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ORAU-30037

AEC/ERDA/DOE-CONTRACTOR DTPA PROGRAM

Miscellaneous Documents
Business File: 1972-1981

Reference: ORAU-30034

1080557

Schedule and Agenda
April 7, 1972 Meeting
of
Atomic Energy Commission
Division of Biology and Medicine
Internal Emitter Treatment - Working Group

Friday, April 7, 1972	Seminar Rooms A, B, C - A Building Monsanto Research Corporation, Mound Laboratory, Miamisburg, Ohio 45342
8:00 a.m.	Opening remarks by Mr. R. Flitcraft, Director, Mound Laboratory, Mr. D. Davis, AEC Dayton Area Office and E. Reagan, Mound Laboratory
8:15	Statement of purposes of meeting, J. Goldstein
8:20	Summary of experimental state-of-the-art, V. Smith
9:15	Discussion (and brief presentations by other laboratory representatives as desired)
9:45	Coffee break and tour of laboratory
10:30	Summary of clinical practices submitted to plutonium registry by clinicians at previous meeting, J. Norcross
11:00	Information needed for new IND, W. Weyzen
11:15	General discussion of the morning session proceedings
11:45	Concept of requirements for experimental research with respect to the different types of treatment and regimens, W. Bair
12:15 p.m.	Lunch - Mound Cafeteria
1:00	Exploration of requirements for best methods of obtaining comparable benefician and adverse clinical data from each of the participants respective to the various treatments used by them, J. Goldstein

REPOSITORY Oak Ridge Institute for Science - Education
COLLECTION Medical Sciences Division AEC/ERDA/DOE - contractor DTTA Program
BOX No.
FOLDER ORAU 30037

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1:45	Coffee break
2:00	Separate subgroup discussions 1. Future experimental concepts with priorities and tentative locations for study, V. Smith, Group Leader 2. Therapeutic protocols - concept of EVALUATION forms for therapy and toxicity, S. Marks, Group Leader
3:00	Presentation of above subgroup discussions by respective Group Leaders as an initial basis for promulgating a responsive DBM program in this area
3:45	Closing remarks, J. Goldstein

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UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
WASHINGTON, D.C. 20545

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DEC 12 1975

Heads of Field Organizations

ERDA-CONTRACTOR HEALTH PROTECTION MEETING, DENVER, COLORADO

The Division of Operational Safety's Health Protection Meeting this year will be held at the Denver Hilton in Denver, Colorado, February 5-7, 1976. The portion of the meeting restricted to ERDA personnel only will be held February 5 from 8 am to 1 pm at the Rocky Flats Plant of Rockwell International. The joint ERDA-Contractor meeting will take place in the Showcase 2 Room of the Denver Hilton Hotel from 8:30 am to 5 pm on Friday and Saturday, February 6 and 7, 1976.

In a departure from previous Health Protection Meeting programs, the contractor attendees are invited to tour the Rocky Flats Plant on Thursday morning, February 5. Bus transportation will leave from the Denver Hilton Hotel at 7 am. During the afternoon (while ERDA personnel are touring the plant) Rockwell staff will convene an informal "contractor only" meeting to discuss health protection problems of mutual interest. The bus will leave the plant at 4:30 pm to return to the Denver Hilton. In preparation for the tour, those attendees with a "Q" clearance should make arrangements through their normal security channels for a Sigma 12 clearance. Attendees without "Q" clearances will be taken on a slightly less comprehensive tour with the sensitive areas eliminated.

Attendance is requested by those who have responsibility for the areas of occupational medicine, industrial hygiene, and health physics. No specific limitations on attendance are being stipulated for this meeting, although prudence would be appreciated.

We are enclosing a tentative listing of the 16 topics to be discussed at the ERDA-Contractor meeting. If you wish to suggest any substitutions, please let us know. Copies of the agenda for the meeting and a list of discussion topics for the ERDA meeting will be sent to you at a later date.

Travel costs will be borne by the participating organizations. Participants are requested to make their own arrangements for accommodations. A block of 60 single rooms at $19/night and 20 double rooms at $27/night has been set aside at the Denver Hilton for the nights of February 4, 5, 6, and 7, 1976. Please reserve these rooms

AMERICAN REVOLUTION BICENTENNIAL 1776-1976

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before January 15 at the Denver Hilton Hotel, 1550 Court Place, Denver, Colorado 80202, telephone 303-893-3333. When making reservations at the Hilton, be sure to identify yourself as a participant in the ERDA meeting so you will be accorded the special rates noted above. Please make reservations as far in advance as possible because this meeting is during the peak of the ski season.

Please provide us with a listing of all attendees, identifying those with and without "Q" clearances.

Martin B. Biles, Director
Division of Operational Safety

Enclosure:
As stated

1080560

Enclosure

HEALTH PROTECTION MEETING

DENVER, COLORADO

FEBRUARY 5-7, 1976

TENTATIVE LIST OF DISCUSSION TOPICS

1. Poisindex - a system for identifying trade name products
2. ERDA goals re energy for the future
3. H&S implications of new energy sources
4. ALAP - in search of guidance
5. EPA and the Federal Radiation Council guidance for Federal agencies
6. A medical and industrial hygiene program for coal conversion plants
7. Chronic diseases - stress preventive medical approach
8. Linking industrial hygiene and medical records
9. Providing advice on toxicological problems
10. Using bacteria to identify carcinogens
11. Medical participation in accident investigations
12. DTPA in plutonium inhalation cases
13. National personnel dosimetry QA program
14. Using the NBS neutron facility
15. Informing employees about hazardous materials
16. Aerosol sampling assistance for ERDA contractors

1080561

OSR 25-5
(REV 1-72)

DTPA files

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
ATOMIC ENERGY DIVISION
SAVANNAH RIVER PLANT
AIKEN, SOUTH CAROLINA 29801
(TWX: 810-771-2670, TEL: 803-824-6331, WU: AUGUSTA, GA.)

January 14, 1976

Dr. Walter H. Weyzen
Medical Research Branch
Division of Biology & Medicine
Energy Research and Development Administration
Washington, DC 20545

Dear Walt:

Our stock of DTPA is down to the point where if we should have anything gross occur we might be embarrassed. What are the chances of getting one or two hundred vials?

Do you have any idea when it will be off I.N.D.?

Sincerely,

George

George A. Poda, M.D.
Medical Superintendent

GAP/bs

00700

1080562

NEN New England Nuclear

Technetium-99m DTPA (Sn) Reagent Kit for use in the preparation of DTPA (Sn) Chelate

Convenient—

no need to administer blocking agent such as perchlorate
DTPA in lyophilized form
no need for refrigeration

Flexible—

kidney imaging
renal perfusion studies
brain imaging
glomerular filtration studies

Instant Use—

inject into vial
shake one minute
ready-to-use

Safe—

each kit supplied with radiation shield

Stable—

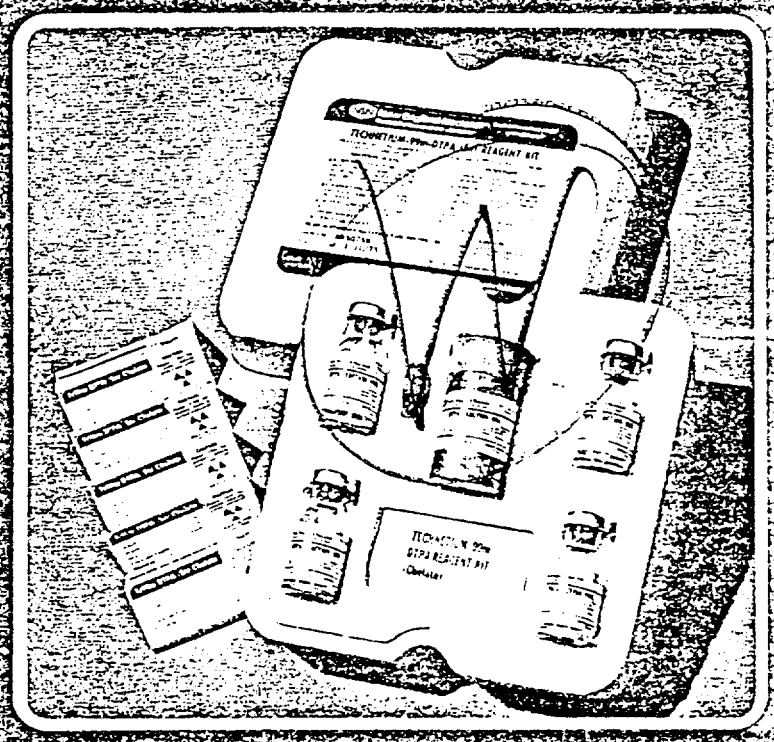
six month shelf life

Reliable—

chelated agents have been found to provide superior tumor to brain ratio

Available—

three major shipping points
Miami — Los Angeles — Boston



NEN's Technetium-99m DTPA (Sn) Reagent Kit provides an instant, convenient and safe means of preparing technetium-99m DTPA (Sn) Chelate. When prepared, the agent is suitable for direct intravenous injection for use in brain and kidney imaging, GFR studies and renal perfusion studies. The kit is intended for use with NEN's Technetium-99m Generator, or with any other approved source of technetium-99m.

Because of the six-hour half-life of technetium-99m, the agent is usually labeled on site on the day of use. Consequently, hospitals employing this nuclear medicine diagnostic technique find it desirable to have a simple, convenient and economical method for the preparation of the labeled agent.

Manufactured by UNION CARBIDE CORPORATION, Tuxedo, N.Y. 10987

ORDERING INFORMATION

NRP-425 NEN Technetium-99m DTPA (Sn) Reagent Kit

1-4 kits	$45 each
5-9 kits	40 each
10-15 kits	35 each

1080563

OVER

Incase you want to do something about this before I can:

U C chemical at Sterling Forest. N.Y. obtain DTPA from Eastman Kodak (but it can be obtained also from Fisher Scientific or Sigma Biochemicals) as a syrup (pH 13.0) as penta valent sa DTPA.

Two chemists Dean Holograf and Ephraim Liebermann (914-351-2131 ext 245) Then neutralize it. acid, dilute and put in vials 10 mg of the DTPA and 0.5 mg Sn.Cl, autoclave, test for pyrogenicity (horse shoe crab serum). They say they'll be glad to be our manufacturer if we can arrange this mutually through Dr. R. Crout (Bu Drugs) and Dr. Gyrafi (301-443-4250). They

1080564

James Potchen 517-353-0120.

PRODUCT MONOGRAPH

Name: Technetium-99m DTPA (Sn) Reagent Kit (Chelate)

DESCRIPTION

kit contains vials of sterile, pyrogen-free diethylenetriamine pentaacetic acid (DTPA) and stannous chloride. When sterile, pyrogen-free sodium pertechnetate Tc-99m is added to a vial, technetium 99m DTPA chelate is formed.

ACTIONS

Following its intravenous administration, technetium 99m DTPA chelate rapidly distributes itself throughout the extracellular fluid space from where it is (promptly) cleared from the body by glomerular filtration. There should be little or no binding of the chelate by the renal parenchyma. There is a variable percentage of the technetium 99m DTPA chelate which binds to serum proteins; this ranges from 3.7% following the single injection to approximately 10% if the material is continuously infused. Although the agent gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured glomerular filtration rate which is lower than the glomerular filtration rate as determined by inulin clearances.

Technetium 99m DTPA chelate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. The agent does not accumulate in the choroid plexus.

Since technetium 99m DTPA chelate is excreted by glomerular filtration, the images of the kidneys obtained in the first few minutes after injection represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collecting system and the renal pelvis.

INDICATIONS

Technetiun 99m DTPA chelate may be used to perform kidney scans, assess renal perfusion, brain scans, and estimate glomerular filtration rate.

CONTRAINDICATIONS

None.

WARNINGS

Technetium 99m DTPA chelate should not be administered to patients who are pregnant, or during lactation unless the benifits to be gained outweigh the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by a nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Sodium pertechnetate Tc-99m may contain oxidants or other contaminants which will prevent the pertechnetate from binding to the DTPA chelate. Although both "instant" and generator-produced pertechnetates have been successfully employed, the user should demonstrate that his source is without adverse effect on the properties of the resulting Tc-99m DTPA chelate before administration to humans.

PRECAUTIONS

To minimize radiation dose to the bladder, the patient should be encouraged to void when the examination is completed and as often thereafter as possible for the next 4-6 hours.

In the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

Technetium 99m DTPA must be formulated within six hours prior to clinical use. For optimum results, this time should be minimized. Intervals longer than one hour should be the exception.

The components of the kit are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic procedures during preparation of the agent.

ADVERSE REACTIONS

None.

DOSAGE AND ADMINISTRATION

The suggested dose range employed in the average adult is: kidney functions and imaging 3 to 5 mCi; brain imaging 10 to 20 mCi. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Technetium 99m decays by isomeric transition with a physical half-life of 6 hours[1]. Photons that are useful for imaging studies are listed in Table I.

(1) Dillman, L.T., Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, Supplement No. 2, MIRD pamphlet No. 4, *J. Nucl. Med.*, p. 22, 1969.

TABLE I
Principal Radiation Emmision Data

Radiation	Mean % Disintegration	Mean Energy (KeV)
M int. con. electron, γ-1	98.6	1.7
Gamma-2	88.3	140.5
K int. con. electron, γ-2	8.8	119.5
L int. con. electron, γ-2	1.1	137.7
Gamma-3	0.03	142.7
K int. con. electron, γ-3	0.96	121.7
K x-rays	6.5	18.4

The specific gamma-ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half-value layer is 0.3 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 4 mm thickness of Pb will attenuate the radiation emitted by a factor of about 10,000.

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table II.

Decay Chart
Technetium 99m, Half-Life 6.0 Hr.

Hours	% Remaining	Hours	% Remaining
—5	177.9	5	56.2
—4	158.7	6	50.0
—3	141.4	7	44.6
—2	126.0	8	39.7
—1	112.2	9	35.4
0	100.0	10	31.5
1	89.1	11	28.1
2	79.4	12	25.0
3	70.7	18	12.5
4	63.0	24	6.3

RADIATION DOSIMITRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 20 millicuries of ^{99m}Tc DTPA are shown in Table III.

(1) Method of Calculation: A Scheme for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, *J. Nucl. Med.*, p. 7, 1968.

TABLE III
Radiation Doses

Tissue	Absorbed Radiatiod Dose (rads/20 mCi)
Kidneys	0.84
Bladder	11.1
Testes	0.32
Ovaries	0.38
Whole-Body	0.32

HOW SUPPLIED

The DTPA $SnCl_2$ is supplied in kit form. The kit consists of 5 serum vials, each containing 10 mg of lyophilized $CaNa_3$-DTPA-$SnCl_2$. When sodium pertechnetate Tc-99m is added to a vial, the drug ^{99m}Tc-DTPA chelate is produced and ready for use.

KIT CONTENTS

- STERILE REACTION VIALS, each containing a lyophilized form of 10 mg $CaNa_3$ DTPA, 0.50 mg $SnCl_2$-$2H_2O$, pH adjusted to 4 with HCl.
- 1 RADIATION SHIELD for preparation and storage of ^{99m}Tc-DTPA (Sn) chelate.
- 10 PRESSURE SENSITIVE LABELS for final ^{99m}Tc-DTPA (Sn) chelate preparation.
- 1 PACKAGE INSERT.

PREPARATION

1. Aseptically swab rubber septum of shielded sterile vial.
2. Aseptically inject up to 60 mCi contained in a maximum of 4 ml of ^{99m}Tc, into sterile vial, withdraw an equal volumn of air.
3. Mix contents of vial for 1 minute.
4. Affix pressure-sensitive label.
5. The ^{99m}Tc-DTPA (Sn) chelate is ready for use.

STORAGE

Store kit contents at room temperature (22°C) or below.

DISPOSAL

The residual materials may be discarded in ordinary trash provided the vials and syringes read background with an appropriate low range survey meter. It is suggested that all identification labels be destroyed before discarding.

Manufactured by UNION CARBIDE CORPORATION
Tuxedo, New York 10987.

1080565

New England Nuclear
Radiopharmaceutical Division

Boston
Atomlight Place
North Billerica, Mass. 01862
617-667-9531

Los Angeles
17210 South Gramercy Place
Gardena, California 90247
213-321-3311

Miami
8119 N.W. 33rd St.
Miami, Florida 33166
305-592-0702

Canada
11475 Côte de Liesse
Dorval, Quebec H9P-1B3
514-636-4971

Europe
D6072 Dreieichenhain
West Germany
Siemensstrasse 1
Langen 06103-85035

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

January 23, 1976

To DTPA Users, Promoters, and Researchers

At the December 1975 IAEA Seminar on Diagnosis and Treatment of Incorporated Radionuclides, it became obvious that there were many more persons in the U. S. interested in the betterment of DTPA therapy than were able to make it to the Vienna meeting. We more fortunate attendees agreed there among ourselves that we would convene a rump session somewhere in the U. S. at the first opportunity, inviting all persons who might be interested in having some input into and exchanging ideas about what might be called "the DTPA problem."

The first opportunity for such a club meeting has now crystallized. The meeting will be held in the Spruce Room in the Denver Hilton Hotel from 1:00 to 4:00 p.m., on Sunday, February 8. This opportunity occurs because of the conjunction there of three other meetings:

1. The ERDA and ERDA-Contractor Health Protection Meeting (February 5, 6, 7) (E and S, Operational Safety).

2. A working session of the NCRP Committee on Radioactive Decontamination (George Voelz) (February 9, 10, 11). NCRP Subcommittee No. 37.

3. The Ninth Midyear Topical Symposium on Operational Health Physics of the Health Physics Society (Feb. 9-12, 1976).

My acting as ad hoc secretary results merely from my availability to get this notice out and help George Voelz, Tom Lincoln, and Vic Smith carry out the planning details. Since I do not know everyone interested in DTPA problems who are also planning to be in Denver that weekend, I am sure that I have overlooked some persons who would like to attend this meeting. If you know people not on the enclosed list of persons receiving this letter whom you would like to have had one, please give them a copy of yours and give me their names later. Also if you cannot come, please fill out the enclosed questionnaire for the purpose of planning future meetings. Everyone contacted so far agrees that these meetings should be as informal as possible and so an agenda for the Denver meeting is non-existent. We hope to have an open discussion on what we think we learned at the Vienna symposium and a free-wheeling round table about research-and-development needs for getting U. S. DTPA therapy on a par with that of our European colleagues.

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division
Directors, REAC/TS

Enc. 2

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Questionnaire

Name _____

Address _____

_____

I cannot make this meeting, but am interested in hearing about other meetings _____

I am not interested _____

I will attend the Denver DTPA Meeting, Sunday, Feb. 8, 1:00 p.m. _____

Send information also to _____

_____

_____

Return to:
C. C. Lushbaugh, M. D.
Chairman, Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

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Distribution List:

G. A. Andrews, ORAU Medical and Health Sciences Division, Oak Ridge, Tennessee
W. J. Bair, Battelle Pacific Northwest Laboratories, Richland, Washington
J. E. Ballou, Battelle Pacific Northwest Laboratories, Richland, Washington
A. J. Barker, General Electric Corp., St. Petersburg, Fla.
W. J. Beck, ORAU Special Training Division, Oak Ridge, Tennessee
J. D. Berger, ORAU Safety Office, Oak Ridge, Tennessee
M. W. Biggs, University of California, Lawrence Livermore Laboratory
S. P. Bliss, Sandia Corporation, P. O. Box 5800, Albuquerque, N. M.
D. W. Brown, University of Colorado Medical Center, Denver, Colorado
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B. I. Griffin, Battelle Pacific Northwest Laboratory
K. F. Hübner, ORAU Medical and Health Sciences Division, Oak Ridge, Tenn.
L. J. Johnson, Rockwell International, Canoga Park, California
G. C. Kealhofer, Ames Laboratory, Iowa State University
F. J. Kelly, Silas Mason Company, Inc., Amarillo, Texas
L. Kreisler, Reynolds Electric and Engineering Co., Inc., Las Vegas
J. F. Leary, Monsanto Research Corporation, Dayton, Ohio
T. A. Lincoln, Oak Ridge National Laboratory, Oak Ridge, Tenn.
A. Lindenbaum, Argonne National Laboratory
R. E. Linnemann, Radiation Management Corporation, Philadelphia
R. L. Levitin, Columbus Laboratories, Columbus, Ohio
R. A. Love, Associated Universities, Inc., Brookhaven National Laboratory, Upton, N
R. O. McClellan, Lovelace Foundation, Albuquerque, N. M.
C. L. McKinney, University of California, Davis
C. W. Mays, University of Utah
J. A. Mewhinney, Lovelace Foundation, Albuquerque, N. M.
W. Moore, Rockwell International, Rocky Flats Plant, Golden, Colorado
B. A. Muggenburg, Lovelace Foundation, Albuquerque, N. M.
I. C. Nelson, Battelle Pacific Northwest Laboratory
H. E. Palmer, Battelle Pacific Northwest Laboratory
G. A. Poda, E. I. du Pont de Nemours and Co., Savannah River Plant, Aiken, S. C.
I. S. Ravin, Boston Edison Co., Boston, Mass.
E. J. Reagan, Monsanto Research Corporation, Miamisburg, Ohio
E. Rothschild, Nuclear Fuel Services, West Valley, New York
J. Rundo, Argonne National Laboratory
E. L. Saenger, Cincinnati General Hospital
D. B. Shipler, Battelle Pacific Northwest Laboratories
V. H. Smith, Battelle Northwest Laboratories
W. Snyder, ORNL, Oak Ridge, Tennessee
H. Spencer, Veterans Administration Hospital, Hines, Ill.
J. H. Spickard, National Reactor Testing Station, Idaho Operations Office
C. J. Sternhagen, Kerr-McGee Corporation, Oklahoma City, Oklahoma
F. W. Strehl, Argonne National Laboratory
G. N. Taylor, University of Utah
F. K. Tomlinson, Monsanto Research Corporation, Mound Laboratory, Miamisburg, Ohio
G. L. Voelz, Los Alamos Scientific Laboratory
N. Wald, University of Pittsburgh
T. W. Walker, New Brunswick Laboratory, New Brunswick, N. J.
W. Weyzen, ERDA Headquarters, Washington, D. C.
M. E. Wrenn, Medical Center, Tuxedo, N. Y.
F. E. Zimmer, The Geisinger Medical Center, Danville, Pa.

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As of 2/3/76
*denotes changes

ERDA/CONTRACTOR HEALTH PROTECTION ATTENDEES

CHICAGO OPERATIONS OFFICE	John H. Pingle	
Argonne National Lab	Donald P. O'Neil C. S. Abrams Dr. Francis W. Strehl (MD)	
Ames Lab	Milo D. Voss	
Atomics International	Robert Tuttle	
Battelle Memorial Institute	Donald A. McKown George Krisch	
Brookhaven National Lab	Otto White, Jr. Charles B. Meinhold	
* Fermi National Accelerator Lab	Robert A. Adams Larry Coulson Paul Neeson	(NO Q) (NO Q) (NO Q)
Princeton Plasma Physics Lab	Harry J. Howe, Jr.	
IDAHO OPERATIONS OFFICE	Dr. C. Q. Writer (MD) (alternate John H. Spickard, MD) Bill Harrie	
Aerojet Nuclear Co.	Richard B. O'Brien Henry Peterson	 (L)
Allied Chemical Corp.	Bryce L. Rich	
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EPA	Jack Coogan	
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Oak Ridge National Lab	Newell E. Bolton Dr. T. A. Lincoln (MD) W. Porter C. E. Bemis, Jr. Doyle M. Davis	
National Lead - NLO	Michael W. Boback	

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Reactive Metals I.	Frank G. VanLoocke	
Union Carbide - K-25	Guy Fortney, (MD) Jack Bailey Herbert F. Higdon	
*		
Union Carbide - Y-12	Jack D. McLendon Gino Zanolli, (MD)	
Union Carbide - Nuclear Division	Robert Jordan	
Goodyear Atomic Corp.	Charles Blackledge Sam H. Eulett	
Paduca Area Office	Dick Baker	
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United Nuclear	L. V. Barker	
BNWL	John J. Jech Jack M. Selby Kenneth R. Heid Carl M. Unruh	
Atlantic Richfield Hanford	Bill J. McMurray	
J. A. Jones Const.	L. L. Crass	
HEDL - Hanford Eng. Dev. Lab	Wally Howell	
HEHF - Hanford Env. Health Found.	Dr. Brice Breitensteine	
SANFRANCISCO OPERATIONS OFFICE	Christine Laszca	
Lawrence Berkeley Lab - LBL	Robert M. Latimer Ralph H. Thomas	
* Lawrence Livermore Lab - LLL	Joseph Tinney	
Stanford Linear Accelerator Center	Charles Beal, MD Richard McCall	(NO Q) (NO Q)
SAVANNAH RIVER OPERATIONS OFFICE	Ken Sasser	
E. I. duPont	Dr. George A. Poda (MD) H. A. McClearin	
SREL - Ecology Lab	Robert I. Nestor Jack Hoy	
ENERGY RESEARCH CENTERS		
Grand Forks	Philip G. Freeman	
Morgantown	Joseph J. Gentile	(NO Q)
Pittsburg	James A. Hultz	

1080570

*	H. D. Bruner, MD, DBER
*	Philip A. Garon, Public Affairs
ERDA HEADQUARTERS	Donald M. Ross, OSD
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	L. Joe Deal, OSD
	William R. Albers (MD), OSD
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	George Ogburn, NRA
	C. Stuart Broad, Dpty Dir of Labor Rel.
	Jack Abrams, Ofc. Asst Adm/Fossil Energy
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	George B. Carroll, OSD
	A. Wendell Holmes, OSD
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Mound Lab	Dr. E. J. Regan
	A. G. Barnett
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Bendix	C. P. McKay
	J. G. Ochoa
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	H. J. Ettinger
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Los Alamos Area Office	William Crismon, Jr.
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General Electric-Pinellas	Dr. A. J. Barker (MD)
Rocky Flats Area Office	N. Richard Glover
	J. G. Stearns
Rockwell	R. J. Yoder
	Dr. W. S. Moore, (MD)
	W. F. McKelvey
	M. A. Thompson
	E. A. Putzier
	J. E. Hill
	C. R. Lagerquist
Sandia Lab - Albuquerque	W. D. Burnett
	D. R. Parker
	D. K. Devlin
Lovelace	J. J. Thompson

SPEAKERS

* George Washington U., St. Louis	Barry Commoner
Denver Poison Control Center	Barry Runack
Dow Chemical - Midland	Ralph Wagner
* EPA (Washington)	James Martin
Bureau of Standards	Greta Ehrich
Lawrence Livermore Lab	Joe Lipara

1080572

FROM:
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NO ACTION NECESSARY ☐
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COMMENT ☐
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BY:

CLASSIF:
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FILE CODE:

DESCRIPTION: (Must Be Unclassified)
Suggestions for the talk you are giving at the banquet, 3/25, at St. Petersburg, Fla., mtg. of ERDA & ERDA contractor occupational physicians

REFERRED TO	DATE	RECEIVED BY	DATE
H. Hollister (1)	2/23		
Dr. Weyzen (1)	2/23		

ENCLOSURES:
Commitment - policy
responsibility
needs - outline
Occ med - good med. prac.
epidem. - use data

REMARKS: to protect man - workers
impact broader responsibilities
DEPO outline these -
connection c̄ research - need for interaction - example

U.S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
MAIL CONTROL FORM
FORM ERDA-326S (4-75)

☆ U.S. GOVERNMENT PRINTING OFFICE: 1975-574-851

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OAK RIDGE NATIONAL LABORATORY

OPERATED BY

UNION CARBIDE CORPORATION

NUCLEAR DIVISION

POST OFFICE BOX X

OAK RIDGE, TENNESSEE 37830

February 20, 1976

Mr. Hal Hollister, Deputy Asst. Administrator
Office of Assistant Administrator for
Environment and Safety
U. S. Energy Research and Development
Administration
Washington, D.C. 20545

Dear Hal:

I forgot to ask you for a title for your presentation at the meeting of occupational physicians in ERDA and ERDA contractors being held in Florida, March 25 and 26, 1976. I used the title, "Occupational Health - The Research-Clinician Interface". If you don't like this title, please call Dr. Art Barker (FTS #350-8101) and give him any changes you may want to make.

We are trying to get the agenda and final announcement in the mail by February 27. If you have any questions about the title or content of your talk, or my suggestions which I sent you February 18, please call me.

Cordially,

Tom

T. A. Lincoln, M.D.
Medical Director

TAL:ph

cc: W. R. Albers, M.D.
W. W. Weyzen, M.D.

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OAK RIDGE NATIONAL LABORATORY
OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION

POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

February 18, 1976

Mr. Hal Hollister
Division of Biomedical and Environmental
Research
U. S. Energy Research and Development
Administration
Washington, D.C. 20545

Dear Hal:

I should like to offer the following suggestions and give you a few points which I think you should make in your talk, which you have kindly agreed to give at the banquet Thursday evening, March 25, at our St. Petersburg, Florida, meeting of ERDA and ERDA contractor occupational physicians:

1. The absolute maximum in time for your formal talk should be 20 minutes. Please feel free to invite questions from the audience for another five minutes.

2. There should be no slides showing organization charts of the ERDA bureaucracy. Nothing "turns off" physicians faster.

3. There should be no slides with bar graphs showing budget distributions, etc. Most occupational medical programs are overhead accounts and money problems are handled with local managements.

4. There will probably be a number of wives at the banquet, so your remarks should not be excessively technical.

5. DBER now has the added responsibility of R&D in health problems related to non-nuclear energy. How to wisely apportion funds between nuclear and non-nuclear energy health research is exceedingly difficult.

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6. ERDA is struggling with its PR. Occupational physicians have a close relationship with employees, other patients and the community. How can we in ERDA help you, the physicians, get well informed so you can respond candidly to those occasionally tough questions about the health and safety of the nuclear power industry.

7. ERDA invests many millions of dollars in biological research, yet the input from occupational physicians in deciding what health problems need to be studied has been minimal. You physicians probably have many ideas, questions, problems, etc. We need to know more about your research needs.

8. You physicians need to be better informed. Although, on a day-to-day basis, your concerns are with backaches, heart attacks, cancer, alcoholism, etc., you need to be aware of what is going on in ERDA research relating to health and safety. Awareness of general principles established in animal studies can help you in dealing with complex human problems following internal radionuclide contamination.

9. Because of the excellent radiation protection programs, there are few accidents. You have been discussing the research scientist-clinician interface today. We need also to think of better ways to help you organize treatment programs so everyone can get maximum information from accidents when they occur.

10. The idea of a newsletter for your organization sounds like a good way to improve communication, but it will only work if you participate. You have to be willing to submit material to the editor. You seem to be getting off to a good start, but maintaining the momentum will require participation by everyone.

11. When one considers the fantastic costs of health care provided to employees by most contractors in terms of sickness and accident, major medical, and total and permanent disability insurance, as well as sick leave, the cost of your efforts is a drop in the bucket. Nevertheless, if you do a good job and have the confidence of your employee patients, you can be of great value to us from a PR standpoint. You have the advantage of the doctor-patient relationship. We want you to know that we regard that as a vital asset. A good occupational medical program can do much to maintain good employee morale and build confidence in the sincerity of management's concern over worker health.

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12. Occupational health programs are expensive. You need to constantly look at what you are doing. Is it cost effective? We only want to get the most we possibly can for every dollar we spend. We may need to spend much more, but before we do, we have to be sure we will get a reasonable return from our investment.

If you have any questions, please call me.

Cordially,

T. A. Lincoln, M.D.
Medical Director

TAL:ph

cc: W. R. Albers, M.D.
A. J. Barker, M.D.
E. J. Reagan, M.D.
W. W. H. Weyzen, M.D.

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OAK RIDGE NATIONAL LABORATORY
OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION

POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

March 2, 1976

To: Distribution

I am sending you a copy of the announcement of Professor Catsch's death, see attached, on February 16 because I was not certain whether you would receive it directly. As you know, we had hoped to have him come to our Florida meeting of ERDA occupational physicians and several of us had gotten to know him quite well while we were in Vienna. We all had been tremendously impressed by his knowledge, enthusiasm and leadership in the field of chelation therapy.

Sincerely,

T. A. Lincoln, M.D.
Medical Director

TAL:ph

Enclosure

Distribution:

W. R. Albers
W. J. Bair
A. J. Barker
A. Lindenbaum
C. W. Mays
J. A. Mewhinney
B. A. Muggenburg
E. G. Reagan
E. Saenger
H. Spencer
G. L. Voelz
N. Wald
W. H. Weyzen

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GESELLSCHAFT FÜR KERNFORSCHUNG MBH KARLSRUHE

KARLSRUHE 24. 2. 76 75

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MIT LUFTPOST PAR AVION

Dr. T. A. Lincoln
Oak Ridge National Laboratory
Nuclear Division
P. O. Box X

Oak Ridge, Tenn. 37830

U.S.A.

Drucksache
Imprimés

Alexander Catsch

Prof. Dr. med.

28. Februar 1913 — 16. Februar 1976

In Dankbarkeit und tiefer Trauer
Gerda Catsch, geb. Hagen
Andreas Catsch
Michael und Tatjana Catsch

Die Beerdigung hat auf Wunsch des Verstorbenen in aller Stille stattgefunden.
Bitte keine Beileidsbesuche.

Karlsruhe-Durlach, im Februar 1976

1080579

UNITED STATES
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

OAK RIDGE OPERATIONS
P. O. BOX E
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8611

March 3, 1976

James L. Liverman, Director, Division of Biomedical and Environmental Research, Headquarters

REPORT OF FOREIGN TRAVEL BY C. C. LUSHBAUGH, ORAU

Enclosed is a copy of the report prepared by Dr. Lushbaugh covering his travel to Vienna, Austria, to attend and present a paper at the IAEA Seminar on Diagnosis and Treatment of Incorporated Radionuclides, during the period December 8-12, 1975. The report has been reviewed and contains no classified information.

This report has been delayed with ERDA approval due to a request from J. H. Kane, OPA-HQ, that Dr. Lushbaugh write a second report on the same meeting. Dr. Lushbaugh had to wait for some data from the other U.S. delegates for preparation of the second report and he wanted to use some of this data in his foreign trip report. The second report was dated February 23, 1976, and was sent directly to Mr. Kane. Additionally, Dr. Lushbaugh was ill and was unable to complete the report as anticipated by the February 16, 1976, extension deadline.

Joseph A. Lenhard, Director
Research and Technical Support Division

OR:MW

Enclosure:
Trip Report

cc: G. F. Helfrich, OIPI-HQ, w/encl (2)
J. G. Poor, ISA-HQ, w/encl (2)
H. E. Lyon, SS-HQ, w/encl
C. A. Keller, w/o encl
W. T. Sergeant, w/encl

ORIGINAL

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Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

February 20, 1976

To: Philip L. Johnson

From: C. C. Lushbaugh

Subject: Foreign Trip Report on IAEA International Seminar on Diagnosis and Treatment of Incorporated Radionuclides, December 8-12, 1975

The purpose of this trip was to attend and participate in this seminar by presenting a paper describing our newly developing REAC/TS program in which the use of chelation agents for the removal of internally contaminated radionuclides is an integral part.

The meeting was held in the main conference hall of IAEA in Vienna, Austria. This room is well outfitted for multilingual conferences. Well-trained, exceedingly fluent translators provide concurrent versions of papers being presented or discussed. The electronics are topnotch also. What difficulties occurred did so as the result of some speakers either not following their text at all, or trying to crowd an hour-long lecture into 15 minutes of allotted time.

There were about 110 attendees from 28 countries. The French were most numerous (18) and the United Kingdom and U.S. next (15 each). While there was some evidence of emotional, as well as scientific differences, all were friendly and no discussions could be classed as "heated." The coffee breaks served as mixers and allowed more penetrating discussions than occurred in the meeting hall. None of the four USSR speakers showed up and their absence was not explained. The U.S. showing was better only because of a greater total number who attended. At least five U.S. speakers did not make it and several who did came at the last minute on nongovernmental, private funds. All of this caused a lot of last-minute program rescheduling and new appointments of program chairmen. Apparently some ERDA operations offices avoid making foreign travel decisions as long as possible but allow abstracts to be submitted without travel monies being budgeted in advance. This results in last-minute cancellations that are baffling in the eyes of attendees from other countries. The IAEA staff seemed inured to this problem but many of the U.S. delegates were not and felt this practice sufficiently embarrassing to U.S. performance to warrant comment and corrective action.

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Although many U.S. attendees came away disappointed from the meeting with the impression that no significant advances had occurred in the last 10 years in improving the removal of incorporated radionuclides from the body, I came away from the meeting feeling that at last I had been briefed as thoroughly as possible on the past and present state-of-this-art, had had the pros and cons of many important questions evaluated thoroughly, and now understood to my satisfaction where we would need to focus our attention in the future.

As a seminar rather than a scientific symposium, some teaching and learning are involved as conference objectives. The main objective was to review all the major aspects of this relatively narrow but important problem. The seminar, in my opinion, achieved this objective well through the device of having well-chosen, invited speakers who were without controversy and truly experts in their fields. These men not only presented scholarly papers in great depth but then led the discussions that followed the presentations of the submitted papers. Some of these men from the U.S. and U.K. were friends and acquaintances of mine with whom I had interacted previously in human radiation biology, while others I knew only from having read their scientific papers. Dr. A. Catsch (Federal Republic of Germany), whom I had never met, was in Dr. Lincoln's and my view the outstanding participant at this conference. His lectures were professorial in the real sense and it was a pleasure to be his student for a week. His insight and plans for future work were brilliant. The experience of meeting and talking with this man alone made the entire trip worthwhile. (I understand from Dr. Lincoln that since the conference Dr. Catsch has had a serious cerebrovascular accident which will prevent his traveling to the U.S. as he had planned. (His recovery seems assured at this time.)

More than 40 papers presented over five days are difficult to summarize individually in detail. I have listed them at the end by senior author or speaker and by title in order of their final presentation. I intend to refer to them only as they contributed in my mind to some "position statements" that I think are important to the future improvement of DTPA usage in the U.S. These position statements have become known to some of us as "Tom Lincoln's gems" and are described further in Dr. Lincoln's trip report. He referred to them as gems because they were crystal clear conclusions that were both unexpected but sorely needed by many of us:

1. $CaNa_3DTPA$ is the drug of choice for plutonium chelation immediately after an accident (Catsch) (Volf) for americium and curium (Seidel). Therapy must start within one hour.

2. CaDTPA is more efficient than ZnDTPA but is more toxic in dose fractionation or protracted use (Catsch) (Cohen) (V. Smith).

3. Contraindications to CaDTPA therapy are pregnancy, aplastic anemia, nephrosis (Catsch) (Mays) (Cohen) (Volf) (Bair) (V. Smith).

4. Present methods of body-burden estimates are woefully inadequate. Urinalysis and Langham's equation grossly overestimate the exposure (Rundo) (Bair) (Catsch) (Dean) (Ramsden) (Voelz) (Werner).

5. No untoward long-term effects have been documented as yet in persons who have received DTPA treatments (Catsch) (Voelz) (Dolphin) (Jammet).

6. In practical therapy, a) treat as quickly as possible, b) dose response is not linear (one gram dose is adequate), c) aerosol prolongs effect and does cause toxicity (Lincoln).

7. Experimentally (at 50-100 times human dose) DTPA toxicity is measured by a) G.I. reaction, b) transitory emphysema (V. Smith), c) decrease in zinc metalloenzymes (Cohen) (Catsch), and d) teratogenicity (Taylor) (Cohen).

8. CaDTPA is locally painful but can be used in wound first aid (Jammet).

The French have developed small first-aid kits for nuclear workers to wear (Jammet) (Nenot) that contain chelation agents for the entire gamut of potential accidental contaminants. DTPA is administered by nasal aspiration of a dry-powdered aerosol generated by a spinning propeller in the vial. While this approach may seem to be quite clever, and perhaps the way to obtain immediate first aid and prevention of absorption, it seemed to the more clinically oriented participants that it puts too much responsibility in the hands of the worker who is ill-prepared to make therapeutic decisions or to decide that an accidental exposure has occurred.

The seminar contained little clinical material or retrospective evaluations that can be used to appraise the effect of DTPA usage in man over the last 10 years. Such material is being collected by the British at their Windscale plant (Schofield) and by the National Radiological Protection Board at Harwell (Dolphin) where, according to Dr. George Voelz who visited there on his way to Vienna, they are planning to start a National Registry for Radiation Workers. This is an obvious need of our nuclear health program, but we are far from achieving such a program in the U.S., even though I understand NRC has this need targeted. In REAC/TS we are attempting to establish, as you know, an overexposure, radiation-worker registry and running into a vacuum containing neither resistance nor support. This meeting suggested to me that we should also be trying to identify for the record those persons who in the past had exposures that led to their having had $CaNa_3DTPA$ treatments. Some observations in dogs at Battelle-Northwest Laboratory (Bair and V. Smith) suggest that there may be long-delayed untoward effects in such cases. The dose-response relations, however, are not defined.

This was my first European trip. I found it an impressive, well-worthwhile experience for which I am quite appreciative. The information I obtained about DTPA and the therapy of accidental contaminations with radioactive substances is extremely applicable to my work in the REAC/TS program, as it is related to assisting ERDA with future development of metallic chelators.

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List of papers in the order they were presented at the IAEA International Seminar on Diagnosis and Treatment of Incorporated Radionuclides. Only the speakers' names are given.

Session I

(Butler, Canada) Review paper: Metabolic excretion and retention patterns of incorporated radionuclides in reference man.

(Rundo, U.S.A.): The excretion rate and retention of plutonium 10,000 days after injection.

(Grimes; U.K.): Aldermaston work on plutonium binding with biological systems.

(Brightwell, U.K.): The translocation to thoracic lymph nodes of inhaled aerosols of plutonium dioxide and of mixed plutonium-sodium oxides.

(Smith, U.K.): Effect of inhaled aerosols of plutonium dioxide and of mixed plutonium-sodium oxide upon thoracic lymph node morphology.

Session II

(Bair, U.S.A.): Review paper: Recent results of animal studies on the deposition, retention and translocation of plutonium compounds.

(Zablotna, Poland): Effects of DTPA on the deposition of ^{65}Zn, ^{60}Co and ^{144}Ce in pregnant rats and in fetoplacental unit.

(Mewhinney, U.S.A.): The effects of varying physical and chemical characteristics of inhaled plutonium aerosols on metabolism and excretion.

(Stojanovic, Yugoslavia): Studies of the effects of ionizing radiation on the penetration of radiocesium through damaged skin and possibilities of decontamination.

(Metivier, France): Experimental study of contamination by a mixture resulting from the combustion of sodium in the presence of plutonium oxide.

(Suzuki-Yasumoto, Japan): Absorption and metabolism of radioactive cobalt compounds through normal and wounded skin.

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Session III

(Ramsden, U.K.): The assessment of plutonium in lungs for both chronic and acute exposure conditions.

(Voelz, U.S.A.): Considerations in the assessment of plutonium deposition in man.

(Sharma, India): Assessment of chest burdens of plutonium.

(Lincoln, U.S.A.): The use of DTPA and induced sputum as diagnostic techniques following internal contamination.

(Smith, for D. B. Shipler et al., U.S.A.): Development of a diagnostic model for inhaled promethium-147--Animal studies.

(Fromheim, Germany): A new approach for an improved short-time localization measurement of low activity, low energy transuranium deposits. in wounds.

(Ohlenschlager, Germany): Review of removal of a four-month old plutonium wound deposition caused by a puncture wound on the left middle finger tip.

Session IV

(Werner, Germany): A whole-body counter with invariant response.

(Rundo, for F. K. Tomlinson, U.S.A.): Plutonium-238 lung counting with Phoswich detectors.

(Lössner, Germany): High sensitivity detection of low energy photon emitters in man by pulse-shape analysis.

(Dean, U.S.A.): Design criteria for phantoms for calibration of external detectors for the in vivo assay of plutonium.

(Rundo, U.S.A.): A rapid method for estimating the effective depth of internally deposited ^{241}Am.

(Schmitt, Germany): Recent developments in lung counting at Karlsruhe.

Session V

(Catsch, Germany): Review paper: Removal of transuranic elements by chelation therapy: Limits, open questions and prospects.

(Volf, Germany): Plutonium decorporation in rats: Experimental evidence and practical implications.

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(Seidel, Germany): The removal of ^{252}Cf and ^{241}Am from the rat by Ca- and ZnDTPA.

(Muggenberg, U.S.A.): The removal of inhaled ^{239}Pu from beagle dogs by lung lavage and chelation treatment.

(Nenot, France): Treatment of accidental inhalation of plutonium oxide by pulmonary lavage.

(Lindenbaum, U.S.A.): Retention of polymeric plutonium in mouse tissues as affected by antiviral compounds and their analogs.

(Stather, U.K.): The experimental use of aerosol and liposomal forms of CaDTPA for removing plutonium.

Session VI

(Dolphin, U.K.): Review paper: Review of some problems and recent research work associated with the use of chelating agents for the removal of incorporated radionuclides from humans.

(Grimes, U.K.): Chelating agents in the removal of radioisotopes from humans.

(Cohen, U.S.A.): Enhanced excretion of Am-241 after intravenous administration of $Na_3CaDTPA$ in man and the baboon; a comparison.

(Smith, for H. E. Palmer, U.S.A.): Rapid removal of sodium isotopes from the body following accidental internal contamination.

(Ohlenschläger, Germany): Comparison study of medicament-therapeutics results from wound contamination by plutonium nitrate.

(Edvardsson, Sweden): Elimination of ^{241}Am following a case of accidental inhalation: Short communication.

(Planas-Bohne, Germany): Toxicological studies on DTPA.

(Smith, U.S.A.): Aspects of inhaled DTPA toxicity in the rat, hamster and beagle dog, and treatment effectiveness for excorporation of Pu from the rat.

(Ducousso, France): Contraindication of CaDTPA in the treatment of radiation-contaminated persons.

(Arndt, Germany): Examination of working places and workers exposed to ^{147}prometheum in dial painting.

(Deworm, Belgium): Ten years' experience of determining internal contamination in plutonium laboratory workers.

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Session VIII

(Jammet, France): Review paper: Principles of medical first-aid of workers who might be exposed to internal contamination.

(Pasquier, France): Emergency treatment of internal radiation contamination: Principles and practice.

(Lushbaugh, U.S.A.): "REAC/TS:": A pragmatic approach for providing physician education for radiation emergencies requiring decontamination and medical care.

(Irlweck, Austria): Tritium levels in urine and blood samples of occupational exposed persons - results of routine checks in R. C. Seibersdorf.

1080587

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

March 19, 1976

Dr. Walter H. Weyzen
Deputy Manager
Physical and Technological Programs
Division of Biomedical and
Environmental Research
Energy Research and Development
Administration
Washington, D. C. 20545

Dear Walt:

As per yesterday's phone conference, I am sending you the updated DTPA insert for you to modify and obtain FDA's concurrence before we print it and send it out to DTPA users. I am also enclosing for your information Xeroxes of the New England folder that indicates that Union Carbide Corporation, Tuxedo, New York, is manufacturing DTPA in this country. Mr. Frank Bruce of UCN here is looking into this for us. It may answer one of our greatest needs. Among the DTPA priorities we discussed, I will try to obtain a consensus of the occupational physicians on the following questions:

1. What routes of administration need to be approved by FDA for therapy?
2. Are there any new research results that would indicate that aerosol usage should not be approved?
3. Are there any that suggest contraindications to its use?
4. What is the true shelf-life of DTPA? What is the best test of DTPA degradation by time, etc.?
5. How do we obtain a new source from an FDA-approved American manufacturer?
6. Usage reporting needs to be standardized.
7. Establishment of a DTPA patient-registry for future monitoring lookng for late untoward effects.
8. Can the group recommend a standard dose and route of administration?
9. Is Zn-DTPA necessary? If so, where are copies of the toxicity report, etc.?

All these questions should require at least five days if it does not rain. I will keep in touch.

Yours sincerely,

C. C. Lushbaugh, M. D.

CCL:fb

1080588

Enc.

P. S. You instructed us in the past to send you any "pink slips" we find in the DTPA material. We found two (enclosed). We are sending Xeroxes of the original notes with them in case you want to answer these (I can't tell if you did--my notes about the Demoleas case indicate that you and I think a modification of the DTPA FDA-IND for use with thorotrast may be required. Can we do that on your and my visit to FDA in April?

CCL

PACKAGE INSERT

(Revised March 1, 1976)

Diethylenetriaminepentaacetic acid or DTPA is a chelating agent for plutonium and transuranic elements. Its structural formula is:

$$(CH_2COOH)_2NCH_2CH_2N(CH_2COOH)CH_2CH_2N(CH_2COOH)_2$$

The following information on DTPA is provided for your use in the treatment of internal contamination by plutonium and other transuranic elements. It should be posted conspicuously and kept available for quick reference where the DTPA is stored.

The DTPA provided is the same as that put out by Geigy Chemicals under the name of Calcium Chel[R] 330 (Brand of trisodium calcium penthamil). The present DTPA is also in this salt form.

1. Each ampoule provided contains 1.0 gram of DTPA in injectable form (4.0 ml of 25% solution). The solution should be clear, colorless, and free of crystalline or other material. The dose for a day should not be fractionated. Intravenous administration should not be protracted over more than 2 hours.

2. The average daily dose is 1.0 gram intravenously per day injected very slowly or added to an intravenous drip as defined in the Investigational New Drug Application (enclosed).

3. A commonly used schedule is five daily injections per week for two weeks adjusted according to the observed excretion of the transuranics in the urine. Other regimens can be used--see enclosed reprint and/or consult with physicians who have used the agent:

C. C. Lushbaugh, M.D., Director
Radiation Emergency Assistance Center/Training Site
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830
FTS: 850-4642, Ext. 215
Commercial: (615) 483-8411, Ext. 215

T. A. Lincoln, M.D., Director
Health Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830
FTS: 850-6681
Commercial: (615) 483-8611, Ext. 3-6681

4. The chelating efficiency is greatest immediately after incorporation (within one hour) when the element is circulating in or available to the tissue fluids and plasma.

5. Contraindication to its use is a history of severe renal damage. Although there is the possibility of hypersensitivity, so far as is known none has been reported. The agent should be injected slowly to obviate the possibility of "colloidocrisis."

6. The urine and renal function should be watched for signs of nephrotoxic reaction.

7. The ampoules should be stored in a cool place and away from sunlight.

8. Any signs of deterioration (discoloration or cloudiness) of the solution or reaction on the part of the patient should be reported at once to one of the following physicians.

W. H. Weyzen, M.D.	FTS: 233-5355, ERDA
W. W. Burr, M.D.	FTS: 233-3153, ERDA
C. C. Lushbaugh, M.D.	FTS: 850-4642, Ext. 215 Commercial: 483-8411, Ext. 215

The Food and Drug Administration requires that ERDA, the holder of the Investigative New Drug authorization, be in a position to account for the ampoules sent to investigator-physicians. Please, therefore, set up an accounting system on the supplies of DTPA and be prepared to report your experience on an annual basis.

Please note also that as an investigator-physician of the DTPA IND you are required to forward to the Division of Biomedical and Environmental Research all observations on the safety and efficacy of the DTPA used by you in agreement with the protocols which you submitted in connection with your original request for DTPA.

List of Attendees at Occupational Physicians in ERDA & ERDA Contractors Meeting - March 25, 1976

A. J. Barker - GEND Pinellas
Bryce Breitenstein - Hanford Environmental Health Foundation
Darrell R. Fisher - University of Florida (formerly Utah group)
Scott E. Calder, - University of Utah Radiobiology Laboratory
C. A. Lang - Fermilab - Batavia, Illinois
F. W. Strehl - Argonne National Laboratory - Argonne, Illinois
H. C. Rogers - Phs./ERDA Germantown, Maryland
H. D. Bruner - DBER/ERDA Germantown, Maryland
A. S. Garrett - ORNL - Oak Ridge, Tennessee
A. Lindenbaum - Argonne National Laboratory
P. D. Klein - Argonne National Laboratory
Robert L. Levitin - Battelle Columbus Laboratories
George A. Poda - DuPont Co. Savannah River Plant, Aiken, S. C.
L. J. Hoge - Knolls Atomic Power Laboratory, Schenectady, N. Y.
E. H. Schnicke - Johnston Atoll, Holmes & Narver, Inc. D. N. A.
George C. Kellhofer - Ames Laboratory - Ames, Iowa
Leonard Kreisler - REECO Las Vegas, Nevada
William R. Albers - DOS/ERDA Headquarters
James F. Park - Battelle Northwest - Richland, Washington
Bernard Zager - GE NED - San Jose, California
S. P. Bliss - Sandia Laboratories - Albuquerque, New Mexico
Gino Zanolli - Y-12 Oak Ridge, Tennessee
R. M. Gastineau - Westinghouse Bettis Lab. - West Miffin, Pennsylvania
Robert W. Bistline - Rockwell Int. - Rocky Flats Plant - Golden, Colorado
Bruce A. Muggenburg - Lovelace Foundation - Albuquerque, N. M.
John J. Downey - Brookhaven National Lab. - Upton, N. Y.
Frank J. Kelly - Mason & Hanger - Amarillo, Texas
Niel Wald - University of Pittsburgh, Pittsburgh, Pennsylvania
E. J. Reagan - Mound Lab - Miamisburg, Ohio
George L. Voelz - Los Alamos Scientific Lab. - Los Alamos, New Mexico
Eugene L. Saenger - University of Cincinnati - Cincinnati, Ohio
John H. Spickard - ERDA/INEL - Idaho Falls, Idaho
Robert H. Esterday - Bendix Corp. - Kansas City, Missouri
Vic Smith - BNWL
C. Lushbaugh - ORAU
T. Lincoln - ORNL
D. Ofte - ERDA/PAO
G. Huffman - ERDA/PAO

1080592

Walter W.

Send me _____ Polyphosphate Kits.

I am ordering these other products. P. O. No. _____

_____

_____

Send me information on:

_____
Signature

- ☐ *Diphosphonate Kit*
- ☐ *Polyphosphate Kit*
- ☐ *Phytate Kit*
- ☒ *DTPA Kit*
- ☐ *Quantity Prices*
- ☐ *Gallium^{67} Citrate*
- ☐ *Xenon^{133} Gas*
- ☐ *Xenon^{133} Saline*
- ☐ *Selenomethionine*
- ☐ *Catalog*

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INFORMED CONSENT FORM

FOR USE OF CA-DTPA, AN INVESTIGATIONAL DRUG

Name:_____ Age:_____

Date:_____ Time:_____AM/PM

I_____, hereby request and authorize_____, M.D. to give to_____the drug calcium-diethylenetriamine-
(myself)
pentaacetic acid (Ca-DTPA) in an attempt to enhance the removal of_____ from my body.

I understand that Ca-DTPA is an investigational drug and not available for general use. This compound has the property to bind with some heavy metals, including iron, lead, plutonium, americium, and the other heavy metals within the body and helps the body to excrete them. Some risks in taking Ca-DTPA with daily doses up to 1 gm are: possible damage to the kidneys and the liver, or additional damage to those organs if they are already diseased. In some persons, the compound may cause a reduction of the platelet count, mild muscle spasms, some hair loss, mouth ulcers, and skin rash, after prolonged therapy. I have been fully informed of these risks and possible consequences and understand that unforeseen results may occur. The alternative methods of treatment such as waiting for spontaneous excretion have been explained to me, and I realize that this drug (Ca-DTPA) is offered to me only after careful deliberation of Dr._____ _____and his colleagues.

I am consenting to its use for the study and/or treatment of my condition with the understanding that the results of this treatment may not necessarily be of benefit to me. The use of Ca-DTPA in the treatment of internal radionuclide contamination is part of a national research program. I do not object if any information relating to my case is used in professional journals or medical books, or for any other purpose in the interest of medical education, knowledge, or research, provided however that it is specifically understood that in any such publication or use I shall not be identified in any way. I am reserving the right to withdraw my permission at any time without prejudicing my further medical care. Dr._____has also offered to answer any of my questions.

Signed_____
(Patient)

Witness_____

The foregoing consent was read, discussed, and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness_____

Date_____

1080595

(This form has been approved for use of noninstitutional physicians by the ORAU/ORNL Committee on Human Studies, Oak Ridge, Tennessee, and ERDA Biomedical Research Division of Safety, Standards, and Compliance.)

Revised

INFORMED CONSENT FORM

FOR USE OF CA-DTPA, AN INVESTIGATIONAL DRUG

NAME: _____ AGE: _____ DATE: _____ TIME: _____ AM/PM

I _____, hereby request and authorize _____, M.D. to give to _____ the drug calcium-diethylenetriamine-pentaacetic
(myself)
acid (Ca-DTPA) in an attempt to enhance the removal of _____ from my body.

I understand that I have been involved in an incident where I was exposed to radioactive _____ and may have been contaminated, to some degree, by this exposure. The above named physician has consulted with me concerning this condition and has advised me that one method of treatment is the use of the drug Ca-DTPA. I understand that I may require repeated doses of this drug several times a week for up to several months depending on the level of contamination that I have experienced, should I decide to accept this method of treatment.

I understand that Ca-DTPA is an investigational drug and not available for general use. The term "investigational drug" means that the drug, Ca-DTPA, is undergoing investigation, under FDA control, to determine its effects on man. It has been explained to me that this compound has the property to bind with some heavy metals, including iron, lead, plutonium, americium, and the other heavy metals within the body and helps the body to excrete them. Some risks in taking Ca-DTPA with daily doses up to 1 gm are: possible damage to the kidneys and the liver, or additional damage to those organs if they are already diseased. I understand that all risks are not known at this time. I have been fully informed of the known risks and possible consequences and understand that unforeseen results may occur. The alternative methods of treatment such as waiting for spontaneous excretion have been explained to me, and I realize that this drug (Ca-DTPA) is offered to me only after careful deliberation of Dr. _____ and his colleagues.

I am consenting to its use for the study and treatment of my condition with the understanding that the results of this treatment may not necessarily be of benefit to me. The use of Ca-DTPA in the treatment of internal radionuclide contamination is part of a national research program. I do not object if any information relating to my case is used in professional journals or medical books, or for any other purpose in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified in any way. I further agree that I will participate in whatever follow-up studies are deemed appropriate by my physician at whatever intervals are found suitable by the investigators. I am reserving the right to withdraw my permission at any time without prejudicing my further medical care. Dr. _____ has also offered to answer any additional questions about this drug and possible delayed effects.

1080596

Signed: _____
(Patient)

Witness: _____

The foregoing consent was read, discussed, and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness _____

Date _____

DTPA ACTIVITIES

I. Management for BER/ERDA of $CaNa_3DTPA$ trials in chelation therapy of Pu and other actinide contaminations by physicians in ERDA plants and contractor facilities.

A. Annual audit of DTPA usage and experience.

1. Number of cases treated (amount of DTPA expended).

2. Stockpiles.

3. Analysis of case histories.

a) initial body-burden estimates.

b) initial urine and fecal excretion

c) increased decorporation by chelation

d) treatment schedule

e) residual body-burden

B. Official report of investigators' experience for FDA. Toxic effects.

C. Upgrading of protocols and consent forms, improvements in routes of administration, re-evaluation of biochemical clinical tests surveying for untoward effects.

D. Procurement of a new pharmaceutical company willing to manufacture DTPA under FDA compliance regulations for human use.

E. Evaluation of scientific literature on specific chelation agents, such as ZnDTPA,to determine if animal toxicity and chelation studies are sufficient to warrant the development of a new FDA-IND for ZnDTPA.

F. Overview of ongoing ERDA-supported research in chelation to determine the need for any redirection or additional projects on special problems.

1080597

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17 D 18 SUBJECT (Unclassified) 49

Req. comments on dft. of Consensus statements developed at the

17 E 18 mtg. of ERDA & ERDA contractor physicians & research scientists 49

17 F 18 at the G. E. Pinellas Plant 49

17 G 18 49

17 H 18 ENCL: as stated 49

17 I 18 SUBJECT (Continued), REMARKS, ENCLOSURES 49

ACTION

17 J 18 49

K 18 49

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~~Dr. Brunner~~	~~4/12~~
Dr Weissgen	4/14

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1080598

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Roy E. Albert	New York University Hospital
John W. Athens	Univ. of Utah Medical Center
Earl M. Best, Jr.	Reynolds Electrical & Engineering Co.
Max W. Biggs	Lawrence Radiation Laboratory
S. P. Bliss	Sandia Corporation
Donald W. Brown	University of Colorado
B. M. Brundage	Atomic International
Thomas F. Budinger	Lawrence Radiation Laboratory
Jerrod P. Commons	Worcester Hahheman Hospital & Laboratory
Asher J. Finkel	Argonne National Laboratory
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T. A. Lincoln	Oak Ridge National Laboratory
Roger E. Linnemann	University of Pennsylvania
David I. Livermore	Kirtland Air Force Base
Robert A. Love	Brookhaven National Laboratory
C. C. Lushbaugh	Oak Ridge Associated Universities

1080599

R. A. MacHaffie	Oregon State University
Raymond E. Masters	Westinghouse Bettis Atomic Power Laboratory
Capt. W. S. Matthews	Naval Hospital, Oakland
Charles L. McKinney	Cowell Student Health Center
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Eugene L. Saenger	Radioisotope Laboratory General Hospital
Frederick H. Shillito	Battelle Columbus Laboratories
William K. Shulte	Space Division of North American Rockwell Corporation
L. N. Spohneimer	Ames Laboratory, Iowa State Univ.
Charles J. Sternhagen	Kerr-McGee Corporation
Francis W. Strehl	Argonne National Laboratory
Niel Wald	University of Pittsburgh
Harry O. Whipple	Los Alamos Scientific Laboratory
Frederick E. Zimmer	Geisinger Medical Center
George L. Voelz	Idaho Operations Office, AEC

1080600

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6 April 1976

To Distribution

Enclosed is a draft of 11 consensus statements developed by Lush and I after hearing your comments on the seven briefly discussed at our recent St. Petersburg, Florida meeting.

The draft has intentionally been double spaced so you can write your comments, corrections and additions directly on this copy. In order to get the final draft completed and forwarded to everyone who attended, as well as appropriate administrators without delay, please send me your comments by April 19.

If I have not received your comments by April 26, I shall assume you have none and approve of the draft as written.

At the bottom of your copy please indicate who, outside the attendees in Florida, should receive the final draft. In the meantime, DO NOT CIRCULATE THIS DRAFT. It is a possibly sensitive item.

Art Barker is working on the transcript of our meeting but this necessarily will take considerable time.

Thank you for your help.

T. A. Lincoln, M. D.
Health Division

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Attached Distribution List

1080601 04559

Consensus Statements Developed at the
Meeting of ERDA and ERDA Contractor Physicians and Research Scientists
at the G. E. Pinellas Plant, St. Petersburg, Fla., March 25 & 26, 1976

1. Ca DTPA should continue to be used for the treatment of internal contamination with radionuclides for which its effectiveness has been demonstrated. Treatment should begin as promptly as possible after exposure.

2. Better guidelines should be developed regarding how much historical information and physical dosimetry estimates are necessary before treatment is started.

3. Further experimental studies are needed concerning the teratogenicity of Ca DTPA in order to develop a better risk benefit basis for deciding whether or not to treat a pregnant woman who has received internal contamination.

4. Additional information uncovered after the Florida meeting indicates that written and signed informed consent is not required for Ca DTPA use. Verbal informed consent, documented with a note in the clinical record, is, of course, needed. Approval by local human studies review committees is also not practical in many locations because clinical research is not conducted in local hospitals or plants. It is recommended that if FDA and/or ERDA decide that written informed consent and human studies committee approval are necessary, guidelines and forms be developed by the DTPA committee.

5. Women in the child bearing age should be informed of the potential hazards to a fetus whenever informed consent for initiating Ca DTPA treatment is requested. Until the risk is better defined, Ca DTPA should not be used in treating a woman who is possibly pregnant.

If the uptake of the radionuclide is expected to be greater than several body burdens, (see 3 above) the risk from the radionuclide may outweigh the potential teratogenicity of the chelating agent. At such times, consideration may have to be given to terminating the pregnancy.

6. An investigative new drug application (IND) for Zn DTPA should be submitted as soon as the necessary animal studies are completed. The IND should include clinical trials of Zn DTPA by intravenous injection, aerosol, wound injection (subcutaneous and intramuscular), injectable slow release form, and topical application (used as a skin decontaminating agent).

7. The status of aerosol administration of Ca DTPA should be unambiguously defined by FDA. In the meantime, administration by this route should be deferred until it is officially approved.

8. Research on the development of new chelating agents, combinations with other chelating agents and ways to get these materials into intracellular compartments needs to be pursued vigorously.

9. The ERDA-Division of Biomedical and Environmental Research-DTPA Committee should develop protocols for the administration of Ca DTPA and a uniform method for reporting its effect in enhancing excretion. Consensus support from ERDA clinicians and research scientists should be obtained, if possible, and then the use of these protocols and reporting methods implemented so maximum human information can be gleaned from the few accidents which occur.

10. The recommended list of chemical, hematological, urinary or other studies which should be performed to detect possible toxic reactions to Ca DTPA needs to be reevaluated.

11. Until the question of human toxicity to Ca DTPA is better defined and an IND for Zn DTPA is approved, a yearly meeting of DTPA users and research scientists involved in chelation therapy should be held to exchange information and review the progress of the DTPA Committee. This meeting need not be a part of ERDA Occupational Physicians' Organization meeting unless they choose to include it on their annual program.

1080604

Distribution List

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IN REPLY REFER TO: H MS 690

April 7, 1976

Clarence C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Division
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, TN 37830

Dear Lush:

Enclosed are the regular and short forms which we use for any procedures or experiments involving human subjects. We do not have standard language for use of DTPA that has passed our Human Studies Committee. I do have our health physics and medical groups looking into the situations and conditions under which we might use DTPA at Los Alamos, and as part of that exercise I would propose to develop the language used in completing the details. The Committee rules on whether the regular or short form can be used. In this case I would try to utilize the short form with the standard sheet describing the indications and contra-indications for use of DTPA. If you plan to develop such a sheet we would like to have the benefit of your work.

Sincerely,

George L. Voelz, M.D.
Health Division Leader

GLV/mjt

Encls. a/s

1080606

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CONSENT TO ACT AS HUMAN SUBJECT

(REGULAR FORM)

Subject's name _____

Date: _____

1. I hereby authorize _____
[name of person(s) who will perform the

_____ and/or such assistants as may
procedure(s) and/or investigation(s)]

be selected by him to perform on _____
(Insert "me" if subject can sign on his own behalf, or the subject's name if the subject is a minor or is otherwise unable to sign)

the following procedure(s) and/or investigation(s):

(Describe in detail, in language which will provide a fair explanation of the procedure(s) and their purposes, including an identification of those procedures which are experimental.)

2. The procedure(s) and/or investigation(s) listed in Paragraph 1

has (have) been explained to me by _____
(Name)

1080607

3. I understand that the procedure(s) and/or investigation(s) described in Paragraph 1 involves (involve) the following possible risks and discomforts:

(Describe in detail)

and that the possible benefits of the procedure(s) and/or investigation(s) are as follows:

(Describe in detail)

4. (To be used when the procedure(s) is (are) intended to be of a possible therapeutic benefit to the patient-subject)

I have been advised of the following appropriate alternative procedures that would be beneficial to _____:
(see 1. above)

(Describe in detail any such alternative procedures)

5. I understand that _____
[Name of person(s) who will perform procedure(s)

_____ and/or such assistants as may be selected by
and/or investigation(s)]

him will answer any inquiries I may have at any time concerning the procedure(s) and/or investigation(s).

1080608

6. I understand that I may terminate participation in the study at any time without prejudice to future care or to any possible reimbursement of expenses, compensation, employment status, or other entitlement, except as provided herein, and that, owing to the scientific nature of the study, the investigator may in his absolute discretion terminate the procedure(s) and/or investigation(s) at any time. In the event that compensation for participation is to be paid, and participation is terminated by the subject or by the investigator, I understand that the subject will be entitled to payment of a sum based upon the scientific value to the study of the information obtained from the participation, provided, however, that in no event shall the subject receive less than _____ per cent of the agreed compensation if he/she continues to participate beyond the _____ (Describe the _____ of the study.
applicable time period)

SUBJECT'S SIGNATURE _____

WITNESS _____

(If subject is a minor, or otherwise unable to sign, complete the following):

Subject is a minor (age ____), or is unable to sign because

_____

_____

_____	_____
Father	Guardian
_____	_____
Mother	~~Other person and relationship~~

1080609

UNIVERSITY OF CHICAGO

CONSENT TO ACT AS HUMAN SUBJECT

(SHORT FORM)

Subject's Name: _____

Date: _____

Name of Project: _____

I hereby consent to be a participant in the activity named above. An explanation of the procedure(s) and/or investigation(s) to be followed, including an identification of those which are experimental, and their purposes, was provided to me by _____. I was provided with a
Name

description of the attendant discomforts and risks to be expected. I was assured that any inquiries concerning the procedure(s) and/or investigation(s) would be answered. I was assured that I am free to withdraw my consent and to discontinue participation in the project or activity at any time without prejudice.

Subject's Signature: _____

Auditor-Witness: _____
(To oral presentation and signature)

(If subject is a minor or otherwise unable to sign, complete the following):

Subject is a minor (age _____), or is unable to sign because

_____

_____

_____ _____
Father Guardian

_____ _____
Mother ~~Other person responsible~~

1080610

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

April 9, 1976

Dr. Walter H. Weyzen
Deputy Manager
Physical and Technological Programs
Division of Biomedical and Environmental
Research
Energy Research and Development
Administration
Washington, D. C. 20545

Dear Walter:

Project "Informed Consent" could not be accomplished this week because there are only three formal informed consents in existence as far as I can determine.

I contacted everyone who had used DTPA in the last calendar year except Reagan who was too busy and the clinician in New York who has been treating the young man and his father in Albany (?). I plan to contact the latter M.D., Reagan, Fuqua, and Spickard in hopes of finding the existence of more. I do not anticipate having much more success than I have had, because everyone except those MDs working under University guidelines which set up committees for evaluation of human subjects in research have not realized the need for such consent forms and do not know how to construct one and get it approved for their use.

As you will note (item 4) in the summary recommendations that will ultimately stem from the Pinellas meeting, the consensus was that we (ERDA, you and me, the DTPA Committee) should get such a form together, have it approved by some institutional committee, and then supply it to the plant physicians for their use. They are quite willing to use such a form but having no HEW assurance agreement on file, the individual plants have no way to meet the compliance requirements themselves without our help.

I would like to suggest to you that you consider having the DTPA "Committee" draft such a form for ERDA physicians and then I would submit it to our ORNL/ORAU Committee on Human Studies, which has an up-to-date HEW assurance agreement on file. If

1080611

approval is obtained, the "Investigators" using the drug would use this form in ERDA plant sites.

Kerr-McGee plant (not in operation now), Dr. Voelz at LASL (where there has been no occasion to use DTPA), and Dr. Wald at the University of Pittsburgh are sending me copies of their consent forms. These are the three that I located in my survey.

In retrospect, historical decisions of 1967 seem to have been so cast in concrete in the minds of the Plant MDs about DTPA that there has seemed to be no need for updating their paper-work procedures. Not being full-time research MDs, these men have not had reason to stay abreast of the changing requirements of HEW and FDA about investigational new drugs. You will recall that all this began under the egis of Dr. William Doran and later Dr. Lionel Liberman (both of DOS). In June 1967, Dr. Lieberman had a letter published in the Federal Registry which provided that plant physicians could obtain consent for DTPA usage orally and this fact merely recorded in the patient record. This has been done "religiously" by everyone as far as I can determine.

I learned from Dr. C. J. Sternhagen, formerly of Kerr-McGee, that at that plant all new hires at the time of training and indoctrination were given the opportunity to sign the DTPA consent form. If a worker did not sign and later a contamination occurred at work decorporation with DTPA was not tried in this case.

The other MDs with whom I talked by phone this week were: George Poda, du Pont; Tom Lincoln, ORNL; George Voelz, LASL; C. Sternhagen, University of New Mexico; Niel Wald, University of Pittsburgh (Wald speaks for Zimmer also); Louis Hempelmann, University of Rochester (to whom I talked principally about other matters and about DTPA and consent forms in passing).

If this DTPA-IND stuff had started as a research project in one of ERDA's laboratories, BER would have had it organized under a 189 proposal. Instead, it started with a pharmaceutical firm who graciously turned it over to DOS that had no procedures for organizing the nation-wide research project that obviously is required. I am carrying out your suggestion that I prepare a new 189 proposal for your and the BER staff approval wherein the REAC/TS core staff would share the responsibilities with you of investigating and controlling the usage of DTPA in cases of Pu contamination. Since I will need some additional guidance from you, I will have a draft ready for your criticism on your return from Holland. We are doing all right financially for the present under our initial REAC/TS 189, a new version of which you will be receiving shortly as scheduled.

I am enclosing at the end of all of this, a draft (which is not to be released yet because Tom Lincoln does not have concurrence of the Pinellas attendees) of our combined thoughts on DTPA needs. I will be using this outline in my 189. A summary of the whole meeting will be made available later by Dr. Art Barker. I enclose also a list of the attendees there and a copy of an article by Fran Schmidtke that Dr. Sidney Wolf apparently does not know of. He says that animal studies previous to the DTPA only involved injectible DTPA. In this 1964 study, DTPA aerosol was shown to be extremely efficient in removing $^{91}YCl_3$ from the lung. Also he does not know of the "Mad Greek" at Hanford in the early 60's who showed in animals that aerosol DTPA was actually more effective than the I.V. route and not toxic. I think this investigator's name is spelled Thrombopolous, but I may have it confused with cardio-vascular pathology.

I have read and re-read the letter by Wolfe, Mazzochi, and Abbotts. My most printable comment is that their requests outline fairly well the course of action you and I have been following since last August and, when met, this information will comprise the report we are intending to make to get DTPA upgraded to an approved new drug.

We are continuing to pursue these matters. I hope your trip home helps you forget such chores for a while.

Yours sincerely,

C. C. Lushbaugh

C. C. Lushbaugh, M. D.

CCL:fb

Enc.

(typed and mailed in Dr. Lushbaugh's absence)

APPLICATION OF DTPA TREATMENT FOR ESTIMATION OF LIVER AND SKELETAL BURDENS FOLLOWING EXPOSURE TO PLUTONIUM AND OTHER ACTINIDE ELEMENTS.

M. H. Bhattacharyya, R. A. Guilmette, and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439

June 21, 1976

Protocol for collection of fecal samples:

Collect fecal samples daily for 7 days after initiation of DTPA treatment. If fecal elimination does not occur daily, collect until seven separate samples are obtained. Collect samples so that there is no contamination of feces by urine. Fecal samples must be collected in their entirety; they must not be pooled. (See accompanying abstract.)

1080614

Abstract of a paper to be presented at the IVth International Congress of the International Radiation Protection Association (IRPA), April 24-30, 1977, Paris, France.

"Estimation of liver and skeletal burdens following exposure to plutonium or americium: use of fecal excretion data following DTPA therapy."

M. H. Bhattacharyya, R. A. Guilmette, and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439*

Prompt treatment of mice and rats with DTPA following the injection of monomeric plutonium results in the quantitative excretion of liver plutonium into the feces by way of the bile (cf. accompanying abstract). This knowledge provides us with a potential diagnostic tool for the estimation of liver and skeletal radionuclide burdens existing prior to DTPA administration. In the present report, we examine the possible application of this analysis to cases of human exposure, using data from mouse, dog, baboon, and one case of inhalation exposure in man.

In the analytical model used, the total amount of radionuclide excreted into the feces during the 7 to 10 days after initiation of DTPA therapy is assumed to be equal to the pretreatment liver burden, which, in turn, is assumed equal to the pretreatment skeletal burden. Using this model to analyze existing data, we find that the estimated skeletal burdens for mouse, dog, and baboon are 120, 65, and 71%, respectively, of levels actually determined in control animals killed just prior to DTPA administration. Thus, in these species, values for total plutonium (mouse and dog data) or americium (baboon data) excreted into the feces in response to DTPA therapy provide a remarkably good measure of pretreatment skeletal burdens. The errors in these determinations are substantially less than those obtainable from models using urinary excretion measurements.

The question still remains, is this type of analysis useful to the human exposure situation? Establishing the validity of the model for human cases is difficult because of uncertainties in estimating whole body and organ burdens of intact individuals. However, excretion data reported for employee A following an accidental inhalation of ^{238}Pu [H. F. Anderson et al., Health Physics 18, 631 (1970)] provide encouraging evidence. Following clearance on days 0 and 1 of very high fecal plutonium levels resulting from the swallowing of inhaled material, there appears a second distinct peak of plutonium, accounting for 0.02 μCi, from days 3 to 6 after DTPA administration. The timing and symmetry of the peak indicate that it probably represents biliary clearance of liver plutonium and therefore can be used to estimate systemic contamination levels at the time of treatment.

(*Work supported by the U. S. Energy Research and Development Administration)

1080615

PROPOSED REGIMEN FOR DTPA DECORPORATION THERAPY OF INDIVIDUALS EXPOSED TO PLUTONIUM OR OTHER ACTINIDES

R. A. Guilmette and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439

June 21, 1976

1. Experimental data (attached) indicate the need for prompt initiation of DTPA therapy, following a known or suspected exposure. Treatment within several hours is strongly recommended.

2. The DTPA should be administered intravenously, as the $CaNa_3$ form.

3. Our animal studies show that early after exposure the currently recommended dose of 0.036 mmole/kg body weight is not an optimum dose. We, therefore recommend the prompt administration of a single dose of 0.18 mmole/kg, or five times the current level.

4. The above recommendations apply only to the first prompt treatment. Subsequent follow-up therapy need not be conducted at doses higher than 0.036 mmole/kg. Since the zinc form of DTPA has been shown to be equally effective as the Ca form, administration of the zinc chelate after the first two days may be advantageous, due to toxicological considerations.

5. The need for sustained daily administration of DTPA has not been demonstrated. For long-term therapy up to two injections per week may be considered maximal.

1080616

"Effectiveness of DTPA Decorporation Therapy, Begun 6 Hours after Injection of Monomeric Plutonium in the Dog." R. A. Guilmette,* A. Lindenbaum, and E. Moretti,* Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois 60439.

For clinical applications of chelation therapy for actinide contamination in man, it is important to improve our understanding of the relationship between the sites of localization of plutonium and the effectiveness of decorporation by various regimens of the chelating agent diethylenetriaminepentaacetic acid (DTPA). Accordingly, groups of three beagle dogs each were treated intravenously (I.V.) with DTPA beginning at 6 hours after I.V. injection of monomeric plutonium (Pu-M). Two groups of dogs were given 24 biweekly injections of $CaNa_3DTPA$, one group receiving 0.25 mMoles/kg (100 mg/kg) and the other 0.036 mMoles/kg (∿ 15 mg/kg); a third group received five daily injections of 0.036 mMoles/kg, followed by biweekly treatments thereafter. Urine and feces were collected daily for the first 7 days. The animals were sacrificed at 90 days, and the bone, soft tissues, and excreta assayed for Pu.

A significant fraction of the injected Pu-M (% ID) was excreted in the urine during the 24 hours following the first DTPA treatment: 61% for the group given the high dose of DTPA, and 40% for both groups given the low dose. The cumulative urinary excretion of Pu during the first week of therapy was 66% ID for the high dose group and 53-58% ID for the low dose groups.

By 90 days, 72-92% of the liver burden at 6 hours had been removed by all treatment regimens. Comparable reductions in Pu were noted in the spleen, kidney, lungs, etc. after each treatment regimen. The effect of DTPA treatment at 6 hours on the skeletal burden was twofold: 1) removal of as much as 60% of the Pu present in the skeleton and 2) prevention of further skeletal uptake. It was further noted that the effectiveness of DTPA begun at 6 hours was superior to similar treatment begun at 6 days or at 90 days.

(Work supported by the U. S. Energy Research and Development Administration.)

1080611

EFFECTIVENESS OF EARLY AND DELAYED DTPA THERAPY ON REMOVAL OF MONOMERIC PLUTONIUM FROM DOG TISSUES

Time Between Injection of Pu and Beginning of DTPA Treatment	Percent of Saline-treated Controls (Percent of Pretreatment Organ Burden Removed)					
	Liver	Spleen	Kidney	Femur	Vertebra (L-3)	Mandible + Teeth
6 hours	2.94 (92.5)	7.35 (88.2)	6.57 (98.4)	8.48 (80.2)	15.7 (53.8)	19.1 (38.0)
6 days	3.85 (96.2)	13.4 (82.4)	18.3 (82.0)	51.7 (50.8)	50.5 (44.4)	60.8 (11.9)
89 days	23.1 (71.4)	38.1 (13.5)	68.1 (56.7)	51.7 (26.4)	52.0 (12.2)	68.6 (32.3)

1080618

DECORPORATION OF MONOMERIC PLUTONIUM IN THE DOG BY DTPA:
EFFECT OF DOSE AND TREATMENT REGIMEN

Treatment	Percent of Saline-Treated Controls					
	Liver	Spleen	Kidney	Femur	Vertebra (L-3)	Mandible + Teeth
0.18 mmole/kg; twice weekly beginning 6 hrs after Pu; 24 injections	2.94	7.35	6.57	8.43	15.7	19.1
0.036 mmole/kg; twice weekly beginning 6 hrs after Pu; 24 injections	10.9	11.5	10.4	14.9	26.0	28.6
0.036 mmole/kg; 5 daily injections beginning 6 hrs after Pu; twice weekly thereafter; 27 injections	7.64	12.3	10.2	13.0	24.4	25.6

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Telephone 615 483-8411

Medical and
Health Sciences
Division

June 30, 1976

Niel Wald, M.D.
University of Pittsburgh
Department of Radiation Health
Graduate School of Public Health
RC-510 Scaife Hall
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

Dear Niel:

Now that Health Physics and Radiation Research meetings are over, please have your secretary return our annual DTPA audit information and anything else you've promised me.

How do you feel about a DTPA Committee meeting on July 22 in Chicago after the NRC meeting?

Enclosed is a copy of a proposal from Art Lindenbaum and some back-up material, all of which seems basic to our Pu body-burden problem.

Sincerely,

Lush

C. C. Lushbaugh, M.D.

CCL:dgb

Enclosure

1080620

Oak Ridge
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Telephone 615 483-8411

Medical and
Health Sciences
Division

June 30, 1976

Dr. G. A. Poda
Medical Superintendent
E. I. du Pont de Nemours and Company
Savannah River Plant
Aiken, South Carolina 28901

Dear George:

Your recent inputs on DTPA and its attendant problems are helpful and are being incorporated in our planning. Could you come to a meeting on DTPA problems at O'Hare Airport on July 22?

I can't determine among all the records I got in response to my May request whether you sent me any case reports along with your response. Perhaps I've lost my mind.

I'm enclosing some material from Art Lindenbaum that looks good to me but needs a clinician's viewpoint for evaluation. Can you give me your opinion?

Sincerely yours,

C. C. Lushbaugh, M.D.

CCL:dgb

Enclosure

1080621

Oak Ridge
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Telephone 615 483-8411

Medical and
Health Sciences
Division

June 28, 1976

Dr. Charles J. Sternhagen
900 Camino de Salud NE
Cancer Research and Training Center
University of New Mexico
Albuquerque, New Mexico 87131

Dear Charles:

In your letter of September 29, 1975, you promised to send me a copy of a paper you presented on DTPA usage. I'd like to have a copy to document ERDA's experience with this drug. Somehow I've not received one, or it's been misfiled and is unretrievable. Would you send me another.

We are again in the audit phase of preparing a report for FDA. Am I correct in assuming that Kerr-McGee will have nothing to report this year? Were any treatments given since May 23, 1975? Is there any program to follow medically the 24 persons whom your previous report indicates having received DTPA therapy?

I realize you are not closely associated with this problem now, but I do need your help in following this up.

Cordially yours,

C. C. Lushbaugh, M.D.

CCL:dgb

cc: Dr. W. Weyzen
RRF

1080622

Oak Ridge
Associated
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Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

July 1, 1976

Walter Weyzen, M.D.
3016 Beaverwood Lane
Wheaton, Maryland 20906

Dear Walt:

Enclosed you'll find a copy of Lindenbaum's proposal for a routine for determining Pu bone burdens. This looks like a good idea to use, but it needs clinical evaluation.

I've asked Wald, Lincoln, and Poda for their opinions.

Sincerely,

C. C. Lushbaugh, M.D.

CCL:dgb

Enclosure

1080623

ARGONNE NATIONAL LABORATORY

June 24, 1976

C. C. Lushbaugh, M.D.
Medical Division
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, TN 37830

Dear Dr. Lushbaugh:

We were delighted to learn, through our telephone conversation last week, that it would be possible for us to have some input into the protocols you said were in process of formulation by Walter Weizen for handling cases of human actinide contamination. To summarize the accompanying information (which includes abstracts of supporting work) we feel we can make the following contribution toward a rational approach to effective clinical practice:

1) Our data, derived from mice, dogs, baboons, and one human case, indicate that early administration of $CaNa_3$ DPTA is not only effective for decorporation of plutonium (and other actinides) but may also serve as a means for estimating the initial skeletal and liver burdens. This work would eliminate the objection to early DTPA therapy based on the need for dosimetric information. Some pros and cons regarding the method are:

   a. It allows immediate treatment with DTPA without sacrificing determination of skeletal burdens.

   b. Errors in the estimation of skeletal burdens are substantially less than when urinary excretion measurements are used to estimate body burdens.

   c. In cases of inhalation exposure, there may be a masking of the peak of liver-derived fecal radionuclide by high levels of swallowed material appearing in the feces, especially if fecal elimination does not occur daily. Perhaps the administration of a rapid-action cathartic would help to avoid this problem.

2) Early intravenous administration of $CaNa_3$ DTPA in a <u>single</u> injection at a level 5 times the amount to be used for prolonged therapy removes significantly greater amounts of Pu from liver, spleen and skeleton than any other regimen of DTPA treatment we have tried. We emphasize <u>early</u> treatment with a <u>single</u>, large dose of $CaNa_3$ DTPA. After this initial dose, low levels are as effective as large, and it is immaterial, insofar as decorporation is concerned, whether the zinc or calcium forms of DTPA are used for subsequent treatment.

1080624

9700 South Cass Avenue, Argonne, Illinois 60439 · Telephone 312-739-7711 · TWX 910-258-3285 · WUX LB, Argonne, Illinois

In connection with item (1) we emphasize the importance of collecting separate daily fecal samples for 7 days after treatment. We of course need feedback from physicians to enable us to gauge the effectiveness of this method of estimating body and organ burdens.

With best wishes,

Art Lindenbaum
Maryka H. Bhattacharyya
R A Guilmette

Arthur Lindenbaum
Maryka H. Bhattacharyya
Raymond A. Guilmette

Division of Biological
and Medical Research

AL/MHB/RAG:mm
Encl.

cc: P. D. Klein
T. E. O'Connor

1080625

APPLICATION OF DTPA TREATMENT FOR ESTIMATION OF LIVER AND SKELETAL BURDENS FOLLOWING EXPOSURE TO PLUTONIUM AND OTHER ACTINIDE ELEMENTS.

M. H. Bhattacharyya, R. A. Guilmette, and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439

June 21, 1976

Protocol for collection of fecal samples:

Collect fecal samples daily for 7 days after initiation of DTPA treatment. If fecal elimination does not occur daily, collect until seven separate samples are obtained. Collect samples so that there is no contamination of feces by urine. Fecal samples must be collected in their entirety; they must not be pooled. (See accompanying abstract.)

1080626

Abstract of a paper to be presented at the IVth International Congress of the International Radiation Protection Association (IRPA), April 24-30, 1977, Paris, France.

"Estimation of liver and skeletal burdens following exposure to plutonium or americium: use of fecal excretion data following DTPA therapy."

M. H. Bhattacharyya, R. A. Guilmette, and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439*

Prompt treatment of mice and rats with DTPA following the injection of monomeric plutonium results in the quantitative excretion of liver plutonium into the feces by way of the bile (cf. accompanying abstract). This knowledge provides us with a potential diagnostic tool for the estimation of liver and skeletal radionuclide burdens existing prior to DTPA administration. In the present report, we examine the possible application of this analysis to cases of human exposure, using data from mouse, dog, baboon, and one case of inhalation exposure in man.

In the analytical model used, the total amount of radionuclide excreted into the feces during the 7 to 10 days after initiation of DTPA therapy is assumed to be equal to the pretreatment liver burden, which, in turn, is assumed equal to the pretreatment skeletal burden. Using this model to analyze existing data, we find that the estimated skeletal burdens for mouse, dog, and baboon are 120, 65, and 71%, respectively, of levels actually determined in control animals killed just prior to DTPA administration. Thus, in these species, values for total plutonium (mouse and dog data) or americium (baboon data) excreted into the feces in response to DTPA therapy provide a remarkably good measure of pretreatment skeletal burdens. The errors in these determinations are substantially less than those obtainable from models using urinary excretion measurements.

The question still remains, is this type of analysis useful to the human exposure situation? Establishing the validity of the model for human cases is difficult because of uncertainties in estimating whole body and organ burdens of intact individuals. However, excretion data reported for employee A following an accidental inhalation of ^{238}Pu [H. F. Anderson et al., Health Physics 18, 631 (1970)] provide encouraging evidence. Following clearance on days 0 and 1 of very high fecal plutonium levels resulting from the swallowing of inhaled material, there appears a second distinct peak of plutonium, accounting for 0.02 μCi, from days 3 to 6 after DTPA administration. The timing and symmetry of the peak indicate that it probably represents biliary clearance of liver plutonium and therefore can be used to estimate systemic contamination levels at the time of treatment.

(*Work supported by the U. S. Energy Research and Development Administration)

1080627

PROPOSED REGIMEN FOR DTPA DECORPORATION THERAPY OF INDIVIDUALS EXPOSED TO PLUTONIUM OR OTHER ACTINIDES

R. A. Guilmette and A. Lindenbaum, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL 60439

June 21, 1976

1. Experimental data (attached) indicate the need for prompt initiation of DTPA therapy, following a known or suspected exposure. Treatment within several hours is strongly recommended.

2. The DTPA should be administered intravenously, as the $CaNa_3$ form.

3. Our animal studies show that early after exposure the currently recommended dose of 0.036 mmole/kg body weight is not an optimum dose. We, therefore recommend the prompt administration of a single dose of 0.18 mmole/kg, or five times the current level.

4. The above recommendations apply only to the first prompt treatment. Subsequent follow-up therapy need not be conducted at doses higher than 0.036 mmole/kg. Since the zinc form of DTPA has been shown to be equally effective as the Ca form, administration of the zinc chelate after the first two days may be advantageous, due to toxicological considerations.

5. The need for sustained daily administration of DTPA has not been demonstrated. For long-term therapy up to two injections per week may be considered maximal.

1080628

OSR 25-5
(REV 1-72)

E. I. DU PONT DE NEMOURS & COMPANY
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(TWX: 810-771-2670, TEL: 803-824-6331, WU: AUGUSTA, GA.)

July 7, 1976

Dr. C. C. Lushbaugh
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, TN 37830

Dear Lush:

Here is something that I have heard no one mention. We worry about Zinc depletion when the average healthy person, except perhaps a pregnant female, can well do with some Zinc deficiency for the time necessary to chelate. However, a huge dose of chelate given rapidly, or one that pulls out Calcium (? Zn DTPA) could cause symptoms and problems of Calcium deficiency.

This should be considered.

Sincerely,

George

G. A. Poda, M.D.
Medical Superintendent

GAP/bs
Attachment

1080629

OSR 25-5
(REV 1-72)

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
ATOMIC ENERGY DIVISION
SAVANNAH RIVER PLANT
AIKEN, SOUTH CAROLINA 29801
(TWX: 810-771-2670, TEL: 803-824-6331, WU: AUGUSTA, GA.)

July 6, 1976

C. C. Lushbaugh, M.D.
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, TN 37830

Dear Lush:

I am delighted to see you are getting input from Art Lindenbaum as did Goodman and Gilman by using his expertise in their article on DTPA.

Art and I are not in any basic disagreement. We collect fecal samples of 5-7 or even more days dependent on the case, and after laxation the first day, use the fecal data in helping determine the initial burden, etc. Where Art talks of his one human case, I have this to say: with a puncture wound as source of entry, the amount of fecal excretion has been proportional to urinary excretion, demonstrating an equilibrium in body fluids, thus the same rate of excretion via liver and kidneys.

There is no argument that early treatment is best. I cannot be dogmatic that I.V. therapy should be used. Also in humans who have received 1 gm. DTPA via aerosol or about 0.25 gm. - 0.50 gm. absorbed dose DTPA, our "decorporation of Pu" has been approximately 60%, whereas Art gets 61% using five times the usual amount for his first dose, so who is to argue an increased dose?

We have no data in humans on Zn DTPA so it is difficult to say what its effectiveness is compared to Ca DTPA. Used judiciously and sparsely, Ca DTPA has shown no apparent problems. No one can argue using a "safer" therapeutic agent if one becomes available.

Hopefully soon I'll have for you a system of dose rate determination from urines while chelation therapy is being used, and the effectiveness.

Sincerely,

George

G. A. Poda, M.D.
Medical Superintendent

GAP/bs

1080630

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Experimental Control of Serum Calcium Levels *in Vivo*.* (17924)

ANTOINETTE POPOVICI, CHARLES F. GESCHICKTER, ALBERT REINOVSKY, AND MARTIN RUBIN (Introduced by M. X. Sullivan)

From Georgetown University Medical Center, Washington, D.C.

The constancy of the total calcium level of the blood is the result of the interplay of numerous factors which include calcium intake, absorption and excretion, Vitamin D economy, parathyroid gland function, and blood phosphate, bicarbonate, protein and pH levels(1). The relations which determine the distribution of the total blood calcium between the ionic and the bound forms are largely unknown. It is generally accepted that the ionic calcium in the blood is the physiologically active form. Were it possible to control the ionic blood-calcium levels by exogenous means further insight into the relationships and mechanisms which govern calcium levels and distribution might be obtained. Soluble oxalates lower blood calcium ions by precipitation of insoluble calcium oxalate. Citrates, tartrates, phthalates, fluorides, polyphosphates, glycine, and other anions lower blood calcium ion by the formation of soluble nonionic complexes(2). The characteristic physiological sequelae attributable to hypocalcemia follow the administration of these agents. However, the use of these materials for quantitative control of calcium ion *in vivo* is subject to certain experimental difficulties. Ethylenediamine tetra-acetic acid (E.D.T.A.A.) forms soluble nonionized complexes with many bivalent cations(3) and behaves as a chelating agent. Dyckerhoff *et al.*(4) have reported that E.D.T.A.A. inhibits blood coagulation *in vitro* probably as the result of the removal of calcium ion by complex formation. At physiological pH we have found that in human or rabbit serum the complex of calcium ion with E.D.T.A.A. forms stoichiometrically. Calcium ion bound in E.D.T.A.A. complex is not precipitated by the addition of oxalates and hence the total remaining non-complexed calcium which may consist of both ionic and protein bound calcium can be determined by oxalate precipitation. We have demonstrated this by numerous *in vitro* experiments. That the same combination occurs *in vivo* is illustrated in Fig. 1 where the physiological action of E.D.T.A.A. was shown to be the consequence of its combination with calcium ion. Rapid (20 sec.) intravenous injection into the marginal ear vein of rabbits of E.D.T.A.A. as the neutral sodium salt, 100 mg/kg, resulted in immediate lowering of the available calcium level with consequent death by hypocalcemic tetany. When the calcium chelation of E.D.T.A.A. has been saturated by admixture with stoichiometric quantities of calcium in the form of its chloride or gluconogluconate salt prior to injection, the previously demonstrated toxic effects did not occur (Fig. 1). A second injection of the neutral sodium salt of E.D.T.A.A. 100 mg/kg, then caused

* Supported by grants from the National Institutes of Health, the Geschickter Fund for Medical Research, and the Bersworth Chemical Co.

1. Cantarow and Trumper, Clinical Biochemistry, W. B. Saunders, Philadelphia, 3rd Ed., 1947, p. 171.
2. Sollmann, A Manual of Pharmacology, W. B. Saunders, Philadelphia, 7th Ed., 1948, p. 779-802; Schmidt and Greenberg, *Phys. Rev.*, 1935, v15, 367.
3. Schwarzenbach and Ackerman, *Helv. Chim. Acta.*, 1948, v31, 1029.
4. Dyckerhoff, Marx and Ludwig, *Z. Ges. Exp. Med.*, 1942, v110, 412.

1080631

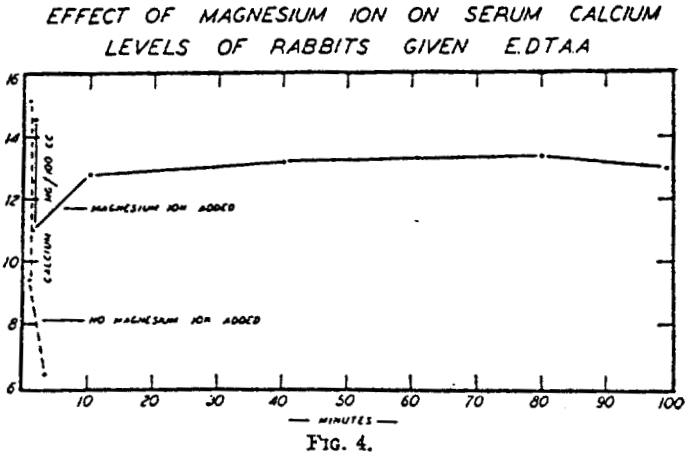

FIG. 4.

function than hitherto available is presented in Fig. 4. It can be noted that simultaneous administration of magnesium ion with an ordinarily lethal dose of E.D.T.A.A. resulted in a rapid replenishment of the blood calcium levels. This effect was noted whether the magnesium was pre-added to the E.D.T.A.A. solution with formation of the magnesium complex of E.D.T.A.A. prior to injection or if magnesium ion in the form of the sulfate was given simultaneously into the opposite ear vein of the rabbit or was injected directly into the heart simultaneously with the intravenous injection of E.D.T.A.A. in the ear vein. That the result was not due to combination of E.D.T.A.A. with magnesium ion rather than calcium ion has been indicated by the demonstration that the complex of calcium ion by E.D.T.A.A. as measured by the precipitation of unbound calcium by oxalate did not change in the presence of magnesium ion in the system when tested *in vitro*. Confirmation of this work was reported in a study by physical means of the preferential complex formation of E.D.T.A.A. with various bivalent cations(7). In the physiological pH range E.D.T.A.A. combines with calcium ion preferentially over magnesium ion.

Summary. The ability of ethylenediamine tetra-acetic acid to form undissociated calcium complexes at physiological pH has been utilized as a tool to regulate available serum calcium levels *in vivo*. Further evidence has been presented for the regulatory action of magnesium ion on serum calcium levels.

5. Mendel and Benedict, *Am. J. Physiol.*, 1909, v25, 25.

6. Becka, *Z. Ges. Exp. Med.*, 1929, v67, 252.

7. Plumb, Martell and Bersworth, to be published.

Received February 14, 1950. P.S.E.B.M., 1950, v74.

1080632

PROTECTION BY CALCIUM AGAINST LETHAL DOSE OF EDTAA GIVEN TO RABBITS

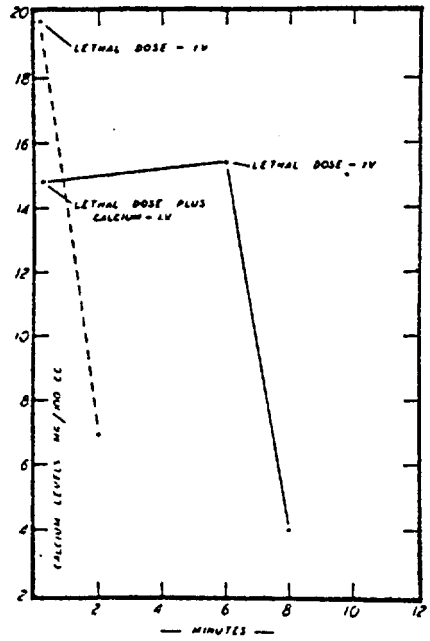

FIG. 1.

RABBIT SERUM CALCIUM LEVELS AFTER EDTAA BY VARIOUS ROUTES

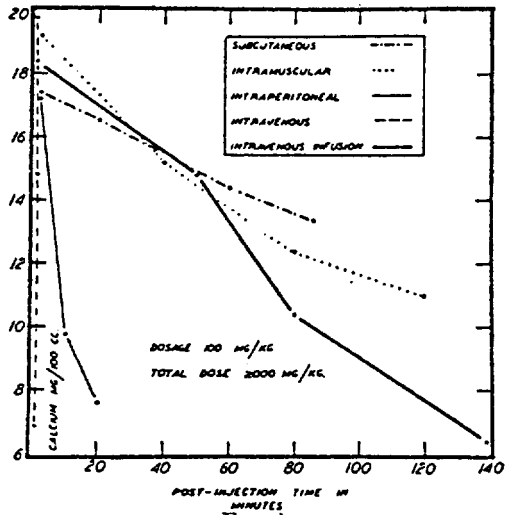

FIG. 2.

death of the rabbit in the typical manner. In numerous experiments it has been demonstrated that complete recovery from the effects of E.D.T.A.A. could be brought about by intravenous or intracardiac administration of calcium salts at any time prior to death. The rapidity with which the calcium level is lowered is a function of the mode of administration of the chelating agent (Fig. 2) and the rate at which it is injected as well as the dose. Intravenous, intraperitoneal, intramuscular and subcutaneous injection, as might be anticipated, resulted in successively diminishing rates of lowering of the available calcium serum levels. By slow intravenous drip it was possible to inject 2,000 mg per kilo of E.D.T.A.A. over a period of 3 hours before the serum calcium fell to a fatal level. By controlling the rates and amounts of chelate given it was possible to lower the available calcium serum level and maintain this level by balancing the complex formation against replenishment of blood calcium from the mobile reserves of the animal. That E.D.T.A.A. may be absorbed through the skin is illustrated in Fig. 3. Daily applications of a 5% water-soluble ointment to 2 human subjects resulted in a gradual fall of the serum calcium to 8 mg per 100 cc in a period of 4 days. Intravenous administration of calcium gluconogluconate resulted in the re-establishment of normal calcium levels.

Magnesium ion may have a regulatory action on calcium metabolism as has been suggested by Mendel and Benedict(5) and Becka(6). More direct evidence for this

HUMAN SERUM CALCIUM LEVELS AFTER EDTAA OINTMENT PERCUTANEOUSLY

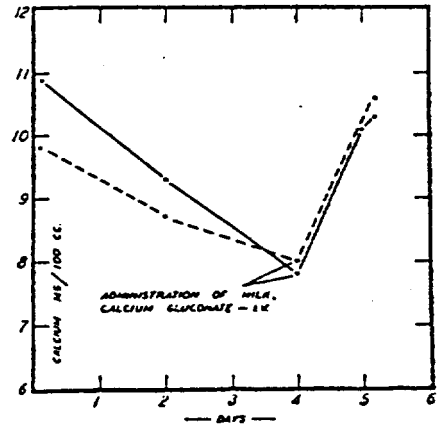

FIG. 3.

1080633

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Medical and
Health Sciences
Division

M E M O R A N D U M

TO: V. Smith, Chairman
W. Weyzen, BER, Ex Officio
W. Albers, DSSC, Ex Officio
N. Wald, Committee Member
G. Poda, Committee Member
G. Voelz, Committee Member
E. Daigneault, Committee Member
A. Lindenbaum, Committee Member
M. Bhattacharyya, Guest
R. Guilmette, Guest
R. Lloyd, Guest
F. Bruenger, Guest
N. Cohen, Guest

RE: DTPA Committee Meeting

DATE: July 16, 1976

I am enclosing a copy of the agenda for the DTPA Committee meeting on Thursday, July 22, at 8 a.m. As stated in my previous letter to you, the meeting will be held in the Hyatt Regency O'Hare and a sign will be placed in the lobby directing you to the assigned conference room.

I look forward to seeing you next Thursday.

C. C. Lushbaugh, M.D.
Executive Secretary

CCL:dgb

Enclosure

1080634

AGENDA

DTPA Study Committee

July 22, 1976

Hyatt Regency O'Hare
Chicago, Illinois

Attendees

Victor Smith, Chairman
C. Lushbaugh, Executive Secretary
W. Weyzen, BER, Ex Officio
W. Albers, DSSC, Ex Officio
N. Wald, Committee Member
G. Poda, Committee Member
G. Voelz, Committee Member
E. Daigneault, Committee Member
A. Lindenbaum, Committee Member
M. Bhattacharyya, Guest
R. Guilmette, Guest
R. Lloyd, Guest
F. Bruenger, Guest
N. Cohen, Guest

Absentees

P. Durbin, Committee Member
C. Mays, Committee Member
T. A. Lincoln, Committee Member

DTPA Agenda

8:00 AM Committee Organization

"Charter" - Goals
Membership - Chairmanship
Tasks/Assignments

8:30 AM Chairman's Remarks

8:45 AM Annual Report

1976 Audit - 31 Users (List Attached)
1976 Stockpile
Shelf Life Study
Identification of a New Manufacturer
DTPA-Case Registry

9:00 AM Compliance with Recent FDA/IND Requirements

New Informed Consent Form and ERDA Plant M.D.'s Comments

Proposed Standard Therapy Protocol

Request for Official Approval for Aerosol Useage

Proposed Bioassay Protocol
G. Poda
A. Lindenbaum

Ca-DTPA Bibliography Update
Effectiveness
Toxicity by Therapy Route (I.M., Wound, Aerosol)
Teratogenicity
Late Effects?

1080635

Zn-DTPA Review of Research Needs for Development of FDA/IND

11:00 AM	Needs for Chelation Research

?Basic Problems
?Loose Ends in Ca-DTPA Studies
?Zn-DTPA Studies
?Search for Better Decorporators
?Search for Intra-Cellularly Active Chelators

12:00 PM	Task Assignments
1:00 PM	Meeting Conclusions

1080636

THE UNIVERSITY OF UTAH

COLLEGE OF MEDICINE
DEPARTMENT OF PHARMACOLOGY
DIVISION OF RADIOBIOLOGY
BUILDING 351
SALT LAKE CITY, UTAH 84112
(801) 581-6600

June 12, 1981

DTPA

Karl F. Hübner, MD
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Oak Ridge, TN 37830

Dear Dr. Hübner,

Your article, "Update on Chelation Therapy," (REACTS Newsletter, April 1981) is most interesting. I'm highly pleased that FDA approval has been obtained for the administration of Ca-DTPA and Zn-DTPA by direct intravenous injection.

If my reading of the IND documents is correct, then all of the transneptunium elements are currently approved by the FDA for chelation therapy by Ca-DTPA or Zn-DTPA. My reasoning is as follows:

Although original IND-4041 for Ca-DTPA seems to have vanished from the face of the earth, the amendment to IND-4041 (A letter from Lionel M. Lieberman to Earl E. Meyers dated 15 August 1967) stated, "DTPA (Calcium Chel 330) will be used as a treatment for persons who receive accidentally internal deposition of plutonium or other transuranic heavy metals." Thus, it appears originally, that DTPA was authorized for neptunium and the transneptunium elements.

Similar wording occurs on page 68 of IND-14603 for Zn-DTPA (approved by the FDA on 24 August 1978). ". . . we propose to conduct a Phase 2 study of the use of Zn-DTPA as a treatment for employees who accidentally receive internal depositions of plutonium or other transuranic heavy metals."

However, buried on page 7 of the huge IND for Zn-DTPA is the following important exception, "Ca-DTPA therapy is not recommended for contamination with uranium or neptunium isotopes. In fact, use of Ca-DTPA therapy in these cases can result in greater uptake by kidney and bone, respectively, with concomitant greater toxicity to these tissues, than if no chelation therapy had been used." Although Zn-DTPA is not specifically mentioned in this regard, it seems prudent to forbid both Ca-DTPA and Zn-DTPA with respect to uranium and neptunium.

If my interpretation is correct, official FDA approval for Ca-DTPA and Zn-DTPA now extends only to the transneptunium elements. These elements and their longest-lived isotopes are as follows:

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Atomic Number	Longest lived Isotope	Physical Half-life
94	Pu-244	81,000,000 years
95	Am-243	7,370 years
96	Cm-247	16,000,000 years
97	Bk-247	1,400 years
98	Cf-251	900 years
99	Es-252	472 days
100	Fm-257	100 days
101	Md-258	56 days
102	No-259	58 minutes
103	Lr-260	3 minutes
104	261	1.1 minute
105	262	0.7 minute
106	263	0.9 second
107	261	~1 millisecond

Since elements of the higher atomic numbers may occasionally be involved in accidental intake, it would seem prudent to continue the FDA approval for DTPA therapy for all of the transneptunium elements. Inside the body they should mainly be in the +3 oxidation state (except for Pu at +4) and all should respond favorably to DTPA chelation therapy. Stated differently, there is nothing to be gained by an arbitrary cutoff of DTPA therapy for the elements beyond californium.

In fact, it might be appropriate to extend FDA approval for Ca-DTPA and Zn-DTPA treatment to the lanthanides and perhaps to thorium and actinium.

Enclosed is a recent review on the status of chelation therapy. We have a small grant from NCI to continue our chelation research, and would be pleased if you, Lush, and Lee Washburn could stop by our lab, collectively or individually, for a half day, or so, to visit.

Sincerely,

Chuck

Charles W. Mays, Ph. D.
Research Professor of Pharmacology

P.S. I would be most grateful if I could have copies of the REACTS newsletter for July 1980 and October 1980, and be put on the mailing list for future issues of the newsletter.

CWM:dm
cc. C.C. Lushbaugh, MD
Patricia W. Durbin
Vladimir Volf
M.E. Wrenn
F.W. Bruenger
G.N. Taylor
R.D. Lloyd
C. Jones

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OS:HP:LML

August 15, 1967

Earl L. Meyers, Ph.D.
Acting Director
Division of Oncology and
Radiopharmaceuticals
Food and Drug Administration
Washington, D. C. 20204

Re: IND 4041

Dear Dr. Meyers:

The following information constitutes an amendment to our IND 4041.

DEFINED OBJECTIVE

DTPA (Calcium Chel 330) will be used as a treatment for persons who receive accidentally internal deposition of plutonium or other tranuranic heavy metals. The clinical use under investigation is the chelation of the heavy metals nuclides to prevent deposition in bone and other body organs.

DOSAGE AND ADMINISTRATION

Ampuls of DTPA, brand of calcium trisodium pentatate are intended for slow intravenous infusion over a period of about one hour after dilution in 100 to 300 ml. of isotonic sodium chloride or five percent dextrose in water solution. In the therapy of plutonium or other transuranic metals deposition adult dosage not exceeding two grams/day is recommended. The usual dose does not exceed one gram/day, and under close supervision may be given for extended periods of time, i.e. weeks. The drug may be used undiluted as an intramuscular injection when intravenous infusion presents unusual difficulties. Absorption is apparently complete, and local tolerance satisfactory, although some pain may be experienced with this route of administration. The addition of one percent or two percent Procaine to the undiluted solution of DTPA, brand of calcium trisodium pentatate, before intramuscular injection has proved helpful.

The use of DTPA is not recommended for children or pregnant women.

AVAILABILITY

DTPA, Calcium Chel 330, brand of calcium trisodium pentatate, is available as ampuls containing one gram in four ml. of a 25 percent solution.

PRECAUTIONS

Caution is indicated in patients with any significant degree of renal or hepatic impairment.

ADVERSE REACTIONS

Occasional instances of diarrhea and nausea have been reported following the administration of calcium trisodium pentatate. Local pain may occur when the intramuscular route is used.

CONTRAINDICATIONS

Safety for the administration of calcium trisodium pentatate, has not been established in pregnancy or children.

PROTOCOL

The subjects in whom the drug is to be used are self-selected and it is not possible to characterize them beforehand. No controls are contemplated in the study. Prior to, during, and after chelation therapy, pertinent measurements for radioactivity will be made. Each case will be studied on an individual basis determined by the particular nuclide, the body burden and the rate of excretion. In addition, complete history, physical examination and one or more of the following laboratory procedures will be done before, during and after therapy. An evaluation of the efficacy of the drug will be made and any side effects noted and recorded.

It is estimated that the number of subjects who might receive DTPA in one year will approximate 75-100. The specific studies are to be chosen by the investigator. Possible studies are:

- Urinalysis
- Hemogram
- Liver function profile
- Renal function profile
- Blood studies
- Pulmonary function studies
- ECG
- EEG
- Bone marrow studies
- Fecal studies
- X-ray studies
- Organ size studies
- Cerebrospinal fluid studies
- Blood pressure and metabolism studies
- Composition of saliva
  - gastric juice
  - pancreatic juice
  - intestinal juice
  - bile

QUALIFIED INVESTIGATORS

The investigational new drug, calcium trisodium pentatate, is being distributed to physicians in charge of medical departments of contractors to the Atomic Energy Commission. It is felt that the following training and experience are considered appropriate to qualify contractor physicians as investigators suitable to participate in the investigation, monitoring and evaluation of the cases.

1. Education: Graduation from an approved medical school

2. Training:

   a. Internship

   b. Residency training and/or a period of experience substantially equivalent

3. Hospital and/or laboratory facilities for appropriate radiological monitoring and clinical testing related to the investigation.

A list of the AEC-contractor physicians who are qualified investigators of DTPA, is attached.

Sincerely yours,

Lionel M. Lieberman, M.D.
Division of Operational Safety

Attachment:
As stated

cc: H. D. Bruner, SM, HQ AEC, w/attach.
L. Dubinski, GO, HQ AEC, " "
H. B. Biles, OS, HQ AEC, " "
G. M. Dunning, OS, HQ AEC," "

OS:HP OS:HF

LIEBERMAN/ck ROSS

8/13/67 8/15/67

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IND-14603 for Zn-DTPA
Approved by the FDA on 24 August 1978

The efficacy of Ca-DTPA is quite good in the case of soluble actinide compounds but is extremely poor or even nil in the case of polymeric or highly insoluble compounds of the radionuclides. For example, Ca-DTPA, administered either by systemic or local methods, is totally ineffective in removing PuO_2 from an intramuscular deposit or from the lung. In such cases, surgical excision of the contaminated tissue and lung lavage, respectively, are the only successful therapeutic methods [Ca76]. The fraction of radionuclide contamination removable with Ca-DTPA becomes progressively smaller as the time interval between incorporation and administration of Ca-DTPA increases. The various actinides show quite different translocation patterns; for example, plutonium is translocated largely to bone whereas americium shows an affinity for liver. The fraction of the radionuclide removable by Ca-DTPA from the skeleton is generally markedly lower than that from the liver. Therefore, because of this effect and the fact that plutonium compounds are generally much more insoluble than those of americium, Ca-DTPA therapy is usually more useful for removal of americium than plutonium, especially if the initiation of therapy is delayed to the extent that the plutonium is largely translocated to bone [Ca76]. Finally, Ca-DTPA chelation therapy is not recommended for contamination with uranium or neptunium isotopes. In fact, use of Ca-DTPA therapy in these cases can result in greater uptake by kidney and bone respectively, with concomitant greater toxicity to these tissues, than if no chelation therapy had been used.

The overall efficacy patterns for Zn-DTPA are expected to be quite similar to those described above for Ca-DTPA. However, Ca-DTPA has a number of contraindications associated with its use (because of its toxicity through trace metal depletion, see Rationale section). Ca-DTPA is contraindicated for minors and for such conditions as pregnancy, nephrosis, and depressed myelopoietic activity, e.g., leukopenia, thrombocytopenia, etc. [Ca76]. These conditions are not contraindications for the use of Zn-DTPA. Perhaps more important is the fact that the toxicity of Ca-DTPA, but not that of Zn-DTPA, is drastically increased with a highly prolonged or fractionated treatment schedule [Ta74, Pl75, Ca76, Pl76a].

The toxicity of Ca-DTPA for protracted administration, coupled with the other contraindications to its use as stated above, form the basis for this application for use of Zn-DTPA in humans.

Zn-DTPA has been shown to effectively remove ^{241}Am from the rat [Se72, 73, Vo74, Se75], the hamster [Vo74], the dog [Ll75a,b, Ll76,77, Ma77], and the baboon [Co76a,b]. The agent has also been used effectively for removal of ^{239}Pu from the rat [Se71,72, Vo74, Ge77], the hamster [Vo74], and the dog [Ll78] and for removal of ^{242}Cm [Se72, Ta77] and ^{252}Cf [Se76] from the rat.

With all actinides studied, comparison of the efficacy of Zn-DTPA with that of Ca-DTPA gives similar results. For prompt treatment with the chelating agent (<24 hours after administration of the isotope), Ca-DTPA is significantly more effective than Zn-DTPA in removing internally

IND-14603 for Zn-DTPA.
approved by the FDA on 24 August 1978

Additional similarly trained investigators may be added to the study after its initiation by filing a completed and signed form 1573. The Food and Drug Administration will be notified as new investigators are added.

10. OUTLINE OF PLANNED CLINICAL INVESTIGATION

Because of the previous clinical use of Zn-DTPA in seven patients and the lack of toxicity encountered, even in the unusually drastic case of one individual who received 432 grams of Zn-DTPA over an 18-month period (see Section 6a), we propose to conduct a Phase 2 study of the use of Zn-DTPA as a treatment for employees who accidentally receive internal depositions of plutonium or other transuranic heavy metals. The clinical use under investigation will be the chelation of the heavy metal nuclides to prevent deposition in bone and other body organs.

Because of the nature of the investigation, each case will be studied on an individual basis determined by the particular nuclide, its chemical form, the route of incorporation, the body burden, and the rate of excretion. Since the subjects in whom the drug is to be used are self-selected, it is not possible to characterize them beforehand. No controls are contemplated in the study. The number of cases expected and the duration of the investigation are undetermined at this time. The usage of Ca-DTPA over the last six years has been approximately 30 cases/year. However, the projected number of patients treated with Zn-DTPA will probably be less than this because many physicians may prefer to treat initially with Ca-DTPA, which has a somewhat better therapeutic efficacy in the case of prompt treatment. Yearly progress reports will be submitted by the sponsor to the Food and Drug Administration.

An informed consent will be obtained from each patient. The consent form to be used is attached as Appendix E. Patients shall not be identified by name in any reports of this work which may be published or presented at medical conferences.

The drug, supplied as ampules containing 4.40 ml of 0.50M Zn-DTPA in water, is to be administered by either intramuscular injection of the undiluted solution, intravenous infusion (dose diluted with 250 ml of D_5W or normal saline) over a period of 60-90 minutes, or inhalation of the nebulized solution (1:1 dilution with water) over a period of 15 minutes or longer. The route of administration will be dependent upon the particular nuclide, its chemical form, and the route of incorporation. Each dose of Zn-DTPA will be 4.00 ml (2.0 mmoles, 1.04 g of Zn-DTPA). No more than two doses of Zn-DTPA will be administered during each 24-hour period (see below).

Administration of Zn-DTPA by inhalation will be done using commercially available micro aerosol devices which develop a 1-3 micron size aerosol particle. The actual equipment to be used will be left to the discretion of the participating investigators and may include the Devilbiss 40 Atomizer, the Bird Respirator Model Mark 7, etc.

Preprinted from Actinides in Man and Animals, M.E. Wrenn, Editor (in press).

STATUS OF CHELATION RESEARCH: A REVIEW

Charles W. Mays, Glenn N. Taylor, Ray D. Lloyd,
and McDonald E. Wrenn

ABSTRACT

The current status of research on the removal of actinide elements from the body is reviewed. Items occurring prior to 1980 include evidence for fetal toxicity from Ca-DTPA; the FDA approval of Zn-DTPA for human therapy, the mixed ligand fiasco, and the abrupt wipeout of chelation funding. This loss of research support severely restricted ongoing studies and almost paralyzed the search for improved new therapeutic procedures in the US.

New concepts that should be explored include improvements in removing radioactivity from lung and bone, the effectiveness of DTPA inside cells, simultaneous therapy with mobilizing agents and chelating agents, prolonging the retention of chelating agents within the body, the oral administration of chelating agents, the effectiveness of LICAM and other new chelating agents, the safety of decorporation procedures, and the effectiveness of chelation therapy on reducing the risk from radionuclide-induced cancer.

Some physicians give DTPA by intravenous injection, a safe procedure that should be officially sanctioned.

INTRODUCTION

Two excellent reviews on the removal of radioactivity from the body have recently appeared: Treatment of Incorporated Transuranium Elements (Vo78) and Management of Persons Accidentally Contaminated with Radionuclides (Voe80). These references are especially useful for researchers and physicians who are involved with decorporation therapy.

In this paper, we discuss the following 14 aspects of decorporation research. The first four are past history; the remainder are unfinished studies that should continue:

1. Ca-DTPA caused brain damage to beagle fetuses. (Page 352)
2. Zn-DTPA approved as an investigational new drug. (352)
3. Mixed ligand chelation. (353)
4. Cutoff of funds for chelation research. (353)

Supported by DOE Contract DE-AC02-76EV 00119 and NCI Grant 1 RO1 CA28314.

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5. Removal of particulates from the lung. (Page 354)
6. Removal ofradioactivity from bone. (355)
7. Intracellular DTPA. (356)
8. Mobilizing agents plus chelating agents. (358)
9. Prolonging the retention of chelating agents. (358)
10. Oral administration of chelating agents. (359)
11. LICAM and other new chelating agents. (359)
12. Safety of decorporation procedures. (360)
13. Reducing cancer risk by radionuclide chelation. (361)
14. Intravenous injection of DTPA. (362)

1. Ca-DTPA CAUSED BRAIN DAMAGE TO BEAGLE FETUSES

Calcium trisodium diethylenetriaminepentaacetate (Ca-DTPA) was injected into pregnant beagles at the daily dosage recommended for humans of 1 g/70 kg of body weight (about 30 μmole Ca-DTPA/kg) each day from 15 days after mating until parturition (Ta78a). Over half of the live-born pups died during the first week with gross and histological evidence of brain damage.

The toxicity of frequently administered Ca-DTPA seems due to the depletion of essential trace metals, especially zinc and manganese, that are essential to cell division (Bö71, Ta74, Pl76). Because of its teratogenicity, Ca-DTPA should not be given to pregnant women (Vo78). In fact, the use of Ca-DTPA is legally restricted to nonpregnant adults (Li67).

2. Zn-DTPA APPROVED AS AN INVESTIGATIONAL NEW DRUG

Zinc-DTPA, unlike Ca-DTPA, does not deplete the body of zinc or manganese.

Zn-DTPA was recently approved as an investigational new drug (IND) by the U.S. Food and Drug Administration for the therapeutic removal of actinides from persons of all ages, including children and pregnant women (Lu79). The efforts of many individuals led to this approval. We regret that Alexander Catsch, who first predicted the safety and effectiveness of Zn-DTPA, did not live to share this moment of triumph (Cat68).

Ca-DTPA is more effective, on an equimolar basis, than Zn-DTPA at early times after internal contamination from plutonium and transplutonium elements, when appreciable radioactivity is still in the circulating blood (Vo78, Ma77, Ta78b). Thus, for the nonpregnant adult, the initial therapy should be about 1 to 2 grams of Ca-DTPA, given intravenously or by aerosol inhalation. The initial therapy should be started as quickly as possible to block the deposition in bone (Se73, Ll79a).

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After 1 day, when most of the retained radioactivity is in tissue, Zn-DTPA and Ca-DTPA seem equally effective (Vo78, Oh76,78). Therefore, and because of its greater safety, Zn-DTPA is presently the chelate of choice for protracted therapy. Daily administration of 1 g Zn-DTPA/70 kg (about 30 µmole Zn-DTPA/kg) may be continued for prolonged times, if necessary (He79, Lu79).

3. MIXED LIGAND CHELATION

Jack Schubert and S. Krogh Derr published a paper claiming that a mixture of Ca-DTPA and salicylic acid had removed from mice virtually 100% of their plutonium burden, including that firmly deposited in bone (Sc78). If confirmed, this would have been the greatest breakthough ever achieved in chelation therapy. Because of its importance, if verified, many chelation investigators at the following laboratories put aside their own research to test the mixed ligand hypothesis:

Argonne National Laboratory (Bh80),
Battelle Pacific Northwest Laboratory (Sm80),
Kernforschungszentrum, Karlsruhe, West Germany (Vo80),
MRC Radiobiology Unit, Harwell, England (Hu80),
National Radiological Protection Board, Harwell, Eng. (Bu79a),
University of Utah (Jo80).

These investigators all found that the effectiveness of a mixture of DTPA and salicylic acid was similar to that from the DTPA alone. When the mixed ligand protocol of Schubert and Derr was carefully followed in mice, the residual retention of plutonium was about 30% (Jo80), not the 0% claimed by Schubert and Derr (Sc78). We estimate that this episode cost, worldwide, about $500,000 in research money and roughly 6 months of each major investigator's time.

Schubert has publicly retracted (Sc79,80) the published paper of Schubert and Derr (Sc78). It seems that Mr. Derr had "invented" the data on which their paper was based (Sc80).

Perhaps one should be grateful that when the mixed ligand paper was published in September 1978, there were still enough funded chelation researchers to prove it wrong. If the paper had appeared 12 months later, it might have been years before the mistake could have been corrected.

4. CUTOFF OF FUNDS FOR CHELATION RESEARCH

Nearly all of the U.S. chelation research was funded by the Human Health and Assessments program of the U.S. Department of Energy. In the summer of 1979, the Congressional Subcommittee on Appropriations ordered a cut of $3.6 million from the $20 million budget of the Human Health program, with the stipulation that the cut could not come from certain epidemiological studies that constituted the bulk of the program.

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Reluctantly, DOE wiped out all of the on-site chelation research in its Human Health and Assessments program. This decision gave the unintended impression that DOE (and the U.S. Congress) were indifferent about reducing the toxicity to people from the internally-deposited radionuclides.

In retrospect, if the $3.6 million budget cut were really necessary, it would have been less disruptive if the Appropriations Subcommittee had distributed the cut over more program categories or, more properly, had left such decisions to the DOE program managers and given these managers the freedom to redistribute funds among their various programs so as to minimize the impact on needed research.

Rather than wiping out the four chelation projects at Albuquerque, Argonne, Richland, and Salt Lake City that had a combined total annual budget of about $500,000, it would have been preferable to have retained a multilaboratory U.S. research capability at a combined total budget of say $100,000. This would have allowed the continued development and testing of new chelates and procedures.

We were fortunate to obtain a small grant from the National Cancer Institute that enabled us to continue our chelation research. The NCI gave very high priority to our studies in beagles on "reducing cancer risk by radionuclide chelation."

The remainder of this paper discusses some of the unfinished research that should be continued.

5. REMOVAL OF PARTICULATES FROM THE LUNG

Inhalation is the most important route of actinide intake by man. When lung deposition is large, the prompt and efficient removal of the radioactivity is desirable, both to reduce the radiation dose to the lung and to minimize the translocation of the radioactivity to liver and bone. Present therapy, however, is only partially successful.

Researchers at Albuquerque have been able to remove about half of the radioactive particulates from the lung by repeated "passive" lavages (Mu81). During each lavage, one of the lungs is filled with isotonic saline by gravity flow. Afterwards, the animal is inverted so that the lavage fluid will drain out. It is unknown how much increased removal might be achieved by a very gentle agitation of the lavage fluid within the lung, perhaps by low intensity ultrasonic vibration. However, the effectiveness of such a procedure would be easy to evaluate in experimental animals. Ultrasonic examinations are now routinely done without known harmful effects in a variety of persons including pregnant women. One might expect that the air bubbles remaining within the lung would provide many air-to-fluid interfaces; these interfaces should convert a part of the ultrasonic energy into vibrational agitation of the lavage fluid. Hopefully, the treatment would be effective at ultrasonic power levels far below those that might damage the lung

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tissue. We have discussed this concept with our colleague, Robert L. Steven, M.D. (Division of Artificial Organs, University of Utah), who has treated many patients using pulmonary lavage. Dr. Steven believes that ultrasonic vibration would probably increase the effectiveness of pulmonary lavage and that the procedure should be evaluated carefully in experimental animals. Indeed, it would be a most important achievement if some innovative investigator could increase the removal of particulates by pulmonary lavage from the present 50% to, say, 90%. Perhaps such success can't be attained, but who can be certain until someone tries?

Pulmonary lavage is especially useful in the removal of relatively insoluble particulates from the lung, whereas relatively soluble particulates are removed most efficiently by a combination of lavage and chelation therapy (Mu81). For highly soluble materials, such as americium nitrate or the mixed oxides of plutonium and sodium, repeated injection of DTPA is remarkably effective in removing radioactivity from the body (He79, Sta80). Because the accidental exposure of people frequently involves the inhalation of particulates that range widely in solubility, it is usually desirable to give chelation therapy as soon as possible. Pulmonary lavage, if indicated, can be given a few days later, after most of the particulates in the alveoli have been phagocytized by pulmonary macrophages.

We are particularly impressed with the recent approach, described by Victor Smith at this workshop, of encapsulating DTPA within tiny lipid vesicles. When inhaled, these vesicles are engulfed by pulmonary macrophages. Thus, the contents of the vesicles are released in intimate proximity to the radioactive atoms inside these cells. This "Trojan Horse" effect also might be used to bring in additional substances to accelerate the solubilization of inhaled particulates. This type of investigation was halted by the funding cutoff, but should continue.

6. REMOVAL OF RADIOACTIVITY FROM BONE

Under present concepts, firmly bound atoms of plutonium and the transplutonium elements can be removed from bone only after the atoms are set free by bone remodeling (Ja71). However, the importance of normal bone remodeling over long time periods should not be discounted. For example, we injected four young adult beagles intravenously with 0.3 μCi/kg of monomeric ^{241}Am in citrate solution at 506 days of age (Ll75;Ma77). Fourteen days later, daily injections of 33 μmole ZnDTPA/kg/day were started. Retention of ^{241}Am in the liver decreased from 43% at the start of therapy to 1% at 2 months of chelation and was undetectable at 1 year. Retention in nonliver tissue (mainly skeleton) decreased from 46% at the start of therapy, to 24% at 2 months of chelation, to 13% at 1 year, and was 7.5% at 3 years. Based on other nonchelated dogs, the ^{241}Am retention at 3 years, without chelation, would have been about 33% in liver, 43% in bone, and 5% in other tissues (Ll78).

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Protracted chelation therapy in humans and baboons was much more effective in removing ^{241}Am from young individuals, who were experiencing rapid skeletal turnover, than from mature adults (Co76,79).

In the event of internal contamination from plutonium or transplutonium elements, the best way to reduce the risk to bone is to block skeletal uptake (a) by prompt chelation therapy to remove the radioactivity that has already reached the bloodstream, (b) by removal of the source of radioactivity by wound excision or pulmonary lavage, and (c) by continued chelation therapy, if necessary, to limit the translocation of radioactivity into the skeleton.

7. INTRACELLULAR DTPA

Although most of the injected DTPA is rapidly excreted in the urine, a very small fraction is retained within the body for longer times. When ^{14}C-labeled DTPA was injected intravenously, most of it left the plasma of rats and beagles with biological half times of less than 1 hour, although a small long-term component was retained with a half time of 1.6 days in rats and 4.4 days in beagles (St78). Based on observations in humans, Hall et al. estimated that in man 99% of the injected DTPA is excreted in the urine with a half time of about 2 hours, while 1% is retained much longer (Ha78). Although they did not directly evaluate the half time of the long-term component for the DTPA itself, it may be similar to their observed half time of about 7 days for the long-term excretion of chelated plutonium from DTPA-treated persons. This enhanced excretion of plutonium continues for weeks to months after the last administration of DTPA (Ha78). The uptake and protracted retention of DTPA within cells could account for much of this continuing excretion of plutonium.

The long-term retention of DTPA within the body is partly inside cells and partly in extracellular compartments that exchange slowly with blood plasma. The relative magnitudes of these two compartments should be evaluated. For purposes of illustration, we tentatively assume that about 0.5% of the injected DTPA might be inside cells and 0.5% might be in slowly exchanging fluids. Even if the amount of intracellular DTPA were 10 times lower, the conclusions from the following calculation would not change appreciably.

There are 1.2×10^{21} molecules of DTPA in the typical therapeutic injection of 1 gram of $CaNa_3DTPA$. If 0.5% of the DTPA entered cells, the cells would contain 6×10^{18} molecules of DTPA. This is nearly 4000 times greater than the 1.6×10^{15} atoms of ^{239}Pu in the permissible body burden of 0.04 μCi of ^{239}Pu. Because only a very small fraction of a firmly deposited body burden is available for chelation at any one time, the number of DTPA molecules entering cells is almost always much larger than the number of plutonium or transplutonium atoms that are then available for chelation.

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The DTPA inside the liver cells is responsible for the enhanced excretion of plutonium from within these cells into the bile as Pu-DTPA (St78, Bh78a,78b,79). This is direct evidence that some of the DTPA molecules get inside of cells. Robinson et al. have shown in tissue culture that the solubilization of the $^{241}AmO_2$ particulates, contained within pulmonary macrophages, was increased appreciably when DTPA was added to the culture medium (Ro80). Thus, it is possible that some DTPA may enter pulmonary macrophages and accelerate the solubilization of actinide atoms from the inhaled particulates that have been phagocytized by these cells. Experimentally, DTPA accelerates the removal of plutonium and americium from the lung when this material is relatively soluble (Mu81, Bu79b). DTPA probably also accelerates the removal of relatively insoluble material, although in this case the accelerated removal rate may still be too low to be of appreciable benefit. The "lipophilic" compound PUCHEL was more effective than Ca-DTPA in removing plutonium from the lung (Bu79b). Presumably, the PUCHEL has an enhanced penetration through the lipid layer of the cell membrane.

If osteoclasts take up DTPA, this might assist in the chelation of plutonium and transplutonium atoms directly at the sites of bone remodeling before these atoms are released into the bloodstream. If so, this should increase the net removal of skeletal radioactivity and decrease its redeposition in bone and other tissues. Experiments should be conducted to confirm or reject this interesting possibility.

More detailed information is needed on the amount of DTPA that gets inside the various types of cells and the subsequent retention of this DTPA. The ^{241}Pu-DTPA chelate might be a suitable tracer. The Pu-DTPA bond is very strong, so very little of the ^{241}Pu should dissociate. The short range β-particles from the ^{241}Pu should enable its precise intracellular localization by autoradiography. The sequential sacrifice of suitable animals injected with high activities of ^{241}Pu-DTPA might establish the uptake and retention times of DTPA among the different types of cells.

It has been recognized that DTPA in the bloodstream is effective in chelating circulating atoms, but only recently has the importance of intracellular DTPA been properly appreciated. Although the exact mechanisms by which DTPA enters cells are still uncertain, pinocytosis (the cellular intake of tiny droplets of fluid by an infolding and pinching off of the cellular membrane) has been suggested as a likely contributor (Ma77; Bh79). Enhanced uptake of DTPA might be expected in phagocytic cells such as the pulmonary macrophages of the lung, the osteoclasts of bone, and the Kupffer cells of the liver (Ma77). Regardless of the mechanisms, it is now clear that some of the DTPA gets inside of cells where the prolonged contact with plutonium and transplutonium atoms increases their chances of being chelated by DTPA and excreted from the body.

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8. MOBILIZING AGENTS PLUS CHELATING AGENTS

Optimum therapy might consist of a mobilizing agent mixed with a chelating agent. The mobilizing agent would loosen the nuclide, while the chelating agent would bind and remove it to prevent redeposition.

For example, Fisher et al. found that parathyroid hormone plus DTPA was slightly more effective than DTPA alone in removing ^{241}Am from the mouse skeleton (Fi76a). In this case, the parathyroid hormone acted as a mobilizing agent in stimulating bone resorption, while the liberated atoms were chelated by the DTPA. However, we do not recommend this treatment for human therapy because of the small additional removal due to the parathyroid hormone and the possible undesirable health effects of induced bone remodeling.

As another example, when a mixture of citrate and Ca-DTPA was injected directly into plutonium-contaminated wounds, more of the plutonium was removed and excreted than when either the citrate or the DTPA was injected alone (Vo78;Har79). The citrate acted as a mobilizing agent, while DTPA chelation prevented redeposition. When the citrate was injected alone, it, unfortunately, spread the plutonium from the wound to the bone and liver. Plutonium binds less firmly to citrate than to DTPA. Furthermore, citrate is broken down within the body, whereas DTPA is not. To prevent such unwanted redeposition, treatment with a mobilizing agent should always be accompanied by simultaneous treatment with a strong chelating agent such as DTPA. Although the direct injection of DTPA with citrate into wounds may be appropriate for special locations that cannot be excised, the surgical excision of the contaminated tissue usually achieves the maximum removal of radioactivity.

Additional mobilizing agents should be investigated, especially those that might accelerate the dissolution of particulates in the lung, mobilize radioactivity from wounds, and loosen the bonding of radionuclides to bone.

9. PROLONGING THE RETENTION OF CHELATING AGENTS

Most of the injected DTPA is rapidly excreted from the body (Ha78; St78;Bh78a,b,79). Therefore, to maintain high levels of DTPA within the body, the frequent administration of relatively high dosages of DTPA may be required. This can be inconvenient and tiresome for both the patient and the physician.

Calder et al. developed an implant that slowly released Zn-DTPA into the circulation (Ca78a). However, to release 1 g Zn-DTPA/day for a year would require a very large implant.

An approach now being investigated by Fred Weitl at Berkeley is to design new chelating agents that will be excreted slowly. If such

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agents are developed, they might be given in smaller doses, with longer times between administrations.

An alternative approach is to make the chelate molecule more "lipophilic" so that more can penetrate into cells (Bru77;Bu79b) where the retention times are longer than in the circulating blood. This, however, would be appropriate only if the increased amounts of the chelate inside of the cells did not cause an unacceptable toxicity.

10. ORAL ADMINISTRATION OF CHELATING AGENTS

If the intestinal absorption of a suitable chelate could be increased, it might be especially convenient for protracted therapy. Most persons don't enjoy being stuck with needles on a daily basis! They would much rather take a pill each day. However, a caution is in order. If an essential metal in the diet is bound by a nonabsorbed chelate, a deficiency of this metal within the body might result. The possibility of such an effect would have to be ruled out before giving people the chelate orally at frequent intervals over a prolonged time. Only about 3% of orally-administered DTPA is absorbed in rats (Tay80). Perhaps the absorption could be increased by a suitable modification of the DTPA molecule.

11. LICAM AND OTHER NEW CHELATING AGENTS

The search for better chelating agents continues. Recently, Kenneth Raymond and Frederich Weitl synthesized a new chelating agent, which was tested in mice by Patricia Durbin (Du80). The compound, called LICAM-S, is [N^1, N^5, N^{10}, N^{14}-tetra (2,3-dihydroxy-5-sulfobenzoyl)-tetraazatetradecane]. Durbin, Weitl, and Raymond kindly provided some to us. We found that LICAM-S was much more effective than Ca-DTPA in removing recently injected plutonium from beagles, but that it caused acute damage to the kidney, as evidenced by renal hemorrhage, edema, and an abrupt rise in blood urea nitrogen (Ll79b). Interestingly, this toxicity was not detected in the initial screening of the compound in mice at Berkeley although, following our results in beagles, the scientists at Berkeley confirmed the toxicity of LICAM-S in rats. This points up the importance of testing a compound in several species before it can be considered for use in man.

Subsequently, Fred Weitl redesigned the LICAM-S molecule, removing the sulfonate groups and locating a carboxyl group on each benzene ring in the 4-position. His modified compound, designated LICAM-C, is [N^1, N^5, N^{10} - tetra (2,3-dihydroxy-4-carboxyl) tetraazatetradecane]. We tested LICAM-C in beagles and found it similar to LICAM-S in removing plutonium, but without evidence of acute toxicity.

Table 1 shows our results. Young adult beagles, 2 males per test group, were injected intravenously with a mixture of ^{237}Pu, ^{239}Pu, and ^{241}Am in citrate solution at about 21 months of age. The 100-keV

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TABLE 1 EFFECTIVENESS OF VARIOUS CHELATING AGENTS ON THE REMOVAL OF PLUTONIUM AND AMERICIUM FROM BEAGLES

	Total-body retention at 7 days	
	Plutonium	Americium
Treatment*	% ± S.D.	% ± S.D.
Untreated	87 ± 5	89 ± 6
CaDTPA	29.7 ± 6.5	20.1 ± 1.1
LICAM-C	11.8 ± 0.6	71.6 ± 2.4
LICAM-S	13.7 ± 0.6	67.2 ± 1.5
LICAM-S plus CaDTPA	11.6 ± 1.3	20.9 ± 1.2

* 30 μmole/kg of each agent was injected intravenously at 30 minutes.

photons from ^{237}Pu and the 60-keV photons from ^{241}Am provided non-destructive assays for plutonium and americium, respectively. Thirty minutes later, 30 μmole/kg of each indicated chelating agent was also injected intravenously. All excreta were collected and, at 7 days, the dogs were total-body counted and sacrificed. The untreated animals (from other experiments) consisted of 14 beagles injected with ^{239}Pu and 6 beagles injected with ^{241}Am.

Each treatment caused a substantial decrease in the retained plutonium. The body burden of plutonium was reduced to 30% by Ca-DTPA and to about 12% for the treatments involving a LICAM compound. These LICAM chelates, however, were less effective than Ca-DTPA in removing americium from the body.

We look forward to the continued testing of promising new chelating agents in our beagles. We hope new agents will be found that are more effective than DTPA and will prove safe enough for use in humans. As Ray Guilmette pointed out in the recorded discussion at the end of this session on decorporation, DTPA is rather ineffective in removing protactinium, uranium, and neptunium from the body. Hence, other agents are needed to remove those elements.

12. SAFETY OF DECORPORATION PROCEDURES

It is not enough for a treatment to be effective; it is also essential that the safety of the treatment be proven. We have conducted extensive investigations on the health effects of Ca-DTPA (Ta74;Fi76b, Ma77;Ta78a) and Zn-DTPA (Brum77;Ma77;Ca78b).

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We tested in pregnant mice the same batch of Zn-DTPA now being used for human therapy (Ca78b). We observed no evidence for effects on the number of births per litter or in the frequency of congenital malformations, even at daily injections of 12,000 μmole Zn-DTPA/kg, which is 400 times the recommended human dosage. When these mouse pups reached maturity, all were found to be fertile and they produced normal-sized litters of clinically healthy offspring. The mice exposed to Zn-DTPA in utero are now being observed throughout their lifespans for delayed effects such as kidney diseases and various types of cancer.

If no damage attributable to Zn-DTPA is seen in these mice, we hope to be able to give a limited number of beagles daily injections of 300 μmole Zn-DTPA/kg (10 times the recommended human dosage) throughout pregnancy to determine whether this treatment has any observable effect on the beagle fetus. The question of whether or not this treatment might increase the fetal burden of plutonium and transplutonium elements should be resolved in large animals such as beagles.

The resulting information should be of value to the physician who must decide whether or not to give Zn-DTPA to a radioactive woman who is pregnant.

We are currently observing throughout their lifespans 15 beagles that received various types of chelation therapy for the removal of ^{239}Pu or ^{241}Am. Ten of these dogs still continue to receive Ca-DTPA or Zn-DTPA. We will continue to observe these beagles for possible effects related to the prolonged administration of DTPA.

As more evidence accumulates on the effectiveness and safety of various decorporation procedures, physicians can improve the therapy for radioactive poisoning by treating sooner, continuing longer, and using better chelating agents.

13. REDUCING CANCER RISK BY RADIONUCLIDE CHELATION

Volf's excellent book on treatment of incorporated transuranium elements (Vo78) lists 353 references. But only 3 of these studies attempted to evaluate experimentally the effect of chelation therapy in reducing the risk of developing radionuclide-induced cancer. Walter Weyzen, the former program manager of Human Health and Assessments at the Department of Energy, often remarked that the goal of chelation research should be the reduction of risk, not just the removal of radioactivity.

We are now involved in evaluating the reduction of risk in 15 beagles and 504 mice that have been partially decorporated by various treatments.

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14. INTRAVENOUS INJECTION OF DTPA

The wording of the present investigational new drug (IND) documents for both Ca-DTPA and Zn-DTPA permits administration (a) by slow intravenous drip over a period of about 1 hour, (b) by intramuscular injection of DTPA with procaine (Novocain), or (c) by inhalation of DTPA as an aerosol (Li67;Lu79;We78). Somehow, the simple and direct administration of DTPA by intravenous injection was not specifically mentioned, although the IND for Zn-DTPA was based extensively on clinical experience with the intravenous injection of DTPA in a man who had been contaminated with massive amounts of ^{241}Am (He79). Special permission was given via telephone by the U.S. Food and Drug Administration (FDA) to treat the subject with Zn-DTPA by i.v. injection (Br76). The prompt and continued therapy undoubtedly saved the man's life by removing over 95% of the 1100 μCi ^{241}Am initially within his body (He79).

Bryce Breitenstein (Br76) has pointed out to us (a) that an i.v. injection usually can be completed more quickly than an i.v. infusion can be started, especially when many patients must be treated, (b) that i.v. drips are awkward to maintain during decontamination procedures such as showering, (c) that i.v. injections cause less vein damage than i.v. infusions, and the maintenance of good veins is very important when daily therapy must be given for many months, (d) that most patients would prefer daily i.v. injections to daily i.v. drips, and (e) that no complications were observed when Breitenstein and his medical assistants gave over 500 i.v. injections of Ca-DTPA or Zn-DTPA to their patients. He gives each injection of 1 g DTPA in 4 ml of solution slowly during an interval of 2 to 4 minutes.

W.D. Norwood stated that the original reason for the i.v. infusion was to avoid the possibility of a sudden drop in blood pressure if high doses of EDTA or DTPA were given too quickly (No80). Norwood believes that no problem exists when 1 g DTPA is given slowly over a minute or more by i.v. injection.

To evaluate whether any appreciable difference existed in the effectiveness of i.v. injection vs. i.v. drip, we intravenously injected 6 male beagles at 18 months of age with a mixture of ^{237}Pu, ^{239}Pu, and ^{241}Am in citrate solution. Thirty minutes later, the dogs were given 30 μmole Ca-DTPA/kg; three animals by i.v. injection of about 10 ml of solution during less than a minute, and the other three animals by i.v. drip in 50 ml during 60 minutes.

Table 2 gives the retention at 7 days. The untreated animals (from other experiments) consisted of 14 beagles injected with ^{239}Pu and 6 beagles injected with ^{241}Am. Intravenous injection and intravenous drip were similar in decorporation efficiency.

In view of the foregoing results and considerations, we hope that the IND's for Ca-DTPA and Zn-DTPA can be amended to permit administration by slow intravenous injection, over a 2-to-4 minute interval.

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TABLE 2 PLUTONIUM AND AMERICIUM RETENTION IN BEAGLES GIVEN 30 μMOLE CaDTPA/kg BEGINNING 30 MINUTES AFTER RADIONUCLIDE ADMINISTRATION

	Total-body retention at 7 days	
	Plutonium	Americium
Treatment	% ± S.D.	% ± S.D.
Untreated	87 ± 5	89 ± 6
i.v. injection	33.2 ± 3.8	19.1 ± 3.8
i.v. drip	32.9 ± 4.5	23.2 ± 1.3

The greater ease of i.v. administration should encourage earlier, more effective therapy. On the other hand, those physicians who prefer intravenous drip, intramuscular injection, or DTPA inhalation may continue to use these routes of administration. The suggested amendment would give physicians greater freedom to select the best treatment for each patient.

SUMMARY

The following one-sentence summaries describe the 14 aspects of decorporation research discussed in this paper: (1) Calcium-DTPA has caused fetal damage to animals and, therefore, should not be administered to pregnant women. (2) Zinc-DTPA is much safer and is approved by the FDA for chelation therapy in persons of all ages, including children and pregnant women. (3) The mixed ligand affair was a scientific disaster. (4) The cutoff of chelation funding severely restricted ongoing studies and almost paralyzed the search for improved new therapeutic procedures in the US. (5) The possible augmentation of pulmonary lavage by ultrasonic vibration should be investigated in experimental animals. (6) Blocking the radionuclides from reaching bone is more effective than trying to remove them after deposition. (7) A small but important fraction of the administered DTPA gets inside of cells where it is highly effective in the chelation of the available plutonium and transplutonium atoms. (8) Mobilizing agents, given simultaneously with chelating agents, may be more effective than either agent alone. (9) Prolonging the retention of chelating agents should increase their effectiveness. (10) Oral administration of an absorbable chelating agent might be especially suitable for repeated therapy over protracted times. (11) Soon after radionuclide injection, the new compound LICAM-C was more effective than Ca-DTPA in removing plutonium from beagles. (12) Suitable decorporation procedures for humans should be both effective and safe. (13) The goal of decorporation therapy is the reduction of risk, not just the removal of radioactivity. (14) The

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IND for DTPA administration should be expanded to permit intravenous injection.

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DISCUSSION

K.W. SKRABLE (University of Lowell):
What is the medical risk of lung lavage?

B.A. MUGGENBURG (Inhalation Toxicology Research Institute):
The risk essentially is that of general anesthesia. I don't know of any additional risk beyond that.

W.D. NORWOOD (Hanford Environmental Health Foundation):
I checked that out at one time and figured about one death in 5,000 lavages.

MUGGENBURG:
That is the overall mortality in lavaged patients. In the case of a worker exposed by inhalation, you probably have a reasonably healthy individual at the time of exposure, so the risk from anesthesia would probably be less than it would in a general hospital population which is being anesthetized for a reason.

EDITORIAL COMMENT (from C.W. Mays):
The following discussion by J.C. Nenot, from page 385 of Diagnosis and Treatment of Incorporated Radionuclides, IAEA, Vienna (1976), relates to the safety of pulmonary lavage in baboons. ". . . Our losses were small: Five deaths in 800 lavages. All of these deaths would have been avoided in human subjects: One death was due to haemorrhage (damage to a large blood vessel), one to 'drowning' through flooding of the lungs (broken catheter), and three anesthesia accidents."

V.H. SMITH (Battelle Pacific Northwest Laboratory):
What is the relative toxicity of the Puchel compared to DTPA?

G.N. STRADLING (National Radiological Protection Board):
I can't give you too much information. All I can tell you is that for acute lethality, Puchel is about twice as toxic as Ca-DTPA.
Our program on Puchel and the development of new chelating agents has been curtailed, so I can't give you more information. I am sorry.

M.E. WRENN (University of Utah):
That is unfortunate. We are faced with two funding curtailments, one in the U.K. and the other in the U.S.

O. RAABE (University of California):
I want to ask about a new chelating agent called "LICAMS," developed by Fred Weitl and Ken Raymond at Berkeley, which they find is more effective than DTPA in binding plutonium.

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F.W. BRUENGER (University of Utah):

LICAMS is a new synthetic chelating agent which is structurally related to a powerful bacterially-produced iron complexing compound called Enterobactin. The agent is composed of 4 sulfonated catechoylamide residues which are linked linearly by 3 straight paraffin chains of specific length. This compound can form a ligand field which appears to be specific for cations with a charge to radius ratio of about 45 electronic charges per nanometer, such as Pu(IV) or Fe(III). This compound is superior to DTPA in removing plutonium, from the body, but it is rather ineffective in removing americium.

WRENN:

That might be a disadvantage in a world of mixed actinides.

C.W. MAYS (University of Utah):

Pat Durbin recently sent us some of their 3,4,3- LICAMS which we tested in beagles that had been injected intravenously with a citrate solution of ^{237}Pu, ^{239}Pu and ^{241}Am (the structural formula of LICAMS and our detailed results are given in COO-119-254, pp. 151-160, 1979). The dogs were injected intravenously with the indicated chelates 30 minutes following radionuclide administration, and the following retentions of Pu and Am were measured 7 days later:

Treatment	TOTAL-BODY RETENTION (%)	
	Pu	Am
Untreated	87	89
CaDTPA (30 μmole/kg)	30	20
LICAMS (30 μmole/kg)	14	67
CaDTPA + LICAMS (30 + 30 μmole/kg)	12	21

Plutonium retention was 30% following CaDTPA, but only 14% following LICAMS. However, Glenn Taylor observed nephrotoxicity in some of the dogs receiving LICAMS, so further research on blocking the toxicity of LICAMS and evaluating its effectiveness at lower doses is indicated. (Subsequent to this workshop, Weitl and Raymond redesigned the LICAM molecule to decrease its toxicity, while maintaining its effectiveness. For results on their new compound in beagles, see the paper by Mays et al. in these proceedings).

R.A. GUILMETTE (Inhalation Toxicology Research Institute):

There are several actinides for which DTPA doesn't work very well. Specifically, they are uranium, protactinium, neptunium, and actinium. We don't have an effective therapy for any of these elements. I think this is one of the areas that could stand some sizable investigation.

EDITORIAL COMMENT (from C.W. Mays):

I consider that Ray Guilmette's comment is the most important point made in this session. Subsequent discussions with Pat Durbin suggest that DTPA usually tightly binds actinide atoms having oxidation states of +3 and +4, but <u>not</u> +5 and +6.

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The following tabulation of oxidation states is an extension from P.W. Durbin (Distribution of the transuranic elements in mammals, Health Phys. 8: 665-671, 1962), and V.H. Smith (Therapeutic removal of internally deposited transuranium elements, Health Phys. 22: 765-778, 1972). The usual oxidation states for physiological conditions within the body are shown.

Atomic No.	Element	Oxidation States			
89	Actinium	+3			
90	Thorium		+4		
91	Protactinium			+5	
92	Uranium				+6
93	Neptunium			+5	
94	Plutonium		+4		
95	Americium	+3			
96	Curium	+3			
97	Berkelium	+3			
98	Californium	+3			
99	Einsteinium	+3			
100	Fermium	+3			

Thus, while DTPA can decrease the body burdens of most of the actinides, it is ineffective in removing protactinium (+5), uranium (+6), and neptunium (+5). To remove these last three elements, other removal agents are needed.

DTPA is less effective in removing actinium than americium. In rats, 1500 μmole DTPA/kg, given at 15 min, 24 hr, and 48 hr after the injection of ^{227}Ac, removed 66% of the body burden, while DTPA, starting 1 hr after exposure to ^{241}Am, reduced the body burden by 87% (D.M. Taylor, The metabolism of actinium in the rat, Health Phys. 19: 411-418, 1970).

GUILMETTE:

There is also the unique problem of removing actinides from wounds. I think to date the most effective approach to chelating a wound is a direct infusion of DTPA into the wound itself. I don't think this has ever been tried on a human.

MAYS:

Vladimir Volf has done a lot of research on this topic, and he has a very good discussion of the wound problem on pages 27-37 of his book, Treatment of Incorporated Transuranium Elements (IAEA, 1978). The optimum treatment is usually surgical excision which removes essentially all of the radioactivity. If a wound is of such a nature that you cannot excise all the material, Volf recommends giving a chelate injection intravenously or by inhalation to prevent translocation from the wound into the skeleton and liver, and he also cautions that if you use a mobilizing agent such as citrate, which is a rather weak chelate, that you must concurrently give DTPA in order to prevent the mobilized nuclide from translocating into other regions. In other words, you want to chelate it so tightly that it is excreted from the body before it

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dissociates and redeposits. I strongly recommend what Volf has written. It is quite good.

K.R. HEID (Battelle Pacific Northwest Laboratories):

Bruce, I am a little confused at the fraction of the initial lung burden that was brought out by lung lavage. What confuses me is that for the dogs inhaling ^{241}Am, only 20 percent remained in the lung at the end of the 64 days without treatment. But you are claiming a 40 percent removal by lavage.

MUGGENBURG:

Some of the americium removed by lavage would otherwise have translocated from the lung and would have redeposited in bone and liver. The americium removed from the lung by lavage will no longer irradiate the lung or any other tissue.

WRENN:

I think in deference to all the hard workers and our reporters who have put in quite a day, we should close tonight's session with thanks to the panelists.

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