follow-up was conducted because of small dose to subjects (see Attachment 1).

References: DeLong, C. W., R. C. Thompson, and H. A. Kornberg, 1954, Percutaneous absorption of tritium oxide. Am. J. Roentgenol. Radium Therapy Nucl. Med. 71, 1038-1045.

Attachment(s): 1 - Memo of 06-22-84 from Roy C. Thompson to Sidney Marks.
2 - Copy of above reference.

DELETED

Battelle
Pacific Northwest Laboratories

Project Number

Internal Distribution

RECEIVED
JUN 22 1984
S. MARKS

Sent to Dr. Paul Cho
DOE-HQ 3/11/86

Date June 22, 1984

To Sid Marks

From Roy C. Thompson RCT

Subject HUMAN EXPERIMENTATION

The only experimentation on humans that I can recall having been done in the Biology Department since 1950 when I joined the Department, is that described in the attached reprint. These were studies of the absorption of tritium-labeled water through the intact skin. Fourteen human subjects (unidentified) were exposed over a small area (~10 cm^2) on the forearm or abdomen to a water vapor atmosphere labeled with tritium oxide; and a single subject (not identified, but known to be DELETED) was similarly exposed over his total skin area, while breathing uncontaminated air.

The purpose of these experiments was to determine the rate of absorption of tritium oxide through the intact skin. Studies had previously been done with rats as subjects. The human data indicated about a 4-fold greater absorption rate than that measured in rats, and were important in establishing the fact that respiratory protection alone was not adequate to protect workers exposed to tritium oxide. As a direct consequences of these studies, the allowable air concentration of tritium oxide was reduced by a factor of two.

Surviving records do not indicate the concentrations of tritium attained in the exposed subjects. It can be estimated from the data reported, however, that single total body exposure must have resulted in an intake of approximately 3.3 mCi of tritium. The ICRP-30 annual limit on intake (ALI) for tritium is 3×10^9 Bq or about 81 mCi. The experimental exposure therefore amounted to about 4% of an ALI, which should have delivered a total body dose

of about 200 mrem. The actual dose delivered was probably less than half of this, since the subject consumed large quantities of water to speed excretion of the tritium oxide. Similar estimates cannot be made for the other subjects, but their exposures, and consequent radiation dose, must have been very much lower than that of the total body exposure.

Because of the very low doses involved, no long-term follow-up was planned or performed.

RCT:pmb

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project involved study of metabolism of promethium in humans and effect of DTPA on metabolism and excretion

Date Started: Sept. 1967
Date Terminated: 1 year after start

Identification: Unknown

Principal Investigator(s): H. E. Palmer, Occupational and Environmental Protection Department, Pacific Northwest Laboratory (PNL), Richland, WA

Responsible Government Official(s):

Objective(s) of test: The study was conducted to determine the uptake, retention, distribution and excretion of promethium in humans following both oral and intravenous administration and to study the effectiveness of DTPA in removing promethium from the body. These considerations were relevant to possible exposure of plant personnel.

Short description: $^{143}PmCl_3$ was administered to 14 volunteers by physicians of the Hanford Environmental Health Foundation (HEHF). Whole body counting and excreta measurements were made by PNL for one year following administration of the ^{143}Pm. Six of the volunteers were also injected with DTPA at various intervals before and after the administration of the ^{143}Pm. Both the HEHF and PNL contributions to the study were funded by AEC.

Follow-up date: There was no follow-up after one year because of the low doses to the human subjects. The estimated doses were .036 rem to the liver, .008 rem to the bone, and .005 to the whole body for injection, and .038 rem to the upper large intestine, and .077 rem to the lower large intestine for the ingestion cases.

References: Palmer, H. E., Nelson, I. C. and Crook, G. H. "The Uptake, Distribution, and Excretion of Promethium in Humans and the Effect of DTPA on these Parameters," Health Physics 18, pp. 53-61 (1970).

Attachment(s): Stated reference.

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project was an investigation of the distribution and excretion of technetium in human subjects.

Date Started: July 1965
Date Terminated: 60 days after start

Identification: Unknown

Principal Investigator(s): T. M. Beasley and H. E. Palmer, Pacific Northwest Laboratory (PNL) and W. B. Nelp, University of Washington Medical School

Responsible Government Official(s):

Objective(s) of test: The study was conducted to measure the long-term retention and localization of technetium in humans following both oral and intravenous administration and to derive mathematical models for excretion, which are very useful in determining the radiation dose to humans from technetium isotopes in the body. They are important from both medical and occupational standpoints.

Short description: ^{95m}Tc and ^{96}Tc were administered to 8 subjects by physicians at the University of Washington Hospital in Seattle. The subjects were hospitalized at the University of Washington Clinical Research Center for the first week. Whole body counting and excreta measurements were made for 60 days. The University of Washington obtained and reimbursed the subjects for their services. The participation by PNL personnel was limited to providing the equipment, making the whole body counting and excreta measurements and analyzing the data. The PNL participation was funded by AEC but not the University of Washington participation.

Follow-up data: Follow-up continued for 60 days. Later follow-up considered unnecessary because of low dose to subjects (estimated to be 0.145 rem)

References: Beasley, T. M., Palmer, H. E., and Nelp, W. B., "Distribution and Excretion of Technetium in Humans," Health Physics 12, pp. 1425-1435 (1966).

0008750 Attachment(s): Stated reference.

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. The project involved the development and calibration of instrumentation for measuring ^{32}P in vivo at environmental levels.

Date Started: Dec. 1963
Date Terminated: Feb. 1964

Identification: Unknown

Principal Investigator(s): H. E. Palmer, Hanford Laboratory, General Electric Company, Richland, WA

Responsible Government Official(s):

Objective(s) of test: To determine the counting rate of a known quantity of ^{32}P as a result of ingestion of fish.

Short description: A calibration factor was needed for measuring the total body content of ^{32}P in people who consumed whitefish and other species of fish taken from the Columbia River during the period when nuclear reactor cooling water was emptied into the River. Five subjects were injected with ^{32}P. Three of the subjects injected were patients at the University of Oregon Medical School and received the ^{32}P as part of the therapy for blood diseases. The other two subjects were injected with very low levels of ^{32}P by physicians from the Swedish Hospital in Seattle for calibration purposes only.

Follow-up date: No follow-up because of low doses to volunteers. The doses to the two volunteers injected for calibration purposes were .025 rem to bone, .009 rem to liver and .005 rem to the total body.

References: H. E. Palmer. "Determination of ^{32}P in In Vivo." Health Physics 12, pp. 605-608 (1966).

Attachment(s): Stated reference

0008751

Pacific Northwest Research Foundation
1102 Columbia Street
Seattle WA 98104

July 19, 1984

Dr. Sidney Marks
Battelle, Pacific Northwest laboratory
P. O. Box 999
Richland, WA 99352

Dear Dr. Marks:

Attached is a brief response to the request made by R. D. Larson in his letter of July 3, 1984.

Sincerely,

Mavis Rowley

MR:rs
Attachment

0008752

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

The Effect of Ionizing Radiation on the Male Reproductive System.

Date Started: 1963
Date Terminated: 1972

Identification:
Principal Investigator(s): Carl G. Heller, M.D., Ph.D. (deceased)

Responsible Government Official(s):

Objective(s) of test:

SEE ATTACHED FOR NARRATIVE

Short description:

Follow-up data:

References:

Attachment(s):

0008753

Objective(s) of test:

1) To determine the exact nature of the cytological defect produced in the development of the germinal epithelium and to relate the extent of the defect to dosage and time;

2) To find the minimal dosage that would affect the germinal epithelium;

3) To determine the time of recovery from any given dosage;

4) To determine whether the higher dosages given would lead to permanent damage of spermatogenic cells;

5) To determine the simultaneous effects of any dosage upon the Leydig cell cytology.

6) To determine the influence of any given dosage upon other parameters such as excretion of total gonadotropic hormone (FSH), lutenizing hormone (LH), estrogens and androgens;

7) To determine the influence of any given dosage upon plasma levels of FSH, LH and testosterone; and

8) To complete a statistical analysis of the results obtained.

Short Description:

In 1963 Dr. Heller initiated a project to determine the effects of graded doses of ionizing radiation upon the human male reproductive system. Actual irradiations were begun in August of 1963 using volunteers. Between 1963 and May of 1971 a total of 67 individuals received acute irradiation in varying doses.

During 1963, 1965 and 1967, ad hoc advisory/review committees were assembled by the Atomic Energy Commission to give overview and direction to this program.

Follow-up data:

After Dr. Heller's acute health failure in December of 1972, several proposals for longterm subject follow-up were presented.

Considerable discussion was held with various agencies about how contact with the volunteers could be maintained in order to allow a life time follow-up. No mechanism was found to allow or implement a long term contact.

References:

There have been numerous publications on this project and its findings beginning in 1963 and extending through 1974. The attached bibliography references to many of them.

0008754

BIBLIOGRAPHY

1. C. G. Heller, G. V. Heller, and M. J. Rowley, Human spermatogenesis: An estimate of the duration of each cell association and of each cell type. III International Congress of Endrocrinology, June 30 - July 5, 1968, Mexico City, Excerpta Med. Found. Int. Congr. Ser. 184, 1012-1018 (1969).

2. C. G. Heller, F. Teshima and M. J. Rowley, Duration of transport of spermatozoa through the human male ductular system. Fert. Steril. 21, 390-396 (1970).

3. M. J. Rowley and C. G. Heller, Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant. Z. Zellforsch. 115, 461-172 (1971).

4. C. G. Heller, P. Wootton, M. J. Rowley, M. F. Lalli, and D. R. Brusca, Action of radiation upon human spermatogenesis. Excerpta Med. Found. Int. Congr. Ser. 112, 408-410 (1966).

5. E. F. Oakberg, Mammalian gametogenesis and species comparisons in radiation response of the gonads. In Effects of Radiation on Meiotic Systems, pp. 3-15. Int. Atomic Energy Agency, Austria, 1968.

6. M. J. Rowley, J. D. Berlin, and C. G. Heller, The ultrastructure of four types of human spermatogonia. Z. Zellforsch, 112, 139-157 (1971).

7. C. G. Heller, M. F. Lalli, J. E. Pearson, and D. R. Leach, A method for the quantification of Leydig cells in man. J. Reprod. Fert., 25, 177-184 (1971).

8. D. R. Brusca, J. M. Kastella, and C. G. Heller, Urinary testosterone excretion as an index of testicular secretion. In Proc. US Endrocinol. Soc., Chicago (F. G. Hofman and N. P. Christy, Eds.) p. 142. J. P. Lipincott, Philadelphia, Pennsylvania, 1966.

9. M. J. Rowley, D. R. Leach, G. A. Warner and C. G. Heller, Effect of graded doses of ionizing radiation on the human testis. [1] Radiat. Res. 59, 665-678 (1974).

UNIVERSITY OF WASHINGTON

School of Medicine
Department of Medicine
Hematology Research, ZD-20

July 17, 1984

Dr. Sidney Marks
Battelle, Pacific Northwest Laboratory
P.O. Box 999
Richland, WA. 99352

Dear Dr. Marks,

During the past twenty years, I don't believe we have had any support from the A.E.C. or Environmental Protection Agency. However, we have collaborated with Earl Palmer in studies of iron absorption, resulting in publication of two articles (#177 and #178). In addition we have recently begun to study iron absorption with a subcontract and loan of equipment for a total body counter. These studies in human subjects are being carried out in Bangkok. Protocols have been approved by our human subjects committee at the University of Washington.

Prior to 1964, we did have one or two contract with the Atomic Energy Commission. One of these had to do with blood preservation and the other with studies of radioiron quantitating erythropoiesis. I don't know the official names of these contracts nor do I know the exact time during which they were awarded. However, I have enclosed two fact sheets indicating the general information available.

Sincerely yours,

Clement A. Finch, M.D.
Professor of Medicine
University of Washington

0008756

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1952
Date Terminated: About 1958

Identification: Contract AT(41-5)-344

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Studies of blood preservation

Short description: This involves evaluation of red cell viability employing Cr-51 tagged cells in human subjects. Cr-51 tagged cells were injected in normal volunteers in quantities equal to those used clinically in blood volume determinations. The number of volunteers is not known but is believed to have been about 50 subjects. These studies led to the use of adenine as a blood preservative.

Follow-up data: None

References: See attached.

Attachment(s): List of publications.

Contract AT(41-5)-344

References:

Gabrio, B.W., Stevens, A.R., Jr., and Finch, C.A.: Erythrocyte Preservation. II. A Study of Extraerythrocyte Factors in the Storage of Blood in Acid-Citrate-Dextroxe. J. Clin. Invest. 33:247-251, 1954.

Gabrio, B.S., Stevens, A.E., Jr. and Finch, C.A.: Erythrocyte Preservation. III. The Reversibility of the Storage Lesion. J. Clin. Invest. 33:252-256, 1954.

Gabio, B.W., Hennessey, M., Thomasson, J. and Finch, C.A.: Erythrocyte Preservation. IV. In Vitro Reversibility of the Storage Lesion. J. Biol. Chem. 215:357-367, 1955.

Donohue, D.M., Motulsky, A.G., Giblett, E.R., Pirzio-Biroli, G., Viranuvatti, V. and Finch, C.A.: The Use of Chromium as a Red-Cell Tag. Brit. J. Haemat. 1:249-263, 1955.

Gabrio, B.W., Donohue, D.M. and Finch, C.A.: Erythrocyte Preservation. V. Relationship between Chemical Changes and Viability of Stored Blood Treated with Adenosine. J. Clin. Invest. 34:1509-1512, 1955.

Gabrio, B.W., Finch, C.A. and Huennekens, F.M.: Erythrocyte Preservation: A Topic in Molecular Biochemistry. Blood 11:103-113, 1956.

Donohue, D.M., Finch, C.A. and Gabrio, B.W.: Erythrocyte Preservation. VI. The Storage of Blood with Purine Nucleosides. J. Clin. Invest. 35:562-567, 1956.

Gabrio, B.W., Donohue, D.M., Huennekens, F.M. and Finch, C.A.: Erythrocyte Preservation. VII. Acid-Citrate-Dextrose-Inosine (ACDI) as a Preservative for Blood during Storage at 4°C. J. Clin. Invest. 35:657-663, 1956.

Donohue, D.M., Gabrio, B.W. and Finch, C.A.: Preservation and Transfusion of Blood. J.A.M.A. 161:784-788, 1956.

Hennessey, M., Finch, C.A. and Gabrio, B.W.: Erythrocyte Preservation. VIII. Metabolic Degradation of Nucleosides in Vitro and in Vivo. J. Clin. Invest. 36:429-433, 1957.

Donohue, D.M. and Finch, C.A.: An Animal Assay Method for the Measurement of Post-Transfusion Survival of Stored Blood. Vox. Sang.2:369-375, 1957.

Donohue, D.M., Gabrio, B.W., Huennekens, F.M. and Finch, C.A.:"The Metabolic Pathways of Purine Nucleosides and the Use of Inosine in Red Cell Preservation" in Int'l Soc. of Blood Transf. (Proc. of 6th Congress). Hollander L, ed. Karger Pub., Basel pp.290-293, 1958.

Lange, R.D., Crosby, W.H., Donohue, D.M., Finch, C.A., Gibson, J.G., II, McManus, R.J. and Stumia, M.M.: Effect of Inosine on Red Cell Preservation. J. Clin. Invest. 37:1485-1493, 1958.

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1955
Date Terminated: Same year

Identification: Contract AT(45-1)-218

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Application of radioiron to quantitation of erythropoiesis

Short description: Fe-55 and Fe-59 were injected in normal and diseased (anemic) subjects. The former are believed to have numbered about 20 and the latter about 60-80 subjects. The quantities used in AEC-sponsored studies were about 5-10 μCi. These studies led to a physiologic classification of red cell production.

Follow-up data: None

References: See attached.

Attachment(s): List of publications.

Contract AT(45-1)-218

References:

Giblett, E.R., Coleman, D.H., Pirzio-Biroli, G., Donohue, D.M., Motulsky, A.G. and Finch, C.A.: Erythrokinetics: Quantitative Measurements of Red Cell Production and Destruction in Normal Subjects and Patients with Anemia. Blood 11:291-309, 1956

Finch, C.A., Giblett, E.R., Donohue, D.M., Hurtado, A.V., Motulsky, A.G. and Reiff, R.H.: Quantitative Aspects of Erythropoiesis in Man. Trans. Assoc. Am. Phys. 69:149-154, 1956.

Sturgeon, P. and Finch, C.A.: Erythrokinetics in Cooley's Anemia. Blood 12:64-73, 1957.

Bothwell, T.H., Hurtado, A.V., Donohue, D.M. and Finch, C.A.: Erythrokinetics. IV. The Plasma Iron Turnover as a Measure of Erythropoiesis. Blood 12:409-427, 1957.

0008760

Battelle
Pacific Northwest Laboratories
P.O. Box 999
Richland, Washington U.S.A. 99352
Telephone (509) 375-2421
Telex 15-2874

August 10, 1984

Paula K. CIark
Richland Operations Office
U. S. Department of Energy
216 Federal Bldg.
Richland, WA 99352

Dear Paula:

I have enclosed the material regarding human experimentation just received from Dr. Paulsen. I believe that this completes our submission since I have received no communication from the University of Oregon and no further word from the University of Washington.

Sincerely yours,

Sidney Marks, M.D.
Associate Manager
Environment, Health and
Safety Research Program

SM:gm

Enclosure

0008761

RECEIVED
AUG 9 1984
S. MARKS

University
of Washington
School of Medicine

Population
Center for
Research in
Reproduction

Seattle
Washington 98195

August 6, 1984

Dr. Sidney Marks
Battelle Pacific Northwest Laboratory
P.O. Box 999
Richland, WA 99352

Dear Sidney:

Enclosed is the material on our AEC supported research that was requested. Sorry to be tardy.

If you require additional information beyond that listed in the questionnaire or require clarification, please let me know.

Finally, the issue of follow-up. There was considerable discussion regarding long-term follow-up. The consensus arrived at between the inmate volunteers and myself was as follows: (1) They did not want compulsory follow-up by law enforcement or governmental authorities by such means as Social Security numbers trace. This was considered an invasion of their rights. (2) They understood that I, as the responsible medical investigator, would be available to any volunteer that wished to see me regarding any health problem. To date, I have only seen a handful of such men in the past 14 years. During the study, we assisted the penitentiary in medical consults on men who were not on our program. Indeed, we arranged for extensive care in two men with serious medical problems unrelated to our program. I mention this to establish the fact that these actions on our part validated our credibility among the inmate population.

Best wishes.

Sincerely,

Alvin

C. Alvin Paulsen, M.D.
Professor of Medicine

CAP:gg
cc: Anne Woolf
Grant & Contract Services
University of Washington

Richard E. Berger
William J. Bremner
Donald K. Clifton
Edward M. Eddy
Charles H. Muller
C. Alvin Paulsen
Edward B. Perrin
Robert A. Steiner

0008762

FACTSHEET HUMAN EXPERIMENTATION

Project Name: The Study of Irradiation Effects on the Human Testis, including Histologic, Chromosomal and Hormonal Aspects

Date Started: 8/63
Date Terminated: 12/70

Identification: Contract #AT(45-1)225, Task Agreement #6
Principal Investigator(s): C. Alvin Paulsen, M.D.

Responsible Government Official(s):

Objective(s) of test: 1) To relate radiation dosage to changes in gonadal function, 2) to utilize the radiation gonadal changes as means for studying pituitary-testis interrelationships, 3) to explore therapeutic and medical protective measures with respect to gonadal irradiation, 4) to explore our current concepts concerning radiation dosage expressed in physical terms and their relation to biologic effects.

Short description: After appropriate baseline studies were performed, subjects received from 7.5r to 400r x-ray irradiation or sham irradiation to the testis only. Testicular biopsies were performed prior to and up to 6 years post-irradiation to assess changes in the germinal epithelium. Seminal fluid specimens were obtained at two-week intervals throughout the study and were analyzed for morphologic changes and changes in total number of sperm. Urine specimens were obtained monthly for evaluation of hormonal changes. Later when the techniques were available, serum LH was measured by radioimmunoassay. Studies of ultrastructure changes in testis tissue were performed using electron microscopy. Subjects were followed until hormonal values returned to normal levels and until sperm counts returned to normal ranges. Vasectomies were performed prior to discharge from the study to eliminate the possibility of defective offspring. Only individuals desiring vasectomy were accepted for the study; but in several instances the volunteers changed their mind and did not desire a vasectomy at the conclusion of the study. Subjects were informed in detail regarding the study and signed consent forms were obtained from subjects and from spouses if subjects were married. Subjects were prison inmates only, thus eliminating the possibility of conception during the study.

Follow-up data:

(see covering letter)

References: Attached is the publication list from our final technical report, dated January 31, 1973.

Attachment(s): covering letter
reference list

0008763

1901/4

Publications supported by this grant

AEC support has been directly involved in each of the publications and presentations listed below, although some are not a part of the AEC contract program. For example, establishment of the chromosome laboratory enabled us to study other aspects of reproductive physiology. Likewise, establishment of the radioimmunoassay and subsequent purchase of the gamma counter allowed us to utilize radioimmunoassay in other endocrine studies as well as in studies directly supported by this contract. Therefore, appropriate credit has been given to the contract for each of the following:

RLO-1781-1 The Determination of Size and Concentration of Human Sperm with an Electronic Particle Counter. D.L. Gordon, D.J. Moore, T. Thorslund and C.A. Paulsen. The Journal of Laboratory and Clinical Medicine, March 1965.

RLO-1781-2 Testicular Biopsy in Man. I. Effect upon Sperm Concentration. D.L. Gordon, Arnold B. Barr, J.E. Herrigel, and C.A. Paulsen, Fertility and Sterility, July 1965.

RLO-1781-3 Effect of X-Irradiation of Testis on Plasma Testosterone in Normal Male Volunteers (abst). C.A. Paulsen, D.L. Gordon, G.R. Halling, A. Barr and H.M. Gandy. Submitted but not presented, Second International Congress on Hormonal Steroids, Milan, Italy, May 1966.

RLO-1781-4 The Effects of X-Ray Irradiation on the Human Testis (abst). C.A. Paulsen. Society for the Study of Fertility, Cambridge, England, July 1966.

RLO-1781-5 Efficacy of Coulter Counter in Determining Low Sperm Concentrations. D.L. Gordon, J.E. Herrigel, D.J. Moore, and C.A. Paulsen. American Journal of Clinical Pathology, January 1967.

RLO-1781-6 Third Year Comprehensive Progress Report, Contract AT(45-1)-1781 March 1966.

RLO-1781-7 Premature Menopause XO/XX/XXX/XXXXX Mosaicism. D.L. Gordon, and C.A. Paulsen. American Journal of Obstetrics and Gynecology, January 1967.

0008764

RLO-1781-8 Klinefelter's Syndrome and Its Variants: A Hormonal and Chromosomal Study. C.A. Paulsen, D.L. Gordon, Richard W. Carpenter, H.M.Gandy, and W.D. Drucker. Recent Progress in Hormone Research, Vol. 24, 1968.

RLO-1781-9 Metabolism of Labelled ^{125}I-HCG by the Rat Ovary. D.H. Espeland, F. Naftolin, and C.A. Paulsen. Gonadotropins 1968, ed. E. Rosemberg, Geron-X, 1968.

RLO-1781-10 Comprehensive Progress Report, April 1969.

RLO-1781-11 Progress Report, An Addendum to Comprehensive Progress Report of April 14, 1969. Prepared March 10, 1970.

RLO-1781-12 Plasma and Urinary Follicle-Stimulating Hormone Levels in Oligospermia. John M. Leonard, Robert B. Leach, Margaret Couture, and C. Alvin Paulsen. J. Clin. Endocr. 34:209-14, 1972.

RLO-1781-13 Effects of X-Ray Irradiation on Human Spermatogenesis. T.W. Thorslund and C.A. Paulsen. From, Proceedings of the National Symposium on Natural and Man-Made Radiation in Space. Ed. E.A. Warman, NASA Document NAS No. 2440, Jan. 1972, pp. 229-232.

RLO-1781-14 Germinal Cell Loss During Human Spermatogenesis. Arnold B. Barr, Donald J. Moore and C. Alvin Paulsen. J. Reprod. Fert. 25: 75-80, 1971.

RLO-1781-15 Electron Microscopy of the Human Seminiferous Tubules. Oscar Vilar, C. Alvin Paulsen and Donald J. Moore. From: The Human Testis, Eds. Eugenia Rosemberg and C. Alvin Paulsen, Plenum Press, New York-London, 1970.

RLO-1781-16 Effects of HCG, HMG, HLH and HGH Administration on Testicular Function. C. Alvin Paulsen, Duane H. Espeland and Edward L. Michals. From: The Human Testis, Eds. Eugenia Rosemberg and C. Alvin Paulsen, Plenum Press, New York-London, 1970.

RLO-225-1 Progress Report and Request for Renewal (Terminal Period) 1970-71.

RLO-225-2 Final Progress Report of AEC Contract No. AT(45-1)-225, Task Agreement No. 6, January 31, 1973.

0008765

MAIL READ UNREAD

To: W.BAIR (DOE617)
Cc: J.ROBERTSON (DOE1217)
Cc: J.THIESSEN (DOE670)
From: J.ROBERTSON (DOE1217) Posted: Tue 21-Aug-84 13:09 EDT Sys 64 (3)
Subject: Reply to: CONGRESSIONAL RESPONSE

--More--

This is regarding Sid Marks' message re follow up in prisoner studies.
This will be useful to have in the record. Thanks much. Regards
JSR

Disposition: File
Filed

Disposition: L

Argument(s) must be specified (eg LINESIZE linmax).

Disposition:

(sent by electronic mail)

375-2461

August 20, 1984

TO: J. Robertson DOE1217

FROM: Sidney Marks, M.D.

SUBJECT: Congressional Response

Mavis Rowley has just informed me that the prisoners at the Oregon State Penitentiary in Salem were followed with regular examinations from the start of the study in 1963 until Dr. Carl Heller suffered a stroke early in 1973. The follow-up examinations were performed on inmates who remained in prison and on any discharged prisoners who were willing to return for the examinations. An assiduous effort was made to obtain such follow-up examinations on all subjects.

Subsequent to Dr. Heller's stroke, an effort was made to continue the follow-up program, but the prison authorities refused to enter into an arrangement with any other physicians, even if associated with the same organization. At that point, they apparently indicated that examinations by the prison physicians would suffice in following the health of the prisoners. They also had no interest in further examinations from a scientific standpoint.

Please call if you have any questions.

SM:gm
..SEND
.SEND

J.ROBERTSON -- Sent

¶OFF
Off

0008767

Battelle
Pacific Northwest Laboratories
P.O. Box 999
Richland, Washington U.S.A. 99352
Telephone (509) 375-4261
Telex 15-2874

September 6, 1984

Paula K. Clark
Energy Programs Division
Richland Operations Office
U. S. Department of Energy
216 Federal Building
Richland, WA 99352

Dear Paula:

I have enclosed a response from Dr. Wil Nelp to the DOE inquiry concerning human experimentation. I believe that this study falls into the class of excluded projects based on the criteria set forth in the memorandum of June 27, 1984, from C. W. Edington to M. J. Lawrence. The study discussed by Dr. Nelp involves the diagnostic use of neutrons as a radiation modality, which differs slightly from the diagnostic use of radiopharmaceuticals mentioned in the memo. However, it is a diagnostic rather than therapeutic technique.

In any event, the material in the letter is available for your consideration.

Sincerely,

Sid

Sidney Marks, M.D.
Associate Manager
Environment, Health and
Safety Research Program

SM:gm

Enclosure

CC: Marjorie Parker (wo/encl)

0008768

RECEIVED
SEP 4 1984
3. MARKS

UNIVERSITY HOSPITAL
UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

DIVISION OF NUCLEAR MEDICINE, RC-70

August 30, 1984

Sidney Marks, M.D.
Battelle, Pacific Northwest Laboratory
P. O. Box 999
Richland, WA 99352

Dear Dr. Marks:

I have received notification from our Grant and Contract Office and I have also talked to Marjorie Parker in Richland regarding your request for information on our previous contract with the A.E.C. that involved human experimentation.

The contract of pertinence was A.E.C.-AT(45-1)-2225. I do not have the contract files at the present time on this work; however, it is my recollection that this work was first funded in 1969 and sponsorship was concluded in approximately 1973.

The project involved total body neutron activation analysis. The first phases revolved around developing the techniques and during the last three years of the contract human subjects were studied by this method.

We originally studied females over the age of 35, most over the age of 55 and most with known bone wasting diseases, commonly osteoporosis. During the course of the AEC sponsorship it is my estimation we studied some 40 to 50 females in this category. We also studied chronically ill individuals suffering from kidney failure who were being treated by artificial kidney dialysis. In these individuals we studied their calcium balance using the techniques. I estimate that some 25 adult patients were studied in this category. The females were non-child bearing.

The procedure involved the exposure of the subjects to a uniform low flux high energy neutron field which delivered a maximum total body exposure of 200 millirads. Using a RBE of 10, we estimate the total body dose to be 2 rems, using a more conservative RBE of 3 or 4, it would make it slightly less than 1 rem.

These patients in the beginning had a one-year follow-up examination of the lens of the eye because of subtle concerns about cataract formation. They were not followed beyond that time for this specific purpose. We

had no long-term follow-up on these individuals. I think it is most unlikely that any of them have borne children and by all of our observations and calculations it would be most unlikely that any adverse effects could be attribtuted to these procedures due to the extremely low levels of radiation.

I am sorry I don't have more detailed data to provide but I think my recollection is reasonably accurate. If you have any further questions I would be happy to speak with you.

Most sincerely,

Wil B. Neip, M.D.
Professor of Medicine and Radiology
Head, Division of Nuclear Medicine

WBN:cf

cc: Grant and Contract Services

Pacific Northwest Research Foundation
1102 Columbia Street
Seattle WA 98104

July 19, 1984

Dr. Sidney Marks
Battelle, Pacific Northwest laboratory
P. O. Box 999
Richland, WA 99352

Dear Dr. Marks:

Attached is a brief response to the request made by R. D. Larson in his letter of July 3, 1984.

Sincerely,

Mavis Rowley

MR:rs
Attachment

0008771

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

The Effect of Ionizing Radiation on the Male Reproductive System.

Date Started: 1963
Date Terminated: 1972

Identification:
Principal Investigator(s): Carl G. Heller, M.D., Ph.D. (deceased)

Responsible Government Official(s):

Objective(s) of test:

SEE ATTACHED FOR NARRATIVE

Short description:

Follow-up data:

References:

Attachment(s):

0008772

Project Name: The Effect of Ionizing Radiation on the Male Reproductive System

Objective(s) of test:

1) To determine the exact nature of the cytological defect produced in the development of the germinal epithelium and to relate the extent of the defect to dosage and time;

2) To find the minimal dosage that would affect the germinal epithelium;

3) To determine the time of recovery from any given dosage;

4) To determine whether the higher dosages given would lead to permanent damage of spermatogenic cells;

5) To determine the simultaneous effects of any dosage upon the Leydig cell cytology.

6) To determine the influence of any given dosage upon other parameters such as excretion of total gonadotropic hormone (FSH), lutenizing hormone (LH), estrogens and androgens;

7) To determine the influence of any given dosage upon plasma levels of FSH, LH and testosterone; and

8) To complete a statistical analysis of the results obtained.

Short Description:

In 1963 Dr. Heller initiated a project to determine the effects of graded doses of ionizing radiation upon the human male reproductive system. Actual irradiations were begun in August of 1963 using volunteers. Between 1963 and May of 1971 a total of 67 individuals received acute irradiation in varying doses.

During 1963, 1965 and 1967, ad hoc advisory/review committees were assembled by the Atomic Energy Commission to give overview and direction to this program.

Follow-up data:

After Dr. Heller's acute health failure in December of 1972, several proposals for longterm subject follow-up were presented.

Considerable discussion was held with various agencies about how contact with the volunteers could be maintained in order to allow a life time follow-up. No mechanism was found to allow or implement a long term contact.

References:

There have been numerous publications on this project and its findings beginning in 1963 and extending through 1974. The attached bibliography references to many of them.

0008713

BIBLIOGRAPHY

1. C. G. Heller, G. V. Heller, and M. J. Rowley, Human spermatogenesis: An estimate of the duration of each cell association and of each cell type. III International Congress of Endrocrinology, June 30 - July 5, 1968, Mexico City, Excerpta Med. Found. Int. Congr. Ser. 184, 1012-1018 (1969).

2. C. G. Heller, F. Teshima and M. J. Rowley, Duration of transport of spermatozoa through the human male ductular system. Fert. Steril. 21, 390-396 (1970).

3. M. J. Rowley and C. G. Heller, Quantitation of the cells of the seminiferous epithelium of the human testis employing the Sertoli cell as a constant. Z. Zellforsch. 115, 461-172 (1971).

4. C. G. Heller, P. Wootton, M. J. Rowley, M. F. Lalli, and D. R. Brusca, Action of radiation upon human spermatogenesis. Excerpta Med. Found. Int. Congr. Ser. 112, 408-410 (1966).

5. E. F. Oakberg, Mammalian gametogenesis and species comparisons in radiation response of the gonads. In Effects of Radiation on Meiotic Systems, pp. 3-15. Int. Atomic Energy Agency, Austria, 1968.

6. M. J. Rowley, J. D. Berlin, and C. G. Heller, The ultrastructure of four types of human spermatogonia. Z. Zellforsch, 112, 139-157 (1971).

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FINCH PROJECTS
C backup

UNIVERSITY OF WASHIN

School of Medicine
Department of Medicine
Hematology Research, ZD-20

July 17, 1984

Dr. Sidney Marks
Battelle, Pacific Northwest Laboratory
P.O. Box 999
Richland, WA. 99352

Dear Dr. Marks,

During the past twenty years, I don't believe we have had any support from the A.E.C. or Environmental Protection Agency. However, we have collaborated with Earl Palmer in studies of iron absorption, resulting in publication of two articles (#177 and #178). In addition we have recently begun to study iron absorption with a subcontract and loan of equipment for a total body counter. These studies in human subjects are being carried out in Bangkok. Protocols have been approved by our human subjects committee at the University of Washington.

Prior to 1964, we did have one or two contract with the Atomic Energy Commission. One of these had to do with blood preservation and the other with studies of radioiron quantitating erythropoiesis. I don't know the official names of these contracts nor do I know the exact time during which they were awarded. However, I have enclosed two fact sheets indicating the general information available.

Sincerely yours,

Clement A. Finch, M.D.
Professor of Medicine
University of Washington

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4-East, Providence Hospital / 500 17th Avenue, C-34008 / Seattle, WA 98124 / Telephone: (206) 326-5521

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1952
Date Terminated: About 1958

Identification: Contract AT(41-5)-344

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Studies of blood preservation

Short description: This involves evaluation of red cell viability employing Cr-51 tagged cells in human subjects. Cr-51 tagged cells were injected in normal volunteers in quantities equal to those used clinically in blood volume determinations. The number of volunteers is not known but is believed to have been about 50 subjects. These studies led to the use of adenine as a blood preservative.

Follow-up data: None

References: See attached.

Attachment(s): List of publications.

Contract AT(41-5)-344

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INTRAERYTHROCYTIC ADAPTATION TO ANEMIA*

J. Torrance, Ph.D., P. Jacobs, M.D., A. Restrepo, M.D., J. Eschbach, M.D., C. Lenfant, M.D., and C. A. Finch, M.D.

Abstract The role of erythrocyte 2,3-diphosphoglycerate (2,3-DPG) in increasing the availability of hemoglobin oxygen in anemia was investigated. Measurements of 2,3-DPG and of oxygen dissociation (P_{50}) were carried out on 57 normal subjects and 114 subjects with anemia. Twenty normal nonsmoking males had a mean hemoglobin of 15.3 g per 100 ml, a mean DPG of 4.83 mM and a mean P_{50} of 27.1 mm of mercury. Twenty normal nonsmoking females had a mean hemoglobin lower by 2.6 g per 100 ml, a DPG higher by 0.5 mM and a P_{50} increased by 0.4 mm of mercury DPG. P_{50} rose progressively with decreasing hemoglobin concentrations. For each gram of hemoglobin fall, there was a DPG increase of about 0.23 mM and a P_{50} increase of about 0.30 mm of mercury. Increases in adenosine triphosphate also occurred but, because of the smaller amount involved, had less effect on the oxygen dissociation curve. A rise in inorganic phosphate level had no demonstrable effect, but in vivo pH changes appear of considerable importance. It was calculated that DPG-induced changes in hemoglobin affinity for oxygen may compensate for up to half the oxygen deficit in anemia.

ANEMIA, by lowering the oxygen-carrying capacity of the blood, reduces the supply of oxygen to tissues. However, the fact that symptoms resulting from anemia are often minimal or absent suggests the existence of mechanisms that compensate for the decrease in arterial blood oxygen content. One of these mechanisms involves a reduced affinity of hemoglobin for oxygen, mediated by an increase in red-cell 2,3-diphosphoglycerate (2,3-DPG).[1-3] The role of this mechanism in the adaptation to anemia is the topic of this report.

Methods

A total of 171 subjects were studied, 119 at sea level in Seattle, Washington, and 52 at 1550 meters in Medellin, Colombia. Medellin subjects were studied because local ecological conditions led to more severe anemia than in the North American patients; Medellin subjects consisted of seven normal males, 22 anemic males and 23 anemic females. The Seattle subjects consisted of 69 subjects with and 50 without anemia, the latter including 20 nonsmoking females and 30 male subjects — 20 nonsmokers and 10 who smoked 10 or more cigarettes daily. In all the anemic patients, the red-cell production rate was below twice the normal level as judged by the reticulocyte index. Of the Seattle patients with anemia, two subgroups of 20 each, all with hemoglobins less than 10 g per 100 ml, were selected for further comparison. One group had hypoproliferative anemia without renal disease and the other had chronic renal disease, all but two patients being under dialysis therapy.

Venous blood was collected and transferred into vacutubes containing 1 mg of heparin per milliliter of blood. In patients undergoing hemodialysis, samples were obtained immediately before dialysis. Hemoglobin concentration was determined as cyanmethemoglobin. A microhematocrit was read from capillary tubes after centrifugation on the Clay–Adams autocrit for 15 minutes at 14,490 × g. Reticulocytes were counted as the percentage of 2000 red cells. For estimates of the rate of erythropoiesis, the reticulocyte count was corrected on the basis of red-cell count and bone-marrow maturation time,[4] except that in patients with renal disease, a normal maturation time was assumed.

Abbreviations Used	
ATP:	adenosine triphosphate
2,3-DPG:	2,3-diphosphoglycerate
O_2-Hb:	oxygen hemoglobin
P_{50}:	oxygen dissociation
Po_2:	oxygen tension
TCA:	trichloroacetic acid

Red-cell extraction for phosphate partition was carried out within one hour and usually within 20 minutes after bleeding. For this purpose, 5 ml of ice-cold, 20 per cent trichloroacetic acid (TCA) was added to 2 ml of whole blood, and after centrifugation, 5 ml of supernatant fluid was taken for analysis. The TCA was removed by five extractions with 2 vol of diethyl ether, and the excess ether was evaporated with a stream of nitrogen; the extracts were then stored at −20°C. A modification of the procedure described by Robinson, Loder and de Gruchy[5] was used for separation of the extract into various fractions. The extract was diluted to twice its volume with distilled water and adjusted to a pH of 7 to 11 with dilute ammonia. The solution was then washed into a column of Dowex 1 × 8, 1 by 5 cm. The stepwise solutions shown in Table 1 were used to obtain their respective fractions. The total phosphate content of each fraction was determined by the method of Bartlett[6] and gave values of DPG

*From the departments of Medicine and of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington, and the Department of Internal Medicine, Universidad de Antioquia, Medellin, Colombia (no reprints of this article will be available).

Supported by a research grant (5-R01-HE-06242) from the U.S. Public Health Service, by training grants (T1-AM-5130 and AM-06741), by a grant (HE-12174) from the National Heart Institute and by the Boeing Employees' Medical Research Fund

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Table 1. Separation of Extract into Fractions.

Fraction	Eluant	Fraction Content
1	50 ml of water & then 50 ml of 0.2% hydrochloric acid	Inorganic phosphate from plasma & red cells, hexose monophosphate, adenosine monophosphate, reduced nicotine adenine dinucleotide & monophosphoglycerate
2	100 ml of 0.1 N ammonium chloride	Hexose diphosphate & adenosine diphosphate
3	200 ml of 0.2 N ammonium chloride	2,3-DPG
4	200 ml of 0.5 N ammonium chloride	ATP
5	100 ml of N hydrochloric acid	Unidentified phosphorus compounds

and adenosine triphosphate (ATP) similar to those reported by him.*

The oxygen-hemoglobin (O_2-Hb) dissociation curve was determined by the mixing technic,* in which oxygen saturation is predetermined by mixture of known amounts of fully oxygenated and fully deoxygenated blood and the oxygen tension (Po_2) of the mixture is directly measured by means of a Po_2 electrode. Hemoglobin affinity for oxygen taken from the O_2-Hb dissociation curve at pH 7.4 was expressed as the P_{50} (7.4) — that is, Po_2 in millimeters of mercury required for 50 per cent saturation of the blood with oxygen at pH = 7.4.

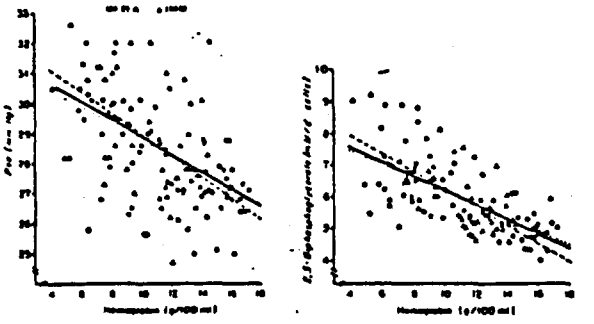

Figure 1. Relation between Hemoglobin Level and Affinity for Oxygen (P_{50}) (A) and between Hemoglobin Level and 2,3-DPG (B), in Seattle Subjects.

In this and in Figures 2 and 3 the triangles represent females, and the open circles males. The solid regression line is for the entire group, the dotted line for males, and the dashed line for females.

Table 2. Changes in Red-Cell Organic Phosphate Compounds in Normal and Anemic Subjects.

Subjects	No. of Subjects Studied	Hemoglobin*	DPG*	ATP*	P_{50}*	Fraction 2*	Fraction 5*
		g/100 ml	mMliter of cells	mMliter of cells	mm Hg	mMliter of cells	mMliter of cells
Seattle:							
Normal subjects:							
Male nonsmokers	20	15.32 ± 1.02	4.83 ± 0.33	0.87 ± 0.20	27.1 ± 0.8	1.12 ± 0.17	1.26 ± 0.26
Female nonsmokers	20	12.68 ± 0.96	5.28 ± 0.40	0.80 ± 0.17	27.5 ± 0.9	1.15 ± 0.16	1.22 ± 0.14
Male smokers	10	15.50 ± 0.94	5.14 ± 0.59	0.89 ± 0.19	27.0 ± 1.3	1.30 ± 0.10	1.33 ± 0.24
Anemic patients:	20	7.62 ± 1.50	6.62 ± 0.86	1.68 ± 0.40	29.1 ± 1.6	1.75 ± 0.53	2.08 ± 0.83
With uremia							
Without uremia	20	7.88 ± 1.38	6.77 ± 1.19	1.48 ± 0.45	30.2 ± 1.9	1.79 ± 0.71	1.95 ± 0.82
Medellin:							
Normal males	7	16.04 ± 1.18	5.48 ± 0.27	0.94 ± 0.09	26.5 ± 0.2	1.13 ± 0.13	0.96 ± 0.12
Anemic patients:	22	8.33 ± 2.35	7.45 ± 1.22	1.32 ± 0.37	28.9 ± 1.4	1.59 ± 0.46	1.37 ± 0.35
Males							
Females	23	7.04 ± 2.81	7.45 ± 1.64	1.32 ± 0.45	29.2 ± 2.3	1.64 ± 0.39	1.52 ± 0.56

*± 1 SD.

Results

The 20 nonsmoking normal males at sea level had a mean hemoglobin of 15.32 g per 100 ml, a mean DPG of 4.83 mM and a mean P_{50} of 27.1 mm of mercury (Table 2). In 20 nonsmoking females the mean hemoglobin was lower by 2.6 g per 100 ml, DPG was higher by 0.5 mM, and the P_{50} was increased by 0.4 mm of mercury. Ten smoking males showed a slight but insignificant increase in hemoglobin and DPG as compared to nonsmoking males. The relation between hemoglobin level and P_{50} (Fig. 1A) and between hemoglobin level and DPG (Fig. 1B) was plotted for the Seattle subjects. The same relation for Medellin subjects is shown in Figures 2A and B. In both groups of subjects there was a progressive increase in P_{50} and DPG as the hemoglobin level fell. In the renal and nonrenal subgroups composed of Seattle subjects with a hemoglobin of less than 10 g per 100 ml, there were similar mean hemoglobin levels, similar elevations in red-cell P_{50} and organic phosphate content (Table 2). As shown in Figures 3A and 3B, there was a close relation between red-cell DPG and P_{50} in both Seattle and Medellin subjects.

Anemia was associated with a rise in red-cell organic phosphates other than DPG as indicated by the regression equations relating the various

*Whole blood rather than washed red cells was extracted because the previously used washing procedure[2] caused a decrease in the recovery of DPG and ATP, and plasma does not contain organic phosphates.

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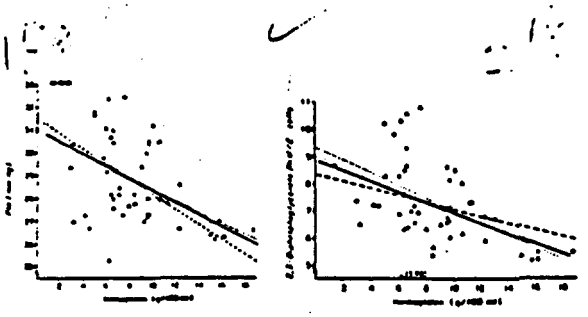


Figure 2. Data in Medellin Subjects.

Table 3. Regression Equations and Correlation Coefficients for All 171 Subjects Studied.

Regression Equation	Standard Error of Estimate	Correlation Coefficient*
Fraction 3 (DPG) = −0.244 hemoglobin + 8.88	± 1.03	−0.654
Fraction 4 (ATP) = −0.066 hemoglobin + 1.92	± 0.37	−0.541
Fraction 2 = −0.072 hemoglobin + 2.24	± 0.39	−0.555
Fraction 5 = −0.071 hemoglobin + 2.29	± 0.56	−0.418

*$p < 0.001$.

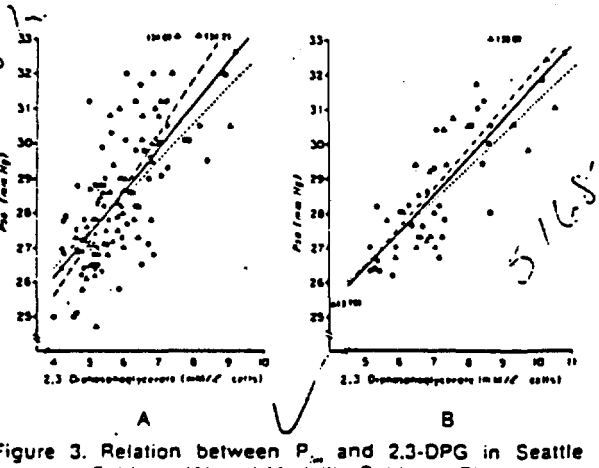
phosphate-containing fractions to hemoglobin concentration (Table 3). All fractions showed a significant correlation (p less than 0.001) with P_{50}. More than 80 per cent of the increased phosphate in the four fractions listed was accounted for by DPG and ATP. Although the percentage increase in red-cell ATP was actually greater than that of DPG, the ATP rise on a molar basis was less than a third of the DPG increase.

The possible relation between arterial pH and changes in red-cell organic phosphate level was evaluated in the Medellin female patients. Any change in pH values in these patients was incidental since they had been selected on the basis of anemia alone. That a relation existed between pH and 2,3-DPG is shown in Figure 4A. In view of this, an attempt was made to show the effect of pH alone by correction of each DPG level for the expected change related to anemia (Fig. 4B). A similar correction is made in the P_{50} level for expected changes related to anemia (Fig. 4C). It is seen that when the pH is 7.4, the changes in DPG and P_{50} are those expected from the degree of anemia; however, with acidosis, the changes in P_{50} and DPG failed to reach the level predicted whereas with alkalosis, the level of P_{50} and DPG exceeds the level predicted from anemia alone.

Discussion

There is convincing evidence that organic phosphate modifies the affinity of hemoglobin for oxygen.[1-3] This effect is evident when the P_{50} curve of hemoglobin in red-cell hemolysates is compared to that of hemoglobin stripped of its organic phosphates,[9] and in the P_{50} measurements on the organophosphate-depleted red cells of stored blood in vitro.[10] Of more physiologic importance is the demonstration that organic phosphates increase in vivo in response to hypoxia and that this rise is associated with a heightened availability of oxygen to tissues. A fall in blood oxygen content due to decreased oxygen loading at high altitudes was shown to be associated with a corresponding rise in both DPG and P_{50}.[7,11] In patients with cardiac disease associated with decreased cardiac output, compensatory increases in both DPG and P_{50} have been demonstrated.[12] The regulation of red-cell DPG content has thus come to be recognized as an important adaptive mechanism to combat tissue hypoxia.[12-14]

In the present study the effect of decreased concentrations of hemoglobin on DPG and P_{50} was examined over a wide range of hemoglobin concentration. The two groups investigated were considered separately, not because of the altitude differences, which had little effect, but because the determinations, although carried out by the same investigators, were under somewhat different laboratory conditions. Normal men and women provided a base line for comparison with anemic subjects. A higher mean DPG was found in females as compared with males in accord with two previous groups of subjects studied,[15-18] but at variance with one other.[16] Since the hemoglobin level in women



A B

Figure 3. Relation between P_{50} and 2,3-DPG in Seattle Subjects (A) and Medellin Subjects (B).

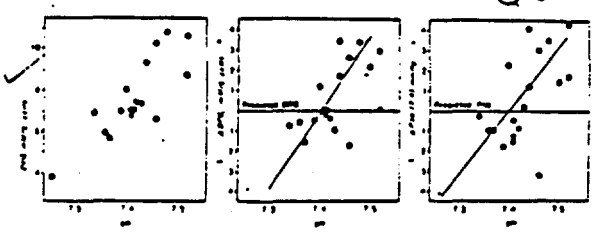


Figure 4. Effect of pH in Medellin Females.
In A DPG level is related to in vivo pH. In B the difference between actual DPG and DPG level predicted on the basis of the subject's hemoglobin concentration is related to in vivo pH.
In C the difference between actual P_{50} and that predicted from the DPG level is related to in vivo pH.

is lower than that in men, the reciprocal increase in DPG appeared consistent with the effect observed in subjects with greater degrees of anemia. The regression curves relating hemoglobin to DPG or P_{50} were similar in male and female anemic subjects.

Anemia is well known to be associated with a decreased affinity of hemoglobin for oxygen.[17-21] These increases are confirmed in the present study, and their interrelations with changes in red-cell organic phosphates are demonstrated. Thus, in the Seattle patients, for every gram per 100 ml of hemoglobin decrease, there is a DPG increase of about 0.23 mM and a P_{50} increase of about 0.30 mm of mercury. For each millimole increase in DPG, there was a corresponding rise of about 1.25 mm of mercury in the P_{50}. ATP was also increased, but on a molar basis was about a third of the DPG increase. Other organic phosphates in the red cell also increase with anemia, but since these increases are much smaller than those of DPG or ATP (Table 2), they probably have little effect in modifying hemoglobin affinity for oxygen.

The rise of these glycolytic intermediates is consistent with the fact that red-cell glycolysis is stimulated by deoxygenation.[22,23] It has been suggested that the Luebering–Rapoport shunt is an alternate to the conversion of 1,3-DPG to 3-phosphoglycerate and that reciprocal changes may occur between the levels of ATP and DPG.[24-26] However, our studies of normal subjects at high altitude[7] and of patients in cardiac failure[14] and the current report of people with anemia all demonstrate increases in both compounds and thus reflect an overall stimulation of glycolysis. This stimulation may be the result of a rise in deoxygenated hemoglobin, which, by binding more organic phosphate than oxyhemoglobin, lowers the free organic phosphate in the cell; alternately, it has been suggested that intracellular pH changes may affect the activity of red-cell enzymes and alter the DPG level.[27] However, there can be little doubt that when there is a rise in the relative amount of deoxygenated hemoglobin in venous blood, there is also a rise in red-cell organic phosphates.

Extracellular inorganic phosphate levels may also have a role in regulating red-cell glycolysis and thus in controlling the level of intermediate compounds such as ATP.[28] This effect was not demonstrable in the 20 patients with renal anemia (Table 2), in which, despite an average increase in plasma inorganic phosphate to 7.4 mM, no significant difference was found in ATP or DPG levels as compared to a similar group of patients with nonrenal regenerative anemia whose plasma inorganic phosphate levels were normal.

Undoubtedly, many variables influence the correlation between hemoglobin and DPG or P_{50}. Smoking, which is known to affect the P_{50} curve, was examined in a group of otherwise normal subjects (Table 2). Since the mean values for DPG and P_{50} in these smokers did not differ significantly from those of the normal subjects, smoking was not taken into consideration in the study of anemic subjects. Another possible cause of variation is the age of the red-cell population. Edwards and Rigas[29] found that young cells separated by centrifugation had a P_{50} of 33.5 mm of mercury as compared with 27 mm in older cells. Because of this observation, subjects with hemolytic anemia as defined by a reticulocyte output of more than twice basal values were excluded from the present study. Likewise, patients with enzyme and hemoglobin abnormalities associated with altered P_{50} were excluded.

Changes in pH are known to affect the P_{50} curve, a shift toward the right accompanying acidosis, and one toward the left accompanying alkalosis (the Bohr effect). Previous workers have also shown that severe acidosis causes a decrease, and alkalosis an increase in DPG.[30] Studies demonstrated such effects in patients in whom pH changes had not been suspected on clinical grounds (Fig. 4). Even though the response to pH change occurs almost instantaneously whereas that to DPG has a half-time of about six hours, the degree of correlation observed in this study is impressive and supports the fact that DPG concentration is subject to the combined effect of hemoglobin concentration and in vivo pH. The regulating effect of DPG thus appears to be the prime mechanism for modifying hemoglobin affinity in adjusting oxygen supply to tissue needs.

The importance of a shift in O_2-Hb dissociation curve in determining Po_2 tension in the tissue capillaries is shown in Figure 5. For instance, a subject with a hemoglobin concentration of 7.5 g per 100

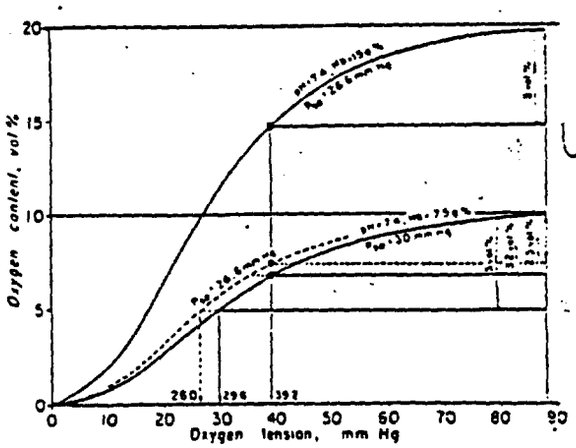


Figure 5. Effects of Anemia on P_{50}.

The normal curve is shown at the top, and the anemic curves below. The dashed line is the unshifted curve, and the solid line indicates the changes in affinity for oxygen observed. If venous oxygen remains at 39.2 mm of mercury, the shift in the curve permits an increased oxygen extraction from 2.5 to 3.5 vol per cent. If the required 5 vol per cent were extracted, oxygen tension would be at 29.6 vol per cent.

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ml and an unshifted curve would release only 2.5 vol per cent of oxygen to maintain a normal end-tissue capillary Po_2 of 39 mm of mercury. A shifted curve, as observed in these studies, yields an oxygen release of 3.2 vol per cent. A normal release of 5 vol per cent either requires an increase in cardiac output of 55 per cent above normal or a lowering in end-tissue capillary Po_2 to 29.6 mm of mercury. In the absence of a shift, the release of 5 vol per cent of oxygen would necessitate doubling the cardiac output or lowering further Pv_{O_2} to 26 mm of mercury. Thus, a shift of the O_2-Hb dissociation curve to the right explains the relatively slight increase in cardiac output and decrease in mixed venous Po_2 observed in anemic patients[31] as well as the minimal symptomatology of moderate anemia.

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FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1955
Date Terminated: Same year

Identification: Contract AT(45-1)-218

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Application of radioiron to quantitation of erythropoiesis

Short description: Fe-55 and Fe-59 were injected in normal and diseased (anemic) subjects. The former are believed to have numbered about 20 and the latter about 60-80 subjects. The quantities used in AEC-sponsored studies were about 5-10 μCi. These studies led to a physiologic classification of red cell production.

Follow-up data: None

References: See attached.

Attachment(s): List of publications.

Contract AT(45-1)-218

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171
178

PHYS. MED. BIOL., 1970, VOL. 15, NO. 3, 457–465

A Whole-Body Counter for Precision *In Vivo* Measurement of Radio-Iron

H. E. PALMER, M.SC.
Pacific-Northwest Laboratory, Battelle Memorial Institute, Richland, Washington

J. D. COOK, M.D.
Department of Medicine, University of Washington, Seattle, Washington

K. G. PAILTHORP, M.SC.
Pacific-Northwest Laboratory, Battelle Memorial Institute, Richland, Washington

and

C. A. FINCH, M.D.
Department of Medicine, University of Washington, Seattle, Washington

Received 28 *July* 1969

ABSTRACT. The *in vivo* counting system described accurately measures the absolute level of total body ^{59}Fe, regardless of body size or isotope distribution. Those results are accomplished by: (1) counting only the Compton scatter radiation omitted from the body rather than the full energy unscattered photons; (2) employing an optimum arrangement of multiple NaI crystal detectors; and (3) surrounding the subject with tissue equivalent plastic pellets. This counting system provides an accurate and efficient means for studying iron absorption or loss in man.

1. Introduction

During the past two decades, ^{59}Fe has been used extensively to measure body iron exchange in man. Its use requires a method that will accurately reflect the total body isotope content regardless of its distribution within the body. Whole-body counters can provide such a method provided the isotope reaches a constant distribution within the body and body size can be standardized or allowance made for differences. ^{40}K, ^{137}Cs and ^{24}Na are good examples of isotopes that can be measured reliably by most whole-body counters, regardless of the type of geometry or radiation detector used, because of their uniform body distribution. Other isotopes, such as ^{59}Fe and ^{65}Zn, do not reach a fixed distribution until one to several weeks after their administration. Thus, changes in counting efficiency may have occurred due to changes in self-absorption of γ-rays within the body. Warner and Oliver (1966) have described a whole-body counting method for ^{59}Fe in which errors due to absorption of γ-rays within the body were minimized by using two opposing collimated detectors and employing the combined count of the Compton scatter and photopeak region. Appreciable changes in detector responses still occurred, however, when comparing a localized with a distributed source of radio-activity.

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Our objective has been to develop a whole-body counter designed specifically for iron absorption measurements, using the principles of the Warner–Oliver counter but attempting to overcome the residual geometrical and self-absorption errors.

2. Preliminary studies

Several counter arrangements have been developed which give a constant count rate from a point source in air when placed in any position normally occupied by the body, but when the source is placed in various positions within a water-filled phantom, the count rates may vary by as much as a factor of two. However, studies with such a counter (Palmer and Langford 1967) show that if the Compton scatter region of the γ-ray spectrum is used, rather than the photopeak region which is normally used, the count rate becomes practically independent of the position of the source. Table 1 shows a comparison of counts in the Compton scatter region versus the photopeak region for a ^{137}Cs source (γ-ray energy = 0·662 Mev) placed in various positions from the centre to the outside of a 25·4 cm diameter phantom. All counts in the Compton scatter region were within ± 1·6%, whereas with photopeak energies, the count in the outside position was 83% higher than the centre.

Table 1. Comparison of count rate in Compton scatter region with that in photopeak region for a point source of ^{137}Cs in cylindrical water phantom

Source position	Compton scatter (counts/min)	Photopeak (counts/min)
Centre of phantom	67,662	30,919
Distance from centre: 2·5 cm	68,170	31,943
5·1 cm	68,357	34,343
7·6 cm	69,231	38,207
10·2 cm	69,453	44,572
12·7 cm	67,216	56,508
Average	68,348	39,398
Range	+1·6% −1·6%	+43% −22%

Since the body is more nearly elliptical in shape, an ellipsoidal water phantom was constructed from styrofoam plastic to provide phantom walls of low mass. The water-filled phantom had a minor axis of 22·9 cm, a major axis of 39·4 cm and was 30·5 cm high. Four 15·2 cm diameter by 10·2 cm thick NaI(Tl) detectors were placed around the phantom as shown in fig. 1; their optimum position was empirically determined such that a point source of ^{59}Fe placed anywhere in the phantom on a plane parallel to the centre of all four detectors

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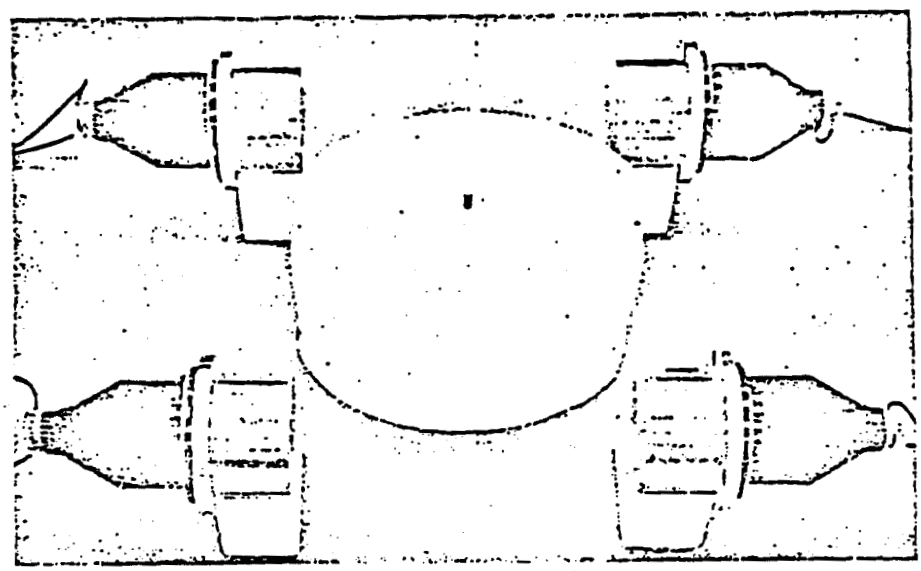

Fig. 1. Water phantom used to determine optimum crystal position.

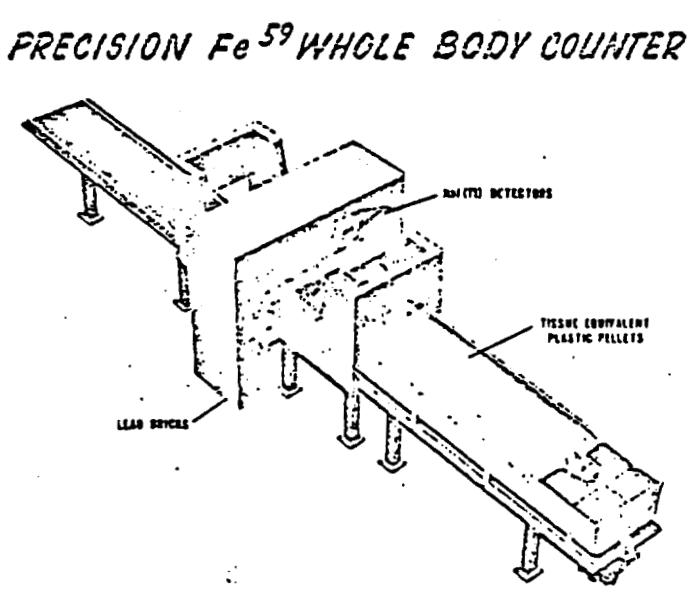

Fig. 2. ^{59}Fe whole-body counter demonstrating the use of Delrin plastic placed around the subject to obtain uniform thickness.

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gave the same count rate in the Compton scatter region. The optimum arrangement of the detectors for ^{59}Fe γ-rays is 43·2 cm between the faces of the two vertical sets of opposing detectors, and 38·1 cm between the sides of the detectors in the two horizontal sets.

3. Whole-body counter

The detectors in the arrangement described above were placed in a shadow shield type (Palmer and Roesch 1965) whole-body counter shown in fig. 2. Diagrammatic scale drawings of the detector and shielding configurations are shown in fig. 3. This counter was designed to minimize the required lead brick shielding. The subject is transported in a mobile carrier through and beyond the major viewing area of the detectors.

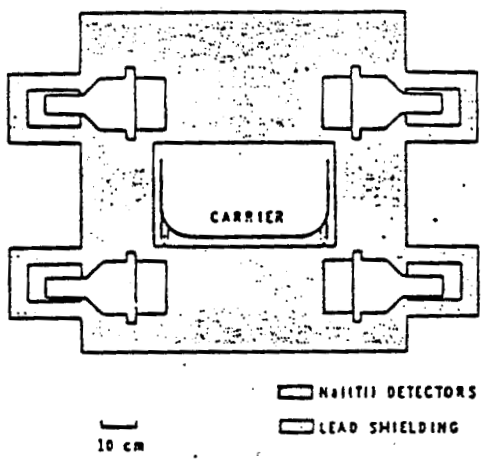

Fig. 3 (*a*). Scale drawing of detectors inside lead shielding (end view).

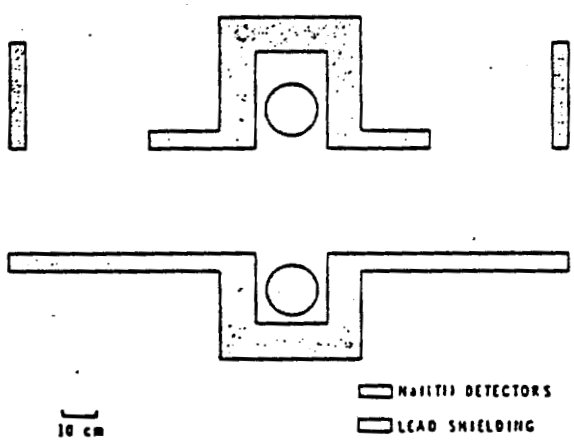

Fig. 3 (*b*). Scale drawing of a cross section of ^{59}Fe counter (side view).

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The shielding weighs about 5 tons. The centre section of 10·2 cm thick lead is 99·1 cm high, 40·6 cm wide and 91·4 cm long. The 5·1 cm thick shadow shielding extends out 61·0 cm from each side of the centre section and is constructed so that background γ-rays from the surrounding room cannot directly enter any of the detectors without going through at least 7·6 cm of lead. The opening through the lead bricks for the patient and carrier to pass through the counter is centred between the four detectors and is 50·8 cm wide and 30·5 cm high. The total length of the counter is 4·72 metres. The carrier is driven by a stepping motor and chain drive that is controlled by a constant speed pulser. When a multi-channel analyser is used, the speed can be controlled by pulses from the live time scaler of the analyser, so that errors caused by the dead time of the analyser are eliminated (Sheen, Palmer and Stringer 1967). The patient carrier is made of 0·32 cm thick aluminium, and the inside dimensions are 20·3 cm deep, 46·4 cm wide and 2·13 metres long. The radius of curvature of bottom corners of the carrier is 7·6 cm. The cost of the counter as shown in fig. 2 without the four detectors and counting instruments was about $3,000, and the cost of the detectors was approximately $10,000.

The rather small tunnel through which the patient travels during a traverse count has not presented any problems. However, the patients would feel less confined during the counting procedure if the tunnel dimensions were enlarged with the addition of more lead bricks to provide a proportional increase in shadow shielding.

4. Characteristics of the counter

The best results with patients would be expected if they were all of the same size and had the same general body contour. The same effect can be accomplished by layering small pellets of a heavy plastic called Delrin over the person until level with the top of the aluminium carrier. The small Delrin plastic has a density of 1·4 but the bulk density of the small 0·32 cm pellets is about the same as the human body. Delrin is a polymer of the molecule—OCH_2—and consists of 53% oxygen, 40% carbon, and 7% hydrogen. A point source of ^{59}Fe placed within a Delrin phantom provides a useful means of assessing the distributional effects of ^{59}Fe activity as they might occur *in vivo*. The Delrin can be easily poured in around the subject, and after counting it can be removed rapidly with a vacuum hose connected to a 40-gallon tank in which the Delrin is stored.

When a source of ^{59}Fe was placed anywhere in the Delrin-filled carrier, the accumulated count rate during a 10-minute traverse of the carrier was within $\pm 4\%$ for all positions in a Delrin thickness of 21·6 cm. This was similar to the results obtained earlier in the water phantom, even though the shape and width of the carrier were slightly different. Fig. 4 shows the relative count rate of the Compton scatter events as a point source is placed in various positions in a vertical cross section of Delrin pellets. This relatively constant counting rate occurs over the entire length of the Delrin-filled carrier, except at 10 cm

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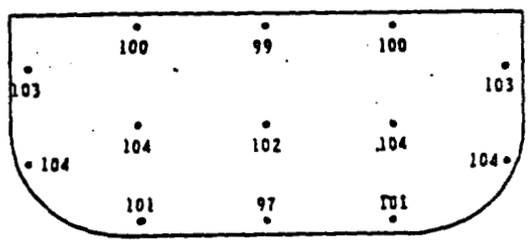

Fig. 4. Relative count rates obtained with different locations of a point source of ^{59}Fe in a vertical cross section of Delrin plastic pellets.

from each end where it begins to drop. 10 cm or more of Delrin on each end of the subject eliminates the end effect that would occur if ^{59}Fe in the top of the head or bottom of the feet did not have scattering material completely surrounding them.

Fig. 5 compares the γ-ray spectra of two measurements of a point source of ^{59}Fe placed at two extreme positions in Delrin. Curve A was obtained when the source was placed on top and near the side of the Delrin phantom, and curve B when it was in the centre. A large reduction in photopeak counts was obtained as the source was moved into the centre because of increased

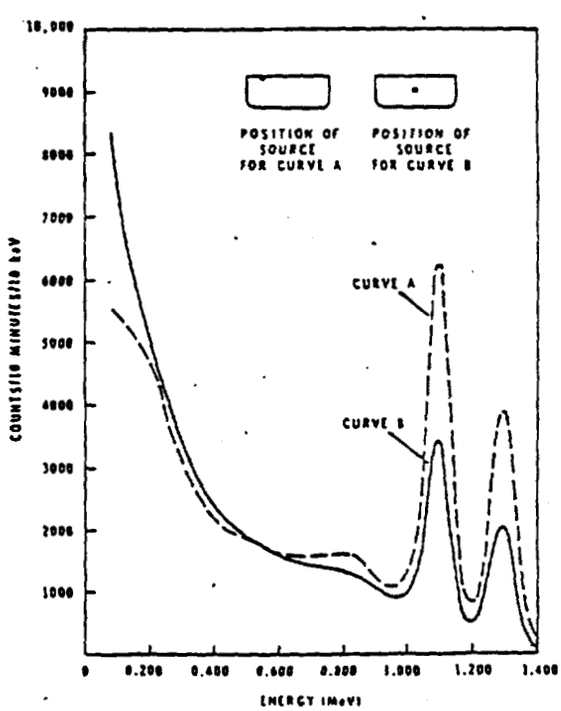

Fig. 5. Gamma-ray spectrum of ^{59}Fe from two different conditions of absorption by tissue equivalent material.

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absorption of the γ-rays, whereas the area under the Compton scatter region remained nearly the same. For the latter region, a slight reduction of counts in the region of 800 kev was offset by a comparable increase in counts below 500 kev, with the result that the integral count rate between 90 and 960 kev remained constant. This explains why the use of the Compton scatter photons provides a count rate that is independent of the location or distribution of the radioactivity.

Fig. 6 shows a spectrum from a 10-minute count of 1 μCi of ^{59}Fe in a human subject packed in Delrin after the background of the counter and the subject have been subtracted. The Compton scatter region of energy used in all studies includes all events between 90 and 960 kev and is shown by the shaded region of the spectrum. The 10-minute net count rate in the Compton scatter region was 144,000 with a background of 30,500, whereas the photopeak measurements gave values of 43,000 and 4,200 respectively. The standard

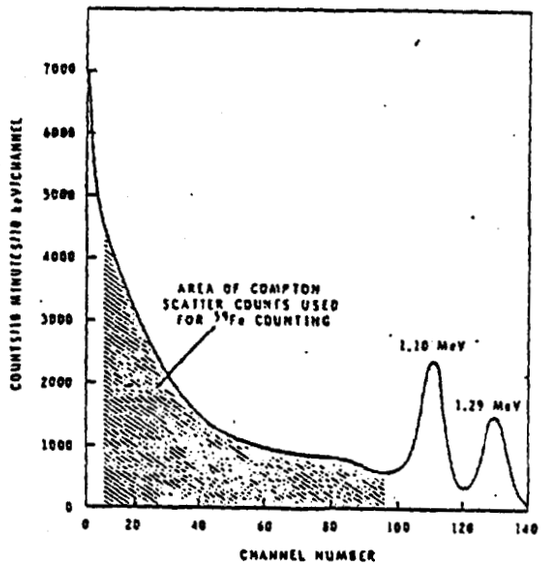

Fig. 6. Gamma-ray spectrum of a whole-body count in a subject containing 1 μCi of ^{59}Fe.

deviation of the net count, considering only counting statistics, is $\pm 0{\cdot}31\%$ and $\pm 0{\cdot}53\%$ for the Compton scatter counts and photopeak counts respectively. Therefore, the use of Compton scatter allows both greater absolute accuracy and precision for determining the total body content of ^{59}Fe. The background for Compton scatter count of a subject added from 1,500 to 2,000 counts to the counter Compton scatter background depending upon the body size. The counter background remained quite constant from day to day within a three-week period. Background counts measured during a 10-minute traverse on

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40 occasions over a one-month interval gave a standard deviation 2·2 times the value for a single background count as determined by the Poisson distribution for radioactive decay, indicating excellent day-to-day stability of counter background. To obtain count rates with low statistical error, a minimum ^{59}Fe whole-body activity of 0·20 μCi is required which gives a net whole-body count rate equal to the counter background and a standard deviation of $\pm 1\%$ for a standard 10-minute traverse.

5. Discussion

Several investigators have obtained improved whole-body counting results with different isotopes using the combined counts of the photopeak and scatter region or just the scatter region (Gibbs, Hodges and Lushbaugh 1966; Warner and Oliver 1966; Genna 1966; Dudley and ben Haim 1968; and Naversten, Lidén, Stahlberg and Norden 1969), and it has been suggested (Dudley and ben Haim 1968) that the majority of γ-rays emitted in the body with energies exceeding 1·0 Mev ultimately emerge from the surface although their energy may be reduced and their angular distribution altered by Compton collisions. Although this suggests that both photopeak and Compton events should be used, much more constant count rates can be obtained when only Compton scatter counts are used. Measurements on phantoms reported here indicate that the total body content of ^{59}Fe can be determined in any size person within a maximum error of $\pm 2\%$ when using the Compton scatter energy band. The application of this technique to γ-rays of other energies has not been investigated. The data shown in table 1 indicate that the method will work with γ-ray energies as low as 0·66 Mev, but a slightly different detector arrangement may be required.

The counter employed here is simple to use and requires rather unsophisticated instrumentation because of the broad band of photon energies used. We used a multi-channel analyser, but a single-channel analyser and scaler will adequately perform the counting. All whole-body counts can be compared directly with that of a standard with identical counting efficiency when placed in a Delrin phantom. Slight instrumental changes affect standard and subject comparably, so that the relationship between the two remains unchanged. Counter materials are relatively inexpensive and easily assembled. Like other types of shadow shield counters it can be disassembled and built up in a different location or can be mounted in a truck to service several locations.

Résumé

Compteur pour le corps entier, employé pour la mesure de précision du radio-fer *in vivo*

Le système pour le comptage *in vivo*, décrit dans ce mémoire, mesure avec précision le niveau absolu de ^{59}Fe contenu dans le corps entier, indépendamment de la grandeur du corps ou de la distribution de l'isotope. Ces résultats sont accomplis en: 1° comptant seulement la radiation diffusée de Compton, émise du corps plutôt que les photons non-diffusés avec énergie complète: 2° employant un arrangement optimum des détecteurs multiples au cristal de NaI; et 3° entourant le sujet de pastilles en matière plastique équivalente au tissu. Ce système de comptage fournit un moyen précis et effectif pour l'étude de l'absorption et de la perte de fer dans l'organisme humain.

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Zusammenfassung

Ein Ganzkörperzähler für genaue Messungen von Radio-Eisen *in vivo*

Das beschriebene System für Zählung *in vivo* misst genau das absolute Niveau des Gesamtkörper-^{59}Fe, unabhängig von der Körpergrösse oder der Isotopenverteilung. Diese Ergebnisse werden zustande gebracht, indem man: (1) nur die vom Körper ausgestrahlte Compton-Streustrahlung zählt, vielmehr als die ungestreuten Photonen mit voller Energie; (2) eine optimale Anordnung der vielfachen NaI-Kristalldetektoren anwendet; und (3) den Subjekt mit den gewebeäquivalenten Kunststoffpastillen umringt. Dieses Zählsystem beschafft ein genaues und effektives Mittel zum Studium der Eisenabsorption und -Verlust im Menschenkörper.

Резюме

Счетчик для измерения активности всего тела, применяемый для точного измерения радиоактивного железа *in vivo*

Описанная система для счета *in vivo* измеряет точно абсолютный уровень полного содержания ^{59}Fe в теле, независимо от величины тела или распределения изотопов. Эти результаты достигаются: (1) счетом одного только рассеянного комптоновского излучения, излучаемого телом, предпочтительно счету нерассеянных фотонов с полной энергией; (2) применением оптимального расположения большого числа детекторов с кристаллами NaI; (3) окружением субъекта тканеэквивалентными пластмассовыми шариками. Эта система счета предоставляет точное и эффективное средство для исследования поглощения или потери железа человеком.

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T.C. - Glenn Finch

^{51}Cr tagged cells
normal volunteers
About 50 subjects
Standard doses for blood volume

---

^{59}Fe - 55 & 59
~~[illegible]~~ 5-10 μCi
~~Longer [illegible] period~~
About 20 normal
60-80 anemia

0008794

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1955
Date Terminated: same year

Identification: Contract AT(45-1)-218

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Application of radioiron to quantitation of erythropoiesis

Short description: Fe-55 and Fe-59 were injected in normal and diseased (anemic) subjects. The former are believed to have numbered about 20 and the latter about 60-80 subjects. The quantities used in AEC-sponsored studies were about 5-10 Ci. These studies led to a physiologic classification of red cell production.

Follow-up data: None

References: See attached.

Attachment(s): List of publications.

0008795

#1

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

Date Started: About 1955
Date Terminated:

Identification: Contract AT(45-1)-218
Principal Investigator(s): C.A. Finch

Responsible Government Official(s):

Objective(s) of test: Application of radioiron to quantitation of erythropoiesis

Short description: These studies ~~lead~~ led to a physiologic classification of red cell production. Cr-51 tagged cells were injected in normal volunteers in quantities equal to those used clinically in blood volume determinations. The number of volunteers is not known but is believed to have been about 50 subjects. See other page #2

Follow-up data: None

References: See attached.

Attachment(s):

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#1

Fe-55 and Fe-59 were injected in normal and diseased (anemic) subjects. The former are believed to have numbered about 20 and the latter about 60-80 subjects. The quantities used in AEC-sponsored studies were about 5-10 μCi.

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#2

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

Date Started: About 1952
Date Terminated: About 1958

Identification: Contract AT(41-5)-344
Principal Investigator(s): C.A. Finch

Responsible Government Official(s):

Objective(s) of test: Studies of blood preservation

Short description: This involves evaluation of red cell viability employing ^{51}Cr Tagged cells in human subjects. These studies ~~lead~~ led to the use of adenine as a blood preservative.

Follow-up data: None

References: See attached.

Attachment(s):

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FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown.

Date Started: About 1952
Date Terminated: About 1958

Identification: Contract AT(41-5)-344

Principal Investigator(s): C. A. Finch

Responsible Government Official(s):

Objective(s) of test: Studies of blood preservation

Short description: This involves evaluation of red cell viability employing Cr-51 tagged cells in human subjects. Cr-51 tagged cells were injected in normal volunteers in quantities equal to those used clinically in blood volume determinations. The number of volunteers is not known but is believed to have been about 50 subjects. These studies led to the use of adenine as a blood preservative.

Follow-up data: None

References: See attached.

Attachment(s): List of publications. ~~Stated reference~~.

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P-32 project

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. The project involved the development and calibration of instrumentation for measuring ^{32}P in vivo at environmental levels.

Date Started: Dec. 1963
Date Terminated: Feb. 1964

Identification: Unknown

Principal Investigator(s): H. E. Palmer, Hanford Laboratory, General Electric Company, Richland, WA

Responsible Government Official(s):

Objective(s) of test: To determine the counting rate of a known quantity of ^{32}P as a result of ingestion of fish.

Short description: A calibration factor was needed for measuring the total body content of ^{32}P in people who consumed whitefish and other species of fish taken from the Columbia River during the period when nuclear reactor cooling water was emptied into the River. Five subjects were injected with ^{32}P. Three of the subjects injected were patients at the University of Oregon Medical School and received the ^{32}P as part of the therapy for blood diseases. The other two subjects were injected with very low levels of ^{32}P by physicians from the Swedish Hospital in Seattle for calibration purposes only.

Follow-up date: No follow-up because of low doses to volunteers. The doses to the two volunteers injected for calibration purposes were .025 rem to bone, .009 rem to liver and .005 rem to the total body.

References: H. E. Palmer. "Determination of ^{32}P in In Vivo." Health Physics 12, pp. 605-608 (1966).

Attachment(s): Stated reference

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Health Physics Pergamon Press 1966. Vol. 12, pp. 605–608. Printed in Northern Ireland

DETERMINATION OF ^{32}P *IN VIVO*

H. E. PALMER
Battelle Memorial Institute, Pacific Northwest Laboratory, Richland, Washington

(*Received* 11 *June* 1965; *in revised form* 14 *September* 1965)

Abstract—A transmission proportional counter and a NaI(Tl) scintillator, operated in coincidence for detection of ^{32}P beta rays emitted from the head, is better for *in vivo* measurements than a bremsstrahlung counter. The background is lower and is much less variable from person to person. Relatively little shielding is required. The ^{32}P body burdens of people who eat whitefish from the Columbia River near Hanford can be measured by this method.

FISH and waterfowl that feed in the Columbia River downstream from the Hanford reactors acquire some radionuclides that enter the river with the effluent water.[1] ^{32}P and ^{65}Zn are the principal nuclides found, and suckers and whitefish usually contain the greatest concentration of these nuclides. Since sportsmen obtain and eat the waterfowl and fish from the Columbia River below Hanford, a method of measuring the low level body burden of these nuclides in humans is needed. Since ^{65}Zn is a gamma emitter, body burdens down to 1 nc can easily be measured in a whole-body counter. FOSTER[2] has described an experiment in which a subject ate a weekly meal of whitefish and the accumulation of the ^{65}Zn in the body was studied. ^{32}P does not emit a gamma ray and it is much more difficult to measure. This paper describes a method by which body burdens of ^{32}P down to 40 nc can be measured.

Several reports have described the determination of ^{32}P in the human body by detection of bremsstrahlung.[3–5] The bremsstrahlung counter we have used is a 4½ in. diameter by 3 mm thick NaI(Tl) scintillator with a 0.001-in. thick aluminum window. Body burdens of ^{32}P down to 200 nc can be detected with it. The principal problem which prevents reliable measurements of lower body burdens is that it is impossible to distinguish between a bremsstrahlung photon and a low energy gamma ray or secondary photon. Therefore, the backgrounds of different people depend on their size, which influences the scattering of surrounding background radiation, and their body burden of gamma-emitting isotopes. Although significant improvement can be made by applying corrections for these two variables, the accuracy with which the individual subject background can be estimated is still the greatest limitation in low level bremsstrahlung measurement.

A typical spectrum obtained with this bremsstrahlung counter placed at the head of a subject containing about 1 mc of ^{32}P is shown in Curve A of Fig. 1. Some of this spectrum, however, is not due to bremsstrahlung. An absorber that absorbs beta rays but does not significantly absorb the bremsstrahlung produced Curve B of Fig. 1 when placed between the counter and the subject's head. Curve B is the true bremsstrahlung spectrum. The difference between A and B, Curve C, is the spectrum due to beta rays emitted from the surface of the head. The areas under curves B and C are equal, i.e. about the same number of counts are obtained from beta rays as from bremsstrahlung. This indicated that counting of only the beta rays should be investigated. If the background could be reduced sufficiently, the minimum detectable amount of ^{32}P might be even lower than for bremsstrahlung counting.

Counting the beta rays emitted through the skin may not work for other pure beta-ray emitters which are metabolized differently than phosphorus. Although phosphorus, like calcium, is associated with bone growth, it is also an

* This paper is based on work performed under U.S. Atomic Energy Commission Contract AT(45-1)-1830. Permission to publish is gratefully acknowledged.

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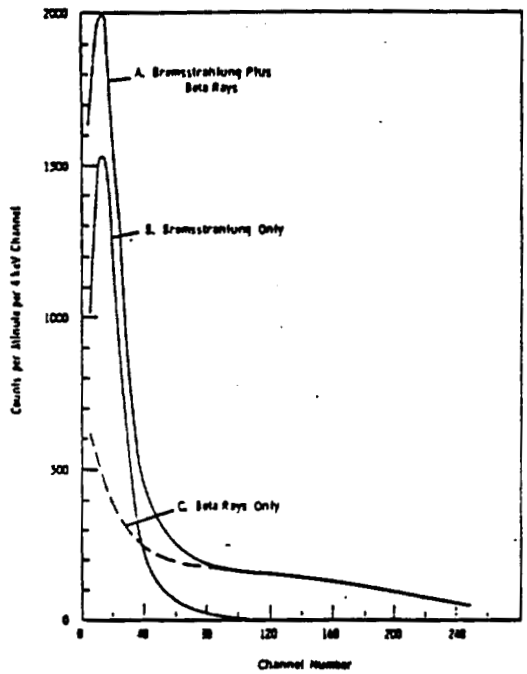

FIG. 1. Bremsstrahlung counter spectra.

essential component of all cells. The blood contains several different compounds of phosphorus. Much of the ^{32}P in the body is circulated in the blood stream and reaches the surface of the body. Deposits of ^{90}Sr on the outside of the skull could probably be measured since the skin and tissue covering the skull is thinner than the range of ^{90}Y beta rays. The low energy beta rays from ^{14}C have been detected from the ear of a mouse.[6]

To reduce the background during the detection of beta rays, we placed a transmission type proportional counter in front of the bremsstrahlung counter. This proportional counter was 1-× 6 × 6 in. and was divided into six small counters, each having a cross section of 1 in.^{2} and a length of 6 in., by means of ground wires. The thin windows were 0.008-in. Mylar plastic. The counter was operated as a flow counter using 90 per cent argon–10 per cent methane. The six anodes were connected together and in coincidence with the NaI scintillator. Figure 2 shows a sketch of the counter. With this arrangement a pulse in the NaI counter is analyzed only when the radiation causes a pulse in the proportional counter at the same time. This discriminates against gamma- and X-rays and counts every charged particle that enters both counters. Inside a good lead shield a large share of the background in the bremsstrahlung counter alone is due to relatively high energy gamma rays that scatter so as to leave only a little energy in the scintillator. The coincidence requirement eliminates this kind of background. Beta rays from the skin can go through the proportional counter with little trouble and are counted nearly as well as before in the NaI scintillator. A NaI scintillator is used rather than a plastic scintillator because the better resolution provides easy energy calibration with low energy photon sources.

The background of this coincidence counter, for 40 to 1000 keV pulses in the NaI, was 12 counts/min when operated in the Hanford iron room with a phantom head made of sugar. With the coincidence circuit turned off it was 130 counts/min. Typically, the coincidence rate was 20 counts/min when counting a subject containing only normal amounts of ^{40}K and ^{137}Cs. A pressed-wood beta absorber $\frac{1}{16}$ in. thick placed between the head and the counter reduced the rate to 15 counts/min, which is 3 counts/min above that of the phantom head. This indicates normal beta background from the head is about 5 counts/min, probably from ^{40}K beta rays. The other 3 counts/min are

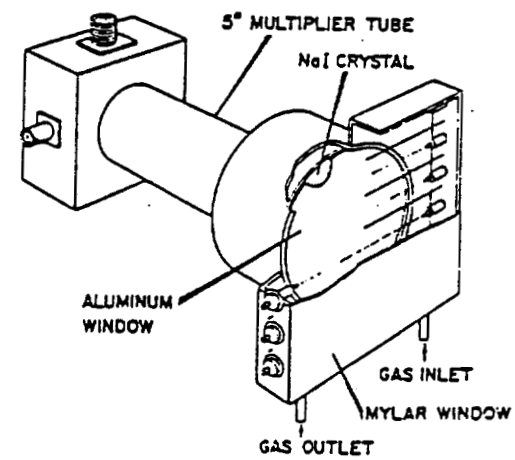

FIG. 2. Beta coincidence counter.

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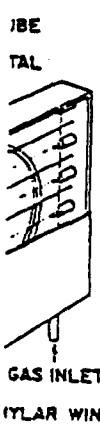

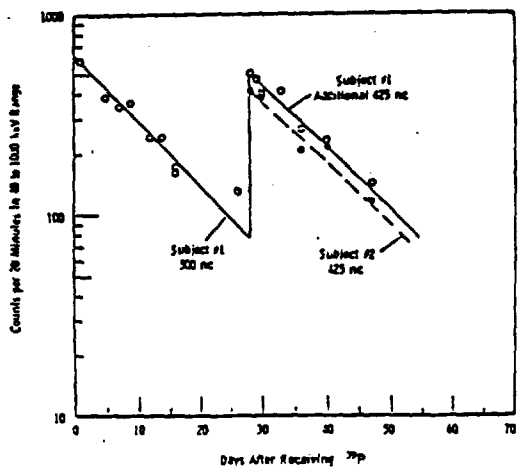

FIG. 3. Retention of low level burdens of ^{32}P.

probably due to Compton recoil electrons produced by gamma rays emitted from the body. The background due to higher than normal gamma radiation in a subject can be determined with the beta ray absorber over the counter. All normal subjects counted so far have had about the same beta ray counting rate, 4–5 counts/min.

The counter was calibrated with five subjects containing known amounts of ^{32}P. The average counting rate at the side of the head is 1.0 counts/20 min per nc of ^{32}P in the body. The range of rates was ± 15 per cent for the five subjects. Figure 3 shows the counts obtained for two subjects. They were studied for several weeks and one of the subjects was reinjected after 28 days. The effective half-life for ^{32}P was about 10 days; this agrees with previous results obtained with the bremsstrahlung counter at higher activity levels of ^{32}P. A detailed study of the influence of body size, excess fat, and different head shapes on the counting rate has not been made. The range of ± 15 per cent in counting rate was obtained from the five subjects who ranged in weight from 160 to 210 lb and in height from 60 to 69 in. For very small or very large people the counting rate per nc of ^{32}P in the body may vary more than 15 per cent. The detection limit for the counter is about 40 nc of ^{32}P at the 95 per cent confidence level. This is much better than the bremsstrahlung counter because the background is lower, shows much less variation from person to person and can be more accurately measured.

The coincidence counter has a higher counting rate over the head than over any other body extremity. In order to stay as far as possible from organs such as the liver, which concentrates potentially interfering isotopes such as ^{65}Zn, it is not used over the torso. Another advantage of using an extremity such as the head is that only that extremity and the counter need be shielded; an iron room is not needed. We found that the counting rate with the head and counter shielded with lead 2 in. thick (total weight 1000 lb) was the same as in the iron room. Such small and light-weight shielding requirements make it feasible to add such a counter to the Hanford Mobile Whole-Body Counter facility.[7]

One reason for developing a sensitive, *in vivo* counter for ^{32}P was to measure people who eat Columbia River fish. The significance of this intake with relation to the maximum permissible body burden has been discussed in another publication.[1] Five subjects ate $\frac{3}{4}$ lb each of whitefish which had been caught in the Columbia River. After allowing 1 day for absorption of the ^{32}P, the subjects were measured for 20 min with the coincidence counter and showed body burdens of 70, 110, 89, 72 and 93 nc. The amount of ^{32}P in the whitefish ingested by the first two subjects was not known but the last three ingested 110 nc. The standard deviation for the measured *in vivo* burdens was about 25 nc. The maximum permissible body burden for occupational exposure is 6000 nc. This counter is in use at the Battelle-Northwest whole-body counting facility and has been used in experiments on ^{32}P uptake from fish.

Acknowledgements—We are indebted to Dr. Oscood of the University of Oregon Medical School and to the Swedish Hospital in Seattle for allowing us to make measurements on people with known burdens of ^{32}P.

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2. R. F. Foster, Accumulation of ^{65}Zn from prolonged consumption of Columbia River fish, *HW-SA-3060* (1963).
3. H. E. Palmer, *Radiology* 78, 115 (1962).

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4. K. Liden, *Proc. 2nd Int. Conf. Peaceful Uses Atom. Energy* 23, 133 (1958).
5. H. E. Palmer, Determination of ^{32}P *in vivo*, *Hanford Radiological Sciences Research and Development Annual Report for* 1962, *HW*-77609 (1963).
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7. D. N. Brady and F. Swanberg, Jr., *Health Phys* 11, 1221 (1965).

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uran project

FACTSHEET HUMAN EXPERIMENTATION

Project Name: The Study of Irradiation Effects on the Human Testis, including Histologic, Chromosomal and Hormonal Aspects

Date Started: 8/63
Date Terminated: 12/70

Identification: Contract #AT(45-1)225, Task Agreement #6
Principal Investigator(s): C. Alvin Paulsen, M.D.

Responsible Government Official(s):

Objective(s) of test: 1) To relate radiation dosage to changes in gonadal function, 2) to utilize the radiation gonadal changes as means for studying pituitary-testis interrelationships, 3) to explore therapeutic and medical protective measures with respect to gonadal irradiation, 4) to explore our current concepts concerning radiation dosage expressed in physical terms and their relation to biologic effects.

Short description: After appropriate baseline studies were performed, subjects received from 7.5r to 400r x-ray irradiation or sham irradiation to the testis only. Testicular biopsies were performed prior to and up to 6 years post-irradiation to assess changes in the germinal epithelium. Seminal fluid specimens were obtained at two-week intervals throughout the study and were analyzed for morphologic changes and changes in total number of sperm. Urine specimens were obtained monthly for evaluation of hormonal changes. Later when the techniques were available, serum LH was measured by radioimmunoassay. Studies of ultrastructure changes in testis tissue were performed using electron microscopy. Subjects were followed until hormonal values returned to normal levels and until sperm counts returned to normal ranges. Vasectomies were performed prior to discharge from the study to eliminate the possibility of defective offspring. Only individuals desiring vasectomy were accepted for the study; but in several instances the volunteers changed their mind and did not desire a vasectomy at the conclusion of the study. Subjects were informed in detail regarding the study and signed consent forms were obtained from subjects and from spouses if subjects were married. Subjects were prison inmates only, thus eliminating the possibility of conception during the study.

Follow-up data: (see covering letter)

References: Attached is the publication list from our final technical report, dated January 31, 1973.

Attachment(s): covering letter
reference list

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Publications supported by this grant

AEC support has been directly involved in each of the publications and presentations listed below, although some are not a part of the AEC contract program. For example, establishment of the chromosome laboratory enabled us to study other aspects of reproductive physiology. Likewise, establishment of the radioimmunoassay and subsequent purchase of the gamma counter allowed us to utilize radioimmunoassay in other endocrine studies as well as in studies directly supported by this contract. Therefore, appropriate credit has been given to the contract for each of the following:

RLO-1781-1 The Determination of Size and Concentration of Human Sperm with an Electronic Particle Counter. D.L. Gordon, D.J. Moore, T. Thorslund and C.A. Paulsen. The Journal of Laboratory and Clinical Medicine, March 1965.

RLO-1781-2 Testicular Biopsy in Man. 1. Effect upon Sperm Concentration. D.L. Gordon, Arnold B. Barr, J.E. Herrigel, and C.A. Paulsen, Fertility and Sterility, July 1965.

RLO-1781-3 Effect of X-Irradiation of Testis on Plasma Testosterone in Normal Male Volunteers (abst). C.A. Paulsen, D.L. Gordon, G.R. Halling, A. Barr and H.M. Gandy. Submitted but not presented, Second International Congress on Hormonal Steroids, Milan, Italy, May 1966.

RLO-1781-4 The Effects of X-Ray Irradiation on the Human Testis (abst). C.A. Paulsen. Society for the Study of Fertility, Cambridge, England, July 1966.

RLO-1781-5 Efficacy of Coulter Counter in Determining Low Sperm Concentrations. D.L. Gordon, J.E. Herrigel, D.J. Moore, and C.A. Paulsen. American Journal of Clinical Pathology, January 1967.

RLO-1781-6 Third Year Comprehensive Progress Report, Contract AT(45-1)-1781 March 1966.

RLO-1781-7 Premature Menopause XO/XX/XXX/XXXXX Mosaicism. D.L. Gordon, and C.A. Paulsen. American Journal of Obstetrics and Gynecology, January 1967.

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RLO-1781-8 Klinefelter's Syndrome and Its Variants: A Hormonal and Chromosomal Study. C.A. Paulsen, D.L. Gordon, Richard W. Carpenter, H.M.Gandy, and W.D. Drucker. Recent Progress in Hormone Research, Vol. 24, 1968.

RLO-1781-9 Metabolism of Labelled ^{125}I-HCG by the Rat Ovary. D.H. Espeland, F. Naftolin, and C.A. Paulsen. Gonadotropins 1968, ed. E. Rosemberg, Geron-X, 1968.

RLO-1781-10 Comprehensive Progress Report, April 1969.

RLO-1781-11 Progress Report, An Addendum to Comprehensive Progress Report of April 14, 1969. Prepared March 10, 1970.

RLO-1781-12 Plasma and Urinary Follicle-Stimulating Hormone Levels in Oligospermia. John M. Leonard, Robert B. Leach, Margaret Couture, and C. Alvin Paulsen. J. Clin. Endocr. 34:209-14, 1972.

RLO-1781-13 Effects of X-Ray Irradiation on Human Spermatogenesis. T.W. Thorslund and C.A. Paulsen. From, Proceedings of the National Symposium on Natural and Man-Made Radiation in Space. Ed. E.A. Warman, NASA Document NAS No. 2440, Jan. 1972, pp. 229-232.

RLO-1781-14 Germinal Cell Loss During Human Spermatogenesis. Arnold B. Barr, Donald J. Moore and C. Alvin Paulsen. J. Reprod. Fert. 25: 75-80, 1971.

RLO-1781-15 Electron Microscopy of the Human Seminiferous Tubules. Oscar Vilar, C. Alvin Paulsen and Donald J. Moore. From: The Human Testis, Eds. Eugenia Rosemberg and C. Alvin Paulsen, Plenum Press, New York-London, 1970.

RLO-1781-16 Effects of HCG, HMG, HLH and HGH Administration on Testicular Function. C. Alvin Paulsen, Duane H. Espeland and Edward L. Michals. From: The Human Testis, Eds. Eugenia Rosemberg and C. Alvin Paulsen, Plenum Press, New York-London, 1970.

RLO-225-1 Progress Report and Request for Renewal (Terminal Period) 1970-71.

RLO-225-2 Final Progress Report of AEC Contract No. AT(45-1)-225, Task Agreement No. 6, January 31, 1973.

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TELE TO C. W. EDINGTON, USDOE-GTN

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FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project involved irradiation of testicles of inmates of Walla Walla State Penitentiary

Date Started: about 1963
Date Terminated: about 1966
Dates are available from Dr. C. A. Paulsen

Identification: Unknown.
Principal Investigator(s): Dr. C. Alvin Paulsen

Responsible Government Official(s):

Objective(s) of test: Study of radiation effects on spermatogenesis in human subjects after x-ray exposure.

Short description:

Staff of the Pacific Northwest Laboratory, Biology Department provided a limited support service to Dr. Paulsen, the principal investigator, by analyzing semen specimens for sperm counts, morphology, etc. The Laboratory did not participate in the design of the study, the arrangements for the use of human subjects or direct the exposure. [N subjects] [PN] A staff member did check the accuracy of exposimeter instruments used in measuring exposure by Dr. Paulsen's staff.

Follow-up data: Unknown

References: Unknown

Attachment(s): None

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Tritium project

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project involved study of absorption of tritium oxide through skin.

Date Started: 1951
Date Terminated: 1951

Identification: Unknown
Principal Investigator(s): Chester W. DeLong, Biology Laboratory, General Electric Company, Richland, WA
Responsible Government Official(s):

Objective(s) of test: To determine the rate of absorption of tritium oxide through the intact skin of man.

Short description: Fourteen human subjects were exposed over a small area ($\sim 10\ cm^2$) on the forearm or abdomen to a water-vapor atmosphere labeled with tritium oxide (HTO). A single human subject was similarly exposed over his total skin area while breathing uncontaminated air. Absorption of tritium oxide was estimated by measurement of tritium oxide subsequently excreted in the subjects' urine. The data from these experiments indicated a 4-fold greater absorption rate than that measured earlier in rats. These studies established the importance of the skin as a route of entry for tritium oxide and led to reductions in the allowable concentration of tritium oxide in air.

Follow-up data: No follow-up was conducted because of small dose to subjects (see Attachment 1).

References:

DeLong, C. W., R. C. Thompson, and H. A. Kornberg, 1954, Percutaneous absorption of tritium oxide. Am. J. Roentgenol. Radium Therapy Nucl. Med. 71, 1038-1045.

Attachment(s): 1 - Memo of 06-22-84 from Roy C. Thompson to Sidney Marks.
2 - Copy of above reference.

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1801/4

Battelle
Pacific Northwest Laboratories

Project Number_____

Internal Distribution

Date June 22, 1984

To Sid Marks

From Roy Thompson RET

Subject HUMAN EXPERIMENTATION

The only experimentation on humans that I can recall having been done in the Biology Department since 1950 when I joined the Department, is that described in the attached reprint. These were studies of the absorption of tritium-labeled water through the intact skin. Fourteen human subjects (unidentified) were exposed over a small area (~10 cm^2) on the forearm or abdomen to a water vapor atmosphere labeled with tritium oxide; and a single subject was similarly exposed over his total skin area, while breathing uncontaminated air.

The purpose of these experiments was to determine the rate of absorption of tritium oxide through the intact skin. Studies had previously been done with rats as subjects. The human data indicated about a 4-fold greater absorption rate than that measured in rats, and were important in establishing the fact that respiratory protection alone was not adequate to protect workers exposed to tritium oxide. As a direct consequence of these studies, the allowable air concentration of tritium oxide was reduced by a factor of two.

Surviving records do not indicate the concentrations of tritium attained in the exposed subjects. It can be estimated from the data reported, however, that single total body exposure must have resulted in an intake of approximately 3.3 mCi of tritium. The ICRP-30 annual limit on intake (ALI) for tritium is 3×10^9 Bq, or about 81 mCi. The experimental exposure therefore amounted to about 4% of an ALI, which should have delivered a total body dose of about 200 mrem. The actual dose

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delivered was probably less than half of this, since the subject consumed large quantities of water to speed excretion of the tritium oxide. Similar estimates cannot be made for the other subjects, but their exposures - and consequent radiation dose - must have been very much lower than that of the total body exposure.

Because of the very low doses involved, no long-term follow-up was planned or performed.

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Battelle
Pacific Northwest Laboratories

Project Number

Internal Distribution

Date June 22, 1984

To Sid Marks

From Roy Thompson

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Surviving records do not indicate the concentrations of tritium attained in the exposed subjects. It can be estimated from the data reported, however, that single total body exposure must have resulted in an intake of approximately 3.3 mCi of tritium. The ICRP-30 annual limit on intake (ALI) for tritium is 3×10^9 Bq, or about 81 mCi. The experimental exposure therefore amounted to about 4% of an ALI, which should have delivered a total body dose of about 200 mrem. The actual dose

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delivered was probably less than half of this, since the subject consumed large quantities of water to speed excretion of the tritium oxide. Similar estimates cannot be made for the other subjects, but their exposures - and consequent radiation dose - must have been very much lower than that of the total body exposure.

Because of the very low doses involved, no long-term follow-up was planned or performed.

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Pacific Northwest Laboratories

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Sent to Dr. Paul Cho DOE-HQ 3/11/86

Date June 22, 1984

To Sid Marks

From Roy C. Thompson RCT

Subject HUMAN EXPERIMENTATION

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of about 200 mrem. The actual dose delivered was probably less than half of this, since the subject consumed large quantities of water to speed excretion of the tritium oxide. Similar estimates cannot be made for the other subjects, but their exposures, and consequent radiation dose, must have been very much lower than that of the total body exposure.

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Pacific Northwest Laboratories

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RECEIVED
JUN 22 1984
S. MARKS

Sent to Dr. Paul Cho
205-HQ 3/11/86

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RCT:pmb

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PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE

BY

CHESTER W. DELONG, ROY C. THOMPSON AND HARRY A. KORNBERG

Reprinted from
The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine
Vol. LXXI, No. 6, June, 1954

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PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE*

By CHESTER W. DELONG,† ROY C. THOMPSON, *and* HARRY A. KORNBERG
Biology Section, Radiological Sciences Department, General Electric Company
RICHLAND, WASHINGTON

TRITIUM, the mass 3 radioactive isotope of hydrogen, promises to become a widely used tracer for hydrogen in biological and chemical studies. Hazards attendant on the handling of this isotope are limited to those from internal radiation, the energy of its beta particle being so weak (maximum energy, 0.0185 mev.) as to constitute no external radiation hazard. In part, then, the problem of hazard evaluation becomes one of studying the various portals through which tritium, or compounds containing tritium, may gain entry to the body. The present paper is concerned with the hazards arising from a tritium oxide contaminated atmosphere.

The two main portals through which atmospheric tritium oxide may enter the body are presumed to be the lungs and the skin. The contribution of pulmonary absorption to the total body uptake from an atmosphere of known tritium oxide content can be readily calculated on the assumption that all tritium oxide entering the lungs is absorbed. This assumption has been experimentally verified by several investigators.[7,12,19] The contribution from absorption through the skin must be measured experimentally. The present investigation was made to determine the rate of percutaneous absorption of tritium oxide, to compare this with the rate of pulmonary absorption, and to investigate the factors which might be important in determining or changing the rate of absorption. While principal attention was focused on absorption from the vapor state, experiments were also performed to compare the rate of absorption of liquid water.

To the extent to which tritium may be considered a legitimate tracer for hydrogen, the results of this study contribute to the general problem of the permeability of the skin to water. Positive proof of the inward passage of liquid water has only recently been reported.[22] A preliminary note on our demonstration of the percutaneous absorption of water vapor has appeared in the literature,[9] and a recent review by Pinson[18] alludes to unpublished studies on percutaneous absorption of tritium oxide performed at the Los Alamos Scientific Laboratory.

METHODS

Subjects and Exposure Procedures. Subjects employed were CF-1 strain mice, rats of the Sprague-Dawley strain, and human, adult, white males. Except for a single total body exposure of a human subject, all exposures were to a circumscribed skin area. Unless otherwise specified, exposures were for one hour at 30° C. Animals were exposed under nembutal anesthesia.

Two systems were employed for exposure of the skin to the tritium oxide-labeled water vapor. The first of these, illustrated in Figure 1, consisted of a small cup containing tritium oxide in water* supported above the skin inside of a containing chamber. This apparatus will be subsequently referred to as the "static" system. Because of inadequate saturation of the air in the system and because of the danger of spilling liquid tritium oxide solution on the skin, a second type of apparatus, illustrated in Figure 2, was employed for the major portion of the investigation. This "dynamic" system consisted of a hydrator into which dried air was passed, via a sintered glass gas dispersion tube, through a water solution of tritium oxide and thence into a connected exposure chamber in which the saturated vapor was passed over the skin and out into a dry ice trap. Control experiments

* It will be recognized that the proportion of tritium oxide in the water solutions was, masswise, extremely small, and that the molecular species present which contained tritium was almost exclusively HTO.

* This paper is based on work performed under Contract No. W-31-109-Eng-52 for the Atomic Energy Commission.
† Present address: The State College of Washington, Pullman, Washington.

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demonstrated that saturation in the dynamic system was maintained at 96 per cent of the theoretical values. In certain of the experiments in which the effect of vapor pressure was to be studied, the solution in the hydrating vessel contained varying proportions of dissolved sodium hydroxide.

The exposure chambers were held against the skin area by application of slight pressure. The juncture was sealed with collodion in early experiments, but this precaution was found to be unnecessary.

Areas exposed were as follows: human subjects, 9.8 cm.^{2} either on volar surface of forearm or on abdomen; rats, 6.6 cm.^{2} on abdomen; mice, 2.8 cm.^{2} on abdomen. The areas to be exposed on rats and mice were shaved a day prior to exposure, and any animal whose skin was nicked in the process was discarded. Exposed areas on human subjects were not shaved.

The total body exposure experiment was conducted in a gas-tight chamber approximately 4 feet on a side. Uncontaminated respiratory air was supplied under slight pressure through a nosepiece and mouthpiece. A continuous stream of tritium oxide-labeled water vapor was passed into the chamber at a rate of approximately 5 liters per minute. Exit air was passed through a large ionization chamber connected to a recording micro-microammeter. Because of the large volume of the exposure chamber it was impossible to maintain exactly constant conditions throughout the fifty-two minute exposure period. The concentration of tritium oxide in the chamber atmosphere varied from 3.7–4.8 μc/liter with a weighted average of 4.2 μc/liter. Temperature of the air averaged 30° C. and the relative humidity averaged 70 per cent.

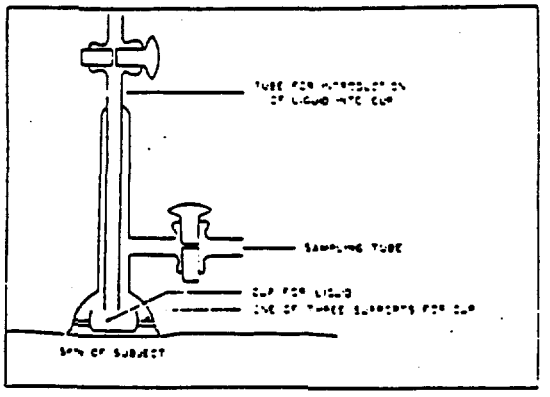

Fig. 1. "Static" skin exposure apparatus.

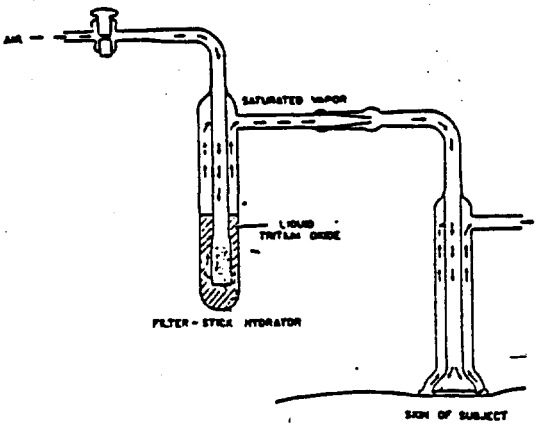

Fig. 2. "Dynamic" skin exposure apparatus.

The subject was unclothed except for loose-fitting shorts, and was perspiring freely during most of the exposure period.

Rats were exposed to liquid physiological saline containing tritium oxide by placing a 2 cm. layer of the liquid confined in the female end of a hemispherical glass joint over the skin area. Solutions employed were warmed to 30° C. before application. Following exposure, the liquid was carefully removed, the exposed area washed with detergent, thoroughly flushed under a tap, and then dried.

Sampling and Counting. Tritium oxide absorption was measured by analyzing samples of body water obtained by several different methods. Rats and mice were sacrificed following exposure, the carcasses ground, and total body water separated by azeotropic distillation with benzene. In the case of rats a cardiac blood sample was also taken immediately following exposure and analyzed as an indication of the rapidity with which absorbed tritium oxide is distributed in the body water. Sampling of human subjects was confined to a series of urine samples taken over a forty-eight hour period following exposure. The peak urine activity, attained several hours following exposure, was used in calculations.

Counting of the samples for tritium activity was accomplished by one or both of the following methods: (a) generation of hydrogen gas by addition of the water, blood serum, or urine sample to calcium metal and counting of the gas in a G. M. tube filled to atmospheric pressure and externally quenched; (b) addition of the sample to calcium carbide for conversion to

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acetylene, which gas was then introduced into an ionization chamber connected to a vibrating reed electrometer. The current produced was measured as a function of the length of time required to discharge a standard negative potential. Currently the hydrogen-filled Geiger counter has supplanted the vibrating reed electrometer because of ease and rapidity of operation and maintenance. Results obtained by either of these methods are reproducible with ±5 per cent. Absolute values may be subject to greater error due to uncertainties in the absolute calibration of the instruments and possibilities of slight isotopic fractionation in the generation of gas samples. Such absolute errors are not of significance in the present study, since all conclusions are based on comparisons of counts. Details of the counting procedure will be described by others.[10]

Expression of Results. Results are expressed in two forms. An absorption rate constant, K, is in units of μc tritium oxide absorbed per cm.² skin area per minute per μc/cc. of tritium oxide in the exposure atmosphere. In terms of experimentally determined quantities, this constant is calculated in the following manner:

$$K = \frac{UC_i}{AtC_e}$$

where U is the total volume of body water (liters), C_i is the activity of the body water (μc/liter), A is the area exposed (cm.²), t is the duration of exposure (minutes), and C_e is the activity of the exposure atmosphere (μc/cc.).

Results are also expressed as the quantity of water absorbed (in μg.) per minute per cm.² skin area. The symbol Δ is employed for this quantity which is calculated in the following manner:

$$\Delta = \frac{UC_i}{AtS}$$

where S is the concentration of tritium in the water employed, in μc/μg. This calculation, of course, assumes that tritium oxide functions as an ideal tracer for water, both in biological absorption and in the physical evaporation to form the saturated atmosphere. While this assumption cannot be strictly valid, error introduced by the assumption is no doubt smaller than other errors inherent in this type of study.

The values for total volume of body water were experimentally determined in the case of the rats and mice, and estimated at 61.8 per cent of total body weight in the case of the human subjects.[20]

The plus-or-minus limits listed with values of K and Δ are standard deviations of the mean at the 95 per cent confidence level.

RESULTS AND DISCUSSION

The results obtained from exposure of the various species to a saturated or near saturated water vapor atmosphere are recorded in Table I. Data for male and female rats and mice were calculated separately, but no sex difference was apparent and the results for both sexes were combined. The results obtained using the static exposure

TABLE I

PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE FROM A SATURATED OR NEAR SATURATED WATER VAPOR ATMOSPHERE AT 30° C.

Subject	Method of Exposure	Site of Exposure	Pre-exposure Treatment	No. of Subjects Exposed	Absorption Rate Constant for Tritium Oxide = K (μc/cm.²/min./μc/cc.)		Water absorption rate = Δ (μg./cm.²/min.)	
					Based on cardiac blood sample	Based on sample of total body water	Based on cardiac blood sample	Based on sample of total body water
Rat	Static	Abdomen	Unshaved	21	.018 ± .003	.055 ± .010	.55 ± .07	1.67 ± .31
Rat	Static	Abdomen	Shaved	25	.082 ± .017	.121 ± .026	2.59 ± .45	4.06 ± .54
Rat	Dynamic	Abdomen	Cloth covering (shaved)	24	.175 ± .029	.189 ± .035	5.31 ± .87	5.70 ± 1.06
Rat	Dynamic	Abdomen	Shaved	30	.134 ± .015	.188 ± .018	4.06 ± .46	5.70 ± .53
Mouse	Dynamic	Abdomen	Shaved	29	—	.67 ± .16	—	22 ± 5
Man	Dynamic	Forearm	Unshaved	12	—	.28 ± .05	—	8.6 ± 1.7
Man	Static	Abdomen	Unshaved	2	—	.34	—	10.4
Man	Dynamic	Total body	Unshaved	1	—	.84	—	17.8

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MICROFORMS

system are low to an uncertain degree for reasons previously discussed. They are included in Table I only for purposes of qualitative comparison. It should be noted that data published previously in a preliminary note[9] were obtained by the static method and are therefore not in agreement with the best values here reported. The "static" data from rats included in Table I do indicate quite clearly the enhanced absorption occasioned by shaving the exposed area.

In all cases the values of K and Δ calculated from cardiac blood samples are lower than the corresponding values calculated from samples of the total body water, indicating a lag in the distribution of the absorbed water. This effect was noted and studied more extensively with short-term exposures by Pinson.[15] With respect to the eventual body burden, however, the values based on samples of total body water are of primary significance, since uniform distribution of the absorbed activity must certainly occur within a period of time which is short compared with the biological half-life of tritium oxide in the body.

The experiment in which a series of rats were exposed with a layer of cloth covering the skin area was designed to evaluate possible effects of clothing on percutaneous absorption. The cloth employed was heavy cotton material of the type commonly found in laboratory coats and coveralls. No effect was observed on total absorption, as indicated by the K values calculated from total body water samples. There does appear to be an increase in the rate at which the absorbed activity appears in the circulation as evidenced by the values of K calculated from the cardiac blood samples.

The data from human subjects are characterized by a lack of agreement between the results obtained for different exposure sites. The agreement between the data from 12 subjects exposed on the forearm was quite good, considering the disparity in physiques and the consequent error in assuming a constant proportion of body water in all subjects. While the two exposures to the abdomen were made using the static system, the results are of qualitative interest, since they indicate a higher rate constant for the abdomen than for the forearm. The quantitative difference is undoubtedly greater than that indicated, since all of the data obtained with the static system were low compared with results obtained using the dynamic system.

The single total body exposure experiment indicates an absorption rate constant about three times as great as the constants calculated from forearm exposures. Several factors must be considered in evaluating this result. First, it is obviously unsafe to generalize too extensively from the results of a single exposure. Second, the conditions of this total body exposure were somewhat different from those which existed in the forearm exposures. While the forearm exposures were performed in an essentially saturated water vapor atmosphere, the average per cent saturation during the total body exposure was only 70 per cent. This difference, while influencing Δ values, should not affect K values, as will be shown in later discussion. Third, the subject involved in the total body exposure was one of the subjects included in the forearm exposure group, the K value from his forearm exposure being 0.23, thus strengthening the evidence for a real difference in absorption rate between different skin areas.

Pinson[15] has suggested that percutaneous absorption of water vapor could be looked upon simply as the reverse phase of the physiological phenomenon of insensible perspiration. If this is the case, and it appears entirely reasonable, then the extensive data previously collected on insensible perspiration should be pertinent to an understanding of percutaneous absorption. Table II lists some of the results obtained over the past thirty-five years, recalculated where necessary to a common basis of μg. water loss per cm.^{2} per minute. Where original data were given in terms of the total body surface an average skin area of 1.8 M^2 was assumed, and it was further

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TABLE II

INSENSIBLE WATER LOSS THROUGH THE SKIN
LITERATURE VALUES

Portion of Body	State of Skin	Rate of Loss (μg./cm.²/min.)	Environment	Reference	Year
Total body	Living	13	—	(21)	1917
Total body	Living	25–30	—	(15)	1931
Total body	Living	25	Liquid, 72° F.	(23)	1932
Index finger tip	Living	120	75° F.	(14)	1941
2nd toe tip	Living	79	50% rel. hum.		
Pinna	Living	32			
Leg	Living	15–20	28° C.	(17)	1942
Ball of foot	Living	180	75° F.	(3)	1943
Plantar surface, heel	Living	160	50% rel. hum.		
Palm	Living	150			
Index finger tip	Living	150			
Lateral surface, arm	Living	140			
Mid plantar, foot	Living	120			
2nd toe tip	Living	88			
Cheek	Living	71			
Mid forehead	Living	70			
Axilla	Living	62			
Posterior surface, leg	Living	53			
Thigh and flank	Living	41			
Mid epigastrium	Living	37			
Volar surface forearm	Living	29			
Epigastrium	Living and dead	100*	75° F.	(24)	1944
Epigastrium	Living and dead	100*	75° F.	(4)	1944
Total body	Living	16	75° F.	(5)	1945
Total body	Dead	9	50% rel. hum.		
Palm	Dead	29	24° C.	(6)	1946
Sole	Dead	18	70% rel. hum.		
Axilla	Dead	10			
Epigastrium	Dead	3.3			
Total body	Living	13	23° C. 51% rel. hum.	(8)	1948
Palm	Living	70–150	27° C.	(16)	1951
Sole	Living	50			
Face	Living	40			
Arm, leg and trunk	Living	7			

* These studies indicate a maximum rate, since dried O_2 was passed over the skin.

assumed that 52 per cent of the total insensible water loss was via the lungs.[5] These figures represent net water loss and constitute the balance between the outward and inward movement of water through the skin. As such, they bear no necessary relationship to the magnitude of either of these individual processes. If, however, the

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TABLE III

EFFECT OF WATER VAPOR PRESSURE ON PERCUTANEOUS ABSORPTION OF TRITIUM OXIDE

Expt. No.	NaOH Molarity	Theoretical		Experimental		No. of rats exposed	K ($\mu c/cm.^2/min./\mu c/cc.$)	Δ ($\mu g./cm.^2/min.$)
		Vapor pressure (mm. Hg)	Conc. of $T = C_v$ ($\mu c/cc.$)	Vapor Pressure (mm. Hg)	Conc. of $T = C_v$ ($\mu c/cc.$)			
1	0	31.8	7.57	30.5	7.28	32	.188 ± .018	5.70 ± .53
2	8	19.4	4.44	20.3	4.65	11	.186 ± .033	3.39 ± .59
3	13	10.7	2.39	10.5	2.34	11	.158 ± .044	1.51 ± .42
4	16	7.2	1.58	7.47	1.64	11	.199 ± .032	1.26 ± .20
5	18	5.0	1.09	5.85	1.31	10	.135 ± .024	.705 ± .124
6	29.4	0.9	0.18	1.73	0.347	11	.245 ± .048	.340 ± .067

mechanism of inward and outward passage of water through the skin is identical or closely similar, one would expect that high net water movement would be associated with high rates of movement in both directions. It is evident from an inspection of the data of Table II that the rate of net water loss varies considerably in different skin areas. The one series of studies which included the volar surface of the forearm shows a lower rate for this area than for any other area measured. It thus appears not unreasonable that the average total body rate of percutaneous absorption should exceed the forearm rate by several fold; and, although based on a single determination, the value of 0.84 $\mu c/cm^2/min/\mu c/cm.^3$ atmosphere is probably a reasonably accurate measure of the total body percutaneous absorption rate constant.

Data on the effect of water vapor pressure on the percutaneous absorption of tritium oxide in rats are summarized in Table III. These experiments were conducted in a manner exactly similar to the other exposures, except that the water vapor pressure in the exposure atmosphere was controlled by addition of sodium hydroxide in various concentrations to the tritium oxide solution in the hydrating chamber of the "dynamic" exposure apparatus. Table III lists both the calculated vapor pressure and tritium concentration of the atmosphere[1,13] and their values as determined experimentally by sampling the atmosphere. Satisfactory agreement was obtained, except for the two highest sodium hydroxide concentrations. In these two cases the theoretical values were based on extrapolation, and the experimental figures are undoubtedly the more accurate of the two. In calculating values of K, theoretical C_v values were used for experiments 1–4 and experimental values for experiments 5 and 6. Values of K and Δ in Table III were based on tritium determinations on the total body water from the exposed animals. Blood samples were also analyzed and led to values of K and Δ which were consistently about 70 per cent of the total body water values, indicating again a time lag in the equilibration of absorbed tritium oxide with the total body water.

It is evident from Table III that the rate of water absorption (Δ) is directly proportional to water vapor pressure. It is also clear that the absorption of tritium oxide from an atmosphere of constant tritium oxide content (K) is independent of total water vapor pressure. The direct proportionality between water absorption and water vapor pressure supports the hypothesis of a simple diffusion mechanism for percutaneous absorption. From the hazard standpoint, the results indicate that humidity is not a factor to be considered in exposure considerations.

The results of liquid water absorption studies on the rat are shown in Table IV. Absorption rates were calculated from analyses on total body water. The much higher values obtained from unshaved animals must be attributed to tritium-labeled

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TABLE IV

PERCUTANEOUS ABSORPTION OF LIQUID WATER BY THE RAT

Expt. No.	No. of Rats	Auxiliary Treatment	(μg./cm.²/min.)
1	17	Shaved prior to exposure	15.2±3.0
2	5	Unshaved	31.3±4.7
3	5	Shaved subsequent to exposure	10.6±3.5

water adsorbed on the hair and included in the total body water determinations. Shaving either before or after exposure reduced the values. The results of experiments 1 and 3 are not significantly different considering the small number of animals in experiment 3. The absorption rate appears to be two to three times larger for liquid water than for saturated water vapor. These results on liquid water should be considered only as preliminary findings; and the possibility of extensive adsorption on the skin, resistant to thorough washing, should not be overlooked. So far as the eventual body burden is concerned, however, any such tightly adsorbed water is practically equivalent to absorption. Pinson[13] has reported no difference in the absorption rate from liquid water or a saturated water vapor atmosphere.

RELATIVE HAZARDS OF PERCUTANEOUS VERSUS PULMONARY ABSORPTION OF TRITIUM OXIDE VAPOR

Using the value of 0.84 for the absorption rate constant for human total body exposure (Table 1), a "standard man"[11] during an eight hour period of exposure to the presently established permissible maximum[11] will absorb 360 μc through his skin:

Absorption rate constant (0.84) × total skin area (1.8×10^4 cm.²)* × time (480 min.) × tritium oxide concentration in atmosphere (5×10^{-4} μc/cc.) = 360 μc.

* This represents the total skin area of a 70 kg. and 170 cm. man.[1]

Similarly, for pulmonary absorption, assuming complete retention of inhaled tritium oxide, a value of 500 μc is obtained:

Volume inspired (10^7 cc.) × tritium oxide concentration in atmosphere (5×10^{-5} μc/cc.) = 500 μc.

From these calculations it is apparent that percutaneous absorption and pulmonary absorption contribute approximately equally to the total body burden of tritium oxide acquired through exposure to an atmosphere contaminated with tritium oxide.

The present permissible maximum level for atmospheric tritium oxide contamination was established without consideration of percutaneous absorption. A reduction in the permissible maximum by a factor of two is therefore suggested by the results of the present investigation. The establishment of percutaneous absorption as a significant hazard also emphasizes the inadequacy of respiratory protection alone in tritium oxide contaminated atmospheres.

SUMMARY

The percutaneous absorption of tritium oxide-labeled water vapor was studied in mice, rats and man. In terms of μg. water absorbed/cm.²/min. from a saturated water vapor atmosphere, the rates found were: for mice (abdomen), 20±5; rats (abdomen) 5.7±1.1; man (forearm) 8.6±1.7. A single total body exposure to a human at 70 per cent relative humidity gave a rate of 18 μg/cm²/min. The rate of water vapor absorption in the rat was found to be directly proportional to water vapor pressure. For a constant level of atmospheric tritium oxide, absorption of tritium oxide was independent of total water vapor pressure.

It was shown that for humans the rate of percutaneous absorption of tritium from a tritium oxide contaminated atmosphere is about the same as the rate of pulmonary absorption from the same atmosphere.

Roy C. Thompson
Radiological Sciences Dept.
General Electric Co.
Richland, Washington

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The authors wish to acknowledge the technical assistance of Mrs. Joan O. Hess and Mrs. Willa D. Oakley in the conduct of much of the experimental work. Counting of tritium samples was performed by the radiochemistry group under the direction of A. C. Case, and assistance in the statistical treatment of the data was obtained from W. C. Healy. Thanks are also due Dr. M. E. Getzendaner and Dr. G. N. Smith for valuable suggestions with regard to apparatus and methods.

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Tc. Project

FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project was an investigation of the distribution and excretion of technetium in human subjects.

Date Started: July 1965
Date Terminated: 60 days after start

Identification: Unknown

Principal Investigator(s): T. M. Beasley and H. E. Palmer, Pacific Northwest Laboratory (PNL) and W. B. Nelp, University of Washington Medical School

Responsible Government Official(s):

Objective(s) of test: The study was conducted to measure the long-term retention and localization of technetium in humans following both oral and intravenous administration and to derive mathematical models for excretion, which are very useful in determining the radiation dose to humans from technetium isotopes in the body. They are important from both medical and occupational standpoints.

Short description: ^{95m}Tc and ^{96}Tc were administered to 8 subjects by physicians at the University of Washington Hospital in Seattle. The subjects were hospitalized at the University of Washington Clinical Research Center for the first week. Whole body counting and excreta measurements were made for 60 days. The University of Washington obtained and reimbursed the subjects for their services. The participation by PNL personnel was limited to providing the equipment, making the whole body counting and excreta measurements and analyzing the data. The PNL participation was funded by AEC but not the University of Washington participation.

Follow-up data: Follow-up continued for 60 days. Later follow-up considered unnecessary because of low dose to subjects (estimated to be 0.145 rem)

References: Beasley, T. M., Palmer, H. E., and Nelp, W. B., "Distribution and Excretion of Technetium in Humans," Health Physics 12, pp. 1425-1435 (1966).

Attachment(s): Stated reference.

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Health Physics Pergamon Press 1966. Vol. 12, pp. 1425–1435. Printed in Northern Ireland

DISTRIBUTION AND EXCRETION OF TECHNETIUM IN HUMANS*

T. M. BEASLEY,† H. E. PALMER‡ and W. B. NELP§
Battelle Memorial Institute, Pacific Northwest Laboratory, Richland, Washington

(*Received* 4 *October* 1965; *in revised form* 10 *December* 1965)

Abstract—Widespread use of ^{99m}Tc as a tracer in medicine and large scale separation of ^{99}Tc from fission product waste require that adequate knowledge of the metabolic properties of technetium be known so that realistic exposure limits can be imposed for the isotopes of interest. The present paper discusses a metabolic experiment using ^{95m}Tc (60 day $T_{1/2}$) and ^{99}Tc (4.3 day $T_{1/2}$) in which long-term excretion, retention and localization of these isotopes were measured using whole-body counting techniques. Following intravenous and oral administration both urinary and fecal excretion rates were measured and mathematical models were derived for technetium elimination. The latter should be helpful in estimating body burdens of the weak beta-emitting ^{99}Tc following inadvertent exposure.

1. INTRODUCTION

THE USE of technetium isotopes in both medicine and metallurgy has recently stimulated interest in the metabolic behavior of this element following intake into the body. ^{99m}Tc which decays by isomeric transition (gamma-ray emission) and has a half-life of 6 hr has found widespread use in biology and medicine both as a tracer and as a diagnostic tool in nuclear medicine. ^{99}Tc which decays by beta emission and has a half-life of 2×10^5 yr is produced in relatively high yield in the fission of uranium-235 and plutonium-239. It is present, therefore, in rather high concentrations in the fission product waste solutions which result from the chemical processing of reactor fuels. ^{99}Tc is currently being separated in kilogram quantities from such wastes at the atomic works near Richland, Washington.

In the event of an inadvertent exposure of plant personnel to ^{99}Tc, measurement of excreta would provide the best means of estimating body deposition, since its decay is not accompanied by gamma-ray emission and therefore cannot be detected by whole-body counting techniques. Technetium metabolism experiments have been performed with humans using the 6.0-hr ^{99m}Tc,[1] but due to the short half-life of this isotope, the duration of the experiments have been 3 days or less. In such a short time period one cannot accurately predict the long-term localization or retention of technetium in any particular organ of the body with any degree of certainty. This information is required to assign exposure limits for personnel who are engaged in the handling of technetium isotopes.

Accidental exposure can lead to deposition of the radioisotope in the body by both inhalation and ingestion. It is therefore of interest to determine the differences, if any, which result in the localization and subsequent metabolic behavior of technetium following oral and intravenous administration. Intravenous administration would simulate the behavior of that portion of the technetium which is rapidly solubilized in the lung and enters the blood stream a short time following exposure. Clearly, neither oral or intravenous administration can simulate the

* This paper is based on work performed under United States Atomic Energy Commission Contract AT(45-1)1830. Permission to publish is gratefully acknowledged.

† Research Scientist, Chemistry Department.

‡ Senior Research Scientist, Physics and Instruments Department, Pacific Northwest Laboratory, operated by Battelle Memorial Institute for the United States Atomic Energy Commission, Richland, Washington.

§ Director, Division of Nuclear Medicine, University of Washington Hospital, Seattle, Washington.

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metabolic behavior of technetium in the lung which is only slightly solubilized.

The present study was undertaken to measure the long-term retention and localization of technetium in humans following both oral and intravenous administration, and to derive mathematical models for the elimination of technetium in the excreta.

II. METHODS

The technetium isotopes used in this experiment were ^{95m}Tc ($T_{1/2}$ = 60 days) and ^{96}Tc ($T_{1/2}$ = 4.3 days). Each isotope decays by electron capture and subsequent gamma-ray emission. The isotopes were prepared by Oak Ridge National Laboratory using high-energy proton irradiation of 95 per cent enriched ^{96}Mo metal. The technetium was separated from the irradiated molybdenum at the Volk Radiochemical Co., Chicago, Illinois, using solvent extraction techniques and was ultimately prepared as sodium pertechnetate in sterile water.

Pertechnetate was chosen as the chemical form in administering the technetium in that this is the most common chemical form of the element currently being used in medical and biological applications, and is the final chemical form in which technetium appears following its purification from fission product wastes. It seemed probable, therefore, that in the event of an accidental release of technetium, its chemical form would be as pertechnetate.

Localization and distribution of the technetium within the body was followed using a shadow shield whole-body counter.[2] Briefly, the counter consists of 400 lead bricks arranged such that a gamma-ray resulting from background cannot directly enter the detector, but a person can be moved past the detector on a movable bed propelled by a ball-bearing screw and electric motor. A 4-in. thick by 9¾-in. diameter NaI(Tl) crystal is used as the detector and the pulses from this crystal are analyzed by a 512-channel multichannel analyzer

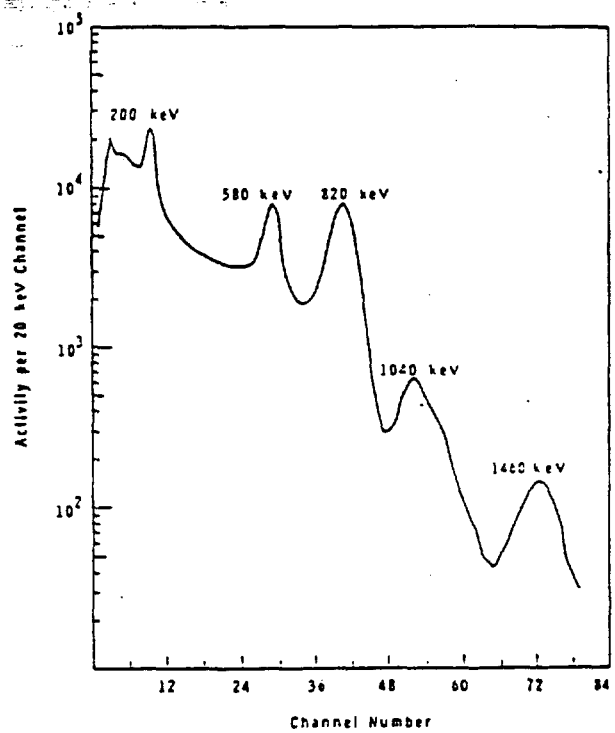

Fig. 1. Gamma-ray spectrum of subject following administration of ^{96}Tc + ^{95m}Tc.

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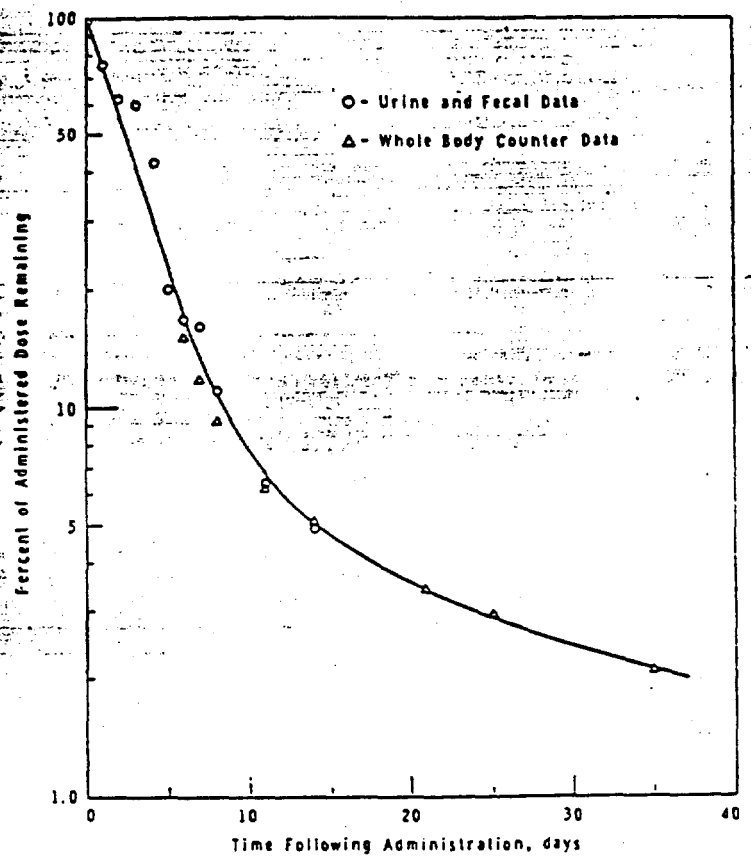

Fig. 2. Per cent original dose of ^{95m}Tc remaining following intravenous administration.

A slit system was employed which covered the majority of the large crystal with 2 in. of lead except for a 1-in. wide slit. This permitted differential scanning of the subject as he traveled under the crystal.

Figure 1 shows a representative gamma-ray spectrum of a subject following administration of the technetium isotopes. The characteristic gamma-ray photons of ^{95m}Tc occur at 0.201, 0.570 and 0.810 MeV while those of ^{96}Tc occur at 0.771, 0.842 and 0.806 MeV. The sum peak at 1.040 MeV is the result of gamma–gamma cascades in the decay of ^{95m}Tc, while the peak at 1.460 MeV arises from the ^{40}K present in all human beings.

Following administration of the technetium, total urine and feces were collected from each subject for a period of 8–10 days. During the first 3 days the distribution and translocation of the technetium was such that the whole-body counter could not be directly calibrated to give technetium retention. Instead, excretion analysis was used to determine body retention during this time by subtracting the measured technetium in the excreta from that in the originally administered dose. Between 3 and 8 days following administration, the whole-body counter results were normalyzed to the retention determined by excretion analysis and after 8 days the whole-body counter was used to measure the retention. Figure 2 shows the good agreement between technetium retention as determined by whole-body counting and subsequent excretion analysis.

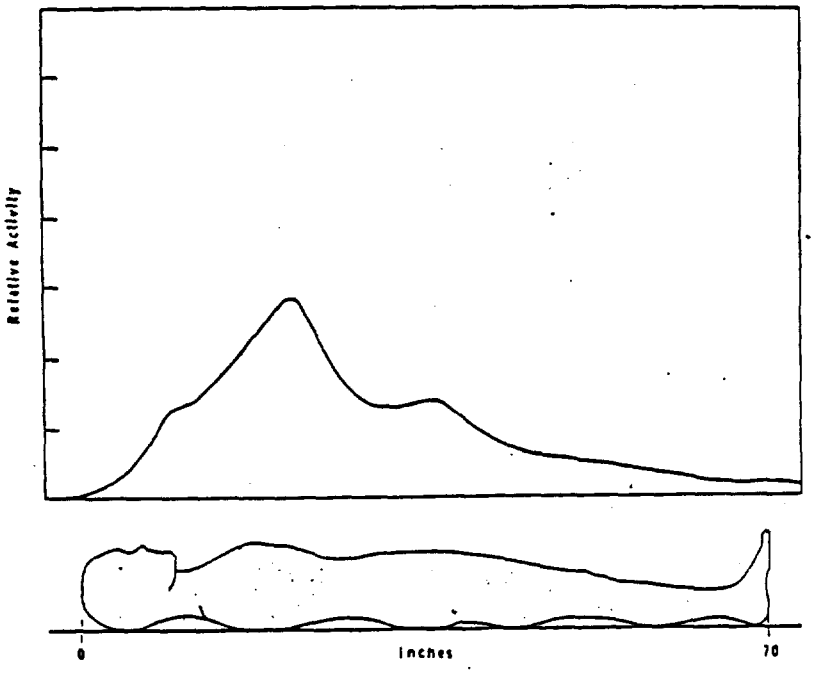

Fig. 3. Subject 10 min post intravenous injection.

The excreta samples collected from each of the subjects were counted beneath the large NaI(Tl) crystal in a fixed geometry and the per cent of the administered dose excreted was determined by comparing the counting rate of a standard counted in an identical fashion. In each instance the standard error of counting never exceeded 5 per cent and usually was less than 3 per cent. Blood and saliva samples were counted in a NaI(Tl) well-type scintillation counter and the per cent of the administered dose present was again determined by comparing the counting rates of the sample and a standard.

III. SUBJECTS

The isotopes were administered as the pertechnetate ion to eight normal human volunteers, ages 22–43 yr. Initially, 20 μc of ^{95m}Tc and 60 μc of ^{96}Tc were administered to the patients. Four subjects received an oral dose after an overnight fast, while the remaining four subjects received the dose intravenously. For the first week, subjects were hospitalized at the Clinical Research Center of the University of Washington Hospital. Samples of plasma, sweat, tears and intestinal mucosa were collected. After the first week, subjects were allowed to collect specimens at home. Observations were made for a period of 60 days on some subjects. Whole-body counts of the subjects prior to administration of the technetium isotopes showed only the presence of ^{137}Cs and ^{40}K, and none of the people had any history of contact with radioactive isotopes prior to the experiment.

IV. RESULTS AND DISCUSSIONS

4.1. *Localization and distribution of technetium*

Figures 3–6 show the distribution of technetium in humans with time following both oral and intravenous administration. In the case of intravenous administration, the technetium has already begun to localize in the area of the bladder as soon as 10 min after injection. Two hours following administration a distribution which was to become characteristic for all of the subjects regardless of administration route had occurred. The technetium had localized in

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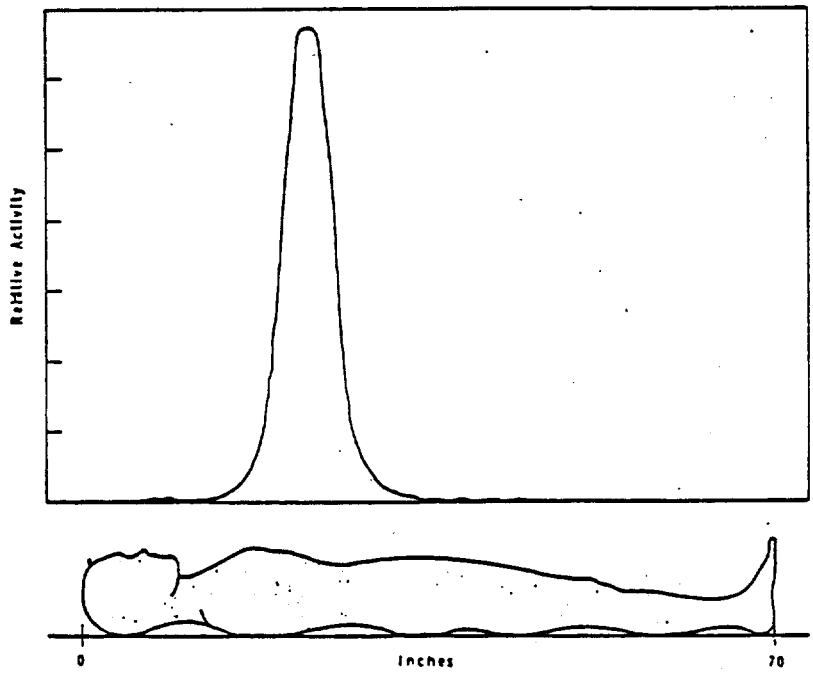

Fig. 4. Subject 10 min post oral administration.

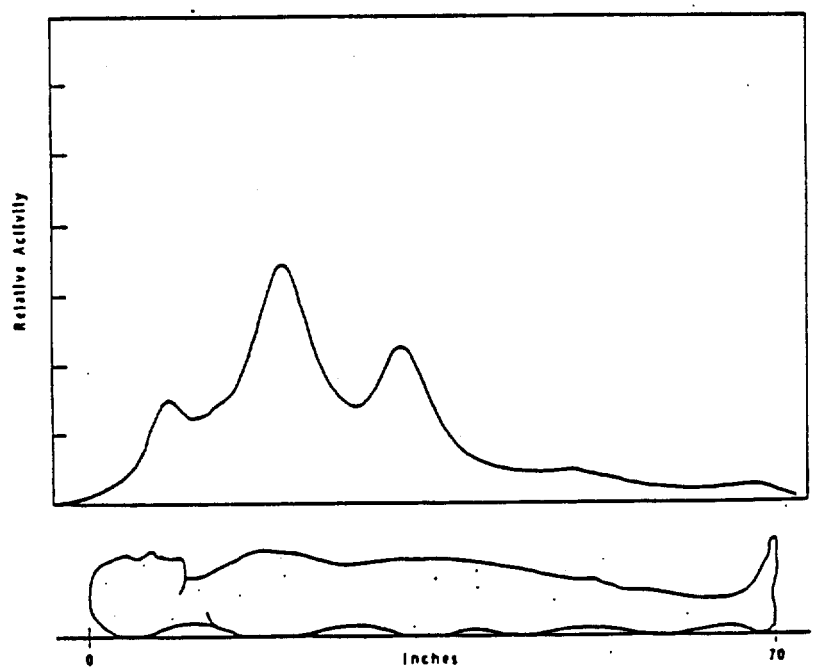

Fig. 5. Subject 2 hr post intravenous injection.

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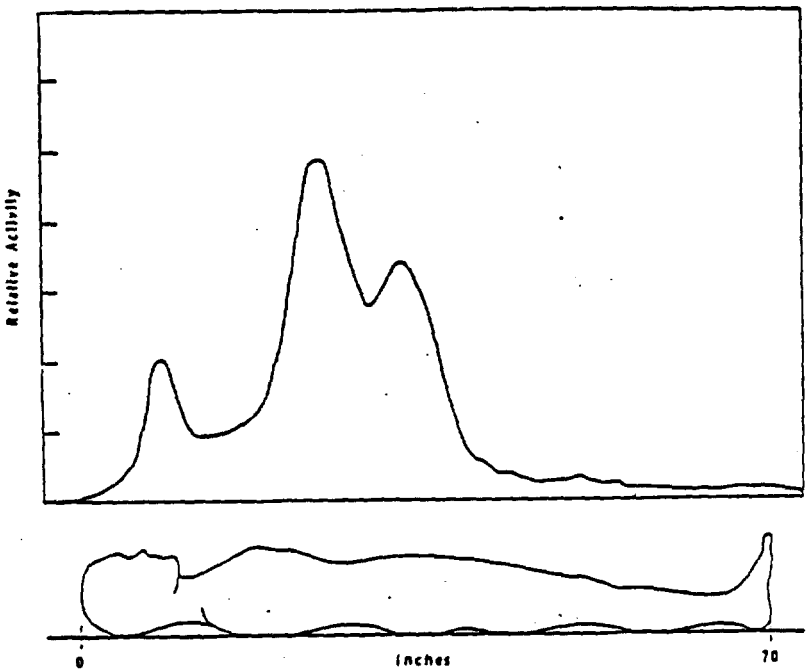

Fig. 6. Subject 2 hr post oral administration.

relatively large concentrations in the region of the salivary-thyroid glands, stomach, liver and bladder. The specific activity of the saliva itself was exceptionally high, approaching 95 per cent of the administered dose per liter of saliva some 2–3 hr following administration. After oral or intravenous doses, the saliva contained 10 to 30 times the concentration of technetium in the plasma. This concentration gradient was maintained for many days, although the total amount in the salivary glands was small after the first day. It was not possible to accurately measure the thyroid concentration of pertechnetate in this experiment due to the counting arrangement employed. The proximity of the thyroid and salivary glands gave rise to the activity peak in the area of the head as seen in Figs. 5–6. The rapid turnover of technetium in the salivary glands was monitored by measuring saliva and showed components of 2–4 hr and 1–2 days. The half-life of the activity in the area of the head was approximately 12–24 hr, indicating some early uptake of technetium into the thyroid, but its removal from this organ is probably quite rapid. When considering the immediate treatment of inadvertent exposure to ^{99}Tc it would appear worthwhile to stimulate salivation, since this could be a very effective means of decreasing the systemic burden of the isotope.

Technetium was not concentrated in the lacrimal or sweat glands; however, the specific activity of the nasal secretions was very large. In this connection it is interesting to point out that in the case of exposure to pertechnetate, nasal and oral swabbing cannot be used as an indication of exposure route due to the high concentrations of technetium which rapidly gets to the saliva and nasal mucosa.

To further define the localization of the technetium as excretion occurred, subjects were studied by photoscanning, localized surface counting with a shielded probe detector and by intestinal biopsy. Figure 7 shows a photoscan of a subject 3 days following oral administration when approximately 30 per cent of the administered dose remained. The photoscan illustrates localization of the technetium predominantly in the bowel and in its contents.

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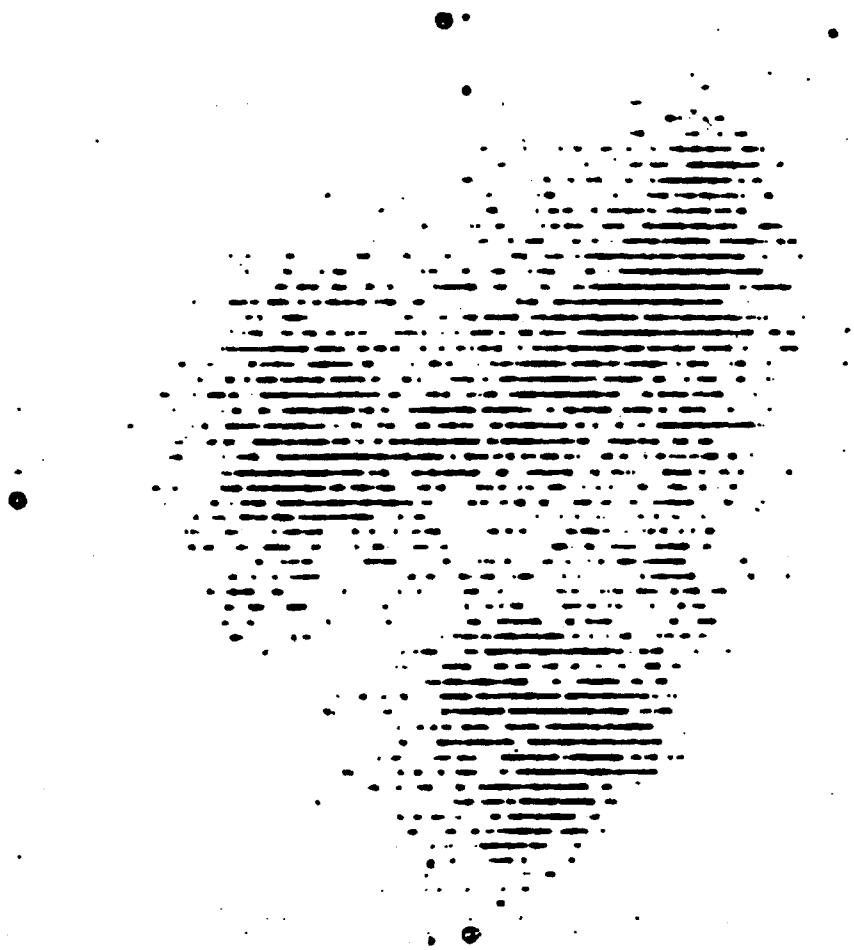

Fig. 7. Photoscan of subject 3 days following oral administration. Abdominal area showing distribution of Tc in transverse and descending colon.

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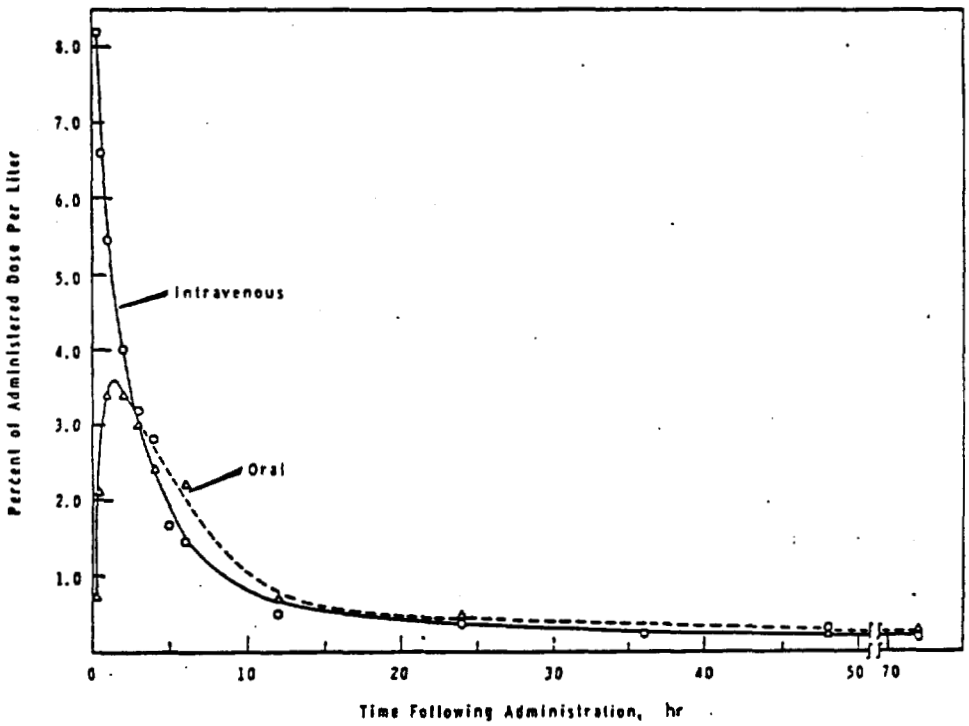

Fig. 8. Variation of blood concentrations of Tc following oral and intravenous administration.

Subsequent photoscans and localized surface counts showed a more diffuse pattern of radioactivity in the total bowel area. There was no evidence of localization of the isotope in either the liver or the kidney.

In three subjects, biopsies of the stomach, duodenum and rectal mucosa were performed at 2, 7 and 19 days following administration. Table 1 contains the results of these measurements and shows the general distribution of the technetium throughout the GI tract. No appreciable activity was observed in rectal mucosa, while stomach and duodenum mucosa had technetium concentrations of some 40–100 times that found in the plasma at comparable times.

Figure 8 shows the blood concentrations of technetium with time and indicates a rapid increase in the blood level of technetium following oral administration. Since no appreciable difference in excretion occurred for the two groups of subjects during this time period, one can estimate the fraction of the orally administered dose absorbed by comparing the areas beneath the plasma concentration curve of the

Table 1. Results of biopsy specimens

Subject	Method of administration	Time following administration (days)	Per cent of administered dose per kilogram of tissue		
			Stomach	Duodenum	Rectum
1	Oral	2	22.4	23.2	0.91
2	Oral	7	8.2	6.3	0.54
3	I.V.	19	1.2	0.45	—

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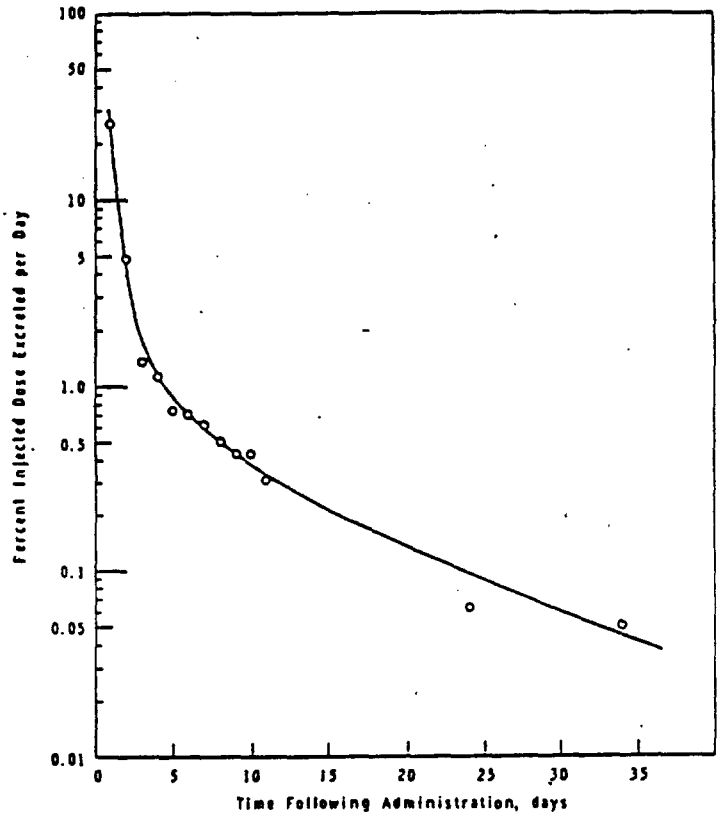

Fig. 9. Daily urinary excretion of intravenously administered ^{99m}Tc.

group to that of the intravenous group. Such a comparison suggests that some 96 per cent of the technetium which was administered orally was absorbed from the gut within the first 2 days. (This comparison was made assuming that the total blood volumes for the respective groups were similar.)

4.2 *Excretion of technetium*

Technetium is excreted very rapidly in the urine following both oral and intravenous administration. In this particular experiment it was not uncommon for a subject to excrete between 8 and 12 per cent of the administered dose in the first 6 hr following intake. By the third day, however, technetium elimination via the urine had decreased to about 1 per cent of the administered dose excreted per day (Table 2).

Fecal excretion, by contrast, reached its maximum value 3–4 days following administration, and thereafter decreased. Figures 9 and 10 show the characteristic excretion patterns obtained from one subject following intravenous administration, while Fig. 11 shows the average cumulative excretion of technetium with time for all subjects investigated.

No difference was detectable between the I.V. and oral groups in relation to the rate, and route of excretion, or to the amount subsequently retained.

The experimental data have been fitted to a three-term exponential expression showing the characteristic initial rapid decrease of the technetium in the urine during the first 3 days, followed by longer half-lived components of 2.0 and 10.0 days respectively. At 28 days following exposure, approximately 0.06 per cent of the dose is excreted per day via the urine.

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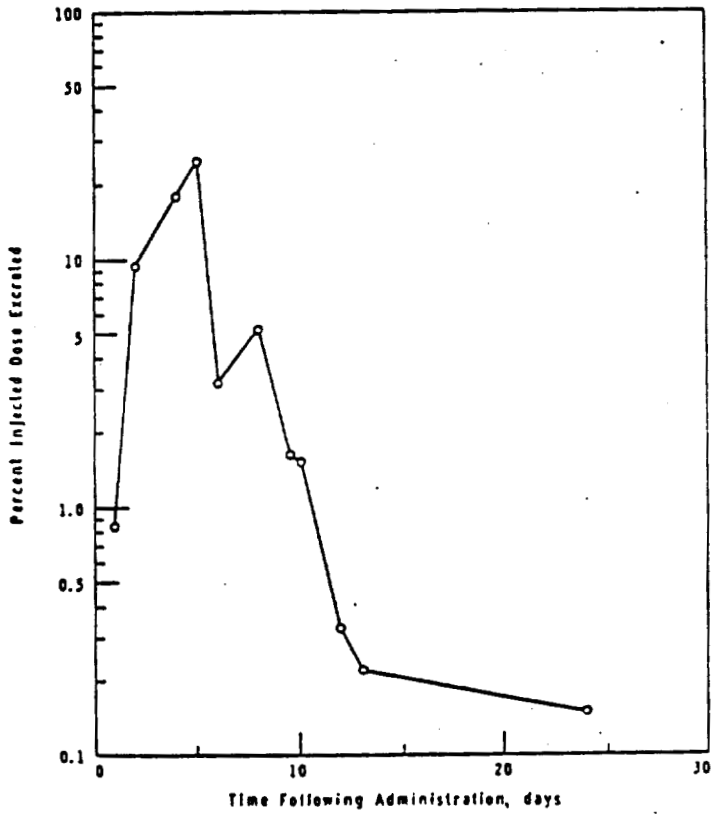

Fig. 10. Fecal excretion of intravenously administerd ^{99m}Tc.

Table 2. Urinary excretion of technetium following oral and intravenous administration as pertechnetate

Days following administration	Average urinary excretion (% administered dose excreted/day)
1	27.76 ± 8.5*
2	2.44 ± 1.55
3	1.17 ± 0.18
4	0.84 ± 0.28
5	0.63 ± 0.20
6	0.52 ± 0.15
7	0.41 ± 0.16
8	0.35 ± 0.10
9	0.37 ± 0.18
10	0.25 ± 0.13
11	0.23 ± 0.08
14	0.16 ± 0.04
16	0.13 ± 0.05
18	0.11 ± 0.04
20	0.09 ± 0.03
22	0.07 ± 0.03
25	0.06 ± 0.02

* Standard error of the mean.

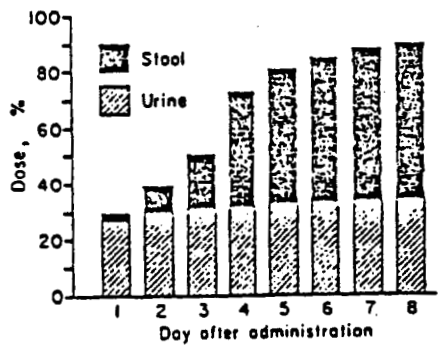

Fig. 11. Cumulative excretion of technetium.

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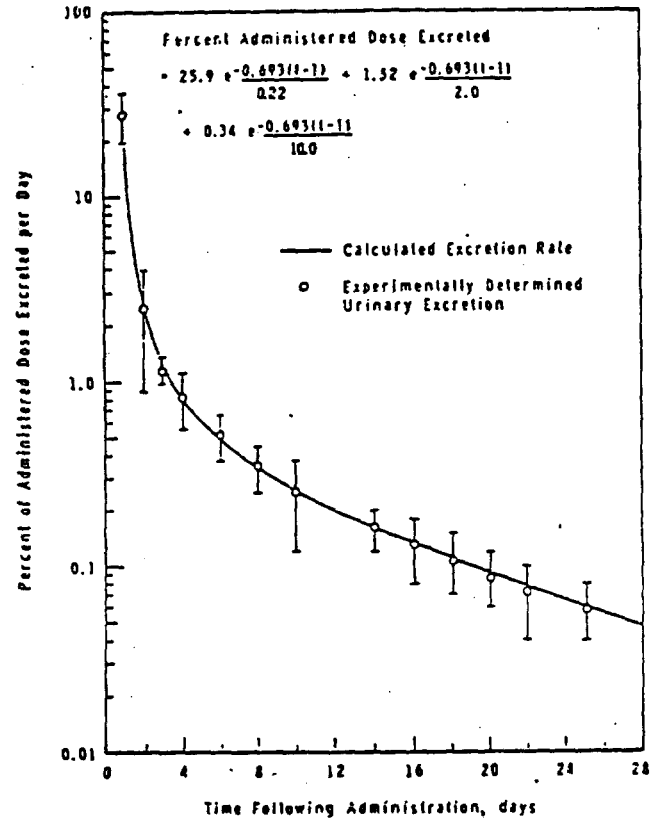

Fig. 12. Variation of the daily urinary excretion of technetium with time. Oral and intravenous.

Figure 12 can be used to estimate an initial exposure to technetium if one knows the time of exposure and the amount of technetium excreted by way of the urine in a 24-hr period following exposure. As an example, if one had measured 0.001 μc in a 24-hr urine specimen obtained from an individual exposed some 28 days prior to the urine sampling, his estimated intake of pertechnetate would have been 1.5 μc.

4.3. *Retention of technetium*

The retention of technetium with time for all eight subjects in this experiment has been averaged and is shown in Fig. 13. Once again the retention has been fitted to a three-term exponential expression. Solution of this equation for the time of 50 per cent retention (and therefore 50 per cent excretion) gives $t = 2$ or a biological $T_{1/2} = 2$ days. The last term in the mathematical expression shows a half-life of 22 days and as previously mentioned is dependent upon the turnover of technetium in the G.I. tract.

SUMMARY

It is of interest to compare the results of the present investigation with the biological parameters published in the ICRP Committee Report II.[3] Table 3 shows such a comparison and indicates, at least in the instance where technetium isotopes are present as pertechnetate, the need for re-evaluating the maximum permissible body burdens, and air and water concentrations to which individuals may be exposed.

There seems to be little, if any, localization of

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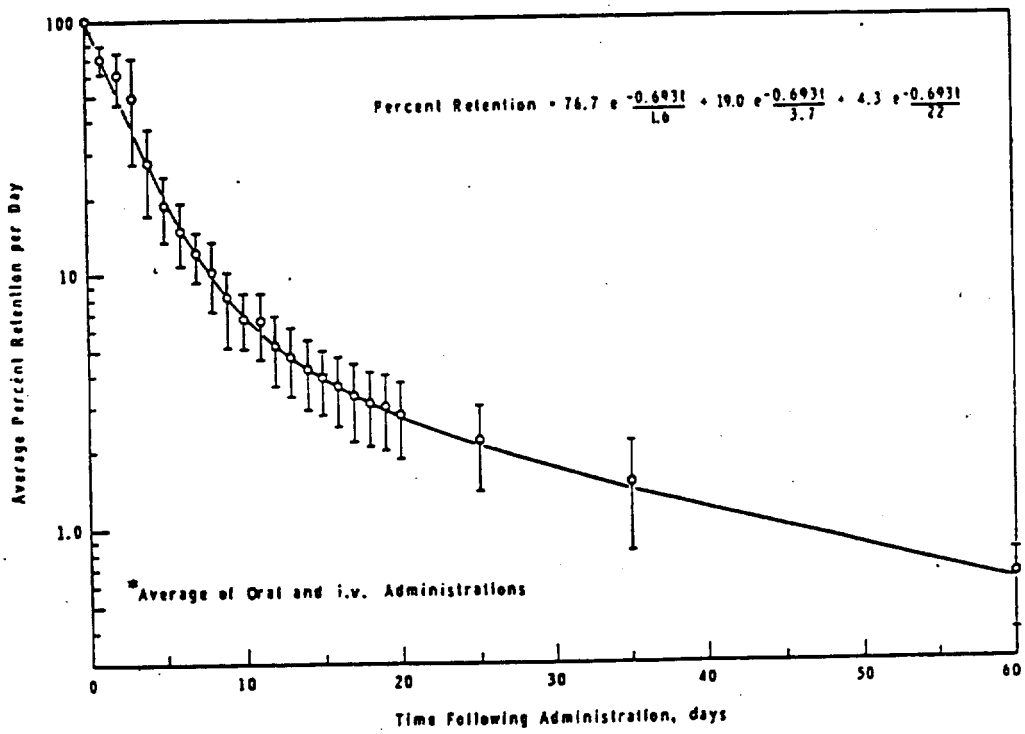

Fig. 13. Retention* of technetium with time.

Table 3. Comparison of biological parameters obtained in present research with ICRP *recommendations*

	ICRP	Present research
Effective half-life in body	1 day	2 days
fraction absorbed on ingestion	0.5	~0.95
organs where technetium localizes	G.I. (LLI)	G.I. (LLI), G.I. (S)
	Kidney	—
	Liver	—

technetium in the kidney or liver, but intsead it seems to concentrate mainly in the GI tract and stomach. Finally, urinalysis coupled with blood analysis at early times provides the best method of assessing body depositions of technetium as pertechnetate following accidental exposure.

REFERENCES

1. P. V. Harper, G. Andros and K. Lathrop, *Preliminary observations on the Use of Six-Hour* ^{99m}Tc *as a tracer in Biology and Medicine*, *ACRH*-18, p. 76 (1962).
2. H. E. Palmer and W. C. Roesch, *Health Phys.* 11, 1213 (1965).
3. K. Z. Morgan (Editor), Report of ICRP Committee II on Permissible Dose for Internal Radiation, *Health Phys.* 3, (1960).
4. E. M. Smith, *J. Nucl. Med.* 6, 231 (1965).
5. J. G. McAfee *et al.*, *J. Nucl. Med.* 5 (1964).

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FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project was an investigation of the distribution and excretion of technetium in human subjects.

Date Started: July 1965
Date Terminated: 60 days after start

Identification: Unknown.
Principal Investigator(s): T.M. Beasley, H.C. Palmer and W.B. Tolp

Responsible Government Official(s):

Objective(s) of test: The study was done to measure the long-term retention and localization of technetium in humans following both oral and intravenous administration and to derive mathematical models for excretion, which are being used in determining the radiation dose to the human from technetium isotopes in the body. They are important from both medical and occupational standpoints.

Short description: ^{95m}Tc and ^{96}Tc were administered to 8 subjects by [illegible] at the U.S. Naval Radiological Defense Laboratory in San Francisco. The subjects were hospitalized at the U.S. Naval Medical Center for the first week [illegible] and remained the subjects for 60 days. The remaining [illegible] were released [illegible] where needed. The participants [illegible] the premises the equipment and [illegible] the data. The [illegible] and excreta measurements and analyzing the data. The [illegible] were funded by AEC but the [illegible] were not funded by AEC.

Follow-up data: Follow-up continued for 60 days. Later follow-up considered unnecessary because of low dose to subjects (estimated to be 0.145 rem

References: Beasley, T.M., Palmer H.C., Tolp, W.B., "Distribution and Excretion of Technetium in Humans", pp. 1225-1234, 1966

Attachment(s): Detail reference.

0008840

1941/66

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FACTSHEET HUMAN EXPERIMENTATION

Project Name: Unknown. Project was an investigation of the distribution and excretion of technetium in human subjects.

Date Started: [illegible]
Date Terminated: [illegible]

Identification: Unknown.
Principal Investigator(s): [illegible]

Responsible Government Official(s):

Objective(s) of test: [illegible]

Short description: [illegible] medical and occupational standpoints. ^{95m}Tc and ^{99}Tc [illegible] AEC.

Follow-up data: [illegible] for 60 days. Later follow-ups considered unnecessary because of [illegible] subjects (estimated [illegible]

References: [illegible]

Attachment(s): Partial reference.

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Department of Energy
Richland Operations Office
P.O. Box 550
Richland, Washington 99352

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JUL 5 1984

Director
Pacific Northwest Laboratory
Richland, Washington

Dear Sir:

INFORMATION ON RESEARCH PROJECTS INVOLVING HUMAN SUBJECTS

The Subcommittee on Energy Conservation and Power of the House Committee on Energy and Commerce has announced an investigation into the health and safety policy of the Department of Energy (DOE). As detailed in the enclosed letter, the Richland Operations Office, DOE (DOE-RL) has been requested to cooperate in collecting information on human experimentation projects funded by DOE and its predecessor agencies through contracts with DOE-RL.

Your assistance is requested in providing best available information on all such research funded by DOE at Hanford Laboratory or PNL. The enclosed letter contains quidance and a format for your response.

As discussed with Dr. Sidney Marks on June 28, 1984, other DOE-RL contractors are receiving requests (copies enclosed) and are being instructed to direct questions and their responses to Dr. Marks. Please compile these responses [redacted] Costs for this effort should be billed to HA programs.

Very truly yours,

Harold E. Ransom

Harold E. Ransom, Director
Energy Programs Division

Enclosures:
1. 6/27/84 memo Edington/Lawrence
2. 7/5/84 letters Larson to RL Contractors (3)

JUL 6 1984

RECEIVED
JUL 09 1984
R. P. MARSHALL

0008842

United States Government Department of Energy

memorandum

DATE: June 27, 1984

REPLY TO ATTN OF: ER-71

SUBJECT: Congressional Investigation into Health and Safety Policies of DOE

TO: Michael J. Lawrence, Manager
Richland Operations Office

The Subcommittee on Energy Conservation and Power of the House Committee on Energy and Commerce has announced an investigation into the health and safety policies of the Department of Energy. Initial discussions with staff of the Subcommittee have made it clear that this investigation will be as broad as they deem necessary, and extend from past to present to future policies.

As a first inquiry in the framework of this investigation, the Department has been asked to provide a list of human experimentation projects funded by DOE and its predecessor agencies, going back to the days of the Manhattan Project. Any support received from other agencies for the support of such projects is also to be provided.

I request your full and expeditious cooperation in collecting the required information, if necessary with the assistance of the national and dedicated laboratories and off-site contractors that may have been involved in human experimentation projects. As there is some question as to the definition of the term "human experiments", I would like — as a first approximation that might be expanded in the future — to include experimental use of ionizing radiation and radioactive materials for purposes of treatment of disease, and for determining hazards of such agents to humans (including experiments aimed at providing information necessary to determine such hazards, e.g., those concerning the metabolic behavior of radioactive materials). For the moment, I would like to exclude clinical feasibility studies concerning radiopharmaceutical compounds for medical diagnostic use.

It is important that a first listing be obtained as soon as reasonably possible, and, in any case, not later than late July 1984. The information to be included should be summarized on factsheets, the format of which is attached to this memorandum. As the Chairman of the Subcommittee, Mr. Richard L. Ottinger, has expressed a particular interest in the specific methods for follow-up and long-term tracking of participants in these projects, I would like your special attention to this item, to be summarized under the heading "Follow-up Data" in the Factsheet. In order to provide us with background materials, useful summaries and reports, and significant

publications related to these projects, I ask you to list such documentation under "References", and to attach copies of particularly informative documents to the Factsheets. You may leave the item "Responsible Government Official(s)" blank, as I intend to identify this/these persons as the Headquarters' Official(s) who had program-management responsibility for the project involved.

I appreciate your personal attention to this request so that we may be most responsive to Mr. Ottinger's inquiry. Dr. J. W. Thiessen, Deputy Associate Director of this Office, may be contacted for further details, if necessary, either by telephone (FTS 233-3153) or by electronic mail (DIALCOM ID DOE670).

J. W. Thiessen

for Charles W. Edington
Associate Director, Office of
Health and Environmental Research
Office of Energy Research

Attachment

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

Date Started:
Date Terminated:

Identification:
Principal Investigator(s):

Responsible Government Official(s):

Objective(s) of test:

Short description:

Follow-up data:

References:

Attachment(s):

Department of Energy
Richland Operations Office
P.O. Box 550
Richland, Washington 99352

JUL 3 1984

Donald K. Baldwin, Director
Office of Grant and Contract Services AS-24
University of Washington
Seattle, WA 98195

Dear Sir:

INFORMATION ON RESEARCH PROJECTS INVOLVING HUMAN SUBJECTS

The Subcommittee on Energy Conservation and Power of the House Committee on Energy and Commerce has announced an investigation into the health and saftey policy of the Department of Energy (DOE). As detailed in the enclosed letter, the Richland Operations Office DOE (DOE-RL) has been requested to cooperate in collecting information on human experimentation projects funded by DOE and its predecessor agencies through contracts with DOE-RL Operations Office.

Your assistance is requested in providing best available information on all such research contracts between your organization and DOE-RL. The enclosed letter contains guidance and a format for your response. Please provide this information as soon as is reasonably possible, but no later than July 17, 1984.

Our contractor for operation of Pacific Northwest Laboratory, Battelle Memorial Institute, will compile the responses. Please send your response to:

Dr. Sidney Marks
Battelle, Pacific Northwest Laboratory
P.O. Box 999
Richland, WA 99352

Questions should also be directed to Dr. Marks at (509) 375-2461.

Very Truly Yours,

R. D. Larson
Contracting Officer

EPD:PKC

Enclosure:
6-27-84 memo Edington/Lawrence

0008846

Department of Energy
Richland Operations Office
P.O. Box 550
Richland, Washington 99352

JUL 3 1984

Pacific Northwest Research Foundation
ATTN: Mavis Rowley
1102 Columbia St.
Seattle, WA 98195

Dear Sir:

INFORMATION ON RESEARCH PROJECTS INVOLVING HUMAN SUBJECTS

The Subcommittee on Energy Conservation and Power of the House Committee on Energy and Commerce has announced an investigation into the health and saftey policy of the Department of Energy (DOE). As detailed in the enclosed letter, the Richland Operations Office DOE (DOE-RL) has been requested to cooperate in collecting information on human experimentation projects funded by DOE and its predecessor agencies through contracts with DOE-RL Operations Office.

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Dr. Sidney Marks
Battelle, Pacific Northwest Laboratory
P.O. Box 999
Richland, WA 99352

Questions should also be directed to Dr. Marks at (509) 375-2461.

Very Truly Yours,

R. D. Larson
Contracting Officer

EPD:PKC

Enclosure:
6-27-84 memo Edington/Lawrence

0008847

United States Government Department of Energy

memorandum

DATE: June 27, 1984

REPLY TO ATTN OF: ER-71

SUBJECT: Congressional Investigation into Health and Safety Policies of DOE

TO: Michael J. Lawrence, Manager
Richland Operations Office

The Subcommittee on Energy Conservation and Power of the House Committee on Energy and Commerce has announced an investigation into the health and safety policies of the Department of Energy. Initial discussions with staff of the Subcommittee have made it clear that this investigation will be as broad as they deem necessary, and extend from past to present to future policies.

As a first inquiry in the framework of this investigation, the Department has been asked to provide a list of human experimentation projects funded by DOE and its predecessor agencies, going back to the days of the Manhattan Project. Any support received from other agencies for the support of such projects is also to be provided.

I request your full and expeditious cooperation in collecting the required information, if necessary with the assistance of the national and dedicated laboratories and off-site contractors that may have been involved in human experimentation projects. As there is some question as to the definition of the term "human experiments", I would like — as a first approximation that might be expanded in the future — to include experimental use of ionizing radiation and radioactive materials for purposes of treatment of disease, and for determining hazards of such agents to humans (including experiments aimed at providing information necessary to determine such hazards, e.g., those concerning the metabolic behavior of radioactive materials). For the moment, I would like to exclude clinical feasibility studies concerning radiopharmaceutical compounds for medical diagnostic use.

It is important that a first listing be obtained as soon as reasonably possible, and, in any case, not later than late July 1984. The information to be included should be summarized on factsheets, the format of which is attached to this memorandum. As the Chairman of the Subcommittee, Mr. Richard L. Ottinger, has expressed a particular interest in the specific methods for follow-up and long-term tracking of participants in these projects, I would like your special attention to this item, to be summarized under the heading "Follow-up Data" in the Factsheet. In order to provide us with background materials, useful summaries and reports, and significant

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publications related to these projects, I ask you to list such documentation under "References", and to attach copies of particularly informative documents to the Factsheets. You may leave the item "Responsible Government Official(s)" blank, as I intend to identify this/these persons as the Headquarters' Official(s) who had program-management responsibility for the project involved.

I appreciate your personal attention to this request so that we may be most responsive to Mr. Ottinger's inquiry. Dr. J. W. Thiessen, Deputy Associate Director of this Office, may be contacted for further details, if necessary, either by telephone (FTS 233-3153) or by electronic mail (DIALCOM ID DOE670).

J. W. Thiessen

for Charles W. Edington
Associate Director, Office of
Health and Environmental Research
Office of Energy Research

Attachment

FACTSHEET HUMAN EXPERIMENTATION

Project Name:

Date Started:
Date Terminated:

Identification:
Principal Investigator(s):

Responsible Government Official(s):

Objective(s) of test:

Short description:

Follow-up data:

References:

Attachment(s):

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To: W.BAIR (DOE617)
From: J.THIESSEN (DOE670) Posted: Tue 19-June-84
16:33 EDT Sys 64 (64)
Subject: Ottinger Inquiry

ATTENTION: Dr. Sidney Marks

Following is a copy of the letter from Ottinger to Hodel:

June 7, 1984

Honorable Donald P. Hodel
Secretary
Department of Energy
Forrestal Building
Washington, D. C. 20585

Dear Mr. Secretary:

As you know, the Subcommittee is investigating the health and safety policies of the Department of Energy. Your assistance is requested for this effort. Please prepare a list of each human experimentation project involving human test subjects and radiation that has been funded by the Atomic Energy Commission, the Energy Research and Development Administration and/or DOE.

The list should include, for each project:

1. the project name, the facility (ies) at which it was conducted, and the dates during which it was conducted;

2. the medical manager of the project, as well as the contracting officer within AEC, ERDA, and DOE who was responsible for monitoring the project;

3. a brief description of the tests, what was done to the participants, including the objectives of the experiments, both therapeutic and experimental;

4. the policy and specific methods for follow-up and long-term tracking of the participants in these projects. Please note if no follow-up review or long-term tracking was conducted.

In addition to the human experimentation projects which the AEC, ERDA, and/or DOE commissioned, please specify each project that these agencies provided support for or conducted jointly with other agencies such as NASA, the Defense Atomic Support Agency, and the Defense Nuclear Agency of the Department of Defense.

Your cooperation is appreciated. Please provide your response by June 25, 1984. If there are any questions regarding this request, please contact Jeanine Hull, Subcommittee counsel, at 226-2424.

Sincerely,

Richard Ottinger
Chairman, Subcommittee on Energy
Conservation and Power of the
Committee on Energy and Commerce

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Thanks for your help.