0RAU-30025

708207

OAK RIDGE ASSOCIATED UNIVERSITIES
MEDICAL DIVISION
MEDICAL RADIONUCLIDE COMMITTEE
INACTIVE PROTOCOLS
AND RELATED DOCUMENTS 1966-1981
(FILE 1)

1048485

708207

REPOSITORY Oak Ridge Institute for Science & Education
Medical Sciences Division

COLLECTION Medical Radionuclide Committee

BOX No. _____

FOLDER _____

1048486

FORM P-4

MEMORANDUM

TO Dr. Lushbaugh DATE April 9, 1975

SUBJECT Medical Radionuclide Committee and Committee on Human Studies

COPIES TO

Originally, the name of the present "Medical Radionuclide Committee" varied from "Human Use Committee" to "Isotopes Committee," and sometimes "Human Studies Committee." When Dr. Kniseley was here he preferred "Isotopes Committee," but after he left and Roger took over as Chairman of the Committee, he and his group gave it a definite name, "Medical Radionuclide Committee." This Committee was functioning quite a while before the "Committee on Human Studies" was formed. I am attaching a memo concerning the establishment of the "Committee on Human Studies".

Present Members of the Medical Radionuclide Committee are:

Bill Gibbs, Chairman
R. L. Hayes
Jim Berger
C. L. Edwards
K. Hubner
D. Swartzendruber

Present Members of the Committee on Human Studies are:

Dr. Brill (Vanderbilt)
Dr. Edwards
Mr. Koons
Dr. Lange (UT, Knoxville)
Dr. Lincoln, ORNL
Dr. Storer
~~Dr. Nelson~~
(It has been suggested that a minister replace Nelson- pending-)

Dr. Hayes had asked me to send copies of the 3-23-67 document to Dr. Andrews, Dr. Edwards, and Dr. Hubner, plus a copy to you. Roger had made some progress on the Committee when he was Chairman, but after he left the Medical Division, Bill Gibbs became Chairman, and I am not knowledgeable about the Committee now. He said the last proposal they reviewed was Iodine-125 for Thyroid Scanning, March 11. If you need anything further on this, let me know.

I hope this has been helpful and not confusing!

See Dr. Andrews notes 1-2-74. attached

Frances

1048487

Table of Contents

MEDICAL RADIONUCLIDE COMMITTEE

April 1972	AEC Licensing Guide - Medical Programs
1966 - 1974	Correspondence
1966 - 1974	Memoranda
Proposal #	
73-1	Use of Technetium-99m Labeled Albumin Microspheres for Lung Scanning. (November 1973)
73-2	Use of Technetium-99m Osteoscan for Bone Scanning. (November 1973)
73-3	Comparison of Indium-111 Chloride and Indium-111 Sulfur Collide in Evaluation of Bone Marrow Disorder. (December 1973)
74-1	Cobalt-57 Vitamin B-12 for the Determination of Vitamin B-12 Absorption in the Intestine, Particularly for the Diagnosis of Pernicious Anemia. (February 1974)
74-2	Iodine-131 to Determine Thyroid Update and Evaluate Thyroid Function. (February 1974)
74-3	Iodine-131 Sodium Iodide as Liquid or in Capsules for Thyroid Scanning. (February 1974)
74-4	Iodine-131 Sodium Iodide as Liquid or in Capsules for Treatment of Hyperthyroidism. (February 1974)
74-5	Iodine-131 Sodium Iodide as a Liquid or in Capsules for Treatment of Thyroid Carcinoma. (February 1974)
74-6	Iodine-131 Macroaggregated Albumin for Lung Scanning. (February 1974)
74-7	Chromium-51 Chromate for Spleen Scanning. (February 1974)

1048488

74-8	Chromium-51 Chromate for Red Blood Cell Volume and Survival Studies. (February 1974)
74-9	Iron-59 as Citrate, Sulfate, or Chloride for Iron Turnover Studies. (February 1974)
74-10	Technetium-99m Sulfur Colloid for Liver and Spleen Scanning. (February 1974)
74-11	Technetium-99m Pertechnetate for Brain Scanning. (February 1974)
74-12	Technetium-99m Pertechnetate for Thyroid Scanning. (February 1974)
74-13	Gallium-67 Citrate for Tumor Imaging. (February 1974)
74-14	Indium-111 Chloride for Tumor Imaging. (February 1974)
74-15	Dysprosium-157 as a Clinical Scanning Agent for the Detection of Osseous and Nonosseous Tumors. April 1974)
74-16	Erbium-171 as a Clinical Scanning Agent for Detecting Osseous and Nonosseous Tumors. (April 1974)
74-17	Thulium-167 as a Clinical Scanning Agent for Detecting Osseous and Nonosseous Tumors. (April 1974)

1048489

AEC LICENSING GUIDE

MEDICAL PROGRAMS

● A Guide For The Preparation Of Applications For The Medical Use Of Radioisotopes.

★ DIVISION OF MATERIALS LICENSING ★
UNITED STATES ATOMIC ENERGY COMMISSION

1048490

NOTE

This document has been compiled by the United States Atomic Energy Commission as an aid in the preparation of applications for byproduct material licenses to receive, possess, and use radiopharmaceuticals. It is not intended as an interpretation of Commission regulations within the meaning of Section 30.5 of Title 10, Code of Federal Regulations, Part 30. Nothing contained in this guide may be construed as having the force and effect of United States Atomic Energy Commission regulations; nor as indicating that applications which follow the recommendations of this document necessarily will be approved; nor as relieving any licensee from the requirements of Title 10, Code of Federal Regulations, Parts 20 and 30, or other pertinent regulations.

This guide supersedes the previously issued booklet with the same title, dated November 1965.

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 - Price 55 cents

1048491

AEC LICENSING GUIDE • MEDICAL PROGRAMS

A GUIDE FOR THE PREPARATION OF APPLICATIONS FOR THE MEDICAL USE OF RADIOISOTOPES

April 1972

DIVISION OF MATERIALS LICENSING
U.S. ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

1048492

1048493

PREFACE

The Atomic Energy Act of 1954, as amended charges the United States Atomic Energy Commission with, among other things, responsibility for regulating the receipt, possession, and use of byproduct material. The Commission is authorized to establish by rule, regulation, or order, such standards, instructions and procedures to govern the possession and use of byproduct material as it may deem necessary or desirable to protect health or to minimize danger to life or property.

In the performance of its regulatory functions, the Commission has promulgated the regulations contained in Title 10 of the Code of Federal Regulations. The following regulations are included in Title 10 and are particularly pertinent to the subject of this guide:

1. Part 20, "Standards for Protection Against Radiation" (10 CFR 20).
2. Part 30, "Rules of General Applicability to Licensing of Byproduct Material" (10 CFR 30).
3. Part 35, "Human Uses of Byproduct Material" (10 CFR 35).

Current copies of Commission regulations may be obtained from the Division of Materials Licensing, U.S. Atomic Energy Commission, Washington, D.C., 20545, or from any of the following U.S. Atomic Energy Commission Regional Compliance Offices:

REGION	ADDRESS
I	Region I, Division of Compliance, USAEC 970 Broad Street Newark, New Jersey 07102
II	Region II, Division of Compliance, USAEC Suite 818, 230 Peachtree St. N.W. Atlanta, Georgia 30303
III	Region III, Division of Compliance, USAEC 799 Roosevelt Road Glen Ellyn, Illinois 60137
IV	Region IV, Division of Compliance, USAEC 10395 West Colfax Avenue Denver, Colorado 80215
V	Region V, Division of Compliance, USAEC 2111 Bancroft Way Berkeley, California 94704

This guide describes the kinds of information to be submitted in applications for the possession and use of radiopharmaceuticals. Its use should result in the submission of more complete applications. The Commission will request additional information if necessary in order to provide reasonable assurance that the applicant has established an adequate radiation safety program. (See Sec. 30.32(b) of 10 CFR 30.) Requests for additional information delay final action on the application and may be avoided by a thorough study of Commission regulations and this guide prior to filing the application.

This guide is intended only for general information and should not be considered a substitute for the applicant's careful evaluation of the proposed use of byproduct material or for assuring that the application correctly and adequately describes the radiation safeguards and procedures to be followed.

1048494

TABLE OF CONTENTS

	PAGE
I. Byproduct Material Licenses for the Medical Use of Radioisotopes	1
II. Filing an Application	3
III. Information to be Submitted	5
IV. Requirements of the Regulations	9

APPENDICES

APPENDIX A. Samples of Typical Licenses	11
APPENDIX B. Medical Isotopes Committee	22
APPENDIX C. Acceptable Training and Experience for Medical Uses of Byproduct Material	23
APPENDIX D. A List of Well Established Medical Uses	26
APPENDIX E. Sample Applications	30
APPENDIX F. Non-Routine Medical Uses of Byproduct Material	45
APPENDIX G. Types of Instruments Needed for Medical Programs	47
APPENDIX H. Information on Facilities and Equipment and Operating Procedures To Be Included with the Application	48
APPENDIX I. Information for Commission Approval of Treatment or Disposal by Incineration	49

1048495

I. BYPRODUCT MATERIAL LICENSES FOR THE MEDICAL USE OF ISOTOPES

The purpose of the guide is to assist persons desiring to use radioactive materials in the practice of nuclear medicine to obtain a byproduct material license. The format of the guide has been established in such a way that it describes the various types of licenses, the types of applications which should be submitted to obtain a license, and the information which should be included in the application.

Licenses may be issued to institutions or to private practitioners. The various types of licenses and their characteristics are as follows:

A. Specific Licenses issued to institutions.*

Specific licenses issued to institutions specify the radioisotopes and the clinical uses which can be performed by physicians named on the institution's license. The regulations in Section 35.11(b) of 10 CFR 35 require that an institutional licensee have a medical isotope committee to evaluate all proposals for clinical research, diagnostic, and therapeutic uses of radioisotopes within the institution. The physicians named on the institution's license conduct their programs with the approval of the isotopes committee. Institutional licenses provide a means whereby nonapproved physicians under the supervision of physicians named on the license may obtain basic and clinical radioisotope training and experience which may enable them to qualify as individual users. Acceptable physician training and experience for the well established uses of radioisotopes in medicine are outlined in appendix C.

B. Broad medical licenses issued to institutions.

Broad medical licenses, i.e., licenses authorizing multiple quantities and types of byproduct material for unspecified uses, are issued to institutions which (1) have had previous experience operating under a specific institutional license and (2) are engaged in medical research, as well as routine diagnosis and therapy using radioisotopes. Such programs operate under the supervision of a medical isotopes committee. No physicians are named as individual users on the license, nor are radioisotopes limited to specified uses. As is the case with specific institutional licenses, physicians may obtain basic and clinical radioisotope training and experience in the use of radiopharmaceuticals in such programs. Since this type of license is not appropriate for most institutions using byproduct material in medical programs and is discussed in a licensing guide dealing specifically with broad licenses now in preparation, no further specific mention will be made of the broad license in this guide.

C. Specific licenses issued to physicians for their private practice.

Licenses issued to physicians for private practice specify the types of isotopes and the clinical uses which may be performed by the physician to whom a license is issued. Usually, private practitioners to whom such licenses are issued are located in offices not on hospital premises. However, this type of license may be appropriate for a physician who conducts a private practice in institutional facilities. It is not required that a medical isotopes committee be formed. The private practice license does not permit other physicians to obtain basic and clinical radioisotope training and experience under it. These licenses are limited to well established uses of byproduct materials and required that the physician so licensed personally conduct the program. Section 35.12, 10 CFR 35, outlines specific requirements for this type of license.

D. General license for certain diagnostic uses.

The general license provided in Section 35.31, 10 CFR 35, authorizes the registrant physician to possess and use limited quantities of prepackaged individual doses of iodine 131 for measurement of thyroid uptake; iodine 125 and iodine 131 for blood and plasma volume determinations; cobalt 60 and cobalt 58 for intestinal absorption of cyanocobalamin; and

**While the "Specific" licenses and the "Broad" licenses referred to in paragraphs A and B are both specific licenses, for purposes of simplicity in this guide only, the former will be referred to as a specific license.*

1048496

chromium 51 for red blood cell volume and survival time determinations. Section 35.31 explains the general license requirements and requires the physician to register with the Commission prior to receiving or using the diagnostic radiopharmaceuticals covered.

E. **Specific licenses for the teletherapy use of radioisotopes.** See licensing guide "AEC Licensing Guide–Teletherapy Programs." These are not discussed herein.

Over 90 percent of the licenses issued for the medical use of radioisotopes are specific licenses to institutions or specific licenses to physicians for their private practice. Accordingly, this guide is orientated toward the needs of these persons. Refer to appendix A for samples of such specific licenses issued to institutions and specific licenses issued to physicians. Note that conditions placed on the licenses vary somewhat depending on whether it is an institutional or private practice license and depending on the scope of the license.

1048497

II. FILING AN APPLICATION

An application for medical uses of byproduct material must be filed in duplicate on the "Application for Byproduct Material License," Form AEC-313. In addition, Form AEC-313a must be filed in duplicate for each physician. The application forms, with supporting documents, should be mailed to the Materials Branch, Division of Materials Licensing, U.S. Atomic Energy Commission, Washington, D.C., 20545. Item 1(a) of Form AEC-313 must name the person (hospital, corporation, partnership, individual, etc.) who will be responsible, as the licensee, for assuring that the byproduct material is used in compliance with the conditions of the license and with the Commission's regulations and the Act. For institutions such as medical schools or hospitals, the applicant will usually be the hospital, medical center, clinic, etc. The name of the applicant must be entered both in items 1(a) and 16 of the Form AEC-313 and the application must be signed by the applicant, or, if the applicant is an institution, by an individual who is authorized to sign on behalf of the institution. *Where a hospital is the applicant, the hospital administrator is normally the individual who signs the application.*

A physician requesting use of byproduct material in private practice or under contract with an institution should be the applicant; his name should be stated in items 1(a) and 16, and the application should be signed by the physician. In case two or more physicians are in a partnership, items 1(a) and 16 should state the name of the partnership and bear the signatures of the partners or the signature of an individual authorized to sign on behalf of the partnership.

Applications for amendments to existing byproduct material licenses are also filed on the Form AEC-313 and the Form AEC-313a. The application for amendment should be completed and signed in the same manner as an initial application except that pertinent information submitted on previous applications may be incorporated by reference. The license number of the license to be amended should be clearly stated in the application.

A physician applying for a diagnostic program under a general license must file Form AEC-482 in triplicate. The registration form should be mailed to the Materials Branch, Division of Materials Licensing, U.S. Atomic Energy Commission, Washington, D.C., 20545. Possession and use of the radiopharmaceuticals covered in the license is not authorized until the physician has filed Form AEC-482 and received from the Commission a validated copy of the form with a registration number assigned.

1048498

III. INFORMATION TO BE SUBMITTED

The information contained in an application must be sufficient to allow the Commission to determined that the applicant's proposed equipment, facilities, procedures, and the training and experience of users are adequate to protect health and minimize danger to life and property. Attached as appendix E are sample applications typical of those appropriate for most medical programs.

The applicant may incorporate by reference information contained in applications, statements, and reports previously filed with the Commission's Division of Materials Licensing or with the former Division of Licensing and Regulation, provided that such reference is clear and specific, indicating the date, page, and paragraph.

FORM AEC-313 APPLICATION FOR BYPRODUCT MATERIAL LICENSE

Item No.

1(a) Explained in section II.

1(b) Self-explanatory. If multiple addresses are to be used, explain the extent of use at each address and the facilities and equipment located at each place of use.

2 Self-explanatory.

3 Self-explanatory.

4 To use byproduct material in humans, an individual must be licensed by a State or territory of the United States, District of Columbia, or the Commonwealth of Puerto Rico to dispense drugs in the practice of medicine (see sec. 30.4(*l*) of 10 CFR 30) and have basic and clinical radioisotope training and experience commensurate with the proposed use of byproduct material. Acceptable training and experience is specified in appendix C for routine medical uses and appendix F for experimental or nonroutine uses.

5 Self-explanatory

6-7 List each isotope, chemical and/or physical form, and possession limit. If the byproduct material is a sealed source, state the name of manufacturer and model number and maximum activity. Under item 7 list each type of *nonhuman* use requested. A specific authorization must be obtained from the AEC to perform studies involving the use of byproduct material in animals. For human uses, refer to item 4 of the instructions for preparing the Form AEC-313.

8-9 See appendix C for the acceptable basic radioisotope training for an institutional user or individual user in a medical radioisotope program. If the Radiation Protection Officer is not a user, list his qualifications to act as Radiation Protection Officer. If the Radiation Protection Officer is a user, his qualifications will be listed elsewhere in the application.

10 List all radiation monitoring or measuring instruments that will be available for the proposed use(s) of byproduct material. This should include instruments for measuring uptake of the isotopes, assaying biological specimens, and making radiation surveys. The manufacturer's name and model number of each instrument should be listed with the number of instruments available, type of radiation detected (beta, gamma, etc.), the sensitivity range (mr/hr, cpm/, etc.), window thickness, if applicable, and use, such as measuring, surveying, etc.

Appendix G contains a list of the types of instruments needed for various medical uses of byproduct material.

11 Self-explanatory.

12 State the name of the organization furnishing film badge service and specify the frequency for changing the badges. If pocket chambers or pocket dosimeters are used, indicate the useful range, frequency of reading the monitoring devices, and the procedures for maintaining the dosimeters.

13-14 Submit sufficiently detailed information

1048499

Item No.

about the facilities and equipment and the radiation protection program to be in effect during use of byproduct materials to permit the Commission to make a determination that the applicant has established an adequate radiation safety program. The degree of detail required depends on the scope of the proposed byproduct material program. See appendix H for guidelines.

15 A specific method for disposing of byproduct material waste should be submitted. A licensee may dispose of waste in the following ways–

(a) Transfer to a person appropriately licensed to receive such waste.

(b) Release into the sanitary sewerage system in conformance with section 20.303 of 10 CFR 20.

(c) Burial in soil in conformance with section 20.304 of 10 CFR 20.

(d) Release into the air in concentrations conforming with section 20.106 of 10 CFR 20.

(e) Other methods specifically approved by the Commission pursuant to section 20.302.

Requests for incineration of byproduct material are handled in accordance with sections 20.106(b) and 20.302 and should include the information outlined in appendix I and section 20.106(c) of 10 CFR 20.

16 Refer to section II

FORM AEC-313a, APPLICATION FOR BYPRODUCT MATERIAL LICENSE–SUPPLEMENT A–HUMAN USE

Item No.

1-3 Self-explanatory.

4 When the Form AEC-313a is used in conjunction with Form AEC-313, state the clinical use and chemical form of each radioactive material. For item 4(c), see appendix H.

5(a) The applicant should state the isotope, chemical and physical form, and dosage range for each condition to be diagnosed or treated. When a byproduct material is proposed for both diagnosis and therapy, the dosage range for each should be stated separately. The statement of dosage is reviewed for appropriateness of the dose range rather than as a specific dosage.

5(b) See appendix F.

6 Self-explanatory.

7 There should be attached either a statement indicating that this application has been reviewed by the institution's medical isotope committee and stating the basis for their action, or a statement indicating that it will be reviewed.

8(a) For private practice programs, state the name and address of the hospital(s) which will admit patients should it become necessary during or after administration of the radioactive material.

8(b) For programs covering more than diagnostic prepackaged doses, the applicant should submit appropriate housekeeping and radiological protection rules to be observed by individuals who must handle radioisotopes or care for patients treated with radioactive pharmaceuticals. Where appropriate, these rules should contain procedures pertaining to surveys, spills, handling of contaminated linens, precautions to be taken with visitors and hospital personnel, collection of urine and excreta, and other radiological safety measures tailored to specific programs and facilities. See appendix E for sample instructions.

9 State the name and address of the physician in item 4 of Form AEC-313. If more than one physician is named in item 4 of Form AEC-313, a separate page 3 of Form AEC-313a (preceptor statement) must be submitted for each individual user.

10 In item 10 *(a)*, *(b)*, *(c)*, and *(d)*, indicate the type of clinical training, the isotope used, condition(s) diagnosed or treated, number of cases observed and the number of cases involving personal participation. If additional space is needed, continue on page 4 of Form AEC-313a.

11 Self-explanatory.

12 State the name of the physician under whom the clinical training was received and the dates of the trainee physician's clinical radioisotope training. Also state the name of

1048500

Item No.

the preceptor's institution and its byproduct material license number. *Item 12 must be signed by the physician(s) under whom the clinical training was received.* This item may not be signed by the individual named in item 9.

Refer to appendix C for the minimum acceptable clinical experience for the well established diagnostic and therapeutic uses and appendix F for nonroutine uses.

FORM AEC-482, APPLICATION FOR REGISTRATION CERTIFICATE–MEDICAL USE OF BYPRODUCT MATERIAL UNDER GENERAL LICENSE

Self-explanatory. A sample certificate is printed in Appendix A. The reverse side of the certificate contains the conditions and limitations of the general license.

IV. REQUIREMENTS OF THE REGULATIONS

Byproduct material programs must be conducted in compliance with 10 CFR 20, "Standards for Protection Against Radiation"; 10 CFR 30, "Rules of General Applicability to Licensing of Byproduct Material"; 10 CFR 35, "Human Uses of Byproduct Material"; the following listed specific requirements in these regulations are not normally submitted with the application; however, attention is directed to these requirements so that they may be considered and procedures adopted to assure compliance with them.

A. *Caution signs, labels, and signals.* (See sec. 20.203 of 10 CFR 20.)

B. *Records of surveys, radiation monitoring, and disposal.* (See sec. 20.401 of 10 CFR 20.)

C. *Reports of theft or loss of licensed material.* (See sec. 20.402 of 10 CFR 20.)

D. *Notifications of incidents.* (See sec. 20.403 of 10 CFR 20.)

E. *Report to former employees of exposure to radiation* (See sec. 20.404 of 10 CFR 20.)

F. *Reports of overexposures and excessive levels and concentrations.* (See sec. 20.405 of 10 CFR 20.)

G. *Notice to employees of exposure to radiation.* (See sec. 20.406 of 10 CFR 20.)

H. *Records.* (See sec. 30.51 of 10 CFR 30.)

1048502

ISOTOPE	CHEMICAL FORM	USE
Chromium 51	Sodium Chromate	Determination of red blood cell volumes and studies of red blood cell survival time
Cobalt 58 or cobalt 60	Cyanocobalamin (Vitamin B-12)	Intestinal absorption studies
Potassium 42	Chloride	Potassium space determinations
Iron 59	Chloride, Citrate or sulfate	Iron turnover studies
	GROUP II	
Iodine 131	Iodinated Human Serum Albumin (IHSA)	Brain tumor localizations Cardiac imaging
Iodine 131	Sodium Iodide	Thyroid imaging
Iodine 131	Macroaggregated Iodinated Human Serum Albumin	Lung imaging
Iodine 131	Colloidal (microaggregated) Iodinated Human Serum Albumin	Liver imaging
Iodine 131	Rose Bengal	Liver imaging
Iodine 131	Iodopyracet, Sodium Iodohippurate, Sodium Diatrizoate, Diatrizoate Methylglucamine, Sodium Diproprizoate, or Sodium Acetrizoate	Kidney imaging
Iodine 131	Sodium Iodipamide	Cardiac imaging
Chromium 51	Sodium Chromate	Spleen imaging
Gold 198	Colloidal Form	Live imaging
Mercury 197	Chlormerodrin	Kidney imaging Brain imaging
Mercury 203	Chlormerodrin	Brain imaging
Strontium 85	Nitrate or Chloride	Bone imaging in patients with known or suspected cancer
Technetium 99m	Pertechnetate	Brain imaging and thyroid imaging Blood pool imaging Salivary gland imaging

1048503

E. This license does not include a specific possession limit for the radioisotopes authorized in Schedule A. The quantities possessed should be those required for the clinical program.

II. A Specific License Issued to an Institution.

A. The license is issued to a hospital and condition 10 names the physicians under whose direction the radioisotopes may be used.

B. Condition 13 requires the sealed sources containing byproduct material to be leak tested every six months.

III. General License Registration Certificate Issued to a Physician in Private Practice.

This certificate authorizes the use of iodine 125, iodine 131, cobalt 58, cobalt 60, and chromium 51 for specific diagnostic purposes provided under the general license in Section 35.31, 10 CFR 35.

1048504

FORM AEC-374 (M-3)
(2/70)
10 CFR 30

U. S. ATOMIC ENERGY COMMISSION
BYPRODUCT MATERIAL LICENSE
(Medical - Groups I & II)

Page 1 of 3 Pages

LICENSE SAMPLE (2) - INSTITUTIONAL LICENSE

Pursuant to the Atomic Energy Act of 1954 and Title 10, Code of Federal Regulations, Chapter 1, Parts 30, 32, 33, 34, and 35, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, own, possess, transfer and import byproduct material listed below; and to use such byproduct material for the purpose(s) and at the place(s) designated below. This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954 as amended, and is subject to all applicable rules, regulations, and orders of the Atomic Energy Commission now or hereafter in effect and to any conditions specified below.

Licensee	
1. Good Hope General Hospital	3. License Number 45-00543-21
2. 2005 South Buran Avenue Richmond, Virginia 22231	4. Expiration date June 30, 1975
	5. Reference No.

6. Byproduct material (element and mass number)	7. Chemical and/or physical form	8. Maximum amount of radioactivity which licensee may possess at any one time
A. Any byproduct material listed in Groups I and II of Schedule A, Section 35.100 of 10 CFR 35	A. Any radiopharmaceutical listed in Groups I and II of Schedule A, Section 35.100 of 10 CFR 35	A. As necessary for uses authorized in Subitem 9. A..
B. Iodine 131	B. Iodide	B. 200 millicuries
C. Iodine 125 or 131	C. Triiodothyronine	C. 1 millicurie
D. Phosphorus 32	D. Soluble Phosphate	D. 25 millicuries
E. Phosphorus 32	E. Colloidal Chromic Phosphate	E. 25 millicuries
F. Gold 198	F. Colloidal	F. 300 millicuries
G. Cobalt 60	G. Wire (Manufacturer and Model No.)	G. 200 millicuries
H. Strontium 90	H. Sealed Source (Manufacturer and Model No.)	H. 50 millicuries
I. Cesium 137	I. Chloride	I. 10 millicuries
J. Molybdenum 99	J. Molybdenum 99/ Technetium 99m Generator (Manufacturer and Model No.)	J. 200 millicuries

Conditions numbered 1, 2, 3, 4 printed on the reverse side of this page shall apply to this license.

For the U. S. Atomic Energy Commission

Date _____ by _____

Division of Materials Licensing
Washington, D. C. 20545

1048505

CONDITIONS

1. Byproduct material may only be used at the licensee's address stated in Item 2 above.

2. The licensee shall comply with the provisions of Title 10, Chapter 1, Code of Federal Regulations, Part 20, "Standards for Protection Against Radiation."

3. Except as otherwise specifically provided by this license, byproduct material to be administered to humans shall be procured in prepackaged, precalibrated form from a supplier who manufactures or repackages the product under appropriate pharmaceutical controls related to assay, identity, quality, purity, sterility, and nonpyrogenicity.

4. Iodine 131 labeled Macroaggregated Iodinated Human Serum Albumin, Chromium 51 labeled Human Serum Albumin, and Iodine 131 labeled Colloidal (Microaggregated) Human Serum Albumin shall be procured from a supplier who holds an unsuspended or unrevoked license issued by the Secretary, Department of Health, Education, and Welfare, to propagate or manufacture and prepare, label, or distribute this material pursuant to Title 42, Chapter 1, Code of Federal Regulations, Part 73, "Biological Products."

5. Needles or standard medical applicator cells containing Cobalt 60 as wire shall not be opened by the licensee unless specifically authorized by a condition in this license.

6. Patients containing Cobalt 60, Cesium 137, and/or Iridium 192 implants shall remain hospitalized until the implants are removed.

7. Patients containing Iodine 131 for the treatment of thyroid carcinoma or patients containing therapeutic quantities of Gold 198 shall remain hospitalized until the residual activity is 30 millicuries or less.

1048506

FORM AEC-374A
(2-68)
10 CFR 30

U. S. ATOMIC ENERGY COMMISSION
BYPRODUCT MATERIAL LICENSE
Supplementary Sheet

License Number 45-00543-21

LICENSE SAMPLE (2) (continued)

9. Authorized use

A. Any diagnostic procedure listed in Groups I and II of Schedule A, Section 35.100 of Title 10, Code of Federal Regulations.
B. Treatment of hyperthyroidism, cardiac conditions, and thyroid carcinoma.
C. In vitro studies.
D. Treatment of polycythemia vera and leukemia.
E. and F. Intracavitary treatment of malignant effusions.
G. Interstitial and intracavitary treatment of cancer as a replacement of radium.
H. Treatment of superficial eye diseases.
I. Brain imaging in 12 patients. Within six weeks after the completion of this study, the licensee is requested to furnish a report to the Commission which briefly summarizes the results of the study.
J. Production of Technetium 99m pertechnetate.

CONDITIONS

10. Byproduct material shall be used by, or under the supervision of, Gerald M. Good, M. D., Franklin D. Lawson, M. D., or Daniel H. Harrington, M. D.

11. Technetium 99m Pertechnetate may be eluted and prepared from a Molybdenum 99/Technetium 99m generator in accordance with statements, representations, and procedures contained in application dated June 4, 1968.

12. Patients containing Cobalt 60 implants shall remain hospitalized until the implants are removed.

13. A. Each sealed source containing byproduct material, other than Hydrogen 3, with a half-life greater than thirty days and in any form other than gas shall be tested for leakage and/or contamination at intervals not to exceed six months. In the absence of a certificate from a transferor indicating that a test has been made within six months prior to the transfer, the sealed source shall not be put into use until tested.

For the U. S. Atomic Energy Commission

Date _____ by _____

Division of Materials Licensing
Washington, D. C. 20545

1048507

FORM AEC-374A
(2-65)
10 CFR 30

U. S. ATOMIC ENERGY COMMISSION
BYPRODUCT MATERIAL LICENSE
Supplementary Sheet

License Number 45-00543-21

LICENSE SAMPLE (2) (continued)

13. continued

B. The test shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the sealed source or from the surfaces of the device in which the sealed source is permanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Commission.

C. If the test reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the sealed source from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the test with the Director, Division of Materials Licensing, U. S. Atomic Energy Commission, Washington, D. C., 20545, describing the equipment involved, the test results, and the corrective action taken. A copy of such report shall also be sent to the Director, Region II, Division of Compliance, USAEC, Suite 818, 230 Peachtree Street, Northwest, Atlanta, Georgia, 30303.

D. Tests for leakage and/or contamination shall be performed by Dr. Gerald M. Good, or by other persons specifically authorized by the Commission or an Agreement State to perform such services.

14. Sealed sources containing byproduct material shall not be opened.

For the U. S. Atomic Energy Commission

te _____

by Materials Branch
Division of Materials Licensing
Washington, D. C. 20545

1048508

LICENSE SAMPLE (3)

Form AEC-482
(7-65)
10 CFR 35

U.S. ATOMIC ENERGY COMMISSION

FORM APPROVED
BUDGET BUREAU NO.
38 R-027

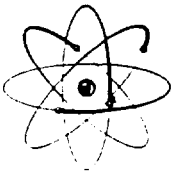
REGISTRATION CERTIFICATE—MEDICAL USE OF BYPRODUCT MATERIAL UNDER GENERAL LICENSE

Section 35.31 of 10 CFR 35 establishes a general license authorizing physicians to possess certain small quantities of I 125, I 131, Co 58, Co 60, and Cr 51 for specified diagnostic uses. Possession of byproduct material under 10 CFR 35.31 is not authorized until the physician has filed Form AEC-482 and received from the Commission a validated copy of Form AEC-482 with registration number assigned.

INSTRUCTIONS

Submit this Form in triplicate to: United States Atomic Energy Commission, Washington, D.C., 20545, Attention: Director, Division of Materials Licensing. *A registration number will be assigned and a validated copy of Form AEC-482 will be returned. Please print or type your name and address* (including ZIP code), *within the shaded area.*

Registration number:



(Leave this space blank—number to be assigned by AEC)

I am a duly licensed physician authorized to dispense drugs in the practice of medicine. My license(s) is (are) valid under the laws of:

STATE(S) OF LICENSURE | LICENSE NUMBER(S)

CERTIFICATE

I hereby certify that:

1. All information in this registration certificate is true and complete.
2. I have appropriate radiation measuring instruments to carry out the diagnostic procedures for which I will use byproduct material under the general license of 10 CFR 35.31 and I am competent in the use of such instruments.
3. I understand that Commission regulations require that any change in the information furnished by a registrant on this registration certificate be reported to the Director, Division of Materials Licensing, within 30 days from the date of such change.
4. I have read and understand the provisions of Section 35.31 of AEC regulations (10 CFR 35) reprinted on the reverse side of this form; and I understand that I am required to comply with those provisions as to all byproduct material which I receive, possess, use, or transfer under the general license for which this Registration Certificate is filed with the Atomic Energy Commission:

Date _____ By _____
(Signature of Registrant)

WARNING.—18 U.S.C., Section 1001, Act of June 25, 1948, 62 Stat. 749: makes it a criminal offense to make a willfully false statement or representation to any department or agency of the United States as to any matter within its jurisdiction

1048509

CONDITIONS AND LIMITATIONS OF GENERAL LICENSE 10 CFR 35.31

§ 35.31 General License for Medical Use of Certain Quantities of Byproduct Material.

(a) A general license is hereby issued to any physician to receive, possess, transfer, or use for any of the following stated diagnostic uses, in accordance with the provisions of paragraphs (b), (c), and (d) of this section, the following byproduct materials in capsules, disposable syringes or other forms of prepackaged individual doses;

(1) Iodine 131 as sodium iodide (NaI^{131}) for measurement of thyroid uptake;

(2) Iodine 131 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(3) Iodine 125 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(4) Cobalt 58 for the measurement of intestinal absorption of cyanocobalamin;

(5) Cobalt 60 for the measurement of intestinal absorption of cyanocobalamin;

(6) Chromium 51 as sodium radiochromate for determination of red blood cell volumes and studies of red blood cell survival time.

Note: Section 32.70 of this chapter requires manufacturers of radiopharmaceuticals which are under the general license in this paragraph to include the following statement in the label affixed to the container or in the leaflet or brochure which accompanies the radiopharmaceutical;

This radioactive drug may be received, possessed, and used only by physicians licensed to dispense drugs in the practice of medicine. Its receipt, possession, use, and transfer are subject to the regulations and a general license of the United States Atomic Energy Commision or of a State with which the Commission has entered into an agreement for the exercise of regulatory authority.

(Name of manufacturer)

(b) No physician shall receive, possess, use, or transfer byproduct material pursuant to the general license established by paragraph (a) of this section until he has filed Form AEC-482, "Registration Certificate—Medical Use of Byproduct Material Under General License" with the Director, Division of Materials Licensing, U.S. Atomic Energy Commission, Washington, D.C., 20545, and received from the Commission a validated copy of the Form AEC-482 with registration number assigned. The registrant shall furnish on Form AEC-482 the following information and such other information as may be required by that form:

(1) Name and address of the registrant;

(2) A statement that the registrant is a duly licensed physician authorized to dispense drugs in the practice of medicine, and specifying the license number and the State in which such license is valid; and

(3) A statement that the registrant has appropriate radiation measuring instruments to carry out the diagnostic procedures for which he proposes to use byproduct material under the general license of § 35.31 of this chapter and that he is competent in the use of such instruments.

(c) A physician who receives, possesses, or uses a pharmaceutical containing byproduct material pursuant to the general license established by paragraph (a) of this section shall comply with the following:

(1) He shall not possess at any one time, pursuant to the general license in paragraph (a) of this section, more than:

(i) 200 microcuries of iodine 131,

(ii) 200 microcuries of iodine 125,

(iii) 5 microcuries of cobalt 58,

(iv) 5 microcuries of cobalt 60, and

(v) 200 microcuries of chromium 51.

(2) He shall store the pharmaceutical until administered in the original shipping container or a container providing equivalent radiation protection;

(3) He shall use the pharmaceutical only for the uses authorized by paragraph (a) of this section;

(4) He shall not administer the pharmaceutical to a woman with confirmed pregnancy or to a person under 18 years of age;

(5) He shall not transfer the byproduct material to a person who is not authorized to receive it pursuant to a license issued by the Commission or an agreement State, or in any manner other than in the unopened, labeled shipping container as received from the supplier, except by administering it to a patient.

(d) The registrant possessing or using byproduct material under the general license of paragraph (a) shall report in duplicate to the Director, Division of Materials Licensing, any changes in the information furnished by him in the "Registration Certificate—Medical Use of Byproduct Material Under General License," Form AEC-482. The report shall be submitted within 30 days after the effective date of such change.

(e) Any person using byproduct material pursuant to the general license of paragraph (a) of this section is exempt from the requirements of Part 20 of this chapter with respect to the byproduct materials covered by the general license.

NOTE

If larger quantities or other forms of byproduct material than those specified in the general license of 10 CFR 35.31 are required, the physician should file an "Application for Byproduct Material License," Form AEC-313 and obtain a specific byproduct material license. Copies of application and registration forms may be obtained from the United States Atomic Energy Commission, Washington, D.C., 20545, Attention: Isotopes Branch, Division of Materials Licensing.

1048510

APPENDIX B

MEDICAL ISOTOPES COMMITTEE

Section 35.11(b), 10 CFR 35, requires the applicant for an institutional license to appoint a medical isotope committee to evaluate all proposals for research, diagnostic, and therapeutic uses of radioisotopes within the institution. The medical isotope committee shall consist of at least three members. This membership should include physicians expert in internal medicine or hematology (or pathology), therapeutic radiology, and a person experienced in assay of radioisotopes and protection against ionizing radiation.

The application should give the names, specialities, and radioisotope experience of each committee member and describe the functions, responsibilities, authority, and administrative procedures of the committee. The following is presented as a typical assignment given to a committee:

A. Committee Authority.

The committee is established by authority of the Hospital Administrator (or Hospital Director) as the administrative body responsible for the safe use of radioisotopes within the institution.

B. Committee Responsibilities.

1. Review and grant permission for, or disapprove, the use of byproduct material for experimental or nonroutine uses within the institution from the standpoint of radiological health and safety of patients or working personnel and other factors which the committee may wish to establish for medical uses of byproduct materials prior to submission of an application to the Commission for licensing action.

2. Prescribe special conditions that will be required during a proposed use of byproduct material such as requirements for bioassays and physical examinations of users, minimum level of training and experience of users.

3. Receive and review records and reports from the radiological safety officer or other individuals delegated responsibility for health safety practices in the instituion.

4. Recommend remedial action to correct safety infractions.

5. Formulate and review the institutional training programs for the safe use of radioisotopes.

6. Maintain written record of actions taken by the committee.

7. Coordinate and supervise the use of isotopes under private practice license. (Although it is not a requirement, the institution may desire to establish a radioisotope committee to assist in the control of radioisotope use if there are multiple private practice licensees permitted to use materials within the institution.)

8. Inform the Commission of any changes in committee membership.

C. Committee Administrative Procedures.

The scope of administrative procedures will depend primarily on the radioisotope program to be undertaken. If the program is initiated on a modest scale, revisions of procedures and organizations may become appropriate, as the program grows over a period of time. The procedures may include–

1. A meeting schedule to review safety aspects of present programs and to consider special cases or problems.

2. Record keeping procedures for committee meetings, actions, recommendations, and decisions.

3. A program for the preparation and dissemination of information pertaining to radiation safety.

4. The delegation of responsibility to a specific individual for the conduct of the day-to-day radiation safety program, including appropriate surveys and maintenance of records.

5. Maintenance of written records of receipts, transfers, and disposal of all radioactive isotopes in the institution and maintenance of an inventory of the total quantity of each radioisotope possessed at the institution.

6. Provisions for initiating corrective action as necessary to assure radiation safety.

1048511

APPENDIX C

ACCEPTABLE TRAINING AND EXPERIENCE FOR MEDICAL USES OF BYPRODUCT MATERIAL

I. GENERAL TRAINING.

Section 35.11 (d) of 10 CFR 35 provides that the Commission will approve a license application by an institution for medical use of byproduct material if it determines, among other things, that the physician designated as the individual user is adequately trained and experienced in (a) basic radioisotope handling techniques and (b) the clinical use of byproduct material proposed in the application. Similar criteria are established in section 35.12(c) of 10 CFR 35 for approval of licenses for medical use of radiopharmaceuticals by individual physicians. Outlined below are training and experience criteria which the Commission, with the assistance of its Advisory Committee on the Medical Uses of Isotopes, has found acceptable for physicians who use radiopharmaceuticals. Each physician's training and experience are examined on a case-by-case basis. If a physician wishes to use radiopharmaceuticals but does not have the training and experience described, he may submit an application listing his specific qualifications and this will be reviewed by the Commission with the assistance of the Medical Advisory Committee.

Training may be obtained in a residency, formal training course, or collaboration in a program using byproduct material. To qualify as adequately trained, a physician's background should include:

A. General Training in Basic Radioisotope Handling Techniques Including–

1. A working knowledge of–

a. Principles and practices of radiological health safety;

b. Radioactivity measurements, standardization, and monitoring techniques and instruments;

c. Mathematics and calculations basic to the use and measurement of radioactivity;

d. Biological effects of radiation; and

2. Experience in the use of byproduct material for the types and quantities for which the application is being made, or equivalent experience.

NOTE: Satisfactory completion of the Oak Ridge Associated Universities "Basic Course in Radioisotope Techniques, or its equivalent, in practical training will serve as evidence of acceptable basic training.

B. Clinical Radioisotope Training Consisting of–

1. Supervised examination of patients to determine the suitability for radioisotope diagnosis and/or treatment and recommendation on dosage to be prescribed;

2. Collaboration in calibration of the dose and the actual administration of the dose to the patient, including calculation of the radiation dose, related measurements, and plotting of data;

3. Adequate period of training to enable the physician to manage radioactive patients and to follow patients through diagnosis and/or the course of treatment;

4. Study and discussion with preceptor of case histories to establish most appropriate diagnostic and/or therapeutic procedures, limitations, contraindications, etc.

II. SPECIFIC TRAINING–BASIC AND CLINICAL.

The following relates to well-established medical uses. Training requirements are the same for physicians in institutional or in private practice programs. See Appendix F for suggested training and experience for nonroutine or experimental medical uses. Training and experience for the specific clinical uses are as follows:

A. Category I–Diagnostic Procedures

The diagnostic procedures covered by Category I are iodide for diagnosis of thyroid function; iodinated human serum albumin for plasma and blood volume determinations; rose bengal for liver function studies; labeled renal function compounds for kidney function studies; triiodothyronine for *in vitro* study of thyroid function; labeled fats and/or fatty acids for fat absorption studies; chromium 51 labeled human

1048512

serum albumin for gastrointestinal protein loss studies; cobalt 60 or 58 labeled cyanocobalamin for intestinal absorption studies; iron 59 as chloride, citrate and/or sulfate for iron turnover studies; potassium 42 as chloride for potassium space determinations; krypton 85 as gas for diagnosis of cardiac abnormalities; and xenon 133 as free gas or in solution for diagnosis of cardiac abnormalities, blood-flow studies and pulmonary function studies. Training and experience criteria for these procedures are—

1. Thirty hours of training in basic radioisotope handling techniques, and

2. Active participation in the performance of five uptake studies, three dilution studies, and three excretion studies involving the use of radiopharmaceuticals on humans.

To be licensed for one or more of the diagnostic procedures listed in Category I, but not the entire category, training and experience should include:

1. Thirty hours of training in basic radioisotope handling techniques, and

2. Active participation in three cases each of the specific diagnostic procedure(s) requested, except that for diagnosis of thyroid function the physician should have actively participated in five cases.

B. Category II—Specialized Diagnostic Procedures (Scans or Tumor Localization)

The specialized diagnostic procedures covered by Category II are iodide for thyroid imaging; iodinated human serum albumin for brain tumor localization, cardiac imaging for determination of pericardial effusions, and placenta localization; sodium iodipamide for cardiac imaging for determination of pericardial effusions; labeled renal function compunds for kidney imaging; chromium 51 for spleen imaging and placenta localization; macroagregated iodinated human serum albumin for lung imaging; microaggregated (colliodal) human serum albumin for liver imaging; strontium 85 as nitrate or chloride for bone imaging in patients with known or suspected cancer; selenium 75 as selenomethionine for pancreas imaging; and mercury 197 for brain and renal imaging; and mercury 203 for brain imaging; technetium 99m as sulfur colloid for liver and spleen imaging; and technetium 99m as pertechnetate for brain, thyroid, salivary, blood pool imaging, and placenta localization.

1. Thirty hours of training in basic radioisotope handling techniques, and

2. Active participation in the performance of three tumor localizations or organ images using byproduct material, except that for pancreas imaging the physician must have been actively engaged in conducting images for at least six months and have participated in at least three (3) pancreas images under the supervision of a physician already experienced in this procedure.

NOTE: Category II procedures require specialized instrumentation and techniques. The physician should, therefore, be familiar with the use of instrumentation for each specialized procedure he requests. The applicant requesting iodinated human serum albumin, chromium 51, or technetium 99m for placenta localization should confirm that the procedure will be performed only if:
1. The patient is in the third trimester of pregnancy;
2. The pateint is bleeding; and
3. The obstetrician recommends the study for the management of the patient.

C. Category III—Iodine 131—Treatment of Hyperthyroidism and/or Cardiac Conditions; Phosphorus 32— Treatment of Blood Dyscrasias.

1. Thirty hours of training in basic radioisotope handling techniques, and

2. For the treatment of hyperthyroidism and/or cardiac dysfunction, clinical experience in the diagnosis of thyroid function and active participation in the treatment of ten patients with hyperthyroidism and/or cardiac dysfunction using iodine 131.

3. For the treatment of polycythemia vera, leukemia, and bone metastases, active participation in the treatment of three patients with one of these conditions using phosphorus 32.

D. Category IV—Treatment of Thyroid Carcinoma; Phosphorus 32 and Gold 198 Intracavitary Therapy.

1. Thirty hours of training in basic radioisotope handling techniques.

2. For the treatment of thyroid carcinoma, clinical experience in diagnosis of thyroid function and treatment of hyperthyroidism and/or cardiac dysfunction, and active participation in the treatment of three patients with thyroid carcinoma using iodine 131.

3. For the intracavitary treatment of carcinomatous patients with gold 198, active participation in three cases.

4. For the intracavitary treatment of carcinomatous patients with phosphorus 32, active participation in three cases.

E. Interstitial Treatment of Carcinomatous Patients With Colloidal Phosphorus 32.

1. Thirty hours of training in basic radioisotope handling techniques.

2. Active participation in the interstitial treatment of three carcinomatous patients with colloidal phosphorus 32 or colloidal gold 198.

NOTE: The interstitial use of colloidal chromic phosphate in the treatment of cancer entails a specialized procedure. Such treatment should, therefore, be carried out only by an appropriate team of specialists including a therapeutic radiologist.

F. Interstitial Treatment of Carcinomatous Patients With Colloidal Gold 198.

1. Thirty hours of basic training in radioisotope handling techniques.

2. Active participation in the interstitial treatment of three carcinomatous patients with colloidal gold 198.

NOTE: The interstitial use of colloidal gold in the treatment of cancer entails a specialized procedure. Such treatment should, therefore, be carried out only by an appropriate team of specialists, including a therapeutic radiologist.

G. Interstitial, Intracavitary, or Surface Treatment of Cancer with Radiation Sources.

Active practice in therapeutic radiology with a minimum of three years' experience.

Note: In lieu of the above experience, the physician should be a qualified specialist in a field appropriate to the proposed use with specialized training and experience in radiation dosimetry and at least three years' experience in interstitial, surface, or intracavitary use of radiation sources.

H. Treatement of Superficial Eye Disease With Beta Ray Applicators.

Active practice in therapeutic radiology or ophthalmology and experience in the therapeutic use of beta rays or soft x-rays.

NOTE: In lieu of the above experience, the physician should have at least three years' experience in the therapeutic use of beta rays or soft x-rays and furnish evidence of knowledge and experience concerning beta ray depth dosage. Such physicians should have actively participated in the treatment of at least three cases of superficial eye diseases.

I. Determination of Blood Volume With Automatic Blood Volume Instruments.

This procedure involves the use of an instrument which automatically measures and directly indicates isotopic dilution and blood volume after injection of prepackaged doses of I-131 as Iodinated Human Serum Albumin.

Training and experience criteria for this procedure are –

1. Three hours of training in the use of the instrument and basic radioisotope handling techniques.

2. Active participation in the performance of three blood volume determination with the instrument.

Uses of other byproduct material not listed in appendix C are considered to be nonroutine. See appendix F for experimental and nonroutine uses of byproduct material.

APPENDIX D

A LIST OF WELL ESTABLISHED MEDICAL USES

ISOTOPE	CHEMICAL FORM	USE
Cesium 137	Encased in Needles and/or Applicator Cells	Interstitial or intracavitary treatment of cancer
Cesium 137	Teletherapy Source	Treatement of cancer
Chromium 51	Chromate	Spleen imaging
Chromium 51	Chromate	Placenta localication
Chromium 51	Chromate	Red blood cell labeling for volume and survival studies
Chromium 51	Labeled Human Serum Albumin	Gastrointestinal protein loss studies
Chromium 51	Labeled Human Serum Albumin	Placenta localization
Chromium 51	Labeled Red Blood Cells	Placenta localization
Cobalt 58 or Cobalt 60	Labeled Cyanocobalamin	Intestinal absorption studies
Cobalt 60	Teletherapy Source	Treatment of cancer
Cobalt 60	Encased in Needles and/or Applicator Cells	Interstitial or intracavitary treatment of cancer
Gold 198	Colloidal	Liver imaging
Gold 198	Colloidal	Intracavitary treatment of malignant effusions
Gold 198	Colloidal	Interstitial treatment of cancer
Gold 198	Seeds	Interstitial treatment of cancer
Iodine 131	Iodide	Diagnosis of thyroid function
Iodine 131	Iodide	Thyroid imaging

1048515

ISOTOPE	CHEMICAL FORM	USE
Iodine 131	Iodide	Treatment of hyperthyroidism and/or cardiac dysfunction
Iodine 131	Iodide	Treatment of thyroid carcinoma
Iodine 131	Iodinated Human Serum Albumin	Blood volume determination
Iodine 131	Iodinated Human Serum Albumin	Brain tumor localization
Iodine 131	Iodinated Human Serum Albumin	Placenta localization
Iodine 131	Iodinated Human Serum Albumin	Cardiac imaging for determination of pericardial effusions
Iodine 131	Iodinated Human Serum Albumin	Cisternography
Iodine 131	Rose Bengal	Liver function studies
Iodine 131	Rose Bengal	Liver imaging
Iodine 131	Iodopyracet, Sodium Iodohippurate Sodium Diatrizoate, Diatrizoate Methyl-glucamine, Sodium Diprotrizoate, Sodium Acetrizoate, or Sodium Iothalamate	Kidney function studies and kidney imaging
Iodine 131	Labeled Fats and/or Fatty Acids	Fat absorption studies
Iodine 131	Sodium Iodipamide	Cardiac imaging for determination of pericardial effusions
Iodine 131	Macroaggregated Iodinated Human Serum Albumin	Lung imaging
Iodine 131	Colloidal Microaggregated Human Serum Albumin	Liver imaging
Iodine 125	Iodide	Diagnosis of thyroid function
Iodine 125	Iodinated Human Serum Albumin	Blood volume determination
Iodine 125	Rose Bengal	Liver function studies

1048516

ISOTOPE	CHEMICAL FORM	USE
Iodine 125	Iodopyracet, Sodium Iodohippurate, Sodium Diatrizoate, Diatrizoate Methyl-glucamine, Sodium Diprotrizoate, Sodium Acetrizoate, or Sodium Iothalamate	Kidney function studies
Iodine 125	Labeled Fats and/or Fatty Acids	Fat absorption studies
Iron 59	Chloride, Citrate and/or Sulfate	Iron turnover studies
Iridium 192	Seeds Encased in Nylon Ribbon	Interstitial treatment of cancer
Krypton 85	Gas	Diagnosis of cardiac abnormalities
Mercury 197	Chlormerodrin	Kidney imaging
Mercury 197	Chlormerodrin	Brain imaging
Mercury 203	Chlormerodrin	Brain imaging
Phosphorus 32	Soluble Phosphate	Treatment of polycythemia vera
Phosphorus 32	Soluble Phosphate	Treatment of leukemia and bone metastasis
Phosphorus 32	Colloidal Chromic Phosphate	Intracavitary treatment of malignant effusions
Phosphorus 32	Colloidal Chromic Phosphate	Interstitial treatment of cancer
Potassium42	Chloride	Potassium space studies
Selenium 75	Selenomethionine	Pancreas imaging
Strontium 85	Nitrate or Chloride	Bone imaging on patients with known or suspected cancer
Strontium 90	Medical Applicator	Treatment of superficial eye conditions
Technetium 99m	Pertechnetate	Brain imaging
Technetium 99m	Pertechnetate	Thyroid imaging
Technetium 99m	Sulfur Colloid	Liver and Spleen imaging

1048517

A LIST OF WELL ESTABLISHED MEDICAL USES

ISOTOPE	CHEMICAL FORM	USE
Technetium 99m	Pertechnetate	Placenta localization
Technetium 99m	Pertechnetate	Blood pool imaging
Technetium 99m	Petechnetate	Salivary gland imaging
Technetium 99m	Iron-Ascorbate-Diethylenetriamine Pentaacetic Acid Complex	Kidney imaging
Xenon 133	Free Gas or in solution	Diagnosis of cardiac abnormalties Blood-flow studies Pulmonary function studies

ADDITIONS TO APPENDIX D

ADDITIONS TO THE LIST OF WELL-ESTABLISHED MEDICAL USES

ISOTOPE	CHEMICAL FORM	USE
Technetium 99m	Human Serum Albumin Microspheres	Lung Imaging
Technetium 99m	Diethylenetriamine Pentaacetic Acid (Sn)	Kidney Imaging Kidney Function Studies
Technetium 99m	Diethylenetriamine Pentaacetic Acid (Sn)	Brain Imaging
Technetium 99m	Polyphosphates	Bone Imaging
Iodine 125	Sealed Source	For Use in Bone Mineral Analyzer
Americium 241	Sealed Source	For Use in Bone Mineral Analyzer
Technetium 99m	Technetated Aggregated Albumin (Human)	Lung Imaging
Fluorine 18	Fluoride	Bone Imaging
Technetium 99m	Disodium Etidronate	Bone Imaging

1048518

APPENDIX E

SAMPLE APPLICATIONS

1. Sample Application No. 1 is a Form AEC-313 and -313a request for an institutional license.
2. Sample Application No. 2 is a Form AEC-313 and -313a request for a private practice license.

1048519

APPLICATION - SAMPLE 1.

Form AEC-313 (11-63) 10 CFR 30	ATOMIC ENERGY COMMISSION **APPLICATION FOR BYPRODUCT MATERIAL LICENSE**	Form approved. Budget Bureau No. 38-R027 4.

INSTRUCTIONS.—Complete Items 1 through 16 if this is an initial application. If application is for renewal of a license, complete only Items 1 through 7 and indicate new information or changes in the program as requested in Items 8 through 15. Use supplemental sheets where necessary. Item 16 must be completed on all applications. Mail three copies to: U.S. Atomic Energy Commission, Washington, D.C., 20545, Attention: Isotopes Branch, Division of Materials Licensing. Upon approval of this application, the applicant will receive an AEC Byproduct Material License. An AEC Byproduct Material License is issued in accordance with the general requirements contained in Title 10, Code of Federal Regulations, Part 30 and the Licensee is subject to Title 10, Code of Federal Regulations, Part 20.

1. (a) NAME AND STREET ADDRESS OF APPLICANT. *(Institution, firm, hospital person, etc.)*

XYZ Hospital
Radioisotope Service
234 West Main Street
Colesville, Illinois

(b) STREET ADDRESS(ES) AT WHICH BYPRODUCT MATERIAL WILL BE USED *(If different from 1 (a).)*

(Same)

2. DEPARTMENT TO USE BYPRODUCT MATERIAL

Radioisotope Service

3. PREVIOUS LICENSE NUMBER(S). *(If this is an application for renewal of a license, please indicate and give number.)*

4. INDIVIDUAL USER(S). *(Name and title of individual(s) who will use or directly supervise use of byproduct material. Give training and experience in Items 8 and 9.)*

John A. Doe, M.D.

5. RADIATION PROTECTION OFFICER *(Name of person designated as radiation protection officer if other than individual user. Attach resume of his training and experience as in Items 8 and 9.)*

Roger D. Doe, M.S.

6. (a) BYPRODUCT MATERIAL. *(Elements and mass number of each.)*	(b) CHEMICAL AND/OR PHYSICAL FORM AND MAXIMUM NUMBER OF MILLICURIES OF EACH CHEMICAL AND/OR PHYSICAL FORM THAT YOU WILL POSSESS AT ANY ONE TIME. *(If sealed source(s), also state name of manufacturer, model number, number of sources and maximum activity per source.)*
A. Iodine 131	A. Iodide (Liquid) 100 millicuries
B. Iodine 131	B. Iodide (Capsules) 5 millicuries
C. Iodine 131	C. IHSA (Capsules) 1 millicurie
D. Iodine 131	D. Labeled Renal Function Compounds (Capsules) 5 millicuries
E. Phosphorus 32	E. Soluble Phosphate (Individual Preparation Doses) 20 millicuries
F. Gold 198	F. Colloidal (Liquid-Individual Prepared Doses) 200 millicuries
G. Cobalt 60	G. Sealed Needles (X Company, Model Z) 200 millicuries
H. Strontium 90	H. Sealed Medical Applicator (X Company, Model B) 1 source of 50 millicuries

7. DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED. *(If byproduct material is for "human use," supplement A (Form AEC-313a) must be completed in lieu of this item. If byproduct material is in the form of a sealed source, include the make and model number of the storage container and/or device in which the source will be stored and/or used.)*

See Supplement 313a for human use.

A-G Research studies in animals.

(Continued on reverse side)

Page Two

TRAINING AND EXPERIENCE OF EACH INDIVIDUAL NAMED IN ITEM 4 (Use supplemental sheets if necessary)

8. TYPE OF TRAINING	WHERE TRAINED	DURATION OF TRAINING	ON THE JOB (Circle answer)	FORMAL COURSE (Circle answer)
a. Principles and practices of radiation protection	University Hospital Durham, Missouri	3 yrs.	(Yes) No	Yes (No)
b. Radioactivity measurement standardization and monitoring techniques and instruments	"	"	(Yes) No	(Yes) No
c. Mathematics and calculations basic to the use and measurement of radioactivity	"	"	(Yes) No	(Yes) No
d. Biological effects of radiation	"	"	(Yes) No	Yes (No)

9. EXPERIENCE WITH RADIATION. (Actual use of radioisotopes or equivalent experience.)

ISOTOPE	MAXIMUM AMOUNT	WHERE EXPERIENCE WAS GAINED	DURATION OF EXPERIENCE	TYPE OF USE
I-131	100 mc.	University Hospital	3 yrs.	Diagnosis, Therapy
P-32	30 mc.	" "	"	Therapy
Au-198	200 mc.	" "	"	Therapy
Co-60	200 mc.	" "	"	Diagnosis, Therapy
Cr-51	100 uc.	" "	"	Diagnosis
Fe-59	100 uc.	" "	"	Diagnosis

10. RADIATION DETECTION INSTRUMENTS. (Use supplemental sheets if necessary.)

TYPE OF INSTRUMENTS (Include make and model number of each)	NUMBER AVAILABLE	RADIATION DETECTED	SENSITIVITY RANGE (mr/hr)	WINDOW THICKNESS (mg/cm²)	USE (Monitoring, surveying, measuring)
Z Instr. Co. Model 1 GM Survey Meter	1	beta, gamma	0 - 20	3.5	Surveying
Z Instr. Co. Model 5 Ionization Chamber	1	beta, gamma	0 - 5000	20	Monitoring
Z Instr. Co. Model 21 Scaler	1	-	-	-	Measuring
Z Instr. Co. Model 18 Well Scintillation	1	gamma	-	-	Measuring
Z Instr. Co. Model 23 Scintillation Probes	2	gamma	-	-	Uptake

11. METHOD, FREQUENCY, AND STANDARDS USED IN CALIBRATING INSTRUMENTS LISTED ABOVE.

Survey Instruments Monthly, Cobalt 60 standards
Measuring and Uptake weekly, Standard Solutions

12. FILM BADGES, DOSIMETERS, AND BIO-ASSAY PROCEDURES USED. (For film badges, specify method of calibrating and processing, or name of supplier.)

Film badges by Johnson Co. (Frequency once per month)
XYZ Co. Dosimeters worn in therapeutic work. Range 0-200 mr/hr (Frequency read daily

INFORMATION TO BE SUBMITTED ON ADDITIONAL SHEETS IN DUPLICATE

13. FACILITIES AND EQUIPMENT. Describe laboratory facilities and remote handling equipment, storage containers, shielding, fume hoods, etc. Explanatory sketch of facility is attached. (Circle answer) (Yes) No See attached.

14. RADIATION PROTECTION PROGRAM. Describe the radiation protection program including control measures. If application covers sealed sources, submit leak testing procedures where applicable, name, training, and experience of person to perform leak tests, and arrangements for performing initial radiation survey, servicing, maintenance and repair of the source.

See attached

15. WASTE DISPOSAL. If a commercial waste disposal service is employed, specify name of company. Otherwise, submit detailed description of methods which will be used for disposing of radioactive wastes and estimates of the type and amount of activity involved. See Section 20.303 of 10 CFR 20
Cobalt 60 and Strontium 90 sources returned to mfg. for disposal. SEE ATTACHED SHEET

CERTIFICATE (This item must be completed by applicant) FOR ANNUAL USES

16. THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATE ON BEHALF OF THE APPLICANT NAMED IN ITEM 1, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PART 30, AND THAT ALL INFORMATION CONTAINED HEREIN, INCLUDING ANY SUPPLEMENTS ATTACHED HERETO, IS TRUE AND CORRECT TO THE BEST OF OUR KNOWLEDGE AND BELIEF.

XYZ Hospital
Applicant named in item 1

Date January 3, 1972

By: Jack R. Jones
Hospital Administrator
Title of certifying official

WARNING.—18 U. S. C., Section 1001; Act of June 25, 1948; 62 Stat. 749; makes it a criminal offense to make a willfully false statement or representation to any department or agency of the United States as to any matter within its jurisdiction.

* U. S. GOVERNMENT PRINTING OFFICE 1968 O—322-213

1048521

FORM AEC-313

Item 13

All isotopes are received and stored in the radioisotope laboratory. This facility is equipped with lead storage containers, portable lead bricks for shielding, remote handling tongs, work benches, sinks, trays, waste containers, and similar equipment. See attached sketch of layout.

The isotopes treatment room is used for the administration of isotopes and for the uptake measurements. The uptake and measuring instruments are located in this room. The room is equipped with examining tables, laboratory bench, sink, and waste container. See attached sheet for animal uses.

Item 14

All isotopes must be procured by the Chief, Radioisotope Service.

Isotopes will be stored in a locked storage container in the radioisotopes laboratory. Only persons authorized by the Medial Isotopes Committee shall have access to the storage container.

Weekly surveys will be made with a GM survey meter in all areas where isotopes are handled, stored, or dispensed. In addition, each room vacated by a patient having received therapeutic doses of material will be surveyed and decontaminated if necessary before occupancy by another patient.

All repair and maintenance of sealed sources as well as leak testing will be performed by the X Company.

When not in use, the cobalt 60 needles will be stored in containers which limit the radiation level at the surface of the container to 200 mr/hr or less and to 10 mr/hr or less at one meter from the center of the container. For portable containers, the radiation level will not exceed 50 mr/hr at six inches from the surface of the container. Portable containers will be equipped with a secure locking device. All transfers of needles from storage containers to transfer containers shall be done behind lead shielding using remote handling equipment. See attached sheet for animal uses.

PROCEDURES FOR USE OF BYPRODUCT MATERIAL IN ANIMAL RESEARCH PROGRAMS

All samples of byproduct materials to be administered to animals will be prepared in the radioisotope laboratory on easily decontaminated surfaces or in a ventilated hood if necessary. Rubber gloves and laboratory coats will be worn by personnel during these preparations. Remote handling tools are available and will be used when necessary. All pipetting of radioactive material will be performed with a remote pipetting device.

Experimental animals will be caged in a room adjacent to the radioisotope laboratory. The animals will be injected with byproduct materials either in the animal room or the radioisotope laboratory. The animals will remain in cages until their excretions contain only background amounts of byproduct material, or until they are sacrificed.

The excreta from the animals will be disposed of into the sanitary sewer in concentrations not exceeding those specified in section 20.303 of 10 CFR 20, with a total disposal not to exceed 1 curie per year.

All dry byproduct material waste will be deposited in properly labeled metal cans provided in the laboratory and animal room. The cans will be lined with disposable polyethylene bags. Short-lived waste will be stored until it emits only background levels of radiation as measured with a survey meter at contact. The waste will then be disposed of in normal trash after all labels denoting radioactivity have been removed.

Sacrificed animals containing byproduct material will be stored in a freezer until they have decayed to background and then buried on hospital property.

Animal cages will be decontaminated with detergent and scrub brushes. Rubber gloves will be worn by personnel. Contaminated water will be flushed down the sink or floor drains in the animal room.

The animal room and laboratory will be surveyed for contamination and radiation levels after each preparation and/or administration of radioisotope(s). The animal room will be locked unless attended by authorized user of byproduct material or the radiation protection officer.

FORM AEC-313a

Item 7

MEDICAL ISOTOPES COMMITTEE

Established by authority of Jack R. Jones, Administrator of XYZ Hospital as the administrative body responsible for safe use of radioisotopes and radiation devices within the XYZ Hospital.

1048522

A. Membership:

JOHN A. D. DOE, M.D., *Chairman*
JOHN Q. PUBLIC, M.D., *Pathologist*
THOMAS N. ANDREWS, M.D., *Internist*
ROGER D. DOE, M.S., *Radiation Protection Officer*

B. Experience:

(1) JOHN A. D. DOE, M.D., *Chairman*

1947–Medical Degree, University of Arkansas School of Medicine.

1952–Diplomate American Board of Radiology with the Medallion in Nuclear Medicine. Attended the Oak Ridge Institute of Nuclear Studies in 1951.

1952-1962– Used iodine 131, phosphorus 32, gold 198, for diagnosis and treatment, cobalt 60 implants, and iridium 192 as encased seeds in nylon ribbon in treatment, and chromium 51 and cobalt 60 for diagnostic procedures.

(2) JOHN Q. PUBLIC, M.D.

1949–B.S. Degree, University of Pittsburgh

1951–M.D. Degree, University of Pittsburgh.

1957–Diplomate of American Board of Pathology.

1958–Attended the Oak Ridge Institute of Nuclear Studies basic radioisotope technique course in 1959 attended the Oscar B. Just Clinical Training Course for Pathologists.

1959-Present–Used iodine 131, chromium 51, cobalt, 60, cobalt 58, and iron 59 for diagnostic studies.

(3) THOMAS N. ANDREWS, M.D.

1949–B.A. Degree, University of Rochester, Rochester, New York.

1953–M.D. Degree, Rochester School of Medicine

1954–Attended the 1954 class of Oak Ridge Institute of Nuclear Studies.

1958–Attended the Columbus University postgraduate course and the clinical use of isotopes under Drs. Feidelberg and Quimby.

1959–Diplomate of American Board of Internal Medicine.

1959-Present–Used iodine 131 and phosphorus 32 for diagnosis and therapy.

(4) ROGER D. DOE, M.S., *Radiation Protection Officer*

1956–Attended the Oak Ridge Institute of Nuclear Studies basic radiation protection course and attended a 16-week course at Purdue University on counting technique and research uses of radioisotopes.

1957–Received a M.S. Degree in Health Physics from Vanderbilt University.

1957-1959–Directed graduate students research and use of isotopes at Purdue University.

1959-1960– Taught the staff and graduate special counting techniques; radiation protection, and radioisotope methodology.

C. Committee Responsibilities:

See appendix B of this guide for typical committee responsibilities.

D. Committee Administrative Procedures:

See appendix B of this guide for subjects to be covered in submitting application.

FORM AEC-313a

Item 4.c

SAMPLE

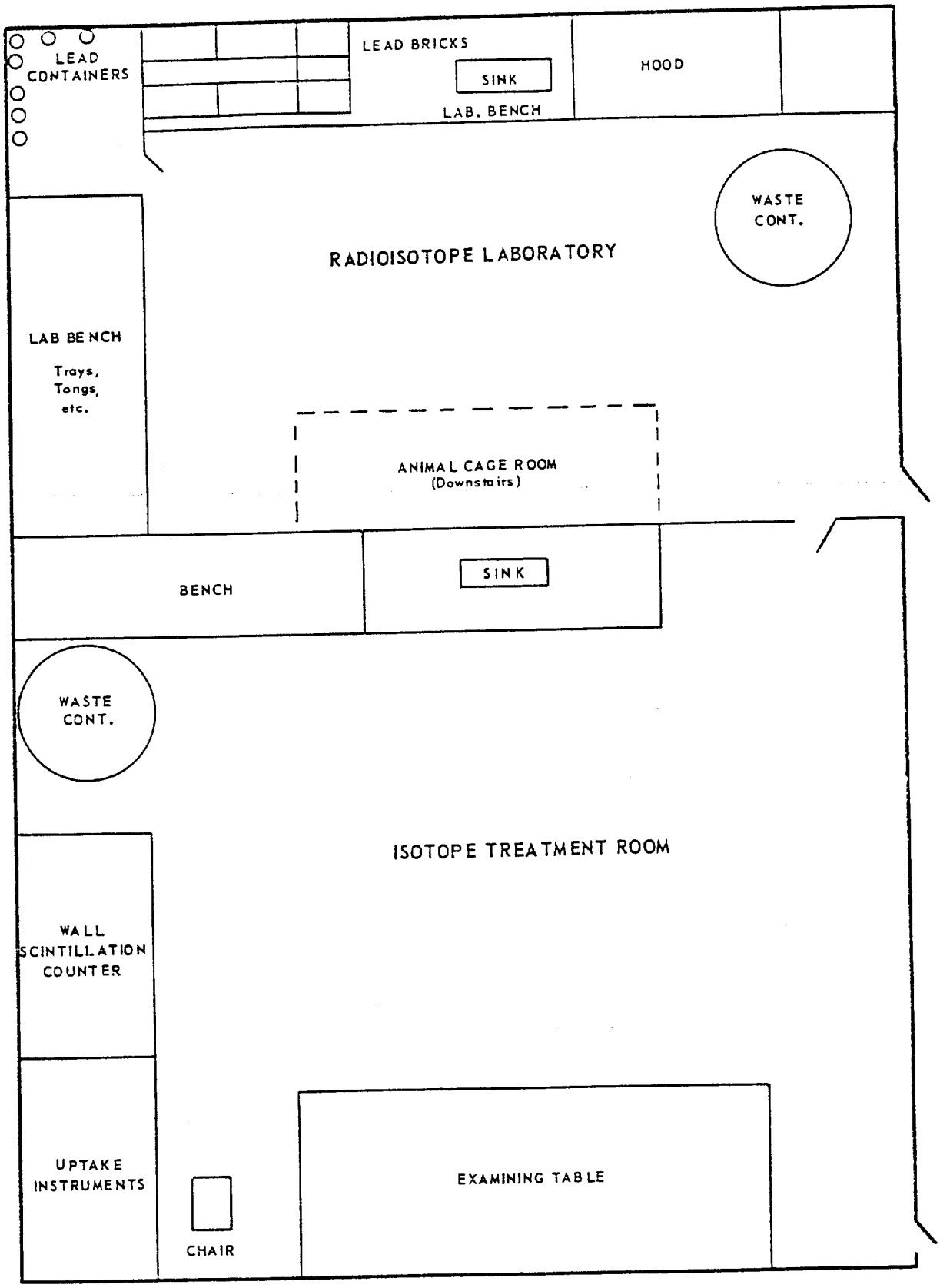
NURSING INSTRUCTIONS FOR PATIENTS RECEIVING COBALT 60

Patient _____
me of *cobalt 60* was inserted on _____

at_____p.m._____

(1) No patient is to be released from the hospital until all radioactive cobalt is removed.
(2) No adjacent patient or visitors shall be within ...feet of this patient.
(3) Nurses or other attendants shall not remain in the immediate proximity of the patient for more than a total of ...hours per day.
(4) Unless otherwise notified, all excreta may be disposed of in the normal manner.
(5) No needles are to be removed by anyone other than the physician(s) named above.
(6) If a source needle is accidentially removed or works itself out, do not handle; immediately contact Dr. Roger D. Doe (Extension 3680).
(7) In the event of death, immediately notify Dr. Roger D. Doe (Extension 3680) or Dr. John A. Doe (Extension 5122) and do not remove the body from the room.

1048523


LEAD CONTAINERS
LEAD BRICKS
SINK
LAB. BENCH
HOOD
WASTE CONT.
RADIOISOTOPE LABORATORY
LAB BENCH
Trays, Tongs, etc.
ANIMAL CAGE ROOM (Downstairs)
BENCH
SINK
WASTE CONT.
ISOTOPE TREATMENT ROOM
WALL SCINTILLATION COUNTER
UPTAKE INSTRUMENTS
CHAIR
EXAMINING TABLE

1048524

FORM AEC-313a
Item 4.c

SAMPLE

NURSING INSTRUCTIONS FOR PATIENTS RECEIVING GOLD 198 AND THERAPEUTIC DOSES OF IODINE 131

Patient _____

This patient was administered _____ mc of _____
(isotope)

on _____ at _____ a.m. p.m.
(date

_____
(name of physician)

(1) If patient's clothes or bed linens are contaminated by fluid originating in the patient, notify the above physician.

(2) Wear rubber gloves while handling contaminated objects. Place gloves in "contaminated" container after use.

(3) Nurses or other attendants shall not remain in the immediate proximity of the patient for more than a total of _____ hours during _____.
(period)

(4) Visitors must remain outside of tape on floor and patient must remain in bed while visitors are in the room during _____.
(period)

(5) Unless otherwise notified, all excreta may be disposed of in the normal manner.

(6) The patient may be released from the hospital after _____ days. The above named physician will make this calculation.

(7) In the event of death, immediately notify Dr. Roger D. Doe (Extension 3680) or Dr. John A. Doe (Extension 5122) and do not remove the body from the room. Dr. Doe will issue appropriate instructions for handling cadaver.

(8) When patient is discharged, room will be surveyed for contamination before remaking room.

SUPPLEMENT SHEET

Item 13

FACILITIES AND EQUIPMENT

Facilities consist of an isotope preparation and storage room and a diagnostic room where doses are administered, uptakes measured, and samples counted.

The storage and preparation room contains a stainless steel table covered with absorbent paper, sink, remote handling equipment, labeled waste disposal containers, and closet where isotopes are stored in shielded containers and behind lead bricks.

Item 14

RADIATION PROTECTION PROGRAM

All radioisotopes are procured in pre-calibrated assayed individual doses and stored prior to use behind lead shields in a closet in the preparation room. During administration of doses to patients, rubber gloves will be worn. The preparation room, storage area, and diagnostic room will be monitored daily or after administration of isotopes to patients. Uptake equipment and portable survey meter will be checked daily and calibrated monthly. Isotope shipments are monitored immediately upon receipt as a check for damage, leakage, or contamination. Permanent records are maintained on all radioisotopes, shipments, doses administered, waste disposal, exposure of individual users, and any transfers of material to other authorized persons.

Item 15

WASTE DISPOSAL

Liquid waste will be disposed of in accordance with section 20.303 of 10 CFR 20.

Solid wastes such as paper cups, tissues, empty isotope containers, etc., will be deposited in labeled waste containers. Contents of containers will be removed daily by user and stored in locked closet for decay to background level as measured by GM survey meter. These articles will be disposed in normal trash after removal or destruction of radiation labels. Contaminated instruments, syringes, etc., stored for decay to background in same closet.

1048525

Form AEC-313a (11-63) 10 CFR 30 PAGE 1

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—HUMAN USE

Form approved. Budget Bureau No. 38-R080 2.

If byproduct material is for "human use" (internal administration of byproduct material, or the radiation therefrom to human beings), complete this supplement and attach to the application for byproduct material license.

1. (a) USING PHYSICIAN'S NAME: John A. Doe, M.D.

(b) NAME AND ADDRESS OF APPLICANT (If different from 1(a)): Same as Item 1(a) of Form AEC-313

2. THE USING PHYSICIAN INDICATED ABOVE IS LICENSED TO DISPENSE DRUGS IN THE PRACTICE OF MEDICINE BY A STATE OR TERRITORY OF THE UNITED STATES, THE DISTRICT OF COLUMBIA, OR THE COMMONWEALTH OF PUERTO RICO. CIRCLE ANSWER (YES) NO

3. A STATEMENT OF USING PHYSICIAN'S CLINICAL RADIOISOTOPE EXPERIENCE (PAGE 3 OF THIS SUPPLEMENT) IS SUBMITTED IN SUPPORT OF THIS APPLICATION. IF ANSWER IS NO, USE PAGE 2 OF THIS SUPPLEMENT TO EXPLAIN OR REFER TO OTHER APPLICATION OR RELATED DOCUMENTS ON WHICH THIS INFORMATION APPEARS. CIRCLE ANSWER (YES) NO

PROPOSED DIAGNOSIS OR TREATMENT

4. (a) DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED INCLUDING SPECIFIC CONDITIONS OR DISEASES TO BE DIAGNOSED OR TREATED (Use page 2 if necessary):

See page 2.

(b) CHEMICAL FORM ADMINISTERED:

See page 2.

(c) DESCRIBE PROCEDURES WHICH WILL BE OBSERVED TO MINIMIZE HAZARD FROM HANDLING, STORAGE, AND DISPOSAL OF THE BYPRODUCT MATERIAL:

1. Stored in lead containers in locked stored area.
2. Handling by remote control and shielded dose cups.
3. Disposal via sanitary sewer system, Cobalt 60 and Strontium 90 returned to supplier for disposal.
4. Sealed sources will not be opened.
5. See attached nursing instructions.

(d) DESCRIPTION AND SKETCHES OF SPECIAL DEVICES TO BE USED FOR ADMINISTERING BYPRODUCT MATERIAL TO HUMAN BEINGS ARE

(1) ATTACHED (LITERATURE REFERENCES WILL SUFFICE) CIRCLE ANSWER YES (NO)

(2) ON FILE WITH THE ISOTOPES BRANCH REFER TO APPLICATION NO _____ CIRCLE ANSWER YES (NO)

5. PROPOSED DOSAGE SCHEDULE

(a) In millicuries for internally administered byproduct material other than discrete fixed sources; and in roentgens or rads, as appropriate, for internal or external irradiation from discrete fixed sources (gold seeds, cobalt needles, etc.) state separately for each condition or disease (use page 2 if necessary):

See page 2.

(b) INVESTIGATIVE PROPOSAL FOR EXPERIMENTAL, NEW OR UNUSUAL HUMAN USES IS ATTACHED. (Attachment should include outline of conditions to be evaluated, including data from animal studies and/or abstract of literature reference if any, number and type of patients (i. e. age group, moribund, etc.)) CIRCLE ANSWER YES (NO)

6. IF BYPRODUCT MATERIAL WILL NOT BE OBTAINED IN PRECALIBRATED FORM FOR ORAL ADMINISTRATION OR IN PRECALIBRATED AND STERILIZED FORM FOR PARENTERAL ADMINISTRATION, DESCRIBE IDENTIFICATION, PROCESSING, AND STANDARDIZATION PROCEDURES:

Obtained in precalibrated form.

7. THE PROPOSED USE OF BYPRODUCT MATERIAL HAS BEEN, OR WILL BE, APPROVED BY THE MEDICAL ISOTOPE COMMITTEE. CIRCLE ANSWER (YES) NO

HOSPITAL FACILITIES FOR INDIVIDUAL PRACTICE USE ONLY

8. (a) THE APPLICANT HAS COMPLETED ARRANGEMENTS FOR A HOSPITAL TO ADMIT RADIOACTIVE PATIENTS WHENEVER ADVISABLE CIRCLE ANSWER YES NO

(b) A COPY OF INSTRUCTIONS TO BE FURNISHED TO THE HOSPITAL AS TO RADIOLOGICAL SAFETY PRECAUTIONS TO BE TAKEN AND AVAILABLE RADIATION INSTRUMENTATION IS ATTACHED. CIRCLE ANSWER YES NO

104852b

Form AEC-313a (11-63) Page 3

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—PRECEPTOR STATEMENT

This page is to be completed by the applicant physician's preceptor. If more than one preceptor is necessary to document experience, obtain a separate statement from each. Back of page may be used for comments.

9. NAME AND ADDRESS OF APPLICANT PHYSICIAN (Include ZIP Code)

John A. D. Doe, M.D.
XYZ Hospital
Colesville, Illinois

10. CLINICAL TRAINING AND EXPERIENCE OF PHYSICIAN NAMED IN ITEM 9 ABOVE

(A) ISOTOPE	(B) CONDITIONS DIAGNOSED OR TREATED	(C) No. Cases Observed (See 1 in key below)	(D) No. Cases Involving Personal Participation (See 2 in key below)
I-131	Diagnosis of thyroid function		
	Dilution studies		
	Excretion studies		
	Brain tumor localization		
	Scanning studies		
	Treatment of hyperthyroidism		
	Treatment of cardiac conditions		
	Treatment of thyroid carcinoma		
P-32 Soluble	Treatment of polycythemia		
	Treatment of leukemia		
	Treatment of bone metastases		
	Tumor localization		
	Intracavitary treatment		
	Interstitial treatment		
Au-198	Intracavitary treatment		
	Interstitial treatment		
	Scanning studies		
Cr-51	Blood determinations		
	Scanning studies		
Co-58 or Co-60	Diagnosis of pernicious anemia		
Co-60	Interstitial treatment		
I-192	Intracavitary treatment		
Co-60 or Cs-137	Teletherapy treatment		
Sr-90	Treatment of superficial diseases of the eye		
Other Isotopes Use back of page			

Key to Column (C) and (D) above

1. Observation should consist of observing radioisotope administration techniques and discussion with preceptor the case histories to establish most appropriate diagnostic and/or therapeutic procedure, limitation, contraindications, etc.

2. Personal participation should consist of (a) supervised examination of patients to determine the suitability for radioisotope diagnosis and/or treatment and recommendation on dosage to be prescribed; (b) collaboration in calibration of the dose and the actual administration of the dose to the patient, including calculation of the radiation dose, related measurements, and plotting of data; and (c) adequate period of training to enable the physician to manage radioactive patients and to follow patients through diagnosis and/or the course of treatment.

11. DATES AND TOTAL NUMBER OF HOURS OF CLINICAL RADIOISOTOPE TRAINING

June 1958 to June 1971 1,000 hours

12. THE TRAINING AND EXPERIENCE INDICATED ABOVE WAS OBTAINED UNDER THE SUPERVISION OF John F. Smith, M.D.,

AT University Hospital, Durham Missouri (Institution) Name and Address 01-00021-01 (Byproduct Material License Number)

John F. Smith
John F. Smith, M.D.
Chairman, Isotope Committee

1048527

Page Two

TRAINING AND EXPERIE OF EACH INDIVIDUAL NAMED IN ITEM 4 (Use ental sheets if necessary)

8. TYPE OF TRAINING	WHERE TRAINED	DURATION OF TRAINING	ON THE JOB (Circle answer)	FORMAL COURSE (Circle answer)
a. Principles and practices of radiation protection	Oak Ridge Institute of Nuclear Studies, Metropolitan Hosp., Colesville, Illinois	1 mo. '54 3 wks '53	Yes No	Yes No
b. Radioactivity measurement standardization and monitoring techniques and instruments	Same	Same	Yes No	Yes No
c. Mathematics and calculations basic to the use and measurement of radioactivity	Same	Same	Yes No	Yes No
d. Biological effects of radiation	Same	Same	Yes No	Yes No

9. EXPERIENCE WITH RADIATION (Actual use of radioisotopes or equivalent experience)

ISOTOPE	MAXIMUM AMOUNT	WHERE EXPERIENCE WAS GAINED	DURATION OF EXPERIENCE	TYPE OF USE
I-131	30 mc.	Metropolitan Hosp., Radioisotope Clinic	3 weeks	Human - Diagnostic and Therapeutic
P-32	5 mc.	State Medical School	1 yr. ('51)	Animal Research
C-14	5 Mc.	State Medical School	1 yr. ('51)	Animal Research

10. RADIATION DETECTION INSTRUMENTS (Use supplemental sheets if necessary)

TYPE OF INSTRUMENTS (Include make and model number of each)	NUMBER AVAILABLE	RADIATION DETECTED	SENSITIVITY RANGE (mr/hr)	WINDOW THICKNESS (mg/cm²)	USE (Monitoring, surveying, measuring)
Model XX Scaler	1				Measuring
Model YY Scint. Detector	1	Gamma			Measuring
Lab. Monitor	1	Beta, Gamma	30,000 cpm	1.2 - 2mg/cm²	Monitoring
Survey Meter	1	Beta, Gamma	0 - 50 mr/hr	30 mg/cm²	Surveying

11. METHOD, FREQUENCY AND STANDARDS USED IN CALIBRATING INSTRUMENTS LISTED ABOVE

Calibrated against Simulated I-131 std. each day.
Calibrated against certified Standard once each month.

12. FILM BADGES, DOSIMETERS, AND BIO-ASSAY PROCEDURES USED (For film badges, specify method of calibrating and processing, or name of supplier.)

XYZ Company Film Badge Service - Frequency -- once per month.

INFORMATION TO BE SUBMITTED ON ADDITIONAL SHEETS IN DUPLICATE

13. FACILITIES AND EQUIPMENT. Describe laboratory facilities and remote handling equipment, storage containers, shielding, fume hoods, etc. Explanatory sketch of facility is attached. (Circle answer) (Yes) No

14. RADIATION PROTECTION PROGRAM. Describe the radiation protection program including control measures. If application covers sealed sources, submit leak testing procedures where applicable, name, training, and experience of person to perform leak tests, and arrangements for performing initial radiation survey, servicing, maintenance and repair of the source.

See attached sheet

15. WASTE DISPOSAL. If a commercial waste disposal service is employed, specify name of company. Otherwise, submit detailed description of methods which will be used for disposing of radioactive wastes and estimates of the type and amount of activity involved.

See attached sheet

CERTIFICATE (This item must be completed by applicant)

16. THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATE ON BEHALF OF THE APPLICANT NAMED IN ITEM 1, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PART 30, AND THAT ALL INFORMATION CONTAINED HEREIN, INCLUDING ANY SUPPLEMENTS ATTACHED HERETO, IS TRUE AND CORRECT TO THE BEST OF OUR KNOWLEDGE AND BELIEF

John A. D. Doe, M.D.
Applicant named in item 1

Date January 30, 1972

By: John A. D. Doe, M.D.
John A. D. Doe
Title of certifying official

WARNING.—18 U S C, Section 1001, Act of June 25, 1948; 62 Stat. 749, makes it a criminal offense to make a willfully false statement or representation to any department or agency of the United States as to any matter within its jurisdiction.

* U S GOVERNMENT PRINTING OFFICE 1968 O—322-213

1048528

Form AEC-313a (11-63) 10 CFR 30 PAGE 1

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—HUMAN USE

Form approved. Budget Bureau No. 38-R080.2.

If byproduct material is for "human use" (internal administration of byproduct material, or the radiation therefrom to human beings), complete this supplement and attach to the application for byproduct material license.

1. (a) USING PHYSICIAN'S NAME: John A. D. Doe, M.D.

(b) NAME AND ADDRESS OF APPLICANT (If different from 1(a)): Same

2. THE USING PHYSICIAN INDICATED ABOVE IS LICENSED TO DISPENSE DRUGS IN THE PRACTICE OF MEDICINE BY A STATE OR TERRITORY OF THE UNITED STATES, THE DISTRICT OF COLUMBIA, OR THE COMMONWEALTH OF PUERTO RICO. CIRCLE ANSWER (YES) NO

3. A STATEMENT OF USING PHYSICIAN'S CLINICAL RADIOISOTOPE EXPERIENCE (PAGE 3 OF THIS SUPPLEMENT) IS SUBMITTED IN SUPPORT OF THIS APPLICATION. IF ANSWER IS NO, USE PAGE 2 OF THIS SUPPLEMENT TO EXPLAIN OR REFER TO OTHER APPLICATION OR RELATED DOCUMENTS ON WHICH THIS INFORMATION APPEARS. CIRCLE ANSWER (YES) NO

PROPOSED DIAGNOSIS OR TREATMENT

4. (a) DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED INCLUDING SPECIFIC CONDITIONS OR DISEASES TO BE DIAGNOSED OR TREATED (Use page 2 if necessary): I-131 as Iodide - Diagnosis of thyroid function; IHSA - blood volume determinations; labeled renal function compounds for renal function studies.

(b) CHEMICAL FORM ADMINISTERED:

Iodine 131 Iodide
Iodine 131 Iodinated Human Serum Albumin
Iodine 131 Labeled Renal Function Compounds

(c) DESCRIBE PROCEDURES WHICH WILL BE OBSERVED TO MINIMIZE HAZARD FROM HANDLING, STORAGE, AND DISPOSAL OF THE BYPRODUCT MATERIAL: Byproduct material procured in individual pre-calibrated and assayed doses. Doses stored behind lead shield in original shipping container prior to use. Handling by remote instruments or in shielded containers. Labeled waste disposal container available. For additional information see attached sheet.

(d) DESCRIPTION AND SKETCHES OF SPECIAL DEVICES TO BE USED FOR ADMINISTERING BYPRODUCT MATERIAL TO HUMAN BEINGS ARE

(1) ATTACHED (LITERATURE REFERENCES WILL SUFFICE) CIRCLE ANSWER YES (NO)

(2) ON FILE WITH THE ISOTOPES BRANCH REFER TO APPLICATION NO _____ CIRCLE ANSWER YES (NO)

5. PROPOSED DOSAGE SCHEDULE

(a) In millicuries for internally administered byproduct material other than discrete fixed sources; and in roentgens or rads, as appropriate, for internal or external irradiation from discrete fixed sources (gold seeds, cobalt needles, etc.) state separately for each condition or disease (use page 2 if necessary):

Iodine 131	Iodide	Up to 25 microcuries
Iodine 131	IHSA	Up to 20 microcuries
Iodine 131	Labeled Renal Function Compounds	Up to 40 microcuries

(b) INVESTIGATIVE PROPOSAL FOR EXPERIMENTAL, NEW OR UNUSUAL HUMAN USES IS ATTACHED. (Attachment should include outline of conditions to be evaluated, including data from animal studies and/or abstract of literature reference if any, number and type of patients (i. e. age group, moribund, etc.)) CIRCLE ANSWER YES (NO)

6. IF BYPRODUCT MATERIAL WILL NOT BE OBTAINED IN PRECALIBRATED FORM FOR ORAL ADMINISTRATION OR IN PRECALIBRATED AND STERILIZED FORM FOR PARENTERAL ADMINISTRATION, DESCRIBE IDENTIFICATION, PROCESSING, AND STANDARDIZATION PROCEDURES:

Not applicable.

7. THE PROPOSED USE OF BYPRODUCT MATERIAL HAS BEEN, OR WILL BE, APPROVED BY THE MEDICAL ISOTOPE COMMITTEE. NONE CIRCLE ANSWER YES NO

HOSPITAL FACILITIES FOR INDIVIDUAL PRACTICE USE ONLY

8. (a) THE APPLICANT HAS COMPLETED ARRANGEMENTS FOR A HOSPITAL TO ADMIT RADIOACTIVE PATIENTS WHENEVER ADVISABLE. See attached sheet CIRCLE ANSWER (YES) NO

(b) A COPY OF INSTRUCTIONS TO BE FURNISHED TO THE HOSPITAL AS TO RADIOLOGICAL SAFETY PRECAUTIONS TO BE TAKEN AND AVAILABLE RADIATION INSTRUMENTATION IS ATTACHED. CIRCLE ANSWER YES (NO)

1048529

Form AEC-313a
(11-63)
Page 3

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—PRECEPTOR STATEMENT

This page is to be completed by the applicant physician's preceptor. If more than one preceptor is necessary to document experience, obtain a separate statement from each. Back of page may be used for comments.

9. NAME AND ADDRESS OF APPLICANT PHYSICIAN (Include ZIP Code)

John A. D. Doe, M.D.
502 Medical Plaza
Colesville, Illinois

10. CLINICAL TRAINING AND EXPERIENCE OF PHYSICIAN NAMED IN ITEM 9 ABOVE

(A) ISOTOPE	(B) CONDITIONS DIAGNOSED OR TREATED	(C) No. Cases Observed (See 1 in key below)	(D) No. Cases Involving Personal Participation (See 2 in key below)
I-131	Diagnosis of thyroid function	5	15
	Dilution studies	1	5
	Excretion studies	1	6
	Brain tumor localization		
	Scanning studies		
	Treatment of hyperthyroidism	2	0
	Treatment of cardiac conditions		
	Treatment of thyroid carcinoma	1	0
P-32 Soluble	Treatment of polycythemia		
	Treatment of leukemia		
	Treatment of bone metastases		
	Tumor localization		
	Intracavitary treatment		
	Interstitial treatment		
Au-198	Intracavitary treatment		
	Interstitial treatment		
	Scanning studies		
Cr-51	Blood determinations		
	Scanning studies		
Co-58 or Co-60	Diagnosis of pernicious anemia		
Co-60	Interstitial treatment		
I-192	Intracavitary treatment		
Co-60 or Cs-137	Teletherapy treatment		
Sr-90	Treatment of superficial diseases of the eye		
Other Isotopes Use back of page			

Key to Column (C) and (D) above

1. Observation should consist of observing radioisotope administration techniques and discussion with preceptor the case histories to establish most appropriate diagnostic and/or therapeutic procedure, limitation, contraindications, etc.

2. Personal participation should consist of (a) supervised examination of patients to determine the suitability for radioisotope diagnosis and/or treatment and recommendation on dosage to be prescribed; (b) collaboration in calibration of the dose and the actual administration of the dose to the patient, including calculation of the radiation dose, related measurements, and plotting of data; and (c) adequate period of training to enable the physician to manage radioactive patients and to follow patients through diagnosis and/or the course of treatment.

11. DATES AND TOTAL NUMBER OF HOURS OF CLINICAL RADIOISOTOPE TRAINING June 30, 1971 to July 21, 1971 hours

12. THE TRAINING AND EXPERIENCE INDICATED ABOVE WAS OBTAINED UNDER THE SUPERVISION OF John Jones, M.D.

AT Metropolitan Hospital (Institution) Name and Address
Colesville, Illinois

02-00034-01 (Byproduct Material License Number)

John Jones, M.D. (Signature of Preceptor)
Chairman, Isotope Committee

1048530

C I T Y H O S P I T A L

January 2, 1972

John A. D. Doe, M.D.
502 Medical Plaza
Colesville, Illinois

Dear Dr. Doe:

We are pleased to advise you that the City Hospital Board of Directors has approved your request for permission to admit patients containing radioactive materials in this hospital.

This agreement is made with the understanding that you will provide the necessary instrumentation, radiological safety and nursing instructions for hospital personnel.

Very truly yours,

J. J. Reem

J. J. Reem, M.D.
Hospital Administrator

1048531

APPLICATION SAMPLE 3 - PRIVATE PRACTICE

Form AEC-313 (11-63) 10 CFR 30	ATOMIC ENERGY COMMISSION **APPLICATION FOR BYPRODUCT MATERIAL LICENSE**	Form approved. Budget Bureau No. 38-R027.4.

INSTRUCTIONS.—Complete Items 1 through 16 if this is an initial application. If application is for renewal of a license, complete only Items 1 through 7 and indicate new information or changes in the program as requested in Items 8 through 15. Use supplemental sheets where necessary. Item 16 must be completed on all applications. Mail three copies to: U.S. Atomic Energy Commission, Washington, D.C., 20545, Attention: Isotopes Branch, Division of Materials Licensing. Upon approval of this application, the applicant will receive an AEC Byproduct Material License. An AEC Byproduct Material License is issued in accordance with the general requirements contained in Title 10, Code of Federal Regulations, Part 30 and the Licensee is subject to Title 10, Code of Federal Regulations, Part 20.

1. (a) NAME AND STREET ADDRESS OF APPLICANT. (Institution, firm, hospital, person, etc.)	(b) STREET ADDRESS(ES) AT WHICH BYPRODUCT MATERIAL WILL BE USED. (If different from 1 (a).)
John A. D. Doe, M.D. 502 Medical Plaza Colesville, Illinois	(Same)
2. DEPARTMENT TO USE BYPRODUCT MATERIAL	**3. PREVIOUS LICENSE NUMBER(S).** (If this is an application for renewal of a license, please indicate and give number.)
Private Use	
4. INDIVIDUAL USER(S). (Name and title of individual(s) who will use or directly supervise use of byproduct material. Give training and experience in Items 8 and 9.)	**5. RADIATION PROTECTION OFFICER** (Name of person designated as radiation protection officer if other than individual user. Attach resume of his training and experience as in Items 8 and 9.)
John A. D. Doe, M.D.	Roger D. Doe, M.S.

6. (a) BYPRODUCT MATERIAL. (Elements and mass number of each.)	(b) CHEMICAL AND/OR PHYSICAL FORM AND MAXIMUM NUMBER OF MILLICURIES OF EACH CHEMICAL AND/OR PHYSICAL FORM THAT YOU WILL POSSESS AT ANY ONE TIME. (If sealed source(s), also state name of manufacturer, model number, number of sources and maximum activity per source.)
Iodine 131	Iodide (Capsule form) 2 millicuries
Iodine 131	Iodinated Human Serum Albumin (vial) 1 millicurie
Iodine 131	Labeled Renal Function Compound (vial) 1 millicurie

7. DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED. (If byproduct material is for "human use," supplement A (Form AEC-313a) must be completed in lieu of this item. If byproduct material is in the form of a sealed source, include the make and model number of the storage container and/or device in which the source will be stored and/or used.)

Human Use - See Form AEC 313a (attached).

(Continued on reverse side)

1048532

Form AEC-313a (11-63) 10 CFR 30 PAGE 1

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—HUMAN USE

Form approved. Budget Bureau No. 38-R080.2

If byproduct material is for "human use" (internal administration of byproduct material, or the radiation therefrom to human beings), complete this supplement and attach to the application for byproduct material license.

1. (a) USING PHYSICIAN'S NAME: John A. D. Doe, M.D.

(b) NAME AND ADDRESS OF APPLICANT (If different from 1(a)): Same

2. THE USING PHYSICIAN INDICATED ABOVE IS LICENSED TO DISPENSE DRUGS IN THE PRACTICE OF MEDICINE BY A STATE OR TERRITORY OF THE UNITED STATES, THE DISTRICT OF COLUMBIA, OR THE COMMONWEALTH OF PUERTO RICO. CIRCLE ANSWER: (YES) NO

3. A STATEMENT OF USING PHYSICIAN'S CLINICAL RADIOISOTOPE EXPERIENCE (PAGE 3 OF THIS SUPPLEMENT) IS SUBMITTED IN SUPPORT OF THIS APPLICATION. IF ANSWER IS NO, USE PAGE 2 OF THIS SUPPLEMENT TO EXPLAIN OR REFER TO OTHER APPLICATION OR RELATED DOCUMENTS ON WHICH THIS INFORMATION APPEARS. CIRCLE ANSWER: (YES) NO

PROPOSED DIAGNOSIS OR TREATMENT

4. (a) DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED INCLUDING SPECIFIC CONDITIONS OR DISEASES TO BE DIAGNOSED OR TREATED (Use page 2 if necessary): I-131 as Iodide - Diagnosis of thyroid function; IHSA - blood volume determinations; labeled renal function compounds for renal function studies.

(b) CHEMICAL FORM ADMINISTERED:

Iodine 131 Iodide
Iodine 131 Iodinated Human Serum Albumin
Iodine 131 Labeled Renal Function Compounds

(c) DESCRIBE PROCEDURES WHICH WILL BE OBSERVED TO MINIMIZE HAZARD FROM HANDLING, STORAGE, AND DISPOSAL OF THE BYPRODUCT MATERIAL: Byproduct material procured in individual pre-calibrated and assayed doses. Doses stored behind lead shield in original shipping container prior to use. Handling by remote instruments or in shielded containers. Labeled waste disposal container available. For additional information see attached sheet.

(d) DESCRIPTION AND SKETCHES OF SPECIAL DEVICES TO BE USED FOR ADMINISTERING BYPRODUCT MATERIAL TO HUMAN BEINGS ARE
(1) ATTACHED (LITERATURE REFERENCES WILL SUFFICE) CIRCLE ANSWER: YES (NO)
(2) ON FILE WITH THE ISOTOPES BRANCH REFER TO APPLICATION NO _____ CIRCLE ANSWER: YES (NO)

5. PROPOSED DOSAGE SCHEDULE
(a) In millicuries for internally administered byproduct material other than discrete fixed sources; and in roentgens or rads, as appropriate, for internal or external irradiation from discrete fixed sources (gold seeds, cobalt needles, etc.) state separately for each condition or disease (use page 2 if necessary):

Iodine 131	Iodide	Up to 25 microcuries
Iodine 131	IHSA	Up to 20 microcuries
Iodine 131	Labeled Renal Function Compounds	Up to 40 microcuries

(b) INVESTIGATIVE PROPOSAL FOR EXPERIMENTAL, NEW OR UNUSUAL HUMAN USES IS ATTACHED. (Attachment should include outline of conditions to be evaluated, including data from animal studies and/or abstract of literature reference if any, number and type of patients (i. e. age group, moribund, etc.)) CIRCLE ANSWER: YES (NO)

6. IF BYPRODUCT MATERIAL WILL NOT BE OBTAINED IN PRECALIBRATED FORM FOR ORAL ADMINISTRATION OR IN PRECALIBRATED AND STERILIZED FORM FOR PARENTERAL ADMINISTRATION, DESCRIBE IDENTIFICATION, PROCESSING, AND STANDARDIZATION PROCEDURES:

Not applicable.

7. THE PROPOSED USE OF BYPRODUCT MATERIAL HAS BEEN, OR WILL BE, APPROVED BY THE MEDICAL ISOTOPE COMMITTEE. NONE CIRCLE ANSWER: YES NO

HOSPITAL FACILITIES FOR INDIVIDUAL PRACTICE USE ONLY

8. (a) THE APPLICANT HAS COMPLETED ARRANGEMENTS FOR A HOSPITAL TO ADMIT RADIOACTIVE PATIENTS WHENEVER ADVISABLE. See attached sheet CIRCLE ANSWER: (YES) NO
(b) A COPY OF INSTRUCTIONS TO BE FURNISHED TO THE HOSPITAL AS TO RADIOLOGICAL SAFETY PRECAUTIONS TO BE TAKEN AND AVAILABLE RADIATION INSTRUMENTATION IS ATTACHED. CIRCLE ANSWER: YES (NO)

1048533

APPENDIX F

NON-ROUTINE MEDICAL USES OF BYPRODUCT MATERIAL

Experimental and nonroutine medical uses of byproduct materials include all human uses not specified in Appendix D. Such uses may be classified into one of two phases of development:

Clinical Research applies to a new use of byproduct material in humans. Little or nothing is known about the procedure and little or nothing has been published on the subject. The basis for proceeding with the new use in humans is derived from knowledge obtained from animals studies. This phase of development includes the initial introduction into humans and initial trials on a limited number of patients.

Clinical Evaluation applies to the planned testing of a new diagnostic or therapeutic procedure in an appropriate series of control and diseased humans. The procedure and results of clinical research will ordinarily have been reported in the literature or at meetings. If adequate information has not been published, the applicant should have spent sufficient time with those who developed the test, to be thoroughly familiar with the details.

The *clinical research* phase of experimental or nonroutine medical use by byproduct material is normally limited to licensees who have broad experience in the use of radioisotopes and who have appropriate facilities and equipment available to conduct research. Research should be pursued by groups of competent investigators representing different disciplines rather than by single individuals. The individual physician to be designated on the license as the authorized user should normally have broad and varied experience in the use of radioisotopes and in clinical research investigation.

The clinical evaluation phase of experimental or nonroutine medical use of byproduct material is normally limited to licensees under the supervision of an individual physician with broad experience in clinical evaluation and the use of radioisotopes and under the guidance of a radioisotope committee representing a number of disciplines. Adequate resources to conduct the trials shall be available.

Applications for experimental or nonroutine uses of byproduct material in humans are reviewed with the assistance of the Commission's Advisory Committee on the Medical Use of Isotopes. Applications should be supported by a research protocol which includes:

1. Title of study.
2. The purpose for conducting the study. Indicate whether the study is to be clinical research or clinical evaluation and explain why.
3. The plan of investigation in sufficient detail to permit a critical evaluation of the methods for conducting the experiments and the controls established.
4. A statement as to whether any planned complementary drug or radioisotope administration is contemplated in conjunction with the study.
5. A statement about the expected fate of the isotope administered and if the procedure is for therapy, a statement about the expected effects.
6. A. *If the application is for clinical research,* an outline of related work conducted by the applicant or others in laboratory animals and in humans, including data on localization, effective half-life, and radiation dosage. If no work has been conducted in animals, explain why. Pertinent references and a brief abstract prepared by the applicant of published or unpublished material should be submitted. (The brochure of a commercial supplier is not a satisfactory authority for this purpose. It is not necessary to include with the application reprints of references.)

   B. *If the application is for clinical evaluation,* pertinent references and a brief abstract prepared by the applicant of published or unpublished material, including information on localization, effective half-life, and radiation dosage. (The brochure of a commercial supplier is not a satisfactory authority for this purpose. It is not necessary to include with the application reprints of references.)

7. A description of the human subjects to be studied:

   A. Persons without manifest disease–number, method of selection, age range.

   B. Persons with manifest disease–number, nature of pathology, method of selection, age range.

   C. Pregnant women shall ordinarily be excluded from any test not involving the condition of

1048534

pregnancy itself. Specify whether or not pregnant women will be tested and if so, explain why.

8. Confirmation that consent of human subjects, or their representatives, will be obtained to participate in the investigation except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

9. The dose range (microcuries or millicuries) to be administered and the method of administration.

10. Calculations of the radiation doses delivered to the whole body and to the critical organ(s). The calculations shall contain information about:

A. The expected half-life in various organs

B. The rationale for using the dose selected.

C. The radiation dose due to other simultaneous or accompanying radioactive isotope test which may be administered.

11. A statement of the institutional resources available to support the study including:

A. Physical facilities and equipment especially suited for the study under consideration.

B. Availability of clinical material.

C. Types of consultation or collaboration available including the name of the sponsor of the study if other than the applicant.

12. Qualifications of the individual physician who will be responsible for the study, including a summary of research training and experience and pertinent training or experience in the use of radioisotopes.

13. Estimated time needed to complete the study.

14. A schedule for reporting results of the study, and an outline of the type of information to be included in the report. The schedule can be in terms of time intervals or number of subjects studied. If studies are to be long range, interim reports should be provided.

Each report should include:

A. A statement of the purpose for conducting the study.

B. A summary of the clinical information provided by the diagnostic or therapeutic procedure which includes the following information:

(1.) The radioisotope administered, its chemical form, and route of administration.

(2.) The number of patients involved in the study, their ages, sex, and clinical diagnosis before administration of the radiopharmaceutical.

(3.) The dosage and frequency of administration.

(4.) Complementary drugs administered, if any.

(5.) The method of preparation of the radiopharmaceutical, if it was not obtained in a prepackaged, precalibrated, sterile and pyrogen-free form from a pharmaceutical supplier.

(6.) Special radiation detection instrumentation used.

(7.) A statement of organ distribution and an estimate of the respective biological half-life of the administered radioisotope as determined during the course of the study. State the rationale behind these estimates or methods used to make the determination.

(8.) A synopsis of the toxicity data obtained.

(9.) Brief clinical histories of all patients exhibiting any adverse reactions to any radiopharmaceutical administered. The investigator should describe the reaction and include his interpretation of the nature and cause of the reaction.

C. An evaluation by the investigator of the safety and efficacy of the diagnostic or therapeutic procedure. This evaluation should include a statement of side effects, toxicity, contraindications, and ineffectiveness. In the case of diagnostic procedures, the investigator should state whether or not the resultant diagnosis was confirmed by other methods.

1048535

APPENDIX G

TYPES OF INSTRUMENTS NEEDED FOR MEDICAL PROGRAMS

The type and quantity of radiation detection instrumentation for a clinical radioisotope program depends upon (1) type and quantity of radioisotopes possessed and the nature of their use, (2) chemical and physical form of the isotopes, and (3) type and volume of work. Certain diagnostic and therapeutic uses of isotopes may involve specialized instrumentation. For example, iodine 131 as iodinated human serum albumin for brain tumor localization and phosphorus 32 for localization of brain and eye tumors involved the use of highly specialized scanning instrumentation including directional collimators or probes.

The attached table lists radiation detection instruments needed for various isotopes and uses.

INSTRUMENTATION NEEDED FOR MEDICAL USES OF BYPRODUCT MATERIAL

Item	I-131		P-32	Au-198	Co-60		Cr-51 Fe-59 S-35	H-3 C-14	Na-24 K-42	Co-58	Sr-85 Hg-197 Hg-203	Mo 99/ to 99m generator	Remarks
	Diag.	Ther.	Ther.	Ther.	Diag.	Ther.	Diag.	Diag.	Diag.	Diag.	Diag.	Diag.	Diag.
Instrumentation:													
A. Measurement:													
1. Uptake	X	X	—	—	—	—	—	—	—	—	X	—	GM or scintillation. Detector and scalers (specialized scanning equipment for special diagnostic procedures).
2. Biological specimens.	X	—	—	—	X	—	X	X	X	X	—	—	Well-type scintillation detection and scaler – Liquid scintillation for H–3 & C–14.
B. Radiation survey:													
1. Low level	X	X	X	X	X	X	X	X	X	X	X	X	GM survey meter.
2. High level	—	X	—	X	—	X	—	—	—	—	—	X	Survey meter capable of measuring up to 1 roentgen per hour.
C. Personnel monitoring:													
1. Film badge	—	X	—	X	—	X	—	—	—	—	—	X	
2. Pocket meters	—	X	—	X	—	X	—	—	—	—	—	X	

X = Needed.
– = Not necessary.

1048536

APPENDIX H

INFORMATION ON FACILITIES AND EQUIPMENT AND OPERATING PROCEDURES TO BE INCLUDED WITH THE APPLICATION

The following indicates the areas in which detailed descriptive information should be submitted in the application.

1. The procedures that ensure that responsible persons are promptly notified of receipt of byproduct material.

2. The method of monitoring packages containing byproduct material to ensure that the contents have not been spilled during transport.

3. The procedures and facilities used to move the byproduct material to storage or the place of use.

4. The storage facilities and security procedures used to restrict access to the byproduct material to authorized users.

5. The facilities, equipment, and procedures that will be available for handling and storage of radioactive material. An explanatory sketch of the work areas and a listing of fume hoods, remote handling equipment, lead brick, or barrier shields, and storage containers should be submitted.

6. The facilities and procedures for storing waste byproduct material prior to disposal.

7. The procedures for removing from storage, transporting, and returning to storage radiation sources for interstitial and intracavitary treatments and the accountability methods used to ensure that all sources are returned to storage.

8. The routine visual and radiation surveys that will be made of areas where byproduct material is used and stored.

9. Since sealed sources of radioactive material are tested for leakage at periodic intervals, information about how the leak tests will be conducted.

NOTE: The application should specify that the leak test shall (1) be made by a person presently authorized by the Commission to perform such leak tests, or (2) describe how the test sample will be taken and confirm that the test will detect 0.005 microcurie of removable activity from the test sample. The applicant can obtain from the supplier of the sealed source information relative to persons and firms authorized to perform leak testing. Radioactive sources such as wire, needles, medical applicator capsules containing wire or needle sources, and metallic seeds do not require leak testing. Beta applicators and encapsulated radioactive material used in radiation effects studies and as calibration sources require leak testing.

10. The method used to keep records of reciept, transfer, and disposal of byproduct material, surveys, and personnel exposures.

11. If therapeutic doses of iodine 131 and gold 198 or cobalt 60 are requested, a copy of the operating instructions to nurses and hospital personnel concerning how to handle these patients and visitors to such patients.

1048537

APPENDIX I

INFORMATION FOR COMMISSION APPROVAL OF TREATMENT OR DISPOSAL BY INCINERATION

I. For compounds containing isotopes such as carbon 14, hydrogen 3, sulfur 35, etc., which volatilize at the temperature at which the incinerator operates.

A. Quantity of each isotope to be disposed of in terms of microcuries per day or similar units.

B. Characteristics of the incinerator such as height of the stack, height of and distance of buildings in the surrounding area, rated air flow of the incinerator in cubic feet per hour or similar units, and expected dilution factors (if necessary).

C. The method of measurement of, or estimation of, the average concentration of radioactive material in the effluent at the point it leaves the stack.

II. For compounds where significant portions of the isotopes may remain in the ash residue.

A. The type, quantity, and chemical form of byproduct material to be incinerated in terms of microcuries per day or similar units.

B. Characteristics of the incinerator such as height of the stack, height of and distance to buildings in the surrounding areas, rated air flow of the incinerator in cubic feet per hour or similar units, and expected dilution factors (if necessary).

C. The method of measurement of, or estimation of, the average concentration of radioactive material in the effluent at the point it leaves the stack.

D. The method of measurement or estimation of the concentration of radioactive material appearing in the ash residue.

E. The procedures which will be followed to prevent overexposure of personnel during all phases of the operation. Include instructions given to persons handling the combustibles and the ashes.

F. The method of disposing of contaminated ash.

1048538

OTHER AEC LICENSING GUIDES

1. Plutonium-Beryllium Neutron Sources for Uses Other Than Well-Logging
2. Fabricated Plutonium Alpha Sources
3. Plutonium-Beryllium Neutron Sources for Well-Logging
4. Fabrication of Thorium-Magnesium Alloys Containing Not More Than 4 Percent Thorium
5. Processing Plutonium and Uranium 233
6. Processing Source Material

*7. Medical Standards for Reactor Operators

*8. Transportation of Irradiated Fuel Elements

*9. General Aspects of Byproduct Material Licensing

*10. Broad Byproduct Material Licenses

11. AEC Licensing Guide—Teletherapy Programs
12. The Purpose, Organization and Contents of Hazards Summary Reports for Power Reactors
13. AEC Licensing Guide—Industrial Radiography

---

*In preparation.

1048539

November 15, 1966

Dr. Constantine J. Maletskos
Harvard University Medical School
Department of Legal Medicine
25 Shattuck Street
Boston, Massachusetts 02115

Dear Costa:

I may have given you and others at the Gatlinburg meetings a somewhat incorrect view of the legal status of our program for human experimentation using radioactive materials. We make no application to anyone for permission to do human studies nor are there legal documents in existence to my knowledge giving us or anyone else permission to do this kind of work. The Office of Legal Counsel of both the Idaho Operations Office and the Washington Headquarters Office have independently reviewed the question of human studies involving deliberate administration of radioactive materials and both concur that they find nothing detrimental to the legal position of the Government in permitting such studies to be undertaken. The larger question seems not to be one of legalities but rather one of popular public opinion. This office takes its guidance in this area from the AEC Division of Biology and Medicine, specifically Dr. H. D. Bruner, who has placed these decisions on a local option basis. So long as the local medical authorities are kept informed of the general philosophies and policies being followed, and have no serious objections to the work being proposed, and so long as the work is carried out in an open and aboveboard manner by competent and knowledgeable scientists acting as a group under competent supervision of their peers, there are no objections on the part of the AEC Division of Biology and Medicine to such programs. The paper I gave at Gatlinburg contained some of the background material upon which our present operating philosophy is based and presents a few of the rules that we have set down for our own guidance.

1048540

I am enclosing a copy of the voluntary consent form that we use, the language of which has been checked and approved through our own legal department. Provided your experiments are carried out by competent people in an open and above-board manner with full knowledge and concurrence of your own local authorities, medical as well as legal and administrative, I would not think that you would need permission from any other source and perhaps the less said about it the better.

I hope this information will be of assistance in clarifying our position out here. If there is any additional information I can give, please do not hesitate to write or call.

Best personal regards,

Claude W. Sill
Ass't Director for Technology
Health and Safety Division

Enclosure:
Voluntary Consent Form

1048541

UNITED STATES ATOMIC ENERGY COMMISSION
IDAHO OPERATIONS OFFICE
P. O. BOX 1183
IDAHO FALLS, IDAHO
83401

IN REPLY REFER TO

November 22, 1965

Mr. Roger A. Cloutier
ORINS Medical Division
P. O. Box 117
Oak Ridge, Tennessee 37830

Dear Roger:

Please accept my sincerest apologies for the delay in sending you the enclosed material on our volunteer program involving radioactive materials. I have just completed some slight revisions of the manuscript in order to get it in shape for reproduction so now is the best for reproduction in the proceedings of the meeting.

As far as the legal approval of this kind of program is concerned, I think the enclosed copy of a letter that I wrote to Costa Maletskos on the same subject will answer your questions adequately. There is nothing in writing anywhere to my knowledge giving anyone legal permission to do this kind of work. Both ID and Washington Headquarters' legal staffs have stated that they do not see anything in this kind of work detrimental to the legal position of the Government. AEC Biology and Medicine in Washington has placed approval on a local option basis, i.e., it may be done provided it has the concurrence of the local medical and administrative authorities. We are doing it, many others over the world are doing it. If your own local authorities say no, then I do not know what recourse you have. I would be most happy to have them call me directly or to call Dr. George Weain who is our resident authority here as the "SOB" who will do whatever he can to convince them of the desirability of this kind of experimental endeavor.

What ?

It was nice seeing you again at Gatlinburg and I regret that we didn't have more time to discuss these programs more in detail.

Best personal regards,

Clayton H. Hill
Asst. Director for Technology
Health and Safety Division

Enclosure: Manuscript

1048542

SOME GUIDELINES FOR STUDIES INVOLVING INTERNAL ADMINISTRATION OF RADIOACTIVE MATERIALS TO HUMAN VOLUNTEERS

Claude W. Gill

Health and Safety Division
U. S. Atomic Energy Commission
Idaho Falls, Idaho

The Health and Safety Laboratory of the U. S. Atomic Energy Commission's [illegible] provides a routine in vivo whole body monitoring program for the protection of the nearly 6,000 employees at the National Reactor Testing Station in Southeastern Idaho. During the five-year period from 1956 through 1960, 7,1[illegible] in vivo determinations were made. Foreign activity has been detected 4,0[illegible] times on 2,2[illegible] individuals including follow-up measurements made on the same individuals when significant exposure has occurred. In all, a total of 31 different radionuclides have been detected in humans, in addition to the naturally-occurring potassium-40 and cesium-137. Virtually all of the exposures have been received inadvertently during the routine performance of their duties. The exposures have generally occurred from inhalation of particulate matter of unknown particle-size distribution under uncertain circumstances.

Of the 4,02[illegible] times that foreign radionuclides have been observed in humans, not more than a half dozen have involved activities greater than about 1 uc. In perhaps 95% of the cases, the activity present was less than 0.1 uc., most of which was eliminated within a very few days. Since the maximum permissible body burden of most beta-gamma emitters is several microcuries or greater for continuous exposure, such levels are of very little physiological significance to the host. As a matter of fact, to save the time and expense of reducing the complex gamma spectra either manually or by a computer program, body burdens lower than about 0.1 uc. are merely recorded qualitatively as being present and are not even quantified. Yet, in almost every case, because of the extreme sensitivity of modern instrumentation, we have been able to determine the mode of excretion from the body, the effective half-life of the specific nuclide involved, and other valuable information from such minute and physiologically insignificant quantities of radioactive materials. This information is of particular importance because it has been obtained on actual human beings under practical conditions and consequently is much more informative and realistic than other data of this kind which is usually obtained by extrapolation from animal data. For example, one of the most important pieces of information derived to date from our routine whole body counting program has been the general philosophy that autopsy is grossly inadequate as a routine monitoring technique for internal contamination in humans where inhalation of insoluble particulates is concerned. Since our experience has also indicated that inhalation of insoluble particulates is the most likely source of contamination to be encountered around operating reactors, routine autopsy has been abandoned in our laboratory as a monitoring technique except for determination of the organ dose from systemically deposited nuclides or detection of certain specific soluble nuclides which are known to be absorbed by the body and excreted in the urine. I wonder how many laboratories would have continued using a technique for detection and [illegible] of internal contamination in humans that does not give

1048543

[illegible] of direct reactor-[illegible] development.

In view of the [illegible] however, [illegible] information concerning the metabolic characteristics [illegible] large number of radioactive [illegible] has been obtained from the minute quantities of material [illegible] day, deliberate exposure of human volunteers [illegible] radioactive materials under controlled conditions would permit a marked increase in the rate of accumulation of such fundamentally important biological data. Almost every dose calculation that I have ever made, or have heard others describe, has contained an apology or a hedge that the validity of the answer depended on whether or not certain assumptions used in the calculations were correct. In many cases, those assumptions were guesses at best, or were derived by extrapolation from animal data and their validity is certainly open to question when applied to humans. Most of the actual human data presently available was obtained from evaluation of human accidents involving intake of radioisotopes. In view of the extremely minute quantities of materials required and the very high sensitivity of modern instrumentation for their detection, why do we continue to penalize ourselves with half truths and calculations that at best border on the ridiculous when the better data is available for the taking in a direct human studies without significant harm to the individual volunteer? Several have made pointed out this need for research programs involving humans to provide better data than is presently available for assessment of the dose received from internally deposited radionuclides (1). I would like to suggest a "Principle of Comparability" that it is both logical and prudent that we should be willing to place at least as much at risk to understand the fundamental effects of internal radiation on humans as we do routinely in developing a nuclear technology. In other words, exposures that are acceptable for day-to-day operation of a reactor should also be acceptable for studies to determine the effect of internal emitters in man.

The use of human subjects in scientific experimentation has generated much controversy concerning the ethics involved, particularly in the medical profession. Throughout much of recorded history, men of medicine have set down principles of good conduct to guide them in their relations with their patients. Many of these precepts apply directly to human studies involving radioactivity. Though by no means the oldest of pagan medical oaths, the oath of Hippocrates is the best known and the most enduring. Traditional and modernized versions continue to be used as a profession pledge of ethical behavior. When the American Medical Association was founded in 1847, it adopted the oath of Hippocrates in its pagan form. At the same time, it adopted a code of medical ethics published in 1803 by the English physician, Thomas Percival. In 1948, the First General Assembly of the World Medical Association appointed a committee to draft an updated wording of the Hippocratic oath. After minor changes, this was adopted in 1949 as Geneva by the Second General Assembly as the "Declaration of Geneva." After World War II, the Nuremberg Code of Ethics in Medical Research was framed by a task group of the American Medical Association to guide the allied military tribunal in the prosecution of 23 Nazi physicians accused of brutal experiments on political prisoners. This code is perhaps the one most frequently quoted where human experimentation is concerned. More recently, another code of ethics on which work was started following World War II was adopted by the Eighteenth World Medical Assembly in June of 1964 in Helsinki, Finland, as the Declaration of Helsinki. According to Dr. Harry H. Gear, Secretary General of the World Medical Association, recommendations in the Declaration of Helsinki "are offered to all medical men and their colleagues [illegible] disciplines [illegible] acceptable scientific and clinical investigations involving human beings." The House of Delegates of the American Medical Association [illegible] endorsed the Declaration of Helsinki as an official guide [illegible] medical investigation. Representatives of the American Medical Association [illegible] members of

1048544

[illegible]

[illegible] being proposed. The [illegible] the subjects must be fully informed [illegible] problems must be in some manner, [illegible] exercise fully his power of choice. [illegible] be witnessed. The investigator must respect the right of each individual to safeguard his own personal integrity and, [illegible] the course of clinical research, the subject or his guardian should be able to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if in his judgment, it may, if continued, be harmful to the individual. The consent of valid informed consent is a [illegible] and [illegible] time is impossible [illegible] and responsibility of the scientist may be [illegible] involved. [illegible] to convey the necessary information and [illegible] in any way lessen the requirement for valid informed consent.

Several items from the Nuremberg Code would seem to be particularly pertinent to our proposed studies. The first item says "The voluntary consent of the human subject is absolutely essential." Item 2 points out a nearly self-evident point of logic and "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment." Item 10 says in part "During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, ..."

The official position of the United Kingdom has been greatly clarified recently by a statement of their Medical Research Council in their annual report for [illegible] and [illegible]. The statement deals primarily with medical investigations in general but is directly applicable to work with radiation and radioactive materials. The council emphasizes the importance of proper safeguards both in procedure and safeguarding to the benefit of the individual and, more specially, [illegible] in which the [illegible] and [illegible] benefit directly from [illegible]. [illegible] particular importance is attached to obtaining the individual's [illegible] consent, by which is meant "consent freely given with proper understanding of the nature and consequences of what is proposed." [illegible] and alone safeguards are ensured, the council clearly endorses the [illegible] of investigations involving volunteers, and concludes that "after adequate explanation, the consent of an adult of sound mind and understanding can be relied upon to be true consent." They further emphasize the responsibility on the professions, on the heads of investigating departments, and on individual investigators, and emphasize the wisdom of all these investigations to be impregnable. The report also points out that the experiment should be conducted only by scientifically qualified persons exercising the highest degree of skill and care throughout all stages of the experiment, and that no experiment should be undertaken where there is any reason to believe that serious injury or death would occur as the result in all of the codes of ethical conduct.

One of the greatest retarding influences on the accumulation of human data has been the [illegible] moral [illegible] in some of the earlier codes, that experiments [illegible] human subjects in union. The subject himself [illegible] informed

[illegible]

The pertinent values are [illegible] rem per quarter or [illegible] rem per year for the whole body or 10 rem per quarter and [illegible] rem per year for the skin. For the sake of simplicity and to eliminate the need for [illegible] when again is evident, which may itself be the principle reason for the experiment, the higher levels permitted for larger organs other than the whole body are not [illegible] of present but the dose [illegible] be the whole [illegible]. Although the [illegible] rem per quarter for the whole body may be exceeded [illegible] the criterion is proposed here single exposure basis, neither the first week [illegible] a value only slightly larger than the average value of 0.[illegible] rem permitted for each of [illegible] consecutive weeks. An extensive table of activities required to produce a dose of 0.[illegible] rem per week to the critical organ from a single exposure has been published (2) and is most helpful and convenient in determining the maximum permissible dose to be used as well as for administrative checking. Another significant point in this connection is that these values and the equations from which they were calculated have been prepared by a well known authority in the field of internal dosimetry, have been published in the open literature and are easily available to others. Another similar and more recent paper entitled "Radiation Doses from Administered Radio Nuclides" is also very useful (3). However, published information tends to become outdated and all final calculations of dose must reflect the most recent methods and information recommended by the Federal Radiation Council and the International Commission on Radiological Protection.

One of the significant differences between doses administered from external or internal sources is the inability to terminate the latter on demand by removal of the source. Both common prudence and most of the national codes suggest that the long-term dose commitment should be restricted to permit either the experimenter or the volunteer to reconsider the decision to continue the test. Consequently, limitations are imposed on the effective half lives that can be employed at a given level of activity so that more than one opportunity is presented to stop the experiment before even a 1-year's maximum permissible dose will have been committed irreversibly.

A summary of the maximum permissible [illegible] made for a single exposure as a function of half life and dose received is given in Table I. Obviously, when the half life is less than that shown in the table, the dose received will also be less than that shown. Specific values then are as follows:

1. The quantity of radioactive material to be taken in a single day shall not exceed that required to deliver a dose to the critical organ of 0.[illegible] rem for the first week after exposure as given in column [illegible] of the published table (2), for ingestion and inhalation, respectively. These values have been chosen to permit integration of the dose received over a time period of one week. Where necessary, the values can be [illegible] to reflect the latest information available.

1048546

2. The maximum level of [illegible] used only with radionuclides having an effective half life in the critical organ shorter than 10 days so that the dose [illegible] exceed the second limitation of 1.25 rem in the first quarter. The dose of 5 rem per year permitted by AEC Manual Chapter 0524 is permitted but only for four separate tests so that the dose can be terminated within a reasonable length of time (one quarter) if either the subject or experimenter should so decide. This limitation also ensures that the total integrated dose will not exceed approximately 5 rem for a maximum of four tests per year.

3. Nuclides with effective half lives longer than 10 days can be used provided the quantities are reduced to limit the long-term commitment. Nuclides with effective half lives in excess of one year are not employed in any case. With nuclides having half lives from 10 days up to 13 weeks, the values given in the published table (2) are reduced by the factor 4.3 so that the dose per year will not exceed 1.25 rem. Again, four tests per year are permitted to restrict the yearly dose to 5 rem and the total integrated infinity dose to only slightly more. For nuclides with half lives of 13 weeks up to one year, only one-tenth the quantity mentioned in the table is permitted per test and only one test is permitted per year to keep the dose for the first year down to about 1 rem and the total infinity dose down to about 2 rem. Use of nuclides with half lives in excess of one year is not likely to be necessary and is undesirable because of inability to terminate the exposure within a reasonable length of time.

4. Nuclides for which the thyroid is the critical organ can be used in quantities three times that specified in the table as permitted by AEC Manual Chapter 0524. Corresponding increases permitted by Manual Chapter for "other organs" can be utilized if the critical organ is known with some assurance. Otherwise, the dose should be limited to that permitted for the whole body.

5. If the source is encapsulated in polyethylene tubing or other impervious material that will not be released in the body and will be eliminated in about 24 hours, the maximum activity used and the number of experiments performed can be adjusted such that the dose received does not exceed 0.3 rem per week or 5 rem per year to that part of the gastrointestinal (G.I.) tract deemed to be the critical organ. As pointed out in the footnote to the table in reference 2, the values given in columns 4 and 7 for a dose rate of 0.043 rem per day may be considered as maximum permissible values for continuous exposure when the G.I. tract is the critical tissue. Consequently, either a single experiment at 7 times this value or 7 experiments at this value could be performed each week. If the source strength is sufficiently high or the nuclides sufficiently long lived to constitute any significant hazard to others if the capsule should be opened, the source will be recovered and properly disposed of after termination of the study.

6. Chemical toxicity is to be considered specifically in each case, and will become a limiting factor when the threshold limit is reached. For example, a solution of methyl iodide containing radioactive iodine tracer could be more toxic chemically than radiochemically if the specific activity were sufficiently low. Both the chemical and radiochemical purity of the activity being administered must be established beyond question.

Since many volunteers will inevitably be obtained from our own subordinates, we must be particularly careful to avoid any suggestion of coercion or mandatory participation as a condition of employment. Consent forms may not even be distributed for signature until the potential volunteer has been

1048547

contacted, the experiment [illegible] and his consent freely given. Similarly, to avoid [illegible] public reaction, the general philosophy of human studies being [illegible] in a given laboratory must have been discussed openly with and concurred in by the local medical authorities without the slightest suggestion of attempted subterfuge. Each specific experiment must be approved by at least two reputable scientists with administrative responsibilities and authority in the organization, one of whom must be a medical officer, and must be carried out openly by the experimenters acting as a group rather than any single individual going it alone. In our laboratory, the Chief of the Medical Branch approves the medical qualifications of the volunteer and assures that all necessary medical aspects of the proposal have been reviewed adequately. The Chief of the Analytical Chemistry Branch approves the project from the standpoint of chemical and radiological toxicities. After the study has been completed the radiation exposure data is entered on the consent form and filed in the individuals medical record.

The above guide lines reflect the maximum quantity of radioactive materials that can be used only with good and sufficient justification and are thought to be relatively conservative. Even so, as a general philosophy, the actual quantity to be used in any given experiment shall not exceed the smallest quantity necessary to achieve the intended results.

LITERATURE CITED

(1) Morgan, K. Z., J. Nucl. Med. 6, 79 (1965).
(2) Morgan, K. Z., Ford, M. R., Nucleonics 12, No. 6, 32 (1954).
(3) Vennart, J., The British Journal of Radiology 35, 372 (1962).

Presented at the Twelfth Annual Bioassay and Analytical Chemistry Meeting, October 14, 1966 at Gatlinburg, Tennessee.

1048548

contacted, the experiment [illegible] explained and his consent freely given. Similarly, to avoid [illegible] public reaction, the general philosophy of human studies being [illegible] in a given laboratory must have been discussed openly with and concurred in by the local medical authorities without the slightest suggestion of attempted subterfuge. Each specific experiment must be approved by at least two reputable scientists with administrative responsibilities and authority in the organization, one of whom must be a medical officer, and must be carried out openly by the experimenters acting as a group rather than any single individual going it alone. In our laboratory, the Chief of the Medical Branch approves the medical qualifications of the volunteer and assures that all necessary medical aspects of the proposal have been reviewed adequately. The Chief of the Analytical Chemistry Branch approves the project from the standpoint of chemical and radiological toxicities. After the study has been completed the radiation exposure data is entered on the consent form and filed in the individuals medical record.

The above guide lines reflect the maximum quantity of radioactive materials that can be used only with good and sufficient justification and are thought to be relatively conservative. Even so, as a general philosophy, the actual quantity to be used in any given experiment shall not exceed the smallest quantity necessary to achieve the intended results.

LITERATURE CITED

(1) Morgan, K. Z., J. Nucl. Med. 6, 79 (1965).
(2) Morgan, K. Z., Ford, M. R., Nucleonics 12, No. 6, 32 (1954).
(3) Vennart, J., The British Journal of Radiology 35, 372 (1962).

Presented at the Twelfth Annual Bioassay and Analytical Chemistry Meeting, October 14, 1966 at Gatlinburg, Tennessee.

1048549

Table I. Radiation Guides for Human Studies Involving a Single Exposure

Effective Half-life	Fraction of Columns 5 or 8[a]	Tests per Year	Maximum Dose Received, rem.				
			First Week	First Year		Total	
				1 Test	Max.	1 Test	Max.
18 days	1	4	0.3	1.29	5.16	1.29	5.16
13 weeks	1/4.3	4	0.069	1.25	5.00	1.33	5.32
1 year	1/10	1	0.03	1.15	1.15	2.3	2.3

[a]Table in Ref. 2

1048550

U. S. Atomic Energy Commission
Health and Safety Division

VOLUNTARY CONSENT FOR PERSONAL PARTICIPATION
IN SCIENTIFIC HUMAN STUDIES

I, _____, do hereby acknowledge that I have volunteered as an AEC employee to participate personally in a scientific investigation promoted by and for the Atomic Energy Commission. I understand the study requires me to take internally a small quantity or quantities of radioisotopes which has been estimated by the investigators and the ID Medical Branch to deliver less than the radiation guide limits permitted me for occupational radiation exposure. I understand that a documented record of these isotope studies will be on file with the ID Health and Safety Division as part of my occupational exposure and/or medical record.

_____
Signature

Witnesses:

_____
Date

_____
Signature

_____
Signature

Experiment No. _____

Nuclide Taken	Quantity, uc.	Date Taken	T 1/2 eff. days	Administration Chemical Form	Physical Form	Route

Approved By: _____ Date: _____
Chief, Analytical Chemistry Branch

_____ Date: _____
Chief, Medical Branch

Study Completed: _____
Date

1048551

Battelle Memorial Institute

P. O. BOX 999 • RICHLAND, WASHINGTON 99352 • TELEPHONE AREA CODE 509, 942-1111

PACIFIC
NORTHWEST
LABORATORY

May 12, 1967

Dr. Gould A. Andrews
Oak Ridge Institute of Nuclear Studies
Oak Ridge, Tennessee

Dear Dr. Andrews:

Carl Unruh mentioned that he had an opportunity to visit with you at a recent meeting of the Committee on "Treatment of Acute Radiation Injury Under Medically Austere Conditions." He also mentioned your interest in conducting studies to relate the uptake, elimination rate, and body burden relationships for radionuclides with some terminal patients at your facility.

The radionuclides of most interest at Hanford are isotopes and compounds of plutonium, uranium, tritium, americium, thorium, strontium, technetium, and promethium. Because of the radiotoxicity of plutonium and because this element is handled in rather large quantities at Hanford, I feel a particular need for more human research in this area.

As you know, existing models relating plutonium deposition in humans to excretion data are of limited use especially when the compounds involved are insoluble in the lung tissues. Also, very little work has been done on how the body metabolizes plutonium deposited at wound sites. Mathematical models are also needed to relate excreta data to internal deposition when the patient is being treated with chelating agents. The normal procedure is to wait until the patient is no longer being treated with chelating agents before making the evaluation. During this period of time, it has been my experience that the patient, his family, and his management become anxious to have an estimate of the patient's internal deposition in order to determine his future work status.

Inhalation experiments are needed to test out the new ICRP lung model (Health Physics 12, pp. 173-207). Particles of known mass median diameter could be administered to volunteers and the deposition in the nasal, pulmonary and tracheobronchial regions evaluated while the patient is living, and the deposition in body organs evaluated at autopsy.

Battelle-Northwest • A PRIME CONTRACTOR FOR THE U.S. ATOMIC ENERGY COMMISSION

My group has recently evaluated several techniques for measuring plutonium deposited in the lung. Data from several types of lung counters indicate a detection level of 10 nCi ^{239}Pu. Also, if 0.5 nCi of ^{241}Am are present and the Am/Pu ratio is known, a 4 inch x 9 inch NaI (TL) crystal can detect 5 nCi of ^{239}Pu. We are also developing several solid state organ counters for detecting ^{237}Pu "in vivo." This isotope has the advantage of a short physical half-life and emits a 100 KeV gamma ray. These "in vivo" techniques may be of assistance to you in determining the quantities administered and the uptake by body organs.

I appreciate the opportunity to make these suggestions. If I can be of further assistance, please don't hesitate to contact me. I will be most anxious to hear about your final plans.

Sincerely,

Howard V. Larson

Manager
Personnel Dosimetry Section
ENVIRONMENTAL HEALTH DEPARTMENT

HV Larson:sg

b. ~~1925~~ 1924, Portland, Ore.
B.S. (Physics) Oregon State Univ. 1950
M.S. 1957
Physicist – Gen. Elec. Co. 1952-1965
Sr. Dev. Engr. – Radiation Protection Dept. Battelle, Mem. Inst. 1965

1048553

FORM P-8A

MEMORANDUM

TO: See Below

DATE: May 24, 1967

SUBJECT: Larson Letter (May 12) - Battelle Institute

COPIES TO: Drs. Edwards, Unisolor, Lushbrugh, Cloutier, Bergner

Please see attached correspondence from Mr. Larson regarding feasibility of us undertaking studies with these isotopes in patients here.

Please let me have your comments.

GAA

I agree we should be doing something here. Yet, unless some new or unknown person in the clinical service is able + willing to be assigned to the project, — ? R

1048554

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
P O BOX 117
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-84

May 25, 1967

Harold V. Larson, Manager
Personnel Dosimetry Section
Environmental Health Department
Battelle Memorial Institute
P. O. Box 999
Richland, Washington 99352

Dear Mr. Larson:

Thank you very much for your letter of May 12. We have a definite interest in trying to provide useful information that can be obtained from human patient volunteers. I will need to talk this over with several members of our staff, and we will let you know as soon as our plans are more clearly worked out.

We would like very much to cooperate with you in this work, and appreciate having heard from you.

Sincerely yours,

Gould A. Andrews, M.D.

GAA/pe

1048555

BROOKHAVEN NATIONAL LABORATORY
ASSOCIATED UNIVERSITIES, INC.
UPTON, L.I., N.Y. 11973
TEL. AREA CODE 516 YAPHANK 4-6262

REFER:

MEDICAL DEPARTMENT

File in: (HUC) Human Use Committee reference file

27 September 1967

Frances see that all members of H.U.C. get a copy of this.

Gould A. Andrews, M. D.
Hospital Division
Oak Ridge Institute Nuclear Studies
Oak Ridge, Tennessee

I am writing to ask your opinion on the problem of the Food and Drug Administration regulations in respect to radiopharmaceuticals. After visits to the FDA and repeated conferences within our own group and with one commercial producer of labeled materials used extensively in clinical research, I have come to the following conclusions. The existing law and regulations make it clear that if a substance is going to be aimed at diagnosis or therapy, that one must, irrespective of its origin, (accelerator or nuclear reactor produced) file for an IND number fulfilling all of the regulations prescribed. If one is using accelerator produced radioisotopes for pure research under conditions in which the steady state equilibrium of the body in the normal or diseased individuals is not disturbed, one would also have to file under existing regulations for an IND number fulfilling all requirements specified. If one takes reactor produced radioisotopes and exclusively within ones own institution processes them up to a form for administration in tracer studies to a sterile pyrogen free entity, one would also have to file for an IND number. However, there is another category namely, where labeled materials are produced by a reputable manufacturer certifying chemical purity, sterility and non-pyrogenicity intended for tracer studies of metabolic processes in which the amount used does not disburb the steady state equilibrium and there is no radiation hazard involved. In this case I feel that the existing FDA regulations are not appropriate. Clearly, when the present exemption for reactor produced isotopes used in medicine is removed and the full responsibility is transferred from the AEC to the Food and Drug Administration some regulatory procedure is required to assure the protection of the patient and that investigators are making the appropriate calculations and studies to assure that there is no radiation hazard.

1048556

PART 130—NEW DRUGS

Consent for Use of Investigational New Drugs on Humans; Statement of Policy

In the FEDERAL REGISTER of March 11, 1967 (32 F.R. 3994), a notice was published proposing a revision of § 130.37, a statement of policy regarding consent for use of investigational new drugs on humans. The comments received in response to the proposal have been considered and the Commissioner of Food and Drugs concludes that, in the public interest and in consonance with the Declaration of Helsinki adopted by the World Medical Association and the "Ethical Guidlines for Clinical Investigation" adopted by the House of Delegates of the American Medical Association, the statement of policy should be revised to read as set forth below.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a)) and under the authority delegated to the Commissioner by the Secretary of Health, Education, and Welfare (21 CFR 2.120), § 130.37 is revised to read as follows:

§ 130.37 Consent for use of investigational new drugs (IND) on humans: statement of policy.

(a) Section 505(i) of the act provides that regulations on use of investigational new drugs on humans shall impose the condition that investigators "obtain the consent of such human beings or their

representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings."

(b) This means that the consent of such humans (or the consent of their representatives) to whom investigational drugs are administered primarily for the accumulation of scientific knowledge, for such purposes as studying drug behavior, body processes, or the course of a disease, must be obtained in all cases and, in all but exceptional cases, the consent of patients under treatment with investigational drugs or the consent of their representatives must be obtained.

(c) "Under treatment" applies when the administration of the investigational drug for diagnostic, therapeutic, or other purpose involves medical judgment, taking into account the individual circumstances pertaining to the patient to whom the investigational drug is to be administered.

(d) "Exceptional cases" as used in paragraph (b) of this section are those relatively rare cases in which it is not feasible to obtain the patient's consent or the consent of his representative, or in which as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent.

(e) "Patient" means the person under treatment.

(f) "Not feasible" is limited to cases wherein the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative; for example, the patient is in a coma or is otherwise incapable of giving consent, his representative cannot be reached, and it is imperative to administer the drug without delay.

(g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's well-being and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought.

(h) "Consent" means that the person involved has legal capacity to give consent, is so situated as to be able to exercise free power of choice, and is provided with a fair explanation of pertinent information concerning the investigational drug, and/or his possible use as a control, as to enable him to make a decision on his willingness to receive said investigational drug. This latter element means that before the acceptance of an affirmative decision by such person the investigator should carefully consider and make known to him (taking into consideration such person's well-being and his ability to understand) the nature, expected duration, and purpose of the administration of said investigational drug; the method and means by which it is to be administered; the hazards involved; the existence of alternative forms of therapy, if any; and the beneficial effects upon his health or per-

administration of the investigational drug.

When consent is necessary under the rules set forth in this section, the consent of persons receiving an investigational new drug in Phase 1 and Phase 2 investigations (or their representatives) shall be in writing. When consent is necessary under such rules in Phase 3 investigations, it is the responsibility of investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug.

(Secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a))

Dated: June 13, 1967.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

[F.R. Doc. 67-6912; Filed, June 19, 1967; 8:47 a.m.]

1048557

PART 130—NEW DRUGS

Consent for Use of Investigational New Drugs on Humans; Statement of Policy

In the FEDERAL REGISTER of March 11, 1967 (32 F.R. 3994), a notice was published proposing a revision of § 130.37, a statement of policy regarding consent for use of investigational new drugs on humans. The comments received in response to the proposal have been considered and the Commissioner of Food and Drugs concludes that, in the public interest and in consonance with the Declaration of Helsinki adopted by the World Medical Association and the "Ethical Guidlines for Clinical Investigation" adopted by the House of Delegates of the American Medical Association, the statement of policy should be revised to read as set forth below.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a)) and under the authority delegated to the Commissioner by the Secretary of Health, Education, and Welfare (21 CFR 2.120), § 130.37 is revised to read as follows:

§ 130.37 Consent for use of investigational new drugs (IND) on humans: statement of policy.

(a) Section 505(i) of the act provides that regulations on use of investigational new drugs on humans shall impose the condition that investigators "obtain the consent of such human beings or their

representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings."

(b) This means that the consent of such humans (or the consent of their representatives) to whom investigational drugs are administered primarily for the accumulation of scientific knowledge, for such purposes as studying drug behavior, body processes, or the course of a disease, must be obtained in all cases and, in all but exceptional cases, the consent of patients under treatment with investigational drugs or the consent of their representatives must be obtained.

(c) "Under treatment" applies when the administration of the investigational drug for diagnostic, therapeutic, or other purpose involves medical judgment, taking into account the individual circumstances pertaining to the patient to whom the investigational drug is to be administered.

(d) "Exceptional cases" as used in paragraph (b) of this section are those relatively rare cases in which it is not feasible to obtain the patient's consent or the consent of his representative, or in which as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent.

(e) "Patient" means the person under treatment.

(f) "Not feasible" is limited to cases wherein the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative; for example, the patient is in a coma or is otherwise incapable of giving consent, his representative cannot be reached, and it is imperative to administer the drug without delay.

(g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's well-being and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought.

(h) "Consent" means that the person involved has legal capacity to give consent, is so situated as to be able to exercise free power of choice, and is provided with a fair explanation of pertinent information concerning the investigational drug, and/or his possible use as a control, as to enable him to make a decision on his willingness to receive said investigational drug. This latter element means that before the acceptance of an affirmative decision by such person the investigator should carefully consider and make known to him (taking into consideration such person's well-being and his ability to understand) the nature, expected duration, and purpose of the administration of said investigational drug; the method and means by which it is to be administered; the hazards involved; the existence of alternative forms of therapy, if any; and the beneficial effects upon his health or per-

administration of the investigational drug.

When consent is necessary under the rules set forth in this section, the consent of persons receiving an investigational new drug in Phase 1[1] and Phase 2[1] investigations (or their representatives) shall be in writing. When consent is necessary under such rules in Phase 3[1] investigations, it is the responsibility of investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug.

(Secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a))

Dated: June 13, 1967.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

[F.R. Doc. 67-6912; Filed, June 19, 1967; 8:47 a.m.]

1048558

PART 130—NEW DRUGS

Consent for Use of Investigational New Drugs on Humans; Statement of Policy

In the FEDERAL REGISTER of March 11, 1967 (32 F.R. 3994), a notice was published proposing a revision of § 130.37, a statement of policy regarding consent for use of investigational new drugs on humans. The comments received in response to the proposal have been considered and the Commissioner of Food and Drugs concludes that, in the public interest and in consonance with the Declaration of Helsinki adopted by the World Medical Association and the "Ethical Guidlines for Clinical Investigation" adopted by the House of Delegates of the American Medical Association, the statement of policy should be revised to read as set forth below.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a)) and under the authority delegated to the Commissioner by the Secretary of Health, Education, and Welfare (21 CFR 2.120), § 130.37 is revised to read as follows:

§ 130.37 Consent for use of investigational new drugs (IND) on humans; statement of policy.

(a) Section 505(i) of the act provides that regulations on use of investigational new drugs on humans shall impose the condition that investigators "obtain the consent of such human beings or their

representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings."

(b) This means that the consent of such humans (or the consent of their representatives) to whom investigational drugs are administered primarily for the accumulation of scientific knowledge, for such purposes as studying drug behavior, body processes, or the course of a disease, must be obtained in all cases and, in all but exceptional cases, the consent of patients under treatment with investigational drugs or the consent of their representatives must be obtained.

(c) "Under treatment" applies when the administration of the investigational drug for diagnostic, therapeutic, or other purpose involves medical judgment, taking into account the individual circumstances pertaining to the patient to whom the investigational drug is to be administered.

(d) "Exceptional cases" as used in paragraph (b) of this section are those relatively rare cases in which it is not feasible to obtain the patient's consent or the consent of his representative, or in which as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent.

(e) "Patient" means the person under treatment.

(f) "Not feasible" is limited to cases wherein the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative; for example, the patient is in a coma or is otherwise incapable of giving consent, his representative cannot be reached, and it is imperative to administer the drug without delay.

(g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's well-being and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought.

(h) "Consent" means that the person involved has legal capacity to give consent, is so situated as to be able to exercise free power of choice, and is provided with a fair explanation of pertinent information concerning the investigational drug, and/or his possible use as a control, as to enable him to make a decision on his willingness to receive said investigational drug. This latter element means that before the acceptance of an affirmative decision by such person the investigator should carefully consider and make known to him (taking into consideration such person's well-being and his ability to understand) the nature, expected duration, and purpose of the administration of said investigational drug; the method and means by which it is to be administered; the hazards involved; the existence of alternative forms of therapy, if any; and the beneficial effects upon his health or per-

administration of the investigational drug.

When consent is necessary under the rules set forth in this section, the consent of persons receiving an investigational new drug in Phase 1[1] and Phase 2[1] investigations (or their representatives) shall be in writing. When consent is necessary under such rules in Phase 3[1] investigations, it is the responsibility of investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug.

(Secs. 505(i), 701(a), 52 Stat. 1053, as amended, 1055; 21 U.S.C. 355(i), 371(a))

Dated: June 13, 1967.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

[F.R. Doc. 67-6912; Filed, June 19, 1967; 8:47 a.m.]

1048559

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

DML:MB:KSD

December 1, 1970

Gentlemen:

The AEC is prepared to receive applications for the use of iodine 131 labeled human serum albumin (IHSA) for cisternography as a well-established diagnostic procedure.

The introduction of IHSA into the cerebrospinal fluid is a highly specialized procedure and should therefore be carried out only by an appropriate team of specialists, including a neurologist or neurosurgeon. Physicians having nuclear medicine responsibilities in cisternography studies should have training and experience as outlined in Appendix C, Section II.B., Category II--Specialized Diagnostic Procedures (Scans or Tumor Localization), of the "AEC Licensing Guide--Medical Programs."

Our Advisory Committee on the Medical Uses of Isotopes recommends that the thyroid gland be blocked and only single entry into the vials containing the iodinated human serum albumin for cisternography be made.

The usual dose range for cisternography is up to 100 microcuries. The quantity of albumin administered should be kept as low as possible and should not exceed a maximum of 4-5 milligrams. An adult dosage of 100 microcuries and a maximum of 4-5 milligrams of albumin necessitates a minimum specific activity of 20-25 microcuries per milligram of albumin at the time of administration. (In terms of the 1% by volume albumin product, this minimum would be 200-250 microcuries per milliliter.)

If the applicant does not obtain IHSA from a manufacturer who is licensed by the Secretary, Department of Health, Education and Welfare, to distribute the material for cisternography, he must determine that in-house IHSA preparations meet the above criteria. In addition, such an applicant should describe in detail the method of preparation and the quality control tests that will be conducted to assure that the product meets the criteria.

Sincerely,

Richard E. Cunningham
Assistant Director for Plans
and Technical Programs
Division of Materials Licensing

1048560

GPO 902-859

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

DML:MB:KSD

November 15, 1971

Gentlemen:

By letter dated July 5, 1966, we announced that molybdenum 99/technetium 99m generators could be authorized for routine use as a source of supply for technetium 99m. This letter enclosed a document entitled "Supplemental Information Required for Licensing Molybdenum 99/Technetium 99m Generators," which set forth certain criteria for the quality of the product. These criteria have now been reevaluated in light of current technology with the assistance of our pharmaceutical consultant and our Advisory Committee on the Medical Uses of Isotopes. The enclosed documents entitled "Radiopharmaceutical Criteria for Molybdenum 99/Technetium 99m Generators Containing Fission Produced Parent Molybdenum 99," and "Radiopharmaceutical Criteria for Molybdenum 99/Technetium 99m Generators Containing Parent Molybdenum 99 Prepared from Irradiated Stable Molybdenum," supersede the criteria enclosed with our 1966 letter. These criteria generally reflect product purity which is technically feasible.

Preliminary tests indicate that the irradiated molybdenum 99/technetium 99m generators which have thus far been approved for routine use meet the revised criteria. If any changes are indicated you will be notified. No fission product molybdenum 99/technetium 99m generators have yet been approved by the AEC for routine use.

Sincerely,

Richard E. Cunningham
Acting Director
Division of Materials Licensing

Enclosures:
1. Fission product criteria
2. Irradiated product criteria

1048561

Radiopharmaceutical Criteria for Molybdenum 99/Technetium 99m Generators Containing Fission Produced Parent Molybdenum 99

1. Molybdenum Breakthrough (2, 3)*

Not more than one microcurie of molybdenum 99 per millicurie of technetium 99m or a maximum of 5 microcuries of molybdenum 99 at the time of administration to each patient. Determination must be accomplished radiometrically because molybdenum 99 is in the carrier-free state; chemical tests therefore lack sufficient sensitivity for this determination. Medical users should assay each elution for molybdenum 99 contamination.

II. Aluminum Breakthrough (2, 3)*

Not more than 10 micrograms per milliliter of generator eluate.

III. Radionuclidic Purity (1, 2)*

A. Gamma Impurities

Iodine 131: 0.05 microcurie per millicurie of technetium 99m at the time of administration to each patient. Ru-103: 0.05 microcurie per millicurie of technetium 99m at the time of administration to each patient. All others: gross gamma activity not more than 0.1 microcurie per millicurie of technetium 99m at the time of administration to each patient.

B. Alpha Impurities

The level of alpha contaminants in fission product molybdenum 99 must be such that not more than 1 nanocurie of gross alpha activity/curie Mo-99 is loaded on any generator by the manufacturer of the generator.

C. Beta Impurities

The nuclides of strontium are of primary concern.

Strontium 89: Not more than 6×10^{-4} microcuries per millicurie of technetium 99m at the time of administration to each patient.

Strontium 90: Not more than 6×10^{-5} microcuries per millicurie of technetium 99m at the time of administration to each patient.

---

* As a convenience to the medical user, information concerning conformity with certain of the specifications may be supplied by the molybdenum 99 producer and molybdenum 99/technetium 99m generator manufacturer. The parenthetical number following each heading suggests who might logically supply information concerning the specification in accordance with the following key: (1) molybdenum 99 producer; (2) generator manufacturer; and (3) medical licensee-user.

1048562

IV. pH (2)

The pH of generator eluates shall be in the range 4.5 to 7.5.

V. Generator Eluant (2)

The eluant to be used in generators shall be sodium chloride injection USP; additives may be present.

VI. Pyrogenicity and Sterility (2)

Generators covered under these specifications shall be constructed so that the eluate resulting therefrom will be free of pyrogens and will be sterile, when the directions of the manufacturer have been followed. Pyrogen and sterility tests, using USP methodology, will be employed for these quality assurances.

VII. Chemical Purity (1, 2)

Assurances must be provided that the generator eluate is not likely to contain substances which would be potentially toxic in the amount any patient is likely to receive. Such toxicity could accrue from the carryover of organic or inorganic reagents used in the molybdenum 99 separation process or in the manufacture of the generator. Evidence of lack of toxicity may be inferred from safety tests of generator eluates in animal species. The producers of molybdenum 99 and the manufacturers of technetium 99m generators must certify that all chemicals used in their respective process are of USP or analytical reagent quality.

VIII. Labeling (2)

In addition to other required information, the labeling of generators under this specification must indicate that the parent molybdenum 99 has been fission product-produced.

November 15, 1971

1048563

Radiopharmaceutical Criteria for Molybdenum 99/Technetium 99m Generators Containing Parent Molybdenum 99 Prepared from Irradiated Stable Molybdenum

I. Molybdenum Breakthrough (2, 3)*

Not more than one microcurie of molybdenum 99 per millicurie of technetium 99m or a maximum of 5 microcuries of molybdenum 99 at the time of administration to each patient. Medical users should assay each elution for molybdenum 99 contamination.

II. Aluminum Breakthrough (2, 3)*

Not more than 20 micrograms per milliliter of generator eluate.

III. Radionuclidic Purity (1, 2)*

Gamma Impurities

Gross gamma contamination not more than 0.5 microcurie per millicurie of eluted technetium 99m or more than 2.5 microcuries per administered dose of technetium 99m at the time of administration to each patient.

IV. pH (2)

The pH of generator eluates shall be in the range 4.5 to 7.5.

V. Generator Eluant (2)

The eluant to be used in generators shall be sodium chloride injection USP; additives may be present.

VI. Pyrogenicity and Sterility (2)

Generators covered under these specifications shall be constructed so that the eluate resulting therefrom will be free of pyrogens and will be sterile when the directions of the manufacturer have been followed. Pyrogen and sterility tests, using USP methodology, will be employed for these quality assurances.

---

* As a convenience to the medical user, information concerning conformity with certain of the specifications may be supplied by the molybdenum 99 producer and molybdenum 99/technetium 99m generator manufacturer. The parenthetical number following each heading suggests who might logically supply information concerning the specification in accordance with the following key: (1) molybdenum 99 producer; (2) generator manufacturer; and (3) medical licensee-user.

VII. Chemical Purity (1, 2)

Assurances must be provided that the generator eluate is not likely to contain substances which would be potentially toxic in the amount any patient is likely to receive. Such toxicity could accrue from the carryover of organic or inorganic reagents used in the molybdenum 99 processing or in the manufacture of the generator. Evidence of lack of toxicity may be inferred from safety tests of generator eluates in animal species. The producers of molybdenum 99 and the manufacturers of technetium 99m generators must certify that all chemicals used in their respective process are of USP or analytical reagent quality.

VIII. Labeling (2)

In addition to other required information, the labeling of generators under this specification must indicate that the parent molybdenum 99 has been prepared from irradiation of stable molybdenum.

November 15, 1971

1048565

GPO 921-787

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

OFFICIAL BUSINESS

POSTAGE & FEES PAID
U.S. Atomic Energy Commission

U.S. MAIL

Return this sheet to above address, if you do NOT wish to receive this material ☐ or if change of address is needed ☐ (indicate change, including ZIP code).

1048566

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

February 18, 1972

DML:MB:KSD

Gentlemen:

The Materials Branch is prepared to receive applications for the use of technetium 99m labeled albumin microspheres (human) for lung imaging as a well-established diagnostic procedure.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C, Section II.B., Category II--Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide--Medical Programs." The usual adult dosage for this procedure is up to 4 millicuries.

Applicants will be required to procure the prepackaged, precalibrated, sterile, pyrogen-free product or a commercial kit used for preparation of the product from a manufacturer who is licensed by the Secretary, Department of Health, Education, and Welfare to distribute the material or kit for the purpose of lung imaging.

Attached is an outline of the information which should be submitted in support of an application for use of a commercial kit to prepare the labeled microspheres.

Sincerely,

Cecil R. Buchanan

Cecil R. Buchanan, Assistant Chief
Materials Branch
Division of Materials Licensing

Enclosure:
As stated

1048567

An application requesting the use of a kit to prepare technetium 99m labeled albumin microspheres (human) for lung imaging should include the following information:

1. The dosage range.

2. The manufacturer's name of the kit to be used to prepare the material.

3. Confirmation that the manufacturer's directions for use of the kit will be followed.

4. A description of radioassay procedures to be followed to assure 90% accuracy.

5. Specification of the source of technetium 99m pertechnetate to be used with the kit.

6. A description of the methods used to control and evaluate radiation exposure to personnel during preparation of the pharmaceutical. In this regard, control and evaluation of hand exposure in the preparation of this radiopharmaceutical, as well as the preparation of other technetium 99m labeled pharmaceuticals, is of particular interest.

7. Confirmation that syringe and vial shields and accessories will be used in accordance with the manufacturer's recommendations.

February 4, 1972

GPO 925-597

1048568

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

DML:MB:KSD

March 30, 1972

Gentlemen:

The Materials Branch is prepared to receive applications for the use of technetium 99m - diethylenetriamine-pentaacetic acid (tin) for kidney function studies, kidney imaging, and brain imaging as well-established diagnostic procedures. This chelate formulation, Tc99m - DTPA(Sn), results from the addition of technetium 99m pertechnetate to a solution containing DTPA and stannous chloride.*

The usual adult dosages for Tc99m - DTPA(Sn) are up to 10 mCi for kidney function studies and kidney imaging and up to 15 mCi for brain imaging. A camera imaging system is required to perform kidney imaging studies due to rapid elimination. Applicants wishing to use a commercial kit to prepare Tc99m - DTPA(Sn) should (1) specify the manufacturer's name, (2) confirm that the manufacturer's directions for use will be followed, (3) describe radioassay procedures to be followed to assure 90% accuracy, (4) specify the source of Tc99m pertechnetate, and (5) describe procedures for determining the radiation dose to arms and hands during preparation.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C, Section II. B., Category II - Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide - Medical Programs."

Sincerely,

Cecil R. Buchanan

Cecil R. Buchanan, Assistant Chief
Materials Branch
Division of Materials Licensing

* An apparently identical product, Tc99m - DTPA(Fe), may be prepared by gel chromatography separation of material prepared from a ferrous sulfate DTPA solution. The Tc99m - iron-ascorbate - DTPA complex previously approved as a well-established agent for kidney imaging exhibits different biological properties and at present, the AEC has not approved this material as a well-established agent for kidney function and brain imaging studies.

1048569

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

L:MB:JEB

JAN 30 1973

Gentlemen:

The Materials Branch is prepared to receive applications for the use of an iodine 125 or americium 241 as a sealed source in a bone mineral analyzer device for the in vivo determination of bone mineral content as a diagnostic aid in aptients with metabolic bone disease.

Applicants wishing to use iodine 125 or americium 241 for the above-clinical procedure should (1) specify the manufacturer's name and model number of the sealed source, (2) specify the manufacturer's name and model number of the bone mineral analyzer device, (3) describe the procedure for installation and source exchange, and (4) describe the leak test procedure for the sealed source.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C, Section II.B., Category II-Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide - Medical Programs."

Sincerely,

James C. Malaro

J. C. Malaro, Chief
Materials Branch
Directorate of Licensing

1048570

GPO 942-519

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

L:MB:KSD

March 12, 1973

Gentlemen:

The Materials Branch is prepared to receive applications for the use of technetium 99m labeled polyphosphates* for bone imaging as a well-extablished diagnostic procedure.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C, Section 11.B., Category 11--Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide--Medical Programs." The adult dosage recommended for this procedure is 5 to 15 millicuries with a usual dosage of 10 millicuries.

An application requesting the use of a commercial kit to prepare Tc 99m labeled polyphosphates should include: (1) the planned dosage range, (2) the manufacturer's name of the kit to be used to prepare the material, (3) confirmation that the manufacturer's directions for use of the kit will be followed, (4) specification of the source of Tc 99m pertechnetate to be used, (5) a description of the radioassay procedures to be followed to assure 90% accuracy, and (6) a description of the methods used to control and evaluate radiation exposure to personnel during preparation, assay, and administration of the radiopharmaceutical.

Sincerely,

James C. Malaro, Chief
Materials Branch
Directorate of Licensing

*The agent intended by this announcement is a sodium polyphosphate polymer prepared by methods similar to those outlined by Subramanian. (See Subramanian, G., McAfee, J. G., Bell, E. G., et al. Tc-Labeled Polyphosphate as a Skeletal Imaging Agent. Radiology 102: 701-704 (1972.) Ethane-1 hydroxy-1, diphosphonate products are not intended.

1048571

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

OCT 9 1973

Gentlemen:

The Materials Branch is prepared to receive applications for the use of Technetated (Tc99m) Aggregated Albumin (Human) for lung imaging as a well-established diagnostic procedure.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C. Section II.B. Category II -- Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide - Medical Programs." The usual adult dosage for this procedure is 1-4 millicuries.

Applicants will be required to procure the prepackaged, precalibrated, sterile, pyrogen-free product or a commercial kit used for preparation of the product from a manufacturer who is licensed by the Secretary, Department of Health, Education, and Welfare, to distribute the material or kit for the purpose of lung imaging.

An application requesting the use of a kit to prepare Technetated (Tc99m) Aggregated Albumin (Human) for lung imaging should include the following information: (1) the dosage range, (2) the manufacturer's name of the kit to be used to prepare the material, (3) confirmation that the manufacturer's directions for use of the kit will be followed, (4) a description of radioassay procedures to be followed to assure 90% accuracy, (5) specification of the source of technetium-99m pertechnetate to be used with the kit, and (6) a description of the methods used to control and evaluate radiation exposure to personnel during preparation, assay, and administration of the radiopharmaceutical.

Sincerely,

James C. Malaro

James C. Malaro, Chief
Materials Branch
Directorate of Licensing
Regulation

1048572

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

October 16, 1973

L:MB:KSD

Gentlemen:

The Materials Branch is prepared to receive applications for the use of technetium-99m labeled disodium etidronate* for bone imaging as a well-established diagnostic procedure.

Physicians desiring to perform these studies should have training and experience as outlined in Appendix C, Section II.B., Category II-Specialized Diagnostic Procedures (Scans or Tumor Localization) of the "AEC Licensing Guide - Medical Programs." The adult dosage recommended for this procedure is 10 to 15 millicuries.

An application requesting the use of a commercial kit to prepare technetium-99m labeled disodium etidronate should include: (1) the planned dosage range, (2) the manufacturer's name of the kit to be used to prepare the material, (3) confirmation that the manufacturer's directions for the use of the kit will be followed, (4) specification of the source of technetium-99m pertechnetate to be used, (5) a description of the radioassay procedures to be followed to assure 90% accuracy, and (6) a description of the methods used to control and evaluate radiation exposure to personnel during preparation, assay, and administration of the radiopharmaceutical.

Sincerely,

James C. Malaro

James C. Malaro, Chief
Materials Branch
Directorate of Licensing
Regulation

*This agent is a complex of technetium-99m pertechnetate and 1-hydroxyethylidene-1, 1-disodium phosphonate in the presence of stannous chloride.

1048573

Mr Cloutier

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

AREA CODE 615
TELEPHONE 483-8611

May 8, 1974

DATE 5-10-74

COPIES TO Andrews
Berger
Potter

Dr. William G. Pollard
Executive Director
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee

Note to Potter - Bob please familiarize yourself with AEC letter of Oct. 11 1972 on reporting.

Dear Dr. Pollard:

UNUSUAL OCCURRENCE REPORT - MISADMINISTRATION OF RADIOPHARMACEUTICALS

Elyn

By letter dated October 11, 1972, OR instituted a program of unusual occurrence reporting for its contractors. It is considered appropriate that we clarify for our contractors involved in clinical or experimental use of radiation certain reporting requirements for such occurrences involving the misadministration of radiation and radioactive material to human patients. For this purpose a misadministration is defined to include administration of:

1. A radiopharmaceutical or radiation from a source other than the one intended.

2. A radiopharmaceutical or radiation to the wrong patient, or

3. A dose of radiopharmaceutical, or exposure from a radiation source, outside the intended dose range prescribed by the physician or by a route of administration other than that intended by the physician.

Verbal notification of such a misadministration should be made to this office as soon as the misadministration is known and prior to notification of individuals or agencies outside the contractor organization. This requirement should not, however, be construed as preventing you from taking immediate emergency corrective action, as you deem necessary, prior to or simultaneous with these notifications. Complete investigation of the incident should be made promptly by the contractor. OR participation in the investigation will be determined by the apparent significance of preliminary findings.

1048574

FEB 8 1974

Dr. William G. Pollard
Executive Director
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee

Dear Dr. Pollard:

RADIOPHARMACEUTICAL PROCEDURES

The above-named procedures have been reviewed by the Research and Technical Support Division and the Safety and Environmental Control Division. The following comments are offered for inclusion in this document to contribute to its present excellent quality:

1. Someone should have the designated responsibility to review compliance with Medical Division procedures and the completeness and accuracy with which Medical Division forms are completed and maintained.

2. The Medical Division chairman should receive a periodic summary of discrepancies encountered during the radiopharmaceutical procurement, preparation, and administration cycle. This would enable the chairman to determine the quality of this facet of his program and identify undesirable trends for correction.

3. A statement should be included to the effect that equipment used to check the prepared dose of a radiopharmaceutical will be properly calibrated in accordance with the ORAU procedures.

4. The person administering the radiopharmaceutical should, prior to administering the drug, be required to verify that each section of the radiopharmaceutical treatment record is complete and within the specified limits of ORAU procedures.

5. This procedure should be expanded to include guidance regarding the notification of the patient, referring physician, and hospital for misadministrations which may or may not cause a demonstrable adverse effect on the patient.

1048575

6. The AEC Research and Technical Support Division should be notified of all misadministrations and prior to the notification of individuals or agencies outside ORAU. OK

7. This procedure should specify the Medical Division chairman or his designee has the responsibility of making the necessary notifications after a misadministration rather than indicating the designees (R&CSO and Chief Clinician) as the procedure does now. why?

8. The procedure should be reworded on Page 1, Section II.C, and on Page 3, Section III.F, to clearly indicate that physicians may delegate the responsibility to administer pre-encapsulated radioisotopes only to qualified personnel. Yes

This procedure delegates the responsibility to the Medical Division chairman and the physicians to assure that technicians are adequately trained. The documented procedure which is used to carry out this responsibility should be transmitted to this office for review. ?

Sincerely,

Joseph A. Lenhard, Director
Research and Technical Support Division

OSH:RDS

cc: W. H. Travis, S&EC

HP Br. Safety Dv. R&TS Dv.

Smith/ndw
2-7-74

1048576

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. L. Edwards, M. D. Proposal No. 74-15

DESCRIPTION:

Dysprosium-157 as a clinical scanning agent for the detection of osseous and nonosseous tumors. The activity administered to a 70-kg man shall not exceed 17.5 mCi.

☒ The Committee approves with the following limitations:

Radiopharmaceutical ~~may~~/may not be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with attached proposal, ORAU/ORNL Committee on Human Studies, Ident. No. 35.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			4/4/74
R. J. Cloutier	RJC			4/4/74
C. L. Edwards	CLE			4/4/74
R. L. Hayes	RLH			4/4/74
C. C. Lushbaugh	CCL			4/4/74

Acknowledgement of Submitter C. L. Edwards Date 4 April 74

- -

Proposal does/~~does not~~ require approval of Committee on Human Studies.

Human Studies approval granted on 11 DEC 1973

1048511

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 35

Project Title Dysprosium-157 as a Clinical Scanning Agent for the Detection of Osseous and Nonosseous Tumors

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are: Radiation and chemical toxicity risks are minimal.

The committee states that adequate safeguards against these risks have been provided.

2. In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons: Possible better diagnostic agent.

3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate: as submitted.

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines: None.

5. Other committee comments: None.

Gerald Andrews
Chairman of Committee

Approve x

Disapprove

11 December 73
Date

1048578

(Revised January 1972)

Ident. No. 35

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: December 10, 1973

Principal Investigator: C. L. Edwards, M. D.

Co-Investigators: R. L. Hayes, Ph. D.
J. K. Poggenburg, Ph. D. (ORNL)

Title of Project: DYSPROSIUM-157 AS A CLINICAL SCANNING AGENT FOR THE DETECTION OF OSSEOUS AND NONOSSEOUS TUMORS.

I. Objectives of Experiment:

To determine whether ^{157}Dy can be used as an effective tumor-localizing agent in humans. Animal experiments indicate that the higher-atomic-number rare-earth radionuclides show unusual affinities for tumor tissue (Fig. 1, appendix), clear rapidly from normal tissue (Table 1, appendix), and may have the same or better tumor-localizing properties as ^{67}Ga in certain tumor types (Table 2, appendix). This radionuclide also has better bone-seeking properties than do technetium phosphate agents, and it may thus be an effective bone scanning agent. It has good decay photons for scanning (Table 3, appendix).

II. Methods of Procedure:

Dysprosium-157 will be obtained from Isotopes Development, ORNL, as the chloride in dilute hydrochloric acid solution. After conversion to the citrate form, sterilization by Millipore filtration (0.22 micron), and testing for pyrogenicity, 0.25 mCi/kg or less will be administered intravenously (1.0-0.1 mg citrate/kg). A group of 20 adult patients with known cancer will initially be studied with this radionuclide. When possible, comparisons will be made with ^{67}Ga and ^{111}In in the same patient. When bone is involved bone scans with ^{99m}Tc Osteoscan will also be made. Further studies with patient volunteers will then be determined after a review by the committee.

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose, and then at 12-hr intervals thereafter through 42 hours.

2. Individual urine specimens will be collected through 2 days.

3. Fecal excreta will be collected through 2 days.

1048579

4. Linear scans will be obtained immediately after the dose, at 3-4 hours, and then daily thereafter through 2 days.

5. Whole body and area scans will be made at 3-4 hours after administration (or as soon as practical) and at 24 hours and 48 hours.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Since ^{157}Dy will be produced by neutron activation of ^{156}Dy (HIFR), stable dysprosium will be present in this radionuclide preparation (although at only microgram levels).

We propose to administer no more than 10 μg/kg of stable dysprosium (and generally much less), since stable rare earths in excess of this amount tend to decrease the relative specificity of these nuclides for tumor tissue (see Table 4, appendix). At a level of 10 μg/kg or less there should be no toxic effects from the I.V. administration of dysprosium, since the I.P. LD_{50} in rats and mice for the chloride and nitrate ranges from 295 to 585 mg/kg (T. J. Haley, J. Pharmaceutical Sciences 54: 663, 1965).

2. Radiation Dose:

The proposed maximum activity doses for ^{157}Dy as stated in II (Methods of procedure) is based on a calculated whole body radiation dose of 1 rad (assuming uniform distribution and no excretion) and is thought to be acceptable for the proposed study. Radiation Physics supplied the radiation dose estimates.

Dysprosium-157 decays to ^{157}Tb which has a half life of 150 y. ^{157}Tb decays by electron capture emitting only gadolinium x rays. The Radiation Physics Office has estimated the maximum permissible body burden for ^{157}Tb to be 150 μCi. The complete decay of 1 mCi of ^{157}Dy would produce only 6×10^{-3} μCi of ^{157}Tb. The radiation dose resulting from the generation of this daughter radionuclide can therefore be disregarded.

IV. Radionuclides and New Drugs:

^{157}DY will be a new radionuclide in our clinical program. Following approval by the Committee on Human Studies and the ORAU Medical Radionuclide Committee, an IND will be filed with the Food and Drug Administration.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. An informed

consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducement will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the test with no promise of continued medical care at ORAU, and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU.

Attached is a copy of the proposed consent form (appendix).

Starting Date: February 1, 1974

Signatures: _____ Principal Investigator

_____ Co-Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature _____

Title _____

Institution _____

Date _____

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon _____
(myself or name of patient)

of the following test: Phase I Radiopharmaceutical Test of Dysprosium-157.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done for my benefit, rather that the test is for experimental purposes and is being done only for gathering information related to my disease, treatment, or both. Further, I understnad that any information learned from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Oak Ridge Associated Universities Medical Division.

DATE: _____

_____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: ^{157}Dy - Dysprosium citrate.

2. The drug contains the element dysprosium in quantities much less than that required to produce any measurable chemical effect in the body. The patients should feel no effects from the drug.

3. The radiation dose will be from approximately 1 rad to the whole body.

4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hrs and 42 hrs.

5. All urine and feces will be saved for two days.

6. Whole body counts and scans will be made at frequent intervals for two days.

7. The patient may withdraw from the test at any time.

DATE: _____

_____
Investigator

1048582

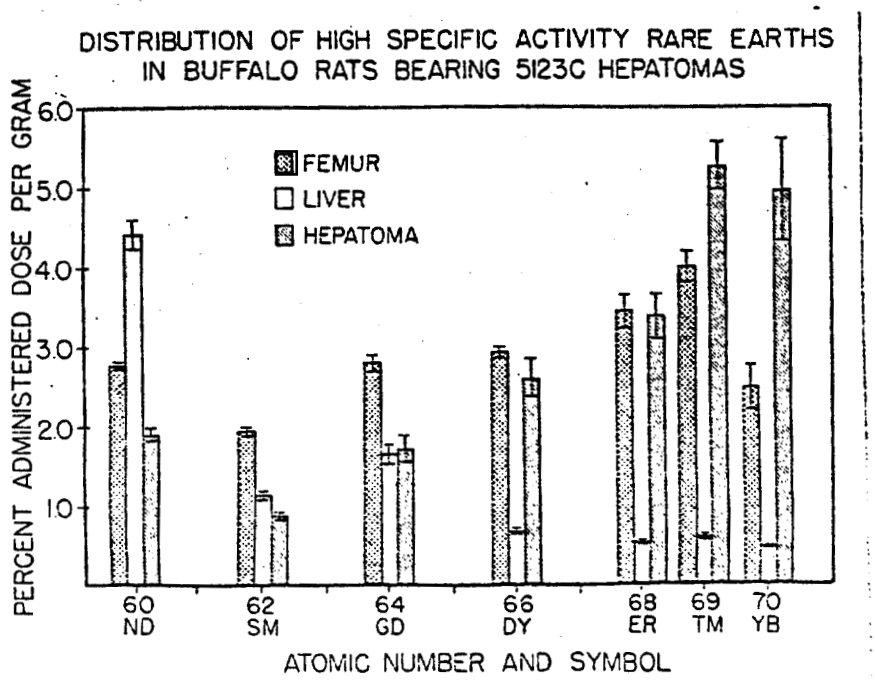
TABLE 1

INFLUENCE OF TIME ON TISSUE DISTRIBUTION OF ^{171}ER AND ^{169}YB IN RATS BEARING 5123C HEPATOMAS

Isotope	Erbium-171			Ytterbium-169	
Time	2 h	4 hr	24 h	4 h	24 h
Tumor conc. (%/g)*	3.3	4.5	3.4**	3.5	4.9**
Ratio tumor conc. to:					
Liver	5.0	5.6	6.7	7.9	11.0
Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
Femur	1.5	1.4	1.0	2.1	2.0
Marrow	7.2	10.1	12.5	5.9	8.0
Blood	6.2	19.0	130.0	9.9	110.0

* Percent administered dose/g normalized to body weight of 250 g.

** Not significantly different from 4 hour value.



1048583

Fig. 1

TABLE 2

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}Yb AND ^{67}Ga (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

TABLE 4

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

1048585

Radiation dose in rads/millicurie of parent administered (24 hr after irradiation) - values in parentheses are the doses in rads for the maximum to be administered to 70 kg man as proposed by Dr. Hayes et al.

Radionuclide	Organ*					
	Total Body	Liver	Kidneys	Spleen	Skeleton*	Marrow
Er-171 + Tm-171	0.36 (3.8)	0.92 (9.7)	1.1 (12)	0.60 (6.3)	1.4 (15)	0.19 (2.0)
Dy-157 + Tb-157	0.065 (1.1)	0.14 (2.4)	0.17 (3.0)	0.11 (1.9)	0.14 (2.4)	0.12 (2.1)
Tm-167	1.8 (1.9)	3.7 (3.9)	5.6 (5.9)	3.4 (3.6)	5.7 (6.0)	2.7 (2.8)

1048586

*skeleton = bone + marrow

[illegible]

E.W.

APPLICATION FOR INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical Division, Oak Ridge Associated Universities

Oak Ridge, Tennessee

May 3, 1974

1. NAME OF DRUG: DYSPROSIUM-157 CITRATE. This preparation diluted in a saline-sodium citrate solution will be administered intravenously in small volumes (< 5 ml).

2. COMPONENTS:

   a. Dysprosium (III)-157 citrate

   b. Stable dysprosium (III) citrate

   c. Sodium citrate

   d. Sodium chloride

   e. Water

3. QUANTITATIVE COMPOSITION (per dose):

   a. Dysprosium (III)-157 citrate: 0.25 millicuries per kilogram of body weight (or less).

   b. Stable dysprosium (III) citrate: 10 micrograms per kilogram of body weight (or less).

   c. Sodium citrate: 1 milligram per kilogram of body weight (or less).

   d. Sodium chloride: 0.2 milligram per kilogram of body weight (or less).

   e. Water: 0.05 milliters per kilogram of body weight (or less).

4. SOURCE OF NEW DRUG SUBSTANCE:

   Enriched dysprosium-156 [supplied by Oak Ridge National Laboratory (ORNL) as the nitrate with the following isotopic abundance: ^{156}Dy, 99.53%; ^{158}Dy, 0.023%; ^{164}Dy, 0.058%] will be activated in the High Flux Isotope Reactor at ORNL for 24 hours. At discharge it is calculated that the radioactivity present per microgram of stable dysprosium will be: ^{157}Dy, $\sim$7 mCi; ^{159}Dy, 0.023 μCi; and ^{165}Dy, 0.15 mCi. The activated dysprosium-156 will be dissolved in dilute

1048587

hydrochloric acid (~0.1N) and then supplied in that form to Medical Division, Oak Ridge Associated Universities (ORAU) after being microfiltered through a 0.22 μ Millipore filter. ORNL will supply ORAU with a radioisotopic assay.

5. METHODS, FACILITIES AND CONTROLS:

The ^{157}Dy chloride solution as received from ORNL will be processed in the following manner: Based on ORNL's assay sufficient sterile 2.5% sodium citrate solution (ampoule 206, Eli Lily Co., Indianapolis, Ind.) will be added to the solution so that each mCi of ^{157}Dy will at that point be associated with 0.1 mg of sodium citrate. The pH of the solution will be brought to 7.0 ± 0.2 with 1N sodium hydroxide using a combination electrode and pH meter. (The stem of the electrode will be stored in 0.9% benzyl alcohol and will be repeatedly rinsed with sterile water before each use.) Following any necessary volume adjustment by the addition of 0.9% sterile nonpyrogenic saline, the solution will be microfiltered through a sterile 0.22 micron Millipore filter into a vial which will then be capped (multipuncture type) and autoclaved at 15 pounds pressure (121°C) for 20 minutes. To insure that the preparation was exposed to adequate heat, Diack controls (Smith and Underwood Laboratories, Troy, Mich.) will be placed in the autoclave next to the ^{157}Dy citrate vial. (A temperature chart will be made a part of the records.) Following autoclaving a portion of the preparation will be withdrawn for a pyrogenicity test (standard USP methods), radioassay (sodium iodide crystal calibrated with NBS standards) and verification of sterility (standard USP methods for radiopharmacy records). The vial of ^{157}Dy citrate will then be labeled as to its contents.

Preparation of each batch of ^{157}Dy citrate will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized. Each batch of ^{157}Dy citrate will be given a batch number and all particulars relative to its preparation and use will be entered in a master log book.

6. STATEMENT ON INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations:

1. Tissue distribution:

Recent reports (1-3) have indicated that the higher-atomic-number rare earth radionuclides show an affinity for nonosseous tumor tissue. R. L. Hayes and ORAU associates have confirmed these results in animals (4) and we now propose to investigate these radionuclides in patients at ORAU Medical Division. This application deals only with ^{157}Dy.

Prior to clinical trials we have studied those factors that influence the distribution of this group of radionuclides in both normal and tumor-bearing animals. Figure 1 shows a histogram of the distribution of various high-specific-activity rare earth radionuclides in liver, bone, and 5123C Morris hepatomas. As has previously been

reported (5), there was a dramatic decrease in the concentration of the rare earths in liver as the atomic number of the nuclides increased. At the same time the concentration in the 5123C hepatoma increased markedly. Table 1 shows the results of this study in a more detailed form. Also shown in Table 1 are the average results obtained for ^{67}Ga with this model tumor system.

Of the higher-atomic-number rare earth radionuclides that might be used for tumor scanning, three are particularly suited for this purpose (^{157}Dy, ^{167}Tm, and ^{171}Er). Their properties are shown in Table 2. Although ^{157}Dy and ^{171}Er would be produced by neutron activation of the stable elements, they could be produced with very high specific activities (mCi/μg). The relatively short half lives of both ^{157}Dy and ^{171}Er do not constitute a problem since the tissue distribution of the higher-atomic-number rare earth radionuclides is essentially complete by 4 hours (Table 3)

From Table 1 it is apparent that radionuclides of dysprosium, thulium, erbium, and ytterbium compare favorable with ^{67}Ga with respect to the tumor-to-nontumor ratios obtained in rats bearing Morris 5123C hepatomas. A further comparison of ^{67}Ga with a rare earth radionuclide (^{169}Yb) in other tumor systems is shown in Table 4. Again, as with the 5123C hepatoma, the absolute concentration of ^{67}Ga was better than that of ^{169}Yb in tumor tissue except in Erhlich ascites (EA) cells where the ^{169}Yb concentration was $\sim$3 times greater than that of ^{67}Ga. Tumor-to-nontumor ratios were, however, approximately the same (except for EA cells). It would thus appear on the basis of this data that rare earth radionuclides might show as high a relative affinity for tumor tissue in human subjects as does ^{67}Ga (6).

It is apparent, however, that rare earth radionuclides concentrate to a much greater extent in bone (and kidney) than does ^{67}Ga, and this may obscure tumor visualization where sites of tumor are under or adjacent to the skeleton. On the other hand, lesions in the bone (both primary and metastatic) should be more readily visualized with rare earth radionuclides than they are with ^{67}Ga. Another advantage of the rare earth radionuclides indicated in Table 2 is that their energies are suitable for use with the gamma camera. Visualization of ^{67}Ga with the camera is poor compared to that obtained with rectilinear systems.

An important requirement for the effective use of rare earth radionuclides for tumor detection will be the use of high-specific-activity preparations. Table 5 shows the rather extreme effect that the simultaneous administration of stable erbium (at the milligram level) had on the tissue distribution of ^{171}Er in rats bearing 7777 hepatomas. The concentration of ^{171}Er in liver and spleen was greatly increased while that in the tumor was correspondingly lowered. Even at a microgram level of stable erbium administration there was a rather dramatic increase in the concentration of ^{171}Er

1048589

in liver and spleen above ∿10 μg Er/kg; the tumor concentration was not affected, however (Table 6). Similar effects were seen with ^{159}Dy (used as tracer for ^{157}Dy). It thus will be important to use carrier-free or high-specific-activity preparations of the rare earth radionuclides in tumor scanning procedures.

The studies discussed above involved administration of rare earth radionuclides in the citrate form at a dose level of 1 mg citrate/kg. Table 7 shows the effect of other forms on the distribution of ^{167}Tm in rats bearing 7777 hepatomas. NTA and HEIDA gave approximately the same tissue distribution patterns as did the citrate while gluconate was somewhat poorer in tumor specificity. HEDTA, a strong chelate, greatly decreased the concentration of ^{167}Tm in tumor tissue and also produced much poorer tumor-to-nontumor ratios (particularly for the spleen, kidney, and blood). Citrate is thus the preferable form for the administration of rare earths, since it is a normal metabolite.

A study has been made of the effect produced by an increase in the citrate dosage on ^{167}Tm tissue distribution. No effect on tumor concentration of ^{167}Tm was observed with a citrate dose as high as 20 mg/kg. There was also no change in the tumor-to-nontumor ratios except for slight increases for spleen and blood.

As with ^{67}Ga the tissue distribution of the higher-atomic-number rare earth radionuclides (as represented by ^{170}Tm) is affected by both sex (Table 8) and age (Table 9). The differences in tissue distribution produced by differences in sex and age were not as pronounced as those seen with ^{67}Ga; however, the differences were highly significant.

2. Toxicity:

The toxicity of the rare-earth metals is low to intermediate, the reported I.P. LD_{50} in rats and mice for dysprosium chloride and nitrate ranging from 295 to 585 mg Dy/kg (7). There is no data available on the toxicity of dysprosium in humans, but stable terbium has been administered to humans at a level of 2.4 mg Tb per dose (∿34 μg Tb/kg) without any symptoms of toxicity (8). The intravenous toxicity of the rare earths decreases with increasing atomic number (9), and, since terbium is directly below dysprosium in the rare earth series, dysprosium should be tolerated by man as well, if not better, than is terbium.

Hepatosplenic degeneration from repeated large doses of rare earths in animals is seen only with the lower-atomic-number rare earths (7). Fatty liver infiltration in the rat from mg/kg doses of rare earths is not seen above samarium in the rare earth series (10).

Certain rare earth salts were used as anticoagulants in Europe during the 1940's and occasionally hemoglobinuria was produced. These were observed at doses of 5-8 mg/kg; slight transient elevations of plasma hemoglobin were occasionally noted at dose levels of 1-2 mg/kg (11).

1048590

Based on these observations in animals and humans, it is anticipated that the related administration of stable dysprosium together with ^{157}Dy at the level proposed (not to exceed 10 μg Dy/kg) would produce a minimal hazard for the subjects receiving dysprosium-157 citrate for tumor localization. The ORAU Committee on Human Studies has approved the use of ^{157}Dy citrate as outlined in this application.

3. Radiation Dosimetry:

The radiation hazard associated with the administration of ^{157}Dy would also be minimal. Its half life is short (8.2 hr). Also it decays by electron capture and has only a minor amount of associated particulate radiation. Table 10 shows the estimated human whole body radiation dose and dose to various organs per millicurie of administered ^{157}Dy. The dose figures in parentheses are those for the maximum admount of activity that will be administered (17.5 mCi in a 70 kg subject). These radiation dose figures and those below were calculated by the ORAU Radiation Dosimetry Group (R. J. Cloutier and E. E. Watson) by extrapolation from tissue distribution data obtained in the rat at 24 hours for maximum organ uptake.

Dysprosium-157 decays to ^{157}Tb which has a half life of 150 yr. ^{157}Tb decays by electron capture emitting only gadolinium X rays. Complete decay of 1 mCi of ^{157}Dy will produce only 6×10^{-3} μCi of ^{157}Tb. The maximum permissible body burden for ^{157}Tb is estimated to be 150 μCi. Any radiation dose resulting from the generation of this daughter radionuclide can therefore be disregarded.

Dysprosium-165 will be a short lived (2.4 h) contaminant in the ^{157}Dy preparation (see section 4). It is anticipated that the earliest possible time that ^{157}Dy citrate can be administered will be 9 hours after removal from the reactor (because of required processing, transportation, preparation, and pyrogen testing). At this earliest administration time each mCi of ^{157}Dy will be associated with 3.5 μCi of ^{165}Dy or 61 μCi for a 17.5 mCi dose of ^{157}Dy. It is estimated that 1 μCi of ^{165}Dy would produce a dose of only 1×10^{-4} rad to the bone, the critical organ for dysprosium. The dose from the ^{165}Dy contamination present can thus be disregarded.

Another slight contaminant, ^{159}Dy, will also be present (see section 4). Since it has a half life of 144 days, it will increase in concentration relative to the ^{157}Dy present in the preparation as the ^{157}Dy decays. We do not anticipate administering ^{157}Dy citrate at a period of much longer than 24 hours after removal from the reactor and certainly not after 36 hours, simply because of production and decay economics. At the 36-hour period each mCi of ^{157}Dy would be associated with approximately 0.07 μCi of ^{159}Dy and a 17.5 mCi dose of ^{157}Dy would contain 1.2 μCi of ^{159}Dy. It is estimated that 1 μCi of ^{159}Dy would yield a radiation dose of 0.15 rad to the bone.

1048591

It is apparent from the above considerations that the radiation dose from the ^{157}Dy citrate preparation when used as proposed will be well within acceptable radiation limits. The ORAU Medical Radionuclide Committee has accordingly approved the use of ^{157}Dy citrate.

b. Previous Marketing:

This drug has not previously been marketed but it has been investigated in humans as a bone scanning agent (8, 12).

c. Drug Combination:

Dysprosium-157 (III) citrate is not a combination of previously investigated or marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The investigators preparing and administering this drug are working in close collaboration at the same institution. Therefore, no formal informational material will be prepared.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See biblographical material in the appendix about Drs. Edwards, Hübner, Goswitz, Vodopick, and Hayes (ORAU), and Poggenburg (ORNL).

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by C. L. Edwards, R. L. Hayes, J. K. Poggenburg, and the sponsor, Gould A. Andrews, M.D., with advice from the ORAU Program Review Committee and the ORAU Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phases I and II, Clinical Pharmacology, in this study will consist of observations on the metabolism and toxicity of ^{157}Dy citrate together with preliminary observations on its tumor-localizing properties. C. L. Edwards, M.D., will be in charge of this clinical investigation.

Patients (30) will be known to have cancer. They will be adults recruited from among our clinical patients and from patients in the Oak Ridge Hospital and surrounding hospitals. Informed consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducements will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the study with no promise of continued medical care at ORAU, and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU.

The principal questions to be answered (during a one year period) are:

1. Is there any unsuspected toxic effect of dysprosium on humans at the dose levels proposed?

2. Will the uptake of ^{157}Dy in human tumors be sufficient to permit tumor detection by scanning?

3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{157}Dy in humans?

4. What is the optimum dose and scanning time?

While it is not anticipated that there will be any toxic effect of dysprosium at the doses to be used in this study, the patients will be observed closely for any unanticipated untoward effects. Particular attention will be given to looking for an effect on the clotting mechanism, because of the known anticoagulant effect of some of the rare earth elements.

To determine the optimum time for scanning and to obtain data for more precise radiation dose estimates, blood levels and whole body counts will be monitored at frequent intervals from multiple blood samples and linear profile scans. All urine and fecal excreta will be collected for 48 hours after dosing and the radioactivity measured by well counting.

The optimum dose for scanning will be determined from data obtained with the use of multiple imaging devices (Anger camera and rectilinear scanners), with scans made at different time intervals.

Should the results of this study be encouraging, a subsequent proposal and application will be filed for clinical trials involving comparison with other tumor detecting techniques.

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{157}Dy citrate prior to 30 days after the date of receipt of the notice by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

References

1. Higasi, T., Ito, K., Tobari, H., and Tomura, K. On the accumulation of rare earth elements in animal tumor. Int. J. Nucl.Med. & Biol. 1: 101-103, 1973.

2. Hisada, K. and Ando, A. Radiolanthanides as promising tumor scanning agents. J. Nucl.Med. 14:615-617, 1973.

3. Hisada, K., Tonami, N., Hiraki, T., and Ando, A. Tumor scanning with ^{169}Yb-citrate. J. Nucl.Med. 14:772-773, 1973.

4. Hayes, R.L. and Byrd, B.L. Factors influencing the distribution of rare earth radionuclides in normal and neoplastic tissue. S. Med. J. 66:1327, 1973, abstr.

5. Durbin, P.W. Metabolic characteristics within a chemical family. Health Physics 2:225-238, 1960.

6. Hayes, R.L. and Edwards, C.L. New applications of tumor-localizing radiopharmaceuticals. In "Medical Radioisotope Scintigraphy 1972", Vol. II, pp. 531-551, International Atomic Energy Agency, Vienna, 1973.

7. Haley, T. J. Pharmacology and toxicology of the rare earth elements. J. Pharm. Sciences 54:663-670, 1965.

8. Yano, Y., Van Dyke, D.C., Verdon, T.A., Jr., and Anger, H.O. Cyclotron-produced ^{157}Dy compared with ^{18}F for bone scanning using the whole-body scanner and scintillation camera. J. Nucl. Med. 12:815-821, 1971.

9. Bruce, D.W., Hietbrink, B.E., and DuBois, K.P. The acute mammalian toxicity of rare earth nitrates and oxides. Toxic Appl. Pharmacol. 5: 750-759, 1963.

10. Snyder, F., Cress, E.A., and Kyker, G.C. Liver lipid response to intravenous rare earths in rats. J. Lipid Res. 1:125-131, 1959.

1048594

11. Beaser, S.B., Segel, A., and Vandam, L. The anticoagulant effects in rabbits and man of the intravenous injection of rare earths. J. Clin. Invest. 21:447-454, 1942.

12. O'Mara, R.E. and Subramanian, G. Experimental agents for skeletal imaging. Seminars Nucl. Med. 2:38-49, 1972.

1048595

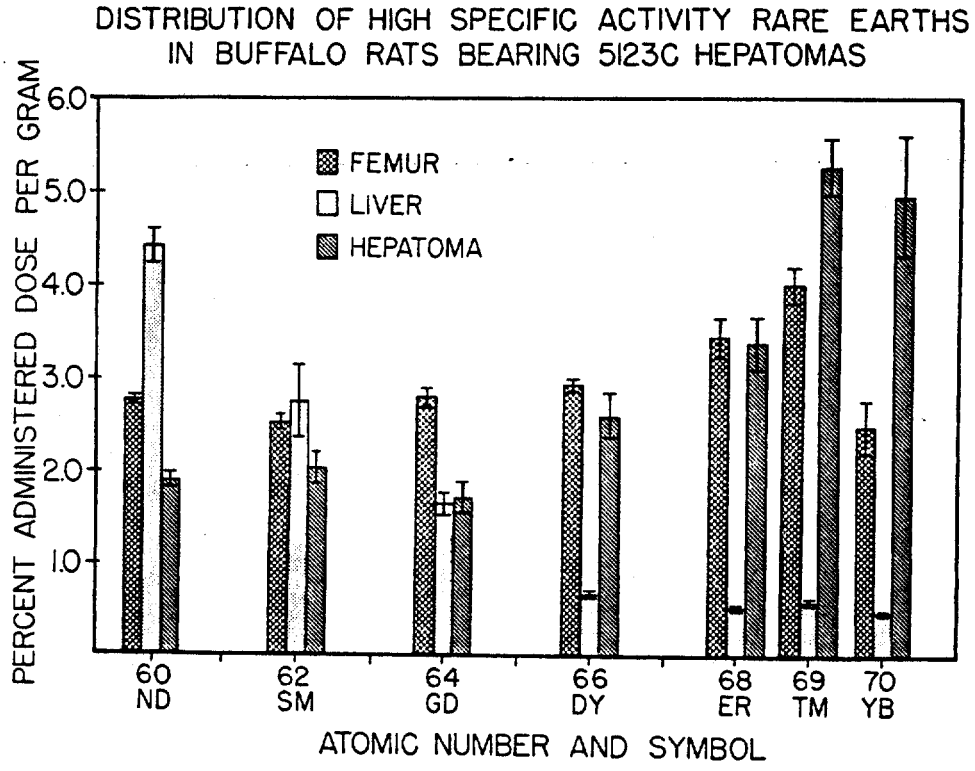


Fig. 1

1048596

TABLE 1

TISSUE DISTRIBUTION OF RARE EARTH ISOTOPES (24 HR) IN RATS BEARING 5123C HEPATOMAS*

Isotope	^{147}Nd	^{153}Sm	^{153}Gd	^{159}Dy	^{171}Er	^{170}Tm	^{169}Yb	^{67}Ga
Atomic Number	60	62	64	66	68	69	70	31
Tumor conc. (%/g)	1.9	2.0	1.7	2.6	3.3	4.3	4.9	9.3
Ratio tumor conc. to:								
Liver	0.4	0.7	1.0	4.0	6.7	10.0	11.0	20.0
Spleen	2.2	6.4	2.5	3.4	6.3	7.5	6.3	8.0
Kidney	0.6	0.5	0.7	1.4	2.1	3.0	4.8	17.0
Lung	6.5	6.4	6.5	13.0	19.0	27.0	25.0	48.0
Muscle	100.0	85.0	110.0	160.0	180.0	120.0	150.0	82.0
Femur	0.7	0.8	0.6	0.9	1.0	1.1	2.0	13.0
Marrow	12.0	9.6	7.4	9.4	12.0	15.0	7.6	8.7
Blood	89.0	76.0	53.0	76.0	120.0	230.0	100.0	150.0

* Groups of 4 animals each.

1048597

TABLE 2

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β^-	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

TABLE 3

INFLUENCE OF TIME ON TISSUE DISTRIBUTION OF ^{171}ER AND ^{169}YB IN RATS BEARING 5123C HEPATOMAS

Isotope	Erbium-171			Ytterbium-169	
Time	2 h	4 hr	24 h	4 h	24 h
Tumor conc. (%/g)*	3.3	4.5	3.4**	3.5	4.9**
Ratio tumor conc. to:					
Liver	5.0	5.6	6.7	7.9	11.0
Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
Femur	1.5	1.4	1.0	2.1	2.0
Marrow	7.2	10.1	12.5	5.9	8.0
Blood	6.2	19.0	130.0	9.9	110.0

* Percent administered dose/g normalized to body weight of 250 g.

** Not significantly different from 4 hour value.

1048598

TABLE 4

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}YB AND ^{67}GA (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

1048599

TABLE 5

EFFECT OF ERBIUM CARRIER ON THE DISTRIBUTION OF ^{171}ER (24 hr) IN THE RAT

Tissue	∿ C.F.	Carrier (mg/kg) 0.1	0.5	1.0
	% Administered Dose/g			
Liver	0.50	3.40	8.00	10.00
Spleen	0.24	0.76	1.60	4.80
Kidney	1.30	3.00	1.40	1.00
Lung	0.19	0.20	0.33	0.64
Muscle	0.02	0.02	0.02	0.01
Femur	4.50	2.61	1.40	1.10
Marrow	0.26	0.56	1.30	2.00
Blood	0.01	0.03	0.13	0.18
Tumor	2.30	1.60	0.88	0.44

TABLE 6

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

TABLE

TISSUE DISTRIBUTION OF ^{167}TM (24 HR) IN RATS BEARING 7777 HEPATOMAS WHEN ADMINISTERED INTRAVENOUSLY IN VARIOUS FORMS*

Tissue/Ratio	Form				
	Gluconate	Citrate	NTA	HEIDA	HEDTA
Tumor (%/g)	2.70	3.20	2.70	2.70	0.17
Ratio tumor conc. to:					
Liver	3.10	7.50	6.90	6.40	2.30
Spleen	3.30	6.10	4.40	4.80	0.44
Kidney	2.60	3.00	3.30	3.40	0.53
Muscle	160	170	140	210	110
Femur	1.10	1.30	1.10	1.10	0.88
Femoral marrow	6.50	8.00	6.70	6.10	4.90
Blood	150	150	140	120	19.0

* 5.2 μM/kg; 4 animals per group.

TABLE 8

TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE AND FEMALE FISCHER RAT*

Tissue	Sex		Significance
	Male	Female	P
	% Administered dose/g**		
Liver	0.74	0.56	0.001 - 0.01
Spleen	0.57	0.31	<0.001
Kidney	0.62	0.52	0.02
Lung	0.13	0.11	-
Muscle	0.03	0.02	<0.001
Femur	5.00	4.30	<0.001
Marrow	0.33	0.22	-
Blood	0.02	0.01	<0.001

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

1048601

TABLE 9

EFFECT OF AGE ON THE TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE BUFFALO RAT*

Tissue	Age		Significance
	2 months	5 months	P
	% Administered dose/g**		
Liver	0.36	0.48	<0.001
Spleen	0.19	0.29	<0.001
Kidney	0.76	2.10	<0.001
Lung	0.14	0.29	<0.001
Muscle	0.02	0.04	<0.001
Femur	4.60	4.30	<0.05 >0.02
Marrow	0.26	0.38	<0.01 >0.001
Blood	0.01	0.02	<0.001
Avg. wt.	190	370	

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

TABLE 10

ESTIMATED HUMAN RADIATION DOSE FROM ^{157}DY IN RAD PER MILLICURIE BASED ON RAT TISSUE DISTRIBUTION DATA

Organ	Rad/mCi
Total Body	0.065 (1.1)*
Liver	0.14 (2.4)
Kidneys	0.17 (3.0)
Spleen	0.11 (1.9)
Skeleton**	0.14 (2.4)
Marrow	0.12 (2.1)

* Values in parentheses are the doses in rads for the maximum activity dose to be administered to a 70 kg subject (17.5 mCi).

** Skeleton = bone + marrow.

1048602

APPENDIX

Chief Investigators:

C. L. Edwards, M.D.
R. L. Hayes, Ph.D.
J. K. Poggenburg, Jr., Ph.D.
F. A. Goswitz, M.D.
K. F. Hübner, M.D.
H. V. Vodopick (Goswitz), M.D.

ORAU Committee on Human Studies:

Gould A. Andrews, M.D.
Chairman, ORAU Medical Division

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

C. Lowell Edwards, M.D.
Chief of Clinical Services
ORAU Medical Division

Melvin E. Koons
Law Department (Y-12 Plant)
Union Carbide Corporation
Oak Ridge, Tennessee

Robert D. Lange, M.D.
Assistant Director
U. T. Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Bill M. Nelson, M.D.
Pathologist, ORAU Medical Division

John B. Storer, M.D.
Scientific Director for Pathology & Immunology
Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

1048603

Program Review Committee:

John G. Conniglio, Ph.D.
Professor, Dept. of Biochemistry
Vanderbilt University Medical School
Nashville, Tennessee 37203

Jane F. Desforges, M.D.
Tufts University Hematology Laboratory
Boston City Hospital
818 Harrison Avenue
Boston, Mass. 02118

R. J. M. Fry, M.D.
Division of Biological and Medical Research
Argonne National Laboratory
Argonne, Illinois 60439

Robert H. Greenlaw, M.D.
Marshfield Clinic
Marshfield, Wisconsin 54449

Leonard A. Sagan, M.D.
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Laboratory of Genetics
University of Wisconsin
Madison, Wisconsin 53706

1048604

BIOGRAPHIES

Name: Gould A. Andrews
Position: Internist, Chairman, Medical Division, ORAU
School: University of Michigan, A.B., 1940
University of Michigan, M.D., 1943
Licensure: Tennessee
Board: Internal Medicine
Memberships: Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club.

Name: A. Bertrand Brill
Position: Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine.
School: Grinnell, A.B., 1949
University of Utah, M.D., 1956
University of California, Berkeley, Ph.D., 1961
Licensure: Tennessee
Memberships: American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association
Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name: John G. Coniglio
Position: Professor of Biochemistry, Vanderbilt School of Medicine
School: Furman, B.S., 1940
Vanderbilt, Ph.D., 1949
Memberships: AAAS; Inst. Nutrit; Oil Chem. Soc.; Soc. Biol. Chem.
Other Indication of Experience and Competence:
Specialist in lipid chemistry.

Name: Jane Fay Desforges
Position: Associate Professor, School of Medicine, Tufts University
School: Wellesley College, B.A., 1942
Tufts University, M.D., 1945
Memberships: Associate Editor, New England Journal Medicine, 1960-; Amer. Fed. Clin. Res.; Amer. Soc. Hemat.; Amer. Soc. Exp. Path. Hemat.

1048605

Name: C. Lowell Edwards
Position: Chief of Clinical Research, Medical Division, ORAU
Schools: Manchester College, A.B., 1950
Indiana University, M.D., 1954
Licensure: Tennessee, Indiana
Board: Internal Medicine
Memberships: Roane-Anderson County Medical Society, Tennessee Medical Association, American Medical Association, Society of Nuclear Medicine, American Association for the Advancement of Science, New York Academy of Sciences.

Name: Richard Jeremy Michael Fry
Position: Senior Scientist, Argonne National Laboratory
Schools: University of Dublin, B.A., 1946
University of Dublin, M.D., 1962
Memberships: Radiation Research Society, American Association Cancer Research, Reticuloendothelial Society

Name: Francis A. Goswitz
Schools: Marquette University, Premedical, B.S., 1952
Marquette University School of Medicine, M.D., 1956
Positions: Intern, University of Iowa Hospitals, 1956-57
Resident, Internal Medicine, University of Iowa Hospitals, 1957-58
Internist, U. S. Army Hospital, Fort Campbell, Ky. 1958-60
Fellow, Nuclear Medicine, ORAU Medical Division, 1960-61
Research Associate, Hematology, University of Utah, 1963-65
Clinician and Coordinator, Medical Radioisotope Courses, ORAU Special Training Division, 1965-68
Senior Clinician and Clinical Research Investigator, ORAU Medical Division, 1968 to present
Interests: Malignant disease, hematology and nuclear medicine
Hematology: chemotherapy of leukemias and lymphomas cytokinetics and cytochemistry of blood cells, iron metabolism
Nuclear Medicine: Uses of radioisotopes in cancer, biological effects of irradiation.

1048606

Name: Helen Vodopick Goswitz
Positions: Internship, University Hospitals, University of Iowa, 1956-57
Residency in Internal Medicine, University Hospitals, 1957-60
Post-residency Fellow in Nuclear Medicine, ORAU Medical Division, 1960-61
Instructor, Internal Medicine and Hematology, Fellow, University of Iowa, 1961-63
Research Associate in Hematology, University of Utah, 1963-65
Assistant Clinican and Head of Clinical Hematology Laboratory, ORAU Medical Division, 1965 to present
Schools: Marquette University, B.S., 1949-1953
Marquette University School of Medicine, M.D., 1952-56
Board: Internal Medicine, 1966
Interests: Hematology: Leukokinetics, especially of "myeloproliferative diseases
Immunology: Histocompatability testing - current work involves in vitro mixed leukocyte cultures
Nuclear Medicine: Liquid scintillation spectrometry and autoradiography in relation to the above two areas of interest.

Name: Robert H. Greenlaw
Position: Physician at Marshfield Clinic, Marshfield, Wisconsin
School: Tufts, B.S., 1948
Rochester, M.D., 1952
Memberships: Amer. Cancer Soc.; Member Med. Adv. Cmt, AEC; Amer. Med. Association; Col. Radiol.; Association Univ. Radiol.; Society of Nuclear Medicine.
Interests: Development of radioisotopes for diagnosis and therapy; radiation biology; clinical development in radiation therapy.

Name: R. L. Hayes
Position: Senior Scientist in charge of medical radioisotope development.
Schools: University of North Carolina, B.S., 1944
University of North Carolina, Ph.D., 1952
Positions: Senior Chemist, U. S. Rubber Co., North Carolina, 1944
U. S. Army, 1944-46
ORAU Medical Division, 1950 - present
Memberships: American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society.
Interests: Development of medical radioisotopic agents; radiation dosimetry.

1048607

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies, (now Oak Ridge Associated Universities) 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961. Admitted to practice of law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966.
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommmittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A. Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	Amer. Assoc. Adv. Sci.; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology, etc.

1048608

Name:	Thomas A. Lincoln
Position:	Director, Health Division, ORNL
School:	Macalester College, B.A., 1946 University of Minnesota, B.S., 1947; B.M., 1949; M.D., 1950 Rotating Internship, Ancker Hospital, St. Paul, Minn. 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, 1963
Memberships:	Fellow, Industrial Medical Association; Tenn. Indust. Med. Assoc.; Amer. Acad. Occupational Med.; AMA; Roane-Anderson County Med. Soc.; Oak Ridge Regional Mental Health Center.

Name:	Bill Nelson
Position:	Research Pathologist
Schools:	University of Kansas, A.B., 1948 University of Chicago, School of Medicine, M.D., 1952
Licensure:	Tennessee
Board:	American Board of Pathology
Memberships:	Amer. Med. Assoc.; Amer. Soc. Clin. Path.; Reticuloendothelial Soc.; Society of Nuclear Medicine; Tennessee Assoc. Pathology

Name:	J. K. Poggenburg, Jr.
Position:	Research Staff, Biomedical Radioisotopes Group, Oak Ridge National Laboratory
Schools:	College of the Holy Cross, Worcester, Mass., B.S., 1956 University of California, Berkeley, Ph.D. - Nuclear Chemistry
Memberships:	Amer. Chem.Soc.; Society of Nuclear Medicine; Sigma Xi.

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fel. American College of Physicians.
Interests:	Late effects of radiation.

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; Amer. Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science.
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance.

1048609

Name:	John B. Storer
Position:	Scientific Director for Pathology and Immunology, Biology Division, Oak Ridge National Laboratory
Schools:	University of Chicago, M.D., 1947
Memberships:	American Association Cancer Research; Amer. Soc. for Exper. Path.; Radiation Res. Soc.; SEBM; Nat. Council on Radiation Protection and Measurements

1048610

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-14

DESCRIPTION: ^{111}In-chloride for tumor imaging. Activities ranging from 350 to 1250 microcuries will normally be administered. This radiopharmaceutical is used under an IND with FDA. A package insert supplied by New England Nuclear is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			8 Feb 74
R. L. Hayes	RLH			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048611

12/73

B. Package Insert Information - Indium-111

1. Name: Indium-111 Chloride (0.45 to 0.9%) in saline solution (pH adjusted to 1 to 3 by addition of HCl) for intravenous injection.

2. Description: This solution contains no-carrier-added Indium-111 chloride in 0.45 to 0.9% saline solution whose pH has been adjusted to 1 to 3 by addition of HCl. Each ml of solution contains 2 mCi (±20%) of Indium-111 less than 2 μCi of Indium-114m and less than 10 μgm of Cadmium at calibration time (calibration time stated on lead shield and vial label). Indium-111 has a physical half life of 2.8 days and decays by electron capture emitting 173 KeV (89% abundant and 247 KeV (94% abundant) gamma rays and characteristic x-rays of Cadmium.

3. Actions (Clinical Pharmacology): Intravenously administered no-carrier-added Indium-111 chloride binds to plasma transferrin, the specific plasma iron binding protein (1). Thus, its initial distribution space is the intravascular space and its plasma clearance half life in man is 6 to 10 hours (1, 2). Subsequent to clearance of activity from plasma approximately one-third accumulates in the bone marrow and one-third in the liver(3). In one study 11% of the administered dose was excreted in the urine and 4% in the feces within ten days after its administration (4).

Lilien, et. al. recently reported evidence suggesting that no-carrier-added Indium-111 concentrated in erythroid precursors in the bone marrow (3). This conclusion was independently reached by Farrer, et. al. (5). Lilien, et. al. found Indium-111 uptake in reticulocytes comparable to that of radioiron and found that radioindium accumulation in human bone marrow could be abrogated by 400 to 800 rads radiation exposure while radiocolloid uptake in such marrow was minimally disturbed. They referred to data in the literature which indicates that once associated with erythroid precursors, Indium appears to be bound to heme. Upon consideration of the biological and physical characteristics they conclude that all of these properties of Indium-111 chloride make it a theoretically ideal bone marrow imaging agent.

Indium-111 Chloride has been used successfully to find tumors scintigraphically (2, 5).

Dosimetry calculations were made by Dr. L.S. Graham of UCLA using the absorbed dose fraction method. Assuming an infinite biological half-life and the in vivo distribution given above, the following absorbed radiation dose estimates were obtained for a standard man.

Organ	Absorbed Dose rads/mCi
Marrow	2.4
Liver	4.5
Total Body	0.5 (gonadal dose is considered equal to whole body dose)
Uterus	0.3

4. Indications: Bone marrow scintigraphy and scintigraphic localization of soft tissue tumors.

5. Contraindications: Indium-111 chloride should not be administered to patients in whom the possible risks of exposure to ionizing radiation outweigh the benefits anticipated from performance of the study.

6. Warnings: The fetus and young child appear to be more susceptible to leukemia-induction by ionizing radiation than the adult. Consequently Indium-111 chloride should not be administered to pregnant females or patients under 18 years of age unless exceptional indication exists for performing the studies involving this radionuclide.

7. Precautions: The use of Indium-111 chloride does not involve any unique hazards. The precautions associated with the use of this material are the same as those associated with the use of any radioactive material with similar physical properties. Appropriate procedures should be used to ensure minimum radiation exposure to the patient and all attending personnel.

1048612

8. Adverse Reactions: Although no adverse reactions are anticipated from use of this product there are no assurances that they will not occur.

9. Dosage: The dosage of Indium-111 chloride for bone marrow scintigraphy should be minimized consistent with the requirements of the study, the instrumentation to be used and the patient's age, size and pathology. Lilian, et. al. used two to five millicuries in their studies. We recommend that no more than 2 mCi be given to adults weighing 70 kgm or more and proportionately less for lighter people. Bone marrow scintigraphy and scintigraphic imaging of soft tissue tumors should be performed 24 to 72 hours after intravenous administration of Indium-111 chloride.

10. Clinical Studies: Bone marrow uptake following intravenous administration of Indium chloride is well known. Lilien et. al. and Farrer, et. al. showed that this uptake was due to accumulation in non-reticuloendothelial cells within the bone marrow.

The presently available clinical studies indicate that Indium-111 chloride administered intravenously is useful in imaging the erythropoietic organ. The clinical significance of erythropoietic organ imaging has been previously demonstrated by scintigraphy with radioisotopes of iron. These studies showed that in normal adults the preponderance of erythropoietic marrow is located in the vertebra, pelvis, proximal femurs and humeri, sternum, ribs and scapulae. In young children and in disease processes where there is extension of erythropoietic bone marrow, sites of erythropoiesis may be seen around the knees (distal femur and proximal tibia) ankles (distal tibia) and elbows (distal femur and proximal radius and ulna). Erythropoiesis in irradiated bone may be temporarily suppressed by several hundred rad and is permanently suppressed by several thousand rad.

11. How Supplied: Indium-111 chloride in acidified 0.45 to 0.9% saline solution (pH 1 to 3) for intravenous injection is prepared according to appropriate manufacturing methods to be sterile and pyrogen free. The product is supplied in 3 ml vials. The specific concentration is 2 mCi/ml at calibration time and each vial contains 1 to 2½ ml as stated on the vial and lead shield label. No preservatives are added.

12. Decay Data (Standard Dosage):

Time from Calibration (Hours)	Specific Concentration of In-111 (mc/ml)	Time from Calibration (Hours)	Specific Concentration of In-111 (mc/ml)
-24	2.56		
-20	2.46		
-16	2.35		
-12	2.27	-72	4.08
- 8	2.17	-48	3.28
- 4	2.07	-24	2.56
0	2	0	2
4	1.92	24	1.56
8	1.84	48	1.22
12	1.76	72	.98
16	1.70		
20	1.62		
24	1.56		

13. References:

1. Wochner, R. D., Adetepe, M., Van Amberg, A. and Potchen, E. J. A new method for estimation of plasma volume with the use of the distribution space of Indium-113m transferrin. The Journal of Laboratory and Clinical Medicine, Vol. 75, No. 5, pp 711-720, May, 1970.

2. Goodwin, D. A., Goode, R., Brown, L. and Imbornone, C. J. ^{111}In-labeled transferrin for the detection of tumors. Radiology, Vol. 100, No. 1, pp 157-179, July, 1971.

1048613

3. Lilien, D.L., Berger, H.G., Anderson, D.P. and Benett, L.R. Indium-111 Chloride: A new agent for bone marrow imaging. Presented in part at the Works in Progress Section, 19th Annual Meeting. Society of Nuclear Medicine, Boston, July 14, 1972.

4. Graham, L.S., ^{111}InCl Dosimetry, private communication.

5. Farrer, P.A., Saha, G.B. and Shibata, H.N. Evaluation of ^{111}In-transferrin as a tumor scanning agent in humans. Journal of Nuclear Medicine, Vol. 13, No. 6, p 429, June 1972.

medi+physics

5855 CHRISTIE AVENUE
EMERYVILLE, CALIFORNIA 94608
(Home Office) — San Francisco Area
(415) 658-2184

1048614

Indium-111 Chloride

Sterile Apyrogenic Aqueous Solution for Intravenous Injection.
Read package insert for ingredients, preparation and dosage information.
CAUTION: New Drug – limited by Federal (USA) law to investigational use.

CAUTION
RADIOACTIVE
MATERIAL

medi+physics Emeryville, Calif. 94608

LABORATORY FACILITIES

SAN FRANCISCO
5855 Christie Avenue
Emeryville, California 94608
(415) 658-2184

LOS ANGELES
1141 Air Way
Glendale, California 91201
(213) 245-5751

CHICAGO
9820 West Bryn Mawr
Rosemont, Illinois 60018
(312) 671-5444

NEW YORK & NEW JERSEY
900 Durham Road
South Plainfield, New Jersey 07080
(201) 757-0500

MPI 9

1048615

New England Nuclear

INDIUM-III CHLORIDE

NAME: Indium-III Chloride for Intravenous Administration.

DESCRIPTION: Indium-III Chloride in 0.05 N hydrochloric acid solution is available in single dose vials containing 3 mCi.

Carrier-free Indium-III, a cyclotron produced product, offers a favorable long-lived complement to Indium-113m with identical chemistry for the study of slow biological processes when observation periods of 24-72 hours after administration are necessary. Indium-113m has a limited application to rapid physiological studies that can be imaged within a maximum of 4-8 hours because of its short half-life (1.66 hours).

Indium-III has very favorable physical decay characteristics for in vivo studies. It decays by electron capture with a physical half-life of 67.7 hours, emits no beta particles and has favorable gamma energies (173, 247 KeV) for use with imaging equipment.

Indium-III injected intravenously at acid pH binds quantitatively to transferrin, competing with iron for the same binding sites. Reported average plasma disappearance half-life values range from 4-16 hours. Little is excreted (In one study 11% in urine and 4% in feces by 10 days) and its tissue retention half-life is much longer than its physical half-life.

According to Lilien (2) transferrin-bound indium is transported into erythroid precursors in a manner similar if not identical to iron. Earlier preliminary work had demonstrated minimal indium uptake by mature red cells and had further indicated that only cell-associated indium appeared to be bound to heme. The similarities of indium and iron suggest that indium is actually incorporated into the metalloporphyrin in the place of iron.

There is no evidence in the literature as noted by Lilien (3) to suggest that Indium-III injected at acid pH behaves as a colloid. Accumulation in marrow then, would depend upon blood flow. It is well known that alteration in hepatic or splenic blood flow produces marked alteration in marrow colloid distribution and further that phagocytic and hematopoietic marrow may not always parallel each other.

INDICATIONS: Indium-III Chloride may be useful for soft tissue tumor localization, evaluation of radiation therapy, delayed brain scanning, visualization of the lymphatic system, blood pool scanning, and especially useful in visualizing bone marrow and other hematopoietic disorders.

At this stage, indications for use are under investigation and critical reports of potential utility beyond those listed above are appearing with greater frequency in the medical literature.

1048616

TOXICITY: Indium has an I.V. LD_{50} in rats of 4.1 mg/Kg (1). The maximum recommended dose of approximately 5 mCi of carrier-free indium corresponds to 12 nanograms of material.

In a long term study on indium, Usher, et al (4), found that rats which received 670 µg/Kg of indium showed loss of weight and a decrease in blood total protein and alkaline phosphate levels. However, he observed no significant physiological, biochemical or histopathologic changes in rats 6 months after the injection of up to 67 µg/Kg of indium, far more than 30 thousand times the single dose of indium used in routine imaging procedures.

CLINICAL STUDIES: Goodwin, et al (5), used Indium-111 for lymph node visualization. They concluded that this technique should offer a simple clinical method of studying quantitatively the kinetics of lymph flow, notably from subcutaneous sites but also from various organs such as the thyroid gland and liver. Indium-111 is an ideal radionuclide for the study of other slow biological events such as radioisotope cisternography with the Anger gamma camera.

Hunter (6) found that Indium-111 appeared to localize in both benign and malignant tumors. In addition, treated lesions were imaged with Indium-111 over a period of 72 hours and were indicated by reduced activity concurrent with other sites of previous malignant disease which demonstrated marked accretion. These findings suggest that Indium-111 Chloride might provide practical evaluation of drug or radiation therapy in cancer patients.

Initial findings suggest that Indium-111 Chloride can serve as a tracer of the exchangeable bone-salt pool during the first 24 hours after injection, thus localizing neoplastic disease which involves the skeleton (6).

After 24 hours, Indium-111 showed an affinity for bone marrow. Lilien, et al (2) reported that Indium-111 appears to be the current bone marrow imaging agent of choice because it does not behave as a colloid, eliminating many of the objections raised with currently available agents and its similarity to iron in disposition leads to a more realistic picture of actual hematopoietic marrow distribution.

CONTRAINDICATIONS: There are no currently known contraindications to the use of Indium-111 Chloride for diagnostic imaging.

WARNING: Pregnant and lactating women should be excluded from studies. Care should be exercised in the use of this radionuclide in children under 18 years of age.

Radiopharmaceuticals should be used only by qualified physicians trained in the use and safe handling of radioisotopes. These physicians must either be approved by the appropriate Federal or State Agency authorized to license the use of radioisotopes or conduct their investigations in institutions already licensed in the use of radioisotopes.

PRECAUTIONS: Indium-111 Chloride should be administered intravenously and slowly. Blood should not be withdrawn into the syringe prior to injection, as it may lead to the formation of an in vitro colloid.

ADVERSE REACTIONS: To date, no adverse reactions have been cited in the cases reported in the medical literature or to New England Nuclear.

DOSIMETRY: Current calculations on dosimetry are as follows:

Total Body	0.39 Rads/mCi
Kidney	5.21 Rads/mCi
Liver	1.76 Rads/mCi
Bladder	3.26 Rads/mCi
Gonads	0.74 Rads/mCi
Marrow (non-penetrating)	3.60 Rads/mCi*

These results will be updated as additional data become available.

DOSAGE: Average dose of Indium-111 is 3 mCi, although it may range from 0.03 to a maximum of 0.07 mCi/Kg, administered intravenously. The maximum dose of about 5 mCi per patient will reduce imaging time because of higher photon yield. Preliminary data indicates that a 48 hour wait prior to imaging is optimal. In many cases, imaging at daily intervals for periods up to 5 days may be advisable.

HOW SUPPLIED: Indium-111 Chloride in 0.05 N hydrochloric acid solution is available in single dose vials containing 3 mCi on the day of calibration. It is sterile and non-pyrogenic.

CAUTION: This product is for intravenous administration only.

Indium-111 Decay Factor

Time from Calibration (Hours)	Decay Factor	Time from Calibration (Hours)	Decay Factor
-72	2.09	4	0.96
-48	1.63	8	0.92
-24	1.28	12	0.88
-20	1.23	16	0.85
-16	1.18	20	0.81
-12	1.13	24	0.78
- 8	1.09	48	0.61
- 4	1.04	72	0.48
- 0	1.00		

* Calculated by Lilien and Graham (2).

1048617

74

References

1. Downs, W.L., Scott, J.F., Steadman, L.T., et al. The toxicity of indium. Office of Technical Services, Commerce Dept., Washington, D. C.

2. Lilien, D. L., Berger, H. G., Anderson, D. P., et al. ^{111}In-Chloride: A new agent for bone marrow imaging. J. Nucl. Med. 14: 184-6 (1973).

3. Lilien, D. L., and Bennett, L. R. A comparison of the uptake and disposition of radioiron and ^{111}In-chloride in human erythrocytes. J. Nucl. Med. 13: 786-7 (1972).

4. Usher, M. W., Westerman, B. R., Ammerman, E. G., et al. Long term effects of indium in rats. J. Nucl. Med. 11: 155-7 (1970).

5. Goodwin, D. A., Finston, R. A., Colombetti, L. G., et al. ^{111}In for imaging: Lymph node visualization. Radiology 94: 175-8 (1970).

6. Hunter, W. W. and Riccabona, X. J. Clinical evaluation of ^{111}In for localization of recognized neoplastic disease. J. Nucl. Med. 11: 328-9 (1970).

7. Goodwin, D. A., Gaade, R., Brown, L., et al. ^{111}In-labeled transferrin for the detection of tumors. Radiology 100: 175-9 (1971).

8. Farrer, P. A., Saha, G. B. and Shibata, H. N. Evaluation of ^{111}In-transferrin as a tumor scanning agent in humans. J. Nucl. Med. 13: 429 (1972).

New England Nuclear
Radiopharmaceutical Division
Atomlight Place, North Billerica, Mass. 01862
Telephone (617) 667-9531

NRP-130P 1073 2MS-601R Printed in U.S.A.

INDIUM-III CHLORIDE

NAME: Indium-III Chloride for Intravenous Administration.

DESCRIPTION: Indium-III Chloride in 0.05 N hydrochloric acid solution is available in single dose vials containing 3 mCi.

Carrier-free Indium-III, a cyclotron produced product, offers a favorable long-lived complement to Indium-113m with identical chemistry for the study of slow biological processes when observations periods at 24-72 hours after administration are necessary. Indium-113m has a limited application to rapid physiological studies that can be imaged within a maximum of 4-8 hours because of its short half-life (1.66 hours).

Indium-III has very favorable physical decay characteristics for in vivo studies. It decays by electron capture with a physical half-life of 2.82 days, emits no beta particles and has favorable gamma energies (173, 247 KeV) for use with imaging equipment.

Indium-III injected intravenously at acid pH binds quantitatively to transferrin, competing with Iron for the same binding sites. Reported average plasma disappearance half-life values range from 4-16 hours. Little is excreted (in one study 11% in urine and 4% in feces by 10 days) and its tissue retention half-life is much larger than its physical half-life.

According to Lilien (26A) transferrin-bound Indium is transported into erythroid precursors in a manner similar if not identical to Iron. Earlier preliminary work had demonstrated minimal Indium uptake by mature red cells and had further indicated that once cell-associated Indium appeared to be bound to heme. The similarities of Indium and Iron suggest that Indium is actually incorporated into the metalloporphyrin in the place of Iron.

1048619

There is no evidence in the literature as noted by Lilien (15) to suggest that Indium-111 injected at acid pH behaves as a colloid. Accumulation in marrow then, would depend upon blood flow. It is well known that alteration in hepatic or splenic blood flow produces marked alteration in marrow colloid distribution and further that phagocytic and hematopoietic marrow further may not always parallel each other.

INDICATIONS: Indium-111 Chloride may be useful for soft tissue tumor localization, evaluation of radiation therapy, delayed brain scanning, visualization of the lymphatic system, blood pool scanning, and especially useful in visualizing bone marrow and other hematopoietic disorders.

At this stage indications for use are under investigation and critical reports of potential utility beyond those listed above are appearing with greater frequency in the medical literature.

TOXICITY: Indium has an I.V. LD_{50} in rats of 4.1 mg/Kg (1). The maximum recommended dose of approximately 5 mCi of carrier-free Indium corresponds to 12 nanograms of material.

Rats which received 670 μg/Kg of Indium showed loss of weight and a decrease in blood total protein and alkaline phosphate levels.

In a long term study on Indium, Usher, et al (5), found no significant physiological, biochemical or histopatholgic changes in rats 6 months after the injection of up to 67 μg/Kg of Indium, far more than 30 thousand times the single dose of Indium used in routine imaging procedures.

CLINICAL STUDIES: Goodwin, et al (19), used Indium-111 for lymph node visualization. They concluded that this technique should offer a simple clinical method of studying quantitatively the kinetics of lymph flow, notably from subcutaneous site but also from various organs such as thyroid gland and liver. The radionuclide Indium-111 is an ideal label for the study of other slow biological events such as radioisotope cisternography with the Anger gamma camera.

Hunter (20) found that Indium-III appeared to localize in both benign and malignant tumors. In addition, treated lesions were imaged with Indium-III over a period of 72 hours and were indicated by reduced activity concurrent with other sites of previous malignant disease which demonstrated marked accretion. These findings suggest that Indium-III Chloride might provide practical evaluation of drug or radiation therapy in cancer patients.

Initial findings suggest that Indium-III Chloride can serve as a tracer of the exchangeable bone-salt pool during the first 24 hours after injection, thus localizing neoplastic disease which involves the skeleton (20).

After 24 hours, Indium-III showed an affinity for bone marrow. Lilien, et al (26A) reported that Indium-III appears to be the current bone marrow imaging agent of choice because it does not behave as a colloid, eliminating many of the objections raised with currently available agents and its similarity to Iron in disposition leads to a more realistic picture of actual hematopoietic marrow distribution.

WARNING: Pregnant and lactating women should be excluded from studies.

Radiopharmaceuticals should be used only by qualified physicians trained in the use and safe handling of radioisotopes. These physicians must either be approved by the appropriate Federal or State Agency authorized to license the use of radioisotopes or conduct their investigations in institutions already licensed in the use of radioisotopes.

PRECAUTIONS: Indium-III Chloride should slowly be administered intravenously. Blood should not be withdrawn into the syringe prior to injection, as it may lead to the formation of an in vitro colloid.

ADVERSE REACTIONS: To date, no adverse reactions have been cited in the cases reported in the medical literature or to New England Nuclear

DOSIMETRY: Current calculations on dosimetry are as follows:

Total Body	0.39 Rads/mCi
Kidney	5.21 Rads/mCi
Liver	1.76 Rads/mCi
Bladder	3.26 Rads/mCi
Gonads	0.74 Rads/mCi

These results will be updated as additional data become available.

DOSAGE: Average dose of Indium-III is 3 mCi although it may range from 0.03 to a maximum of 0.07 mCi/Kg, administered intravenously. The maximum dose of about 5 mCi per patient will reduce imaging time because of higher photon yield. Preliminary data indicates that a 48 hour wait prior to imaging is optimal. In many cases, imaging at daily intervals for periods up to 5 days may be available.

HOW SUPPLIED: Indium-III Chloride in 0.05 N hydrochloric acid solution is availabel in single dose vials with specific concentration of 3 mCi/1-1/2 ml on the day of calibration.

CAUTION: This product is for intravenous administration only.

1048622

DECAY DATA (Standard Dosage)

Time from Calibration (Hours)	Specific Concentration of In-111 (mc/ml)	Time from Calibration (Hours)	Specific Concentration of In-111 (mc/ml)
-72	4.08	4	1.92
-48	3.26	8	1.84
-24	2.56	12	1.76
-20	2.46	16	1.70
-16	2.35	20	1.62
-12	2.27	24	1.56
-8	2.17	48	1.22
-4	2.07	72	0.98
0	2.00		

3/73

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

IND 5489

FEB 27 1969

The Medical Division, Oak Ridge Associated Universities
Attention: Gould A. Andrews, M. D.
P. O. Box 117
Oak Ridge, Tennessee 37830

Gentlemen:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for the following:

Sponsor: The Medical Division, Oak Ridge Associated Universities

Name of drug: Gallium-67 Citrate

Date of notice: February 4, 1969

Date of receipt: February 11, 1969

Please identify all future communications concerning this Notice with the IND number shown above.

All submissions should be forwarded in triplicate.

As sponsor of the clinical study proposed in this exemption, you are now free to obtain supplies of the investigational drug and to initiate clinical studies. If deficiencies are found during our review of the information you have furnished, you will be notified and invited to make corrections.

The use of the assigned IND number may assist you in obtaining shipment of the drug from your supplier or in clearing import shipments through U.S. customs.

The interstate distribution of this drug for investigational use is subject to all of the applicable provisions of the Act and regulations.

1048624

This includes the immediate reporting of any alarming reaction in either animal or human studies and submission of progress reports at intervals not to exceed one year. A copy of the Investigational Drug Regulations is enclosed for your information.

Sincerely yours,

R. Barzilai

Enclosure

Raymond E. Barzilai, M. D.
Acting Director
Division of Oncology and
Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine

703-557-2464

1048625

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
WASHINGTON, D.C. 20204

FOOD AND DRUG ADMINISTRATION

IND: 5489

JUL 28 1969

The Medical Division, Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830

Attention: Gould A. Andrews, M.D.

Gentlemen:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Gallium-67 Citrate, IND 5489

We also acknowledge your communication dated April 3, 1969, amending the Notice.

Any data available (i.e. reprints) to support the safety of gallium citrate and explain its metabolism should be submitted for incorporation into the IND. Reports on the tumor studies in animals now in progress would also be useful to establish the safety of the proposed human trials.

The Notice is unsatisfactory in that it fails to contain a full statement of the components and quantitative composition of the drug and adequate information concerning the methods used in the synthesis, extraction, isolation, or purification of the new drug substance to determine its identity, strength, quality and purity.

The Notice is unsatisfactory in that it fails to contain complete information on the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

1048626

Included in whatever information you submit pertaining to the two paragraphs above, you should submit a description of how the isotope is made and also a statement of the total gallium in the final dosage form and possibly limits of acceptance for this area.

Your prompt attention to this matter is requested in order that your Notice may be in conformity with the provisions of section 130.3 of the New Drug Regulations.

Sincerely yours,

R. Barzilai

Raymond E. Barzilai, M.D.
Acting Director
Division of Oncology and
Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine

The reference to the communication dated April 3, 1969, amending the notice has to do with a special submission (not included here) providing that some doses of gallium-67 prepared for administration could be shipped to Donner Laboratory for studies employing their special scanning equipment.

1048627

OAK RIDGE ASSOCIATED UNIVERSITIES
INCORPORATED
P. O. BOX 117
OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-0411

October 20, 1969

Dr. Raymond E. Barzilai
Director,
Division of Oncology and Radiopharmaceuticals
Office of New Drugs, Bureau of Medicine
Consumer Protection and Environmental Service
Public Health Service
Department of Health, Education, and Welfare
Washington, D. C. 20204

Dear Doctor Barzilai:

In accordance with your letter of July 1969 concerning our IND 5489 we are submitting the following supplementary material:

1. Copies of articles from the literature concerning the toxicity and metabolism of gallium in both animals and humans.

2. Reprints of our recent publications concerning gallium distribution in and interaction with mammalian tissue.

3. A copy of a manuscript on the localization of gallium-67 in rat and mouse tumors that we have submitted for publication.

We trust that this material will satisfy your request for additional information as outlined in the third paragraph of your letter.

To overcome the objections to our application noted in paragraphs four and five of your letter, we are submitting herewith revised versions of sections 4 and 5 in Form FD-1571. These should be substituted for sections 4 and 5 in our original Notice of Clinical Investigational Exemption for Gallium-67

1048628

citrate. You will note that details are included on the preparation of gallium-67 and the amount of stable gallium present in patient doses of gallium-67 citrate as called for in paragraph six of your letter.

May we hope that this further information will place our Notice (IND-5489) in conformity with regulations.

Sincerely yours,

Gould A. Andrews

Gould A. Andrews, M.D.
Chairman,
The Medical Division

Enclosures:

Supplementary Material I. Papers on the toxicity and metabolism of gallium in animals and humans.

Supplementary Material II. Recent reprints on gallium tissue distribution and its interaction with mammalian tissue.

Supplementary Material III. Manuscript on localization of gallium-67 in rat and mouse tumors.

Amendment to FDA Form FD-1571 for IND-5489.

1048629

IND-5489 Supplementary Material I.

Papers on the toxicity and metabolism of gallium in animals and humans.

H. C. Dudley and Milton D. Levine. Studies of the toxic action of gallium. J Pharmacol Exp Therap 95:487-492, 1949.

H. C. Dudley, et al. Studies of the metabolism of gallium. J Pharmacol Exp Therap 96:135-138, 1949.

H. C. Dudley, et al. Studies of the metabolism of gallium. II. J Pharmacol Exp Therap 98:105-110, 1950.

H. C. Dudley, et al. Studies of the toxic action of gallium. II. J Pharmacol Exp Therap 98:409-417, 1950.

W. C. Mulry and H. C. Dudley. Studies of radiogallium as a diagnostic agent in bone tumors. J Lab Clin Med 37:239-252, 1951.

Frederick R. Lang. A study of the use of radioactive gallium in medicine. Ann Int Med 35:1237-1249, 1951.

E. R. King, et al. A preliminary report on the use of gallium^{72} in clinical tracer studies. Radiology 59:844-847, 1952.

H. C. Dudley and H. H. Marrer. Studies of the metabolism of gallium. III. Deposition in and clearance from bone. J Pharmacol Exp Therap 106:129-134, 1952.

E. R. King, et al. Therapeutic trials of radiogallium (Ga^{72}). Arch Int Med 785-789, 1952.

Marshall Brucer and Others. A study of gallium^{72}. Radiology 61:534-613, 1953.

IV. Toxicity of gallium citrate in dogs and rats. H. D. Bruner, B. M. Cooper, D. J. Rehbock, 550-555.

V. Distribution studies on gallium^{72} in rats. H. D. Bruner, J.D. Perkinson, J E. R. King, G. A. Andrews, J.B. Nash, and M. Brucer. 555-570.

VI. Clinical studies with gallium^{72}. G. A. Andrews, S. W. Root, and H. D. Kerman. 570-588.

VII. Studies of the urinary excretion of gallium^{72} in man. H. D. Bruner J. Gray, S. W. Root, and M. Brucer. 588-590.

VIII. Autopsy studies of distribution of gallium^{72}. M. Brucer, G. A. Andrews, D. J. Rehbock, S. W. Root, and J Gray. 590-595.

IX. Autoradiographic studies. J. C. Gallimore, Jr., G. A. Boyd, G. A. Andrews, and M. Brucer. 595-601.

X. Preliminary data on gallium^{67}. H. D. Bruner, R. L. Hayes, and J. D. Perkinson, Jr. 602-613.

OAK RIDGE ASSOCIATED UNIVERSITIES
INCORPORATED
P.O. BOX 117
Oak Ridge, Tennessee 37830

1048630

IND-5489 Supplementary Material II.

Recent reprints on gallium tissue distribution and its interaction with mammalian tissue.

IND-5489 Supplementary Material III

Manuscript on localization of gallium-67 in rat and mouse tumors.

R. L. Hayes, et al. Bone scanning with gallium-68: A carrier effect. J Nucl Med 6:605-610, 1965.

C. L. Edwards and R. L.Hayes. Tumor scanning with ^{67}Ga citrate. J Nucl Med 10:103-105, 1969.

R. E. Hartman and R. L. Hayes. The binding of gallium by blood serum. J Pharmacol Exp Therap 168:193-198, 1969.

R. M. Kniseley, et al. Bone-marrow and skeletal scanning. Radiologic Clinics of North America 7:265-280, 1969.

R. L. Hayes. Radioisotopes of gallium. IN Radioactive Pharmaceuticals, G. A. Andrews, R. M. Kniseley, and H. N. Wagner, Jr., Eds. AEC Symposium Series No. 6, CONF-651111, pp 603-618.

OAK RIDGE ASSOCIATED UNIVERSITIES
INCORPORATED
P.O. BOX 117
Oak Ridge, Tennessee 37830

1048631

IND-5489

Amendment to FDA Form FD-1571 for IND-5489

October 15, 1969

The following two sections should be substituted for Sections 4 and 5 of Form FD-1571.

4. Gallium-67 is the only new drug substance in the preparation. It is obtained from Oak Ridge National Laboratory (ORNL), Oak Ridge, Tennessee. They list the following product specifications: "Half-life: 78 hr; Production method: $^{68}Zn(p,2n)^{67}Ga$; Chemical form: $GaCl_3$ in dilute HCl; Concentration: ∿3 mCi/ml; Specific Activity: no added gallium carrier; Purity: >99% exclusive of ^{66}Ga."

The following details have been supplied by ORNL concerning their production and purification of ^{67}Ga: "Zinc cyclotron targets are fabricated in the form of tubes by extrusion using 99.99% pure natural zinc metal. After bombardment the center section (∿10 g) is cut from the zinc tube and dissolved in 5 *N* HCl. Titanous chloride solution (20%) is added dropwise (5 to 10 drops) to the acid solution of zinc until a permanent blue color is obtained (to insure a 2+ oxidation state of any iron present) and the gallium is extracted into three separate portions of 4-methyl-2-pentanone preequilibrated with 5 *N* HCl. The combined organic fractions are then washed three times with 6 *N* HCl (preequilibrated with organic phase) to remove the zinc either extracted by the organic solvent or dissolved in the acid and present in the organic phase. The gallium is stripped from the organic phase by shaking it with three separate portions of water. The combined aqueous phase containing the gallium is reduced in volume to about 5 ml and charged to a washed Bio-Rad AG-1 X2 (Bio-Rad Laboratories, Richmond, California) anion exchange column in the chloride form. Gallium is eluted from the column with 2 *N* HCl, while any trace of zinc is retained by the resin.

All of the radioactivity determinations are performed by the method described by Heath (Scintillation Spectrometry, 2nd ed., Vol. 1, USAEC Report IDO-16880-1, Idaho Operations Office, August 1964) using a 9.3-cm source distance from a calibrated 3x3-in. NaI(Tl) crystal detector coupled with a multichannel analyzer.

1048632

The ^{67}Ga is assayed using the 0.296 MeV photon (22 photons per 100 nuclear transformations). The contribution to the peak area from the 0.511 MeV annihilation photons of ^{66}Ga is substracted using a ^{22}Na ($\beta+$) source. The ^{66}Ga is assayed using the 0.511 MeV annihilation photon (114 photons per 100 nuclear transformations).

The purity of the gallium product is ascertained by examining the gamma spectrum using a 21-cm^3 active volume Ge(Li) detector coupled with a 4096-channel analyzer."

Because of its modest half-life (78 hr), the actual weight of gallium due to the presence of ^{67}Ga in this preparation will be negligible. On the other hand, in the process of chemical separation, any stable gallium present as a trace contaminant in the zinc target will of necessity be separated with the ^{67}Ga. Since the zinc used is 99.99% pure the maximum gallium contamination resulting from processing the bombarded zinc (10 g) would be approximately 1 mg. Assay by ORNL of the zinc used indicates a gallium contamination of only 10 parts per million thus limiting the amount of gallium present in the processed solution to 0.1 mg. The resulting concentration in the final preparation supplied by ORNL is thus approximately 4 μg/ml (25 ml batch volume). In actual practice the normal ^{67}Ga preparation for each patient will contain only approximately 10 μg (∿2.5 ml per patient dose). In view of the clinical experience detailed in the attached reprints (particularly reports of diagnostic use) it is considered that the administration of even the total amount of stable gallium present in any one batch (0.1 mg to 1.0 mg maximum) to a 70-kg human would be innocuous.

5. The initial ^{67}Ga and ^{66}Ga radioassay provided by ORNL will be checked on receipt of each new batch of ^{67}Ga by our Radiation Safety Office. The radiation spectrum will also be surveyed for any radioisotopic contaminants other than ^{66}Ga. Doses will not be prepared for human use until the ^{66}Ga level is less than 1% of the ^{67}Ga content on a disintegration basis. As a further safeguard, each dose will be assayed for radioactivity content by the ORAU Radiation Safety Office just before it is administered to a patient.

Although all doses will be terminally sterilized by microfiltration, each batch (∿25 ml) will on receipt be filtered through a sterile 0.22-micron Millipore Swinex-25 filter (#SXGS0250S, Millipore Corporation, Bedford, Massachusetts) into a sterile multientry vial. This vial will be labeled so as to identify the isotope, ORNL batch number, date, and radioassay of both ^{67}Ga and ^{66}Ga. This information will also be entered into a master log book on a separate page. Calculated volumes of ^{67}Ga solution for individual doses will be removed

using a sterile disposable syringe and hypodermic needle; the name of the patient, patient number, date, and volume removed will be recorded in the master log book on the page for that particular batch. In addition, non-radioisotopic ingredients in the final dose will also be recorded.

Each batch of ^{67}Ga will be tested on receipt for pyrogenicity using standard United States Pharmacopeia techniques (Seventeenth revision, 1965, p. 863). Preparation of all ^{67}Ga doses will be carried out in a recirculating laminar-flow clean-box (Abbott Clean Air Center, Model HR) equipped with an ultraviolet light for surface sterilization of equipment and containers. Except for a pH meter combination-electrode (Corning #476050, or equal) all glassware and equipment coming in contact with the preparation will be cleaned, packaged, and sterilized (autoclaved) between uses. The stem of the electrode will be stored in an aqueous 0.9% benzyl alcohol solution and will be repeatedly rinsed in sterile pyrogen-free distilled water just before use. Mock doses will be periodically prepared and tested for sterility and pyrogenicity. Doses will be routinely made up in excess so that 10% of the preparation can be held back for testing should there be any question of patient reaction to the dose.

The dose for each patient will be prepared individually as follows: A magnetically stirred (teflon-coated stirring bar) aqueous mixture of the required amounts of ^{67}Ga (5 mCi is usually less than 2.5 ml) and sterile pyrogen-free 4% sodium citrate solution (Baxter Laboratories, Morton Grove, Illinois, or equal) is brought to pH of 7.0 ± 0.2 by adding 1 *N* sodium hydroxide (prepared from reagent grade NaOH and sterile pyrogen-free distilled water) using the combination-electrode and pH meter. The resulting solution is drawn into a sterile pyrogen-free, disposable syringe (Becton-Dickinson and Co., Rutherford, New Jersey, or equal) using a sterile pyrogen-free disposable 3-way stopcock and tubing assembly (#2C0481, Travenol Laboratories, Morton Grove, Illinois, or equal) and filtered through an attached sterile disposable 0.22-micron Millipore Swinex-25 filter into a partially emptied 150-ml bottle of sterile, pyrogen-free 0.9% sodium chloride (#4124, Abbott Laboratories, North Chicago, Illinois, or equal) containing sufficient retained saline to make the final volume approximately 100 ml. The dose bottle will then be sealed with the original cap and the filter assembly bubble tested to check for leakage. The saline bottle will have been stored in the laminar-flow clean-box and uncapped just before filtration. The operator will wear sterile gloves during the entire preparation procedure.

A label identifying the preparation as to isotope, patient name, patient number, total volume, and assay will be attached to the container and the dose released to the Radiation Safety Office for transport to the administration site. There a final check of the dose will be made using a calibrated ionization chamber. All doses will be administered within one hour after preparation; if a longer waiting period is anticipated the preparation will be autoclaved. Doses will be administered to patients by slow intravenous infusion using disposable venoclysis sets (Abbott #4622 and #4613, or equal).

^{67}Ga CITRATE IND-8377

INFORMATION FOR INVESTIGATORS

PHASE III

INDICATIONS FOR USE: The attached sheet summarizing the informational material available to date outlines the major uses for gallium-67 citrate as a tumor imaging agent. The mechanism of localization is poorly known at present and many investigators are actively exploring the use of the radionuclide.

PRECAUTIONS, CONTRAINDICATIONS, ETC.: These are also outlined in the attachment. It should be noted that a significant portion of the administered dose is excreted via the feces and laxatives should be prescribed, not only to avoid interference in imaging abdominal areas, but also to lower the internal absorbed radiation dose to this area of the body.

GOVERNMENT REGULATIONS: The medical use of gallium-67 citrate is regulated by the Food and Drug Administration. It is necessary that each investigator maintain careful records for every patient receiving the drug. New England Nuclear is responsible for monitoring and retaining copies of this information for ultimate submission to the FDA. Copies of simplified case report forms will be supplied to each investigator and must be completed to account for each administered dose. These forms must be forwarded as they are completed to New

INFORMATIONAL MATERIAL

A. Name - Gallium-67, as the citrate, for intravenous administration.

B. Description - Gallium-67 citrate is supplied in isotonic solution as a sterile, non-pyrogenic radiopharmaceutical. It is cyclotron produced by the proton irradiation of enriched zinc oxide and is essentially carrier free. The only radionuclidic impurities seen in early product lots have been ^{66}Ga (less than 1%) and ^{65}Zn (less than 0.05%).

^{67}Ga decays by electron capture, emitting several gamma rays of moderate energy, suitable for camera imaging and rectilinear scanning. The moderately short half-life (78 hours) is sufficiently long to allow widespread distribution from a central manufacturing facility.

C. Actions (Clinical Pharmacology) - Carrier-free gallium-67 is presently under intensive investigation to determine the scope of utility in tumor imaging. The radionuclide appears to concentrate mainly in viable rather than necrotic tumor areas. The basic process appears to be binding, either to protein inside the tumor, or to a carrier that in turn concentrates there (1), but the precise mechanism of tumor concentration is not completely understood. It has been theorized that the bone seeking properties of gallium-67 are due to exchange for calcium in newly formed bone crystal (2).

1048637

centrate in human breast milk (12).

F. Warnings - As with most radiological procedures, the physician must weigh the relative value of the information to be obtained against the potential radiation damage to the fetus in pregnant women, to lactating women, or to children.

Radiopharmaceuticals should be used only by qualified physicians trained in the use and safe handling of radioisotopes. These physicians must either be approved by the appropriate Federal or State agency authorized to license the use of radioisotopes or conduct their investigations in institutions already licensed in the use of radioisotopes.

G. Precautions - Gallium-67 citrate should be administered intravenously, either directly or as part of a slow infusion diluted with isotonic saline.

Approximately 10% of the administered dose may be excreted via the feces over the first few days. In order to allow scanning in the abdominal area, a laxative should be administered on the day of dosing and continued daily until scans are completed. It may be desirable to administer an enema just prior to scanning in order to rid the bowel of radioactivity.

Langhammer, et al (10), have reported on 194 scans and found the highest incidence of positive gallium-67 accumulation in the RES diseases, in carcinomas of the bronchus, thyroid, and stomach, and in the demonstration of metastases. In some untreated categories, a high percentage of positive scintigraphic findings were reported. As a final example Winchell and his co-workers (11) summarized their results with 18 patients and suggested that gallium-67, among other carrier free chelated radionuclides, would prove effective in both the diagnosis of and, anatomical distribution of malignant neoplasms in humans.

K. How Supplied - Gallium-67 is supplied as the citrate complex in saline solution at from 0.5 to 5 mCi/ml in 10 ml multidose vials. The formulation contains 2 mg of sodium citrate per milliliter and sufficient sodium chloride to assure isotonicity. The pH is controlled to 4.5-7.5 and the formulation certified sterile and pyrogen-free.

M. References

1. 1969 Research Report, Medical Division, ORAU-110, pages 81-102.
2. Dudley, H.C., Imirie, G.W., and Istock, J.T., Deposition of radio-gallium (^{72}Ga) in proliferating tissues. Radiology, 55:571 (1950)
3. Edwards, C.L., Hayes, R.L., Nelson, B.M., and Tehranian, N. Clinical Investigation of ^{67}Ga for tumor scanning. Abstracted in J. Nucl. Med., 11:316 (1970)
4. Cloutier, R.J., Watson, E.E., Hayes, R.L., and Nelson, B. Radiation doses from isotopes of gallium. Abstracted in J. Nucl. Med., 12:348 (1971)
5. Popham, M.G., Taylor, D.M., and Trott, N.G. Evaluation of the dosimetry of intravenously administered ^{67}Ga-citrate from measurements of the distribution in male August-Marshall Hybrid Rats. Brit. J. Radiol., 43:807 (1970)
6. Nelson, B., Hayes, R.L., Edwards, C.L., et al. Distribution of ^{67}Ga in human tissues at autopsy, Abstracted in J. Nucl. Med., 12:452 (1971)
7. Edwards, C.L, and Hayes, R.L. ^{67}Ga for scanning and staging tumors. Abstracted in J. Nucl. Med., 12:355 (1971)
8. Edwards, C.L., and Hayes, R.L. Tumor scanning with gallium-67 citrate. J. Nucl. Med., 10:103 (1969)
9. 1970 Research Report, Medical Division, ORAU-113, pages 78-115.
10. Langhammer, H., et al. Cited from Duphar Isotips, Number 17.
11. Winchell, H.S., et al. Visualization of tumors in humans using ^{67}Ga-citrate and the Anger whole body scanner, scintillation camera and tomographic scanner. J. Nucl. Med., 11:459 (1970)
12. Larson, S.M., and Schall, G.L. Gallium-67 concentration in human breast milk. J. Am. Med. Assoc., 218(2):257 (1971)

NEN New England Nuclear
Radiopharmaceutical Division
Atomlight Place, North Billerica, Mass. 01862
Telephone (617) 667-9531

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-13

DESCRIPTION: ^{67}Ga-citrate for tumor imaging. Activities ranging from 1.5 to 5.0 millicuries will normally be administered. This radiopharmaceutical is used under an IND with FDA. A package insert supplied by New England Nuclear is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	[signature]			2/8/74
R. J. Cloutier	[signature]			2-8-74
C. L. Edwards	[signature]			8 Feb 74
R. L. Hayes	[signature]			2/8/74
C. C. Lushbaugh	[signature]			2/8/74

Acknowledgement of Submitter [signature] Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048641

12/73

74-13

New England Nuclear

GALLIUM-67 CITRATE

DESCRIPTION

Gallium-67 Citrate is supplied in isotonic solution as a sterile, non-pyrogenic radiopharmaceutical. The aqueous solution contains 3mCi ^{67}Ga-citrate per 1.5ml, adjusted to pH 4.5-7.5 and made isotonic with sodium chloride. It is cyclotron produced by the proton irradiation of enriched zinc oxide and is essentially carrier free. The only radionuclidic impurities seen in early product lots have been ^{66}Ga (less than 1%) and ^{65}Zn (less than 0.05%).

^{67}Ga decays be electronic capture, emitting several gamma rays of moderate energy, suitable for camera imaging and rectilinear scanning. The moderately short half life (78 hours) is sufficiently long to allow widespread distribution from a central manufacturing facility.

ACTIONS

Carrier free gallium-67 is presently under intensive investigation to determine the scope of utility in tumor imaging. The radionuclide appears to concentrate mainly in viable rather than necrotic tumor areas. The basic process appears to be binding, either to protein inside the tumor, or to a carrier that in turn concentrates there (1), but the precise mechanism of tumor concentration is not completely understood. It has been theorized that the bone seeking properties of gallium-67 are due to exchange for calcium in newly formed bone crystal (2). Recent investigations have pointed to the accumulation of ^{67}Ga in the lysosomes of white blood cells (13).

Gallium is excreted relatively slowly from the body. The average whole body retention is 65% after 7 days, with 26% being excreted in the urine and 9% in the stools (3). The dosimetry of gallium isotopes has been discussed by a few authors (4, 5). The whole body dose is approximately 0.18-0.34Rads/mCi. It has been noted, however, that the variable uptake within the body combined with the relative contribution from internal conversion and Auger electrons makes precise dosimetric evaluation difficult (6).

INDICATIONS

Imaging with radioactive gallium-67 appears to be useful in the staging of Hodgkin's disease. The isotope does not localize in malignancies in general but rather in tumors of specific cellular types. A relatively high percentage of positive scans have been seen with reticulum cell sarcoma, lymphoblastoma and squamous cell carcinoma of the lung (7). These same authors found false negative scans in cases of carcinoma of the ovary, colon, pancreas, and a variety of other malignancies. In addition ^{67}Ga may be particularly useful in delineating inflammatory processes and infections. In addition, pneumonia and tuberculosis may also be visualized.

At this stage, indications for use are under very intensive investigation and critical reports of the potential utility beyond those listed above are appearing with great frequency in the medical literature.

CONTRAINDICATIONS

To our knowledge, the only contraindication is restriction in

1048642

74-13

nursing women as gallium has been shown to concentrate in human breast milk (12).

WARNINGS

As with most radiological procedures, the physician must weigh the relative value of the information to be obtained against the potential radiation damage to the fetus in pregnant women, to lactating women, or to children.

Radiopharmaceuticals should be used only by qualified physicians trained in the use and safe handling of radioisotopes. These physicians must either be approved by the appropriate Federal or State agency authorized to license the use of radioisotopes or conduct their investigations in institutions already licensed in the use of radioisotopes.

PRECAUTIONS

Gallium-67 citrate should be administered intravenously, either directly or as part of a slow infusion diluted with isotonic saline.

Approximately 10% of the administered dose may be excreted via the feces over the first few days. In order to allow scanning in the abdominal area, a laxative should be administered on the day of dosing and continued daily until scans are completed. It may be desirable to administer an enema just prior to scanning in order to rid the bowel of radioactivity.

ADVERSE REACTIONS

None have been cited in the cases reported in the medical literature.

DOSAGE

Average doses of gallium-67 have ranged from 0.03 to 0.07 mCi/kg, administered intravenously. The higher dose of about 5mCi per patient will reduce scanning time because of higher photon yield. Preliminary data indicates that a 48 hour wait prior to scanning is optimal. In many cases, scans at later periods (72 hours up to 5 days) may be valuable.

CLINICAL STUDIES

In 1969, Edwards and Hayes published a paper showing uptake of carrier free ^{67}Ga citrate in certain soft tissue tumors (8). Since this report, laboratories throughout the world have begun intensive studies into the diagnostic utility of this radionuclide. To select some reports, Edwards and his co-workers summarized results with 78 patients with at least 20 different neoplasms (1) and showed that the poorly differentiated lymphomas, reticulum cell sarcomas and lymphoblastic lymphsarcomas concentrated the gallium consistently. In addition, concentration was observed in squamous cell carcinomas, some adenocarcinomas, and in Hodgkin's disease. By the following year, a total of 165 doses had been administered to 116 patients by this same Oak Ridge group (9) and the data refined to show that although gallium is extremely useful in tumor diagnosis, it does not localize in malignancies in general but rather in specific histological types.

Langhammer, et al (10), have reported on 194 scans and found the highest incidence of positive gallium-67 accumulation in the RES diseases, in carcinomas of the bronchus, thyroid, and stomach, and in the demonstration of metastases. In some untreated categories, a high percentage of positive

1048643

74-13

scintigraphic findings were reported. As a final example, Winchell and his co-workers (11) summarized their results with 18 patients and suggested that gallium-67, among other carrier free chelated radionuclides, would prove effective in both the diagnosis of and anatomical distribution of malignant neoplasms in humans.

Higasi, et al (14) performed scintiscans on 149 cases with a variety of malignant, benign, and inflammatory lesions. They noted, however, that ^{67}Ga-citrate accumulates in inflammatory and granulomatous lesions, thereby making the differentiation between malignant tumor and these two groups difficult.

DOSIMETRY

^{67}Ga decays with a physical half-life of 78 hours. The principle gamma emissions are 93 KeV (40%), 184 KeV (24%), 296 KeV (22%), 388 KeV (7%). Characteristic x-rays of zinc are also emitted.

	Cloutier's Values* Rads/mCi	NEN Values Rads/mCi
Whole Body	0.27	0.23
Skeleton	0.46	0.44
Liver	0.52	0.53
Gonads	–	0.22
Bone Marrow	0.56	–
Spleen	0.59	–
Kidney	0.48	–

*The radiogallium distribution and retention in various organs of the body has been described by Dr. Cloutier and his associates (4) in their dosimetry calculations.

DECAY DATA

Time from calibration (hours)	Specific Concentration ^{67}Ga(mCi/ml)
-72	3.81
-48	3.07
-24	2.48
-16	2.31
-8	2.14
0	2.00
8	1.86
16	1.73
24	1.61
48	1.30
72	1.05

HOW SUPPLIED

Gallium-67 citrate is supplied sterile and non-pyrogenic in containers for intravenous use. Each ml contains 2mCi of gallium-67 on the calibration date, 2mg sodium citrate, and 6.8mg of sodium chloride. The pH is adjusted to between 4.5-7.5 with either hydrochloric acid or sodium hydroxide solution. Benzyl alcohol 0.9% is added as a preservative.

REFERENCES

1. 1969 Research Report, Medical Division, ORAU-110, pages 81-102.
2. Dudley, H. C., Imirie, G. W., and Istock, J. T., Deposition of radiogallium (^{72}Ga) in proliferating tissues. Radiology *55*: 571 (1950).
3. Edwards, C. L., Hayes, R. L., Nelson, B. M., and Tehranian, N. Clinical Investigation of ^{67}Ga for tumor

1048644

scanning. Abstracted in J. Nucl. Med. 11: 316 (1970).
4. Cloutier, R. J., Watson, E. E., Hayes, R. L., and Nelson, B., Internal radiation doses to man from isotopes of gallium. Personal communication.
5. Popham, M. G., Taylor, D. M., and Trott, N. G. Evaluation of the dosimetry of intravenously administered ^{67}Ga-citrate from measurements of the distribution in male August-Marshall Hybrid Rats. Brit. J. Radiol., *43*: 807 (1970).
6. Nelson, B., Hayes, R. L., Edwards, C. L., et al. Distribution of ^{67}Ga in human tissue at autopsy. Abstracted in J. Nucl. Med., *12*: 452 (1971).
7. Edwards, C. L., and Hayes, R. L. ^{67}Ga for scanning and staging tumors. Abstracted in J. Nucl. Med. *12*: 355 (1971).
8. Edwards, C. L., and Hayes, R. L Tumor scanning with gallium-67 citrate. J. Nucl. Med. *10*: 103 (1969).
9. 1970 Research Report, Medical Divison, ORAU-113, pages 78–115.
10. Langhammer, H., et al. Cited from Duphor Isotips, No. 17.
11. Winchell, H. S., et al. Visualization of tumors in humans using ^{67}Ga-citrate and the Anger whole body scanner, scintillation camera and tomographic scanner. J. Nucl. Med., *11*: 459 (1970).
12. Larson, S. M., and Schall, G. L. Gallium-67 concentration in human breast milk. J. Am. Med. Assoc. *218*(2): 257 (1971).
13. Dr. Littenberg, Personal communication to NEN.
14. Higasi, T. and Nakayama, Y., et al. Clinical evaluation of ^{67}Ga-citrate scanning. J. Nucl. Med. *13*(3): 196–200 (1972).

GALLIUM-67 DECAY CHART
Half-Life – 78 Hours

HOURS	0	2	4	8	6
0	1.000	0.982	0.965	0.948	0.931
10	0.915	0.899	0.883	0.867	0.852
20	0.837	0.822	0.808	0.794	0.780
30	0.766	0.753	0.739	0.726	0.714
40	0.701	0.689	0.677	0.665	0.653
50	0.641	0.630	0.619	0.608	0.598
60	0.587	0.577	0.567	0.557	0.547
70	0.537	0.528	0.518	0.509	0.500
80	0.492	0.483	0.474	0.466	0.458
90	0.450	0.442	0.434	0.427	0.419
100	0.412	0.404	0.397	0.390	0.383
110	0.377	0.370	0.364	0.357	0.351
120	0.345	0.339	0.333	0.327	0.321
130	0.315	0.310	0.304	0.299	0.294
140	0.289	0.284	0.279	0.274	0.269
150	0.264	0.259	0.255	0.250	0.246
160	0.242	0.237	0.233	0.229	0.225
170	0.221	0.217	0.213	0.210	0.206
180	0.202	0.199	0.195		

New England Nuclear
Radiopharmaceutical Division
Atomlight Place, North Billerica, Mass. 01862

1048645

Original IND-5489

1. Name: gallium-67 citrate

   Route of Administration: intravenous

2. The preparation will contain the following components:

   (a) Trivalent gallium-67 (^{67}Ga)

   (b) Sodium citrate

   (c) Sodium chloride

   (d) Water

3. Quantitative composition (per dose):

   (a) Trivalent ^{67}Ga (half life 78 hr): up to 5 mCi/70 kg body weight

   (b) Sodium citrate: 7 mg/kg body weight

   (c) Sodium chloride: approximately 900 mg

   (d) Water: sufficient to bring final volume to 100 ml

If preclinical studies (animal tumors) now in progress indicate an advantageous effect, the sodium citrate dosage might reasonably be increased to a level of 20 mg/kg body weight. If, on the other hand, these studies indicate that lowering the citrate dosage below the proposed 7 mg/kg does not adversely effect tumor localization, the preparation will be adjusted accordingly.

4. Gallium-67 is the only new drug substance in the preparation. It is produced by proton bombardment of zinc at the Oak Ridge National Laboratory (ORNL), Oak Ridge, Tennessee, and is supplied to this installation as a dilute (~0.1N) HCl solution of carrier-free ^{67}Ga free of zinc and spectrometrically pure except for small amounts of gallium-66.

5. The initial radioassay provided by ORNL will be checked upon receipt of each batch of ^{67}Ga, and the ^{66}Ga (half life 9 hr) content of each batch will be determined spectrometrically. Doses will not be prepared for human use until the ^{66}Ga level is less than 1% of the ^{67}Ga content on a disintegration basis. As a further safeguard each dose will be assayed for radioactivity content by the ORAU Radiation Safety Office prior to its being given.

1048646

Although all doses are terminally sterilized by microfiltration, each batch upon receipt will be filtered through 0.22 micron sterile Millipore filter into a sterile multientry vial. Volumes of ^{67}Ga solution for individual doses will be removed using a sterile disposable syringe and hypodermic needle.

Each batch of ^{67}Ga will be tested upon receipt for pyrogenicity using standard United States Pharmacopeia techniques. Preparation of all ^{67}Ga doses will be carried out in a recirculating laminar flow clean box (Abbott Clean Air Center, Model HR). Except for a pH meter combination electrode (Corning #476050) all re-used glassware and equipment coming in contact with the preparation will be cleaned, packaged, and sterilized (autoclaved) between uses. The stem of the electrode will be stored in an aqueous 0.9% benzyl alcohol solution. It will be repeatedly rinsed in sterile pyrogen-free distilled water just prior to use. Mock doses will be periodically prepared and tested for sterility and pyrogenicity. Doses will be routinely made up in excess so that 10% of the preparation can be held back for testing should there be any question of a pyrogenic reaction.

The dose for each patient will be prepared individually as follows: A magnetically stirred aqueous mixture of the required amounts of ^{67}Ga (5 mCi is usually less than 5 ml) and sterile nonpyrogenic sodium citrate solution (either 2.5% Lilly or 4.0% Baxter) is brought to pH of 7.0 ± 0.2 by adding 1N sodium hydroxide using a combination electrode and pH meter. The resulting solution is drawn into a sterile, pyrogen-free, disposable syringe using a sterile, pyrogen-free disposable 3-way stopcock and tubing assembly, and filtered through an attached sterile disposable 0.22 micron Millipore Swinex-25 filter into a partially emptied 150 ml bottle of sterile, pyrogen-free 0.9% sodium chloride for injection (Abbott) containing sufficient solution to make the final volume approximately 100 ml. The filter assembly will then be bubble tested to check for leakage prior to release of the dose for administration.

6. (a) Previous studies at this installation with gallium radionuclides in both animals and humans with bone neoplasms have been reported in the open literature (Brucer, Marshall, et al., "A Study of Gallium^{72}," Radiology 61, 534-613, 1953). The tissue distribution of intravenously administered ^{67}Ga in animals bearing various soft tissue tumors has recently been studied. Table 1 (attached) shows the distribution in rats

bearing a transplanted poorly differentiated carcinoma. Table 2 (attached) shows the tissue distribution of intravenously administered carrier-free gallium radionuclides in the rat through a period of 17 days (5 half-lives of ^{67}Ga). The latter two investigations were conducted under the supervision of R. L. Hayes (biography attached). The Human Use Committee of the ORAU Medical Division has concluded that it is reasonably safe to initiate a clinical investigation with ^{67}Ga. (A list of members of this Committee and their biographies is attached.) No pharmacologic effect is expected from this drug preparation. The ^{67}Ga used will be carrier-free. The only chemically detectable ingredient in addition to the physiologic saline will be sodium citrate. The concentration of citrate present will be approximately that in stored blood treated with ACD solution as an anticoagulant.

(b and c) Do not apply.

7. All doses are to be prepared and used in the hospital of the ORAU Medical Division. After preparation each dose will be released directly to a member of the health physics staff who after assaying the dose will transport it to the attending physician and monitor the administration. A form will accompany the dose designating the dose in millicuries and in milliliters together with the patient's name and identification number.

8. The investigators are: (biographies are attached)

C. L. Edwards, M.D.
R. L. Hayes, Ph.D.
Ryosaku Tanida, M.D.
Helen A. Vodopick, M.D.
Francis Goswitz, M.D.
Nasser Tehranian, M.D.

9. The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by Gould A. Andrews, M.D., Chairman of the Medical Division (see biography) with advice from the Program Review Committee (see attached list and biographies), and the Human Use Committee.

10. This preparation is intended as a diagnostic aid to the clinician in locating neoplastic tumors, either primary or metastatic in soft tissue as well as the skeleton. Its efficacy will be judged solely on the basis of its localization in tumor tissue in sufficient concentration to permit visualization of tumor sites with clinical scanning equipment.

(a) Clinical Pharmacology. Being free of carrier gallium, the drug's only pharmacologically active ingredient is citrate,

which is not toxic in this amount. Slow infusion (15 to 20 minutes) will minimize any symptomatic hypocalcemia which may occur due to the temporary binding of ionized calcium by the citrate.

The radiation exposure resulting from the ^{67}Ga is expected to be less than 2.1 rads/mCi to the skeleton and less than 0.4 rads/mCi to the whole body; that from ^{68}Ga (see Section 5) will not exceed 0.05 rads/mCi to bone and 0.007 rads/mCi to the whole body. These figures assume the worst possible conditions, i.e., no excretion and 100% localization in the skeleton for the first figure and 100% uniform distribution with no excretion for the second. Animal data and earlier human data obtained with other isotopes of gallium indicate at least 40% excretion within the first half-life and no more than 50% localization in the skeleton. More precise human data for this preparation is unavailable but will be obtained from the initial patients.

Phase I, therefore, includes giving up to 5 mCi/70 kg body weight of the radiopharmaceutical to approximately 50 patients with known malignant neoplasms. Blood clearance, whole body retention, and urine and fecal excretion data will be compiled where possible for each patient. Differential counts over such organs as liver, spleen, heart, and thigh will be combined with serial profile scans to obtain more precise data regarding localization and hence the radiation dose to specific organs. Terminal patients will not be excluded from the study and data obtained from external counting will be supplemented with assay of tissues obtained at autopsy and surgery when available.

Phase II. The initial trials will be limited to patients with known malignant neoplasms that can be presumed to be life shortening, i.e., excluding curable skin cancers, carcinoma of the cervix, and other cancers believed to have been cured by excision. The objective of Phase II is finding which types of human neoplasms can be detected with this preparation and the limits of size, time, location, and other factors affecting the localization of this radionuclide in tumor tissue. Of particular interest are carcinoma of the lung and of the pancreas, as well as Hodgkin's disease and other lymphomas. We plan to study between 50 to 100 patients in a year, although more will be necessary to obtain all the data necessary to satisfy the major objectives of Phase II.

(b) Clinical Trial. It is understood that this application is for Phases I and II only and that a subsequent application

will be forthcoming prior to beginning Phase III which will extend these trials to patients suspected of having but not known to have cancer or other malignant tumors. Phase III will have to wait compilation of adequate evidence of safety from Phase I and sufficient evidence of efficacy from Phase II to justify exposure of patients not known to have a life-shortening disease to even this amount of radiation. Precise data regarding the radiation doses to internal organs must be made available to the Human Use Committee before the decision to go ahead with this phase is made.

Assuming the results of Phases I and II warrant extension to Phase III, the objective of Phase III will be to determine, 1) if a neoplasm is detectable by other means, e.g. coin lesions seen on chest X-ray, or a palpable breast tumor, can be distinguished from benign lesions; 2) if metastatic lesions not detected by X ray can be found prior to radical resectional surgery (e.g. radical mastectomy or pneumonectomy).

Appendix (not copied for present distribution) included names of Medical Division review committees with brief bibliographies of the members and also of the investigators on the gallium project.

1048650

Table 1

DISTRIBUTION OF GALLIUM-67 IN RATS WITH TRANSPLANTED POORLY DIFFERENTIATED CARCINOMA*

Tissue	Intraperitoneal Implant	Intramuscular Implant
	% Administered Dose/g	
Liver	1.03 ± 0.04**	1.04 ± 0.02
Spleen	1.49 ± 0.07	1.50 ± 0.05
Kidney	0.94 ± 0.04	0.90 ± 0.02
Lung	0.36 ---	0.35 ---
Muscle	0.27 ± 0.01	0.26 ± 0.01
Rib	2.26 ± 0.09	2.22 ± 0.23
Femur	1.93 ± 0.08	1.86 ± 0.05
Calvaria	0.92 ± 0.04	0.85 ± 0.01
Marrow	1.19 ---	1.00 ---
Blood	0.19 ± 0.01	0.23 ± 0.01
Tumor	8.20 ± 0.49	4.35 ± 0.29
Ratio Tumor to:		
Blood	43	19
Muscle	31	17
Liver	8	4
Bone	5	3

* Fischer rats; killed 24 hours; 7 mg Sodium citrate/kg; 5 animals per group.

** Standard Deviation of the mean

1048651

Tab 2

EFFECT OF TIME ON THE TISSUE DISTRIBUTION OF GALLIUM RADIONUCLIDES IN THE RAT

Tissue	Time After Intravenous Administration					
	2 Hours*	1 Day	3 Days*	5 Days	10 Days	17 Days
	% Administered dose/g					
Liver	0.33 ± 0.02**	0.61 ± 0.08	0.56 ± 0.06	0.50 ± 0.08	0.31 ± 0.03	0.20 ± 0.04
Spleen	0.55 ± 0.02	0.41 ± 0.08	0.59 ± 0.10	0.52 ± 0.07	0.59 ± 0.06	0.59 ± 0.11
Kidney	0.38 ± 0.02	0.53 ± 0.06	0.56 ± 0.03	0.57 ± 0.03	0.43 ± 0.02	0.28 ± 0.03
Lung	0.50 ± 0.04	0.21 ± 0.03	0.16 ± 0.03	0.14 ± 0.01	0.15 ± 0.03	0.12 ± 0.02
Muscle	0.20 ± 0.01	0.08 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.07 ± 0.02	0.04 ± 0.01
Rib	1.65 ± 0.08	3.45 ± 0.16	3.39 ± 0.18	2.44 ± 0.07	2.22 ± 0.20	1.93 ± 0.08
Femur	1.25 ± 0.02	2.49 ± 0.05	2.44 ± 0.09	2.31 ± 0.08	1.91 ± 0.10	1.70 ± 0.07
Calvaria	0.69 ± 0.03	1.39 ± 0.06	1.34 ± 0.08	1.30 ± 0.08	1.11 ± 0.09	1.13 ± 0.04
Marrow	--- 0.51	0.51 ± 0.06	0.38 ± 0.08	0.29 ± 0.01	0.32 ± 0.02	0.29 ± 0.06
Blood	1.22 ± 0.05	0.16 ± 0.02	0.03 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01

* 2 Hours - ^{68}Ga; 3 Days - ^{72}Ga; Other Groups ^{67}Ga; 2 Hours CFN Rats, Other Groups CDBS rats; 5 or more animals per group.

** Standard Deviation of the mean.

1048652

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-12

DESCRIPTION: ^{99m}Tc-pertechnetate for thyroid scanning. Activities ranging from 1 to 10 millicuries will normally be administered. This radiopharmaceutical is included in the AEC List of Well-Established Medical Uses. An FDA Sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical may/~~may not~~ be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			8 Feb 74
R. L. Hayes	R.L.H			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards, Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048653

74-12

FDA Sample Package Insert

SAMPLE LABELING

SODIUM PERTECHNETATE TC 99m INJECTION

DESCRIPTION

Sodium pertechnetate Tc-99m injection is available as a sterile, pyrogen-free isotonic sodium chloride solution which should be crystal clear. Hydrochloric acid or sodium hydroxide may be present for pH adjustment.

ACTIONS:

The pertechnetate ion distributes in the body similarily to the iodide ion but is not organified when trapped in the thyroid gland. Pertechnetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It also concentrates in thyroid gland, salivary glands, stomach and choroid plexus. After intravascular administration it remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

INDICATIONS

Sodium pertechnetate Tc-99m is used for brain imaging, thyroid imaging, salivary gland imaging, placenta localization and blood pool imaging.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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.

1048654

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by 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.

PRECAUTIONS

As in the use of any other 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.

At the time of administration the solution should be crystal clear.

AVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

Sodium pertechnetate Tc-99m is usually administered by intravascular injection but can be given orally. The dosage employed varies with each diagnostic procedure.

The suggested dose range employed for various diagnostic indications in average patient (70 kg) is:

brain imaging:	10 to 20 mCi
thyroid gland imaging	1 to 10 mCi
salivary gland imaging:	1 to 5 mCi
placenta localization:	1 to 3 mCi
blood pool imaging:	10 to 20 mCi

Note: Up to 1 gram of reagent grade potassium perchlorate in a suitable base or capsule may be given orally prior to administration of Sodium Pertechnetate Tc-99m injection for brain imaging, placenta localization and blood pool imaging.

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.

Table I. Principal Radiation Emission 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
Kα x rays	6.5	18.4

[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.

The specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half value layer is 4 mm of Pb.

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.

Table II. Physical Decay Chart; ^{99m}Tc, half life 6 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.779	5	.562
-4	1.587	6	.500
-3	1.414	7	.446
-2	1.260	8	.397
-1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

1048656

RADIATION DOSIMETRY

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 are shown in Table III. For placental localization studies when a maximum dose of 3 millicuries is used, it is assumed to be uniformly equilibrated between maternal and fetal tissues.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/20 mCi)	(rads/3 mCi)
Thyroid	12.0	
Large Bowel	2.94	
Stomach	2.14	
Liver	0.30	
Testes	0.27	
Ovaries	0.28	
Placenta		0.05
Fetus		> 0.05
Brain	0.24	
Whole-body	0.27	

[1]Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048657

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-11

DESCRIPTION: ^{99m}Tc-pertechnetate for brain scanning. Activities ranging from 10 to 20 millicuries will normally be administered. This radiopharmaceutical is included in the AEC List of Well-Established Medical Uses. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical may/~~may not~~ be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. C. Berger	[illegible]			2/8/74
R. J. Cloutier	[illegible]			2/8/74
C. L. Edwards	[illegible]			2/8/74
R. L. Hayes	[illegible]			2/8/74
C. C. Lushbaugh	[illegible]			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date Mar 5, 1974

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048658

12/73

74-11

FDA Sample Package Insert

SAMPLE LABELING

SODIUM PERTECHNETATE TC 99m INJECTION

DESCRIPTION

Sodium pertechnetate Tc-99m injection is available as a sterile, pyrogen-free isotonic sodium chloride solution which should be crystal clear. Hydrochloric acid or sodium hydroxide may be present for pH adjustment.

ACTIONS:

The pertechnetate ion distributes in the body similarily to the iodide ion but is not organified when trapped in the thyroid gland. Pertechnetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It also concentrates in thyroid gland, salivary glands, stomach and choroid plexus. After intravascular administration it remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

INDICATIONS

Sodium pertechnetate Tc-99m is used for brain imaging, thyroid imaging, salivary gland imaging, placenta localization and blood pool imaging.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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.

1048659

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by 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.

PRECAUTIONS

As in the use of any other 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.

At the time of administration the solution should be crystal clear.

AVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

Sodium pertechnetate Tc-99m is usually administered by intravascular injection but can be given orally. The dosage employed varies with each diagnostic procedure.

The suggested dose range employed for various diagnostic indications in average patient (70 kg) is:

brain imaging:	10 to 20 mCi
thyroid gland imaging	1 to 10 mCi
salivary gland imaging:	1 to 3 mCi
placenta localization:	1 to 3 mCi
blood pool imaging:	10 to 20 mCi

Note: Up to 1 gram of reagent grade potassium perchlorate in a suitable base or capsule may be given orally prior to administration of Sodium Pertechnetate Tc-99m injection for brain imaging, placenta localization and blood pool imaging.

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.

Table I. Principal Radiation Emission 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
Kα x rays	6.5	18.4

[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.

The specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half value layer is 4 mm of Pb.

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.

Table II. Physical Decay Chart: ^{99m}Tc, half life 6 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.779	5	.562
-4	1.587	6	.500
-3	1.414	7	.446
-2	1.260	8	.397
-1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

104861

RADIATION DOSIMETRY

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 are shown in Table III. For placental localization studies when a maximum dose of 3 millicuries is used, it is assumed to be uniformly equilibrated between maternal and fetal tissues.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/20 mCi)	(rads/3 mCi)
Thyroid	12.0	
Large Bowel	2.94	
Stomach	2.14	
Liver	0.30	
Testes	0.27	
Ovaries	0.28	
Placenta		0.05
Fetus		0.05
Brain	0.24	
Whole-body	0.27	

[1]Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048662

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-10

DESCRIPTION: ^{99m}Tc-sulfur colloid for liver and spleen scanning. Activities ranging from 1 to 8 millicuries will normally be administered. This radiopharmaceutical is included in the AEC List of Well-Established Medical Uses. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/5/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			8 Feb 74
R. L. Hayes	RLH			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048663

SAMPLE LABELING

TECHNETIUM Tc-99m SULFUR COLLOID

DESCRIPTION

The kit contains all of the non-radioactive reagents required to prepare a sterile, non-pyrogenic preparation of Tc-99m Sulfur Colloid suitable for direct intravenous injection. When sterile, pyrogen-free Sodium Pertechnetate Tc-99m is added to the reaction vial Technetium Tc-99m Sulfur Colloid is formed with the non-radioactive reagents.

ACTIONS

Following intravenous administration, Technetium Tc-99m Sulfur Colloid is rapidly cleared by the reticuloendothelial system from the blood with a nominal clearance half time of approximately 2 1/2 minutes. Uptake of the radioactive colloid by organs of the reticuloendothelial system is dependent upon both their relative blood flow rates and the functional capacity of the phagocytic cells. In the average normal patient 80 to 90% of the injected colloidal particles are phagocytized by the Kupffer cells of the liver, 5 to 10% by the spleen and the balance by the bone marrow.

INDICATIONS

Technetium Tc-99m Sulfur Colloid is used as an agent for imaging areas of functioning reticuloendothelial cells in the liver, spleen, and bone marrow.

CONTRAINDICATIONS

None.

WARNINGS

The contents of the two unit dose syringes, one syringe containing the appropriate acidic solution and the second syringe containing the appropriate buffer solution, are intended only for use in the preparation of the Tc-99m sulfur colloid and are not to be directly administered to the patient.

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc-99m is added, adequate shielding of the final preparation must be maintained.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by 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.

This radiopharmaceutical preparation should not be administered to patients who are pregnant or during lactation unless the benefits 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.

PRECAUTIONS

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 colloid.

The stability of the colloidal preparation may be decreased in the presence of polyvalent cations, thus resulting in the agglomeration of the individual colloidal particles. These larger particles are likely to be trapped by the pulmonary capillary bed following intravenous injection.

It is recommended that pertechnetate solutions containing more than 10 micrograms/ml of aluminum ion not be used for formation of the Technetium Tc-99m Sulfur Colloid.

Technetium Tc-99m Sulfur Colloid is physically unstable and as such the particles will settle with time. Failure to agitate the vial adequately before use may result in non-uniform distribution of radioactivity.

It is also recommended that because of the increasing probability of agglomeration with aging a batch of Technetium Tc-99m Sulfur Colloid not be used after six hours from the time of formulation.

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

ADVERSE REACTIONS

Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving sulfur colloid preparation. Although rare, pyrogen reactions have been reported following the administration of the drug stabilized with gelatin.

PREPARATION

The following directions must be carefully followed for optimum preparation of the Technetium Tc-99m sulfur colloid.

1. Aseptically inject 0.1-5.0 ml of sterile sodium pertechnetate Tc-99m, which must contain less than 10 micrograms of aluminum, into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air. Mix the solution.

2. Assemble the acid syringe and inject the total contents into the reaction vial with gentle agitation. Relieve the excess pressure by withdrawing an equal volume of air and remove the needle.

3. Immerse the reaction vial in a vigorously boiling water bath, deep enough to cover the entire liquid contents of the vial. Keep the vial in the water bath for 10 plus or minus 2 minutes.

4. Remove the vial from the water bath and place in a lead shield and allow to cool for 5 minutes.

5. Assemble the buffer syringe and aseptically inject the total contents into the reaction vial with gentle agitation. Reduce the pressure by withdrawing an equal volume of air.

6. Allow to cool to room temperature before use and then affix the descriptive label to the reaction mixture vial. Maintain adequate shielding of the radioactive colloid preparation. Do not use the preparation after 6 hours from the time of formulation.

7. The radioactivity concentration of the final Tc-99m Sulfur Colloid preparation may be calculated by using the following formula:

C = A/V where C equals radioactivity concentration of the sulfur colloid preparation (millicuries/ml)

A = Tc-99m activity added to the reaction mixture vessel (millicuries)

1048666

V = Total volume in the final maxture (ml).

DOSAGE AND ADMINISTRATION

The suggested intravenous dose range used in the average patient (70 kg) is 1 to 8 millicuries of Technetium Tc-99m sulfur colloid.

When orally administered, the technetium Tc-99m sulfur colloid is not absorbed from the G.I. tract.

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.

Table I. Principal Radiation Emission 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	[illegible]	121.7
K x rays	[illegible]	18.4

[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.

The specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half value layer is 4 cm of Pb.

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.

Table II. Physical Decay Chart; ^{99m}Tc, half life 6 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.779	5	.562
-4	1.587	6	.500
-3	1.414	7	.446
-2	1.260	8	.397
-1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 8 millicuries of ^{99m}Tc sulfur colloid are shown in Table III. For comparison, the estimated radiation doses from a maximum dose of 300 microcuries of colloidal ^{198}Au used as a liver imaging agent are also included.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/8 mCi ^{99m}Tc)	(rads/300 uCi ^{198}Au)
Liver	2.8	12.0
Spleen	1.2	6.2
Bone marrow	0.36	0.91
Testes	0.002	0.005
Ovaries	0.046	0.047
Whole-body	0.13	0.40

[1]Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

1048668

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-9

DESCRIPTION: ^{59}Fe as citrate, sulfate, or chloride for iron turnover studies. Activities ranging from 5 to 10 microcuries will normally be administered. This radiopharmaceutical is included in the AEC List of Well-Established Medical Uses. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			8 Feb 74
R. L. Hayes	RJH			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal does/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048669

12/73

FDA Sample Package Insert

SAMPLE LABELING

Ferrous Citrate Fe-59 Injection

DESCRIPTION

Ferrous Citrate Fe-59 Injection is a sterile, pyrogen-free aqueous solution containing 0.9% benzyl alcohol as a preservative. It is made isotonic with sodium chloride. Sodium hydroxide or hydrochloric acid may be present for adjustment of the pH. It contains trace amounts of ascorbic acid and not more than 0.5 mg/ml of sodium citrate as a buffer.

ACTIONS

Following injection, iron from the administered ferrous citrate is bound to the plasma protein, transferrin. In this transport form, iron is carried to the blood forming organs where it is utilized to form hemoglobin or is deposited in the reticuloendothelial cells of the liver and spleen.

INDICATIONS

Ferrous Citrate Fe-59 is indicated for iron turnover studies. These include clearance of iron from the plasma, appearance of iron in newly synthesized red blood cells and in various body sites, and the absorption of iron from the intestine.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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 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 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.

PRECAUTIONS

As in the use of any other 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.

ADVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

The suggested dose range for intravenous or oral administration employed in the average patient (70 kg) is 5 to 10 microcuries of ferrous citrate Fe-59.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iron-59 decays by beta and gamma emissions with a physical half life of 45 days.[1] Photons that are useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean % Disintegration	Mean Energy MeV
Gamma-2	[illegible]	0.192
Gamma-4	[illegible]	1.095
Gamma-5	[illegible]	1.292
Beta -2	[illegible]	0.081
Beta -3	[illegible]	0.153

[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. 18, 1969.

The specific gamma ray constant for ^{59}Fe is 6.4 R/mCi-hr at 1 cm. The half value layer is 1.1 cm of Pb.

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

Table II. Physical Decay Chart; ^{59}Fe, half life 45 days.

Days	Fraction Remaining	Days	Fraction Remaining
-7	1.113	7	.898
-5	1.080	10	.857
-3	1.048	15	.794
-1	1.018	20	.735
0*	1.000	25	.681
1	.985	30	.630
2	.970	35	.584
3	.955	40	.540
4	.940	45	.500
5	.926	50	.464

*Calibration day

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 10 microcuries of ^{59}Fe are shown in Table III.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/10 uCi ^{59}Fe)*
Liver	0.29
Kidneys	0.45
Spleen	0.58
Bone Marrow	0.65
Testes	0.34
Ovaries	0.33
Whole-body	0.23

*90% of the dose becomes incorporated into red blood cells with 120-day cell life. Doses will be about 10-25% of the above following oral administration.

[1]Method of calculation: A schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048672

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-8

DESCRIPTION: ^{51}Cr-chromate for red blood cell volume and survival studies. Activities ranging from 10 to 200 microcuries will normally be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{51}Cr-chromate. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/5/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			Feb 8 '74
R. L. Hayes	R.L.H			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048613

FDA Sample Package Insert

SAMPLE LABELING

Sodium Chromate Chromium 51 Injection

DESCRIPTION

Sodium Chromate Chromium Cr 51 (hexavalent) injection is a sterile pyrogen-free aqueous solution made isotonic with sodium chloride and may contain 0.9% benzyl alcohol as a preservative. Sodium hydroxide or hydrochloric acid may be present for the adjustment of the pH.

ACTIONS

Chromium is present in the hexavalent (+6) state, in which form it readily penetrates the red blood cell, attaches to the hemoglobin, and is reduced to the trivalent (+3) state. This state is maintained until the red blood cell is sequestered by the spleen, at which time the chromium is released to the plasma and is readily excreted in the urine. In the trivalent state, chromium 51 is not reutilized for tagging of additional red blood cells. Since the product has a high specific activity, adequate red blood cell tagging is secured in minimum time without demonstrable effect on cell life.

INDICATIONS

Sodium chromate Cr 51 may be used in the determination of red blood cell volume or mass, the study of red blood cell survival time, and evaluation of blood loss.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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 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 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.

PRECAUTIONS

As in the use of any other 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.

In order to obviate or minimize the possibility of contamination and of increased fragility of the tagged red blood cells, sterile techniques should be employed throughout the collection, tagging, rinsing, suspending, and injection of red blood cells. If used, the number of washes and transfers should be kept to a minimum, and only sterile, pyrogen-free isotonic diluent should be employed throughout the tagging procedure.

Specific activity should be not less than 10 millicuries per milligram (10 microcuries per microgram) of sodium chromate at the time of use.

ADVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

The usual dosages for the above indications in the average patient (70 kg) are as follows:

The determination of red blood cell volume or mass: 10 to 30 microcuries.

The study of red blood cell survival time: 150 microcuries.

The evaluation of blood loss: 200 microcuries.

PHYSICAL CHARACTERISTICS

Chromium 51 decays by electron capture and gamma emission with a physical half life of 27.8 days[1]. The primary gamma energy of Cr 51 is 320 KeV.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Gamma -1	8.99	319.8

[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. 27, 1969.

The specific gamma ray constant for Cr 51 is 0.15 R/mCi-hr at 1 cm. The half value layer is 2 mm of Pb.

1048676

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

Table II. Physical Decay Chart; Cr 51, half life 27.8 days

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-8	1.221	8	.819	50	.288
-4	1.105	15	.688	55	.254
-2	1.051	20	.607	60	.224
-1	1.025	25	.536	65	.198
0*	1.000	30	.473	70	.175
1	.975	35	.418	75	.154
2	.951	40	.369	80	.136
4	.905	45	.326	85	.120

*Calibration day

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 200 microcuries of Cr 51 are shown in Table III.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/200 uCi)
Blood	0.20
Spleen	2.64
Testes	0.056
Ovaries	0.056
Whole-body	0.055

[1]Method of calculation: A Schema for Absorbed-dose Calculations for Biologically-Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

1048677

HOW SUPPLIED

Revised 5/1/73

1048678

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-7

DESCRIPTION: ^{51}Cr-chromate for spleen scanning. Activities ranging from 300 to 500 microcuries will normally be administered. This radiopharmaceutical is included in the AEC List of Well-Established Medical Uses. An FDA sample package insert is attached.

☐ The Committee approves with the following limitations:

Radiopharmaceutical may/may not be administered to patients under 18 years of age.

Radiopharmaceutical may/may not be administered to pregnant patient.

Other:

☒ The Committee disapproves for the following reasons:

Spleen scanning with ^{51}Cr-chromate no longer performed at Medical Division. Package inserts for ^{51}Cr-chromate do not list spleen scanning as recommended procedure.

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger				2/8/74
R. J. Cloutier				2/8/74
C. L. Edwards				2/8/74
R. L. Hayes				2/8/74
C. C. Lushbaugh				2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 5 Mar '74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048619

FDA Sample Package Insert

SAMPLE LABELING

Sodium Chromate Chromium 51 Injection

DESCRIPTION

Sodium Chromate Chromium Cr 51 (hexavalent) injection is a sterile pyrogen-free aqueous solution made isotonic with sodium chloride and may contain 0.9% benzyl alcohol as a preservative. Sodium hydroxide or hydrochloric acid may be present for the adjustment of the pH.

ACTIONS

Chromium is present in the hexavalent (+6) state, in which form it readily penetrates the red blood cell, attaches to the hemoglobin, and is reduced to the trivalent (+3) state. This state is maintained until the red blood cell is sequestered by the spleen, at which time the chromium is released to the plasma and is readily excreted in the urine. In the trivalent state, chromium 51 is not reutilized for tagging of additional red blood cells. Since the product has a high specific activity, adequate red blood cell tagging is secured in minimum time without demonstrable effect on cell life.

INDICATIONS

Sodium chromate Cr 51 may be used in the determination of red blood cell volume or mass, the study of red blood cell survival time, and evaluation of blood loss.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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 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 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.

PRECAUTIONS

As in the use of any other 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.

In order to obviate or minimize the possibility of contamination and of increased fragility of the tagged red blood cells, sterile techniques should be employed throughout the collection, tagging, rinsing, suspending, and injection of red blood cells. If used, the number of washes and transfers should be kept to a minimum, and only sterile, pyrogen-free isotonic diluent should be employed throughout the tagging procedure.

Specific activity should be not less than 10 millicuries per milligram (10 microcuries per microgram) of sodium chromate at the time of use.

ADVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

The usual dosages for the above indications in the average patient (70 kg) are as follows:

The determination of red blood cell volume or mass: 10 to 30 microcuries

The study of red blood cell survival time: 150 microcuries.

The evaluation of blood loss: 200 microcuries.

PHYSICAL CHARACTERISTICS

Chromium 51 decays by electron capture and gamma emission with a physical half life of 27.8 days[1]. The primary gamma energy of Cr 51 is 320 KeV.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Gamma -1	8.99	319.8

[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. 27, 1969.

The specific gamma ray constant for Cr 51 is 0.15 R/mCi-hr at 1 cm. The half value layer is 2 mm of Pb.

1048682

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

Table II. Physical Decay Chart; Cr 51, half life 27.8 days

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-8	1.221	8	.819	50	.288
-4	1.105	15	.688	55	.254
-2	1.051	20	.607	60	.224
-1	1.025	25	.536	65	.198
0*	1.000	30	.473	70	.175
1	.975	35	.418	75	.154
2	.951	40	.369	80	.136
4	.905	45	.326	85	.120

*Calibration day

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 200 microcuries of Cr 51 are shown in Table III.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/200 uCi)
Blood	0.20
Spleen	2.64
Testes	0.066
Ovaries	0.066
Whole-body	0.055

[1]Method of calculation: A Schema for Absorbed-dose Calculations for Biologically-Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

104883

HOW SUPPLIED

Revised 5/1/73

1048684

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-6

DESCRIPTION: ^{131}I-macroaggregated albumin for lung scanning, detection of emboli, diagnosis of malignancies, and evaluation of other pulmonary problems. Activities ranging from 150 to 300 microcuries will normally be administered. This radiopharmaceutical is included in the AEC list of well-established medical uses. A package insert distributed by Squibb is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	[illegible]			2/8/74
R. J. Cloutier	[illegible]			2-8-74
C. L. Edwards	[illegible]			2-8-74
R. L. Hayes	[illegible]			2/8/74
C. C. Lushbaugh	[illegible]			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb '74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048685

14-6

SQUIBB

J2-540B

AGGREGATED RADIO-IODINATED (^{131}I) ALBUMIN (HUMAN) ALBUMOTOPE®-LS

FOR LUNG SCANNING

Aggregated Radio-Iodinated (^{131}I) Albumin (Human) [Albumotope-LS] is intended for intravenous administration in scintillation scanning of the lungs. It is a sterile, non-pyrogenic aqueous suspension providing, in each cc., approximately 0.5 mg. aggregated human serum albumin labeled with Iodine-131. The product has been heated under carefully controlled conditions to produce aggregates, not less than 90% of which fall between 10 and 90 microns in size and none of which are larger than 150 microns. The potency ranges from 250 to 450 microcuries per cc. on the date of assay. The preparation also contains less than 0.01 mg./cc. potassium iodide as a carrier, 0.9% (w/v) benzyl alcohol as a preservative, less than 0.01 mg./cc. sodium thiosulfate, less than 0.16 mg./cc. sodium acetate as a buffer to adjust pH to 5.0-6.0, and propylene glycol for isotonicity; trace amounts of sodium bicarbonate, sodium hydroxide, simethicone, glyceryl monostearate, polyethylene glycol monostearate, and sorbic acid are present; trace amounts of hydrochloric acid may be present.

The activity at the time of administration can be calculated easily by consulting the radioactivity decay factors provided in this monograph and the activity data provided on the label.

This product is prepared by adjusting the pH of Radio-Iodinated (^{131}I) Serum Albumin (Human) and subjecting it to heat under controlled conditions. The size of the resultant aggregates is a function of pH and temperature. The aggregates are apparently composed of loosely-knit, fragile clusters of smaller particles. Electrophoretic studies of similar material with aggregates of smaller size have shown that the material has patterns similar to those of normal human serum albumin except for reduced mobility. The radioactive iodine has been found to be strongly bound to the tyrosine moiety of the protein, and remains bound *in vivo* until the material is metabolized by the body.

PHYSICAL PROPERTIES OF IODINE-131

Iodine-131 is produced during the fission reaction of Uranium-235 or by the irradiation of tellurium. It disintegrates by a complex decay scheme emitting beta particles and gamma rays. The major radiation energies are 0.36 Mev and 0.61 Mev for the principal gamma ray and beta particle, respectively. ^{131}I has a half-life of 8.08 days.

1048686

'14-6

RADIOACTIVITY DECAY FACTORS

The activity at the time of administration can be calculated by multiplying the assay value stated on the label by the appropriate factor found in the following table:

Days	Factor	Days	Factor	Days	Factor
1	0.918	11	0.390	21	0.165
2	0.843	12	0.358	22	0.152
3	0.774	13	0.328	23	0.139
4	0.710	14	0.301	24	0.128
5	0.652	15	0.277	25	0.117
6	0.598	16	0.254	26	0.108
7	0.549	17	0.233	27	0.099
8	0.504	18	0.214	28	0.091
9	0.463	19	0.196	29	0.083
10	0.425	20	0.180	30	0.076

ACTION, DISTRIBUTION AND EXCRETION

Following intravenous injection, Aggregated Radio-Iodinated (^{131}I) Albumin (Human) is rapidly transported by the blood stream to the lungs. The aggregates do not enter the tissues of the lungs, but remain in the pulmonary vasculature. When pulmonary blood flow is normal, the material is carried throughout the entire lung field; when pulmonary blood flow is diminished or obstructed by a disease process, the particles are correspondingly prevented in part or in whole from passage through the affected portion of the pulmonary vasculature.

Aggregated radioalbumin remains in the lungs for variable amounts of time depending on particle size. The particles disappear from the lungs in exponential fashion with the larger sized aggregates having the longer half-life; particles ranging from 10 to 90 microns in diameter usually have a half-life of 2 to 8 hours.[1,2] Apparently, the aggregates are temporarily trapped by the narrow pulmonary capillaries where the particles are broken down until they are small enough to pass.

Although the particles of radioalbumin remain for a time in the pulmonary capillaries, they do not appear to interfere even temporarily with pulmonary blood flow or ventilation in the dosage required for lung scanning. This is evidenced by the fact that these doses do not produce any respiratory distress nor any tachycardia, even in patients severely ill with pulmonary and/or cardiac disorders.

Once the albumin particles leave the lungs, they are carried to the liver, where they are removed from the blood stream primarily by the Kupffer cells. There, the particles are phagocytized and rapidly metabolized. Thyroid accumulation of ^{131}I resulting from metabolic deiodination of the protein can be minimized by prior administration of Lugol's Solution.

RATIONALE FOR USE

Aggregated radioalbumin is an ideal substance for visualizing the pulmonary vasculature by means of lung scanning techniques. The material is selectively concentrated in the lungs, and specifically in only those areas with an adequate blood supply, so that there is a clearly visible distinction between normal lung fields and areas obstructed by a morbid process. The aggregates remain in the lungs for ample time to complete one or more scans, and there is essentially no interference from radioactivity in other organs or in the general circulation throughout this scanning period. Moreover, the material clears rapidly from the lungs after scanning, and is readily metabolized and rapidly excreted, so that the radiation dose to the patient is minimal (for an administered dose of 300 microcuries, the radiation dose to the lungs and whole body is reported to be 1.9 rads and 0.008 rads, respectively[3]). Finally, the material is non-toxic and therefore presents no pharmacologic hazards to the patient.

1048687

74-6

Because aggregated radioalbumin is non-toxic and the radiation dose is low, lung scanning may be repeated in 24 hours, when necessary, enabling the physician to follow the course of a disease or to evaluate the benefits of therapy.

Lung scanning with aggregated radioalbumin provides essentially the same information as pulmonary arteriography, but without any of the dangers attendant on the administration of radiopaque material or on cardiac catheterization.

INDICATIONS

Scintillation scanning of the lungs with Aggregated Radio-Iodinated (^{131}I) Albumin (Human) is indicated as an adjunct to other diagnostic procedures whenever information about pulmonary vasculature is desired. The most useful clinical applications of lung scanning have been outlined by Wagner:* 1) The diagnosis of pulmonary embolism; 2) differentiation of focal conditions such as bullae or cysts from diffuse pulmonary disorders; 3) determination of the degree of pulmonary vascular obliteration in parenchymal disease; 4) diagnosis and management of congenital heart disease as, for example, quantification of the degree of shunting; and 5) evaluation of the patient's ability to withstand pulmonary surgery.

Perhaps the most frequently useful indication for the lung scan has been the early detection of pulmonary emboli. The lung scan is uniquely able to demonstrate the existence of an embolism before radiological signs become apparent. Although an area of increased radiolucency on the chest film may suggest an embolism, X-ray findings do not usually become apparent until the embolism has produced signs of ischemia or infarction. Once an embolism has been diagnosed, information obtained from the scan is of value in determining the desirability of surgical embolectomy, while subsequent scans provide information on the effectiveness of surgical or anticoagulant therapy.

Lung scanning is similarly helpful in the diagnosis of various types of malignancies affecting the lungs. Again, scanning is of value in locating the affected areas, in determining the need for and probable effectiveness of surgery or of radiation therapy, and in following up the benefits of treatment.

Useful information is also provided by the scan in the diagnosis or evaluation of other pulmonary problems, such as pneumonia, cysts or bullae, abscesses, atelectasis, pleural effusion, pulmonary tuberculosis, parenchymal disease, emphysema, and chronic asthmatic bronchitis.

CONTRAINDICATIONS

Radiopharmaceuticals should not be administered to pregnant women or to persons under the age of 18 years unless the indications are very exceptional.

Because iodide is excreted in human milk, aggregated radioalbumin should not be administered to nursing mothers.

ADVERSE REACTIONS

Although the immunological properties of serum albumin are believed to be virtually unaltered by the iodination process, there is a possibility that hypersensitivity reactions may occur in patients receiving additional doses a number of weeks after an initial dose.

The hypothetical possibility that particles of large size might induce deleterious cardiovascular or cerebrovascular effects, postulated by some investigators, has not been borne out in extensive clinical use with Aggregated Radio-Iodinated (^{131}I) Albumin (Human).

DOSAGE AND PROCEDURE

A thyroid-blocking iodine preparation such as Lugol's Solution will minimize the uptake of radioactive iodine by the thyroid.

Dosage of aggregated radioalbumin is dependent on detection equipment available; doses of 150 to 300 microcuries have been used most frequently. *The vial must be shaken just before use, to insure resuspension of the particles.* Aggregated radioalbumin is administered by slow intravenous injection.

J. Amer. Med. Assoc. 189: ad. p. 35 (Aug. 17, 1964).

1048688

74-6

Scanning procedures, as well as the characteristic appearance of scans of normal lungs and of those with various disorders, are described in the literature. However, the physician should familiarize himself with the appearance of normal lung scans performed anteroposteriorly, posteroanteriorly, and laterally for purposes of comparison, and should establish for himself the procedure which provides optimal results.

The scan is usually performed from the anteroposterior position with the patient supine. In the A-P lung scan there is an area of decreased radioactivity corresponding to the heart, and another which corresponds to the superior mediastinum. Bands of decreased activity correlating with the rib cage may be avoided by careful adjustment of the detector. When the scan is performed P-A the cardiac area is diminished in size and a larger area of the lungs is visualized. In some cases, a lateral scan may provide additional useful information. It is anticipated that the large particle size of Albumotope-LS [Aggregated Radio-Iodinated (^{131}I) Albumin (Human)] will allow ample time to scan from all 3 positions when this is considered advisable.

Many of the reports appearing in the literature have recommended scanning immediately after injection, beginning caudad and progressing cephalad in order to avoid interference from accumulating liver radioactivity. However, these reports are based on work which was done with material having a smaller particle size than Albumotope-LS [Aggregated Radio-Iodinated (^{131}I) Albumin (Human)]; the material currently in use has an extended lung half-time, which delays liver interference and permits scanning throughout a longer period of time. While most may still prefer to scan immediately, in other instances the clinician may find it preferable to begin the scan 1 to 1½ hours after dosage is administered. Occasionally the later scan will pick up a "cold" area that was missed during scanning at the earlier time when lung radioactivity was heavier.

Occasionally, small areas of increased radioactivity may appear on lung scans: this may be due to the inadvertent static mixing of blood in the syringe containing the drug or to freezing or exposure of the product to excessive heat during storage or shipping.

REFERENCES

1. Haddad RG, Luchsinger PC: Disappearance rate of ^{131}I-tagged macroaggregated albumin from the lung. *J Nucl Med* 10:560-561, 1969
2. Furth ED, Okinaka AJ, Focht EF, *et al:* The distribution, metabolic fate, and radiation dosimetry of ^{131}I labeled macroaggregated albumin. *J Nucl Med* 6:506-518, 1965

E. R. Squibb & Sons, Inc.

Radiopharmaceutical Dept.

New Brunswick, N.J. 08903

U.S. License No. 52

Printed in U.S.A. Revised July 1970 J2-540B

1048689

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. L. Edwards Proposal No. 74-5

DESCRIPTION: ^{131}I-sodium iodide as a liquid or in capsules for treatment of thyroid carcinoma. Activities ranging from 85-150 millicuries may be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{131}I-sodium iodide. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2-8-74
C. L. Edwards	CLE			Feb 8 '74
R. L. Hayes	RLH			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter [signature] Date 8 Feb. '74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048690

12/73

FDA Sample Package Insert

SAMPLE LABELING

SODIUM IODIDE I 131 CAPSULES AND SOLUTION THERAPEUTIC

DESCRIPTION

Sodium Iodide I 131 is available in capsules and aqueous solution for oral administration.

ACTIONS

Sodium Iodide is readily absorbed from the gastrointestinal tract. Following absorption, the iodide is distributed primarily within the extracellular fluid of the body. It is concentrated and organified by the thyroid, and trapped but not organified by the stomach and salivary glands. It is also promptly excreted by the kidneys. About 90% of local irradiation is caused by beta radiation and 10% is caused by gamma radiations.

INDICATIONS

Sodium Iodide I 131 is indicated for the treatment of hyperthyroidism and selected cases of carcinoma of the thyroid.

CONTRAINDICATIONS

Vomiting and diarrhea represent contraindications to the use of radioiodide, Antithyroid therapy of a severely hyperthyroid patient is usually discontinued 3 to 4 days before administration of radioiodide.

Therapeutic doses of Sodium Iodide I 131 are contraindicated in pregnancy.

WARNINGS

Sodium Iodide I 131 is not usually used for treatment of hyperthyroidism in patients under 30 years of age. This radiopharmaceutical agent should not be administered to patients who are pregnant or during lactation.

Ideally, therapy 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 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.

PRECAUTIONS

As in the use of any other 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.

The uptake of iodine 131 will be affected by recent intake of stable iodine in any form, or by the use of thyroid, anti-thyroid and certain other drugs. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media.

ADVERSE REACTIONS

Depression of the hematopoietic system may occur when large doses are employed. Such potential side effects include radiation sickness, increase in clinical symptoms, bone marrow depression, acute leukemia, anemia, chromosomal abnormalities, acute thyroid crises, blood dyscrasia, leukopenia, or thrombocytopenia.

DOSAGE AND ADMINISTRATION

For hyperthyroidism the usual dose range is 4 to 10 millicuries. Toxic nodular goiter and other special situations will require the use of larger doses.

For thyroid carcinoma 50 millicuries is the usual dose for ablation of normal thyroid tissue, and 100 to 150 millicuries is the usual subsequent therapeutic dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iodine 131 decays by beta and gamma emissions with a physical half-life of 8.05 days[1]. Photons that are useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Beta-1	1.6	70.1
Beta-2	6.9	95.5
Beta-4	90.4	191.7
Gamma-6	83.3	364.5

104863

[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. 26, 1969.

The specific gamma ray constant for ^{131}I is 2.2 R/mCi-hr at 1 cm. The half value layer is 6 mm of Pb.

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

Table II. Physical Decay Chart; ^{131}I, half life 8.05 days.

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-7	1.825	7	.548	19	.195
-5	1.538	8	.502	20	.179
-3	1.295	9	.461	21	.164
-2	1.188	10	.423	22	.150
-1	1.089	11	.389	23	.138
0*	1.000	12	.356	24	.127
1	.918	13	.326	25	.116
2	.842	14	.299	26	.107
3	.772	15	.275	27	.098
4	.708	16	.252	28	.090
5	.650	17	.231	29	.082
6	.596	18	.212	30	.076

*Calibration day

RADIATION DOSIMETRY

Following oral administration of I-131 sodium iodide, about 40% of the activity has an effective half life of 0.34 days and 60% has an effective half life of 7.61 days. On this basis the estimated absorbed radiation doses[1] to an average patient (70 kg) from an oral dose of 10 millicuries of I-131 are shown in Table III.

1048694

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/10 mCi ^{131}I)
Thyroid	35,000
Testes	9.2
Ovaries	9.3
Whole-body	16

[1]Method of calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-4

DESCRIPTION: ^{131}I-sodium iodide as liquid or in capsules for treatment of hyperthyroidism. Activities ranging from 1 to 10 millicuries will normally be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{131}I-sodium iodide. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2/8/74
C. L. Edwards	CLE			2/8/74
R. L. Hayes	RLH			2/8/74
C. C. Lushbaugh	[illegible]			2/8/74

Acknowledgement of Submitter C Lowell Edwards Date 6 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048696

FDA Sample Package Insert

SAMPLE LABELING

SODIUM IODIDE I 131 CAPSULES AND SOLUTION THERAPEUTIC

DESCRIPTION

Sodium Iodide I 131 is available in capsules and aqueous solution for oral administration.

ACTIONS

Sodium Iodide is readily absorbed from the gastrointestinal tract. Following absorption, the iodide is distributed primarily within the extracellular fluid of the body. It is concentrated and organified by the thyroid, and trapped but not organified by the stomach and salivary glands. It is also promptly excreted by the kidneys. About 90% of local irradiation is caused by beta radiation and 10% is caused by gamma radiations.

INDICATIONS

Sodium Iodide I 131 is indicated for the treatment of hyperthyroidism and selected cases of carcinoma of the thyroid.

CONTRAINDICATIONS

Vomiting and diarrhea represent contraindications to the use of radioiodide, Antithyroid therapy of a severely hyperthyroid patient is usually discontinued 3 to 4 days before administration of radioiodide.

Therapeutic doses of Sodium Iodide I 131 are contraindicated in pregnancy.

WARNINGS

Sodium Iodide I 131 is not usually used for treatment of hyperthyroidism in patients under 30 years of age. This radiopharmaceutical agent should not be administered to patients who are pregnant or during lactation.

Ideally, therapy 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 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.

PRECAUTIONS

As in the use of any other 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.

The uptake of iodine 131 will be affected by recent intake of stable iodine in any form, or by the use of thyroid, anti-thyroid and certain other drugs. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media.

ADVERSE REACTIONS

Depression of the hematopoietic system may occur when large doses are employed. Such potential side effects include radiation sickness, increase in clinical symptoms, bone marrow depression, acute leukemia, anemia, chromosomal abnormalities, acute thyroid crises, blood dyscrasia, leukopenia, or thrombocytopenia.

DOSAGE AND ADMINISTRATION

For hyperthyroidism the usual dose range is 4 to 10 millicuries. Toxic nodular goiter and other special situations will require the use of larger doses.

For thyroid carcinoma 50 millicuries is the usual dose for ablation of normal thyroid tissue, and 100 to 150 millicuries is the usual subsequent therapeutic dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iodine 131 decays by beta and gamma emissions with a physical half-life of 8.05 days[1]. Photons that are useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Beta-1	1.6	70.1
Beta-2	6.9	95.5
Beta-4	90.4	191.7
Gamma-6	83.3	364.5

1048699

[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. 26, 1969.

The specific gamma ray constant for ^{131}I is 2.2 R/mCi-hr at 1 cm. The half value layer is 6 mm of Pb.

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

Table II. Physical Decay Chart; ^{131}I, half life 8.05 days.

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-7	1.825	7	.548	19	.195
-5	1.538	8	.502	20	.179
-3	1.295	9	.461	21	.164
-2	1.188	10	.423	22	.150
-1	1.089	11	.389	23	.138
0*	1.000	12	.356	24	.127
1	.918	13	.326	25	.116
2	.842	14	.299	26	.107
3	.772	15	.275	27	.098
4	.708	16	.252	28	.090
5	.650	17	.231	29	.082
6	.596	18	.212	30	.076

*Calibration day

RADIATION DOSIMETRY

Following oral administration of I-131 sodium iodide, about 40% of the activity has an effective half life of 0.34 days and 60% has an effective half life of 7.61 days. On this basis the estimated absorbed radiation doses[1] to an average patient (70 kg) from an oral dose of 10 millicuries of I-131 are shown in Table III.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/10 mCi ^{131}I)
Thyroid	35,000
Testes	9.2
Ovaries	9.3
Whole-body	16

[1]Method of calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048701

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-3

DESCRIPTION: ^{131}I-sodium iodide as liquid or in capsules for thyroid scanning. Activities ranging from 5 to 100 microcuries will normally be administered; however, for localizing extrathyroidal metastases, up to 1 millicurie may be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{131}I-sodium iodide. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	[illegible]			2/8/74
R. J. Cloutier	RJC			2/8/74
C. L. Edwards	CLE			2/8/74
R. L. Hayes	RLH			2/8/74
C. C. Lushbaugh	[illegible]			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048702

FDA Sample Package Insert

SAMPLE LABELING

SODIUM IODIDE I 131 CAPSULES AND SOLUTION - DIAGNOSTIC

DESCRIPTION

Sodium Iodide I 131 is available in capsules and aqueous solution for oral administration.

ACTIONS

Sodium iodide is readily absorbed from the gastrointestinal tract. Following absorption, the iodide is distributed primarily within the extracellular fluid of the body. It is concentrated and organified by the thyroid, and trapped but not organified by the stomach and salivary glands. It is also promptly excreted by the kidneys.

INDICATIONS

Sodium Iodide I 131 is indicated for use in the diagnosis of thyroid function and for thyroid imaging. Diagnostic doses may also be employed in localizing metastases associated with thyroid malignancies.

CONTRAINDICATIONS

None

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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 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.

PRECAUTIONS

As in the use of any other 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.

The uptake of iodine 131 will be affected by recent intake of stable iodine in any form, or by the use of thyroid, anti-thyroid and certain other drugs. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media.

ADVERSE REACTIONS

None

DOSAGE AND ADMINISTRATION

The suggested oral dose range employed in the average patient (70 kg) for various diagnostic procedures for thyroid function is 5 to 100 microcuries.

1048704

For localization of extra thyroidal metastases the usual dose is 1000 microcuries.

The patient dose should be measured by a suitable radioactivity calabration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iodine 131 decays be beta and gamma emissions with a physical half-life of 8.05 days[1]. Photons that are useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Beta-1	1.6	70.1
Beta-2	6.9	95.5
Beta-4	90.4	191.7
Gamma-6	83.3	364.5

[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. 26, 1969.

The specific gamma ray constant for ^{131}I is 2.2 R/mCi-hr at 1 cm. The half value layer is 6 mm of Pb.

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

Table II. Physical Decay Chart; ^{131}I, half life 8.05 days.

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-7	1.825	7	.548	19	.195
-5	1.538	8	.502	20	.179
-3	1.295	9	.461	21	.164
-2	1.188	10	.423	22	.150
-1	1.089	11	.389	23	.138
0*	1.000	12	.356	24	.127
1	.918	13	.326	25	.116
2	.842	14	.299	26	.107
3	.772	15	.275	27	.098
4	.708	16	.252	28	.090
5	.650	17	.231	29	.082
6	.596	18	.212	30	.076

*Calibration day

RADIATION DOSIMETRY

Following oral administration of I-131 sodium iodide, about 80% of the activity has an effective half life of 0.34 day and 20% has an effective half life of 7.61 days. On this basis the estimated absorbed radiation doses[1] to an average patient (70 kg) from an oral dose of 100 microcuries of I-131 are shown in Table III. This table also shows the corresponding absorbed radiation doses from an oral dose of 100 microcuries of I-125.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/100 uCi ^{131}I)	(rads/100 uCi ^{125}I)
Thyroid	120	87
Testes	0.042	0.035
Ovaries	0.042	0.037
Whole-body	0.061	0.049

1048706

[1]Method of calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048707

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. C. Lowell Edwards Proposal No. 74-2

DESCRIPTION: ^{131}I-sodium iodide as liquid or in capsules to determine thyroid uptake and evaluate thyroid function. Activity ranging from 1 to 25 microcuries will normally be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{131}I-sodium iodide. A package insert supplied by Squibb is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2/8/74
C. L. Edwards	CLE			2/8/74
R. L. Hayes	R.L.H			2/8/74
C. C. Lushbaugh	[illegible]			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048108

SQUIBB

J3-170

IODOTOPE®

Sodium Iodide I 131 Capsules U.S.P.

Diagnostic • Oral

DESCRIPTION

Sodium Iodide I 131 Capsules U.S.P. contain radioactive iodine (^{131}I) processed in the form of sodium iodide from products of uranium fission or the neutron bombardment of tellurium.

PHYSICAL PROPERTIES

Iodine 131 is produced during the fission reaction of Uranium 235 or the irradiation of tellurium. It disintegrates by a complex decay scheme emitting beta particles and gamma rays. The major radiation energies are 0.36 Mev and 0.61 Mev for the principal gamma ray and beta particle, respectively. Iodine 131 has a half-life of 8.08 days and the final disintegration product is Xenon 131.

ACTIONS

Iodine 131 is chemically identical to naturally-occurring stable iodine and is handled by the body in the same manner as stable iodine.

The thyroid gland has a high affinity for iodine in the form of inorganic iodide. Ingested iodide is rapidly absorbed from the intestinal tract and is removed from the blood stream almost exclusively by the thyroid cells and the kidneys. It can generally be detected in the thyroid within minutes after oral administration. The normal thyroid concentrates approximately 20% of the

iodide again become
again be incorporate
Iodide is also conc
glands and the stom
secretions from these
stream. Sensitive scan
tions of iodine also o
female-breast (inclu
intestine. Presumabl
tions of inorganic io
of circulating thyroid
Iodide is ultimately
amounts are detectal
are excreted in the m
hours after administ

INDICATIONS

Iodotope (Sodium Io
use in performance o
evaluate thyroid func
scintillation scanning
in localizing metast

WARNINGS

Radiopharmaceutica
qualified by specific
radioisotopes and w
approved by the ap
to license the use of
Radiopharmaceut
less than 18 years of
the hazards.
Since iodide is exc
be substituted for bre
to the mother durin
Usage in pregnanc
be administered to w
pregnant or during
tional and the need f
risks from the radia

1048709

with radioiodine for hyperthyroidism, but the tests should be interpreted with caution, particularly if the results do not agree with clinical evidence. Both falsely elevated and falsely depressed uptakes have been known to occur after radioiodine therapy, regardless of true thyroid status. Such tests should therefore *not* be used as the sole basis for determining either the need for additional doses of ^{131}I or the need for replacement therapy. During the course of treatment for hyperthyroidism, a chemical determination of the serum PBI and a basal metabolism test are suggested in conjunction with the thyroid uptake test. A chemical determination of the serum PBI may be the most reliable laboratory test for the detection of late-onset hypothyroidism several years after therapy. In any patient treated with radioiodine, the clinical state is probably the best indicator of thyroid status.

Renal impairment may decrease urinary excretion of radioiodine and increase its levels in the plasma, thyroid, and feces, but it does not usually affect 24-hour uptake studies to a significant extent. Mercurial diuretics seldom influence the uptake test. Malabsorption states and other gastrointestinal disorders have little, if any, effect on thyroid uptake of ^{131}I. However, thyroid uptake of radioiodine may be markedly increased in chronic cirrhosis, possibly because of a dietary deficiency of the element. Congestive heart failure may decrease uptake of radioiodine while cardiac patients on low sodium diets may show elevated uptake.

While thyroid uptake of radioiodine is generally not altered by small daily fluctuations in iodide intake derived from foods, it will be significantly changed by recent administration of drugs or other preparations containing iodine in any form, by thyroid and antithyroid drugs, and by many other compounds. Even though such preparations may not influence thyroid function, they will invalidate ^{131}I uptake test results and may alter other thyroid function tests as well. The patient should therefore be questioned carefully regarding previous medication. The following substances may alter the uptake of ^{131}I by the thyroid:

- Iodine preparations for internal or external use such as solutions, ointments, or tinctures of iodine or iodides
- Radioiodine preparations given either diagnostically or therapeutically
- Asthma and cough preparations containing iodine
- Vitamin-mineral preparations containing iodine or vitamin A
- Antiparasitic drugs such as diiodohydroxyquin or iodochlorhydroxyquinoline
- Cod liver oil preparations
- Iodized salt
- Radiographic contrast media
- Thyroid and antithyroid drugs
- p-amino benzoic acid
- p-aminosalicylic acid (PAS)
- Corticosteroids
- Thiopental
- Sulfobromophthalein
- Cobalt, mercury, and other heavy metals
- Estrogens
- Progesteron
- Phenylbuta
- Resorcinol
- Suntan loti

NOTE: It is difficult to estimate how lon mentioned compounds will continue to aff tests. In general, the effect of inorganic iodi will persist for several weeks, although in iodine turnover rate may be high enough t time somewhat. On the other hand, the m and excretion rates of iodine present in org highly variable and these compounds can a tests for extended periods of time, some e

Medication such as perchlorates or thiocy iodine concentration by the thyroid, or ant prevent the formation of thyroid hormon bound" phenomenon, with a period of ex following the initial suppression of upt phenomenon may also occur following t desiccated thyroid or synthetic thyroid p after cessation of iodine medication; with bound" may be delayed at times or may

If the patient has recently received a p radioiodine (e.g. radio-iodinated serum alb bengal, etc.), a count should be made over to the administration of sodium iodide I 131 uptake test. The test should be postponed i the count indicates low residual activity, per minute should be recorded and the thyr in computing the thyroid uptake of ^{131}I, th be corrected for further decay and then thyroid uptake data.

Information regarding factors that ma of the results of the radioiodide uptake function tests is contained in various ref

DOSAGE AND ADMINISTRATION

Dosage depends on the instrumentation nique employed. Radioiodide thyroid require doses of ^{131}I ranging from 1 to tional procedures, which may be perfor concurrently, often provide useful co regarding the status of thyroid function. T tion of urinary excretion of ^{131}I, measure ^{131}I (PBI), and the measurement of th

1048710

tion of primary thyroid malignancies. The usual dose for thyroid scanning is 50 to 100 microcuries of sodium iodide I 131. Doses of several hundred microcuries are usually required for the localization of metastases associated with thyroid malignancies.

Dosimetry

Seltzer[5] calculated the average radiation doses that would be delivered to the whole body and the thyroid in patients of various ages following the administration of sodium iodide I 131 for thyroid function studies. The calculations are based upon the following assumptions: 1) the sodium iodide I 131 is completely absorbed following oral administration, 2) except in the case of newborns, 30% of the administered nuclide is metabolized by the thyroid; the thyroid uptake and percent of nuclide metabolized in newborns is higher, 3) radioiodide not taken up by the thyroid is rapidly excreted by the kidneys (biological half-life of 10 hours), 4) the radioiodine concentrated in the thyroid has a biological half-life of about 50 days in the normal adult, 5) after a short time the thyroid contains 87% of the administered dose of radioiodide with the remainder of the body containing the other 13%, 6) absorption, thyroid uptake, and distribution of the nuclide are instantaneous, and 7) the thyroid mass is considered as a single sphere located in the midline of the neck.

The radiation dose to the *thyroid* is calculated solely from the ^{131}I that is within the gland. The dose delivered to the *whole body* is the sum of the radiation dose delivered by: 1) the beta and gamma radiation from ^{131}I not taken up by the thyroid and thus rapidly excreted, 2) beta and gamma radiation from the fraction of radioiodine in the organic form (biological half-life of 50 days), and 3) gamma radiation from ^{131}I within the thyroid. The calculated average radiation doses (per microcurie of sodium iodide I 131 administered) delivered to the thyroid and the whole body of subjects of various ages are presented in Table 1.

TABLE 1

Age	Average dose to the thyroid (rads/microcurie)	Average whole-body dose (millirads/microcurie)
Newborn	32.0	10.0
1 year old	10.0	2.0
5 years old	4.3	1.3
10 years old	3.1	0.81
15 years old	1.7	0.53
Standard man	1.3	0.45

$$D_{(B+\gamma)} = \frac{T(eff)}{m}(73.8\,E_B + 0.034 \times g)$$

where:

$D_{(B+\gamma)}$ = total absorbed dose from radiation (rads per μCi ad

T(eff) = 6 days

m = 30 grams

E_B = 0.178 Mev/disintegration

g = 14.6

k = 2.18 roentgens/mCi/hr. (

Riccabona[7] calculated the radia thyroid following the administratio with different sized thyroids in vari tion. The status of glandular functio tion since this affects the percentag of radioiodine turnover which in half-life of ^{131}I in the thyroid gland radiation dose delivered to the th thyroid function following the adm of Iodine 131:

TABLE

State of thyroid function	Weight of gland (g.)	% Uptake
Normal	20	20
Thyrotoxicosis	70	70
Hypothyroidism	10	10

The absorbed dose by the thyroi any other body tissue. Pochin[6] re curie of ^{131}I ingested, approximatel be absorbed by the blood and delivered to the salivary glands, breast, and certain joint cavities temporarily concentrated.

HOW SUPPLIED

Iodotope (Sodium Iodide I 131 C available in several potencies. Co package of diagnostic capsules are activity at the time of administr multiplying the assay value stated priate factor found in Table 3. U

1048711

74-2

TABLE 3

Days	Pre-Calibration Decay Factor	Post-Calibration Decay Factor
1	1.089	.9177
2	1.187	.8423
3	1.293	.7730
4	1.409	.7095
5	1.535	.6512
6	1.673	.5976
7	1.823	.5485
8	1.986	.5034
9	2.164	.4620
10	2.358	.4240
11	2.569	.3892
12	2.799	.3572
13	3.050	.3278
14	3.324	.3008
15	3.621	.2761
16	3.946	.2534
17	4.299	.2326
18	4.686	.2134
19	5.104	.1959
20	5.561	.1798

REFERENCES

1. Grayson R. R.: Factors which i
thyroidal uptake test. Amer. J.
2. Silver S.: Radioactive Isotopes
2: Medicine, 2nd ed., Philadel
pp. 15-169
3. Blahd W. H., Bauer F. K., Cass
Medicine, Springfield, Ill., Ch
4. Sisson J. C.: Principles of, an
tests. J. Nucl. Med. 6:853, 196
5. Ben Porath M., Hochman A.
Iodine-125 and Iodine-131 as
thyroid disease. I. Physical aspe
6. Pochin E. E.: Chronic and acu
late effects of radioiodine in ma
1967
7. Riccabona G.: ^{125}I in the clini
ease. New Eng. J. Med. 273:1
8. Seltzer R. A. et al: Radiation e
pounds in pediatrics. Brit. J. R

1048712

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. Lowell Edwards Proposal No. 74-1

DESCRIPTION: ^{57}Co-vitamin B_{12} for the determination of vitamin B_{12} absorption in the intestine, particularly for the diagnosis of pernicious anemia. Normally activity ranging from 0.5 to 1.0 microcurie will be administered. Major radiopharmaceutical manufacturers have NDA's approved by FDA for ^{57}Co-vitamin B_{12}. FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may/~~may not~~ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			2/8/74
R. J. Cloutier	RJC			2/8/74
C. L. Edwards	CLE			2/8/74
R. L. Hayes	R.L.H			2/8/74
C. C. Lushbaugh	CCL			2/8/74

Acknowledgement of Submitter C. Lowell Edwards Date 8 Feb 74

- -

Proposal ~~does~~/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048713

FDA Sample Package Insert

SAMPLE LABELING

CYANOCOBALAMIN Co 57 or Co 60 Solution or Capsules

DESCRIPTION

Cyanocobalamin is a sterile pyrogen-free aqueous solution or a capsule of radioactive cyanocobalamin (vitamin B-12) labeled with Co 57 or Co 60. The solution is made isotonic with saline and may contain a suitable preservative.

ACTIONS

Orally administered cyanocobalamin is normally complexed to intrinsic factor and absorbed by the distal ileum.

Following parenteral administration cyanocobalamin is bound to plasma proteins and distributed to the liver and blood-forming organs.

INDICATIONS

Cyanocobalamin Co 57 - Co 60 is used for diagnosis of Addisonian (pernicious) anemia and as a diagnostic adjunct in other defects of intestinal absorption.

CONTRAINDICATIONS

None.

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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 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 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.

PRECAUTIONS

As in the use of any other 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.

The test should not be started within 24 hours of a therapeutic dose (1000 ug) of vitamin B-12 or within 24 hours of a loading dose of vitamin B-12 given for the Schilling test.

ADVERSE REACTIONS

None.

DOSAGE AND ADMINISTRATION

The suggested dose range employed for intravenous or oral administration in the average patient (70 kg) is up to 1.0 microcurie of cyanocobalamin Co 57 - Co 60.

In younger patients, the need should be carefully evaluated before a test (or test sequence) is repeated using cyanocobalamin Co 60 in the same patient.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Cobalt - 57 decays by electron capture with a physical half life of 270 days. The primary gamma energy of Co 57 is 122 KeV. Cobalt - 60 decays by beta and gamma emissions with a physical half life of 5.26 years. Photons that are useful for imaging studies are listed in Table I.[1]

Table I. Principal Radiation Emission Data

	Radiation	Mean %/disintegration	Mean Energy (KeV)	(MeV)
Co 57	Gamma -2	87.1	121.9	
	Gamma -3	9.6	136.3	
Co 60	Beta -1	99.8	94.1	
	Gamma -1	99.8		1.173
	Gamma -2	100.0		1.333

[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. 27, 1969.

The specific gamma ray constant for Co 57 is 1.0 R/mCi-hr at 1 cm. For Co 60 it is 13.0 R/mCi-hr at 1 cm. The half value layer for Co 57 is 0.2 mm of Pb. For Co 60 it is 1.2 cm of Pb.

To correct for physical decay of these radionuclides, the fractions that remain at selected time intervals before and after the day of calibration are shown in Table II.

1048716

Table II. Physical Decay Chart: Co 57, half life 270 days; Co 60, half life, 5.26 years

Days	Fraction Remaining		Days	Fraction Remaining	
	Co 57	Co 60		Co 57	Co 60
-15	1.039	1.005	60	.857	.979
-10	1.025	1.004	75	.825	.973
- 5	1.013	1.002	90	.794	.968
0*	1.000	1.000	105	.764	.963
5	.987	.998	120	.735	.958
10	.975	.996	135	.707	.952
15	.962	.995	150	.680	.947
30	.926	.989	165	.654	.942
45	.891	.984	180	.630	.937

*Calibration day

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous administration of 1 microcurie of Co 57 or Co 60 Vitamin B_{12} are shown in Table III.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/uCi Co 57)		(rads/uCi Co 60)	
	Normal	Pernicious Anemia	Normal	Pernicious Anemia
Liver	0.13*	0.026	3.4	0.65
Stomach	0.000031	0.00011	0.00085	0.0013
Small Intestine	0.00013	0.00040	0.0013	0.0039
Upper Large Intestine	0.00025	0.00076	0.0022	0.0066
Lower Large Intestine	0.00060	0.0018	0.0055	0.167
Testes	0.0052	0.00012	0.18	0.0052
Ovaries	0.0065	0.00057	0.24	0.020
Whole-body	0.0099	0.0013	0.32	0.040

1048711

*The administration of a flushing dose of nonradioactive Vitamin B_{12} will decrease the dose to the liver, gonads, and whole-body from Co 57 and Co 60 by about 30%.

[1]Method of calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: November 28, 1973

Principal Investigator: Francis A. Goswitz, M.D.

Co-Investigators:

Title of Project: Comparison of Indium-111 Chloride and Indium-111 Sulfur Colloid in Evaluation of Bone Marrow Disorders

I. Objectives of Experiment

A. Purpose

The objective is to determine which agent is superior or whether both agents are necessary to evaluate patients with bone marrow disorders or potential marrow abnormalities before and after treatment of their primary disease.

B. Background Information

The marrow can be scanned by labeling the reticulo-endothelial system with radiocolloids (e.g. ^{198}Au) or by labeling the erythron with ^{52}Fe. The ^{198}Au colloid is usually uniform in size but presents a radiation hazard to the liver; ^{99m}TcS colloid is a larger-size particle and often accumulates in the lung making interpretation between rib and lung uptake difficult. Production problems and a short half-life make ^{52}Fe unavailable for routine use. Iron-59 is unsuitable for conventional imaging. Indium-111, which binds to transferrin, possesses ideal physical and radiobiological characteristics as a tracer. Farrer and associates found selective uptake by bone marrow from ^{111}In-transferrin to be far superior to those of ^{99m}Tc S colloid in hematologically normal patients (J. Nuc. Med 13: 429, 1972 abstract). Liver and spleen visualized poorly suggesting that ^{111}In was not labeling the reticulo-endothelial system. Non-red marrow of the bones was also poorly visualized. The tracer disappeared from the plasma with a net half-time of about 11 hours, considerably longer than the normal half-disappearance time of 1-2 hours for radioactive iron. There was no incorporation of the tracer into erythrocytes up to 96 hours (certainly some radioiron is utilized normalized by 96 hours), but then it appeared in circulating erhythrocytes and leukocytes; white blood cells do not incorporate significant amounts of radioiron (Farrer, American Society of Hematology program, p. 56, abstract 70, 1972).

1048719

Lilien et al (J. Nucl. Med. 14: 184-186, 1973) also felt indium-111 chloride had several properties ideal for marrow imaging and that ionic indium metabolized similarly to iron. When injected intravenously at acid pH, indium binds virtually quantitatively to transferrin and appears to compete with iron for the same binding sites. Reported average plasma half-time disappearance values ranged from 6-10 hours, also longer than radioiron. They suggested that indium is actually incorporated into the metalloporphyrin in the place of iron.

II. Methods of Procedure:

The ^{111}In chloride is supplied in dilute hydrochloric acid, approximately 0.03 N HCl from the Oak Ridge National Laboratory or as a radiopharmaceutical from a commercial manufacturer (Medi-Physicis, Inc. or New England Nuclear). If the agent is obtained as a radiochemical, the product will be sterilized by autoclaving and Millipore filtration, radioassayed, and then injected intravenously in a dose of 0.5-2 mCi per patient. If it is obtained as a radiopharmaceutical, the compound will be injected as already prepared at its acid pH.

The ^{111}In sulfur colloid will be prepared by converting the chloride to the sulfur colloid by the sodium thiosulfate method using the same "Kit" procedure now used in the preparation of ^{99m}Tc sulfur colloid from pertechnetate. If the thiosulfate method fails to provide a satisfactory radiocolloid, we will use the hydrogen sulfide method as developed at Brookhaven National Laboratory (W. Hauser et al: New York State J. Med. 70: 848-854, 1970) or as previously performed by Hayes and his group at the ORAU Medical Division. Pinsky and co-authors (Southern Med. J. Proceedings of Southeastern Soc. N. Med. Meeting November 1-4, 1972) found sulfur colloid prepared by the hydrogen sulfide method to be superior in reticuloendothelial marrow uptake to sulfur colloid prepared by the sodium thiosulfate method.

Total-body rectilinear scans will be performed about 15-60 minutes after injection of the ^{111}In chloride. The indium-111 sulfur colloid scan will be done 24 hours after injection of the dose. We anticipate doing 100 scans in patients with a variety of marrow disorders. With our present nuclear medicine staff and their commitments to other studies, the time to accomplish this work would require at least 12 and possibly 18 months.

In 10 patients external organ counting, whole-body retention, and blood samples collected at 1/2, 1, 2, 4, 8, and 24 hours, 5 and 12 days, will be done to compare distribution and disappearance times with the two agents.

III. Possible Hazards and Their Evaluation:

Lilien states that preliminary dosmetry calculations according to Graham indicates a dose of 3.6 rads/mCi to marrow, 4.5 rads/mCi to the liver, and 0.5 rad/mCi to the total body (J. Nuc. Med. 14: 186, 1973). These calculations are based on highly conservative estimates of the biodistribution of indium, studies of which are being undertaken. Indium-111 has a physical half-life of 2.8 days. It decays by electron capture with the emission of two gamma photons, 173 Kev (89% per distintegration) and 247 Kev (94% per distintegration). It is produced by proton bombardment of enriched ^{111}Cd at Oak Ridge National Laboratory and supplied to the Medical Division free of cadmium in the carrier-free form.

1048120

The proposed dosage for both indium-111 chloride and sulfur colloid to the patient will be 0.75 mCi/M^2 body surface area. Both agents will be administered intravenously. Standard man is approximately 1.6 M^2 so that the total dose injected would be 1.2 millicuries.

No reports can be found in the literature pertaining to the organ distribution of ^{111}In sulfur colloid. If it follows the same distribution as ^{113m}In radiocolloid or ^{99m}Tc S colloid, then approximately 80% would distribute to the liver. (Goodwin, Nucleonics, Nov. 1966). He estimates that the radiation dose to the liver is ~0.55 rads/mCi ^{113m}In administered. The biologic half-life is approximately 30 days.

IV. Radioisotopes and New Drugs:

No new radioisotopes or new drugs are requested. No reports regarding the uses of ^{111}In sulfur colloid in patients have appeared in the literature to my knowledge, but ^{113m}In colloid has been shown to be an attractive liver and spleen scanning agent. (Goodwin, Stern and Wagner: A new radiopharmaceutical for liver scanning, Nucleonics, Nov. 1966) (Potchen and Adatepe: Liver and Spleen Scintiscanning with 113m-Indium: A Clinical Pathologic Correlation, Am. J. Roentgenol. 106: 739-744, August 1969).

V. Responsibility of Principal Investigator:

The same ORAU consent form as is required for our other experimental agents will be used in this study to obtain approval from the patient.

Starting Date: January 1, 1974

Signatures: Francis A. Gosnell, MD Principal Investigator

_____ Co-Investigator

_____ Co-Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Signature_____

Title _____

Institution_____

Date _____

1048721

FORM P-4

MEMORANDUM

TO Isotope Committee DATE November 28, 1973

SUBJECT COMPARISON OF INDIUM-111 CHLORIDE AND INDIUM-111 SULFUR COLLOID IN EVALUATION OF BONE MARROW DISORDERS (See proposal on this topic submitted to Human Use Committe

COPIES TO

1. Proposal:

Farrer and associates found selective uptake by the bone marrow from ^{111}In - transferrin to be far superior to those of ^{99m}Tc S colloid in hematologically normal patients (J. Nucl. Med. 13: 429, 1972 (abstract); Blood, December 1972, American Soc. Hematology (abstract). Lilien and co-authors (J. Nucl Med. 14: 184-186, 1973) confirmed this finding and reported on the value of ^{111}In-chloride as a new agent for bone marrow imaging. Our proposed study is to determine whether ^{111}In-sulfur colloid is superior as a scanning agent or whether both agents are necessary to evaluate patients with bone marrow disorders before and after treatment of their primary disease. ^{111}In-chloride supposedly labels the erythropoietic system of the bone marrow, ^{111}In-sulfur colloid the reticulo-endothelial system.

2. Radioisotope:

Indium-111 has a half-life of 2.8 days. It decays by electron capture with the emission of two gamma photons, 173 Kev (89%/disinteg) and 247 Kev (94%/disinteg.). It may be supplied to the Medical Division free of cadmium in the carrier-free form from the Oak Ridge National Laboratory where it will be produced by proton bombardment of enriched ^{111}Cd. It may also be obtained commercially as radiopharmaceuticals from either Medi-Physics, Inc. New England Nuclear Company.

3. Chemical Form:

The isotope will be received in the chloride form in dilute HCl. Both Farrer at Montreal and Lilien at UCLA injected ^{111}In-chloride intravenously into humans at an acid pH. We propose to do the same. With the ^{111}In-sulfur colloid we would first try to prepare this agent by the sodium thiosulfate "kit" method as in the case of ^{99m}Tc S colloid; if this preparation is unsatisfactory, then we will attempt the hydrogen sulfide method of the Brookhaven protocol modified by Hayes and his group.

4. Administration:

Intravenous injection using the same technique as employed now for administration of ^{99m}Tc S colloid.

5. Dosage:

Farrer used 1-2 mCi of ^{111}In-chloride but Lilien injected 2-5 mCi into each patient. We propose a dose of 0.75 mCi/M^2 body surface area which means initially a dose range from 0.5-2 mCi per patient. If this dose is too low, then it will be doubled if possible in some patients provided that the patient has a disease which will accept this amount of increased radioactivity.

6. Experimental protocol:

a. Number and selection of patients: 100 scanning studies, divided between those having positive and negative ^{111}In-chloride and ^{111}In-sulfur colloid scans. Ten patients would be studied with external organ counting (heart, liver, spleen, sacrum), blood sampling at 1, 2, 4, 8, and 24 hours, 5 and 12 days to evaluate plasma disappearance and red-cell utilization, and whole-body counting to determine total-body retention.

b. Duration of studies: 12-18 months with our pesent nuclear medicine staff.

c. Type and frequency of assay: See 6a above. The urines and stools will not be collected unless we find total-body retention less than 80% by 10 days. Wochner and coworkers in a study for estimation of plasma volume with the use of indium-113m-transferrin found little indium was excreted, 11% in the urine and 4% in the feces. (J. Lab. Clin. Med. 75: 711-720, 1970).

d. Special procedures: Whole-body scans will be performed in all studies. Liver and spleen scintiphotos with the Anger camera will be requested in all studies since time will not permit always the obtainment of rectilinear scans.

7. Distribution Studies:

Farrer and his associates found that indium-111 chloride disappeared from the plasma with a net half-time of about 11 hours. The plasma disappearance curve had two exponetial components, an initial one with a half-time of about 4 hours followed by a slow component with a half-time of about 30 hours. There was no incorporation of the tracer into erythrocytes up to 96 hours. The liver and spleen were poorly visualized according to Farrer, but the liver on the two illustrations in Lilien's article was well-visualized. No information has been reported to my knowledge involving the distribution of indium-111 sulfur colloid in man; we are assuming that its distribution will simulate other radiocolloids.

8. Radiation Dose:

Lilien in his March 1973 article (J. Nucl. Med.) reported that preliminary dosimetry calculations according to Graham would indicate a dose of 3.6 rads/mCi to the marrow, 4.5 rads/mCi to the liver, and 0.5 rad/mCi to the total body. These calculations he stated were based on highly conservative estimates of the biodistribution of indium, studies of which are being undertaken.

9. Related and Pertinent Human Data:

The only total-body scan reports involving the use of indium-111 chloride (transferrin) as a bone-marrow imaging agent are the ones by Farrer and Lilien. Kinetic information on the degree of the agent's utilization in red cells is lacking. Comparison with indium's distribtuion as a sulfur colloid would help determine the chloride's labeling of non-reticulo-endothelial elements only.

10. Chemical, Radiation and Infectious Hazards:

The ^{111}In will be carrier-free since it is produced by proton bombardment; chemical toxicity from indium is therefore not relevant. A microanalytical test for cadmium will be made on each batch of ^{111}In on receipt. Spectrometric verification of radionuclide purity of each batch will also be made.

A trace amount of ^{114}In will be present in the preparation due to the presence of small amount of ^{114}Cd in the separated ^{111}Cd target material. This is estimated by Oak Ridge National Laboratory to be approximately 0.02% of the ^{111}In level (0.2 Ci/mCi ^{111}In) at one half-life after termination of the target bombardment. The radiation dose from ^{114}In per Ci is estimated by the Radiation Safety Office to be 0.042 rads to the whole body and 0.41 rad to the bone. Thus, the whole-body dose contribution from the presence of this contaminant will be 0.008, 0.015, and 0.03 rad per mCi of ^{111}In administered

1048723

at one, two and three half-lives after termination of bombardment. The dose to the bone 1 be 0.082, 0.157, and 0.305 rad/mCi ^{111}In at the same intervals. The total dose due both ^{111}In and ^{114}In will then be: Bone 2.4, 2.5, and 2.6 rads/mCi ^{111}In, and whole body 0.49, 0.5 and 0.51 rad/mCi ^{111}In at these time intervals.

The ^{111}In solution will be milipore filtered (0.22 micron) into an autoclaved, sealed vial on receipt and tested for pyrogenecity. The preparation of the ^{111}In dose will be carried out in a laminar-flow hood using sterile equipment. Final sterilization will be made through milipore filtration. Ten percent of the preparation will be withheld for testing should the patient show any reaction.

No test for pyrogenecity and no milipore filtration will be performed if the radiopharmaceutical is obtained from a commercial supplier. Ten percent of the preparation will be withheld for testing, however, should the patient show any reaction.

Same procedure for the ^{111}In sulfur colloid preparation will be performed as is now being done to prepare ^{99m}Tc sulfur colloid using the sodium thiosulfate procedure.

Starting date: January 1, 1974 pending approval of study by Human Use Committee.

Francis A. Goswitz, M.D.

1048724

FORM P-4

MEMORANDUM

Medical Radionuclide Committee DATE 3 December 1973

SUBJECT INDIUM-111 CHLORIDE AND INDIUM-111 SULFUR COLLOID

COPIES TO Dr. Andrews, file

Dr. Goswitz has submitted the attached proposal for use of In-111 chloride and In-111 sulfur colloid for our review. He hopes that we will approve the proposal at our 4 December 1973 meeting so that he can submit the proposal to the Committee on Human Studies before their 11 December 1973 meeting. I have also attached Dr. Goswitz's proposal to the Committee on Human Studies.

Roger J. Cloutier

RJC:vrs

Members:
- Berger
- Cloutier ✓
- Edwards
- Harmon
- Hayes
- Lushbaugh

1048725

12-4-73

Radiation Dose (rads per millicurie administered)

	Total Body*	Liver	Spleen	Skeleton	Marrow	Gonads	
						Testes	Ovaries
In-S-colloid	0.55	12	4.7	0.35	0.84	0.012	0.15
In-chloride	0.55	0.93	1.7	1.7	3.8	0.89	0.87

* based on uniform distribution in body.

1048726

FORM F-4

MEMORANDUM

TO Medical Radionuclide Committee

DATE 6 December 1973

SUBJECT DR. GOSWITZ'S PROPOSALS

COPIES TO Dr. Andrews, Dr. Goswitz, file

The Medical Radionuclide Committee has scheduled a special meeting for Friday, December 7, 1973 at 1:30 p.m. in the second floor conference room to hear Dr. Goswitz present his proposal to use ^{111}InCl and ^{111}In sulfur colloid in humans at ORAU. The proposal was distributed to committee members on 3 December 1973.

Roger J. Cloutier

Roger J. Cloutier

Members:
- Berger
- Cloutier ←
- Edwards
- Harmon
- Hayes
- Lushbaugh

1048727

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Francis A. Goswitz, M.D. PROPOSAL NO. 73-4

DESCRIPTION:

Comparison of In-111 chloride and In-111 sulfur colloid in evaluation of bone marrow disorders (Memo of Nov. 28, 1973).

This proposal was considered in two parts. This disapproval is for the the use of In-111 sulfur colloid in humans.

☐ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not___ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not___ be administered to pregnant patients

Other:

☒ The Committee disapproves for the following reasons:

Additional work needs to be done on the preparation of the sulfur colloid and its distribution and retention in animals.

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
Berger		[signature]		12/7/73
Cloutier		[signature]		12/7/73
Edwards		[signature]		12/7/73
Harmon			✓	
Hayes		[signature]		12/7/73
Lushbaugh			✓	

Acknowledgement of Submitter Francis A. Goswitz Date 12/10/73

- -

Proposal does ___ does not ___ require approval of Committee on Human Studies.

Human Studies approval granted on 1048728

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Francis A. Goswitz, M.D. PROPOSAL NO. 73-3

DESCRIPTION: Comparison of In-111 chloride and In-111 sulfur colloid in evaluation of bone marrow disorders (Memo of Nov. 28, 1973.

This proposal was considered in two parts. This approval is given for the use of In-111 chloride.

[X] The Committee approves with the following limitations:

Radiopharmaceutical may ✓ ~~may not~~ ___ be administered to patients under 18 years of age/ only if the patient has a malignant hematologic disorder.

Radiopharmaceutical ~~may~~ may not ___ be administered to pregnant patient.

Other: Radiopharmaceutical may not be used if In-114m is present in an amount that would contribute more than 10% of the In-111 dose.

[ ] The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
Berger	[illegible]			12/7/73
Cloutier	[illegible]			12-7-73
Edwards	[illegible]			12-7-73
Harmon			✓	
Hayes	[illegible]			12/7/73
Lushbaugh			✓	

Acknowledgement of Submitter Francis A. Goswitz Date 12/10/73

- -

Proposal does ___ ~~does not~~ ___ require approval of Committee on Human Studies.

Human Studies approval granted on Withdrawn 11 Dec 73

1048729

FORM P-4

MEMORANDUM

TO File DATE 16 January 1974

SUBJECT MEDICAL RADIONUCLIDE COMMITTEE MEETING OF 7 DECEMBER 1973

COPIES TO

Committee members Berger, Cloutier, Edwards, and Hayes met with Dr. Goswitz to discuss his proposals to administer ^{111}In-chloride and ^{111}In-sulfur colloid to humans. After considerable discussion of the merits of the proposal and the adequacy of the presented data, the committee voted unanimously to permit the use of ^{111}In-chloride at ORAU provided the proposal is subsequently approved by the Committee on Human Studies. The committee did not approve the use of ^{111}In-sulfur colloid in humans because it felt that sufficient data does not exist to prove that an adequate colloid could be produced. The committee therefore disapproved the proposal. A record of both actions was recorded on the form developed by the committee for recording such action.

Roger J. Cloutier

Roger J. Cloutier

RJC:vrs

1048730

FORM P-4

MEMORANDUM

TO File DATE 16 January 1974

SUBJECT MEETING OF MEDICAL RADIONUCLIDE COMMITTEE ON 4 DECEMBER 1973

COPIES TO

Committee members Berger, Cloutier, Edwards, Lushbaugh, and Hayes met to discuss the draft of the proposed responsibilities and operating rules for the committee. Many different comments were made regarding the distributed draft. Cloutier was assigned the task of rewriting the draft to take into account the new comments. The committee then reviewed the proposals submitted by Dr. Goswitz on ^{111}In-chloride and ^{111}In-sulfur colloid. It was decided that before taking action on these proposals the committee should meet with Dr. Goswitz so that he could present his proposals. This meeting was scheduled for 7 December 1973.

Roger J. Cloutier

Roger J. Cloutier

RJC:vrs

1048731

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. L. Edwards, M.D. PROPOSAL NO. 73-2

DESCRIPTION:

Use of Tc-99m Osteoscan for bone scanning.

Kit to be used is described on attached package insert distributed by Procter and Gamble Co.

[X] The Committee approves with the following limitations:

Radiopharmaceutical ~~may~~ xxx may not___ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~ xxx may not___ be administered to pregnant women.

Other:
none

[ ] The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. Berger	JB			11/14/73
R. Cloutier	RC			11/14/73
C. L. Edwards	CLE			11/14/73
H. Harmon			✓	
R. Hayes	RH			11/14/73
C. Lushbaugh			✓	

Acknowledgement of Submitter [signature] Date 28 Nov 73

- -

Proposal ~~XXXXXXXXX~~ does not ___ require approval of Committee on Human Studies.

Human Studies approval granted on

1048132

NDC 37000-400-01

73-2

PROCTER & GAMBLE

OSTEOSCAN

(5.9 MG DISODIUM ETIDRONATE 0.16 MG STANNOUS CHLORIDE)

SKELETAL IMAGING AGENT

DESCRIPTION

Each vial of OSTEOSCAN contains 5.9 mg disodium etidronate and 0.16 mg stannous chloride as active ingredients. Upon addition of ADDITIVE-FREE ^{99m}Tc-pertechnetate, these ingredients combine with ^{99m}Tc to form a stable soluble complex.

ACTIONS (CLINICAL PHARMACOLOGY)

When injected intravenously, ^{99m}Tc-labeled OSTEOSCAN has a specific affinity for areas of altered osteogenesis. Areas of bone which are undergoing neoplastic invasion often have an unusually high turnover rate which may be imaged with ^{99m}Tc-labeled OSTEOSCAN.

Three hours after intravenous injection of 1 ml ^{99m}Tc-labeled OSTEOSCAN, an estimated 40-50% of the injected dose has been taken up by the skeleton. At this time approximately 50% has been excreted in the urine and 6% remains in the blood. A small amount is retained by the soft tissue. The level of ^{99m}Tc-labeled OSTEOSCAN excreted in the feces is below the level detectable by routine laboratory techniques.

INDICATIONS

OSTEOSCAN is a skeletal imaging agent used to demonstrate areas of altered osteogenesis.

CONTRAINDICATIONS

None.

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or lactating unless the information to be gained outweighs 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 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.

The ^{99m}Tc- generator should be tested routinely for molybdenum breakthrough and aluminum. If either is detected, the eluate should not be used.

PRECAUTIONS

Both prior to and following ^{99m}Tc-labeled OSTEOSCAN administration, patients should be encouraged to drink fluids. Patients should void as often as possible after the ^{99m}Tc-labeled OSTEOSCAN injection to minimize background interference from accumulation in the bladder and unnecessary exposure to radiation.

As in the use of any other 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.

ADVERSE REACTIONS

None.

DOSAGE AND ADMINISTRATION

The recommended adult dose of ^{99m}Tc-labeled OSTEOSCAN is 1 ml with a total activity range of 10-15 mCi. ^{99m}Tc-labeled OSTEOSCAN should be given intravenously by slow injection over a period of 30 seconds within three (3) hours after its preparation. Optimum scanning time is 3-4 hours postinjection.

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.

Table I. Principal Radiation Emission 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
Kα X-rays	6.5	18.4

[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.

The specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half value layer is 4 mm of Pb.

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.

Table II. Physical Decay Chart; ^{99m}Tc, half-life 6 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.779	5	.562
-4	1.587	6	.500
-3	1.414	7	.446
-2	1.260	8	.397
-1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 15 millicuries of ^{99m}Tc-labeled OSTEOSCAN are shown in Table III. For comparison, the estimated radiation doses from a maximum dose of 4 millicuries of ^{18}F used as a bone imaging agent are also included.

Table III. Radiation Doses

Tissues	Absorbed Radiation Dose	
	^{99m}Tc-OSTEOSCAN (rads/15 mCi)	^{18}F (rads/4 mCi)
Skeleton*	0.59	0.64
Testes	0.32	0.83
Ovaries	0.33	0.65
Total Body	0.13	0.18
Bladder 4.8 hour void	8.4	
Bone Marrow	0.14	

*Local dose may be a factor of 10 or more greater.

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

HOW SUPPLIED

The OSTEOSCAN kit contains five (5) vials. Each vial contains 5.9 mg disodium etidronate and 0.16 mg stannous chloride as active ingredients. The contents of each vial are prepared by appropriate manufacturing procedures to be sterile and pyrogen-free.

PREPARATION FOR USE

The following aseptic procedure should be followed in the preparation of the ^{99m}Tc-labeled OSTEOSCAN skeletal imaging agent:

STEP 1.
Remove central metal disc of the OSTEOSCAN vial and swab the top of the vial with alcohol to sterilize the surface of the closure.

STEP 2.
Place the OSTEOSCAN vial in a radiation shield. In a sterile syringe, collect 5 ml of sterile pyrogen-free ^{99m}Tc-pertechnetate from an additive-free ^{99m}Tc-pertechnetate source which has been checked for molybdenum breakthrough. Check the activity of the ^{99m}Tc-pertechnetate to avoid exceeding 50-75 mCi/5 ml. If the activity exceeds this level, dilute with ADDITIVE-FREE sterile saline only such that a 5 ml portion will contain the 50-75 mCi activity.

STEP 3.
Add the ^{99m}Tc-pertechnetate to the vial. After adding the ^{99m}Tc-pertechnetate to the vial, withdraw an equivalent amount of air to equalize the pressure inside the vial to prevent spray contamination. CAUTION: DO NOT USE ^{99m}Tc-PERTECHNETATE WHICH CONTAINS AN OXIDIZING AGENT. INTRODUCTION OF AN OXIDANT MAY RESULT IN A SOLUTION UNSUITABLE FOR SKELETAL IMAGING. Commercial sources of ^{99m}Tc-pertechnetate that have been used in clinical trials with OSTEOSCAN include the New England Nuclear Technetium-99m Generator, the Mallinckrodt Technetium-99m Generator, the Squibb Hi-Con Generator, Medi+Physics Instant Technetium, and Cambridge Nuclear Instant Technetium.

STEP 4.
Shake the vial well for three (3) minutes to assure complete dissolution of the contents. Minimal exposure can be obtained by use of either an ultrasonic agitator or mechanical shaker.

STEP 5.
Record the time and date of preparation and the activity of the ^{99m}Tc-labeled OSTEOSCAN on the radiation shield label contained in the kit and affix this label to the shield.

STEP 6.
Use within three (3) hours of preparation. Discard excess material.

1048733

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. L. Edwards, M.D. PROPOSAL NO. 73-1

DESCRIPTION:

Use of Tc-99m labeled albumin microspheres for lung imaging.

Kit to be used is described on attached package insert distributed by 3M Co.

[x] The Committee approves with the following limitations:

Radiopharmaceutical ~~may~~ may not___ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~ may not___ be administered to pregnant women.

Other:

none

[ ] The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. Berger	JB			11/14/73
R, Cloutier	RC			11/14/73
C. L. Edwards	CLE			11/14/73
H. Harmon			✓	
R. Hayes	RH			11/14/73
C. Lushbaugh			✓	

Acknowledgement of Submitter C L Edwards Date 18 Nov 73

- -

Proposal ~~does~~ does not ___ require approval of Committee on Human Studies.

Human Studies approval granted on _____

10481 3H

73-1

Table IV. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/7 mCi)
Lungs	2.03
Bladder Wall	0.39
Liver	0.12
Spleen	0.12
Testes	0.04
Ovaries	0.05
Total Body	0.11

[1] Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD Pamphlet No. 1, p. 7, 1968.

HOW SUPPLIED

Kit Contents

The Albumin Microspheres kit for labeling with sodium pertechnetate Tc 99m consists of:

5 labeling vials, each containing 5 mg Albumin Microspheres (Human), 100-250 micrograms tin in the form of stannous chloride and stannic chloride pentahydrate, and 6 mg Pluronic F-68.

10 "CAUTION-RADIOACTIVE MATERIAL" and radioassay labels (pressure sensitive).

1 Package Insert

Directions for Preparation

The technetium-99m used for labeling the Albumin Microspheres is furnished by the user. Sterile, non-pyrogenic solutions of sodium pertechnetate Tc 99m can be obtained by elution of a commercially available generator or delivered daily from a commercial supplier.

SOLUTIONS OF SODIUM PERTECHNETATE Tc 99m WHICH CONTAIN OXIDIZING AGENTS SHOULD NOT BE USED.

In choosing the amount of Tc 99m radioactivity to be used in the preparation of the Technetium Tc 99m Albumin Microspheres Injection, the number of patients, administered radioactive dose and radioactive decay must be taken into account.

Procedure

1. Add 15-60 mCi sodium pertechnetate Tc 99m to the shielded vial (the shield should have at least a 4 mm lead wall and cap). If the volume is less than 4 ml, add Sodium Chloride Injection U.S.P. to a total volume of 4-10 ml.
2. Put the shield cap on the shield and vigorously shake the vial (5-15 seconds).
3. Using forceps (at least 9" in length), remove the vial from the shield and place in center of an operating ultrasonic bath containing 3/4" of water. The bath should be protected by lead glass or bricks. Ultrasound for 5 minutes.

The vial should be visually inspected before removing the dose of Technetium Tc 99m Albumin Microspheres Injection. The vial should be adequately shielded during the visual inspection. If aggregates are present, the vial should be sonicated or shaken vigorously. Do not use the preparation after 8 hours from the time of formulation.

Storage

After labeling, store the Albumin Microsphere labeling vial in a lead shield at 2-8°C.

This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.14 and Section 35.100 Group III of 10 CFR, Part 35 or under equivalent licenses of Agreement States.

34-7009-1802-1A (491.5) BPH

Litho in U.S.A. with 3M BRAND Photo Offset Plates, Film and Chemicals.

Diagnostic Products
Medical Product Division/3M
3M Center, St. Paul, MN 55101

3M

1048735

ALBUMIN MICROSPHERES (HUMAN)
FOR LUNG IMAGING
(15 – 30 MICRON)

3M BRAND ALBUMIN MICROSPHERE
^{99m}Tc LABELING KIT

3M Brand Albumin Microspheres are provided in a dry, sterile, pyrogen-free vial designed for rapid and efficient labeling with technetium-99m. The ^{99m}Tc-labeled Albumin Microspheres are intended for gamma scintillation imaging of the lungs following intravenous administration.[1-4] The Albumin Microspheres are produced from Normal Serum Albumin (Human), U.S.P., and their size is controlled in such a manner that 100 percent are within a diameter range of 5-50 microns, 90 percent falling within a diameter range of 15 to 30 microns. A labeling efficiency of 60 percent is possible.

The Albumin Microspheres are produced by agitating Normal Serum Albumin (Human), U.S.P., in heated vegetable oil. The resultant spherical Albumin Microspheres are processed to a dry and free-flowing state which allows sieving to the desired size range (15 to 30 microns diameter). Each Albumin Microsphere ^{99m}Tc-Labeling Vial contains 5 mg of Albumin Microspheres. The Labeling Vial, the Rinsing and Suspending Solution Vial, the special 3/8 inch 25 gauge needle and a radioactive warning label are the components of a single Albumin Microsphere ^{99m}Tc Labeling Unit.

IDENTIFICATION

The Albumin Microspheres are packaged in a dry, sterile, pyrogen-free, two-compartment Labeling Vial. One compartment contains a cation-exchange resin which produces sufficient hydrochloric acid for the technetium-99m labeling procedure when the pertechnetate solution is introduced into the compartment. The second compartment contains 5 mg of Albumin Microspheres and a reagent tablet. The two compartments are separated by a glass filter that prevents passage of the Albumin Microspheres into the compartment containing the ion-exchange resin, and vice versa. A 25 gauge, 3/8 inch disposable needle is also provided to facilitate introduction of the technetium-99m solution into the Labeling Vial. When dry, 100 percent of the Albumin Microspheres are between 5-50 microns in diameter, with at least 90 percent between 15-30 microns. After labeling with technetium-99m using the recommended labeling instructions and soaking for 30 minutes in 3M Rinsing and Suspending Solution, the increase in mean diameter does not exceed 50 percent of the mean diameter of the dry form.

The Rinsing and Suspending Solution is contained in a separate vial and is used for rinsing the ^{99m}Tc-labeled Albumin Microspheres and for preparing the final suspension. The Rinsing and Suspending Solution is sterile, pyrogen-free and consists of Sodium Chloride for Injection, U.S.P., polysorbate 80 and benzyl alcohol.

1048736

ALBUMIN MICROSPHERES (HUMAN)

TECHNETIUM-99M FOR LABELING 3M BRAND ALBUMIN MICROSPHERES

The technetium-99m used for labeling the Albumin Microspheres is furnished by the user. Sterile, non-pyrogenic solutions of ^{99m}Tc sodium pertechnetate can be obtained by aseptic elution of commercially available generators.

PHARMACOLOGY AND METABOLISM

The intravenous LD_{50} for Albumin Microspheres is 72.2 mg/kg in the mouse and 43.8 mg/kg in the rat. The MLD for the intravenous administration of Albumin Microspheres is 68.1 mg/kg in the dog and 82.6 mg/kg in the monkey. The toxic doses employed were at least 1000 times the estimated maximum recommended adult dose of 0.04 mg/kg.

At necropsy, the most consistent findings were pulmonary edema with histological evidence of the Albumin Microspheres in pulmonary arterioles and capillaries. Their presence was also observed in the brain, heart, liver and kidney with congestion of the liver and kidneys.

The Albumin Microspheres were administered intravenously to dogs and monkeys once every other day for a total of eight doses at levels of 1, 7 and 20 mg/kg. No consistent or distinctive product-related effects were observed with regard to physical appearance and behavior, appetite, and body weight in any of the test animals.

Clinical laboratory studies did not reveal any definite product-related effects. Gross necropsy findings in the monkey were negative. Gross findings in the dog at necropsy showed product-related alterations of the lungs (hemorrhagic-appearing areas) at the 20 mg/kg level, the cervical and mediastinal nodes (medullas reddened), and the attachment between the liver and gallbladder (appeared deep red) at the 7 and 20 mg/kg levels.

In both the dog and monkey, histopathologic examination revealed the presence of Albumin Microspheres as represented by eosinophilic-staining, globular material in the vascular bed of the lungs at all three dosage levels. The presence of this eosinophilic material was accompanied by endothelial cell proliferation and focal perivascular lymphoreticular cell proliferation.

Following intravenous administration, 99 percent of the Albumin Microspheres administered to mice are cleared from the lungs within 29 hours. The effective half-life of the technetium-99m in the lung of the mouse is 5.5 hours. The radiation dose to the human lung is approximately 0.4 rads/mCi of ^{99m}Tc administered.[3]

1048737

ALBUMIN MICROSPHERES (HUMAN)

INDICATIONS

Scintillation imaging of the lungs with ^{99m}Tc-labeled Albumin Microspheres is indicated as an adjunct to other diagnostic procedures whenever information about pulmonary circulation is desired. [4, 5] The most useful clinical applications of lung imaging are in the diagnosis of 1) pulmonary embolism, 2) chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis, 3) pathological conditions which impede pulmonary blood flow such as carcinoma and pulmonary abscess, and 4) other pulmonary diseases such as pneumonia and tuberculosis.

PRECAUTIONS

To ensure minimum radiation exposure to all personnel including physicians, patients, technicians and nurses, radiopharmaceuticals should be used only by physicians who are qualified by specific training in the use and safe handling of radioisotopes and whose experience and training have been approved by an individual agency or institution already licensed in the use of radioisotopes.

CONTRAINDICATIONS

The use of radiopharmaceuticals is contraindicated in pregnant women, nursing mothers, or patients under 18 years of age unless exceptional conditions exist.

The safety of Albumin Microspheres in patients with a known right-to-left cardiac shunt has not been established and its use in such patients is contraindicated.

SIDE EFFECTS

Although no anaphylactoid reactions have been reported in patients following the administration of Albumin Microspheres, the possibility should be considered that hypersensitivity reactions may occur rarely in patients who, after the initial administration, receive additional doses a number of weeks after the initial dose. In the clinical evaluation of the Albumin Microspheres, a total of 175 patients received two to eight injections with no anaphylactoid reactions. The time between injections ranged from 1 to 232 days. The majority of repeat lung scans occurred within one to seven days and a very few repeat scans were spaced more than 90 days apart.

1048738

ALBUMIN MICROSPHERES (HUMAN)

Two patients experienced adverse reactions following the administration of Albumin Microspheres. One patient with a history of acute myocardial infarction, cough and weakness, experienced an episode of severe coughing and shortness of breath with head and neck cyanosis shortly after administration of the Albumin Microspheres. Following diagnosis of acute pulmonary embolism, the patient was treated with anticoagulants and experienced no evidence of long term effects. A second patient experienced an episode of flushing and rapid breathing following administration of Albumin Microspheres. Lung imaging procedures were completed when the symptoms subsided spontaneously within three minutes. No adverse effects could be documented and an anxiety reaction to the injection procedure is a possible cause. The patient was treated with heparin for the presumptive diagnosis of pulmonary embolus. Both patients recovered completely from these episodes.

DOSAGE AND PROCEDURE

The recommended adult dose of ^{99m}Tc-labeled Albumin Microspheres is 1-4 mCi (0.2 – 2 mg Albumin Microspheres). The usual adult dose is 2.0 mCi (0.8 mg Albumin Microspheres).

It is not necessary to block the thyroid prior to administration of the ^{99m}Tc-labeled Albumin Microspheres.[6]

In choosing the amount of ^{99m}Tc radioactivity to be used in the preparation of the ^{99m}Tc-labeled Albumin Microspheres, the labeling efficiency, number of patients, administered radioactive dose and radioactive decay must be taken into account. The recommended amount of ^{99m}Tc radioactivity to be added to the Labeling Vial is 40 mCi. Assuming an average ^{99m}Tc uptake of 60 percent, this will yield 5 mg of ^{99m}Tc-labeled Albumin Microspheres with a specific activity of approximately 5 mCi/mg at the time of labeling and approximately 2 mCi/mg eight hours later.

Labeling is accomplished according to the instructions provided with each kit.

Though aggregation of the Albumin Microspheres seldom occurs (only 9 out of 1400 administrations during the clinical trials), the Labeling Vial should be visually inspected before removing the dose of Albumin Microspheres to be administered. If aggregation is observed, the Labeling Vial should be returned to the ultrasonic bath for one minute. The Labeling Vial should be adequately shielded during the visual inspection.

The ^{99m}Tc is slowly leached from the Albumin Microspheres on standing. In order to minimize the possible interference from liver and spleen uptake due to the free ^{99m}Tc, it is recommended that the Microspheres be rerinsed once if they have stood for more than three hours after labeling. This rinse step should be performed just prior to injection to minimize free ^{99m}Tc. The Microspheres need not be rinsed again if they are used within the recommended time limit of eight hours from the time of labeling. Again, 1-2 minutes before withdrawing the Microspheres from the Labeling Vial for injection, shake well or ultrasonically agitate for one minute and reinspect for aggregation.

1048739

Albumin Microspheres labeled with technetium-99m are injected intravenously over a 10-20 second period using a plastic syringe. Glass syringes should be avoided because the Albumin Microspheres may interfere with the free action of the plunger.

For optimum results, lung imaging should begin as soon as possible and not more than one hour after administration of the Albumin Microspheres.

The physician should be familiar with lung imaging and its use in the diagnostic process.[5, 7-9] He should establish for himself the imaging procedure which provides optimal results.

HOW SUPPLIED

The Albumin Microsphere ^{99m}Tc Labeling Kit consists of the following items:

5 LABELING VIALS

Each Labeling Vial contains 5 mg Albumin Microspheres (Human) and the necessary reagents for labeling the Microspheres with technetium-99m.

5 RINSING AND SUSPENDING SOLUTION VIALS

Each vial contains 30 cc of Rinsing and Suspending Solution.

5 NEEDLES (25 g) for injecting technetium-99m into the Labeling Vial.

5 RADIOACTIVE WARNING LABELS (pressure sensitive).

1048740

REFERENCES

1. Buck A. Rhodes, Ilse Zolle, Julia W. Buchanan and Henry N. Wagner, Jr.: Radioactive Albumin Microspheres for Studies of the Pulmonary Circulation, Radiology 92: 1453-1460 (1969).

2. Julia W. Buchanan, Buck A. Rhodes and Henry N. Wagner, Jr.: Labeling Albumin Microspheres with ^{113m}In, J. Nuc. Med. 10: 487-490, (1969).

3. J. A. Burdine, R. E. Sonnemaker, L. A. Ryder and H. J. Spjut: Perfusion Studies with Technetium-99m Human Albumin Microspheres (HAM), Radiology 95: 101-107 (1970).

4. J. A. Burdine, L. A. Ryder, R. E. Sonnemaker, G. DePuey and M. Calderon: ^{99m}Tc-Human Albumin Microspheres (HAM) for Lung Imaging, J. Nuc. Med. 12: 127-130 (1971).

5. L. M. Freeman, et al: Radionuclide Studies of the Lung, Seminars in Nuclear Medicine 1: No. 2, 1-262 (1971).

6. J. G. McAfee, C. F. Fruger, H. S. Stern, H. N. Wagner and T. Migita: Tc-99m Pertechnetate for Brain Scanning, J. Nuc. Med. 5: 811-27, (1964).

7. H. N. Wagner, Jr.: Principles of Nuclear Medicine, W. B. Saunders Co., Philadelphia (1968).

8. J. L. Quinn: The Lung: The Challenge of Nuclear Medicine, Am. J. Roent. 105: 251-259 (1969).

9. E. R. Weibel: Morphometry of the Human Lung, Academic Press, New York (1963).

File Copy
File Copy

FORM P-8A

MEMORANDUM

TO: Dr. W. G. Pollard

DATE: March 24, 1967

SUBJECT: Use of Radioisotopes in Humans

COPIES TO: File

We are attaching a draft of a policy of the committee for use of radioisotopes in humans, and a policy concerning the recruitment of human volunteers.

After you have read this material we would like to talk with you about the next steps to take in informing the Commission of our plans.

Gould A. Andrews

attachment -

1048742

3. A reimbursement may be offered to the volunteer.

III. Release Form - An agreement signed and witnessed that:

1. Participation is of the person's own volition,
2. Subject understands that this experience is for experimental purposes, not for diagnosis or treatment,
3. Subject understands the nature, procedures, and probable effects, if any, of the experiment. (These features should be listed or described briefly in the agreement.)
4. The volunteer, whether or not he is an employee of ORAU, is not considered an employee insofar as the experiment is concerned.

XXXXX

1048743

MEMORANDUM

TO: [illegible]

DATE: July [illegible], 19[illegible]

SUBJECT: RADIOHEALTH PHYSICS DETERMINATION OF PERMISSABLE DOSE TO EMPLOYEE - VOLUNTEERS IN RADIOASSAY PROGRAM

COPIES TO: William Gibbs and file

Recently in consideration of the upper limit of radioiodine that can be given to employee-volunteers under existing AEC rules of maximum permissable occupational exposure, it appeared that our radiation safety office was applying guide lines that extended the intentions of the AEC committee. The reasons for this action seemed based on the generally accepted concept that the least dose is the best dose. While no one can argue against this truism, I would like to argue that a dose reduction that makes the statistical validity of research results questionable should not be accepted unless there are reasons other than unsupported opinions, emotional bias and matter of taste. An arbitrary safety factor of 5 put upon existing permissable quarterly exposure limits makes it impossible for us to correlate organ and whole-body radioactivity for a sufficiently long period of time to obtain the answers we need in our whole-body iodine retention study.

C. C. Lushbaugh, M.D.

bbc

1048744

FORM P-4

MEMORANDUM

TO: G. A. Andrews

DATE: July 1, 1966

SUBJECT: "HUMAN USE COMMITTEE"

COPIES TO: William Gibbs and file

We believe the temporary "Human Use Committee" should be made permanent. It is a good idea to have an in-house group review proposed research programs involving radioisotopes in man, particularly in normal volunteers. We (William Gibbs and C. C. Lushbaugh) should not be members as we are users. Also, any member of the standing committee should be disqualified when a proposal of his own is under consideration. An important member of this committee would be Roger Cloutier or a substitute when he is out of town.

New experimental procedures should be proposed formally in a written protocol to this committee through your office. This protocol should explain the problem or question that the research might help answer: the minimum numbers of normal subjects and patients needed for valid interpretation of results; dosage levels forced by instrumental and temporal requirements; and the frequency and duration of radioassays. This committee should be empowered to veto a proposal, but the proposer should have the opportunity to argue his position and reach a justifiable compromise in such a case.

C. C. Lushbaugh, M.D.

bbc

William Gibbs

1048745

FORM P

TO R. M. Kniseley
C. C. Lushbaugh
C. L. Edwards
R. J. Cloutier

MEMORANDUM

DATE June 29, 1966

SUBJECT TRACER DOSE OF RADIOISOTOPES IN VOLUNTEERS

COPIES TO File

Recently, discussions have focused on the need for clear-cut policies in connection with the giving of tracer doses of radioisotopes to volunteers. Some months ago, in the face of an urgent problem, a procedure was set up to deal with the ethical and legal aspects of some doses of cesium which were given for an intercalibration study on the whole-body counter. These procedures seemed to serve admirably, but after the initial problem, we did not take any particular action in setting them up as general policy. It may be that these procedures, or a somewhat modified version of them, will be entirely satisfactory for the very small tracer doses, but if we wish to give volunteers doses in the neighborhood of those used for ordinary clinical diagnostic tests, certain other problems would arise. There are also questions concerning how the volunteers should be recruited (I am inclined to believe that some sort of bulletin board announcement, rather than personal contacts, would be more free of any suggestion of coercion) and whether they should be reimbursed for serving in this way.

Within the next month we will try to establish a policy and make it available to all of our staff members. Meanwhile, in order not to delay any prospective studies, I believe that the procedure followed in the earlier cesium measurements should be followed, and that for each experiment agreement should be reached among at least three members of the group to whom this memorandum is addressed.

GAA

Gould A. Andrews, M. D.

GAA:fb

1048746

FORM - 4

MEMORANDUM

TO Bruce Ketelle, ORNL

DATE November 8, 1974

SUBJECT COMPARISON OF RADIATION DOSES FROM ER-165 AND TC-99M

COPIES TO File

The attached table gives our comparison of the radiation doses to the skeleton from ^{99m}Tc and ^{165}Er. We have calculated the dose for three situations: (1) the radionuclide uniformly distributed in the body, (2) 50% of the radionuclide in the skeleton and 50% uniformly distributed in the remainder of the body, and (3) the radionuclide uniformly distributed in the skeleton. For each situation we assumed that the effective half-time was equal to the physical half-life of the nuclide.

I am also sending you a copy of the Dillman print-out of the decay scheme of ^{165}Er and a copy of an abstract of a paper presented at the June 1974 meeting of the Society of Nuclear Medicine on the possible use of ^{165}Er for tumor localization.

If you have any questions concerning these dose estimates or if we can be of further help, please call me or Evelyn Watson at 3-4642, ORAU extension 263.

Roger J. Cloutier

Roger J. Cloutier, Chairman
Special Training Division

EEW:ras
Attachments

Cos:

I checked that the correct energies and intensities of radiations were used in these dose calculations. The high absorption of low-energy X-Rays and Auger electrons results in the rather surprisingly high comparative dose. They did not the radiations or intensities for 99m Tc but I assume they are correct

Bruce K

I have had no time till now to check the 165 Er intensities hence the delay 12-3-74

1048747

FORM P-4

MEMORANDUM

TO William D. Gibbs DATE 20 August 74

SUBJECT Medical Radionuclide Committee

COPIES TO J. Berger, C. L. Edwards, R. Cloutier
File

This memo is a follow-up on our telephone conversation concerning the Medical Radionuclide Committee. We are pleased that you are willing to become chairman of this, and this memo is to indicate your appointment to this job.

I will be glad to discuss with you the scope of the work of the committee, or to be of help in any way possible.

Gould A. Andrews

Gould A. Andrews

pe

1048748

Dose to Skeleton
rad/mCi adm.

	^{99m}Tc	^{165}Er	% difference
uniform in body	0.020	0.022	+10%
50% in skeleton; 50% uniform in rem. of body	0.038	0.046	+21%
100% in skeleton	0.064	0.080	+25%

11-7-74

Radiopharmaceutical
Internal Dose Center

1048749

USAEC-ORO

HEALTH PROTECTION APPRAISAL

OAK RIDGE ASSOCIATED UNIVERSITIES

MARCH 1974

by

R. D. SMITH
R. W. POE
J. T. DUFOUR
R. O. EDDINS

1048750

I. Purpose and Scope

The annual health protection and environmental pollution appraisal was conducted during March 11-15, 1974. This appraisal was conducted by Messrs. R. D. Smith, R. W. Poe, J. T. Dufour of the Health Protection Branch, and R. O. Eddins of the Environmental Protection Branch, Safety and Environmental Control Division. The areas covered by this appraisal include health physics, industrial hygiene, environmental pollution, pesticides, and with special emphasis being placed this year on medical research.

II. Summary

The health physics and industrial hygiene programs of ORAU are considered to be very good. The Medical Division program in the area of human experimentation is undergoing some reorganization and has the earmarks of developing into a well organized program capable of fulfilling DHEW guidelines concerning the participant's safety. Two recommendations in the area of documentation and a suggestion in the findings should aid in this reorganization. Although pesticide use at ORAU is minimal, there are certain minimum health protection requirements applicable for their use, and a 1973 appraisal recommendation concerning these requirements had not been implemented at the time of the 1974 appraisal. This was pointed out during the critique and ORAU management assured the reviewers this recommendation would receive timely attention. In the area of environmental protection, ORAU is conforming to all applicable state and federal emission criteria.

III. Recommendations

A. Recommendations of the 1973 Appraisal

It was recommended that:

1. The responsibilities of the Radiation and Chemical Safety Officer and the General Safety Officer be formally documented in enough detail to eliminate

1048751

any jurisdictional discrepancies, and eliminate the dual responsibility concept now utilized in some areas in favor of a singly responsible officer.

An internal memorandum was prepared delineating each safety officer's responsibilities. An industrial hygiene safety manual was prepared which fully defines the program responsibilities and standards. This recommendation is considered implemented.

2. A respiratory protection program be established in accordance with ANSI Z88.2-1969 and, further that one individual be given the responsibility for coordination of all facets of the program.

   The R&CSO has been given this responsibility, and the program is considered to be in compliance with ANSI Z88.2-1969. This recommendation is considered to be implemented.

3. Training procedures be developed covering the proper use of pesticides, health hazards, and the necessary protective equipment to be used by employees, and that records of training and retraining be maintained.

   This recommendation has not been implemented and is repeated in this report.

4. The dose information form used by the Medical Division for ordering radioisotopes for patients be initiated in writing by the requesting physician.

A radioisotope order form has been developed which the physician initiates in writing, and the form has check off points at each major step up to and including administration. These forms are maintained in the patient's medical folder and in a master file. This recommendation is considered implemented.

B. Recommendations of the 1974 Appraisal

It is recommended that:

1. The Human Studies Committee document its procedure(s) used to assure the adequate implementation of its recommendations and/or limitations and conditions placed upon research proposals. (Section IV.C.3.)

2. Research proposals for studies involving human subjects include not only an evaluation of the physical harm but also an opinion of the psychological, and sociological harm associated with the proposed research. (Section IV.C.3.)

3. Training procedures be developed covering the proper use of pesticides, health hazards, and the necessary protective equipment to be used by employees, and that records of training and retraining be maintained (a repeated recommendation from the 1973 appraisal). (Section IV.F.2.)

IV. Findings

A. Organization

The ORAU health physics, industrial hygiene, and environmental protection programs are operated by the Radiation and Chemical Safety Officer, two technicians, and a half-time secretary. Collectively, their 3-1/2 man year effort is distributed approximtely

1.75 for health physics, 0.75 for industrial hygiene, 0.5 for environmental pollution, and 0.5 for miscellaneous special projects, teaching, and committee work.

B. Health Physics

The health physics program was found to be in good shape and run in a professional manner. A review of the records and tour of most ORAU facilities support this finding. Radiation exposures continue to remain quite low with a maximum exposure of about 470 mRem and an average of about 92 mRem. ORAU changes film badges on a quarterly basis and due to the minimum sensitivity of the film (20 mRem) all zeros are recorded as 20 mRem. Therefore, the minimum recorded exposure of ORAU employees is 80 mRem/year.

About five employees are monitored for neutron exposure. During the changeout of a 4 mg ^{252}Cf source for an 18.8 mg ^{252}Cf source, two employees received the only neutron exposure recorded for ORAU. The maximum was 150 mRem.

Internal exposures are determined through applicable Carbon-14 breath analysis, tritium bioassay analysis, and whole body counting. The results of all these techniques indicate no significant internal exposure among ORAU employees.

Course participants are monitored for internal and external radiation exposure when necessary. These exposures are comparable to those received by ORAU employees.

C. ORAU Medical Division

1. Patient Safety Program

The emphasis of this year's health protection appraisal was on programs in the Medical Division designed to protect human subjects from possible hazards in medical research with experimental drugs and procedures. These programs were reviewed using the "Institutional Guide to Department of Health, Education, and Welfare Policy on Protection of Human Subjects" as a guide. The Medical Division has two established committees, with separate responsibilities, to review research proposals and to ensure that adequate precautions will be taken in all medical research at ORAU. First, the Medical Radionuclide Committee must approve all medical radionuclide used at ORAU. Secondly, the Human Studies Committee must review and approve research proposals primarily to ensure that the benefit outweighs the risk, which includes an assessment of the hazards, precautions, and the information to be presented to the patient to gain informed consent.

2. Medical Radionuclide Committee

Since the last appraisal the Committee for Use of Radioisotopes in Humans has been renamed the Medical Radionuclide Committee and is also operating under a revised charter. This committee is charged with the responsibility, as defined by its charter, to ensure that the administration of radionuclides to humans at ORAU is adequately controlled and to ensure the safety of each person administered a radionuclide. To

1048755

aid the committee in carrying out this responsibility, researchers are required to submit a research proposal with sufficient information for the committee to make a determination on the safety of the radionuclide for its intended use. Proposals must be submitted not only for radionuclides used in experimental procedures but also those used in well established procedures which have been approved by the FDA and the AEC. The committee assigns a dose range to each radionuclide it considers safe for a given procedure, within which the researcher must operate. To go beyond this range, the research must again receive committee approval.

One significant change in the revised committee's charter is the deletion of ORAU policy guidelines defining the maximum radiation dose to human subjects not receiving medical benefit from their participation in medical research programs. These radiation dose guidelines limited the maximum dose to these persons to occupational exposure limits. It is the understanding of the chairman of this committee that considerations of maximum doses are now done solely by the Committee on Human Studies. The Committee on Human Studies documented guidelines, however, have not yet been revised to include any dose guidelines. Thus, it is suggested that guidelines representing ORAU policy be incorporated in the Committee on Human Studies guidelines.

3. Committee on Human Studies

A review of the minutes of the Committee on Human Studies (CHS) meetings pointed up documentation deficiencies in the handling of committee recommendations. These minutes

represent the records of actions taken by the committee. In cases where the CHS made recommendations and/or placed conditions on research proposals, their records did not always indicate what decision had been made by the committee as to the adequacy of the implementation. In most cases it is not readily apparent what action was taken with regard to the recommendation, except the committee may have given approval for continuation of the research. It is felt by the reviewers that formal procedures stating steps to be followed in gaining approval for recommendation implementation is a necessary part of the CHS operating guidelines, and further that the committee's records reflect the actions taken by the committee. Thus, it is recommended that the CHS formally document procedures used to assure the adequate implementation of its recommendations and/or conditions placed upon research proposals.

One of the primary functions of the CHS is to make an assessment of the risk versus benefit of all research proposals at ORAU. Inherent in this assessment is the obligation to make sure that adequate steps are taken to minimize the risk, if possible. In this respect, this committee is doing a commendable job. There is, however, a responsibility on the researcher to identify the possible risk to human subject associated with the research he proposes. In reviewing several research proposals, it became apparent that only the physical risks to patient were being presented in the proposal for assessment by the committee. The reviewers were informed that many times the committee has had questions with regard to psychological

1048757

hazard, and on occasions patients have been restricted from some research, by the researcher, for psychological reasons. While it appears that a valid effort is being made to minimize psychological risk of some research, the proper documentation has not been kept. Thus, it is recommended that research proposals and the minutes of committee meetings for studies involving human subjects include not only an evaluation of the physical harm but also an opinion on the possible psychological and sociological harm associated with the proposed research.

4. ORAU Radiopharmaceutical Procedure

As a result of a misadministration of a radionuclide to two Oak Ridge Hospital patients last year, ORAU was requested to formalize a procedure dealing with the administration of radionuclides. The draft of this procedure was discussed during the appraisal. The definition of misadministration and the action to be taken was the only exception taken by the reviewers. As a result of the discussion, ORAU agreed to modify the procedure to require an internal investigation of any administration of a radionuclide which differed by ± 20% of the prescribed amount and not approved by the attending physician before administration. Additionally, any administration of a radionuclide exceeding the maximum amount approved by the ORAU Medical Radionuclide Committee will require notification of the AEC.

The procedure additionally assigns the Chief Clinician the responsibility of advising the patient or a responsible relative of a misadministration, if in the doctor's opinion,

it could cause a demonstrably adverse effect on the patient, and if so advising would not be contrary to the patient or relative's best interest.

D. Industrial Hygiene

During the appraisal, extensive discussions held with the R&CSO indicated that problem areas at ORAU have been dealt with in an effective manner. The major IH problem is the control of toxic chemicals as used in research and daily activities at ORAU. Other major areas of concern are shops, (dust from wood, metal, paints, lead) animal handling (infections, allergies to dander, use of ether, and the associated biohazards). Many of these areas have resulted in specific programs as described below. Others like carcinogens, precipitated by the Emergency Temporary Standard issued in May 1973, have been handled in a way which can be endorsed by the reviewers. The only carcinogen still being used at ORAU is benzidine. Its use is the subject of a safety bulletin which includes practices consistent with ORO interpretations of the permanent carcinogen standard. Other carcinogens found on site have been disposed of in an acceptable manner. Another area of discussion was the ORAU pesticide program. This subject will be covered in detail in Section IV.F.E. of this report.

1. Trouble Shooting

A considerable amount of time is devoted to checking out new operations, investigating incidents, complying with requests for information from the AEC, making requested inspections, etc. These activities are an essential part of an active IH program, and have been performed effectively during the past year.

1048759

2. Toxic Chemical Labeling

An effective program for labeling of both large and small quantities of toxic chemicals has been initiated. The R&CSO staff actively survey areas to assure that labels are being applied and that employees are aware of the program and its purpose. The continuing effectiveness of this program will be assessed in future appraisals.

As an integral part of the toxic chemical labeling and control program, the R&CSO receives copies of all relevant purchase orders for chemicals, compressed gases, insecticides, pesticides, herbicides, germicides, paint thinner, degreasers, solvents and cleaners, housekeeping chemicals, etc. They are also in the process of requesting the same for ultra-violet sources, lasers, and microwave sources. This information assists in both the early implementation of required controls, and in some cases the suggested substitution of a less hazardous item.

3. Noise

The only major noise source at ORAU is the emergency generator which has been monitored at 113dB. A sign has been posted and earmuffs are required during operation. The effectiveness of this administrative control is being evaluated by the R&CSO.

4. Hood Surveys

Laboratory hoods are checked for maintenance of designed flow rates every six months. Appreciable decrements in performance are investigated and repaired.

1048760

5. Ultra-Violet

There are a considerable number of sources at ORAU; most are used for sterilization. R&CSO is evaluating any potential hazard associated with these devices. At this time only the units at the Marmoset Facility warrant concern. In the near future signs will be posted and the appropriate instructions issued to affected employees.

6. Industrial Hygiene Manual

During the past year, R&CSO has prepared and issued and Industrial Hygiene Manual. This document which includes policies, standards, responsibilities, and procedures is considered by the reviewers to be an excellent description of the ORAU industrial hygiene program.

7. Manuals and Safety Bulletins

R&CSO periodically issues documents on safety, film badges, radiation safety, radiation warning signs, respirator protection program, laboratory safety, perchloric acid safety and benzidine. This is regarded as an effective means of communicating safety information to new employees and to inform and reemphasize safety practices to veteran employees.

8. Respirators

The R&CSO has been assigned the responsibility of administering ORAU's respiratory protection program. ORAU's written procedure further delegates the responsibility of employee training and equipment maintenance

1048761

to division chairman and department heads. Respirator usage at ORAU is minimal, and most respirators are for emergency use and training. A number of respirators have been purchased which considerably increases the protection capabilities of this program. The application of pesticides, etc., by Technical Services, is the only function routinely requiring the use of a respirator. Additional training in regard to the proper care and storage of this equipment appears necessary for the routine users in Technical Services (see Section IV.F.2.). ORAU's compliance with ANSI Z88.2-1969 is considered adequate for their needs.

E. Facilities

Tours of ORAU facilities included the hospital, Tyrone Road Laboratory, Special Training Division, Museum and the associated shops, and the Lipid Lab. These tours were interesting and informative and afforded the opportunity to assess the effectiveness of ORAU health protection programs in its most practical field applications. The reviewers were satisfied that a safe and healthful working environment is being maintained by the R&CSO in cooperation with supervisors and employees.

F. Environmental Management

1. General

ORAU continues to have minimal impact on the local air quality since natural gas is utilized for heating at all its facilities. Liquid radioactive effluents continue

1048762

to be very small from the Medical Division. ORAU conducts no incineration or open burning of waste. All non-contaminated dry trash is disposed of in the Oak Ridge municipal landfill and has only minor impact.

2. Pesticides

ORAU has modified its pesticide program in that a contract pest control company now performs all termite treatment in addition to indoor treatment. The R&CSO should review the contract to ensure that the pesticide used is registered for the intended use and complies with all legal and environmental requirements. The R&CSO presently performs this review on pesticides purchase requests and this would just be an extension of this task. In addition, the pesticide contractor shall be licensed and furnish ORAU with the following information on the pesticide used:

a. trade name and chemical name,
b. EPA registration number, and
c. complete analysis

The lockers utilized for pesticide storage are to be labeled. Respirators and solvents are not to be stored in the lockers as was observed during this appraisal. All unlabeled containers (bottles, coffee cans, etc.) are to be discarded and are not to be stored in the lockers. The dieldrin on hand is to be disposed of since this pesticide has been banned by EPA.

The General Safety Officer should (1) initiate periodical pesticide training, (2) document such training, and (3) formalize instructions in a document to include safety precautions, the proper use and care of safety equipment, hazards associated with the chemicals used, symptoms of overexposure, and first aid. The latter was a recommendation from the 1973 appraisal and was not implemented. Upon completion of the document in Item 3 above, it is requested that a copy be timely provided to the S&EC Division for review.

Reviewers:

R. D. Smith
Health Physicist

R. W. Poe
Health Physicist

J. T. Dufour
Industrial Hygienist

R. O. Eddins
Safety Engineer

1048764

No. 74-1

FORM P-4

R. Cloutier

MEMORANDUM

Senior Staff of Medical Division

DATE January 8, 1974

SUBJECT MEDICAL RADIONUCLIDE COMMITTEE

COPIES TO File

The Division's Medical Isotope Committee has in the past been chaired by Dr. Kniseley. Because of his absence, I have asked the committee to review its mission which is to assist in the introduction of new radiopharmaceuticals at ORAU.

The committee has asked that its name be changed to Medical Radionuclide Committee and has prepared an operating procedure that I have approved (copy attached). I have appointed J. Berger, R. Cloutier, C. L. Edwards, R. Hayes, and C. Lushbaugh to the new committee and have asked Roger Cloutier to serve as its chairman.

Staff members are reminded that all proposals to administer radionuclides to humans must be reviewed by the Medical Radionuclide Committee. Experimental procedures will also require the approval of the ORAU-ORNL Committee on Human Studies.

Gould Andrews

Gould A. Andrews, M.D.

Attachment

To:
D. Brown
R. Cloutier
C. L. Edwards
N. Gengozian
F. Goswitz
R. Hayes
T. C. Lee
G. Littlefield
C. C. Lushbaugh
B. Nelson
R. Ricks
F. Snyder
D. C. Swartzendruber
R. Tyndall
P. Urso
H. Vodopick
R. Wykle
Information copies to: Ms. Bingham, Ms. Banner, Mr. Harmon, Mr. Crockett

1048765

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PURPOSE:

The Medical Radionuclide Committee evaluates all proposals to administer radionuclides to humans at ORAU.

RESPONSIBILITIES:

The committee is responsible to the Medical Division Chairman for ensuring that the administration of radionuclides to humans at ORAU is adequately controlled to ensure the safety of each person administered a radionuclide. The committee does not have responsibility for other aspects of radiation safety since these are already assigned by the ORAU Health and Safety Committee.

MEMBERSHIP:

The committee, appointed by the Medical Division Chairman, shall consist of at least three members selected to provide the committee with competence in nuclear medicine, radiation effects, dosimetry, and safety.

QUORUM:

A quorum shall consist of three members.

POLICY:

Unanimous approval by the committee members present at the meeting is required before a proposal can be instituted at ORAU. The committee will issue authorization on a form similar to that given in Appendix I. Persons whose proposals are disapproved by the committee may submit them to the Division Chairman who can countermand the committee decision.

OPERATING PROCEDURE:

The person proposing the use of a radionuclide in humans at ORAU must submit a written proposal to the committee. The proposal must contain sufficient information to permit the committee to evaluate the safety of the procedure.

1. Established clinical procedures

   If the AEC* or FDA† have already approved the radionuclide and procedure for routine use in patients, the proposal need only consist of the radiopharmaceutical package insert and a statement that the instructions contained in the package insert will be followed.

2. Experimental clinical procedures

   The proposal submitted may be the same as that required by the Committee on Human Studies (Appendix II).

---

* AEC's list of well established medical uses.

† Radionuclides distributed under an FDA new drug authorization.

Approved January 2, 1974

G. A. Andrews, M. D.
Medical Division Chairman

1048766

Appendix I

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL _____ Proposal No. _____

DESCRIPTION:

☐ The Committee approves with the following limitations:

Radiopharmaceutical may/may not be administered to patients under 18 years of age.

Radiopharmaceutical may/may not be administered to pregnant patient.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE

Acknowledgement of Submitter _____ Date _____

- -

Proposal does/does not require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048161

Appendix II

Ident. No._____

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date_____

Principal Investigator: _____

Co-Investigators: _____

_____

_____

_____

Title of Project: _____

_____

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

1048768

Title of Project: _____

Ident. No. _____

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date_____

Signatures: _____ Principal Investigator

_____ Co-Investigator

_____ "

_____ "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature_____

Title _____

Institution_____

Date _____

1048769

FORM P-4

MEMORANDUM

Roger Cloutier DATE 3 December 73

SUBJECT Medical Radionuclide Committee

COPIES TO File

I note with appreciation your work on the Medical Radionuclide Committee. The draft outlining the duties and functions of the committee sounds good to me. I have only one minor question. Under the heading Quorum, in the middle of the first page, it says, "All actions shall require the approval of all members present." I wonder if there is some hazard here that we might foresee. All the people now on the committee are reasonable and nonobstructive, but if we should at some future date have a member who was unreasonably in opposition to something it seems that we should have a method of over-riding him, particularly if the large majority of the whole committee thought he was in the wrong. I can't think of any straightforward method of doing this and I don't think a great deal of time should be wasted on it, since it will probably never arise. Perhaps some procedure for calling in an outside consultant could be briefly mentioned, simply to imply that a technique of appeal could be developed if it seemed needed.

C 147

Gould A. Andrews

pe

1048770

Please keep for quick reference. Mr Clautier

RADIOPHARMACEUTICAL PROCEDURES - ORAU MEDICAL DIVISION

ADMINISTRATION PROCEDURES AND RADIATION SAFETY PRECAUTIONS

I. INTRODUCTION

The administration of medical radionuclides to humans requires certain precautions to ensure the patient's safety. Also, during the administration of radiopharmaceuticals, there is the potential for contaminating facilities and equipment and unnecessarily exposing staff, visitors, and other patients. Even after the radionuclide has been administered, the patient may cause contamination or exposure problems for some time. To minimize these radiation safety problems, the Medical Division observes the following policies and procedures.

II. RESPONSIBILITIES

A. Division Chairman

The Chairman of the Medical Division is responsible for ensuring that work involving the administration of radionuclides to humans is performed in accordance with Association and Division policies and procedures. He must ensure that employees are familiar with these policies and procedures and that adequate instruction, training, and monitoring or protective devices are provided.

B. Medical Radionuclide Committee

The Medical Radionuclide Committee evaluates proposals for the use of radionuclides in humans. Only those procedures which have received approval by this Committee may be employed at ORAU Medical Division.

C. Physicians

The physician is responsible for the safety and welfare of the patient with regard to the administration of radiopharmaceuticals. He must personally prescribe all radioisotope procedures and interpret the results of such procedures. The physician may delegate certain activities such as preparation and measurement of radiopharmaceuticals, administration of some preencapsulated materials, and operation of appropriate data collecting instruments to qualified technicians and other medical personnel. It is the physician's duty to assure that these personnel are adequately trained.

1048771

D. Radiation and Chemical Safety Office

The Radiation and Chemical Safety Office (R&CSO) assists the Medical Division in carrying out its radiation safety duties. The R&CSO evaluates procedures and operations to ensure compliance with the Association's radiation safety policies as established in the CRAU Radiation Safety Manual and provides monitoring, training, and consulting services for all operations involving the use of radiation or radioactive materials.

III. RADIOPHARMACEUTICAL ADMINISTRATION PROCEDURES

A. Prescription of Test or Treatment

The patient's physician will:

Prescribe all nuclear medicine procedures using section 1 of the radiopharmaceutical treatment form (Figure 1). Notify and transmit the form to the radiopharmaceutical section so that the radiopharmaceutical may be procured or prepared.

Explain the procedure in detail to the patient, including a discussion of potential risks.

Obtain consent of the patient or his guardian. If the procedure is not designated by the AEC or FDA as an established use, written consent for an experimental test or treatment must be obtained (Figure 2).

B. Preparation of Radiopharmaceuticals

Radiopharmaceuticals are prepared by the radiopharmaceutical section upon request by the physician.

The preparer of the dose will:

Complete section 2 of the treatment form

Notify the nurses' station that the dose is ready.

C. Preparation of Patient

The nursing staff will perform the necessary setup and preparation. To reduce the potential for spreading contamination, the number of locations where radiopharmaceuticals are administered should be kept to a minimum. Unless required for a particular procedure, administrations should be performed in the treatment room (Room 303).

1048772

The use of absorbent paper, secondary containers, syringe shields, "hot" waste containers, gloves, etc. will also minimize unnecessary exposure and the spread of contamination.

D. Transport of Radiopharmaceuticals to the Treatment Area

Low activity, preencapsulated radiopharmaceuticals may be transported to the treatment area by the physician or technician preparing or administering the dose.

Whenever the radiopharmaceutical is in the liquid form or contains more than 1 millicurie of activity, the radiopharmaceutical section should notify the requesting physician who will then contact the Radiation and Chemical Safety Office to transport the radionuclide and assist in its administration.

The radiopharmaceutical must be properly shielded during transport to limit radiation exposures.

E. Dose Check

The Radiation and Chemical Safety Office representative or the person administering the dose will:

> Verify the quantity of each radioisotope to be administered. Verification must be performed by an individual who was not involved in preparing the dose or performing the calculations of volume or activity. An independent check of the activity reduces the potential for introducing bias into the dose calibration procedure.

The person making the dose verification completes part three of the radiopharmaceutical treatment form. He must call to the attention of the person administering the dose, any abnormalities or discrepancies in the activity greater than 10%.

When abnormalities or activity discrepancies are identified, the requesting physician is responsible for the decision whether or not to administer the radiopharmaceutical.

F. Administration

A physician will personally administer all radionuclides except for low activity, preencapsulated forms used for function tests. The physician may delegate the responsibility for administration of preencapsulated materials to qualified technicians or other medical personnel.

The person administering the dose will check the identity of the patient receiving the radionuclide against the prescription form.

1048773

Involved personnel will wear appropriate protective clothing and monitoring devices.

Unnecessary persons will be prohibited from the treatment room.

The person administering the dose will complete the bottom section of the treatment form.

Copies of the treatment form will be distributed in the following manner:

Original (yellow)	-	patient record
1st Copy (pink)	-	radiopharmaceutical section
2nd Copy (green)	-	scanning
3rd Copy (blue)	-	nurses

Nurses will complete the warning sign (Figure 3) and affix it to the patient's bed.

After the administration of the radioisotope, the staff involved will:

Check for contamination of themselves and the equipment used.

Place disposable items in the radioactive-waste containers.

The person who transported the radiopharmaceutical to the treatment area is responsible for the return of any unused portion of it to the storage vault.

Nurses will:

Notify the scanning and counting equipment operators of the administration time and arrange schedules with them.

Place the treatment form and consent form (if required) in the patient's record.

IV. MISADMINISTRATIONS

The following constitute misadministrations of radiopharmaceuticals and are to be reported by the individual discovering the error to the chief clinician, the chairman of the Medical Division, and the Radiation and Chemical Safety Officer.

1048774

1. Administration of a defective radiopharmaceutical

2. Administration of other than the prescribed radionuclide or to other than the intended patient

3. Administration of a radiopharmaceutical in other than the prescribed form or manner

4. Administration of a radiopharmaceutical in a quantity which exceeds the activity range established by the ORAU Medical Radionuclide Committee for the specific procedure.

The R&CSO will initiate an internal investigation of each misadministration and has the responsibility for notification of the Executive Office and other agencies if required.

When a misadministration could cause a demonstrably adverse effect on the patient, the chief clinician is responsible for advising the patient or a responsible relative regarding the misadministration, unless, in the clincian's professional judgment, such notification would be contrary to the best interests of the patient or the responsible relative.

V. CONTROL AND RESTRICTIONS OF PATIENTS

To reduce unnecessary radiation exposure to others in the vicinity, patients administered radionuclides may be restricted in their movements until the radiation levels and risks of contamination are within acceptable limits. Exceptions to the following guides are, of course, necessary. For instance, patients may be required to visit other hospital areas for diagnostic tests. In such instances the patient's physician with the help of radiation safety personnel will determine the precautions to be observed.

The general AEC requirement is that patients receiving radionuclides must be hospitalized until their body content is less than 30 millicuries. Below this level of activity, they may be released with instructions from their physician for limiting radiation exposures to others in the household.

If the patient remains in the ORAU facilities, the following restrictions will be applied.

A. Facilities

Patients receiving a dose larger than 1 millicurie normally occupy room 302-315 at the south end of the hospital wing, thereby limiting potential contamination to smaller areas.

Since patients who have received large quantities of radionuclides, e.g. 100 mCi ^{131}I, pose an external radiation hazard to staff, visitors, and other patients, two single-occupancy rooms, 311 and 315, are provided for their use.

B. Control of Contamination

Patients administered more than 1 millicurie of a rapidly excreted radiopharmaceutical are restricted to their rooms for at least 24 hours after administration. The physician will inform the patient of the precautions necessary to restrict the spread of contamination.

All hospital personnel and visitors should minimize the frequency of entries to rooms during this time. Hospital staff will:

Frequently use the instruments in the treatment room or nurses' station to monitor hands and feet.

Dispose of all waste according to radioactive waste disposal procedures. Urine from such patients during the first 24 hours is to be collected and placed in the special hot-waste drains.

When the potential for contamination is high, the Radiation and Chemical Safety Office will assist in determing necessary steps to control the release and spread of contamination and will increase area monitoring to ensure its early detection.

C. Control of External Radiation

When a patient receives therapeutic quantities of radioactive material, he may emit significant levels of external radiation. When possible such patients will occupy rooms 311 or 315. Patients administered radionuclides will remain in their rooms until radiation levels measured at one meter from them are below 2 milliroentgens per hour.

D. Release from Restrictions

The R&CSO will determine when radiation levels or contamination potential permit the lifting of the above restrictions and will notify the nursing staff.

VI. VISITOR CONTROL

Visitors to patients restricted for contamination control should be kept to a minimum especially during the 24 hours after administration of more than 1 millicurie of excretable activity. For protection

from external radiation exposure, visitors should not enter areas where radiation levels exceed 2 milliroentgens per hour.

VII. SURGERY

The R&CSO should be notified of all intended surgical procedures on patients who may contain more than 5 millicuries of radionuclide so that appropriate radiation and contamination control procedures can be instituted. Whenever possible, surgery involving potential spread of contamination should be performed within ORAU facilities.

VIII. DECEASED PATIENTS

When a patient containing more than 5 millicuries of radionuclides dies, the nursing staff will notify the R&CSO to survey bodies and determine the need for handling precautions or restrictions during autopsy procedures.

Approval:

G.A. Andrews, Chairman
ORAU Medical Division
Date [illegible]

C.L. Edwards, Chief Clinican
ORAU Medical Division
Date 10 Dec 73

J.D. Berger
Radiation and Chemical
Safety Officer
Date Dec 11, 1973

1048777

RADIOPHARMACEUTICAL TREATMENT RECORD

1. PRESCRIPTION:

Name of Patient (last, first, middle) 1 [ ] 25 Sex (M or F) 26 [ ]
(leave space between names; omit punctuation marks)

Hospital [ ] 27 (1. ORAU, 2. ORH, 3. Other (specify) _____)

ORAU Patient No. (if applicable) 28 [ ] 31

Radionuclide 32 [ ] 33 — 34 [ ] 36 37 [ ]
element *atomic wt.* *enter "M" if isomeric state*

Activity 38 [ ] 40 • 41 [ ] 44 mCi

Compound _____ Route _____ Date to be Given _____

Procedures *(enter corresponding numerical identification)*

45 [ ] [ ] 46
47 [ ] [ ] 48
49 [ ] [ ] 50
51 [ ] [ ] 52

01 Brain scan
02 Liver scan
03 Lung scan
04 Skeletal scan
05 Spleen scan
06 Thyroid scan
07 Linear scan
08 Torso scan
09 Total body scan
10 Area scan (specify) _____
11 Whole body count
12 Red cell survival
13 Schillings test
14 Thyroid uptake
15 Other (specify) _____

Additional tests or instructions _____

Prescribing physician _____ Date _____
(signature)

2. RADIOPHARMACEUTICAL IDENTIFICATION: Supplier _____ Lot No. _____

Volume to be administered _____ capsules, cup, or cc

Calculation or preparation by _____

3. DOSE CALIBRATION: Activity (from dose calibrator) _____ mCi

Measured by _____

4. ADMINISTRATION RECORD: Date 53 [ ] 54 *Mo.* 55 [ ] 56 *Day* 57 [ ] 58 *Year* Time _____

Administering Physician or Technician _____

Remarks _____

1048778

Figure 1. Radiopharmaceutical Treatment Record Form

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to administer to _____ the following radioactive substance _____ _____

Nuclide Chemical

_____ _____

Dose Route of administration

The purpose of this procedure has been explained to me as being:

_____

_____

_____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

_____

Name of patient

_____

Date

104817 9

Figure 2. Informed consent form.

CAUTION

ADMINISTERED

RADIOACTIVE

MATERIAL

PATIENT _____

DOCTOR _____ DATE _____

RADIOACTIVE MATERIAL _____

QUANTITY _____ FORM _____

ROUTE: ORAL _____ IV _____ IP _____ OTHER _____

SPECIAL PRECAUTIONS _____

_____

_____

_____

REMOVE SIGN ON _____

Figure 3. Warning sign for patient bed.

FORM P-4

MEMORANDUM

Those listed below

DATE 7 November 1973

SUBJECT MEETING OF MEDICAL ISOTOPE COMMITTEE

COPIES TO Dr. Andrews, file

Edwards ✓
Lushbaugh ✓
Hayes ✓
Cloutier ←
Berger
Harmon

The ORAU Medical Isotope Committee will meet at 2:00 p.m. on Wednesday, November 14, 1973 in the second floor conference room to review its present status. At this meeting we will consider:

1. What is the role of the Medical Isotope Committee today?
   a. Approve all routine medical uses of radionuclides?
   b. Approve experimental uses of radionuclides for submission to Human Use Committee?
   c. Approve all medical uses of radionuclides?
   d. Review all medical uses of radionuclides routinely?
   e. Investigate all misadministrations?
   f. Decide what action is required on NDA's and IND's?
2. What is the committee's relationship to the Human Use Committee?
3. Who should be members of the Medical Isotope Committee?
4. Any other pertinent topics.

After the meeting, I will update the description of the committee's responsibilities. A copy of the committee's responsibilities as outlined in March 1967 is attached.

The committee will meet at a later date to take action on a number of items that require review.

Roger J. Cloutier

Roger J. Cloutier

RJC:vrs

Attachment

1048781

REVISED & REPRINTED DEC. 73
CALLED RADIOPHARMACEUTICAL PROCEDURE

RADIATION SAFETY PRECAUTIONS FOR ADMINISTERED RADIOPHARMACEUTICALS

I. INTRODUCTION

The administration of medical radionuclides to humans requires certain precautions to ensure the patient's safety. Also, during the administration of radiopharmaceuticals, there is the potential for contaminating facilities and equipment and unnecessarily exposing staff, visitors, and other patients. Even after the radionuclide has been administered, the patient may cause contamination or exposure problems for some time. To minimize these radiation safety problems, the Medical Division observes the following policies and procedures.

II. RADIOPHARMACEUTICAL ADMINISTRATION

The physician is responsible for the safety and welfare of the patient with regard to the administration of radiopharmaceuticals. He must personally prescribe all radioisotope procedures and interpret the results of such procedures. The physician may delegate certain activities such as preparation and measurement of radiopharmaceuticals, administration of some preencapsulated materials, and operation of appropriate data collecting instruments to qualified technicians and other medical personnel. It is the physician's duty to assure that these personnel are adequately trained.

A. Prescription of Test or Treatment

The patient's <u>physician</u> will:

Prescribe all nuclear medicine procedures. Only those procedures designated by the AEC as established uses (see Appendix A) and those having received approval by the ORAU Human Isotope Use Committee may be employed at the ORAU Medical Division.

Explain the procedure in detail to the patient including a discussion of potential risks.

Obtain consent of the patient or his guardian. If the procedure is not designated by the AEC as an established use, written consent for an experimental test or treatment must be obtained (Figure 1).

1048782

Prescribe the isotope, activity, chemical form, and desired administration time using section 1 of the radiopharmaceutical prescription form (Figure 2). Notify and transmit copies one through three (1-3) of the form to the radiopharmaceutical section so that the radiopharmaceutical may be procured or prepared.

Post the fourth copy of the form at the nurses station. This copy will serve to notify scanning, nursing, and other laboratory personnel of upcoming procedures.

B. Preparation of Radiopharmaceuticals

Radiopharmaceuticals are prepared by the radiopharmaceutical section upon request by the physician.

The preparer of the dose will:

Complete section 2 of the prescription form.

Notify the nurses' station that the dose is ready.

C. Preparation of Patient

The nursing staff will perform the necessary setup and preparation. To reduce the potential for spreading contamination, the number of locations where radiopharmaceuticals are administered should be kept to a minimum. Unless required for a particular procedure, administrations should be performed in the treatment room (Room 303).

The use of absorbent paper, secondary containers, syringe shields, "hot" waste containers, gloves, etc. will also minimize unnecessary exposure and the spread of contmination.

D. Transport of Radiopharmaceuticals to the Treatment Area

The radiopharmcautical will be transported to the treatment area in the shielded cart. If the radiopharmaceutical is in liquid form or contains more than 1 millicurie of activity, the radiopharmaceutical section should notify the requesting physician who will then contact the Radiation and Chemical Safety Office to transport the radionuclide and assist in its administration. Low activity, preencapsulated radiopharmaceuticals may be transported to the treatment area by the physician or technician preparing or administering the dose.

1048783

E. Dose Check

The Radiation and Chemical Safety Office representative or the person administering the dose will:

Verify the quantity of each radioisotope to be administered, using a dose calibrator, and complete the third section of the dose prescription form.

Call to the attention of the person administering the dose, abnormalities or discrepancies in the activity greater than 10%. Where abnormalities or activity discrepancies are identified, the requesting physician is responsible for the decision whether or not to administer the radiopharmaceutical.

Whenever possible verification of the activity being administered should be performed by an indivdual who was not involved in preparing the dose or performing the calculations of volume or activity. An independent check of the activity will reduce the potential for intoducing bias into the dose calibration procedure.

F. Administration

The physician will personally perform all radioisotope administrations involving other than the low activity, preencapsulated forms for function tests. The physician may delegate the responsibility for administrations of these preencapsulated materials to qualified technicians or other medical personnel.

Involved personnel will wear appropriate protective clothing and monitoring devices.

Unnecessary persons will be prohibited from the treatment room.

The person administering the dose will complete the bottom section of the dose prescripption form.

Three copies of the prescription form will be distributed in the folllowing manner:

Original	-	left with nurses for patient record
1st Copy	-	sent to scanning
2nd Copy	-	returned to radioassay for filing

Nurses will complete the warning sign (Figure 3) and affix it to the patient's bed.

After the administration of the radioisotope, the staff involved will:

Check for contamination of themselves and the equipment used.

Place disposable items in the radioactive-waste containers.

The person who transported the radiopharmaceutical to the treatment area is responsible for the return of any unused portion of it to the storage vault.

Nurses will:

Notify the scanning and counting equipment operators of the administration time and arrange schedules with them.

Place the dose prescription form and consent form (if required) in the patient's record.

III. CONTROL AND RESTRICTIONS OF PATIENTS

To reduce unnecessary radiation exposure to others in the vicinity, patients administered radioisotopes may be restricted in their movements until the radiation levels and risks of contamination are within acceptable limits. Exceptions to the following guides are, of course, necessary. For instance, patients may be required to visit other hospital areas for diagnostic tests. In such instances the patient's physician with the help of radiation safety personnel will determine the precautions to be observed.

The general AEC requirement is that patients receiving radioisotopes must be hospitalized until their body content is less than 30 millicuries. Below this level of activity, they may be released with instructions from their physician for limiting radiation exposures to others in the household.

If the patient remains in the ORAU facilities, the following restrictions will be applied.

A. Facilities

Patients receiving a dose larger than 1 millicurie normally occupy rooms 302-315 at the south end of the hospital wing, thereby limiting potential contamination to smaller areas. Since patients who have receivied large quantities of radioisotopes, e.g., 100 mCi ^{131}I pose an external radiation hazard to staff, visitors, and other patients, two single-occupancy rooms, 311 and 315, are provided for their use.

B. Control of Contamination

Patients administered more than 1 millicurie of a rapidly excreted isotope are restricted to their rooms for at least 24 hours after administration. The physician will inform the patient of the precautions necessary to restrict the spread of contamination.

All hospital personnel and visitors should minimize the frequency of entries to rooms during this time. Hospital staff will:

Frequently use the instruments in the treatment room or nurses' station to monitor hands and feet.

Dispose of all waste according to radioactive waste disposal procedures. Urine from such patients during the first 24 hours is to be collected and placed in the special hot-waste drains.

When the potential for contamination is high, the Radiation and Chemical Safety Office will assist in determining necessary steps to control the release and spread of contamination and will increase area monitoring to ensure its early detection.

C. Control of External Radiation

When a patient receives therapeutic quantities of radioactive material, he may emit significant levels of external radiation. When possible such patients will occupy rooms 311 or 315. Patients administered radioisotopes will remain in their rooms until radiation levels measured at one meter from them are below 2 milliroentgens per hour.

D. Release from Restrictions

The R&CSO will determine when radiation levels or contamination potential permit the lifting of the above restrictions and will notify the nursing staff.

IV. VISITOR CONTROL

Visitors to patients restricted for contamination control should be kept to a minimum especially during the 24 hours after administration of more than 1 millicurie of excretable activity. For protection from external radiation exposure, visitors should not enter areas where radiation levels exceed 2 milliroentgens per hour.

1048786

V. SURGERY

The R&CSO should be notified of all intended surgical procedures on patients who may contain more than 5 millicuries of radionuclide so that appropriate radiation and contamination control procedures can be instituted. Whenever possible, surgery involving potential spread of contamination should be performed within ORAU facilities.

VI. DECEASED PATIENTS

When a patient dies, the nursing staff will notify the R&CSO, who will survey bodies containing more than 5 millicuries of radioisotopes and will determine the need for handling precautions or restrictions during autopsy procedures.

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to administer to _____ the following radioactive substance _____ _____

Nuclide Chemical

_____ _____

Dose Route of administration

The purpose of this procedure has been explained to me as being:

_____

_____

_____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

_____

Name of patient

_____

Date

Figure 1. Consent form.

1048788

AUTHORIZATION FOR THE ADMINISTRATION OF RADIOACTIVE SUBSTANCE MED-148(2-67)

RADIOPHARMACEUTICAL TREATMENT RECORD

1. PRESCRIPTION:

Name of Patient (last, first, middle) 1 [ ] 25 *(leave space between names; omit punctuation marks)* Sex (M or F) 26 [ ]

Hospital [ ] 27 (1. ORAU, 2. ORH, 3. Other (specify) _____)

ORAU Patient No. (if applicable) 28 [ ][ ][ ][ ] 31

Radionuclide 32 [ ][ ] 33 — 34 [ ][ ][ ] 36 37 [ ]
element *atomic wt.* *enter "M" if isomeric state*

Activity 38 [ ][ ][ ] 40 • 41 [ ][ ][ ][ ] 44 mCi

Compound _____ Route _____ Date to be Given _____

Procedures *(enter corresponding numerical identification)*

45 [ ] [ ] 46
47 [ ] [ ] 48
49 [ ] [ ] 50
51 [ ] [ ] 52

01 Brain scan
02 Liver scan
03 Lung scan
04 Skeletal scan
05 Spleen scan
06 Thyroid scan
07 Linear scan
08 Torso scan
09 Total body scan
10 Area scan (specify) _____
11 Whole body count
12 Red cell survival
13 Schillings test
14 Thyroid uptake
15 Other (specify) _____

Additional tests or instructions _____

_____

Prescribing physician _____ Date _____
(signature)

2. RADIOPHARMACEUTICAL IDENTIFICATION: Supplier _____ Lot No. _____

Volume to be administered _____ capsules, cup, or cc

Calculation or preparation by _____

3. DOSE CALIBRATION: Activity (from dose calibrator) _____ mCi

Measured by _____

4. ADMINISTRATION RECORD: Date 53 [ ][ ] 54 55 [ ][ ] 56 57 [ ][ ] 58 Time _____
Mo. *Day* *Year*

Administering Physician or Technician _____

Remarks _____

1048789

CAUTION

ADMINISTERED

RADIOACTIVE

MATERIAL

PATIENT _____

DOCTOR _____ DATE _____

RADIOACTIVE MATERIAL _____

QUANTITY _____ FORM _____

ROUTE: ORAL _____ IV _____ IP _____ OTHER _____

SPECIAL PRECAUTIONS _____

_____

_____

_____

REMOVE SIGN ON _____

Figure 3 Warning sign for patient bed.

ISOTOPE	CHEMICAL FORM	USE
Iodine 125	Iodopyracet, Sodium Iodohippurate, Sodium Diatrizoate, Diatrizoate Methyl-glucamine, Sodium Diprotrizoate, Sodium Acetrizoate, or Sodium Iothalamate	Kidney function studies
Iodine 125	Labeled Fats and/or Fatty Acids	Fat absorption studies
Iron 59	Chloride, Citrate and/or Sulfate	Iron turnover studies
Iridium 192	Seeds Encased in Nylon Ribbon	Interstitial treatment of cancer
Krypton 85	Gas	Diagnosis of cardiac abnormalities
Mercury 197	Chlormerodrin	Kidney imaging
Mercury 197	Chlormerodrin	Brain imaging
Mercury 203	Chlormerodrin	Brain imaging
Phosphorus 32	Soluble Phosphate	Treatment of polycythemia vera
Phosphorus 32	Soluble Phosphate	Treatment of leukemia and bone metastasis
Phosphorus 32	Colloidal Chromic Phosphate	Intracavitary treatment of malignant effusions
Phosphorus 32	Colloidal Chromic Phosphate	Interstitial treatment of cancer
Potassium42	Chloride	Potassium space studies
Selenium 75	Selenomethionine	Pancreas imaging
Strontium 85	Nitrate or Chloride	Bone imaging on patients with known or suspected cancer
Strontium 90	Medical Applicator	Treatment of superficial eye conditions
Technetium 99m	Pertechnetate	Brain imaging
Technetium 99m	Pertechnetate	Thyroid imaging
Technetium 99m	Sulfur Colloid	Liver and Spleen imaging

1048791

ISOTOPE	CHEMICAL FORM	USE
Technetium 99m	Pertechnetate	Placenta localization
Technetium 99m	Pertechnetate	Blood pool imaging
Technetium 99m	Petechnetate	Salivary gland imaging
Technetium 99m	Iron-Ascorbate-Diethylenetriamine Pentaacetic Acid Complex	Kidney imaging
Xenon 133	Free Gas or in solution	Diagnosis of cardiac abnormalties Blood-flow studies Pulmonary function studies

1048792

Committee for Use of Radioisotopes in Humans

Medical Division
Oak Ridge Associated Universities

March 23, 1967

I. Committee's Mission

To receive, evaluate, approve, and monitor proposals for new uses of radioisotopes in human beings. This committee will replace the earlier, less formal, arrangement that has been operating.

II. Committee Membership

The committee, appointed by the Division Chairman, consists of Dr. Edwards, Dr. Lushbaugh, Mr. Cloutier, Dr. Kniseley, Dr. Hayes, and Mr. Harmon (ex officio). A member of the Health Physics group - Mr. Cloutier or his delegate - must be present or represented by his document. Of the other four voting members, at least three persons should be present, one of whom may be replaced by the Division Chairman.

III. Protocol for a Proposal for a New Use

A. A written proposal should be submitted in advance of any meeting for study by each committee member.

B. The following outline should be used:

1. Question that the research might answer
2. Radioisotope
3. Chemical form
4. Route of administration
5. Proposed dosage (chemical and radioisotopic)
6. Experimental protocol:
   a. Number and selection of subjects
   b. Duration of studies
   c. Types and frequency of assays

C. To make an evaluation of the proposal, the following information must accompany it:

1. Animal distribution data and calculation of radiation dose to whole body and critical organs

2. Related and pertinent human data

3. Appraisal of chemical radiation and infectious hazards.

1048793

IV. Guidelines for Dosage

A. The investigator must provide general information about the age, sex, weight, and state of health of the volunteers to be selected. The best estimate of the retention of the isotope in the body and critical organ(s) must also be submitted so that the committee might evaluate the anticipated exposure.

B. Prior to the initiation of the experimental program, the volunteer's exposure record should be submitted to the committee so that it may be assured that the volunteer has not already exceeded the accumulated exposure of 5(N - 18) when N is the age in years.

C. The committee will not approve the administration of any exposure that when added to the individual's anticipated occupational exposure during the period of the proposed experiment will exceed the following limits that are in accordance with the ICRP occupational exposure limits:

	Whole body, blood-forming organs, gonads	Thyroid, skin, bone	Other internal organs
1. Normal Adult			
rem/week	0.3	0.6	0.3
rem/13 consecutive weeks	3.0	10.0	4.0
rem/year	5.0	30.0	15.0
2. Women of Reproductive Age			
rem/week	0.3		
rem/13 consecutive weeks	1.3		
rem/year	5.0		

1048794

V. Selection of Subjects

Recruitment of volunteers must fall within policies established in the Division (See Policy Statement Attached.)

VI. Approval of protocol will consist of a concise written summary of its extent signed by the participating members, and will reflect complete committee concurrence.

Frank Andrews M.D.

Chairman, Medical Division

Note: Mr. Harmon and Mr. Elza prepared this for the file on April 12, 1973. He has a Xerox copy and also gave one to Dr. Edwards and one to Mr. Elza.

1048795

FORM P-4

MEMORANDUM

TO: Medical Radionuclide Committee

DATE: 29 November 1973

SUBJECT: DATE OF NEXT MEETING

COPIES TO: Members, Dr. Andrews, file

The Medical Radionuclide Committee will meet at 2:00 p.m. on Tuesday, 4 December 1973 in the second floor conference room. This is a change in the date from that announced (Dec. 5, 1973) in my earlier memo. The main purpose of the meeting is to discuss the draft of the committee's responsibilities and operating rules distributed earlier.

Roger J. Cloutier

Roger J. Cloutier

Members:
- Berger
- Cloutier ✓
- Edwards
- Harmon
- Hayes
- Lushbaugh

1048796

FORM A-4

MEMORANDUM

Medical Radionuclide Committee
(Medical Isotope Committee)

DATE 23 November 1973

SUBJECT PROPOSED RESPONSIBILITIES AND OPERATING RULES

COPIES TO Members, Dr. Andrews, file

Attached is a draft of the proposed responsibilities and operating rules for the Committee. It is also proposed that the Committee be known as the ORAU Medical Radionuclide Committee. Would you look over the draft and be prepared to discuss any changes you feel are necessary at the 5 December 1973 meeting of the Committee. This meeting will be held at 2:00 p.m. in the second floor conference room.

Roger J. Cloutier

Roger J. Cloutier

RJC:vrs

Committee Members:
Berger
Cloutier
Edwards
Harmon
Hayes
Lushbaugh

1048797

DRAFT 11/23/73

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PURPOSE:

The Medical Radionuclide Committee evaluates all proposals to administer radionuclides to humans at ORAU.

RESPONSIBILITIES:

The Committee is responsible to the Medical Division Chairman for ensuring that the administration of radionuclides to humans at ORAU is adequately controlled to ensure the safety of each person administered a radionuclide. The Committee does not assume any other role for the control of other aspects of radiation safety since these are already assigned by the ORAU Health and Safety Committee.

MEMBERSHIP:

The Committee, appointed by the Medical Division Chairman, shall consist of at least three members selected to provide the Committee with competence in nuclear medicine, radiation effects, dosimetry, and safety.

QUORUM:

The Committee may take action at any meeting at which three or more members are present. All actions shall require the approval of all members present. Div chairman

OPERATING PROCEDURE:

1. Well established clinical procedures

   All proposals to use radionuclides and procedures already approved by the AEC* or the FDA† shall be submitted to the Committee for approval before being used at ORAU. The person proposing the use of the procedure should give the Committee a short written description of how the procedure will be used at ORAU; the submission of the radiopharmaceutical package insert will usually be sufficient. Generally, the Committee will approve the use of established procedures at ORAU; however, it may impose specific limitations. The Committee will issue authorization on a form similar to that given in Appendix I.

2. Experimental clinical procedures

   All other proposals for use of radionuclides that in patients & VoC (1) have not been approved for routine use in patients by the AEC or FDA, or (2) are to be administered to volunteers must be submitted to

---

*AEC's list of well established medical uses.

†Radionuclides distributed under an FDA new drug authorization.

1048198

the ~~Human~~ Medical Radionuclide Committee for evaluation of ~~efficacy and~~ their safety. This Committee will review the proposal and submit its recommendation for or against the proposal to the ~~Committee on Human Studies.~~ Chairman of the Medical Division. ~~The Medical Radionuclide Committee shall list~~ any limitation on the study that it ~~deems~~ including necessary in its report to the Committee on Human ~~Studies.~~ The Committee on Human Studies ~~has~~ ultimate responsibility for approving all experimental programs involving humans at ORAU.

To properly evaluate each proposal, the Medical Radionuclide Committee will require a written detailed description of the proposal. This report may be the same as that required by the Committee on Human Studies (Appendix II). Approval of the proposal by both groups shall not relieve the investigator from the FDA requirement for submitting ~~an IND.~~

January 2, 1974

G. A. Andrews, M.D.
Medical Division Chairman

Review - annually.

1048799

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL _____ PROPOSAL NO._____

DESCRIPTION:

☐ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not___ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not___ be administered to pregnant patient:

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE

Acknowledgement of Submitter _____ Date_____

- -

Proposal does ___ does not ___ require approval of Committee on Human Studies.

Human Studies approval granted on

1048800

Appendix II

Ident. No._____

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date_____

Principal Investigator: _____

Co-Investigators: _____

_____

_____

_____

Title of Project: _____

_____

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

1048801

Title of Project: _____

Ident. No. _____

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date_____

Signatures: _____ Principal Investigator

_____ Co-Investigator

_____ "

_____ "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature_____

Title _____

Institution_____

Date _____

1048802

(Revised January 1972)

FORM P-4A

MEMORANDUM

TO: Dr. Edwards
Dr. Kniseley

DATE: June 28, 1967

SUBJECT:

COPIES TO:

Dr. Bill Myers, of Ohio State, says that he has a new isotope preparation that he wants to try on some patients and would like to try it out in our hospital as soon as we have our Anger camera set up. I told him that we would be glad to cooperate but that we had to have approval by our committee before giving any unfamiliar radioactive material to patients. However, he did not seem to want to start any negotiations until after our camera had arrived and was in operation. Apparently he is getting some very short half- lived material with the help of Art Rupp.

I think it would be desirable to cooperate with him if it seems feasible after we know what this is all about.

Gould A. Andrews

pe

1048803

April 1967

Committee for Use of Radioisotopes in Humans

Medical Division, Oak Ridge Associated Universities

I. Committee's Mission

To receive, evaluate, approve, and monitor proposals for new uses of radioisotopes in human beings. This committee will replace the earlier, less formal, arrangement that has been operating.

II. Committee Membership

The committee, appointed by the Division Chairman, consists of Dr. Edwards, Dr. Lushbaugh, Mr. Cloutier, Dr. Kniseley, Dr. Hayes, and Mr. Harmon (ex officio). A member of the Health Physics group, Mr. Cloutier or his delegate, must be present, or a written report of his findings submitted to the committee. Of the other four voting members, at least three persons should be present, one of whom may be replaced by the Division Chairman.

III. Protocol for a Proposal for a New Use

A. A written proposal should be submitted in advance of any meeting for study by each committee member.

B. The following outline should be used:

1. Question that the research might answer
2. Radioisotope
3. Chemical form
4. Route of administration
5. Proposed dosage (chemical and radioisotopic)
6. Experimental protocol:
   a. Number and selection of subjects
   b. Duration of studies
   c. Types and frequency of assays

C. To make an evaluation of the proposal, the following information must accompany it:

1. Animal distribution data and calculation of radiation dose to whole body and critical organs
2. Related and pertinent human data
3. Appraisal of chemical, radiation, and infectious hazards.

IV. Guidelines for Dosage

A. The investigator must provide general information about the age, sex, weight, and state of health of the volunteers to be selected. The best estimate of the retention of the isotope in the body and critical organ(s) must also be submitted so that the committee might evaluate the anticipated exposure.

1048804

B. Prior to the initiation of the experimental program, the volunteer's exposure record should be submitted to the committee so that it may be assured that the volunteer has not already exceeded the accumulated exposure of 5 (N - 18) when N is the age in years.

C. The committee will not approve the administration of any exposure that when added to the individual's anticipated occupational exposure during the period of the proposed experiment will exceed the following limits that are in accordance with the ICRP occupational exposure limits:

	Whole body, blood-forming organs, gonads	Thyroid, skin, bone	Other internal organs
1. Normal Adult			
rem/week	0.3	0.6	0.3
rem/13 consecutive weeks	3.0	10.0	4.0
rem/year	5.0	30.0	15.0
2. Women of Reproductive Age			
rem/week	0.3		
rem/13 consecutive weeks	1.3		
rem/year	5.0		

V. Selection of Subjects

Recruitment of volunteers must fall within policies established in the Division. (See Policy Statement Attached.)

VI. Approval of protocol will consist of a concise written summary ot its extent signed by the participating members, and will reflect complete committee concurrence.

Approved by G. A. Andrews, Chairman
March 31, 1967

1048805

Committee for Use of Radioisotopes in Humans

Medical Division
Oak Ridge Associated Universities

I. Committee's Mission

To receive, evaluate, approve, and monitor proposals for new uses of radioisotopes in human beings. This committee will replace the earlier, less formal, arrangement that has been operating.

II. Committee Membership

The committee, appointed by the Division Chairman, consists of Dr. Edwards, Dr. Lushbaugh, Mr. Cloutier, Dr. Kniseley, Dr. Hayes, and Mr. Harmon (ex officio). A member of the Health Physics group - Mr. Cloutier or his delegate - must be present or represented by his document. Of the other four voting members, at least three persons should be present, one of whom may be replaced by the Division Chairman.

III. Protocol for a Proposal for a New Use

A. A written proposal should be submitted in advance of any meeting for study by each committee member.

B. The following outline should be used:

1. Question that the research might answer
2. Radioisotope
3. Chemical form
4. Route of administration
5. Proposed dosage (chemical and radioisotopic)
6. Experimental protocol:
   a. Number and selection of subjects
   b. Duration of studies
   c. Types and frequency of assays

C. To make an evaluation of the proposal, the following information must accompany it:

1. Animal distribution data and calculation of radiation dose to whole body and critical organs

2. Related and pertinent human data
3. Appraisal of chemical radiation and infectious hazards.

1048806

-more

IV. Guidelines for Dosage

A. The investigator must provide general information about the age, sex, weight, and state of health of the volunteers to be selected. The best estimate of the retention of the isotope in the body and critical organ(s) must also be submitted so that the committee might evaluate the anticipated exposure.

B. Prior to the initiation of the experimental program, the volunteer's exposure record should be submitted to the committee so that it may be assured that the volunteer has not already exceeded the accumulated exposure of 5 (N - 18) when N is the age in years.

C. The committee will not approve the administration of any exposure that when added to the individual's anticipated occupational exposure during the period of the proposed experiment will exceed the following limits that are in accordance with the ICRP occupational exposure limits:

	Whole body, blood-forming organs, gonads	Thyroid, skin, bone	Other internal organs
1. Normal Adult			
rem/week	0.3	0.6	0.3
rem/13 consecutive weeks	3.0	10.0	4.0
rem/year	5.0	30.0	15.0
2. Women of Reproductive Age			
rem/week	0.3		
rem/13 consecutive weeks	1.3		
rem/year	5.0		

-more

1048807

V. Selection of Subjects

Recruitment of volunteers must fall within policies established in the Division. (See Policy Statement Attached.)

VI. Approval of protocol will consist of a concise written summary of its extent signed by the participating members, and will reflect complete committee concurrence.

Corrected Draft Approved by Members - March 23, 1967

1048808

Recruitment of Human Volunteers

Policy of the Medical Division, Oak Ridge Associated Universities

I. Definition of Normal Human Subject Volunteer -

A person in apparent sound physical and mental health, 21 years of age or older, participating without coercion as a subject in a medical research project. This category is to be distinguished from a "patient volunteer" who registers in the Medical Division as a patient for the investigation and possible treatment of a medical disorder.

II. Recruitment -

1. Methods shall be discreet and in the bounds of propriety. Solicitation in public communications media can be made only through the Human Use Committee.

2. Conscious efforts will be made with ORAU employees to have recruitment free of any suggestion of coercion or implication that participation is expected. For example, announcements that ask for volunteers will be used rather than personal solicitation. Participation or non-participation shall have no bearing on merit evaluations, status, or promotion in ORAU. An ORAU employee should have concurrence of his supervisor so that regular work assignments are not handicapped.

3. Compensation may be offered to the volunteer, and will require prior authorization by the Division Chairman.

III. Release Form - An agreement signed and witnessed that:

1. Participation is of the person's own volition,
2. Subject understands that this experience is for experimental purposes, not for diagnosis or treatment,
3. Subject understands the nature, procedures, and probable effects, if any, of the experiment. (These features should be listed or described briefly in the agreement.)
4. The volunteer, whether or not he is an employee of ORAU, is not considered an employee insofar as the experiment is concerned.

Approved by G. A. Andrews, Chairman
March 31, 1967

1048809

(Draft - 23 March 67)

Policy of Medical Division, Oak Ridge Associated Universities, Concerning Recruitment of Human Volunteers

I. Definition of Normal Human Subject Volunteer -

A person in apparent sound physical and mental health, 21 years of age or older, participating without coercion as a subject in a medical research project. This category is to be distinguished from a "patient volunteer" who registers in the Medical Division as a patient for the investigation and possible treatment of a medical disorder.

II. Recruitment -

1. Methods should be discreet and in the bounds of propriety. Solicitation in public communications media can be made only through the Human Use Committee.

2. Conscious efforts will be made with ORAU employees to have recruitment free of any suggestion of coercion or implication that participation is expected. For example, announcements that ask for volunteers will be used rather than personal solicitation. Participation or non-participation shall have no bearing on merit evaluations, status, or promotion in ORAU. An ORAU employee should have concurrence of his supervisor so that regular work assignments are not handicapped.

1048810

-more

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. L. Edwards, M. D. Proposal No. 74-16

DESCRIPTION:

Erbium-171 as a clinical scanning agent for the detection of osseous and nonosseous tumors. The activity administered to a 70-kg man shall not exceed 10.5 mCi.

☒ The Committee approves with the following limitations:

Radiopharmaceutical ~~may~~/may not be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with attached proposal, ORAU/ORNL Committee on Human Studies, Ident. No. 33.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	[illegible]			4/4/74
R. J. Cloutier	[illegible]			4/4/74
C. L. Edwards	[illegible]			4/4/74
R. L. Hayes	[illegible]			4/4/74
C. C. Lushbaugh	[illegible]			4/4/74

Acknowledgement of Submitter Charles Edwards Date 4 April 74

- -

Proposal does/~~does not~~ require approval of Committee on Human Studies.

Human Studies approval granted on 11 DEC. 1973

1048811

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 33

Project Title Erbium-171 as a Clinical Scanning Agent for the Detection of Osseous and Nonosseous Tumors

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are: Radiation and chemical toxicity risks are minimal.

The committee states that adequate safeguards against these risks have been provided.

2. In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons: Possible better diagnostic agent.

3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate: as submitted.

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines: None

5. Other committee comments: None

Approve X

Disapprove

Gerald Andrews
Chairman of Committee

11 December 73
Date

1048812

(Revised January 1972)

Ident. No. 33

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: December 10, 1973

Principal Investigator: C. L. Edwards, M.D.

Co-Investigator: R. L. Hayes, Ph.D.

J. K. Poggenburg, Ph.D. (ORNL)

Title of Project: ERBIUM-171 AS A CLINICAL SCANNING AGENT FOR THE DETECTION OF OSSEOUS AND NONOSSEOUS TUMORS

I. Objectives of Experiment:

To determine whether ^{171}Er can be used as an effective tumor-localizing agent in humans. Animal experiments indicate that the higher-atomic-number rare-earth radionuclides show unusual affinities for tumor tissue (Fig. 1, appendix), clear rapidly from normal tissue (Table 1, appendix), and may have the same or better tumor-localizing properties as ^{67}Ga in certain tumor types (Table 2, appendix). This radionuclide also has better bone-seeking properties than do technetium phosphate agents. The half-life of ^{171}Er is sufficiently short so that it may be an effective bone scanning agent. It has good decay photons for scanning (Table 3, appendix).

II. Methods of Procedure:

^{171}Er will be obtained from Isotopes Development, ORNL, as the chloride in dilute hydrochloric acid solution. After conversion to the citrate form, sterilization by Millipore filtration (0.22 micron) and testing for pyrogenicity, 0.15 mCi/kg or less will be administered intravenously (1.0-0.1 mg citrate/kg). A group of 20 adult patients with known cancer will initially be used to evaluate this radionuclide. When possible, comparisons will be made with ^{67}Ga and ^{111}In in the same patient. When bone is involved scans with ^{99m}Tc Osteoscan will also be made. Further studies with patient volunteers will then be determined after a review by the committee.

1048813

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose and at 12-hr intervals thereafter through 42 hours.

2. Individual urine specimens will be collected through the first 2 days.

3. Fecal excreta will be collected through 2 days.

4. Linear scans will be obtained immediately after the dose, at 3-4 hours, and then daily thereafter through 2 days.

5. Whole body and area scans will be made at 3-4 hours after administration (or as soon as practical) and at 24 hours and 48 hours.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Since ^{171}Er will be produced by neutron activation of ^{170}Er (HIFR), stable erbium will be present in this radionuclide preparation (although at only microgram levels).

We propose to administer no more than 10 μg/kg of stable erbium (and generally much less), since stable rare earths in excess of this amount tend to decrease the relative specificity of rare earth nuclides for tumor tissue (see Table 4, appendix). At a level of 10 μg/kg or less there should be no toxic effects from the I.V. administration of erbium, since the I.V. LD_{50} in rats for the nitrate is reported to be 36 mg/kg in the female and 52 mg/kg in the male (T. J. Haley, J. Pharmaceutical Sciences 54: 663, 1965).

2. Radiation Dose:

The proposed maximum activity dose as stated in II (Methods of Procedure) is based on a calculated whole body radiation dose of 4 rads (assuming uniform distribution and no excretion) and is thought to be acceptable for the proposed study. Radiation Physics supplied the radiation dose estimates.

^{171}Er decays to ^{171}Tm (1.9 y half-life) which is a weak-beta emitter (0.1 MeV). Dose estimates by E. Watson indicate that the whole-body radiation dose to be expected from the ^{171}Tm generated by the decay of 1 mCi of pure ^{171}Er would be about 8.5×10^{-3} rads. If we assume neutron activation of ^{170}Er for 3 half-lives of ^{171}Er (87.5% saturation) and a decay period of 1 day before administration, the radiation dose from the ^{171}Tm associated with and generated by the decay of 1 mCi of ^{171}Er would be approximately 20 times that produced by the complete decay of 1 mCi of pure ^{171}Er. This would give a radiation dose of 1.8 rads from ^{171}Tm for the maximum activity dose proposed for ^{171}Er. Accordingly, no ^{171}Er will be administered after an individual preparation has decayed for more than 1 day after removal from the pile.

1048814

Ident. No. 33

IV. Radionuclides and New Drugs:

^{171}Er will be a new radionuclide in our clinical program. Following approval of this application by the Committee on Human Studies and the ORAU Medical Radionuclide Committee an IND will be filed with the Food and Drug Administration.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. An informed consent will be obtained from the patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducement will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the test with no promise of continued medical care at ORAU, and the ORAU patients will be assured that their participation is not a prerequisite of their continuing to receive treatment at ORAU.

Attached is a copy of the proposed consent form (appendix).

Starting Date: February 1, 1974

Signatures: _____ Principal Investigator

_____ Co-Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature: _____

Title _____

Institution _____

Date _____

1048815

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon _____
(Myself or name of patient)

of the following test: Phase I Radiopharmaceutical Test of Erbium-171.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done for my benefit, rather that the test is for experimental purposes and is being done only for gathering information related to my disease, treatment, or both. Further, I understand that any information learned from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Oak Ridge Associated Universities Medical Division.

DATE: _____

_____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: ^{171}Er - Erbium citrate.
2. The drug contains the element erbium in quantities much less than that required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. The radiation dose will be approximately 2 rads to the whole body.
4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hr, and 42 hrs.
5. All urine and feces will be saved for 2 days.
6. Whole body counts and scans will be made at frequent intervals for 2 days.
7. The patient may withdraw from the test at anytime.

DATE: _____

_____
Investigator

1048816

TABLE 1

INFLUENCE OF TIME ON TISSUE DISTRIBUTION OF ^{171}ER AND ^{169}YB IN RATS BEARING 5123C HEPATOMAS

Isotope	Erbium-171			Ytterbium-169	
Time	2 h	4 hr	24 h	4 h	24 h
Tumor conc. (%/g)*	3.3	4.5	3.4**	3.5	4.9**
Ratio tumor conc. to:					
Liver	5.0	5.6	6.7	7.9	11.0
Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
Femur	1.5	1.4	1.0	2.1	2.0
Marrow	7.2	10.1	12.5	5.9	8.0
Blood	6.2	19.0	130.0	9.9	110.0

* Percent administered dose/g normalized to body weight of 250 g.

** Not significantly different from 4 hour value.

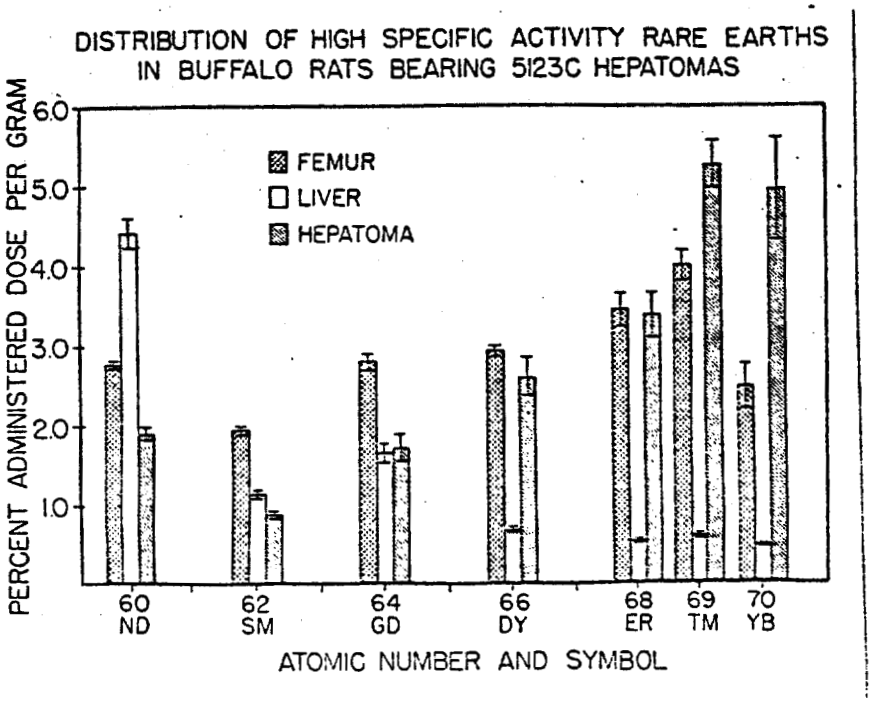


Fig. 1

1048817

TABLE 2

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}YB AND ^{67}GA (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

1048818

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

TABLE 4

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

1048819

Radiation dose in rads/millicurie of parent administered (24 hr after irradiation) - Values in parentheses are the doses in rads for the maximum to be administered to 70 kg man as proposed by Dr. Hayes et al.

Radio-nuclide	Total Body	Liver	Kidneys	Spleen	Skeleton*	Marrow
	Organ *					
Er-171 + Tm-171	0.36 (3.8)	0.92 (9.7)	1.1 (12)	0.60 (6.3)	1.4 (15)	0.19 (2.0)
Dy-157 + Tb-157	0.065 (1.1)	0.14 (2.4)	0.17 (3.0)	0.11 (1.9)	0.14 (2.4)	0.12 (2.1)
Tm-167	1.8 (1.9)	3.7 (3.9)	5.6 (5.9)	3.4 (3.6)	5.7 (6.0)	2.7 (2.8)

1048820

* skeleton = bone + marrow

* concentration based on [illegible] data by Dr. Hayes

E.W.

APPLICATION FOR INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical Division, Oak Ridge Associated Universities

Oak Ridge, Tennessee

May 21, 1974

1. NAME OF DRUG: ERBIUM-171 CITRATE. This preparation, dissolved in a saline-sodium citrate solution, will be administered intravenously in small volumes (< 5 ml).

2. COMPONENTS:

   a. Erbium (III)-171 citrate

   b. Stable erbium (III) citrate

   c. Sodium citrate

   d. Sodium chloride

   e. Water

3. QUANTITATIVE COMPOSITION (per dose):

   a. Erbium (III)-171 citrate: 0.10 millicuries per kilogram of body weight (or less).

   b. Stable erbium (III) citrate: 10 micrograms per kilogram of body weight (or less).

   c. Sodium citrate: 1 milligram per kilogram of body weight (or less).

   d. Sodium chloride: 0.2 milligram per kilogram of body weight (or less).

   e. Water: 0.05 milliters per kilogram of body weight (or less).

4. SOURCE OF NEW DRUG SUBSTANCE:

   Enriched erbium-170 [supplied by Oak Ridge National Laboratory (ORNL) as the nitrate with the following isotopic abundance: ^{170}Er, 96.06%; ^{168}Er, 1.93%; ^{167}Er, 0.97%; ^{166}Er, 1.04%; ^{164}Er, <0.1%; and ^{162}Er, <0.1%] will be activated in the High Flux Isotope Reactor at ORNL for 20 hours. At discharge in one run the main radioactivities present

1048821

per microgram of stable erbium were: ^{171}Er, 2.2 mCi and ^{172}Er, 4.1 μCi (the latter from double neutron capture). It is calculated that each microgram of stable erbium will also be associated at discharge with 1.1 μCi of ^{169}Er and 2.3 μCi of ^{165}Er. The activated erbium-170 will be dissolved in dilute hydrochloric acid (∿0.1N) and then supplied in that form to the Medical Division, Oak Ridge Associated Universities (ORAU) after being microfiltered through a 0.22 μ Millipore filter. ORNL will also supply ORAU with a radioisotopic assay for the ^{171}Er present plus the erbium content.

5. METHODS, FACILITIES AND CONTROLS:

The ^{171}Er chloride solution as received from ORNL will be processed in the following manner: Based on ORNL's assay, sufficient sterile 2.5% sodium citrate solution (ampoule 206, Eli Lily Co., Indianapolis, Ind.) will be added to the solution so that each mCi of ^{171}Er will at that point be associated with 0.1 mg of sodium citrate. The pH of the solution will be brought to 7.0 ± 0.2 with 1 N sodium hydroxide using a combination electrode and pH meter. (The stem of the electrode will be stored in 0.9% benzyl alcohol and will be repeatedly rinsed with sterile water before each use.) Following any necessary volume adjustment by the addition of 0.9% sterile nonpyrogenic saline, the solution will be microfiltered through a sterile 0.22 micron Millipore filter into a vial which will then be capped (multipuncture type) and autoclaved at 15 pounds pressure (121°C) for 20 minutes. To insure that the preparation was exposed to adequate heat, Diack controls (Smith and Underwood Laboratories, Troy, Mich.) will be placed in the autoclave next to the ^{171}Er citrate vial. (A temperature chart will be made a part of the records.) Following autoclaving a portion of the preparation will be withdrawn for a pyrogenicity test (standard USP methods), radioassay (sodium iodide crystal calibrated with NBS standards) and verification of sterility (standard USP methods for radiopharmacy records). The vial of ^{171}Er citrate will then be labeled as to its contents.

Preparation of each batch of ^{171}Er citrate will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized. Each batch of ^{171}Er citrate will be given a batch number and all particulars relative to its preparation and use will be entered in a master log book.

6. STATEMENT ON INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations:

1. Tissue distribution:

Recent reports (1-3) have indicated that the higher-atomic-number rare earth radionuclides show an affinity for nonosseous tumor tissue. R. L. Hayes and ORAU associates have confirmed these results in animals (4) and we now propose to investigate these radionuclides in patients at ORAU Medical Division. This application deals only with ^{171}Er.

1048822

Prior to clinical trials we have studied those factors that influence the distribution of this group of radionuclides in both normal and tumor-bearing animals. Figure 1 shows a histogram of the distribution of various high-specific-activity rare earth radionuclides in liver, bone, and 5123C Morris hepatomas. As has previously been reported (5), there was a dramatic decrease in the concentration of the rare earths in liver as the atomic number of the nuclides increased. At the same time the concentration in the 5123C hepatoma increased markedly. Table 1 shows the results of this study in a more detailed form. Also shown in Table 1 are the average results obtained for ^{67}Ga with this model tumor system.

Of the higher-atomic-number rare earth radionuclides that might be used for tumor scanning, three are particularly suited for this purpose, ^{171}Er, ^{157}Dy, and ^{167}Tm. Their properties are shown in Table 2. Although ^{171}Er and ^{157}Dy would be produced by neutron activation of the stable elements, they could be produced with very high specific activities (mCi/μg). The relatively short half lives of both ^{171}Er and ^{157}Dy do not constitute a problem since the tissue distribution of the higher-atomic-number rare earth radionuclides is essentially complete by 4 hours (Table 3).

From Table 1 it is apparent that radionuclides of erbium, dysprosium, thulium, and ytterbium compare favorably with ^{67}Ga with respect to the tumor-to-nontumor ratios obtained in rats bearing Morris 5123C hepatomas. A further comparison of ^{67}Ga with a rare earth radionuclide (^{169}Yb) in other tumor systems is shown in Table 4. Again, as with the 5123C hepatoma, the absolute concentration of ^{67}Ga was better than that of ^{169}Yb in tumor tissue except in Erhlich ascites (EA) cells where the ^{169}Yb concentration was $\sim$3 times greater than that of ^{67}Ga. Tumor-to-nontumor ratios were, however, approximately the same (except for EA cells). It would thus appear on the basis of this data that rare earth radionuclides might show as high a relative affinity for tumor tissue in human subjects as does ^{67}Ga (6).

It is apparent, however, that rare earth radionuclides concentrate to a much greater extent in bone (and kidney) than does ^{67}Ga, and this may obscure tumor visualization where sites of tumor are under or adjacent to the skeleton. On the other hand, lesions in the bone (both primary and metastatic) should be more readily visualized with rare earth radionuclides than they are with ^{67}Ga. Another advantage of the rare earth radionuclides indicated in Table 2 is that their energies are suitable for use with the gamma camera. Visualization of ^{67}Ga with the camera is poor compared to that obtained with rectilinear systems.

An important requirement for the effective use of rare earth radionuclides for tumor detection will be the use of high-specific-activity preparations. Table 5 shows the rather extreme effect that the simultaneous administration of stable erbium (at the milligram level) had on the tissue distribution of ^{171}Er in rats bearing 7777 hepatomas.

1048823

The concentration of ^{171}Er in liver and spleen was greatly increased while that in the tumor was correspondingly lowered. Even at a microgram level of stable erbium administration there was a rather dramatic increase in the concentration of ^{171}Er in liver and spleen above ∿10 μg Er/kg; the tumor concentration was not affected, however (Table 6). It thus will be important to use carrier-free or high-specific-activity preparations of the rare earth radionuclides in tumor scanning procedures.

The studies discussed above involved administration of rare earth radionuclides in the citrate form at a dose level of 1 mg citrate/kg. Table 7 shows the effect of other forms on the distribution of ^{167}Tm in rats bearing 7777 hepatomas. NTA and HEIDA gave approximately the same tissue distribution patterns as did the citrate while gluconate was somewhat poorer in tumor specificity. HEDTA, a strong chelate, greatly decreased the concentration of ^{167}Tm in tumor tissue and also produced much poorer tumor-to-nontumor ratios (particularly for the spleen, kidney, and blood). Citrate is thus the preferable form for the administration of rare earths, since it is a normal metabolite.

A study has been made of the effect produced by an increase in the citrate dosage on ^{167}Tm tissue distribution. No effect on tumor concentration of ^{167}Tm was observed with a citrate dose as high as 20 mg/kg. There was also no change in the tumor-to-nontumor ratios except for slight increases for spleen and blood.

As with ^{67}Ga the tissue distribution of the higher-atomic-number rare earth radionuclides (as represented by ^{170}Tm) is affected by both sex (Table 8) and age (Table 9). The differences in tissue distribution produced by differences in sex and age were not as pronounced as those seen with ^{67}Ga; however, the differences were highly significant.

2. Toxicity:

The toxicity of the rare-earth metals is low to intermediate, the reported I.P. LD_{50} in male and female rats and mice for erbium chloride and nitrate ranging from 225 to 535 mg/kg (7). The I.V. LD_{50} toxicity in male and female rats was respectively 52.5 and 35.8 mg/kg for the nitrate. Stable terbium has been administered to humans at a level of 2.4 mg Tb per dose (∿34 μg Tb/kg) without any symptoms of toxicity (8). The intravenous toxicity of the rare earths decreases with increasing atomic number (9), and, since terbium is below erbium in the rare earth series, erbium should be tolerated by man as well, if not better, than is terbium. O'Mara and Subramanian (10) have administered reactor-produced ^{171}Er to humans together with small amounts of stable erbium. They give no exact stable erbium dose in their publication. However, based on the specific activity they achieved (20-40 mCi/mg Er) and assuming that the latest their ^{171}Er was administered after removal from the reactor was at ∿3 half lives, they probably administered 10-20 μg of stable erbium per kilogram of body weight. They reported no untoward effects from the administration of their preparation.

1048824

Hepatosplenic degeneration from repeated large doses of rare earths in animals is seen only with the lower-atomic-number rare earths (7). Fatty liver infiltration in the rat from mg/kg doses of rare earths is not seen above samarium in the rare earth series (11).

Certain rare earth salts were used as anticoagulants in Europe during the 1940's and occasionally hemoglobinuria was produced. These were observed at doses of 5-8 mg/kg; slight transient elevations of plasma hemoglobin were occasionally noted at dose levels of 1-2 mg/kg (12).

Based on these observations in animals and humans, it is anticipated that the related administration of stable erbium together with ^{171}Er at the level proposed (not to exceed 10 μg Er/kg) would produce a minimal hazard for the subjects receiving erbium-171 citrate for tumor localization. The ORAU Committee on Human Studies has approved the use of ^{171}Er citrate as outlined in this application.

3. Radiation Dosimetry:

The radiation hazard associated with the administration of ^{171}Er (T 1/2 = 7.5 h) will also be minimal. Table 10 shows the estimated human total body radiation dose and radiation dose to various organs per millicurie of administered ^{171}Er. The dose figures in parentheses are those for the maximum amount of activity that will be administered (7 mCi ^{171}Er for a 70 kg subject). These radiation dose figures and those below were calculated by the ORAU Radiation Dosimetry Group (R. J. Cloutier and E. E. Watson) by extrapolation from tissue distribution data obtained in the rat.

Erbium-171 decays to ^{171}Er which is a weak beta emitter (0.1 Mev) with a 1.9 year half life. Thulium-171 is necessarily produced during the production of ^{171}Er and because of its long half life will build up in the ^{171}Er product as the ^{171}Er decays following removal from the reactor. Table 10 also shows, in addition to the radiation dose produced by ^{171}Er itself, the associated radiation dose to be expected from the ^{171}Tm that would be present due to its production during activation (20 h) and from decay of ^{171}Er for 24 hours after removal from the reactor. At this 24-hour period each mCi of ^{171}Er will be associated with 56 μCi of ^{171}Tm. The permissible body burden of ^{171}Tm is given as 90 μCi in NBS Handbook 69. In no case will this level of ^{171}Tm be exceeded. It should be pointed out that the ^{171}Tm contamination level could be considerably decreased by using a shorter activation period, although the yield of ^{171}Er would be somewhat decreased.

As indicated in section 4, small amounts of 49 day ^{172}Er (producing daughter ^{172}Tm, T 1/2 = 64 d), 9 day ^{169}Er, and 10 hour ^{165}Er will also be present in the ^{171}Er preparation. At 24 hours after removal from the pile the total body radiation dose from these contaminants for administration of the maximum ^{171}Er dose (7 mCi) is estimated to be as follows: ^{172}Er, ^{172}Tm, 0.24; ^{169}Er, 0.02; and ^{165}Er, 0.0003 rads. Also a small amount of ^{163}Er (20 μCi/mCi ^{171}Er) will be produced from

the ^{162}Er present in the target erbium. But, since this radionuclide decays by electron capture with essentially no gamma emissions and has a 75 m half life, the radiation dose from it may be disregarded.

It is apparent from the above considerations that the radiation dose from ^{171}Er citrate when used as proposed will be within acceptable radiation limits. The ORAU Medical Radionuclide Committee has accordingly approved the clinical use of ^{171}Er citrate in humans.

b. Previous Marketing:

This drug has not previously been marketed but it has been investigated in humans as a bone scanning agent (10).

c. Drug Combination:

Erbium (III) citrate is not a combination of previously investigated or marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The investigators preparing and administering this drug are working in close collaboration at the same institution. Therefore, no formal informational material will be prepared.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See bibliographical material in the appendix about Drs. Edwards, Hübner, Goswitz, Vodopick, and Hayes (ORAU), and Poggenburg (ORNL).

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by C. L. Edwards, R. L. Hayes, J. K. Poggenburg, and the sponsor, Gould A. Andrews, M.D., Chairman of the ORAU Medical Division with advice from the ORAU Program Review Committee and the ORAU Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phases I and II, Clinical Pharmacology, in this study will consist of observations on the metabolism and toxicity of ^{171}Er citrate together with preliminary observations on its tumor-localizing properties. C. L. Edwards, M.D. will be in charge of this clinical investigation.

Patients (30) will be known to have cancer. They will be adults recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. Informed consent will be obtained from each patient (minors and adults incapable of giving

an informed consent will be excluded from the study). No inducements will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the study with no promise of continued medical care at ORAU, and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU.

The principal questions to be answered are:

1. Is there any unsuspected toxic effect of erbium on humans at the dose levels proposed?

2. Will the uptake of ^{171}Er in human tumors be sufficient to permit tumor detection by scanning?

3. For the purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{171}Er in humans?

4. What is the optimum dose and scanning time?

While it is not anticipated that there will be any toxic effect of erbium at the doses to be used in this study, the patients will be observed closely for any unanticipated untoward effects. Particular attention will be given to looking for an effect on the clotting mechanism, because of the known anticoagulant effect of some of the rare earth elements.

To determine the optimum time for scanning and to obtain data for more precise radiation dose estimates, blood levels and whole body counts will be monitored at frequent intervals from multiple blood samples and linear profile scans. All urine and fecal excreta will be collected for 48 hours after dosing and the radioactivity measured by well counting.

The optimum dose for scanning will be determined from data obtained with the use of multiple imaging devices (Anger camera and rectilinear scanners), with scans made at different time intervals.

Should the results of this study be encouraging, a subsequent proposal and application will be filed for clinical trials involving comparison with other tumor detection techniques.

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{171}Er citrate prior to 30 days after the date of receipt of the notice by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

References

1. Higasi, T., Ito, K., Tobari, H., and Tomura, K. On the accumulation of rare earth elements in animal tumor. Int. J. Nucl. Med. & Biol. 1:101-103, 1973.

2. Hisada, K. and Ando, A. Radiolanthanides as promising tumor scanning agents. J. Nucl. Med. 14:615-617, 1973.

3. Hisada, K., Tonami, N., Hiraki, T., and Ando, A. Tumor scanning with ^{169}Yb-citrate. J. Nucl. Med. 14:772-773, 1973.

4. Hayes, R.L. and Byrd, B.L. Factors influencing the distribution of rare earth radionuclides in normal and neoplastic tissue. S. Med. J. 66:1327, 1973, abstr.

5. Durbin, P.W. Metabolic characteristics within a chemical family. Health Physics 2:225-238, 1960.

6. Hayes, R.L. and Edwards, C.L. New applications of tumor-localizing radiopharmaceuticals. In "Medical Radioisotope Scintigraphy 1972", Vol. II, pp. 531-551, International Atomic Energy Agency, Vienna, 1973.

7. Haley, T.J. Pharmacology and toxicology of the rare earth elements. J. Pharm. Sciences 54:663-670, 1965.

8. Yano, Y., Van Dyke, D.C., Verdon, T.A., Jr., and Anger, H.O. Cyclotron-produced ^{157}Dy compared with ^{18}F for bone scanning using the whole-body scanner and scintillation camera. J. Nucl. Med. 12:815-821, 1971.

9. Bruce, D.W., Hietbrink, B.E., and DuBois, K.P. The acute mammalian toxicity of rare earth nitrates and oxides. Toxic Appl. Pharmacol. 5: 750-759, 1963.

10. O'Mara, R.E. and Subramanian, G. Experimental agents for skeletal imaging. Seminars Nucl. Med. 2:38-49, 1972.

11. Snyder, F., Cress, E.A., and Kyker, G.C. Liver lipid response to intravenous rare earths in rats. J. Lipid Res. 1:125-131, 1959.

12. Beaser, S.B., Segel, A., and Vandam, L. The anticoagulant effects in rabbits and man of the intravenous injection of rare earths. J. Clin. Invest. 21:447-454, 1942.

1048829

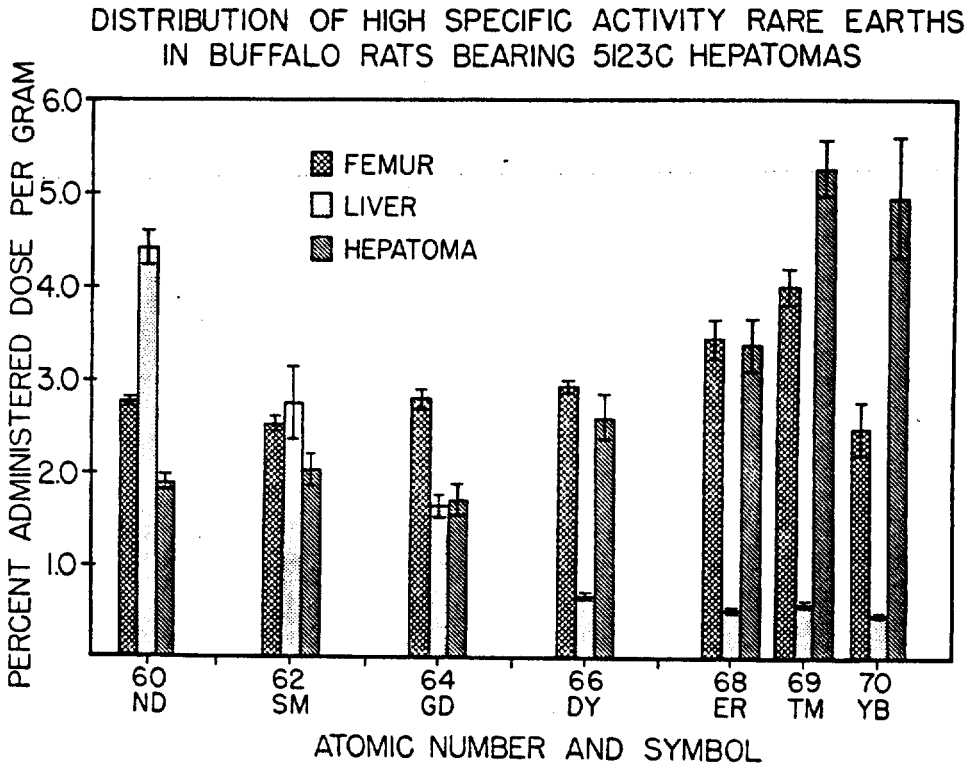


Fig. 1

1048830

TABLE 1

TISSUE DISTRIBUTION OF RARE EARTH ISOTOPES (24 HR) IN RATS BEARING 5123C HEPATOMAS*

Isotope	^{147}Nd	^{153}Sm	^{153}Gd	^{159}Dy	^{171}Er	^{170}Tm	^{169}Yb	^{67}Ga
Atomic Number	60	62	64	66	68	69	70	31
Tumor conc. (%/g)	1.9	2.0	1.7	2.6	3.3	4.3	4.9	9.3
Ratio tumor conc. to:								
Liver	0.4	0.7	1.0	4.0	6.7	10.0	11.0	20.0
Spleen	2.2	6.4	2.5	3.4	6.3	7.5	6.3	8.0
Kidney	0.6	0.5	0.7	1.4	2.1	3.0	4.8	17.0
Lung	6.5	6.4	6.5	13.0	19.0	27.0	25.0	48.0
Muscle	100.0	85.0	110.0	160.0	180.0	120.0	150.0	82.0
Femur	0.7	0.8	0.6	0.9	1.0	1.1	2.0	13.0
Marrow	12.0	9.6	7.4	9.4	12.0	15.0	7.6	8.7
Blood	89.0	76.0	53.0	76.0	120.0	230.0	100.0	150.0

* Groups of 4 animals each.

1048831

TABLE 2

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β^-	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

TABLE 3

INFLUENCE OF TIME ON TISSUE DISTRIBUTION OF ^{171}ER AND ^{169}YB IN RATS BEARING 5123C HEPATOMAS

Isotope	Erbium-171			Ytterbium-169	
Time	2 h	4 hr	24 h	4 h	24 h
Tumor conc. (%/g)*	3.3	4.5	3.4**	3.5	4.9**
Ratio tumor conc. to:					
Liver	5.0	5.6	6.7	7.9	11.0
Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
Femur	1.5	1.4	1.0	2.1	2.0
Marrow	7.2	10.1	12.5	5.9	8.0
Blood	6.2	19.0	130.0	9.9	110.0

* Percent administered dose/g normalized to body weight of 250 g.

** Not significantly different from 4 hour value.

1048832

TABLE 4

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}YB AND ^{67}GA (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

TABLE 5

EFFECT OF ERBIUM CARRIER ON THE DISTRIBUTION OF ^{171}ER (24 hr) IN THE RAT

Tissue	∿ C.F.	Carrier (mg/kg) 0.1	0.5	1.0
	% Administered Dose/g			
Liver	0.50	3.40	8.00	10.00
Spleen	0.24	0.76	1.60	4.80
Kidney	1.30	3.00	1.40	1.00
Lung	0.19	0.20	0.33	0.64
Muscle	0.02	0.02	0.02	0.01
Femur	4.50	2.61	1.40	1.10
Marrow	0.26	0.56	1.30	2.00
Blood	0.01	0.03	0.13	0.18
Tumor	2.30	1.60	0.88	0.44

TABLE 6

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

1048834

TABLE 7

TISSUE DISTRIBUTION OF ^{167}TM (24 HR) IN RATS BEARING 7777 HEPATOMAS WHEN ADMINISTERED INTRAVENOUSLY IN VARIOUS FORMS*

Tissue/Ratio	Form				
	Gluconate	Citrate	NTA	HEIDA	HEDTA
Tumor (%/g)	2.70	3.20	2.70	2.70	0.17
Ratio tumor conc. to:					
Liver	3.10	7.50	6.90	6.40	2.30
Spleen	3.30	6.10	4.40	4.80	0.44
Kidney	2.60	3.00	3.30	3.40	0.53
Muscle	160	170	140	210	110
Femur	1.10	1.30	1.10	1.10	0.88
Femoral marrow	6.50	8.00	6.70	6.10	4.90
Blood	150	150	140	120	19.0

* 5.2 μM/kg; 4 animals per group.

TABLE 8

TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE AND FEMALE FISCHER RAT*

Tissue	Sex		Significance
	Male	Female	P
	% Administered dose/g**		
Liver	0.74	0.56	0.001 - 0.01
Spleen	0.57	0.31	<0.001
Kidney	0.62	0.52	0.02
Lung	0.13	0.11	-
Muscle	0.03	0.02	<0.001
Femur	5.00	4.30	<0.001
Marrow	0.33	0.22	-
Blood	0.02	0.01	<0.001

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

TABLE 9

EFFECT OF AGE ON THE TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE BUFFALO RAT*

Tissue	Age		Significance	
	2 months	5 months	P	
	% Administered dose/g**			
Liver	0.36	0.48	<0.001	
Spleen	0.19	0.29	<0.001	
Kidney	0.76	2.10	<0.001	
Lung	0.14	0.29	<0.001	
Muscle	0.02	0.04	<0.001	
Femur	4.60	4.30	<0.05	>0.02
Marrow	0.26	0.38	<0.01	>0.001
Blood	0.01	0.02	<0.001	
Avg. wt.	190	370		

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

TABLE 10

ESTIMATED HUMAN RADIATION DOSE FROM ^{171}ER AND ITS DECAY PRODUCT ^{171}TM.

Radionuclide	Total Body*	Organ				
		Liver	Kidneys	Spleen	Skeleton+	Marrow
^{171}Er ‡	0.18	0.45	0.54	0.29	0.64	0.14
	(1.3)	(3.2)	(3.8)	(2.0)	(4.5)	(1.0)
^{171}Tm δ	0.15	0.40	0.51	0.26	0.60	0.042
	(1.1)	(2.8)	(3.6)	(1.8)	(4.2)	(0.29)

* Uniform distribution with no excretion.

\+ Skeleton = bone + marrow.

‡ Rads per mCi ^{171}Er. Figures in parentheses are total rads for the maximum dose to a 70 kg subject (7.0 mCi ^{171}Er).

δ Rads from ^{171}Tm per mCi of ^{171}Er administered at 24 hours after removal of target from reactor (20 h activation). Figures in parentheses are total rads for the maximum dose to a 70 kg subject (7.0 mCi ^{171}Er).

APPENDIX

Chief Investigators:

C. L. Edwards, M.D.
R. L. Hayes, Ph.D.
J. K. Poggenburg, Jr., Ph.D.
F. A. Goswitz, M.D.
K. F. Hübner, M.D.
H. V. Vodopick (Goswitz), M.D.

ORAU Committee on Human Studies:

Gould A. Andrews, M.D.
Chairman, ORAU Medical Division

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

C. Lowell Edwards, M.D.
Chief of Clinical Services
ORAU Medical Division

Melvin E. Koons
Law Department (Y-12 Plant)
Union Carbide Corporation
Oak Ridge, Tennessee

Robert D. Lange, M.D.
Assistant Director
U. T. Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Bill M. Nelson, M.D.
Pathologist, ORAU Medical Division

John B. Storer, M.D.
Scientific Director for Pathology & Immunology
Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

1048837

Program Review Committee:

John G. Conniglio, Ph.D.
Professor, Dept. of Biochemistry
Vanderbilt University Medical School
Nashville, Tennessee 37203

Jane F. Desforges, M.D.
Tufts University Hematology Laboratory
Boston City Hospital
818 Harrison Avenue
Boston, Mass. 02118

R. J. M. Fry, M.D.
Division of Biological and Medical Research
Argonne National Laboratory
Argonne, Illinois 60439

Robert H. Greenlaw, M.D.
Marshfield Clinic
Marshfield, Wisconsin 54449

Leonard A. Sagan, M.D.
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Laboratory of Genetics
University of Wisconsin
Madison, Wisconsin 53706

1048838

BIOGRAPHIES

Name: Gould A. Andrews
Position: Internist, Chairman, Medical Division, ORAU
School: University of Michigan, A.B., 1940
University of Michigan, M.D., 1943
Licensure: Tennessee
Board: Internal Medicine
Memberships: Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club.

Name: A. Bertrand Brill
Position: Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine.
School: Grinnell, A.B., 1949
University of Utah, M.D., 1956
University of California, Berkeley, Ph.D., 1961
Licensure: Tennessee
Memberships: American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association
Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name: John G. Coniglio
Position: Professor of Biochemistry, Vanderbilt School of Medicine
School: Furman, B.S., 1940
Vanderbilt, Ph.D., 1949
Memberships: AAAS; Inst. Nutrit; Oil Chem. Soc.; Soc. Biol. Chem.
Other Indication of Experience and Competence:
Specialist in lipid chemistry.

Name: Jane Fay Desforges
Position: Associate Professor, School of Medicine, Tufts University
School: Wellesley College, B.A., 1942
Tufts University, M.D., 1945
Memberships: Associate Editor, New England Journal Medicine, 1960-; Amer. Fed. Clin. Res.; Amer. Soc. Hemat.; Amer. Soc. Exp. Path. Hemat.

1048839

Name: C. Lowell Edwards
Position: Chief of Clinical Research, Medical Division, ORAU
Schools: Manchester College, A.B., 1950
Indiana University, M.D., 1954
Licensure: Tennessee, Indiana
Board: Internal Medicine
Memberships: Roane-Anderson County Medical Society, Tennessee Medical Association, American Medical Association, Society of Nuclear Medicine, American Association for the Advancement of Science, New York Academy of Sciences.

Name: Richard Jeremy Michael Fry
Position: Senior Scientist, Argonne National Laboratory
Schools: University of Dublin, B.A., 1946
University of Dublin, M.D., 1962
Memberships: Radiation Research Society, American Association Cancer Research, Reticuloendothelial Society

Name: Francis A. Goswitz
Schools: Marquette University, Premedical, B.S., 1952
Marquette University School of Medicine, M.D., 1956
Positions: Intern, University of Iowa Hospitals, 1956-57
Resident, Internal Medicine, University of Iowa Hospitals, 1957-58
Internist, U. S. Army Hospital, Fort Campbell, Ky. 1958-60
Fellow, Nuclear Medicine, ORAU Medical Division, 1960-61
Research Associate, Hematology, University of Utah, 1963-65
Clinician and Coordinator, Medical Radioisotope Courses, ORAU Special Training Division, 1965-68
Senior Clinician and Clinical Research Investigator, ORAU Medical Division, 1968 to present
Interests: Malignant disease, hematology and nuclear medicine
Hematology: chemotherapy of leukemias and lymphomas cytokinetics and cytochemistry of blood cells, iron metabolism
Nuclear Medicine: Uses of radioisotopes in cancer, biological effects of irradiation.

1048840

Name: Helen Vodopick Goswitz
Positions: Internship, University Hospitals, University of Iowa, 1956-57
Residency in Internal Medicine, University Hospitals, 1957-60
Post-residency Fellow in Nuclear Medicine, ORAU Medical Division, 1960-61
Instructor, Internal Medicine and Hematology, Fellow, University of Iowa, 1961-63
Research Associate in Hematology, University of Utah, 1963-65
Assistant Clinican and Head of Clinical Hematology Laboratory, ORAU Medical Division, 1965 to present
Schools: Marquette University, B.S., 1949-1953
Marquette University School of Medicine, M.D., 1952-56
Board: Internal Medicine, 1966
Interests: Hematology: Leukokinetics, especially of "myeloproliferative diseases
Immunology: Histocompatability testing - current work involves in vitro mixed leukocyte cultures
Nuclear Medicine: Liquid scintillation spectrometry and autoradiography in relation to the above two areas of interest.

Name: Robert H. Greenlaw
Position: Physician at Marshfield Clinic, Marshfield, Wisconsin
School: Tufts, B.S., 1948
Rochester, M.D., 1952
Memberships: Amer. Cancer Soc.; Member Med. Adv. Cmt, AEC; Amer. Med. Association; Col. Radiol.; Association Univ. Radiol.; Society of Nuclear Medicine.
Interests: Development of radioisotopes for diagnosis and therapy; radiation biology; clinical development in radiation therapy.

Name: R. L. Hayes
Position: Senior Scientist in charge of medical radioisotope development.
Schools: University of North Carolina, B.S., 1944
University of North Carolina, Ph.D., 1952
Positions: Senior Chemist, U. S. Rubber Co., North Carolina, 1944
U. S. Army, 1944-46
ORAU Medical Division, 1950 - present
Memberships: American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society.
Interests: Development of medical radioisotopic agents; radiation dosimetry.

1048841

Name: Karl F. Hübner
Schools: 2 years of college (last 2 years of German "high school") 1952-54
University of Heidelberg, Germany, M.D., 1959
Positions: Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present
Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70
Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67
Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies, (now Oak Ridge Associated Universities) 1962-64
Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Interests: Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name: Melvin E. Koons
Position: Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School: University of North Dakota, B.A., 1955; Juris doctor, 1961.
Admitted to practice of law:
North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966.
Memberships: American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommmittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name: Robert Lange
Position: Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools: Macalester College, B.A.
Washington University, M.D., 1944
Licensure: Tennessee, Minnesota, Missouri, Georgia
Board: Internal Medicine
Memberships: Amer. Assoc. Adv. Sci.; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology, etc.

1048842

Name:	Thomas A. Lincoln
Position:	Director, Health Division, ORNL
School:	Macalester College, B.A., 1946 University of Minnesota, B.S., 1947; B.M., 1949; M.D., 1950 Rotating Internship, Ancker Hospital, St. Paul, Minn. 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, 1963
Memberships:	Fellow, Industrial Medical Association; Tenn. Indust. Med. Assoc.; Amer. Acad. Occupational Med.; AMA; Roane-Anderson County Med. Soc.; Oak Ridge Regional Mental Health Center.

Name:	Bill Nelson
Position:	Research Pathologist
Schools:	University of Kansas, A.B., 1948 University of Chicago, School of Medicine, M.D., 1952
Licensure:	Tennessee
Board:	American Board of Pathology
Memberships:	Amer. Med. Assoc.; Amer. Soc. Clin. Path.; Reticuloendothelial Soc.; Society of Nuclear Medicine; Tennessee Assoc. Pathology

Name:	J. K. Poggenburg, Jr.
Position:	Research Staff, Biomedical Radioisotopes Group, Oak Ridge National Laboratory
Schools:	College of the Holy Cross, Worcester, Mass., B.S., 1956 University of California, Berkeley, Ph.D. - Nuclear Chemistry
Memberships:	Amer. Chem.Soc.; Society of Nuclear Medicine; Sigma Xi.

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fel. American College of Physicians.
Interests:	Late effects of radiation.

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; Amer. Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science.
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance.

1048843

Name:	John B. Storer
Position:	Scientific Director for Pathology and Immunology, Biology Division, Oak Ridge National Laboratory
Schools:	University of Chicago, M.D., 1947
Memberships:	American Association Cancer Research; Amer. Soc. for Exper. Path.; Radiation Res. Soc.; SEBM; Nat. Council on Radiation Protection and Measurements

1048844

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL C. L. Edwards, M. D. Proposal No. 74-17

DESCRIPTION:

Thulium-167 as a clinical scanning agent for detecting osseous and nonosseous tumors. The activity administered to a 70-kg man shall not exceed 1.05 mCi.

☒ The Committee approves with the following limitations:

Radiopharmaceutical ~~may~~/may not be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~/may not be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with attached proposal, ORAU/ORNL Committee on Human Studies, Ident. No. 34.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. D. Berger	JDB			4/4/74
R. J. Cloutier	RJC			4/4/74
C. L. Edwards	CLE			4/4/74
R. L. Hayes	RLH			4/4/74
C. C. Lushbaugh	CCL			4/4/74

Acknowledgement of Submitter [signature] Date 4 April 74

- -

Proposal does/~~does not~~ require approval of Committee on Human Studies.

Human Studies approval granted on 11 DEC 1973

1048845

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 34

Project Title Thulium-167 as a Clinical Scanning Agent for Detecting Osseous and Nonosseous Tumors

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are: Radiation and chemical toxicity risks are minimal.

The committee states that adequate safeguards against these risks have been provided.

2. In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons: Possible better diagnostic agent.

3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate: as submitted.

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines: None.

5. Other committee comments: None.

Approve X

Disapprove

Gerald Cantrell
Chairman of Committee

11 Dec. 73
Date

1048846

(Revised January 1972)

Ident. No. 24

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES:
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: December 10, 1973

Principal Investigator: C. L. Edwards, M. D.

Co-Investigators: R. L. Hayes, Ph. D.
L. C. Brown, Ph. D. (ORNL)

Title of Project: THULIUM-167 AS A CLINICAL SCANNING AGENT FOR DETECTING OSSEOUS AND NONOSSEOUS TUMORS.

I. Objectives of Experiment:

To determine whether ^{167}Tm can be used as an effective tumor-localizing agent in humans. Animal experiments indicate that the higher-atomic-number rare-earth radionuclides show unusual affinities for tumor tissue (Fig. 1, appendix), clear rapidly from normal tissue (Table 1, appendix), and may have the same or better tumor-localizing properties as ^{67}Ga in certain tumor types (Table 2, appendix). It has good decay photons for scanning (Table 3, appendix).

II. Methods of Procedure:

^{167}Tm will be obtained from Isotopes Development, ORNL, as the chloride in dilute hydrochloric acid solution. After conversion to the citrate form, sterilization by Millipore filtration (0.22 micron) and testing for pyrogenicity, 0.015 mCi/kg or less will be administered intravenously (1.0-0.1 mg citrate/kg). A group of 20 adult patients with known cancer will initially be used to evaluate this radionuclide. When possible, comparisons will be made with ^{67}Ga and ^{111}In in the same patient. When skeletal lesions are present bone scans with ^{99m}Tc Osteoscan will also be made. Further studies with patient volunteers will then be determined after a review by the committee.

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose and at 12-hr intervals thereafter through 42 hours and then daily through 7 days.

2. Individual urine specimens will be collected through the first 24 hr and pooled 24-hr samples thereafter for 7 days.

3. Fecal excreta will be collected through 7 days.

4. Linear scans will be obtained immediately after the dose, at 3-4 hours, and then daily thereafter through 7 days.

1048847

5. Whole body and area scans will be made at 3-4 hours after administration (or as soon as practical), at 24 hours, 48 hours, and at later times as called for by the physician in charge.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Since ^{167}Tm will be produced by a p,2n interaction on ^{168}Er and then separated from the erbium target material, it will be carrier free with respect to thulium; however, a small amount of erbium (micrograms) will be present as a contaminant from an ion exchange separation procedure.

We propose to administer no more than 10 μg/kg of stable erbium (and generally much less) since stable rare earths in excess of this amount tend to decrease the relative specificity of these nuclides for tumor tissue (see Table 4, appendix). At a level of 10 μg/kg or less there should be no toxic effects from the I.V. administration of erbium, since the I.V. LD_{50} in rats for the nitrate is reported to be 36 mg/kg in the female and 52 mg/kg in the male (T. J. Haley, J. Pharmaceutical Sciences 54: 663, 1965).

2. Radiation Dose:

The proposed maximum activity dose for ^{167}Tm as stated in II (Methods of Procedure) is based on a calculated whole body radiation dose of 2 rads (assuming uniform distribution and no excretion) and is thought to be acceptable for the proposed study. Radiation Physics supplied the radiation dose estimates.

IV. Radionuclides and New Drugs:

^{167}Tm will be a new radionuclide in our clinical program. It decays by electron capture with a $T_{1/2}$ of 9 days giving off a 208 KeV photon in 43% of its disintegrations (Table 3, appendix). Following approval of this application by the Committee on Human Studies and the ORAU Medical Radionuclide Committee, an IND will be filed with the Food and Drug Administration.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. An informed consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducement will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the test with no promise of continued medical care at ORAU and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU. Attached is a copy of the proposed consent form (appendix A).

Ident. No. 3d

Starting Date: February 1, 1974

Signatures: C. Joseph Edwards Principal Investigator

R. L. Hayes Co-Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature _____

Title _____

Institution _____

Date _____

1048849

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon _____
(myself or name of patient)

of the following test: Phase I Radiopharmaceutical Test of Thulium-167.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done for my benefit, rather that the test is for experimental purposes and is being done only for gathering information related to my disease, treatment, or both. Further, I understand that any information learned from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Oak Ridge Associated Universities Medical Division.

DATE: _____ _____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: ^{167}Tm - Thulium citrate.
2. The drug contains the element thulium in quantities much less than that required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. The radiation dose will be approximately 2 rads to the whole body.
4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hr, 42 hr, and then daily for a total of 12 samples.
5. All urine and feces will be saved for one week.
6. Whole body counts and scans will be made at frequent intervals for one week.
7. The patient may withdraw from the test at any time.

DATE: _____ _____
Investigator

1048850

TABLE 1

INFLUENCE OF TIME ON TISSUE DISTRIBUTION OF ^{171}ER AND ^{169}YB IN RATS BEARING 5123C HEPATOMAS

Isotope	Erbium-171			Ytterbium-169	
Time	2 h	4 hr	24 h	4 h	24 h
Tumor conc. (%/g)*	3.3	4.5	3.4**	3.5	4.9**
Ratio tumor conc. to:					
Liver	5.0	5.6	6.7	7.9	11.0
Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
Femur	1.5	1.4	1.0	2.1	2.0
Marrow	7.2	10.1	12.5	5.9	8.0
Blood	6.2	19.0	130.0	9.9	110.0

* Percent administered dose/g normalized to body weight of 250 g.

** Not significantly different from 4 hour value.

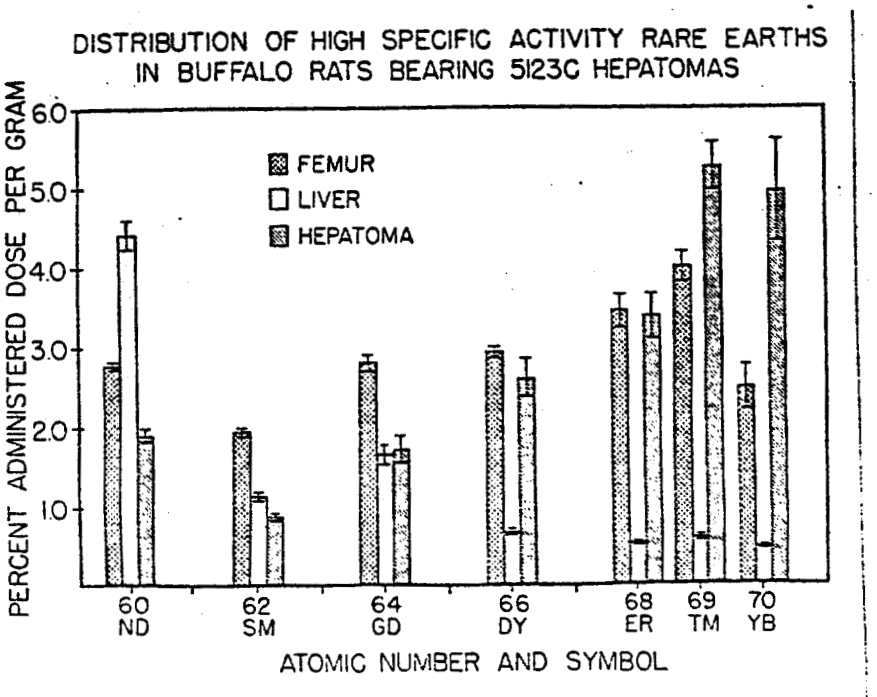


Fig. 1

1048851

TABLE 2

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}Yb AND ^{67}Ga (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

1048852

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

TABLE 4

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

1048853

Radiation dose in rads/millicurie of parent administered (24 hr after irradiation) - values in parentheses are the doses in rads for the maximum to be administered to 70 kg man as proposed by Dr. Hayes et al.

Radionuclide	Organ*					
	Total Body	Liver	Kidneys	Spleen	Skeleton*	Marrow
Er-171 + Tm-171	0.36 (3.8)	0.92 (9.7)	1.1 (12)	0.60 (6.3)	1.4 (15)	0.19 (2.0)
Dy-157 + Tb-157	0.065 (1.1)	0.14 (2.4)	0.17 (3.0)	0.11 (1.9)	0.14 (2.4)	0.12 (2.1)
Tm-167	1.8 (1.9)	3.7 (3.9)	5.6 (5.9)	3.4 (3.6)	5.7 (6.0)	2.7 (2.8)

1048854

*skeleton = bone + marrow

+ [illegible] based on [illegible]

E.W.

APPLICATION FOR INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical Division, Oak Ridge Associated Universities

Oak Ridge, Tennessee

May 21, 1974

1. NAME OF DRUG: THULIUM-167 CITRATE. This preparation, dissolved in a saline-sodium citrate solution, will be administered intravenously in small volumes (< 5 ml).

2. COMPONENTS:

   a. Thulium (III)-167 citrate

   b. Stable erbium (III) citrate

   c. Sodium citrate

   d. Sodium chloride

   e. Water

3. QUANTITATIVE COMPOSITION (per dose):

   a. Thulium (III)-167 citrate: 0.015 millicuries per kilogram of body weight (or less).

   b. Stable erbium (III) citrate: 10 micrograms Er per kilogram of body weight (or less).

   c. Sodium citrate: 1 milligram per kilogram of body weight (or less).

   d. Sodium chloride: 0.2 milligram per kilogram of body weight (or less).

   e. Water: 0.05 milliters per kilogram of body weight (or less).

4. SOURCE OF NEW DRUG SUBSTANCE:

   Thulium-167 will be produced by a p, 2n proton interaction with 96.7% enriched ^{168}Er oxide using the Oak Ridge National Laboratory (ORNL) 86" cyclotron. Following bombardment and dissolution of the ^{168}Er target material in HCl, the ^{167}Tm will be separated from the erbium by double-passage high-pressure ion exchange chromatography using α-hydroxyisobutyric acid. The separated ^{167}Tm will then be converted

1048855

to the chloride form in another ion exchange step and the final solution adjusted to ∿ 0.1 N with respect to HCl. It will be supplied in that form to Oak Ridge Associated Universities (ORAU) after first being microfiltered through a sterile 0.22 μ Millipore filter. The exact level of any contamination of the ^{167}Tm with target erbium will be determined spectrophotometrically with PAR reagent (1). The erbium concentration and a radioisotopic assay will be supplied to ORAU by ORNL at the time of delivery.

5. METHODS, FACILITIES AND CONTROLS:

The ^{167}Tm chloride solution as received from ORNL will be processed in the following manner: Based on ORNL's assay sufficient sterile 2.5% sodium citrate solution (ampoule 206, Eli Lily Co., Indianapolis, Ind.) will be added to the solution so that each mCi of ^{167}Tm will at that point be associated with 5 mg of sodium citrate. The pH of the solution will be brought to 7.0 ± 0.2 with 1 N sodium hydroxide using a combination electrode and pH meter. (The stem of the electrode will be stored in 0.9% benzyl alcohol and will be repeatedly rinsed with sterile water before each use.) Following any necessary volume adjustment by the addition of 0.9% sterile nonpyrogenic saline, the solution will be microfiltered through a sterile 0.22 micron Millipore filter into a vial which will then be capped (multipuncture type) and autoclaved at 15 pounds pressure (121°C) for 20 minutes. To insure that the preparation was exposed to adequate heat, Diack controls (Smith and Underwood Laboratories, Troy, Mich.) will be placed in the autoclave next to the ^{167}Tm citrate vial. (A temperature chart will also be made a part of the records.) Following autoclaving a portion of the preparation will be withdrawn for a pyrogenicity test (standard USP methods), radioassay (sodium iodide crystal calibrated with NBS standards) and verification of sterility (standard USP methods) for radiopharmacy records. The vial of ^{167}Tm citrate will then be labeled as to its contents.

Preparation of each batch of ^{167}Tm citrate will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized. Each batch of ^{167}Tm citrate will be given a batch number and all particulars relative to its preparation and use will be entered in a master log book.

6. STATEMENT ON INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations:

1. Tissue distribution:

Recent reports (2-4) have indicated that the higher-atomic-number rare earth radionuclides show an affinity for nonosseous tumor tissue. R. L. Hayes and ORAU associates have confirmed these results in animals (5) and we now propose to investigate these radionuclides in patients at the ORAU Medical Division. This application deals only with ^{167}Tm.

1048856

Prior to clinical trials we have studied those factors that influence the distribution of this group of radionuclides in both normal and tumor-bearing animals. Figure 1 shows a histogram of the distribution of various high-specific-activity rare earth radionuclides in liver, bone, and 5123C Morris hepatomas. As has previously been reported (6), there was a dramatic decrease in the concentration of the rare earths in liver as the atomic number of the nuclides increased. At the same time the concentration in the 5123C hepatoma increased markedly, thulium showing the highest tumor concentration. Table 1 shows the results of this study in a more detailed form. Also shown in Table 1 are the average results obtained for ^{67}Ga with this model tumor system. Figure 2 shows the tissue distribution of thulium in the rat over a 28-day period.

Of the higher-atomic-number rare earth radionuclides that might be used for tumor scanning, three are particularly suited for this purpose, ^{167}Tm, ^{171}Er, and ^{157}Dy. Their properties are shown in Table 2.

From Table 1 it is apparent that radionuclides of thulium, erbium dysprosium, and ytterbium compare favorably with ^{67}Ga with respect to the tumor-to-nontumor ratios obtained in rats bearing Morris 5123C hepatomas. A further comparison of ^{67}Ga with a rare earth radionuclide (^{169}Yb) in other tumor systems is shown in Table 3. Again, as with the 5123C hepatoma, the absolute concentration of ^{67}Ga was better than that of ^{169}Yb in tumor tissue except in Erhlich ascites (EA) cells where the ^{169}Yb concentration was $\sim$3 times greater than that of ^{67}Ga. Tumor-to-nontumor ratios were, however, approximately the same (except for EA cells). It would thus appear on the basis of this data that rare earth radionuclides might show as high a relative affinity for tumor tissue in human subjects as does ^{67}Ga (7).

It is apparent, however, that rare earth radionuclides concentrate to a much greater extent in bone (and kidney) than does ^{67}Ga, and this may obscure tumor visualization where sites of tumor are under or adjacent to the skeleton. On the other hand, lesions in the bone (both primary and metastatic) should be more readily visualized with rare earth radionuclides than they are with ^{67}Ga. Another advantage of the rare earth radionuclides indicated in Table 2 is that their energies are suitable for use with the gamma camera. This is particularly true for ^{167}Tm. Visualization of ^{67}Ga with the camera is poor compared to that obtained with rectilinear systems.

An important requirement for the effective use of rare earth radionuclides for tumor detection will be the use of high-specific-activity preparations. Table 4 shows the rather extreme effect that the simultaneous administration of stable erbium (at the milligram level) had on the tissue distribution of ^{171}Er in rats bearing 7777 hepatomas. The concentration of ^{171}Er in liver and spleen was greatly increased while that in the tumor was correspondingly lowered. Even at a microgram level of stable erbium administration there was a rather

1048857

dramatic increase in the concentration of ^{171}Er in liver and spleen above ∿10 μg Er/kg; the tumor concentration was not affected, however (Table 5). It thus will be important to use carrier-free or high-specific-activity preparations of the rare earth radionuclides in tumor scanning procedures.

The studies discussed above involved administration of rare earth radionuclides in the citrate form at a dose level of 1 mg citrate/kg. Table 6 shows the effect of other forms on the distribution of ^{167}Tm in rats bearing 7777 hepatomas. NTA and HEIDA gave approximately the same tissue distribution patterns as did the citrate while gluconate was somewhat poorer in tumor specificity. HEDTA, a strong chelate, greatly decreased the concentration of ^{167}Tm in tumor tissue and also produced much poorer tumor-to-nontumor ratios (particularly for the spleen, kidney, and blood). Citrate is thus the preferable form for the administration of rare earths, since it is a normal metabolite.

A study has been made of the effect produced by an increase in the citrate dosage on ^{167}Tm tissue distribution. No effect on tumor concentration of ^{167}Tm was observed with a citrate dose as high as 20 mg/kg. There was also no change in the tumor-to-nontumor ratios except for slight increases for spleen and blood.

As with ^{67}Ga the tissue distribution of the higher-atomic-number rare earth radionuclides (as represented by ^{170}Tm) is affected by both sex (Table 7) and age (Table 8). The differences in tissue distribution produced by differences in sex and age were not as pronounced as those seen with ^{67}Ga, but the differences were highly significant, however.

2. Toxicity :

The toxicity of the rare-earth metals is low to intermediate, the reported I.P. LD_{50} in female rats and mice for thulium nitrate ranging from 255 to 285 mg/kg (8). Male mice had an I.P. LD_{50} of 485 mg/kg for thulium chloride. Stable terbium has been administered to humans at a level of 2.4 mg Tb per dose (∿34 μg Tb/kg) without any symptoms of toxicity (9). The intravenous toxicity of the rare earths decreases with increasing atomic number (10), and, since terbium is below thulium in the rare earth series, thulium should be tolerated by man as well, if not better, than is terbium.

Hepatosplenic degeneration from repeated large doses of rare earths in animals is seen only with the lower-atomic-number rare earths (8). Fatty liver infiltration in the rat from mg/kg doses of rare earths is not seen above samarium in the rare earth series (11).

Certain rare earth salts were used as anticoagulants in Europe during the 1940's and occasionally hemoglobinuria was produced. These were observed at doses of 5-8 mg/kg; slight transient elevations of plasma hemoglobin were occasionally noted at dose levels of 1-2 mg/kg (12).

1048858

Based on these observations in animals and humans, it is anticipated that the related administration of stable erbium together with ^{167}Tm at the level proposed (not to exceed 10 μg Er/kg) would produce a minimal hazard for the subjects receiving thulium-167 citrate for tumor localization. The ORAU Committee on Human Studies has approved the use of ^{167}Tm citrate as outlined in this application.

3. Radiation Dosimetry:

The radiation hazard for ^{167}Tm at the dose level proposed will be minimal. Table 9 shows the estimated total body radiation dose and the radiation dose to various organs per mCi of administered ^{167}Tm (maximum proposed dose for a 70 kg subject = 1 mCi).

Due to a p, n interaction with ^{168}Er there will be a slight production of ^{168}Tm which will necessarily be a contaminant in the final ^{167}Tm preparation. Measurements by ORNL indicate that the level of ^{168}Tm contamination will be less than 0.4% (4 μCi of ^{168}Tm per 1 mCi of ^{167}Tm) at the end of the production bombardment. Although the radiation dose from ^{168}Tm at this level will be minor, its concentration in the ^{167}Tm preparation will continuously rise as the ^{167}Tm decays, since its half life is 93 days while that of ^{167}Tm is 9.3 days. It is necessary, therefore, to establish a maximum level for this contaminant beyond which a particular ^{167}Tm preparation will not be used. For our purposes in this study we propose a maximum level of 4% (40 μCi of ^{168}Tm per 1 mCi of ^{167}Tm). The estimated radiation dose from ^{168}Tm at this level of contamination is also shown in Table 9 for the maximum dose of ^{167}Tm (1 mCi).

It is apparent from the above considerations that the radiation dose from ^{167}Tm citrate when used as proposed will be within acceptable radiation limits. The ORAU Medical Radionuclide Committee has accordingly approved the clinical use of ^{167}Tm citrate in humans.

b. Previous Marketing:

This drug has not previously been marketed but it has been investigated in humans as a bone scanning agent (13).

c. Drug Combination:

Thulium-167 (III) citrate is not a combination of previously investigated or marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The investigators preparing and administering this drug are working in close collaboration at the same institution. Therefore, no formal informational material will be prepared.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See bibliographical material in the appendix about Drs. Edwards, Hübner, Goswitz, Vodopick, and Hayes (ORAU) and Poggenburg (ORNL).

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by C. L. Edwards, R. L. Hayes, J. K. Poggenburg, and the sponsor, Gould A. Andrews, M.D., Chairman of the ORAU Medical Division, with advice from the ORAU Program Review Committee and the ORAU Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phases I and II, clinical pharmacology, in this study will consist of observations on the metabolism and toxicity of carrier-free ^{167}Tm citrate containing erbium citrate together with preliminary observations on its tumor-localizing properties. C. L. Edwards, M.D. will be in charge of the clinical investigation.

Patients (30) will be known to have cancer. They will be adults recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. Informed consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducements will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the study with no promise of continued medical care at ORAU, and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU.

The principal questions to be answered are:

1. Is there any unsuspected toxic effect of erbium on humans at the dose levels proposed?

2. Will the uptake of ^{167}Tm in human tumors be sufficient to permit tumor detection by scanning?

3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{167}Tm in humans?

4. What is the optimum dose and scanning time?

While it is not anticipated that there will be any toxic effect of erbium at the doses to be used in this study, the patients will be observed closely for any unanticipated untoward effects. Particular attention will be given to looking for an effect on the clotting mechanism, because of the known anticoagulant effect of some of the rare earth elements.

To determine the optimum time for scanning and to obtain data for more precise radiation dose estimates, blood levels and whole body counts will be monitored at frequent intervals from multiple blood samples and linear profile scans. All urine and fecal excreta will be collected and measured for radioactivity by well counting for up to two weeks after dosing.

The optimum dose for scanning will be determined from data obtained with the use of multiple imaging devices (Anger camera and rectilinear scanners), with scans made at different time intervals.

Should the results of this study be encouraging, a subsequent proposal and application will be filed for clinical trials involving comparison with other tumor detection techniques.

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{167}Tm citrate prior to 30 days after the date of receipt of the notice by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

1048861

References

1. Munshi, K.N. and Dey, A.K. Spectrophotometric determination of rare earth metals with 4-(2-pyridylazo) resorcinol. Anal. Chem. 36: 2003-2004, 1964.

2. Higasi, T., Ito, K., Tobari, H., and Tomura, K. On the accumulation of rare earth elements in animal tumor. Int. J. Nucl. Med. & Biol. 1: 101-103, 1973.

3. Hisada, K. and Ando, A. Radiolanthanides as promising tumor scanning agents. J. Nucl. Med. 14:615-617, 1973.

4. Hisada, K., Tonami, N., Hiraki, T., and Ando, A. Tumor scanning with ^{169}Yb-citrate. J. Nucl. Med. 14:772-773, 1973.

5. Hayes, R.L. and Byrd, B.L. Factors influencing the distribution of rare earth radionuclides in normal and neoplastic tissue. S. Med. J. 66:1327, 1973, abstr.

6. Durbin, P.W. Metabolic characteristics within a chemical family. Health Physics 2:225-238, 1960.

7. Hayes, R.L. and Edwards, C.L. New applications of tumor-localizing radiopharmaceuticals. In "Medical Radioisotope Scintigraphy 1972", Vol. II, pp. 531-551, International Atomic Energy Agency, Vienna, 1973.

8. Haley, T.J. Pharmacology and toxicology of the rare earth elements. J. Pharm. Sciences 54:663-670, 1965.

9. Yano, Y., Van Dyke, D.C., Verdon, T.A., Jr., and Anger, H.O. Cyclotron-produced ^{157}Dy compared with ^{18}F for bone scanning using the whole-body scanner and scintillation camera. J. Nucl. Med. 12:815-821, 1971.

10. Bruce, D.W., Hietbrink, B.E., and DuBois, K.P. The acute mammalian toxicity of rare earth nitrates and oxides. Toxic Appl. Pharmacol. 5: 750-759, 1963.

11. Snyder, F., Cress, E.A., and Kyker, G.C. Liver lipid response to intravenous rare earths in rats. J. Lipid Res. 1:125-131, 1959.

12. Beaser, S.B., Segel, A., and Vandam, L. The anticoagulant effects in rabbits and man of the intravenous injection of rare earths. J. Clin. Invest. 21:447-454, 1942.

13. Chandra, R., Braunstein, P., Duhov, Lucy, and Tilbury, R.S. Evaluation of ^{167}Tm HEDTA as a bone scanning agent in humans and its comparison with ^{18}F. Brit. J. Rad. 47:51-53, 1974.

1048862

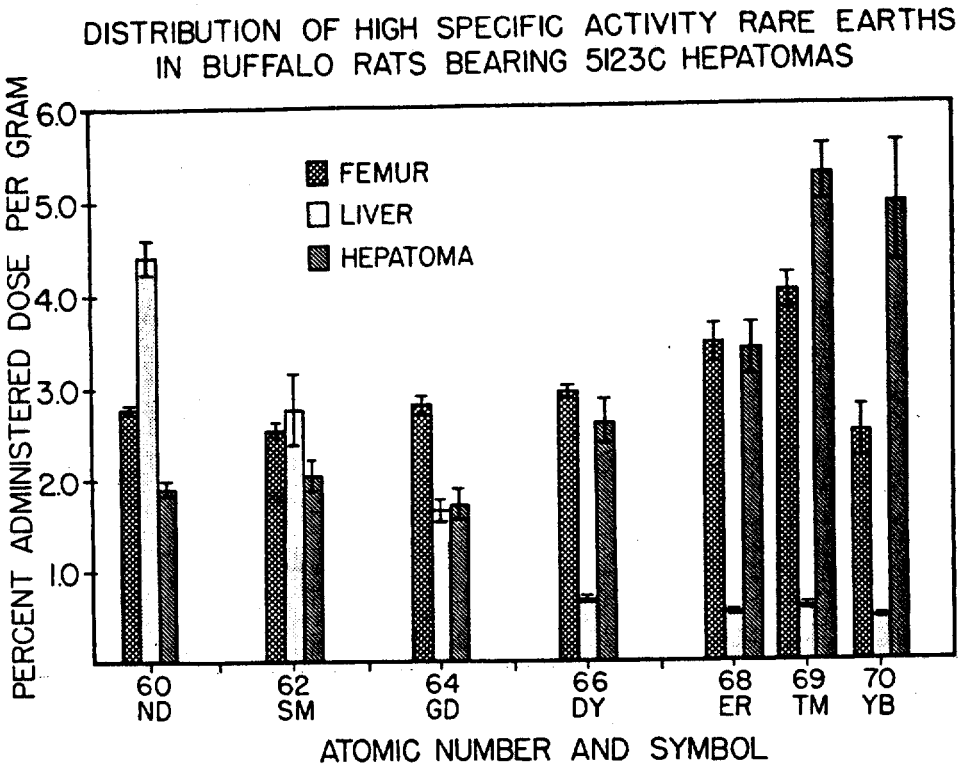
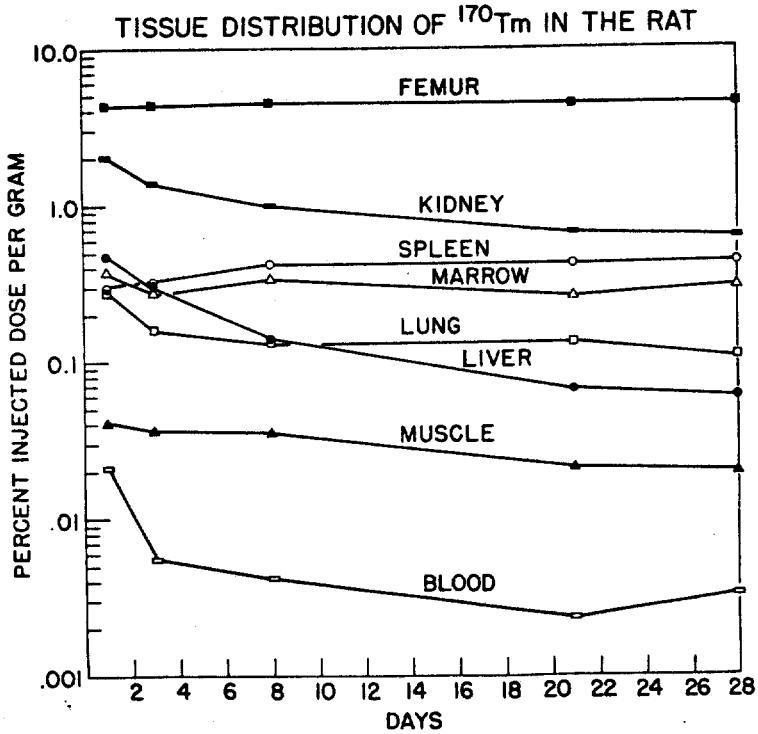


Fig. 1



1048863

Fig. 2

TABLE 1

TISSUE DISTRIBUTION OF RARE EARTH ISOTOPES (24 HR) IN RATS BEARING 5123C HEPATOMAS*

Isotope	^{147}Nd	^{153}Sm	^{153}Gd	^{159}Dy	^{171}Er	^{170}Tm	^{169}Yb	^{67}Ga
Atomic Number	60	62	64	66	68	69	70	31
Tumor conc. (%/g)	1.9	2.0	1.7	2.6	3.3	4.3	4.9	9.3
Ratio tumor conc. to:								
Liver	0.4	0.7	1.0	4.0	6.7	10.0	11.0	20.0
Spleen	2.2	6.4	2.5	3.4	6.3	7.5	6.3	8.0
Kidney	0.6	0.5	0.7	1.4	2.1	3.0	4.8	17.0
Lung	6.5	6.4	6.5	13.0	19.0	27.0	25.0	48.0
Muscle	100.0	85.0	110.0	160.0	180.0	120.0	150.0	82.0
Femur	0.7	0.8	0.6	0.9	1.0	1.1	2.0	13.0
Marrow	12.0	9.6	7.4	9.4	12.0	15.0	7.6	8.7
Blood	89.0	76.0	53.0	76.0	120.0	230.0	100.0	150.0

* Groups of 4 animals each.

TABLE 2

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	$T_{1/2}$	γ Energy (%)	Comments
^{167}Tm	EC	9d	208 Kev (43%)	^{168}Er p, 2n
^{171}Er	β^-	7.5h	∿300 Kev (90%)	σ ^{170}Er = 5.7; ^{171}Tm $T_{1/2}$ = 1.9y
^{157}Dy	EC	8.2h	326 Kev (91%)	σ ^{156}Dy (0.05%) = 3

1048864

TABLE 3

COMPARISON OF THE RELATIVE AFFINITIES OF ^{169}YB AND ^{67}GA (24 HR) FOR VARIOUS TUMOR TISSUES

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
Fluid	-	-	-	-	-	-	3.60	0.36

TABLE 4

EFFECT OF ERBIUM CARRIER ON THE DISTRIBUTION OF ^{171}ER (24 hr) IN THE RAT

Tissue	∿ C.F.	Carrier (mg/kg) 0.1	0.5	1.0
	% Administered Dose/g			
Liver	0.50	3.40	8.00	10.00
Spleen	0.24	0.76	1.60	4.80
Kidney	1.30	3.00	1.40	1.00
Lung	0.19	0.20	0.33	0.64
Muscle	0.02	0.02	0.02	0.01
Femur	4.50	2.61	1.40	1.10
Marrow	0.26	0.56	1.30	2.00
Blood	0.01	0.03	0.13	0.18
Tumor	2.30	1.60	0.88	0.44

TABLE 5

EFFECT OF CARRIER ERBIUM ON TISSUE DISTRIBUTION (21 hr) OF ^{171}ER IN THE RAT

Tissue	∿ C.F.	Carrier (μg/kg) 1.7	11	17	34
	% Administered Dose/g				
Liver	0.68	0.72	0.61	1.30	3.70
Spleen	0.57	0.66	0.32	0.67	1.10
Kidney	1.40	1.60	1.80	2.60	2.70
Lung	0.19	0.23	0.18	0.19	0.23
Muscle	0.03	0.03	0.02	0.03	0.03
Femur	4.50	4.70	4.20	4.10	3.50
Marrow	0.24	0.28	0.30	0.39	0.65
Blood	0.02	0.02	0.02	0.02	0.06
Tumor	4.00	5.00	3.80	4.00	3.70

1048866

TABLE 6

TISSUE DISTRIBUTION OF ^{167}TM (24 HR) IN RATS BEARING 7777 HEPATOMAS WHEN ADMINISTERED INTRAVENOUSLY IN VARIOUS FORMS*

Tissue/Ratio	Form				
	Gluconate	Citrate	NTA	HEIDA	HEDTA
Tumor (%/g)	2.70	3.20	2.70	2.70	0.17
Ratio tumor conc. to:					
Liver	3.10	7.50	6.90	6.40	2.30
Spleen	3.30	6.10	4.40	4.80	0.44
Kidney	2.60	3.00	3.30	3.40	0.53
Muscle	160	170	140	210	110
Femur	1.10	1.30	1.10	1.10	0.88
Femoral marrow	6.50	8.00	6.70	6.10	4.90
Blood	150	150	140	120	19.0

* 5.2 μM/kg; 4 animals per group.

TABLE 7

TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE AND FEMALE FISCHER RAT*

Tissue	Sex		Significance
	Male	Female	P
	% Administered dose/g**		
Liver	0.74	0.56	0.001 - 0.01
Spleen	0.57	0.31	<0.001
Kidney	0.62	0.52	0.02
Lung	0.13	0.11	-
Muscle	0.03	0.02	<0.001
Femur	5.00	4.30	<0.001
Marrow	0.33	0.22	-
Blood	0.02	0.01	<0.001

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

1048867

TABLE 8

EFFECT OF AGE ON THE TISSUE DISTRIBUTION (24 HR) OF ^{170}TM IN THE MALE BUFFALO RAT*

Tissue	Age		Significance	
	2 months	5 months	P	
	% Administered dose/g**			
Liver	0.36	0.48	<0.001	
Spleen	0.19	0.29	<0.001	
Kidney	0.76	2.10	<0.001	
Lung	0.14	0.29	<0.001	
Muscle	0.02	0.04	<0.001	
Femur	4.60	4.30	<0.05	>0.02
Marrow	0.26	0.38	<0.01	>0.001
Blood	0.01	0.02	<0.001	
Avg. wt.	190	370		

* Groups of 5 animals each.

** Percent administered dose/g normalized to body weight of 250 g.

TABLE 9

ESTIMATED HUMAN RADIATION DOSE FROM ^{167}TM AND ASSOCIATED ^{168}TM

Radionuclide	Total Body*	Organ				
		Liver	Kidney	Spleen	Skeleton+	Marrow
^{167}Tm‡	1.8	3.7	5.6	3.4	5.7	2.7
^{168}Tm$^{\delta}$	1.9	2.5	3.0	2.3	2.8	2.7

* Uniform distribution with no excretion.

\+ Skeleton = bone + marrow.

‡ Rads per mCi of ^{167}Tm.

δ Rads per 40 μCi of ^{168}Tm (see section 6-a-3).

APPENDIX

Chief Investigators:

C. L. Edwards, M.D.
R. L. Hayes, Ph.D.
J. K. Poggenburg, Jr., Ph.D.
F. A. Goswitz, M.D.
K. F. Hübner, M.D.
H. V. Vodopick (Goswitz), M.D.

ORAU Committee on Human Studies:

Gould A. Andrews, M.D.
Chairman, ORAU Medical Division

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

C. Lowell Edwards, M.D.
Chief of Clinical Services
ORAU Medical Division

Melvin E. Koons
Law Department (Y-12 Plant)
Union Carbide Corporation
Oak Ridge, Tennessee

Robert D. Lange, M.D.
Assistant Director
U. T. Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Bill M. Nelson, M.D.
Pathologist, ORAU Medical Division

John B. Storer, M.D.
Scientific Director for Pathology & Immunology
Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

1048869

Program Review Committee:

John G. Conniglio, Ph.D.
Professor, Dept. of Biochemistry
Vanderbilt University Medical School
Nashville, Tennessee 37203

Jane F. Desforges, M.D.
Tufts University Hematology Laboratory
Boston City Hospital
818 Harrison Avenue
Boston, Mass. 02118

R. J. M. Fry, M.D.
Division of Biological and Medical Research
Argonne National Laboratory
Argonne, Illinois 60439

Robert H. Greenlaw, M.D.
Marshfield Clinic
Marshfield, Wisconsin 54449

Leonard A. Sagan, M.D.
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Laboratory of Genetics
University of Wisconsin
Madison, Wisconsin 53706

1048870

BIOGRAPHIES

Name: Gould A. Andrews
Position: Internist, Chairman, Medical Division, ORAU
School: University of Michigan, A.B., 1940
University of Michigan, M.D., 1943
Licensure: Tennessee
Board: Internal Medicine
Memberships: Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club.

Name: A. Bertrand Brill
Position: Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine.
School: Grinnell, A.B., 1949
University of Utah, M.D., 1956
University of California, Berkeley, Ph.D., 1961
Licensure: Tennessee
Memberships: American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association
Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name: John G. Coniglio
Position: Professor of Biochemistry, Vanderbilt School of Medicine
School: Furman, B.S., 1940
Vanderbilt, Ph.D., 1949
Memberships: AAAS; Inst. Nutrit; Oil Chem. Soc.; Soc. Biol. Chem.
Other Indication of Experience and Competence:
Specialist in lipid chemistry.

Name: Jane Fay Desforges
Position: Associate Professor, School of Medicine, Tufts University
School: Wellesley College, B.A., 1942
Tufts University, M.D., 1945
Memberships: Associate Editor, New England Journal Medicine, 1960-; Amer. Fed. Clin. Res.; Amer. Soc. Hemat.; Amer. Soc. Exp. Path. Hemat.

1048871

Name: C. Lowell Edwards
Position: Chief of Clinical Research, Medical Division, ORAU
Schools: Manchester College, A.B., 1950
Indiana University, M.D., 1954
Licensure: Tennessee, Indiana
Board: Internal Medicine
Memberships: Roane-Anderson County Medical Society, Tennessee Medical Association, American Medical Association, Society of Nuclear Medicine, American Association for the Advancement of Science, New York Academy of Sciences.

Name: Richard Jeremy Michael Fry
Position: Senior Scientist, Argonne National Laboratory
Schools: University of Dublin, B.A., 1946
University of Dublin, M.D., 1962
Memberships: Radiation Research Society, American Association Cancer Research, Reticuloendothelial Society

Name: Francis A. Goswitz
Schools: Marquette University, Premedical, B.S., 1952
Marquette University School of Medicine, M.D., 1956
Positions: Intern, University of Iowa Hospitals, 1956-57
Resident, Internal Medicine, University of Iowa Hospitals, 1957-58
Internist, U. S. Army Hospital, Fort Campbell, Ky. 1958-60
Fellow, Nuclear Medicine, ORAU Medical Division, 1960-61
Research Associate, Hematology, University of Utah, 1963-65
Clinician and Coordinator, Medical Radioisotope Courses, ORAU Special Training Division, 1965-68
Senior Clinician and Clinical Research Investigator, ORAU Medical Division, 1968 to present
Interests: Malignant disease, hematology and nuclear medicine
Hematology: chemotherapy of leukemias and lymphomas cytokinetics and cytochemistry of blood cells, iron metabolism
Nuclear Medicine: Uses of radioisotopes in cancer, biological effects of irradiation.

1048872

Name:	Helen Vodopick Goswitz
Positions:	Internship, University Hospitals, University of Iowa, 1956-57 Residency in Internal Medicine, University Hospitals, 1957-60 Post-residency Fellow in Nuclear Medicine, ORAU Medical Division, 1960-61 Instructor, Internal Medicine and Hematology, Fellow, University of Iowa, 1961-63 Research Associate in Hematology, University of Utah, 1963-65 Assistant Clinican and Head of Clinical Hematology Laboratory, ORAU Medical Division, 1965 to present
Schools:	Marquette University, B.S., 1949-1953 Marquette University School of Medicine, M.D., 1952-56
Board:	Internal Medicine, 1966
Interests:	Hematology: Leukokinetics, especially of "myeloproliferative diseases Immunology: Histocompatability testing - current work involves in vitro mixed leukocyte cultures Nuclear Medicine: Liquid scintillation spectrometry and autoradiography in relation to the above two areas of interest.

Name:	Robert H. Greenlaw
Position:	Physician at Marshfield Clinic, Marshfield, Wisconsin
School:	Tufts, B.S., 1948 Rochester, M.D., 1952
Memberships:	Amer. Cancer Soc.; Member Med. Adv. Cmt, AEC; Amer. Med. Association; Col. Radiol.; Association Univ. Radiol.; Society of Nuclear Medicine.
Interests:	Development of radioisotopes for diagnosis and therapy; radiation biology; clinical development in radiation therapy.

Name:	R. L. Hayes
Position:	Senior Scientist in charge of medical radioisotope development.
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U. S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society.
Interests:	Development of medical radioisotopic agents; radiation dosimetry.

1048873

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies, (now Oak Ridge Associated Universities) 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961. Admitted to practice of law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966.
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommmittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A. Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	Amer. Assoc. Adv. Sci.; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology, etc.

1048874

Name:	Thomas A. Lincoln
Position:	Director, Health Division, ORNL
School:	Macalester College, B.A., 1946 University of Minnesota, B.S., 1947; B.M., 1949; M.D., 1950 Rotating Internship, Ancker Hospital, St. Paul, Minn. 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, 1963
Memberships:	Fellow, Industrial Medical Association; Tenn. Indust. Med. Assoc.; Amer. Acad. Occupational Med.; AMA; Roane-Anderson County Med. Soc.; Oak Ridge Regional Mental Health Center.

Name:	Bill Nelson
Position:	Research Pathologist
Schools:	University of Kansas, A.B., 1948 University of Chicago, School of Medicine, M.D., 1952
Licensure:	Tennessee
Board:	American Board of Pathology
Memberships:	Amer. Med. Assoc.; Amer. Soc. Clin. Path.; Reticuloendothelial Soc.; Society of Nuclear Medicine; Tennessee Assoc. Pathology

Name:	J. K. Poggenburg, Jr.
Position:	Research Staff, Biomedical Radioisotopes Group, Oak Ridge National Laboratory
Schools:	College of the Holy Cross, Worcester, Mass., B.S., 1956 University of California, Berkeley, Ph.D. - Nuclear Chemistry
Memberships:	Amer. Chem.Soc.; Society of Nuclear Medicine; Sigma Xi.

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fel. American College of Physicians.
Interests:	Late effects of radiation.

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; Amer. Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science.
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance.

1048875

Name:	John B. Storer
Position:	Scientific Director for Pathology and Immunology, Biology Division, Oak Ridge National Laboratory
Schools:	University of Chicago, M.D., 1947
Memberships:	American Association Cancer Research; Amer. Soc. for Exper. Path.; Radiation Res. Soc.; SEBM; Nat. Council on Radiation Protection and Measurements

1048876

0RAU-30025

OAK RIDGE ASSOCIATED UNIVERSITIES
MEDICAL DIVISION
MEDICAL RADIONUCLIDE COMMITTEE
INACTIVE PROTOCOLS
AND RELATED DOCUMENTS 1966-1981
(FILE 2)

1048877

FORM P-4

MEMORANDUM

TO Dr. Lushbaugh DATE April 9, 1975

SUBJECT Medical Radionuclide Committee and Committee on Human Studies

COPIES TO

Originally, the name of the present "Medical Radionuclide Committee" varied from "Human Use Committee" to "Isotopes Committee," and sometimes "Human Studies Committee." When Dr. Kniseley was here he preferred "Isotopes Committee," but after he left and Roger took over as Chairman of the Committee, he and his group gave it a definite name, "Medical Radionuclide Committee." This Committee was functioning quite a while before the "Committee on Human Studies" was formed. I am attaching a memo concerning the establishment of the "Committee on Human Studies."

Present Members of the Medical Radionuclide Committee are:

Bill Gibbs, Chairman
R. L. Hayes
Jim Berger
C. L. Edwards
K. Hubner
D. Swartzendruber

Present Members of the Committee on Human Studies are:

Dr. Brill (Vanderbilt)
Dr. Edwards
Mr. Koons
Dr. Lange (UT, Knoxville)
Dr. Lincoln, ORNL
Dr. Storer
~~Dr. Nelson~~
(It has been suggested that a minister replace Nelson- pending-)

Dr. Hayes had asked me to send copies of the 3-23-67 document to Dr. Andrews, Dr. Edwards, and Dr. Hubner, plus a copy to you. Roger had made some progress on the Committee when he was Chairman, but after he left the Medical Division, Bill Gibbs became Chairman, and I am not knowledgeable about the Committee now. He said the last proposal they reviewed was Iodine-125 for Thyroid Scanning, March 11. If you need anything further on this, let me know.

I hope this has been helpful and not confusing!

See Dr. Andrews notes 1-2-74. attached

Frances

1048878

Table of Contents

MEDICAL RADIONUCLIDE COMMITTEE

Proposal #	
68	Gallium-68 Labeled Hydrous Ferric Oxide Colloid for Tomographic Imaging of the Reticuloendothelial System. (October 1981)
39b	Amendment to existing IND 12,967: Physiological studies of pancreas and brain using "C-L-Tryptophan." (October 1981)
75-1	Iodine-125 for Thyroid Scanning as liquids or capsules. (March 1975)
75-2	Carbon-11 ACPC for the detection of tumors in humans. (April 1975)
76-1	Xenon-133 gas inhalation for Lung ventilation and washout studies. (April 1976)
76-2	Xenon-133 gas for Lung perfusion studies. (April 1976)
76-3	Carbon-11 DL-Valine-1 for visualization of the pancreas. (April 1976)
76-4	(1) Fluorine-18 as Fluoride ion in Saline solution. Oral administration for Skeletal imaging. (2) Iodine-131 Sodium rose bengal for Liver function and Liver imaging. (3) Iodine-125. (April and June 1976)
76-5	Selenium-75 for pancreas imaging. (June 1976)
76-6	Carbon-11 DL - Tryptophan for visualization of the pancreas. (October 1976)
76-7	Technetium-99m - Iron - Ascorbate - DTPA (Renotec R) for Renal Scanning. (November 1976)
77-1	Gallium-68 EDTA for studies of Brian lesions, Soft tissue Malignancies, and Kidneys. (March 1977)
77-2	Emission Computerized Tomography studies of Gallium-68 citrate.
77-3	To Investigate Carbon-11 ACBC for the positron tomography detection of

1048879

tumors in humans and to compare its efficacy with Carbon-11 ACBC and Gallium-67 citrate. (September 1977) (May 1977)

78-1 Gallium-68 Labeled Microspheres - Preparation for the study of Lung perfusion in subjects with Pneumoconiosis. (July 1978)

78-1a Gallium-68 Labeled Microspheres - Change previous approved Level. (March 1979)

79-1 Gallium-68 EDTA aerosol for Lung Ventilation studies by positron tomography. (May 1979)

79-2 Technetium-99m Pertechnetate for Peripheral Vascular imaging and blood pool imaging in patients with probable Radiation injury. (December 1979)

80-1 Ytterbium-169 Citrate for the detection of in Flammatory Lesions. (April 1980)

81-1 L-Valine-1 "Carbon to study the rate of protein synthesis by Positron Emission Computerized Tomography in Neoplastic Lesions and in the Brain. (January 1981)

1048880

Ident No. 68

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities (ORAU)
and Oak Ridge National Laboratory (ORNL)

Date: October 15, 1981

Principal Investigator: Karl F. Hübner, M.D. (ORAU)

Co-Investigators: Raymond L. Hayes, Ph.D. (ORAU)

Francis Goswitz, M.D. (Oak Ridge Medical Clinic)

Title of Project: USE OF ^{68}GA-LABELED HYDROUS FERRIC OXIDE COLLOID FOR TOMOGRAPHIC IMAGING OF THE RETICULOENDOTHEIAL SYSTEM.

I. Objective of Experiment:

The objective of this study is to determine the benefits that may be derived from the administration of ^{68}Ga-labeled hydrous ferric oxide colloid and subsequent scanning with an ORTEC ECAT-II positron tomograph for determining the functional status of the reticuloendotheial system (RES) in patients afflicted with cancer. The results obtained in each patient will be compared with those obtained with conventional ^{99m}Tc sulfur colloid scanning using a Searle FOCON-II scanner (a single photon tomographic instrument). These latter studies will be performed by Dr. Goswitz. Gallium-68 is a positron emitter with a 68-min half life that is available from a long-lived ($T_{1/2}$ = 288 d) ^{68}Ge/^{68}Ga generator.

II. Methods of Procedure:

The ^{68}Ga-labeled hydrous ferric oxide colloid (mean diameter of particles = ∿9 nm) will be prepared by heat hydrolysis of dilute ferric chloride solutions that contain ^{68}Ga chloride. The ^{68}Ga chloride will be produced from ^{68}Ga EDTA which in turn will be obtained from a ^{68}Ge/^{68}Ga generator (procedure covered in ORAU IND 13,533 for ^{68}Ga citrate). The colloid will be stabilized with gelatin (obtained from a Mallinckrodt TechneColl Sulfur Colloid kit) and brought to pH 6.0 with sodium acetate. The intra-

1048881

venously injected volume of the preparation will not exceed 3.4 ml nor contain more than 1.4 mg of iron for a 70 kg subject (20 μg Fe/kg body weight). Each preparation will be tested for pyrogens before it is administered. The amount of ^{68}Ga injected will not exceed 3.0 mCi for a 70 kg subject (43 μCi/kg body weight). This preparation has been shown in animals to localize specifically in the liver, spleen, and bone marrow (see Tables 1 and 2).

A total of 15-20 patients will be studied. These patients will be referred to the Medical and Health Sciences Division by Dr. Francis Goswitz or other oncologists in the area. Before referral, when possible, the patients will receive ^{99m}Tc sulfur colloid single-photon tomographic FOCON scans in Goswitz's facilities. Ideally these patients will also be scanned with the Medical and Health Sciences Division's (M&HSD) Pho-Gamma V camera immediately following these ^{99m}Tc studies. Two to three days after the ^{99m}Tc RES studies the patients will be studied at M&HSD using the ECAT-II scanner and the ^{68}Ga-labeled colloid agent detailed above. Scanning will commence 10-15 minutes after administration. Scan sections (1.8 cm in thickness) will be made through the body over those postions of the trunk that the previous ^{99m}Tc sulfur colloid scans indicate are of interest or that clinical assessment dictates. Informed consent will be obtained from each patient before the study is performed (see attached consent form).

III. Possible Hazards and Their Evaluation:

The stable components of this radiopharmaceutical preparation will be similar to those of several drugs that are currently being used for intravenous treatment of iron deficiency anemia where oral iron administration has been found to be ineffective or impractical, i.e., Imferon and Astrafer. Both of these preparations contain hydrous ferric oxide colloid stabilized with high molecular carbohydrates. The ^{68}Ga-labeled hydrous ferric oxide colloid to be used in these studies will be stabilized with gelatin (Mallinckrodt), the agent of choice in ^{99m}Tc sulfur colloid preparations. Imferon and Astrafer are normally administered at dose levels of approximately 1 mg Fe/kg body weight. The amount of iron administered with this preparation will not exceed 20 μg Fe/kg body weight (1/50th the usual iron dose for Imferon and Astrafer). No untoward effects should therefore be expected as the result of the administration of ^{68}Ga-labeled hydrous ferric oxide colloid. A study of the acute effects of this preparation administered at a level 50 times that to be used in human subjects using male and female rats gave negative results.

IV. Radioisotopes and New Drugs:

The radioisotope used in this preparation will be ^{68}Ga ($T_{1/2}$ = 68 m). It will be obtained from a New England Nuclear $^{68}Ge/^{68}Ga$ generator. This proposal will be submitted to the ORAU Medical Isotopes Committee on October 20, 1981. The Committee on Human Studies will be notified of its action when the committee meets on October 29, 1981. The ORAU Internal Dose Information Center estimates on the basis of the data contained in Table 1 that the radiation dose to the human liver will

1048882

be 1.7 rads/mCi of ^{68}Ga (5 rads for the proposed dose of 3 mCi of ^{68}Ga-labeled hydrous ferric oxide colloid per 70 kg subject).

V. Responsibility of Principal Investigator:

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study (see attached consent form). The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or the development of unexpected risks will be immediately brought to the attention of the Committee on Human Studies.

Starting Date December 15, 1981

Signatures _____ Principal Investigator

_____ Co-Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature: _____

Title: Chairman, Medical and Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: _____

TABLE 1

Tissue Distribution of ^{68}Ga-Labeled Hydrous Ferric Oxide Colloid in Male Fischer-344 Rat at Various Times After Administration.

Tissue or Organ	Time (min)		
	15	30	60
Liver	10.6* ± 0.6†(88.4)§	11.3 ± 0.9(91.7)	9.9 ± 0.3(94.1)
Spleen	2.70 ± 0.42	3.12± 0.42	3.11± 0.14
Kidney	0.13 ± 0.01	0.10± 0.01	0.08± 0.01
Lung	0.16 ± 0.01	0.21± 0.05	0.14± 0.02
Muscle	0.01 ± 0.00	0.01± 0.00	0.02± 0.00
Femur	0.14 ± 0.01	0.18± 0.02	0.29± 0.05
Bone marrow	0.95 ± 0.10	1.19± 0.19	1.16± 0.10
Blood	0.14 ± 0.03	0.07± 0.01	0.09± 0.01
Testis	0.01 ± 0.00	0.01± 0.00	0.01± 0.00

* Percent administered ^{68}Ga/g normalized to 250 g body weight; 5 animals per group.

† Standard error.

§ Percent administered ^{68}Ga/organ.

1048884

TABLE 2

^{68}Ga-Labeled Hydrous Ferric Oxide Colloid

	Ratio of ^{68}Ga activity in liver, spleen and marrow to that in other organs*		
	Liver to:	Spleen to:	Marrow to:
Liver	-	0.3	0.1
Spleen	4	-	0.4
Kidney	110	31	12
Lung	54	15	6
Muscle	1100	310	120
Femur	63	17	7
Marrow	10	3	-
Blood	160	45	17
Testis	1100	310	120

* 30 Minutes after intravenous administration.

1048885

Oak Ridge Associated Universities

MEMORANDUM

Ray Hayes

FROM Jack Coffey Jack

DATE September 30, 1981

COPIES TO File

SUBJECT Radiation Dose from Ga-68 Hydrous Ferric Oxide Colloid

Listed below are the radiation dose estimates for Ga-68 Hydrous Ferric Oxide Colloid based on the rat data you supplied.

Organ	Radiation Dose (rad/mCi)
Liver	1.7
Red Marrow	0.085
Spleen	0.33
Testes	0.0026
Total Body	0.0011

JLC/fs

1048886

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner PROPOSAL NO. 68

DESCRIPTION: ^{68}Ga-Labeled hydrous ferric oxide colloid for tomographic imaging of the reticuloendothelial system.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not X be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not X be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
James A. Kenger	X			10/29/81
William D. Gibbs	X			10/21/81
Russell J. Di Zio	X			10/21/81

Acknowledgement of submitter Karl F. Hübner Date

Proposal does X does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on

1048887

PROPOSAL 39b

The material accompanying this proposal includes the proposal itself, consent forms, and a letter to Dr. Gyarfas of FDA. The Gyarfas letter has not been sent and will not be sent until the Committee has made a decision regarding the proposal. It is included for your information.

dg

1048888

Ident. No. 39b

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date 10/12/81

Principal Investigator: K. F. Hübner

Co-Investigators: Lee Washburn

R. L. Hayes

Title of Project: Amendment to existing IND 12,967: physiological studies of the pancreas and brain using ^{11}C-L-tryptophan

I. Objectives of Experiment:

1. To determine whether the ^{11}C-L-tryptophan localizes to a higher degree in normal pancreatic tissue than in neoplastic or inflammatory lesions, and whether ^{11}C-L-tryptophan in conjunction with ^{11}C-1-aminocyclobutane-carboxylic acid (^{11}C-ACBC) or ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC) can be used for the differential diagnosis of pancreatic disease by positron tomography.

2. To study the metabolic activity of the brain or specific structures of the brain in patients with Phenylketonuria (PKU), Huntington's Disease (HD), and brain tumors by measuring the rate of protein synthesis using ^{11}C-L-tryptophan as a precursor.

There are "no good large animal models" for any of these diseases. Large animals would be required for meaningful ECAT studies. In vivo measurement of metabolic activity as based on amino acid (L-tryptophan) utilization should provide a better understanding of pancreatic disease and brain damage and might form the basis for new information needed for improved treatment of these diseases.

II. Methods of Procedure

The protocols and procedures are described in detail in the attached drafted letter to FDA.

1048889

III. Possible Hazards and Their Evaluation

There are no chemical risks from injecting L-tryptophan in the amounts proposed in this investigation. Adherence to quality control procedures (sterility, pyrogenicity testing) prior to i.v. injection of ^{11}C-L-tryptophan should eliminate any side effects.

IV. Radioisotopes and New Drugs

L-tryptophan, a natural essential amino acid, will be labeled with carbon-11. The whole body radiation doses from the injection of carbon-11 labeled L-tryptophan in the amounts proposed are comparable to radiation doses from conventional pancreas and brain scans (200 to 500 millirad total body dose). The compound and doses have been approved by the ORAU/M&HSD's Radionuclide Committee. The attached amendment will be submitted to FDA subsequent to approval by the ORAU/ORNL Committee on Human Studies.

V. Responsibilities of Principal Investigator

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be immediately brought to the attention of the Committee on Human Studies.

Starting Date: December 1, 1981

Signatures: Karl F. Hubner, M.D. — Principal Investigator

Lee C. Washburne — Co-Investigator

R. L. Hayes (per LCW) — "

DIVISION REVIEW:

The application described above has been reviewed and approved for submission to the ORAU/ORNL Committee on Human Studies.

Official signing for the institution:

Signature

Title: Chairman, M&HSD

Institution: Oak Ridge Associated Universities

Date: 10/12/81

1048890

#37b

Medical and Health Sciences Division
OAK RIDGE ASSOCIATED UNIVERSITIES

Adult ____ Guardian ____ Parent ____ Patient ____

Child ____ Controls ____

CONSENT FOR RESEARCH STUDY

Title of Project: _____

_____

Principal Investigator: _____

Name of Volunteer: _____ Age: _____

_____

To persons who agree to participate in this study:

The information on this and on the attached form has been given to me to inform me about this research project and my participation in it. I have been asked to read these forms carefully. All my questions about the study, the procedures required to do the study, and the information provided on the attached form have been answered.

I understand the purpose of the study, the procedures involved, and the possible risks and potential benefits. Further, I understand that, while my rights and privacy will be maintained, any information gained in this test becomes the property of ORAU and may be published in the scientific literature or used for other purposes which ORAU deems proper in the interest of medical education, knowledge, or research.

I have been informed that I may, at any time withdraw from continued participation in this study. I understand further that in the event of physical injury resulting from the procedure essential medical treatment including hospitalization is provided free of charge, but monetary compensation for wages lost because of injury is not available from either ORAU or Union Carbide Corporation, ORNL. I freely and voluntarily choose to participate.

Date _____

_____
Signature of Volunteer

_____
Signature of parents and guardian
(when applicable)

_____
Signature of Witness

1048891

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Amino Acid (valine) Utilization in Pancreatic Diseases

The purpose of this study: is to measure the rate of protein fomation (synthesis) in the pancreas and in pancreatic tumors in order to gain a better understanding about the nature of pancreas disease. On a voluntary basis a brain scan will be done following the completion of the pancreas scan for the purpose of collecting data on valine uptake by normal brain structures.

The procedures to be done: are as follows.

(1) I (she/he) should not eat anything after breakfast, but may have water and continue all important medications. Thirty minutes before the study I (she/he) will be asked to drink a milkshake.

(2) First I (she/he) am (is) going to have several pancreas and had scans to be done with a ECAT scanner. I (she/he) will be instructed to hold still: my (her/his) eyes will be covered with pads, and I (she/he) will be asked to listen to music through a head phone and try to stay awake.

(3) Injection needles will be placed in a vein in each hand for the injection of tryptophan (a normal component of the body) and for obtaining several small (2 ml) blood samples. My (her/his) hands will be kept warm during the 30-minute blood sampling period. At the beginning of the actual test a small amount of radioactive valine will be injected. Following the injection blood samples will be taken and a series of scans of my (her/his) pancreas will be made. When the pancreas scans are completed, several head scans will be made.

Duration of this study: The entire examination should take approximately 1-1/2 to 2 hours. I (she/he) understand(s) that I (she/he) may have to return for one or two more examinations (same procedure as done today) within the next few weeks.

Discomforts, inconveniences and/or risks that can be reasonably expected are: the slight pain from the insertion of the injection needles, and perhaps a slight discomfort from having to lie on the scanning table for over an hour. There is no chemical risk from the injection of the valine and the radiation dose to my whole body is equivalent to the dose I would receive for an ordinary pancreas scan in a local hospital.

Potential benefits of the study: I understand that this test is not a treatment but rather a research method that might lead to new insights into my disease and perhaps diseases of the brain.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1048892

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Local Brain Metabolism in Brain Tumors

The purpose of this study: is to measure the rate of protein formation (synthesis) in different regions of the brain in order to gain a better understanding about the nature of the brain tumors and possibly find an improved treatment for patients who have brain tumors.

The procedures to be done: are as follows.

(1) I (she/he) should not eat anything after breakfast, but may have water and continue all important medications.

(2) First I (she/he) am (is) going to have several head scans to be done with an ECAT scanner. I (she/he) will be instructed to hold still. My (her/his) eyes will be covered with pads, and I (she/he) will be asked to listen to some music through a head phone and try to stay awake.

(3) Injection needles will be placed in a vein in each hand for the injection of tryptophan (a normal component of the body) and for obtaining several small (2 ml) blood samples. My (her/his) hands will be kept warm during the 30-minute blood sampling period. At the beginning of the actual test a small amount of radioactive valine will be injected. Blood samples will be taken and a series of scans of my (her/his) brain will be made.

Duration of this study: The entire examination should take approximately 1-1/2 to 2 hours, and I (she/he) understand(s) that I (she/he) will have another examination (same procedure as done today) also using radioactively labeled valine but in a slightly different chemical form.

Discomforts, inconveniences and/or risks that can be reasonably expected are: the slight pain from the insertion of the injection needles, and perhaps a slight discomfort from having to lie on the scanning table for over an hour. There is no chemical risk from the injection of either of the two types of valine and the radiation dose to the whole body is equivalent to the dose one would receive from two ordinary brain scans in a local hospital.

Potential benefits of the study: I understand that this test is not a treatment but rather a research method that might lead to new insights into brain tumor growth for a better understanding of the disease process and its treatment.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1048893

Medical and Health Sciences Division
Oak Ridge Associated Universities

rincipal Investigator: _____

Title of Project: Local Brain Metabolism in Phenylketonuria (PKU)

The purpose of this study: is to measure the rate of protein formation (synthesis) in different regions of the brain in order to gain a better understanding about the nature of the brain damage from PKU and possibly find an improved treatment for PKU patients.

The procedures to be done: are as follows.

(1) She/He should not eat anything after breakfast, but may have water and continue all important medications.

(2) First she/he is going to have several head scans to be done with a ECAT scanner. She/He will be instructed to hold still her/his eyes will be covered with pads, and she/he will be asked to listen to music through a head phone and try to stay awake.

(3) Injection needles will be placed in a vein in each hand for the injection of tryptophan (a normal component of the body) and for obtaining several small (2 ml) blood samples. Her/His hands will be kept warm during the 30-minute blood sampling period. At the beginning of the actual test a small amount of radioactive valine will be injected. Following the injection blood samples will be taken and series of scans of her/his brain will be made.

Duration of this study: The entire examination will take approximately 1-1/2 to 2 hours, and I understand that she/he may have to return for another examination (same procedure as done today) in about eight to 16 weeks.

Discomforts, inconveniences and/or risks that can be reasonably expected are: the slight pain from the insertion of the injection needles, and perhaps a slight discomfort from having to lie on the scanning table for over an hour. There is no chemical risk from the injection of the valine and the radiation dose to the whole body is equivalent to the dose one would receive from an ordinary brain scan in a local hospital (200 millirad).

Potential benefits of the study: I understand that this test is not a treatment but rather a research method that might lead to new insights into PKU and perhaps other diseases of the brain for a better understanding of the disease process and its treatment.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1048894

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Local Brain Metabolism in Huntington's Disease (HD)

The purpose of this study: is to measure the rate of protein formation (synthesis) in different regions of the brain in order to gain a better understanding about the nature of the brain damage from HD and possibly find an improved treatment for HD patients.

The procedures to be done: are as follows.

(1) I (she/he) should not eat anything after breakfast, but I (she/he) may have water and may continue all important medications.

(2) First I (she/he) am (is) going to have several head scans to be done with an ECAT scanner. I (she/he) will be instructed to hold still. My (her/his) eyes will be covered with pads, and I (she/he) will be asked to listen to music through a head phone and try to stay awake.

(3) Injection needles will be placed in a vein in each hand for the injection of tryptophan (a normal component of the body) and for obtaining several small (2 ml) blood samples. My (her/his) hands will be kept warm during the 30-minute blood sampling period. At the beginning of the actual test a small amount of radioactive valine will be injected. Blood samples will be taken and a series of scans of my (her/his) brain will be made.

Duration of this study: The entire examination will take approximately 1-1/2 to 2 hours, and I (she/he) understand(s) that I (she/he) may have to return for another examination (same procedure as done today) in about eight to 16 weeks.

Discomforts, inconveniences and/or risks that can be reasonably expected are: the slight pain from the insertion of the injection needles, and perhaps a slight discomfort from having to lie on the scanning table for over an hour. There is no chemical risk from the injection of the valine and the radiation dose to the whole body is equivalent to the dose (she/he) would receive from an ordinary brain scan in a local hospital (200 millirad).

Potential benefits of the study: I understand that this test is not a treatment but rather a research method that might lead to new insights into Huntington's Disease and perhaps other diseases of the brain for a better understanding of the disease process and its treatment.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1048895

#590

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

October 9, 1981

William J. Gyarfas, M.D., Director
Division of Oncology and Radio-
pharmaceutical Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: IND 12,967

Dear Dr. Gyarfas:

The following information, submitted in triplicate, constitutes an amendment to IND 12,967. The proposed amendment involves the resolution of ^{11}C-DL-tryptophan, the previously approved drug, by high-performance liquid chromatography and the intravenous administration of an optically active form of the approved drug, ^{11}C-L-tryptophan, for physiological studies of the pancreas and brain.

Background

^{11}C-DL-Tryptophan was shown in animal studies (1) to be potentially useful as a pancreas-imaging agent and was subsequently approved for human studies. Clinical trials with ^{11}C-DL-tryptophan and a similar agent, ^{11}C-DL-valine (IND 12,459), have shown that both agents concentrate very selectively in the pancreas (2); however, differential diagnosis of pancreatic carcinoma has not been feasible, apparently because of similarly high uptakes in the pancreas and tumor.

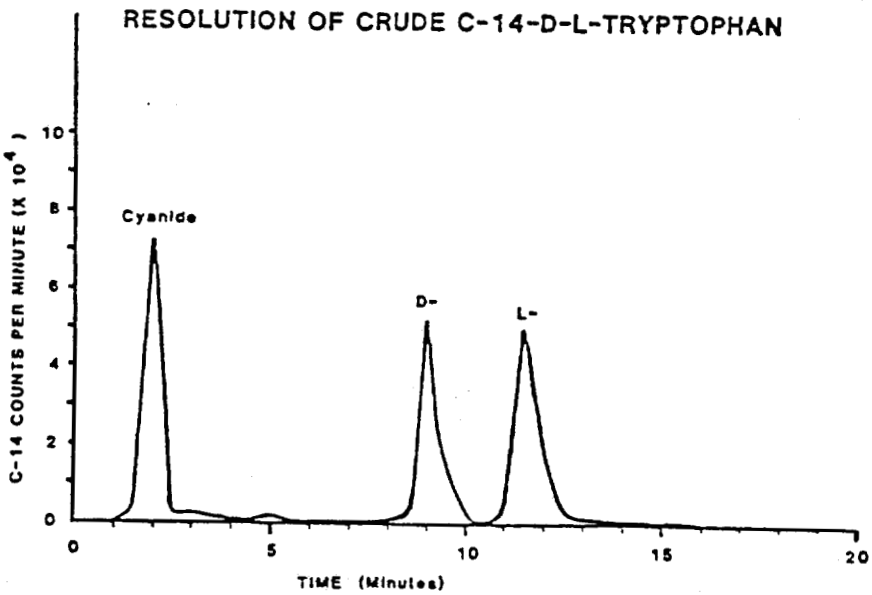
Tamemasa and co-workers (3) have found that D-amino acids are concentrated selectively by tumor tissue. Therefore, it appears that the uptake of ^{11}C-DL-tryptophan by pancreatic carcinoma may be due to the presence of ^{11}C-D-tryptophan in the mixture. We anticipate that use of ^{11}C-L-tryptophan may overcome these difficulties and permit detection of pancreatic carcinoma as a defect rather than a "hot spot" in pancreas scans. Availability of ^{11}C-L-tryptophan will also permit studies of L-tryptophan metabolism in the brain.

1048896

Production of ^{11}C-L-tryptophan

^{11}C-L-Tryptophan is produced by separation of the two optical isomers of ^{11}C-carboxyl-labeled DL-tryptophan by high-performance liquid chromatography (HPLC) using a chiral mobile phase. Crude ^{11}C-DL-tryptophan is prepared as previously described (4, IND,967) with the exception that measures are taken to minimize the volume of the reaction mixture: (1) The gas absorption column is not rinsed with water; and (2) 0.3 ml of 12 N NaOH (Fisher Scientific Co., Fair Lawn, N.J.) is used in place of 1.0 ml of 6.25 N NaOH for hydrolysis of the hydantoin. In addition, because of the insolubility of the copper complex with tryptophan and proline, the amount of carrier potassium cyanide used in the production of ^{11}C-DL-tryptophan was reduced to <0.1 mg, which results in the synthesis of a ^{11}C-labeled compound having much higher specific activity.

The HPLC (LC/System Support Unit I, Laboratory Data Control, Riviera Beach, FL) is fitted with a preparative [10 mm (i.d.) x 25 cm (length)] Spherisorb ODS, 5 μ column (Laboratory Data Control). The column is equilibrated with the mobile phase [0.007 M cupric acetate (Fisher Scientific Co.), 0.015 M L-proline (Sigma Chemical Co., St. Louis, MO), and 0.03 M sodium acetate (J. T. Baker Chemical Co., Phillipsburg, N.J.) in 85% distilled water - 15% ethanol. The flow rate is adjusted to 7.2 ml/minute, giving a pressure of 3200-3300 psi. The crude ^{11}C-DL-tryptophan reaction mixture (1.3 ml) is combined with 3.2 mg of cupric acetate and 3.9 mg of L-proline in 100 μl of distilled water and 300 μl of ethanol. This mixture is adjusted to pH 5 using concentrated HCl (Fisher Scientific Co.), microfiltered, and loaded onto the HPLC column using a 3-ml disposable syringe and a 2-ml sample injection loop. The elution of the ^{11}C-labeled mixture is monitored using a shielded gamma probe. The figure below shows the elution pattern which is typically obtained. In this case, a ^{14}C-labeled DL-tryptophan reaction mixture was used. The elution time for commercially available ^{14}C-L-tryptophan (New England Nuclear Corp., Boston, MA) was identical to that of the ^{14}C-L-tryptophan component of the crude reaction mixture.



1048897

Final purification by cation-exchange chromatography, as in the production of ^{11}C-DL-tryptophan, effectively removes both copper and L-proline and gives ^{11}C-L-tryptophan in a radiopharmaceutically pure form. The L-amino acid fraction from HPLC is acidified with HCl and loaded onto a prewashed 1.0 cm (dia.) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation-exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydrogen form. Cationic ^{11}C-L-tryptophan is retained while neutral and anionic materials, including the copper complex with L-proline, pass through the column. After washing with 100 ml of 1 N HCl and 100 ml of distilled water, the column is eluted with 0.2 N NaOH, the process being monitored using a shielded gamma probe to minimize the volume of eluate containing the product (∿ 15 ml), which is collected in a sterile bottle. Final radiopharmaceutical processing (neutralization, microfiltration, and Limulus Lysate pyrogen testing) is done as detailed in the original IND 12,967.

Toxicity

As mentioned above, the cation-exchange column quite effectively removes the cupric ions and L-proline which are present in the HPLC mobile phase. ^{14}C-Labeled L-proline was used to determine quantitatively the removal of L-proline. The 1 N HCl wash contained 99.3% of the total carbon-14 counts loaded onto the column, while the product fraction contained 2.3%. (The total recovery of 101.6% is within experimental error of the theoretical 100%.) Assuming 20 ml of HPLC eluate, 35 mg of L-proline would be present if none was removed. However, only 2.3% of this amount, or 0.8 mg, remains following cation-exchange purification. Assuming that blood comprises 7% of the total human body weight and a hematocrit of 40, there is an average of 69.4 mg of L-proline in the blood stream of a normal 70-kg human (5). Therefore, the quantity of L-proline which we propose to administer would increase the blood L-proline level by only 1.2%.

Likewise human blood contains 98 (72-124) μg of copper per 100 ml (6). Assuming again that blood comprises 7% of the total human body weight, there is an average of 4.8 mg of copper in the blood stream of a normal 70-kg human. Analysis (Galbraith Laboratories, Inc., Knoxville, TN) of a typical product solution which had undergone final purification by cation exchange chromatography showed 0.9 mg Cu/liter. Therefore, the typical 15-ml product would contain 13.5 μg of copper, and administration of this quantity would increase the normal level of copper in the blood by only 0.3%.

Chemical toxicity from unlabeled L-tryptophan will also be negligible. L-Tryptophan, of course, is one of the essential, naturally occurring amino acids, and, as such, it is present to the extent of 0.274 (0.269-0.289) mg per 100 ml of normal human blood (5). Assuming that blood comprises 7% of total human body weight, there is ∿ 13.4 mg of L-tryptophan in the blood stream of a normal 70-kg human. We propose to administer no more than 0.2 mg of L-tryptophan per 70 kg subject, and, therefore, we will be increasing the blood level of L-tryptophan by no more than 1.5%. This amendment has been approved by the ORAU/ORNL Committee on Human Studies.

1048898

Radiation Dosimetry

Because of the short half-life of carbon-11 (20.4 minutes), the radiation dose to patients from ^{11}C-DL-tryptophan will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center that the complete decay of 1 mCi of ^{11}C-L-tryptophan uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.01 rads or a total of 0.20 rads per 20 mCi (the maximum proposed administered dose of ^{11}C-L-tryptophan. The table below gives the expected radiation dose to various organs in the human estimated from animal data. Use of ^{11}C-L-tryptophan was approved by the M&HSD, ORAU Medical Radionuclide Committee.

Estimated Radiation Dose from ^{11}C-L-Tryptophan to Organs in Man*

Tissue	Radiation Dose (rads/mCi)
Total body	0.011
Pancreas	0.25
Liver	0.035
Spleen	0.020
Kidney	0.023
Bone marrow	0.017
Lung	0.017
Small intestine	0.042
Ovary	0.019
Testis	0.010

* Based on 30-minute tissue distribution in male and female rats following intravenous administration of L-tryptophan [side chain-3-^{14}C] (0.01 mg/kg) assuming immediate uptake and no further change in distribution.

Clinical Studies

In this amendment we request permission by FDA to use the diagnostic radiopharmaceutical ^{11}C-L-tryptophan in patients with different proven or suspected diseases: tumors of different types, pancreatic diseases and neurological disease.

Patient selection criteria for patients with pancreatic diseases. During the first year 10 patients with suspected cancer of the pancreas will be studied with L-tryptophan-1-^{11}C. Each patient is scheduled to have a tomographic pancreas scan with this amino acid and in addition will be scanned using the tumor scanning agents ^{11}C-ACBC and ^{11}C-ACPC (IND Nos. 13,867 and 11,848, respectively) to determine whether L-tryptophan-1-^{11}C in conjunction with ^{11}C-ACPC or ^{11}C-ACBC is of value in the differential diagnosis of pancreatic disease. Criteria for suspicion of neoplastic pancreatic disease are pain, weight loss, steatorrhea, jaundice, and existing metastatic disease with suspected primary carcinoma of the pancreas. Patients are expected to be referred by the Oak Ridge/Knoxville medical community and Vanderbilt University, Nashville, TN.

In addition to the patients with suspected pancreatic cancer, 10 patients with proven pancreas tumors undergoing chemotherapy and/or radiation therapy will be studied three times: before, during and after the first course of treatment.

Some of the patients will be asked to volunteer for a brain scan after completion of the L-tryptophan-1-^{11}C pancreas scan for the purpose of collecting information on the normal intracerebral distribution of this amino acid which might also be useful in studying neoplastic and non-neoplastic brain diseases.

Protocol/procedures for patients with pancreatic diseases.

1. Patients will be instructed to have nothing by mouth after breakfast except water, and will be encouraged to drink one milkshake 30 minutes before the L-tryptophan-1-^{11}C dose for the pancreas scan.

2. A series of transmission ECAT scans of the abdomen (and head) will be done prior to the injection of the dose. The patient will be asked to be quiet but to stay awake.

3. Intracatheters will be placed into a vein in each hand and one hand will be kept in a thermostatically controlled water bath (44°C) during the transmission scans and for an additional 30 minutes after injection of the dose.

4. A dose of 20 mCi of L-tryptophan-1-^{11}C in a volume of 10 to 20 ml physiological saline will be injected by slow push (30 to 60 seconds) into one hand.

5. Blood samples from the hand opposite to that injected (2 ml heparinized) will be drawn at 1, 5, 10, 20 and 30 minutes for radioassay. The last sample will also be used to determine the absolute L-tryptophan concentration in plasma by HPLC.

6. ECAT scanning of the abdomen (pancreas) will be started one minute after injection and carried out for 30 minutes. Thereafter, tomographic scans of the head (brain) will be made over another period of 20 to 30 minutes.

7. The entire procedure should not exceed 2 hours. Some of the patients will be asked to be examined 3 times during the course of their disease.

8. General considerations for human subjects participating in this study: Pregnant women and patients under 18 years of age will not be included. Only patients capable of giving informed consent will be accepted for participation.

After initial discussion with their primary physician, the patients will be informed about the procedures and tests about 1 to 2 hours prior to the examination. The consent forms (see Attachment A) have been approved by the ORAU/ORNL Committee on Human Studies. Consent will usually be obtained by a physician involved in the project. The purpose of the procedure, the chemical aspects with regard to the amino acids and the radiological aspects with regard to the ^{11}C-label of the radiopharmaceuticals as well as the scanning procedure will always be discussed with the patient. The discussion will usually take place in the presence of a nurse, and the patient will be encouraged to ask questions and reminded that she/he can withdraw from the study at any time. The signed consent forms are to be kept in the patient's record.

There are no physical risks other than the radiation dose; there are no psychological, social or legal risks. There are no alternative methods for the in vivo metabolic studies proposed in this amendment.

The activity level will be kept at 20 mCi which is less than 50% of the doses approved by FDA (^{11}C-DL-valine, ^{11}C-ACPC and ^{11}C-ACBC) for a 70 kg person.

Potential benefits include information on the extent of the disease, possible useful metabolic information on tumor growth for therapeutic decisions, and valuable data on protein synthesis in normal brain. The risk as related to the potential benefits is minimal.

Selection criteria and scanning protocols for patients with non-malignant neurological diseases and for patients with brain tumors.

Non-malignant neurological diseases to be studied under the amended IND are: phenylketonuria, and possibly Huntington's disease. The principle rationale is to study the metabolic activity of the brain or specific structures of the brain in such patients by measuring protein synthesis using L-tryptophan-1-^{11}C as a precursor.

Phenylketonuria (PKU), a metabolic disease in which abnormally high blood levels of phenylalanine interfere with uptake and utilization of other amino acids by the brain, especially the developing brain, can serve as a unique model for a number of human diseases in which protein metabolism of the brain is disturbed. This observation and rationalization forms the basis for using patients with PKU in this study. The patient will be selected by Dr. Richard J. Allen, Professor of Pediatrics and Director of Pediatric Neurology at The University of Michigan. The patients will be over 18 years of age and untreated at the time of study.

Huntington's Disease (HD) is an autosomal dominant disorder associated with progressive dementia and involuntary movements, usually beginning in midlife. The underlying metabolic defect is poorly understood and there is no predictive test that could identify asymptomatic gene carriers. This disease in which abnormalities of cerebral glucose metabolism have been

demonstrated may also have an abnormal protein synthesis (especially in the caudate nucleus) that most likely antedate the onset of symptoms. Positron emission computerized tomographic scans using L-tryptophan-1-^{11}C in patients with established HD and patients at risk appear to offer the opportunity to gain a better understanding of this disease and inspire the hope that carriers of HD may be detectable. The patients to be studied will be selected by Dr. Anne B. Young, Assistant Professor at the Department of Neurology at The University of Michigan.

Brain tumors, notably malignant gliomas seem to express a preference for some essential amino acids as has been demonstrated by in vitro analysis, and dietary elimination of these preferentially utilized amino acids has shown a favorable effect on the survival of patients with malignant gliomas. PETT studies (done under the existing IND) have confirmed high uptake of DL-valine-1-^{11}C and DL-tryptophan-1-^{11}C in several glioma patients.

To use the natural L-form of valine and tryptophan as scanning agents would be highly desirable for the obvious reason that the natural form would more closely reflect amino acid utilization and protein synthesis of neoplastic lesions in the brain. For this study patients with brain tumors or strongly suspected brain tumors will be selected and referred by Dr. J. Purvis, neurosurgeon (Knoxville), Dr. J. Robertson, neurosurgeon at UT Memphis, and Dr. N. S. Mahaley, The University of North Carolina.

Protocols/Procedures for patients with non-malignant neurological diseases and patients with brain tumors.

Phenylketonuria. Only 4 patients with PKU may be studied under this IND at Oak Ridge during the first year. If funds permit, these patients, all older than 18 years, will be examined at least twice, once while on an uncontrolled diet and again while on a controlled diet, i.e., a diet low in phenylalanine and supplemented with isoleucine.

1. The patients will be kept fasting after a light breakfast (according to their previously determined diet), if the L-tryptophan-1-^{11}C injection is to be given at around noon. Water will be allowed ad libitum.

2. Approximately 30 minutes prior to the injection of the dose, 4 transmission scans for attenuation correction purposes are to be performed.

3. Pads will be placed over both eyes and a stethoscope headset (with sound control) will be put into the ears.

4. The subject will be instructed to remain quiet and not to move for the rest of the examination, but to stay awake.

5. An intracatheter will be inserted in a vein of each hand. One hand will be kept in a 44°C water bath prior to injection and for about 30 additional minutes. One 2 ml blood sample will be taken for plasma phenylalanine determination.

6. At the completion of the transmission scans a dose of 20 mCi of L-tryptophan-1-^{11}C will be injected by i.v. push into one hand. Blood samples are to be taken from the catheter of the other hand at 1, 5, 10, 20 and 25 minutes for radioassay and at 30 minutes for phenylalanine and valine determination in the plasma.

7. Thirty minutes after the L-tryptophan-1-^{11}C injection, four PETT scans each with 18 mm thickness starting 7.5 cm above to the O.M. line will be started.

8. Four more scans may be obtained if remaining activity permits. The entire scanning procedure should not exceed 90 to 120 minutes (including transmission scans).

9. General considerations for human subjects included in this study: Informed consent is to be obtained from the patient's parents or legal guardians. There are no known risks from chemical toxicity of L-tryptophan and the overall risk continues to be limited to an acceptably small radiation dose. At the age of 18 or above, a PKU patient is not at a disadvantage when taken off a controlled diet for a short period of time as suggested in this study.

Huntington's Disease. In a preliminary study, the rate of protein synthesis in the brain and especially in the basal ganglia will be studied in 4 patients with HD during the first year following approval of this amendment. The scanning and blood sampling protocol is as follows:

1. The patients will be asked to remain fasting (except for water) after breakfast. All essential medications will be continued.

2. Approximately 30 minutes prior to the injection of L-tryptophan-1-^{11}C a series of tomographic transmission scans will be made to obtain data for attenuation correction of the final images.

3. The eyes of the subjects will be covered and a stethoscope headset will be placed in the ears. The patient will be instructed to remain quiet but awake and not to move his/her head if at all possible.

4. An intracatheter will be placed into a vein of each hand for injection of the radiopharmaceutical in one hand and blood samples from the other hand which will be kept in a "water bath" (40°C) to arterialize the venous blood. Samples will be taken several times during the first 30 minutes postinjection (for radioassay) and at time 0 and at the end of the 30-minute period for determination of plasma L-tryptophan concentration by HPLC.

5. Following the transmission scans the patient will remain on the scanning table. A dose of 20 mCi of L-tryptophan-1-^{11}C will be injected by i.v. push, and time-activity data (counts per 10 seconds) will be collected for plane 1 using the ECAT as a count rate meter.

6. Blood samples (2 ml each) are to be drawn at time 0, 1, 5, 10, 20, 25 and 30 minutes after injection of the dose.

7. Positron emission computerized tomographic scans of the head will be started 30 minutes after the dose. Four consecutive "slices", each 18 mm thick will be obtained, starting with "plane 1" approximately 7.5 cm above the OM line with subsequent slices in a caudad direction.

8. Depending on remaining activity and the count rate from the brain/head, the same four planes of the head will be scanned a second time. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time to establish "longitudinal" information on protein synthesis in hypertonia.

9. General considerations for human subjects selected for this research project: Informed consent will be obtained from the patient's parents or legal guardians. The risk from the radiation associated with the procedure will be explained and discussed. There may be a psychological risk, especially for subjects who have no signs of the disease but could conceivably be found to be a carrier of HD. The results of psychological counseling in conjunction with genetic advice should, however, outweight this risk.

Brain Tumors. During the first year 5 patients with brain tumors will be selected for this test prior to surgical removal of the tumor (surgery will not be delayed because of the ECAT studies).

1. The patients will be N.P.O. after a light breakfast.

2. Tomographic transmission scans will be made starting about 30 minutes before dose application.

3. Subject will remain on the scanning table, eyes will be covered and a stethoscope type headphone music system with volume control will be put in the ears. The patients will be instructed to remain quiet but to stay awake.

4. Intracatheters are to be placed, one in each hand for the same purpose as for the patients with non-malignant neurological diseases.

5. A dose of 20 mCi of L-tryptophan-1-^{11}C will be injected by i.v. push when transmission scans are completed.

6. Blood samples (2 ml each) will be drawn at 1, 5, 10, 20, 25 and 30 minutes for radioassays and plasma valine determination. During the first 30 minutes a time-activity curve - using the ECAT as a count rate meter - will be obtained for one "slice".

7. PETT scans of the head will be started 30 minutes after injection of the dose. Four slices, each 18 mm thick, will be scanned; slice level will depend on location of the tumor. Scans will be repeated if enough activity is left after the first 4 scans.

8. General considerations for human subjects selected for this study: Informed consent to be obtained from the patients will be based on discussion of this protocol and the points mentioned in the attached consent form and material. Each patient will be scanned also with L-valine-1-^{11}C or DL-tryptophan-1-^{11}C on the same day.

We are not aware of any chemical toxicity from either the DL- or L-form of tryptophan in the amounts to be used in this proposed study. The risk from radiation exposure involved in the diagnostic procedure will be discussed and explained.

The data analysis, in addition to image interpretation, will include a calculation of the rate of protein synthesis of specific regions of interest in the brain. Calculations will be based on an equation derived by Sokoloff et al. The protocols outlined above indicate that all the information required to calculate the rate of protein synthesis can be obtained using the ECAT/L-tryptophan-1-^{11}C or L-valine-1-^{11}C approach. The necessary input data are: the integral value for blood amino acid radioactivity from time 0 - 30 minutes, blood amino acid level at time 0 and at 30 minutes, and the brain radioactive uptake at 30 minutes as based on the scan data.

As mentioned above, all of the protocols have been approved by our Institutional Review Board and the ORAU Medical Radionuclide Committee.

Please consider each of the applications and protocols for approval as an amendment for IND 12,967. If you need additional information, do not hesitate to contact me.

Sincerely,

ORIGINAL SIGNED BY:
C. C. LUSHBAUGH, M. D.

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:bbc

References

1. L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, and T. A. Butler. J. Nucl. Med. 20:857, 1979.

2. K. F. Hubner, G. A. Andrews, E. Buonocore, R. L. Hayes, L. C. Washburn, I. R. Collmann, and W. D. Gibbs. J. Nucl. Med. 20:507, 1979.

3. O. Tamemasa, R. Goto, and T. Suzuki. Gann 69:517, 1978.

4. L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, T. A. Butler, and A. P. Callahan. In Radiopharmaceuticals II, Soc. Nucl. Med., New York, 1979, pp. 767-777.

5. "Blood and Other Body Fluids", D. S. Ditner, ed., Federation of American Societies for Experimental Biology, Washington, D.C., 1961, p. 73.

6. Ibid., p. 21.

1048906

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Amendment to existing IND 12,967: Physiological Studies of the Pancreas ~~and Brain Using ^{11}C-L-tryptophan~~ PROPOSAL NO. 39b

DESCRIPTION:
The proposed amendment to IND 12,967 involves the resolution of ^{11}C-DL-tryptophan, a previously approved drug, by high-performance liquid chromatography and the intravenous administration of up to 20 mCi of ^{11}C-L-tryptophan, an optically active form of the approved drug, for physiological studies of the pancreas and brain. A copy of the radiation dosimetry data for the proposed agent is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not X___ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not X___ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
[illegible]	X			10/20/81
William D. Tibbs	X			10/21/81
[illegible]	X			10/21/81

Acknowledgement of submitter [illegible] Date ~~10/16/81~~ 10/21/81

Proposal does X does not _____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048907

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL G. A. Andrews PROPOSAL NO 75-1

DESCRIPTION:

^{125}I-sodium iodine as liquid or in capsules for thyroid scanning. Activities ranging from 5 to 100 microcuries will normally be administered; however, for localizing extrathyroidal metastases, up to 1 millicurie may be administered. Major radiopharmaceutical manufacturers have NDA's approved FDA for ^{125}I-sodium iodide. An FDA sample package insert is attached.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may ✓ ~~may not~~ ___ be administered to patients under 18 years of age.

Radiopharmaceutical ~~may~~ ___ may not ✓ be administered to pregnant patient.

Other:

Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William W. Tobias	W.D.T.			3/11/75
D. C. Swartzendruber	DCS			3/11/75
R. L. Hayes	RLH			3/11/75
Karl F. Hubner	KFH			3/11/75
[illegible]	[illegible]			11 March '75
JIM BERGER			✓	

Acknowledgement of Submitter _____ Date _____

- -

Proposal does ___ does not ___ require approval of Committee on Human Studies.

1048908

SAMPLE LABELING

SODIUM IODIDE I 125 CAPSULES AND SOLUTION - DIAGNOSTIC

DESCRIPTION

Sodium Iodide I 125 is available in capsules and aqueous solution for oral administration.

ACTIONS

Sodium iodide is readily absorbed from the gastrointestinal tract. Following absorption, the iodide is distributed primarily within the extracellular fluid of the body. The iodide is concentrated and organified by the thyroid and trapped but not organified by the stomach and salivary glands. It is also promptly excreted by the kidneys.

INDICATIONS

Sodium Iodide I 125 is indicated for use in the diagnosis of thyroid function, for thyroid imaging, and for determination of protein bound iodine. Diagnostic doses may also be employed in localizing metastases associated with thyroid malignancies.

CONTRAINDICATIONS

None.

WARNINGS

This radiopharmaceutical agent should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs the potential hazards.

1048909

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 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.

PRECAUTIONS

As in the use of any other 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.

The uptake of iodine 125 will be affected by recent intake of stable iodine in any form or by the use of thyroid, anti-thyroid and certain other drugs. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media.

ADVERSE REACTIONS

None.

DOSAGE AND ADMINISTRATION

The suggested oral dose range employed in the average patient (70 kg) for various diagnostic procedures for thyroid function is 10 to 100 microcuries.

1048910

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iodide-125 decays be electron capture with a physical half-life of 60 days[1]. Photons useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean %/disintegration	Mean Energy (KeV)
Gamma-1	6.8	35.5
K int. con. electron, γ-1	74.6	3.7
L int. con. electron, γ-1	10.7	30.9
M int. con. electron, γ-1	8.0	34.7
Kα-1 x rays	73.8	27.5
Kα-2 x rays	37.8	27.2
Kβ-1 x rays	19.9	31.0
Kβ-2 x rays	4.1	31.8

[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. 25, 1969.

The specific gamma ray constant for ^{125}I is 1.23 R/mCi-hr at 1 cm. The half value layer is 0.04 mm of Pb.

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

1048911

Table II. Physical Decay Chart; ^{125}I, half life 60 days.

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
-14	1.176	1	.989	18	.812
-12	1.149	2	.977	20	.794
-10	1.122	3	.966	22	.776
-8	1.097	4	.955	25	.950
-7	1.084	5	.944	30	.708
-6	1.072	6	.933	35	.668
-5	1.059	7	.922	40	.630
-4	1.047	8	.912	45	.595
-3	1.035	10	.891	50	.562
-2	1.023	12	.871	55	.530
-1	1.012	14	.851	60	.500
0*	1.000	16	.831	75	.421

*Calibration day

RADIATION DOSIMETRY

Following oral administration of I-125 sodium iodide, about 80% of the activity has an effective half life of 0.35 day and 20% has an effective half life of 41.8 days. On this basis the estimated absorbed radiation doses[1] to an average patient (70 kg) from an oral dose of 100 microcuries of I-125 are shown in Table III. This table also shows the corresponding absorbed radiation doses from an oral dose of 100 microcuries of I-131.

Table III. Radiation Doses

Tissue	Absorbed Radiation Dose (rads/100 uCi ^{125}I)	Rads/100 uCi ^{131}I)
Thyroid	87	120
Testes	0.035	0.042
Ovaries	0.037	0.042
Whole-body	0.049	0.061

1048912

[1]Method of calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, J. Nucl. Med., p. 7, 1968.

HOW SUPPLIED

Revised 5/1/73

1048913

APPLICATION FOR INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee

August 19, 1975

1. NAME OF DRUG: CARBOXYL-LABELED ^{11}C-1-AMINOCYCLOPENTANECARBOXYLIC ACID. This drug, dissolved in saline solution, will be administered intravenously.

2. COMPONENTS:

   a. Carboxyl-labeled ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC).

   b. 1-Aminocyclopentanecarboxylic acid (ACPC).

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION: Since the ^{11}C present in the labeled 1-aminocyclopentanecarboxylic acid is radioactive ($T_{\frac{1}{2}}$ = 20.4 min), we cannot state an exact relationship between the components of this preparation. From radiation dosimetry considerations, however, we have determined that the maximum ^{11}C activity administered will not exceed 0.357 mCi per kilogram of body weight (a 25 mCi dose for a 70 kg subject). The actual amount of stable ACPC that will be administered will be determined by the amount of ^{11}C used in labeling ACPC and also the time that elapses from the time of ^{11}C-ACPC preparation to the time of its administration. The composition stated below, therefore, represents the dosage limits that will be adhered to for the components in this radiopharmaceutical preparation.

   a. Carboxyl-labeled ^{11}C-1-aminocyclopentanecarboxylic acid: maximum of 0.357 mCi per kilogram of body weight (25 mCi for a 70 kg subject).

   b. 1-Aminocyclopentanecarboxylic acid: maximum of 0.1 mg per kilogram of body weight (7 mg for a 70 kg subject).

   c. Sodium chloride: maximum of 3 mg per kilogram of body weight (210 mg for a 70 kg subject).

   d. Water: maximum of 0.5 ml per kilogram of body weight (35 ml for a 70 kg subject).

1048914

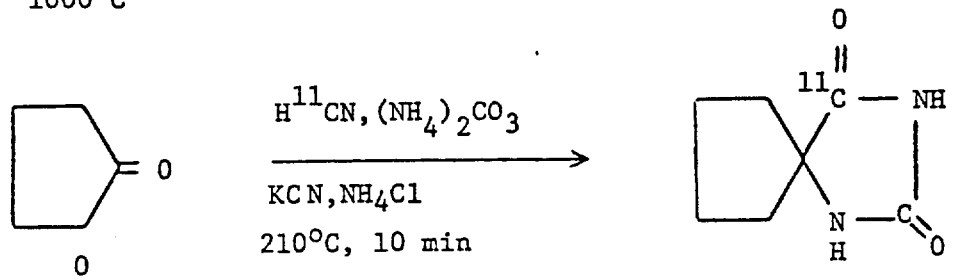
4. SOURCE OF NEW DRUG SUBSTANCE:

Carboxyl-labeled ^{11}C-1-aminocyclopentanecarboxylic acid will be synthesized in a hot cell at the 86-inch Oak Ridge National Laboratory (ORNL) 22 Mev proton cyclotron complex using the following series of reactions:

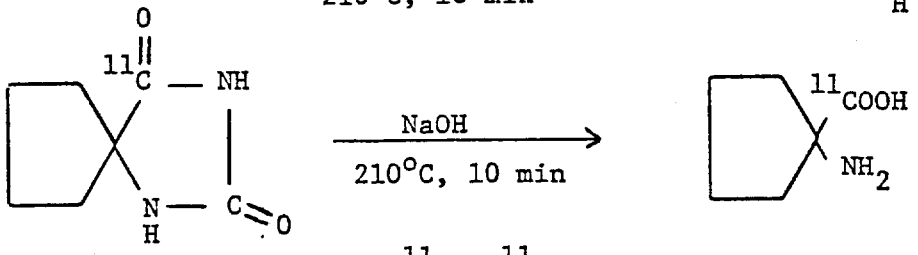
$$B_2O_3 \xrightarrow{^{11}B(p,n)^{11}C} {}^{11}CO_2/{}^{11}CO \qquad \text{Step I}$$

$$^{11}CO_2/{}^{11}CO \xrightarrow[\text{Ni, } 370^\circ C]{H_2} {}^{11}CH_4 \qquad \text{Step II}$$

$$^{11}CH_4 \xrightarrow[1000^\circ C]{Pt, NH_3} H^{11}CN \qquad \text{Step III}$$



Step IV



Step V

Targetry and Production of $^{11}CO_2/^{11}CO$ (Step I): B_2O_3, prepared by heating H_3BO_3 (Fisher Scientific Co., Fair Lawn, N.J.), is fused onto the fins of a multifin molybdenum metal (99.9%) target support. During bombardment the B_2O_3 melts and a series of fine cuts in the fins aids in maintaining the correct distribution of the fluid B_2O_3 during bombardment through surface tension effects. This also aids in the release of ^{11}CO and $^{11}CO_2$ from the target. The molybdenum target support is mounted in an aluminum annulus-type header so that a water coolant flow of 15 liters/min can be maintained. The header assembly is connected to a gas flow loop that has provisions for on-line gas purge or recirculation. The outlet of the loop is located in a remote control hot cell that is adjacent to the cyclotron. During bombardment, when He (Lif-O-Gen Inc., Cambridge, Md.) is used as the carrier gas in the loop, a $^{11}CO_2/^{11}CO$ ratio of approximately 4 is obtained. Outgassing of target ^{11}C activity into the gas flow loop during bombardment is approximately 50% complete. With a beam current of 150-175 μA approximately 3 Ci of usable $^{11}CO_2/^{11}CO$ activity is produced.

Production of $^{11}CH_4$ and $H^{11}CN$ (Steps II and III): Both $^{11}CH_4$ and $H^{11}CN$ are produced by contact catalysis. A 50 ml/min He stream from the cyclotron gas loop is mixed with a 50 ml/min H_2 (Lif-O-Gen Inc.) stream and fed through a quartz tube containing Ni catalyst on kieselguhr (Ventron Alpha Products, Beverly, Mass.) held at a temperature of 370°C. The output gas from this conversion (containing $^{11}CH_4$) is passed through a $CaSO_4$/NaOH trap and then mixed with a 50 ml/min stream of anhydrous NH_3 (Lif-O-Gen Inc.). This mixture is then passed through another quartz tube containing Pt catalyst on alumina (Ventron Alpha Products) heated to 1000°C. The output from this conversion (containing the desired $H^{11}CN$) is finally trapped in a pressure reaction vessel for synthesis of ^{11}C-ACPC.

Synthesis of ^{11}C-ACPC (Steps IV and V): Prior to the start of a ^{11}C-ACPC production run a stainless steel (type 316) pressure vessel having an internal volume of 3 ml and fitted with a ball valve is charged with a mixture of 1 ml distilled water, 31.8 mg cyclopentanone (99+ %, b.p. 130.5°C, Aldrich Chemical Co., Inc., Milwaukee, Wis.), 72 mg $(NH_4)_2CO_3$ (certified A.C.S., Fisher Scientific Co.), 6.7 mg NH_4Cl and 8.2 mg KCN (both Baker Analyzed Reagents, J. T. Baker Chemical Co., Phillipsburg, N.J.). The gas stream from Step III, containing $H^{11}CN$, is bubbled into the mixture in the reaction vessel through a Teflon tube placed through the opened valve. After trapping of $H^{11}CN$ is complete (as monitored by an ion chamber), the valve is closed and the vessel rapidly heated to a temperature of 210°C and maintained at that temperature for 10 min after which it is rapidly cooled. The valve is then opened, 1.0 ml of 6.25 N NaOH is introduced, the valve is closed and the vessel is again heated at 210°C for another period of 10 min.

Purification of ^{11}C-ACPC: After completion of Step V the cooled reaction mixture is filtered and then loaded directly onto a 1.5 cm (diameter) x 5 cm (length) prewashed AG 1-X2, 100-200 mesh,anion exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydroxyl form. Anionic components, including ^{11}C-ACPC, are retained by the column while cationic and nonionic components pass through. After washing repeatedly with distilled water (∿ 50 ml) the column is then eluted with 1 N HCl, the process being monitored by means of an ion chamber. The acidic eluate is loaded onto a prewashed 0.9 cm (diameter) x 4 cm (length) AG 50-X2, 50-100 mesh, cation exchange bed (Bio Rad Laboratories) in the hydrogen form. Cationic ^{11}C-ACPC is retained while anionic material passes through the column. After washing repeatedly with distilled water (∿ 30 ml), the column is finally eluted with 0.2 N NaOH, the process again being monitored with an ion chamber to minimize the volume of eluate containing the product (∿ 10 ml). This solution is collected in a sterile bottle for transport to Oak Ridge Associated Universities (ORAU) for final processing.

In developmental studies prior to actual production of ^{11}C-ACPC, it had previously been determined by carbon, hydrogen and nitrogen determinations and by infrared spectrophotometry that the synthesis and purification processes did indeed yield pure ACPC. The purity of the ^{11}C-ACPC product has been assessed by thin layer chromatography (tlc) (Eastman silica gel, Chromagram Sheet 13179) using an n-butanol: water: acetic acid (100:10:5)

development system and also by comparison of its tissue distribution in tumor-bearing animals with those that had previously been obtained with commercially available ^{14}C-labeled ACPC (New England Nuclear Corp., Boston, Mass.). Pyrogenicity tests of the ^{11}C-ACPC product by standard USP techniques have been negative. There has also been no indication of decomposition of ^{11}C-ACPC as the result of radiolysis.

^{11}C-ACPC (from a run spiked with $K^{14}CN$ prior to synthesis) gave a tlc pattern that was similar to that of ^{14}C-labeled ACPC with no indication of any impurities when the two tlc patterns were viewed with a spark chamber. Ninhydrin development of the tlc chromatograms also gave similar results. Figure 1 shows a scan obtained with a Buffalo rat bearing a 5123C Morris hepatoma killed 25 min after intravenous administration of ^{11}C-ACPC. Table 1 shows the tissue distribution in this animal using counts from the ^{14}C spike that had been introduced as $K^{14}CN$ in the production run for later assay purposes. Table 1 also includes tissue concentration data at 30 min on a hepatoma rat given commercial ^{14}C-ACPC. (See section 6 for further animal data.)

5. METHODS, FACILITIES AND CONTROLS:

The solution containing the purified ^{11}C-ACPC will be transported from the ORNL cyclotron complex to the ORAU Medical and Health Sciences Division located on Vance Road in Oak Ridge proper (trip time, 6-8 min). After being transferred to a conical beaker the pH of the solution will be adjusted to 7.0 ± 0.2 with 1 N HCl using a combination electrode and pH meter. (The stem of the electrode will be stored in 0.9% benzyl alcohol and will be rinsed with sterile water before each use.) The solution will then be filtered through a sterile 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (multipuncture type, Wheaton Glass Co., Millville, N.J.). A portion of the solution will be removed for final radioassay using a sodium iodide crystal calibrated with NBS standards (a previous preliminary ion chamber assay will have been made at the cyclotron facility). The solution will also be tested for pyrogens using the Pyrotest limulus amebocyte lysate technique (Difco Laboratories, Detroit, Mich.). The short half-life of ^{11}C (20.4 min) precludes testing with rabbits in the conventional USP manner, and, although this particular limulus technique normally requires an hour for completion, it should act as a test for gross pyrogen contamination during the period of time required for assay and transport of the preparation to the site of administration ($\sim$ 15 min). The full test will become part of the record as will standard USP sterility tests. The vial containing the ^{11}C-ACPC will finally be labeled as to its content and assay (see section 7).

Preparation of each batch of ^{11}C-ACPC for clinical use will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized. Fresh ion exchange resins will be used for purification in each ^{11}C-ACPC run. Each batch will be given a batch number and all particulars relative to its preparation and use will be entered into a master log book.

6. STATEMENT ON INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations

1. Animal studies

The insertion of radioisotopic labels into the intrinsic structure of organic compounds and biological substances that have high affinities for specific tissues is an ideal method of labeling, since structures are not altered. The radionuclides ^{11}C, ^{13}N, and ^{15}O, are all candidates for use in labeling such agents for nuclear medical diagnosis by scanning. Their decay is accompanied by photon emission in the form of positron annihilation radiation which can be utilized for coincidence detection techniques such as positron emission transaxial tomography utilizing computer reconstruction. This is an instrumentation technique that may shortly come into its own in nuclear medical technology (1). Of these three radionuclides, ^{11}C is the obvious choice as a label because of its longer half-life (20.4 min), although, even with this radionuclide, rapid tissue distribution is necessarily required of any radiopharmaceutical agent that is labeled with it.

The synthetic amino acid, 1-aminocyclopentanecarboxylic acid (ACPC, also referred to as "cycloleucine") was reported by Berlinguet et al. (2) to concentrate rapidly at high levels in the tumor tissue of mice bearing sarcoma-180 tumors. Their investigation was carried out autoradiographically with ^{14}C-labeled ACPC and was prompted by the fact that this compound had shown chemotherapeutic potential against animal tumors (3). ACPC, when labeled with a suitable gamma-emitting radionuclide, could, therefore, be an effective external tumor-localizing agent. ^{11}C-labeling of this compound was an obvious approach, since ^{11}C-labeled ACPC would be quite stable chemically and furthermore the presence of ^{11}C in its structure would not be expected to produce alterations in its biological behavior.

Before initiating a program designed to develop a method for the synthesis of ^{11}C-ACPC, we carried out studies of the tissue distribution of ^{14}C-labeled ACPC in tumor-bearing animals for corroborative purposes. The results of these studies (supervised by R. L. Hayes) were in agreement with the report of Berlinguet et al. (2) (Table 2). We also substantiated the rapidity of uptake that they had reported (Table 3). The specific activity of ^{11}C-ACPC (or dose of stable ACPC per unit body weight) will not affect its tissue distribution in tumor-bearing rats (Table 4).

We have also observed by rectilinear scanning good uptakes of ^{11}C-ACPC in other tumor tissues, similar to that shown in Fig. 1: H-35 Reuber hepatoma (better), Morris 7794 and 7787 hepatoma, RFT rat tumor, B-16 mouse melanoma, Novikoff hepatoma, and R-325 giant cell sarcoma (somewhat less). A *S. aureus* 6339 abscess in the rat did not show any preferential uptake of ^{11}C-ACPC.

1048918

2. Toxicity

ACPC is an agent with antitumor activity which was discovered through the screening program of the Cancer Chemotherapy Service Center of the National Cancer Institute (3). It was reported that the drug inhibits the growth of adenocarcinoma 755, 6C3HED ascites lymphosarcoma and ascites leukemia L4946 in mice but has no effect on sarcoma 180 and Ehrlich ascites carcinoma.

Cancer chemotherapy trials with ACPC have also given variable results. The toxicity of the drug has been one of the main problems associated with its use in therapy, but the toxicity seems to follow an all-or-none pattern (see NCI Chemotherapy Fact Sheet, July 1970, which is attached). Thus dogs given sublethal doses show little evidence of toxicity, whereas dogs given lethal doses characteristically become anorectic, lose weight, and die.

Humans also show no toxicity to small or moderate doses of ACPC. A large amount of data exists as the result of the clinical trials that have been carried out (see Chemotherapy Fact Sheet). Few, if any, toxic symptoms have been seen in patients at intravenous doses up to 60 mg/kg/day, even after a series of 5-10 daily doses. At slightly higher doses such symptoms as anorexia, nausea, vomiting, weight loss, thrombocytopenia, anemia, and a fall in total serum proteins are seen. ACPC is less toxic in man than in small animals, such as mice and rats, apparently because of a faster excretion rate in man.

At the dose level of the drug which we would use for tumor scanning (0.1 mg/kg or less), we would expect no toxicity, since we will be below the threshold of toxicity by a factor of approximately 600. The ORAU-ORNL Committee on Human Studies has approved these studies (see Appendix for membership).

3. Radiation Dose

Carbon-11 has a 20.4 min half life decaying by positron emission (99+ %). Because of its short half life the radiation dose to patients will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Dosimetry Center (headed by R. J. Cloutier) that the complete decay of 1 mCi of a ^{11}C-labeled substance uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.01 rads or a total of 0.25 rads per 25 mCi (the maximum administered dose of ^{11}C-ACPC). Table 5 gives details of the expected radiation dose to various organs in the human estimated from animal data. The ORAU ~~Radioisotopes~~ Committee has approved the use of ^{11}C-ACPC.
MEDICAL RADIONUCLIDE [redacted]

b. Previous Marketing:

This ^{11}C-labeled drug has not been marketed before, but the unlabeled material has been used in clinical cancer chemotherapy trials (as noted in 6-a-2 above).

c. Drug Combination:

^{11}C-ACPC is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with ^{11}C-ACPC will have the following form:

^{11}C-1-AMINOCYCLOPENTANECARBOXYLIC ACID

Assay:_____mCi/ml as of_____ a.m. p.m. _____
time date

Total Volume_____ ml ACPC_____mg/ml

Expiration Date_____

FOR REGULATED USE ONLY FDA IND_____

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal information material will be prepared; however, each participant will of course be issued a copy of this Application.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See bibliographical material in the appendix about Drs. Andrews, Hayes, Hübner, Washburn, and Wieland.

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by G. A. Andrews, R. L. Hayes, K. F. Hübner, and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Acting Chairman of the ORAU Medical and Health Sciences Division, with advice from the ORAU Medical Advisory Committee and the ORAU-ORNL Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phases I and II, clinical pharmacology, in this study will consist of observations on the metabolism and toxicity of ^{11}C-ACPC together with preliminary observations on its tumor-localizing properties. K. F. Hübner, M.D. will be in charge of the initial phase of the clinical investigation which will be done on an out-patient basis at the ORAU Medical and Health Sciences Division Hospital Facility, Vance Road, Oak Ridge, Tennessee.

A total of 30 patients with known cancer will be studied. They will be adult patients referred for tumor scans by physicians in the Oak Ridge Hospital, East Tennessee Chest Disease Hospital (Knoxville), and the University of Tennessee Memorial Hospital (Knoxville). Informed consent will be obtained from each patient (adults incapable of giving an informed consent will be excluded from the study). No inducements will

be offered to obtain voluntary consent. Patients will be recruited specifically for the study with no promise of continued medical care by ORAU.

The principal questions to be answered are:

1. Is there any unsuspected toxic effect of ^{11}C-ACPC on humans at the dose levels proposed?

2. Will the uptake of ^{11}C-ACPC in human tumors be sufficient to permit tumor detection by scanning?

3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{11}C-ACPC in humans?

4. What is the optimum dose and scanning time?

While it is not anticipated that there will be any toxic effect of ^{11}C-ACPC at the doses to be used in this study (see sections 2 and 6-a-2), the patients will be observed closely for any unanticipated untoward effects.

To determine the optimum time for scanning and to obtain data for more precise radiation dose estimates, blood levels and whole body counts will be monitored at frequent intervals from multiple blood samples and whole body counts.

The optimum dose and time for scanning will be determined from scans made at different time intervals using multiple imaging devices (Anger camera with positron attachment and a rectilinear scanner modified for coincidence detection).

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{11}C-ACPC prior to 30 days after the date of receipt of notice by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

References

1. M. M. Ter-Pogossian, M. E. Phelps, E. J. Hoffman, and N. A. Mullani. Radiol. 114, 89 (1975).
2. L. Berlinguet, N. Begin, and L. M. Babineau, Can. J. Biochem. Phys. 40, 1111 (1962).
3. T. A. Connors, L. A. Elson, and W.C.J. Ross, Biochem. Pharmacol. 1. 239 (1958); R. B. Ross, C. I. Noll, W.C.J. Ross, M.V. Nadkarni, B. H. Morrison, and H. W. Bond, J. Med. Pharm. Chem. 3, 1 (1961); also see attached NCI Chemotherapy Fact Sheet dated July 1970, by S. K. Carter.

Table 1

Early Tissue Distribution of Labeled ACPC in Male Buffalo Rats Bearing Morris 5123C Hepatomas after I.V. Administration

Tissue	Commerical ^{14}C-ACPC	^{11}C-ACPC Preparation
	Percent administered dose/g	
Liver	0.43	0.46
Spleen	0.46	0.71
Kidney	0.71	0.49
Muscle	0.47	0.41
Marrow	0.53	0.67
Blood	0.42	-
S. intestine	0.74	0.54
Pancreas	2.54	2.22
V. tumor	3.55	3.11
N. tumor	-	0.62

Table 2

Effect of Tumor Type on the Tissue Distribution of ^{14}C-ACPC at 30 Minutes Postinjection

Nontumor Tissue	Tumor to Nontumor Tissue Conc. Ratio		
	5123C	RFT	B-16
Liver	6.8	2.0	2.7
Spleen	5.5	3.2	3.7
Kidney	5.1	-	5.8
Lung	5.7	-	4.7
Muscle	6.7	3.0	5.4
S. intestine	3.9	2.3	3.8
Marrow	5.7	2.9	-
Blood	5.8	4.0	4.0
Pancreas	1.0	0.6	0.5

Table 3

Tissue Distribution of ^{14}C-ACPC After Intravenous Administration in Male Buffalo Rats Bearing the Morris 5123C Hepatoma

Tissue	Percent administered dose/g at various times postinjection			
	10 min.	20 min.	30 min.	60 min.
Liver	0.728	0.565	0.426	0.488
Spleen	0.700	0.597	0.461	0.485
Kidney	0.821	0.827	0.706	0.707
Muscle	0.447	0.541	0.466	0.543
Marrow	0.825	0.718	0.525	0.498
Blood	0.517	0.584	0.422	0.487
Tumor	3.216	2.818	3.549	3.415
Small intestine	1.484	1.102	0.739	0.634
Pancreas	2.840	5.092	2.538	2.009
Plasma	0.583	0.574	0.449	0.503

Table 4

Effect of Specific Activity on the Tissue Distribution of ^{14}C-ACPC in Buffalo Rats Bearing the 5123C Hepatoma at 30 Minutes Postinjection

Nontumor Tissue	Tumor to Nontumor Tissue Conc. Ratio		
	0.14 mg/kg	1.0 mg/kg	5.0 mg/kg
Liver	3.7	4.1	5.0
Spleen	3.2	3.4	4.2
Kidney	2.9	3.1	3.6
Lung	3.5	3.8	4.7
Muscle	3.7	4.0	4.9
Small intestine	2.1	1.9	2.9
Marrow	2.8	3.1	3.7
Blood	3.6	4.3	4.4
Pancreas	0.6	0.5	0.7

Table 5

Estimated Radiation Dose to Specific Tissue and Organs in Humans Following Administration of 25 mCi of ^{11}C-Labeled 1-Aminocyclopentanecarboxylic* Acid (ACPC)

Tissue	rads
Liver	0.305
Spleen	0.358
Kidney	0.388
Lung	0.323
Muscle	0.308
Bone marrow	0.404
Blood	0.318
Small intestine	0.534
Pancreas	2.006
Tumor	1.140

* Based on tissue distribution following intravenous administration of ^{14}C-labeled ACPC (0.138 mg/kg) in rats at 30 minutes postinjection.

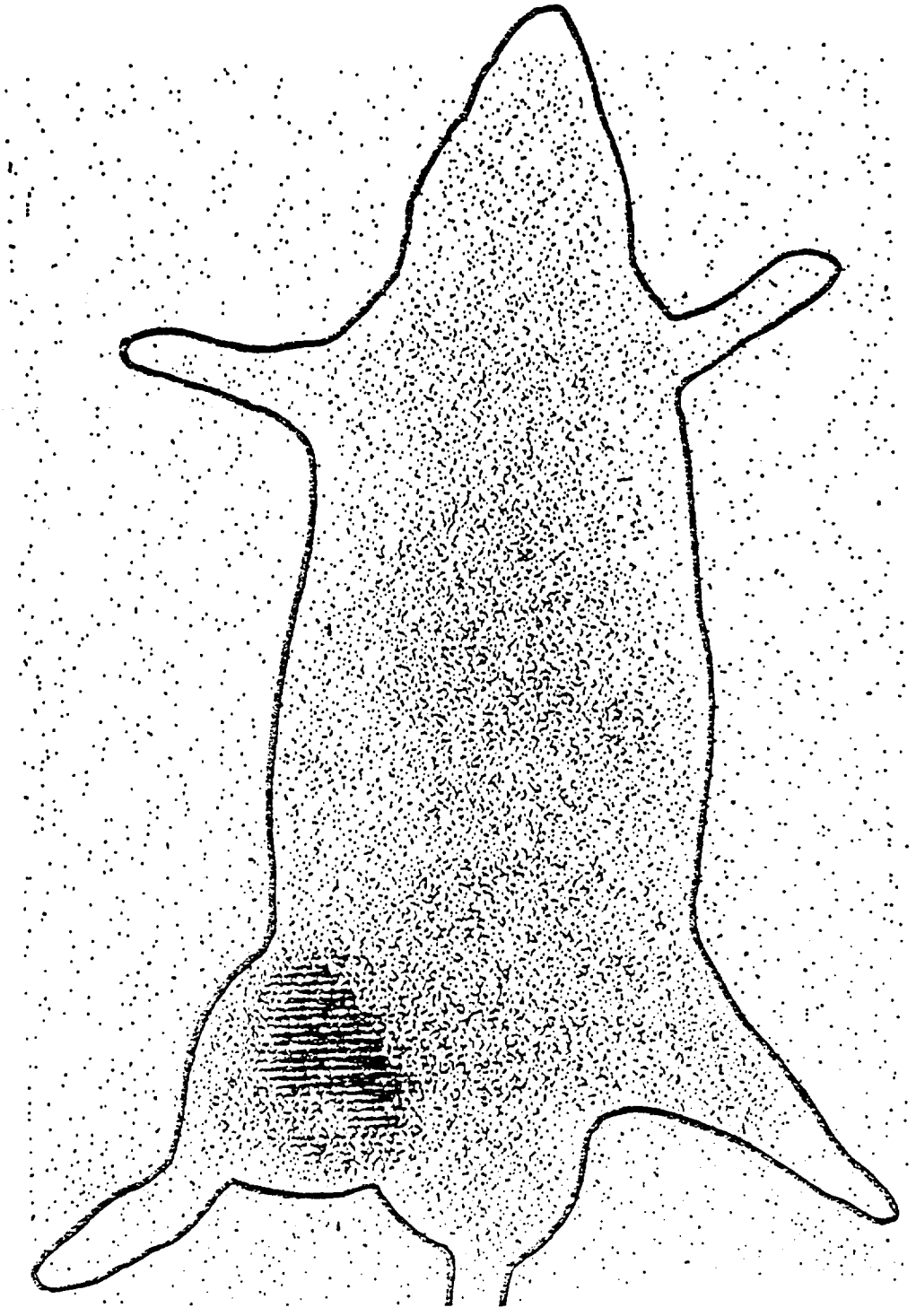


Fig. 1 Rectilinear photoscan of a male Buffalo rat (365 g) bearing a transplanted Morris 5123C hepatoma (left side of scan, 12 g) that had received intravenous ^{11}C-ACPC (750 μCi) 25 minutes before being killed by an overdose of sodium pentobarbital. The scan was made with a fine focus collimator. The area of decreased density in the tumor was necrotic.

1048926

APPENDIX

Chief Investigators:

G. A. Andrews, M.D.
R. L. Hayes, Ph.D.
K. F. Hübner, M.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

ORAU-ORNL Committee on Human Studies:

Gould A. Andrews, M.D.
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Y-12 Area
Union Carbide Nuclear Company
P. O. Box Y
Building 9704-2
Oak Ridge, Tennessee 37830

Robert D. Lange, M.D.
Assistant Director
University of Tennessee
Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

1048927

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

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

ORAU Medical Advisory Committee:

Richard J. Michael Fry, Chairman
Physiology/Radiation Biology (M.D., Dublin, 1962)
Senior Scientist
Division of Biological and Medical Research
Argonne National Laboratory

Robert H. Greenlaw
Nuclear Medicine (M.D., University of Rochester, 1952)
Marshfield Clinic

Leonard A. Sagan
Internal Medicine, Research Administration (M.D., Chicago, 1955)
Associate Director, Department of Environmental Medicine
Palo Alto Medical Clinic

William H. Stone
Genetics, Immunology (Ph.D., University of Wisconsin, 1953)
Professor of Genetics
University of Wisconsin

John F. Volker (ex officio member from the ORAU Board of Directors)
President
University of Alabama
Birmingham

1048928

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews
Position:	Internist, Director of Clinical Applications
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association

Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name:	Richard Jeremy Michael Fry
Position:	Senior Scientist, Argonne National Laboratory
Schools:	University of Dublin, B.A., 1946 University of Dublin, M.D., 1962
Memberships:	Radiation Research Society; American Association Cancer Research; Reticuloendothelial Society

Name:	Robert H. Greenlaw
Position:	Physician at Marshfield Clinic, Marshfield, Wisconsin
School:	Tufts, B.S., 1948 Rochester, M.D., 1952
Memberships:	American Cancer Society; Member Med. Adv. Cmt, AEC; Amer. Med. Association; Col. Radiol.; Association Univ. Radiol.; Society of Nuclear Medicine
Interests:	Development of radioisotopes for diagnosis and therapy; radiation biology; clinical development in radiation therapy

1048929

Name:	R. L. Hayes
Position:	Senior Scientist in charge of medical radioisotope development.
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U. S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961. Admitted to practice of law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A., 1941 Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association For the Advancement of Science; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology.

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry),1946 University of Minnesota, Minneapolis, Minnesota, B.S., 1949, M.D., 1950. Rotating Internship, Ancker Hospital, St. Paul, Minnesota, 1949-50.
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination, June 5, 1963
Memberships:	Fellow Industrial Medical Association; Past President, Tennessee Industrial Medical Association; American Academy of Occupational Medicine; American Medical Association; Past President, Roane-Anderson County Medical Society; Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Acting Chairman, Medical and Health Sciences Division Director, Radiation Emergency Assistance Center/Training Site (REAC/TS)
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; American Society for Experimental Pathology; Associated Researchers and Clinicians in Cancer; Society for Experimental Biology and Medicine; Health Physics Society; Radiation Research Society; Society of Nuclear Medicine; American Medical Society; Tennessee State Medical Society

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fel. American College of Physicians
Interests:	Late effects of radiation

1048931

Name: William Harold Stone
Position: Genetics, Immunology
Schools: Brown University, A.B., 1948
Maine, M.S., 1949
Wisconsin, Ph.D., 1953
Memberships: Genetics Soc.; Soc. Human Genetics; American Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science
Interests: Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name: John B. Storer
Position: Director, Biology Division, Oak Ridge National Laboratory
School: University of Chicago, M.D., 1947
Memberships: American Association for Cancer Research; American Society for Experimental Pathology; Radiation Research Society; Society for Experimental Biology and Medicine; National Council on Radiation Protection and Measurements

Name: Joseph F. Volker
Position: President, University of Alabama, Birmingham, Alabama
Schools: Indiana University, D.D.S, 1936
University of Rochester, A.B., 1938
University of Rochester, M.S., 1939
University of Rochester, Ph.D., 1942
Univ. Med. Sci., Bankok, hon. D.Sc, 1967
Univ. Lund, hon. Dr. Ontol., 1968
University of Alabama, hon. D. Sci., 1970
Indiana Univ., hon. D. Sci., 1970
Louis Pasteur Univ., hon. Dr., 1972
Memberships: Mem. Unitarian Med. Teaching Mission, Czech., 1946, Ger., 1948
Specialist, U. S. Dept. State, Thailand, 1951-.
Dir. Arizona Med. Sch. Study, 1960-1961
Mem. Inst. Med. Nat. Acad. Sci., 1971
Mem. Order of White Lion, Czech, 1946
Comdr., Order of Crown, 1959
Fel., Royal Col. Surg., 1961
Comdr., Order of Falcon, Repub. Iceland, 1969
AAAS; Soc. Expl. Biol. and Med.; Int. Asn. Dent. Res.

Name: Lee Cross Washburn
Position: Associate Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools: Murray State University, B.A., 1968
Vanderbilt University, Ph.D., 1972
Membership: American Chemical Society
Interests: Synthetic organic chemistry; chromatography; radiopharmaceutical tissue distribution studies; radioprotective drugs

1048932

Name:	Bruce W. Wieland
Position:	Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools:	Iowa State University, B.S., 1960 Ohio State University, Ph.D., 1973
Membership:	Society of Nuclear Medicine
Interests:	Production and utilization of short-lived positron-emitting isotopes for nuclear medical applications. Development of hot cell equipment for the synthesis of labeled compounds. Isotope imaging instrumentation, including coincidence detection and computer reconstruction techniques for tomography.

1048933

chemotherapy fact sheet

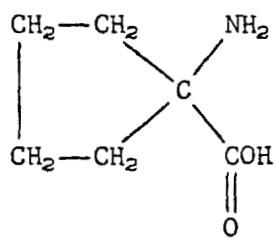
Program Analysis Branch, Chemotherapy, National Cancer Institute

July 1970

1-Aminocyclopentanecarboxylic Acid (NSC-1026)

A Review

1-Aminocyclopentanecarboxylic acid (cycloleucine) is a synthetic amino acid that is thought to act as an antagonist to the amino acid valine. It can be looked upon as an amino acid lacking the usual α-hydrogen atom. Its structure is shown below:



The mobility of cycloleucine in paper chromatography is strikingly different from that of the naturally occurring amino acids. Leucine has the most similar R_f value but the two are readily distinguishable (1).

In 1961, Ross was the first to suggest that this compound might function as an amino acid antagonist (1). Mickelson failed to find any evidence of amino acid antagonism with a bacterial assay (2). Berlinguet et al presented evidence that cycloleucine antagonizes the in vitro and in vivo incorporation of valine into the proteins of the rat, indicating also that the site of its action is the prevention of the attachment of valine to transfer ribonucleic acid (3).

Contributions to the *Fact Sheet* are welcome.
They should be submitted to the Publications Section,
Program Analysis Branch, National Cancer Institute, Bethesda, Md 20014.

1048934

Machlin et al supported this with work in chickens (4). They showed that the addition of as little as 0.15% cycloleucine to normal chicken diets inhibited growth. When the effect of protein level was examined on this phenomenon, it was clearly demonstrated that increasing the protein content of the diet reduced the growth inhibition. It was then found that the addition of valine was as effective as high levels of protein in preventing growth inhibition. None of the essential amino acids except valine replaced the protein effect and the addition of leucine resulted in a more severe growth retardation from cycloleucine. Since leucine is also known to antagonize the effect of valine in animals, the increased toxicity from the combination of these 2 amino acids is understandable.

Sterling and Henderson have studied the mechanism of action of cyclophosphamide in ascites tumor cells in vitro (5). They reported that cycloleucine replaced no natural amino acid in protein synthesis nor did it interfere with the endogenous synthesis of natural amino acids from glucose. The drug appeared to be concentrated in the cells by an active transport system utilized by some natural amino acids. They demonstrated participation in a heteroexchange diffusion process with DL-leucine and DL-valine. Although high concentrations of cycloleucine partially inhibited the incorporation of amino acids into proteins in ascites tumor cells in vitro, it was felt that this was due to inhibition of transport of these amino acids into the cells. The drug inhibited the uptake of leucine and valine in a competitive fashion and is probably transported by the same carrier system in the cell that transports leucine and valine. The question arises whether this is the antitumor mechanism of action. It has been shown that tumor cells concentrate amino acids to a greater extent than do normal tissues, both in vivo (6) and in vitro (7), and it has been suggested that this gives the tumor a competitive advantage during growth. Thus a drug that inhibits amino acid supply might have more uniform effects on tumors than on normal tissue. This is supported by the experience with L-asparaginase (NSC-109229) with which it is generally accepted that the tumor effect is due to a lowering of asparagine in tumor cells that are unable to synthesize this nonessential amino acid themselves.

Clark et al reported that growth inhibition with cycloleucine in rats was relieved by force feeding and concluded that the drug does not effect the distribution of a number of amino acids in rat tissues when food intake is maintained (8).

Recently Brown reported that cycloleucine administration in cancer patients resulted in a reversible, marked aminoaciduria consisting predominantly of cystine, ornithine, lysine, and arginine, with only minor elevations of other amino acids (9). Plasma levels of amino acids were essentially unchanged except for slight decreases in ornithine and lysine. This aminoaciduria is most likely due to a blockage by the drug of the renal tubular reabsorption of cystine, ornithine, lysine, and arginine, resulting in an aminoaciduria of the type seen in cystinuria. In the same study, administration of the drug resulted in the appearance of large peaks of unmetabolized compound in chromatograms of both plasma and urine; no other peaks appeared, confirming other reports that the drug is not metabolized. After several days of drug administration, patients usually excreted about 90% of the daily dose in the urine;

1048935

at that time concentration of drug in the urine ranged from 72.4 to 172 millimol/day for the 5 patients studied most extensively, and plasma levels ranged from 3.73 to 10.8 μmol/ml of plasma.

The rate of excretion of drug from the body after cessation of therapy could be approximated by a straight line on a semilogarithmic plot with a half-life of 2.4 days for both plasma and urinary decay rates. This excretion rate is considerably greater than the rate in rats and mice, for which a half-life of 22 days was reported. This difference in rate of excretion probably explains the lesser toxicity of the drug in man than in rats and mice.

Cycloleucine is active against leukemia L1210. A single dose of 400 mg/kg intraperitoneally (ip) gives a 69% increased lifespan (ILS); 100 mg/kg/day X 5 ip, a 52% ILS; and 100 mg/kg/day X 9 ip, a 51% ILS. When 300 mg/kg is given ip every 4 days (Days 1, 5, and 9) a 50% ILS is observed. Various other schedules against the L1210 give essentially the same results, indicating a lack of schedule dependency with this compound.

The drug has also been reported to inhibit the growth of Adenocarcinoma 755, 6C3HED ascites lymphosarcoma, and ascites leukemia L4946 in mice as well as Walker carcinosarcoma 256 in rats (1,10).

In rats both single and repeated doses of cycloleucine produce a course characterized by decrease in food intake, weight loss, and at higher levels, death. These phenomena are delayed in appearance and, in survivors, slow in abating. No acute organic lesions have been discovered that might have contributed to the wasting and delayed death of the rats. Hematologic toxicity is manifested by depletion of neutrophils, both in the marrow and peripheral blood. Gross pathologic findings in the rats are negligible. When cycloleucine is given orally and intravenously (iv) to dogs, the effects follow an all-or-none pattern. Dogs receiving sublethal doses show little evidence of toxicity; on the other hand, dogs given lethal doses characteristically become anorectic, lose weight, and die. The hematologic picture is one of hemoconcentration thrombocytopenia, reticulocytopenia, and in some animals, increased immaturity of peripheral leukocytes. The most frequent pathologic change is gastrointestinal ulceration, hemorrhage, and atrophy. Moderate atrophic hepatic and pancreatic changes are observed in some animals. Bone marrow pathology is characterized by varying degrees of erythroid depletion, and in some cases immaturity of the myeloid series.

Monkeys respond to cycloleucine like the dog, though higher doses are required and toxic abnormalities are less pronounced. Fatal doses in the monkey induce malaise; weight loss; diarrhea; moderate degrees of leukopenia, thrombocytopenia, and hemoconcentration; and occasionally local areas of gastrointestinal hemorrhage. The only toxic effects in animals given sublethal doses were diarrhea and weight loss which were seen in 2 monkeys.

A summary of the single dose lethal to 50% of the animals (LD50) and the maximum tolerated single dose is given in table 1 [Report from the Federal Drug Administration to the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute (NCI)].

Table 1.--Summary of single dose LD50 and maximum tolerated single dose of cycloleucine in animals

Species	Dose (mg/kg) iv	Dose (mg/kg) oral
LD50, Single Dose		
Mouse		309
Rat	316	261
Guinea pig		119
Dog	300	300
Maximum Tolerated Single Dose		
Mouse		199
Rat	125	158
Guinea pig		79.4

At Pfizer, groups of 4 female rabbits received single iv doses of 50, 100, and 200 mg/kg cycloleucine (Morrison, M. J., personal communication). Four rabbits died; 2 at the 100 mg/kg level and 2 at the 200 mg/kg level. At the 100 mg/kg level, they died on Days 20 and 29 and pathologic studies showed extensive purulent pneumonia in one animal and edema of the anterior mediastinal tissues in the other. At the 200 mg/kg level, death was on Days 6 and 7; both animals had friable livers with areas of marbling. One rabbit had extensive hemorrhage into the right mesosalpinx.

When serum levels are studied in dogs and monkeys given single iv doses of cycloleucine a surprising phenomenon is observed. In all animals there is a rapid fall in serum levels followed by a sustained rise at 4 hours to peaks, in some animals, far exceeding those noted shortly after injection. Levels then begin to decline slowly between 8 and 24 hours. Even at 48 hours, however, substantial concentrations of the drug can be measured in the serum. Two examples are shown below:

Serum levels of cycloleucine (mg/ml) after iv dose of 120 mg/kg

Animal	1/2 hr	1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
Monkey	30.36	26.68	14.72	33.12	22.08	21.16	11.96
Dog	21.16	22.08	16.56	19.32	53.36	59.80	28.52

As yet this phenomenon is unexplained. Paper chromotographic studies detect the drug (or another material with nearly the same mobility) in serum. There is no evidence that an outpouring of amino acids with similar patterns of mobility are instrumental in the apparent increase in the concentration of cycloleucine.

1048937

When rats are given 40 mg/kg/day x 3 orally, glucose determinations made at Days 0, 4, 7, and 14 show that the glucose levels rise directly after treatment, as food consumption drops. Glucose levels in pair-fed controls drop during the same period. A transitory rise in blood glucose occurs when rats are given injections of leucine and valine (11) but the rise with cycloleucine is more consistent. After adrenalectomy, leucine and valine still cause a slight hyperglycemic response but cycloleucine produces a steady fall in glucose levels with all rats dying after 5 days; no deaths occur in controls or in rats treated with leucine or valine. This evidence and the observation of drastic loss of body protein and fat deposits in rats imply the possibility of excessive secretion of adrenocortical hormones and stimulation of gluconeogenesis and liver glycogen storage after lethal doses of cycloleucine.

One of the initial studies with cycloleucine was done in the Veterans' Administration hospitals (12). They treated 71 patients who had far-advanced malignant disease with oral and iv doses of 10-150 mg/kg/day x 5-10. Toxicity was limited to anorexia, nausea, and vomiting, which were observed in some patients given doses of 60 mg/kg/day or more. The tumor types treated included carcinoma of the bowel, stomach, and lung, as well as a whole range of other solid tumors. No improvement was observed except in one patient with malignant melanoma who sustained an improvement in performance status and decrease in the size of a neck lesion.

Benefiel and his associates reported on the use of cycloleucine in 3 patients with multiple myeloma (13). Two patients were refractory to treatment with steroids, X rays, and urethan (NSC-746; ethyl carbamate). Two were in a preterminal state. Cycloleucine was given iv for 10 days at a dose of 80 mg/kg/day. All 3 patients noted almost complete disappearance of pain within 2 weeks after completion of treatment. A steady increase in hemoglobin levels was noted. No changes in bone lesions or abnormal serum proteins were observed. No toxic effects were seen. Several additional patients with myeloma treated by the author also had a remarkable relief of bone pain though there was no good evidence of reversal of the basic disease process (Benefiel, W. B., personal communication to the CCNSC, June 1961). Severe thrombocytopenia with gastrointestinal hemorrhage was observed in a few patients, with platelets returning to normal upon discontinuance of therapy.

Bergsagel studied cycloleucine in 11 patients with multiple myeloma at a dose of 80 mg/kg/day iv x 10 (16). Marked pain relief was reported in 3 of 5 patients who complained of this symptom. No objective improvement was noted in any patient. Toxic effects were anorexia, weight loss, thrombocytopenia, anemia, and a fall in total serum proteins (TSP). The fall in TSP is interesting in light of recent data on this with L-asparaginase as shown by Canellos et al (14) and Haskell et al (15). The TSP fell from 0.8 to 5.7 g/100 ml in 8 patients. The maximum fall in serum proteins was noted within 15-34 days; it gradually returned toward pretreatment levels. No consistent effect was noted in the albumin to abnormal globulin ratio. The serum electrophoresis patterns did not reveal a selective depression of the abnormal serum globulin. The fall in serum proteins appeared to affect all the proteins (16).

1048938

Miss studied 15 patients who had plasmocytic myeloma treated with cycloleucine. Three treatment regimens were used: (1) 750-1000 mg/kg/day orally to toxicity; (2) 600-1000 mg/kg every other day iv to toxicity; and (3) 80 mg/kg/day iv X 5 every 1-3 months.

Six patients on regimen 1 showed no effect except relief of bone pain in 2 patients. Toxic effects developed in all 6. Thrombocytopenia developed in 2 patients, causing discontinuance of drug. Leukopenia was reason for stopping the drug in 2 other patients. In addition, nausea and weight loss were observed.

Six patients were treated on regimen 2, and the only response was partial relief of bone pain in one patient. Thrombocytopenia was noted in 3 patients, but no leukopenia developed.

On regimen 3, one patient had relief of bone pain and decrease in size of an osteolytic skull lesion. No other parameters of improvement were noted (17).

In 1963, Bigley reported on treating 7 patients who had multiple myeloma with doses of 0.5-1.0 g/day orally and iv (Bigley, R. H., personal communication to P. Waalkes). Five patients had fair to good decrease in bone pain. One patient had definite disappearance of a 5 X 7 cm palpable myeloma tumor on the chest wall after iv therapy. No change in abnormal proteins was noted. Toxic effects were aggravation of mild diabetes (noted in one other study) and nausea and thrombocytopenia in one patient.

Krant et al treated 7 patients who had myeloma with cycloleucine at a dosage of 40-60 mg/kg/day X 6-10. Good relief of bone pain was seen in 5 patients. Despite this alleviation of pain, progression of disease was relentless. Severe bone marrow toxicity developed in 3 patients, with virtual pancytopenia resulting in clinical bleeding in 2 patients. Despite the marrow depression, plasma cells were not affected (18).

The Central Drug Evaluation Program has done extensive testing of cycloleucine in solid tumors (19). Initially they treated 33 patients with 1 or 2 courses of 80 mg/kg/day X 10 iv. Wherever possible a second course of therapy was given 28 days after the first course was completed. Of the 33 treated, 13 completed 2 courses, 11 completed 1 course, and 9 did not satisfactorily complete a full course. One patient with a chondrosarcoma of the pelvis and inguinal node metastasis had a greater than 50% decrease in the size of an inguinal node. A palpable vaginal mass seemed to decrease in size but could not be measured accurately. The tumor returned to its pretreatment size 3 months after therapy began. The condition of 9 of the other patients treated with cycloleucine remained unchanged and 23 had progression of disease.

Little significant toxicity was noted. Two patients had a drop in platelets to 75,000 and 62,000. One patient lost 36 pounds during 2 full courses of therapy, but this was thought to be due to progressive disease.

In view of this lack of toxicity and tumor response the group felt that further evaluation at this dose level was not warranted and decided to do a phase I study at higher dosage levels.

1048939

Forty-seven patients were then treated at dosage levels ranging from 60 to 350 mg/kg/day x 10 iv as follows (20):

Dose (mg/kg/day)	*Number of courses*
60-100	3
100-200	17
200-300	38
300-350	5

Subjective improvement, manifested by relief from pain or improved appetite and weight gain, was noted in 7 patients; 6 of them received more than 200 mg/kg/day. Gastrointestinal toxicity included nausea and vomiting in 14 patients, bleeding in 8, anorexia in 6, and diarrhea in 4. Thrombocytopenia of less then 100,000 was observed in 6 of 47 patients and leukopenia was noted in one patient after 2 days of 350 mg/kg/day. The most serious toxic manifestation observed was the infrequent occurrence of neurologic effects. At doses above 220 mg/kg/day, signs and symptoms of active degeneration of the spinal cord and peripheral nerves were noted. These effects included ataxia, Romberg's sign, nystagmus, vertigo, delirium, and paresthesia.

A phase II study was then started at 300 mg/kg/day x 8-10. A total of 140 patients were treated in this study (21). A summary of the toxicity follows [GI = gastrointestinal, GU = genitourinary, CNS = central nervous system]:

Degree	*Blood*	*GI*	*GU*	*Liver*	*CNS*	*Oral*	*Other*
None	99	80	124	126	79	125	85
Slight to moderate	14	31	4	2	26	2	10
Severe	16	19	0	0	30	0	5
Degree not specified	1	1	0	0	0	0	2
Not reported	10	9	12	12	5	13	38
Percent incidence	23	38	3	1	41	1	16

Partial responses were noted in 1 of 4 head and neck tumors, 2 of 16 colorectal tumors, 1 of 2 ovarian tumors, 1 of 11 melanomas, and 1 of 5 tumors with unknown primary.

Most interesting are the results seen in the treatment of proven leiomyosarcomas with cycloleucine. Fourteen patients (5 men, 9 women) have been treated, most of them receiving 300 mg/kg/day. Of the 14 patients, 13 had measurable lesions; 10 of the 13 showed a definite decrease in measurable lesions. Of these, 6 had a 50% reduction in size of the lesions when compared with the pretherapy measurement. The duration of remission was 24 months in 1 patient and 23 months in another. Two patients were treated not only with 2 courses of 300 mg/kg/day x 10 but with weekly therapy as well; the remission lasted 21 months in 1 patient and the other was still in partial remission at last report. It is interesting that all patients who showed evidence of response had toxic effects: vertigo, slurring of speech, ataxia, or disorientation.

1048940

In summary, cycloleucine is a compound whose clinical history dates back to 1960. It is of special interest at present because of the renewed interest in amino acid antagonist such as L-asparaginase. Cycloleucine is thought to inhibit valine and, like L-asparaginase, is seen to lower serum protein in patients in whom this has been observed. Its mechanism of amino acid antagonism is not the same as that of L-asparaginase, and unlike L-asparaginase, cycloleucine is active in leukemia L1210.

Cycloleucine appears to consistently dimish bone pain in multiple myeloma while not affecting any objective parameters. It is worth noting that all myeloma studies were done at dosage levels that were probably suboptimal and a further evaluation at 300 mg/kg/day might be worthwhile.

The striking effects reported in leiomyosarcoma by the Clinical Drug Evaluation Program and the response in the case of chondrosarcoma would indicate that further evaluation of the compound in sarcomas would be of interest. In addition, cycloleucine has had no clinical trials against acute leukemia or lymphomas. Since it is active against leukemia L1210, is an amino acid antagonist, and has myelosuppressive potential, a trial in these diseases would also be indicated. The experimental evaluation of combinations of cycloleucine with L-asparaginase or the so-called glutamine antagonists, such as azaserine (NSC-742) and azotomycin (NSC-56654), would be still another field of interesting endeavor.

Despite the fact that this compound is one of the oldest compounds in the Chemotherapy program of the NCI, it may well be that it still has a significant future.

REFERENCES

1. Ross, R. B., Noll, C. I., Ross, W. C. J., Nadkarni, M. V., Morrison, B. H., Jr., and Bond, H. W. Cycloaliphatic amino acids in cancer chemotherapy. J Med Pharm Chem 3:1-23, 1961.
2. Mickelson, M. N. Effect of 1-aminocyclopentanecarboxylic acid on amino acid utilization in various bacterial test systems. Biochem Pharmacol 5:165-166, 1960.
3. Berlinguet, L., Begin, N., and Sarkar, N. K. Mechanism of antitumour action of 1-amino-cyclopentane carboxylic acid. Nature 194:1082-1083, 1962.
4. Machlin, L. J., Gordon, R. S., and Puchal, F. Alleviation of 1-aminocyclopentane-1-carboxylic acid (NSC-1026) toxicity by valine. Nature 198:87-88, 1963.
5. Sterling, W. R., and Henderson, J. F. Studies of the mechanism of action of 1-aminocyclopentane-1-carboxylic acid. Biochem Pharmacol 12:303-316, 1963.
6. Christensen, H. N., and Henderson, M. E. Comparative uptake of free amino acids by mouse-ascites carcinoma cells and normal tissues. Cancer Res 12:229-231, 1952.

1048941

7. Christensen, H. N., and Riggs, T. R. Concentrative uptake of amino acids by the Ehrlich mouse ascites carcinoma cell. J Biol Chem 194:57-68, 1952.
8. Clark, A. J., Matsutani, O., and Swendseid, M. E. Food intake, weight gain and amino acid pools of rats receiving 1-aminocyclopentane-1-carboxylic acid. Proc Soc Exp Biol Med 124:1093-1096, 1967.
9. Brown, R. R. Aminoaciduria resulting from cycloleucine administration in man. Science 157:432-434, 1967.
10. Connors, T. A., Elson, L. A., and Ross, W. C. J. The tumour growth inhibitory activity of 1-amino-cyclopentane-1-carboxylic acid and related peptides. Biochem Pharmacol 1:239-240, 1958.
11. Ciofalo, L. M., and Roberts, M. E. Some evidence for pancreatic-adrenal interaction following lethal doses of 1-aminocyclopentanecarboxylic acid. Experientia 22:97-98, 1966.
12. Preliminary clinical notes--1-Aminocyclopentanecarboxylic acid (NSC-1026). Cancer Chemother Rep 6:59-60, 1960.
13. Benefiel, W. W., Helsper, J. T., and Sharp, G. S. Apparent control of multiple myeloma by 1-aminocyclopentane-1-carboxylic acid (NSC-1026). Cancer Chemother Rep 9:21-22, 1960.
14. Canellos, G. P., Haskell, C. M., Arseneau, J., and Carbone, P. P. Hypoalbuminemic and hypocholesterolemic effect of L-asparaginase (NSC-109,229) treatment in man--a preliminary report. Cancer Chemother Rep 53:67-69, 1969.
15. Haskell, C. M., Canellos, G. P., Leventhal, B. G., Carbone, P. P., Serpick, A. A., and Hansen, H. H. L-Asparaginase toxicity. Cancer Res 29:974-975, 1969.
16. Bergsagel, D. E., Ross, S. W., and Baker, D. T. Evaluation of new chemotherapeutic agents in the treatment of multiple myeloma. V. 1-Aminocyclopentanecarboxylic acid (NSC-1026). Cancer Chemother Rep 21:101-106, 1962.
17. Mass, R. E. Clinical evaluation of 1-aminocyclopentanecarboxylic acid (NSC-1026) in plasmocytic myeloma. Cancer Chemother Rep 28:17-19, 1963.
18. Krant, M. J., Iszard, D. M., Abadi, A., and Carey, R. W. Treatment of multiple myeloma with 1-aminocyclopentanecarboxylic acid (NSC-1026). Cancer Chemother Rep 22:59-64, 1962.
19. Johnson, R. O. Preliminary phase II trials with 1-aminocyclopentanecarboxylic acid (NSC-1026). Cancer Chemother Rep 32:67-71, 1963.
20. Aust, J. B., and Roux, K. Phase I study of 1-aminocyclopentanecarboxylic acid (NSC-1026) in cancer patients. Cancer Chemother Rep 49:63-64, 1965.
21. Aust, J. B., Andrews, N. C., Schroeder, J. M., and Lawton, R. L. Clinical note: phase II study of 1-aminocyclopentanecarboxylic acid (NSC-1026) in patients with cancer. Cancer Chemother Rep, 1970. In Press.

Stephen K. Carter
Cancer Therapy Evaluation Branch
Chemotherapy, NCI

1048942

PUBLICATIONS AVAILABLE

The following are past issues of the *Chemotherapy Fact Sheet* which can be obtained from the Publications Section, Program Analysis Branch, Chemotherapy, National Cancer Institute:

Streptonigrin (NSC-45388)
Streptozotocin (NSC-85998)
Daunomycin (NSC-82151)

1048943

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL R. L. Hayes PROPOSAL NO. 75-2

DESCRIPTION:
Carboxyl-labeled ^{11}C-1-aminocyclopentanecarboxylic acid (ACPC). This agent will be used for the detection of tumors in humans using conventional rectilinear and positron coincidence scanning techniques.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may ___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may ___ may not ✓ be administered to pregnant patient.

Other: PHYSICIANS MAY NOT ADMINISTER MORE THAN TWICE THE NORMALLY RECOMMENDED ACTIVITY WITHOUT SPECIFIC APPROVAL OF THE MEDICAL RADIONUCLIDE COMMITTEE.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William D. Dibble	✓			Aug. 21, 1975
D. C. Swartzendruber	✓			Aug 21, 1975
James R. Berger	✓			8/21/75
KARL HUBNER			✓	
R. L. HAYES	NOT VOTING			

Acknowledgement of Submitter R. L. Hayes Date 8/21/75

- -

Proposal does ✓ does not ___ require approval of Committee on Human Studies.

1048944

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. Karl Hübner PROPOSAL NO. 76-1

DESCRIPTION: ^{133}Xe gas inhalation for lung ventilation and washout studies. Studies will include imaging with a gamma camera and/or digital collection of dynamic data for functional analysis. The usual dose will not exceed 30 millicuries in accordance with attached package insert.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may ___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may ___ may not ✓ be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. ~~Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee~~.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William D. Fitz	✓			April 9, 1976
D C Swartzendruber	✓			4/9/76
G D Berger	✓			4/9/76
KARL HUBNER	NOT VOTING			
RAYMOND HAYES			✓	

Acknowledgement of Submitter Karl F. Hübner Date 4/9/76

- -

Proposal does ___ does not ✓ require approval of Committee on Human Studies.

1048945

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to an average patient (70 kg) for pulmonary perfusion and cerebral blood flow studies from a maximum dose of 30 millicuries of Xenon Xe 133 in 3 liters of air are shown in Table III.

Table III
Radiation Doses

	Effective Half-time	Lungs*	Brain	Whole Body
		rads/30mCi		
Pulmonary Perfusion	2 min.	0.25	0.0014	0.0027
Cerebral Blood Flow	5 min.	0.63	0.0035	0.0068

*99% of activity is in lungs

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

HOW SUPPLIED

The Xenon Xe 133 gas is supplied as part of the Calidose® system, consisting of 2 ml unit dose vials and the Calidose dispenser* for shielded dispensing.

Normally vials containing either 10 or 20 mCi/vial, packed up to 5 vials per shield tube, are supplied. Vial sets containing up to 100 mCi/vial are available.

*Patent Pending

New England Nuclear
Radiopharmaceutical Division
Atomlight Place
North Billerica, Mass. 01862

JO 127 7-75 Rev 1 Printed in U.S.A.

10M775S-734R

1048946

XENON Xe 133 GAS

Catalog Number NRP-127

New England Nuclear

DESCRIPTION

'non Xe 133 for diagnostic use is available as 5% gas in rbon dioxide diluent 95%.

ACTIONS

Xenon Xe 133 is a readily diffusible gas which is neither utilized nor produced by the body. It passes through cell membranes and freely exchanges between blood and tissue. It tends to concentrate more in body fat than in blood, plasma, water or protein solutions. In the concentrations used for diagnostic purposes it is physiologically inactive. Inhaled Xenon Xe 133 gas will enter the alveolar wall and enter the pulmonary venous circulation via the capillaries. Most of the Xenon Xe 133 that enters the circulation from a single breath is returned to the lungs and exhaled after a single pass through the peripheral circulation.

INDICATIONS

Inhalation of Xenon Xe 133 gas has proved valuable for the evaluation of pulmonary function and for imaging the lungs. It may also be applied to assessment of cerebral flow.

CONTRAINDICATIONS

To date, no known contraindications to the use of Xenon Xe 133 gas have been reported.

WARNINGS

This radiopharmaceutical should not be administered to pregnant or lactating women unless the benefits to be gained outweigh the potential hazards.

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

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

PRECAUTIONS

As in the use of any other 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. Expired Xenon Xe 133 gas should be controlled in a manner that is in compliance with the appropriate governmental agency regulations.

Xenon Xe 133 adheres to some plastics and rubber and should not be allowed to stand in tubing or respirator containers. Such unrecognized loss of radioactivity from the dose for administration may render the study non-diagnostic. Xenon Xe 133 gas delivery systems, i.e., respirators or spirometers, and associated tubing assemblies must be leakproof to avoid loss of radioactivity into the laboratory environs not specifically protected by exhaust systems.

ADVERSE REACTIONS

To date, no adverse reactions based on the use of Xenon Xe 133 gas have been reported.

DOSAGE AND ADMINISTRATION

n Xe 133 gas is administered by inhalation from closed respirator systems or spirometers.

The suggested activity range employed for inhalation by the average adult patient (70 kg) is:

Pulmonary function including imaging: 2-30 mCi in 3 liters of air.

Cerebral blood flow: 10-30 mCi in 3 liters of air.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Xenon Xe 133 decays by beta and gamma emissions with a physical half-life of 5.27 days[1]. Photons that are useful for imaging studies are listed in Table I.

Table I
Principal Radiation Emission Data Xenon Xe 133

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta-2	99.3	100.6
Gamma-2	34.99	81.0
K int. con. electrons, -2	47.24	45.0
L int. con. electrons, -2	7.87	75.7
M int. con. electrons, -2	9.84	80.0
K x-rays	34.70	30.8
K x-rays	7.67	35.2

(1) Dillman, L.T., Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, Part 2, Supplement No. 4, MIRD pamphlet No. 6, J. Nucl. Med., p. 28, 1970.

The specific gamma ray constant for Xenon Xe 133 is 0.44 R/mCi-hr. at 1 cm. The half value layer is 1 mm of Pb.

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

Table II
Xenon Xe 133 Physical Decay Chart
(Half-life 5.27 days)

Day	Fraction Remaining	Day	Fraction Remaining
-5	1.930	8	.349
-4	1.693	9	.302
-3	1.483	10	.268
-2	1.300	11	.235
-1	1.140	12	.206
0*	1.000	13	.181
1	.877	14	.159
2	.769	15	.139
3	.674	16	.122
4	.591	17	.107
5	.518	18	.094
6	.454	19	.082
7	.398	20	.072

*Calibration Day

1048947

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. Karl Hübner PROPOSAL NO. 76-2

DESCRIPTION: ^{133}Xe administered intravenously in saline for lung perfusion studies. These studies will include imaging with a gamma camera and/or collection of digital data for functional analysis. The usual dose will not exceed 30 millicuries in accordance with the attached package insert.

☒ The Committee approves with the following limitations:

Radiopharmaceutical may ___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may ___ may not ✓ be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. ~~Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee~~.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William D. Bibb	✓			April 9, 1976
H. C. Hartzler	✓			4/9/76
G. M. Berger	✓			4/9/76
Karl Hubner	NOT VOTING			
Raymond Hayes			✓	

Acknowledgement of Submitter Karl F. Hubner Date 4/9/76

- -

Proposal does ___ does not ✓ require approval of Committee on Human Studies.

1048448

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to an average patient (70 kg) for pulmonary perfusion and cerebral blood flow studies from a maximum dose of 30 millicuries of Xenon Xe 133 in 3 liters of air are shown in Table III.

Table III
Radiation Doses

	Effective Half-time	Lungs*	Brain	Whole Body
		rads/30mCi		
Pulmonary Perfusion	2 min.	0.25	0.0014	0.0027
Cerebral Blood Flow	5 min.	0.63	0.0035	0.0068

*99% of activity is in lungs

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

HOW SUPPLIED

The Xenon Xe 133 gas is supplied as part of the Calidose® system, consisting of 2 ml unit dose vials and the Calidose dispenser* for shielded dispensing.

Normally vials containing either 10 or 20 mCi/vial, packed up to 5 vials per shield tube, are supplied. Vial sets containing up to 100 mCi/vial are available.

*Patent Pending

New England Nuclear
Radiopharmaceutical Division
Atomlight Place
North Billerica, Mass. 01862

7 7-75 Rev 1

Printed in U.S.A.

10M7755-734R

1048949

XENON Xe 133 GAS

Catalog Number NRP-127

New England Nuclear

DESCRIPTION

on Xe 133 for diagnostic use is available as 5% gas in on dioxide diluent 95%.

ACTIONS

Xenon Xe 133 is a readily diffusible gas which is neither utilized nor produced by the body. It passes through cell membranes and freely exchanges between blood and tissue. It tends to concentrate more in body fat than in blood, plasma, water or protein solutions. In the concentrations used for diagnostic purposes it is physiologically inactive. Inhaled Xenon Xe 133 gas will enter the alveolar wall and enter the pulmonary venous circulation via the capillaries. Most of the Xenon Xe 133 that enters the circulation from a single breath is returned to the lungs and exhaled after a single pass through the peripheral circulation.

INDICATIONS

Inhalation of Xenon Xe 133 gas has proved valuable for the evaluation of pulmonary function and for imaging the lungs. It may also be applied to assessment of cerebral flow.

CONTRAINDICATIONS

To date, no known contraindications to the use of Xenon Xe 133 gas have been reported.

WARNINGS

This radiopharmaceutical should not be administered to pregnant or lactating women unless the benefits 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 the menses.

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

PRECAUTIONS

As in the use of any other 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. Expired Xenon Xe 133 gas should be controlled in a manner that is in compliance with the appropriate governmental agency regulations.

Xenon Xe 133 adheres to some plastics and rubber and should not be allowed to stand in tubing or respirator containers. Such unrecognized loss of radioactivity from the dose for administration may render the study non-diagnostic. Xenon Xe 133 gas delivery systems, i.e., respirators or spirometers, and associated tubing assemblies must be leakproof to avoid loss of radioactivity into the laboratory environs not specifically protected by exhaust systems.

ADVERSE REACTIONS

To date, no adverse reactions based on the use of Xenon Xe 133 gas have been reported.

DOSAGE AND ADMINISTRATION

a Xe 133 gas is administered by inhalation from closed respirator systems or spirometers.

The suggested activity range employed for inhalation by the average adult patient (70 kg) is:

Pulmonary function including imaging: 2-30 mCi in 3 liters of air.

Cerebral blood flow: 10-30 mCi in 3 liters of air.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Xenon Xe 133 decays by beta and gamma emissions with a physical half-life of 5.27 days[1]. Photons that are useful for imaging studies are listed in Table I.

Table I
Principal Radiation Emission Data Xenon Xe 133

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta-2	99.3	100.6
Gamma-2	34.99	81.0
K int. con. electrons, -2	47.24	45.0
L int. con. electrons, -2	7.87	75.7
M int. con. electrons, -2	9.84	80.0
K x-rays	34.70	30.8
K x-rays	7.67	35.2

(1) Dillman, L.T., Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, Part 2, Supplement No. 4, MIRD pamphlet No. 6, J. Nucl. Med., p. 28, 1970.

The specific gamma ray constant for Xenon Xe 133 is 0.44 R/mCi-hr. at 1 cm. The half value layer is 1 mm of Pb.

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

Table II
Xenon Xe 133 Physical Decay Chart
(Half-life 5.27 days)

Day	Fraction Remaining	Day	Fraction Remaining
-5	1.930	8	.349
-4	1.693	9	.302
-3	1.483	10	.268
-2	1.300	11	.235
-1	1.140	12	.206
0*	1.000	13	.181
1	.877	14	.159
2	.769	15	.139
3	.674	16	.122
4	.591	17	.107
5	.518	18	.094
6	.454	19	.082
7	.398	20	.072

*Calibration Day

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 76-3

DESCRIPTION:
DL-VALINE-1-^{11}C. We propose to use this new radiopharmaceutical agent in clinical studies for visualization of the pancreas. The IND we propose to submit to FDA is attached (see Table 10 for radiation dosimetry).

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William R. Bibbo	✓			April 9, 1976
D. C. Aronchambers	✓			4/9/76
S. P. Berger	✓			4/9/76
KARL HUBNER	NOT	VOTING		
RAYMOND HAYES			✓	

Acknowledgement of submitter Karl F. Hübner Date 4/9/76

Proposal does ✓ does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048951

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division (MHSD), Oak Ridge

Associated Universities (ORAU), Oak Ridge, Tennessee

March , 1976

1. NAME OF DRUG: DL-VALINE-1-^{11}C. This drug will be administered intravenously, dissolved in a sterile nonpyrogenic saline solution.

2. COMPONENTS:

   a. DL-Valine-1-^{11}C (active radioactive drug).

   b. DL-Valine [nonradioactive carrier (stable) drug].

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION: Since the ^{11}C present in labeled DL-valine-1-^{11}C is radioactive ($T_{1/2}$ ^{11}C = 20.4 min), we cannot state a completely exact relationship between the components of this preparation at the time of administration. From radiation dosimetry considerations, however, we have determined that the maximum ^{11}C activity that will be administered will not exceed 0.714 mCi per kilogram of body weight (a 50 mCi dose for a 70 kg subject). The actual amount of stable DL-valine that will be administered will be determined by the amount of ^{11}C used in labeling DL-valine and also the time that elapses from the time of DL-valine-1-^{11}C preparation to the time of its administration to the patient. The composition stated below, therefore, represents the dosage limits that will be adhered to for the components in this radiopharmaceutical preparation:

   a. DL-Valine-1-^{11}C: maximum of 0.714 mCi per kilogram of body weight (50 mCi total for a 70 kg subject).

   b. DL-Valine: maximum of 0.1 mg per kilogram of body weight (7 mg total for a 70 kg subject). The weight of DL-valine-1-^{11}C administered (a, above) will be negligible compared to that of stable DL-valine.

   c. Sodium chloride: maximum of 3 mg per kilogram of body weight (210 mg total for a 70 kg subject).

   d. Water: maximum of 0.5 ml per kilogram of body weight (35 ml total for a 70 kg subject).

1048952

4. SOURCE OF NEW DRUG SUBSTANCE:

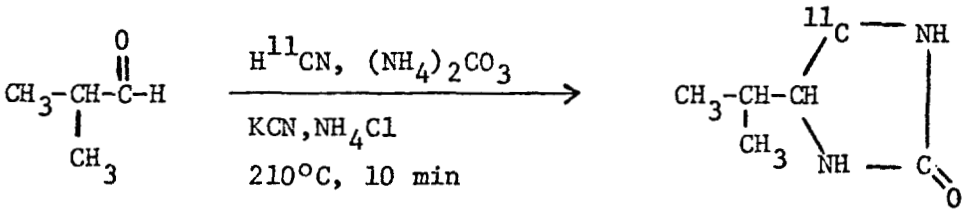
Reference should be made to the details of synthesis and purification of ^{11}C-ACPC in our IND 11848 (dated 16 September 1975) application for a similarly prepared radiopharmaceutical. (^{11}C-ACPC has been under clinical investigation at MHSD, ORAU, since November 1975.)

DL-Valine-1-^{11}C will be synthesized in the preparatory hot cell at the 86-Inch Oak Ridge National Laboratory(ORNL)'s 22 Mev proton cyclotron complex using the following series of reactions:

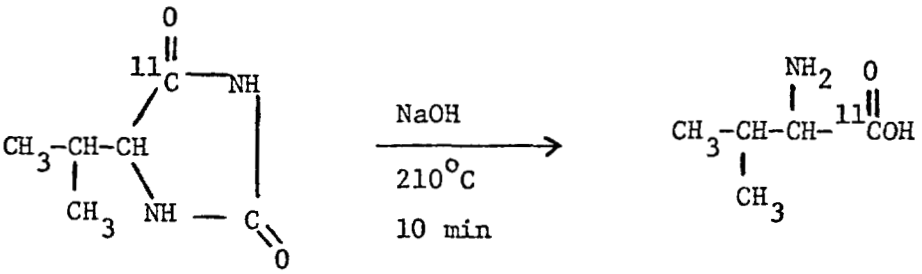
$$B_2O_3 \xrightarrow{^{11}B(p,n)^{11}C} {}^{11}CO_2/{}^{11}CO \qquad \text{Step I}$$

$$^{11}CO_2/{}^{11}CO \xrightarrow[\text{Ni, } 370^\circ C]{H_2} {}^{11}CH_4 \qquad \text{Step II}$$

$$^{11}CH_4 \xrightarrow[900\text{-}950^\circ C]{\text{Pt, } NH_3} H^{11}CN \qquad \text{Step III}$$



Step IV



Step V

Targetry and Production of $^{11}CO_2/^{11}CO$ (Step I): B_2O_3, prepared by heating H_3BO_3 (Fisher Scientific Co., Fair Lawn, N.J.), is fused onto a graphite substrate, which is mounted in an aluminum annulus-type header. The annulus provides a water coolant flow of 15 liters/min. The header assembly is connected in turn to a gas flow loop that has provisions for on-line gas purge or recirculation. The outlet of the loop is located in the remote control preparatory hot cell that is adjacent to the cyclotron. During bombardment, when He (Lif-O-Gen Inc., Cambridge, Md.) is used as the carrier gas in the loop, a $^{11}CO_2/^{11}CO$ ratio of approximately 4 is obtained. Outgassing of target ^{11}C activity into the gas flow loop during bombardment is approximately 50% complete. With a beam current of 150-175 μA approximately 3 Ci of usable $^{11}CO_2/^{11}CO$ activity is produced.

Production of $^{11}CH_4$ and $H^{11}CN$ (Steps II and III): Both $^{11}CH_4$ and $H^{11}CN$ are produced by contact catalysis. A 100 ml/min He stream introduced into the cyclotron gas flow loop is mixed at the loop outlet with a 50 ml/min H_2 (Lif-O-Gen Inc.) stream and fed through a quartz tube containing Ni catalyst on kieselguhr (Ventron Alpha Products, Beverly, Mass.) held at a temperature of 370°C. The output gas flow from this conversion (containing $^{11}CH_4$) is passed through a $CaSO_4$/NaOH trap and then mixed with a 50 ml/min stream of anhydrous NH_3 (Lif-O-Gen Inc.). This mixture is then passed through another quartz tube containing Pt catalyst on alumina (Ventron Alpha Products) heated to 900-950°C to complete the conversion of $^{11}CH_4$ to $H^{11}CN$.

Synthesis of DL-Valine-1-^{11}C (Steps IV and V): Prior to the start of a DL-valine-1-^{11}C production run a stainless steel (type 316) pressure vessel having an internal volume of 3 ml and fitted with a ball valve is charged with a mixture of 35 µl (27.8 mg) isobutyraldehyde (98%, b.p. 63°, Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, redistilled before use), 72 mg $(NH_4)_2CO_3$ (certified A.C.S., Fisher Scientific Co.), 6.7 mg NH_4Cl and 8.2 mg KCN (both Baker Analyzed Reagents, J. T. Baker Chemical Co., Phillipsburg, N.J.). The gas stream from Step III, containing $H^{11}CN$ is bubbled into a gas absorption column containing 1 ml of 0.005 N NaOH. This solution is then introduced into the charged reaction vessel and the closed vessel then rapidly heated to 210°C and maintained at that temperature for 10 min, after which it is rapidly cooled. One ml of 6.25 N NaOH (Fisher Scientific Co.) is then introduced and the vessel again heated at 210°C for another period of 10 min.

Purification of DL-Valine-1-^{11}C: After completion of Step V the cooled reaction mixture is withdrawn remotely by means of a syringe and then loaded directly onto a 1.5 cm (dia.) x 5 cm (length) prewashed AG 1-X2, 100-200 mesh, anion exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydroxide form. Anionic components, including DL-valine-1-^{11}C, are retained by the column while cationic and nonionic components pass through. After washing repeatedly with distilled water (∿50 ml) the column is then eluted with 1 N HCl, the process being monitored by means of a shielded gamma probe. The acidic eluate is loaded onto a prewashed 1.0 cm (dia.) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation exchange bed (Bio Rad Laboratories) in the hydrogen form. Cationic DL-valine-1-^{11}C is retained while anionic material passes through the column. After washing repeatedly with distilled water (∿30 ml), the column is finally eluted with 0.2 N NaOH, the process again being monitored with a shielded gamma probe to minimize the volume of eluate containing the product (∿15 ml). This solution is collected in a sterile bottle for transport to MHSD, ORAU for final processing.

Assessment of Purity. The purity of the DL-valine-1-^{11}C product has been assessed by thin layer chromatography (tlc) (Eastman silica gel, Chromagram Sheet 13179) using an n-butanol:water:acetic acid (100:10:5 v/v) solvent system and also by comparison of its tissue distribution in animals with those that have previously been obtained with commercially available DL-valine-1-^{14}C (New England Nuclear Corp., Boston, Mass.). Pyrogenicity tests of the DL-valine-1-^{11}C product by standard USP techniques have been negative. There has also been no indication of decomposition of DL-valine-1-^{11}C as the result of radiolysis.

1048954

DL-Valine-1-^{11}C (from a run spiked with K^{14}CN prior to synthesis) gave a tlc pattern that was similar to that of DL-valine-1-^{14}C with no indication of any impurities when the two tlc patterns were viewed with a spark chamber (Burchover Instruments, Ltd., Bancroft, England). Ninhydrin development of the tlc chromatograms also gave similar results (single amino acid spots with the same rf values).

Figure 1 shows a torso scan of a dog obtained with intravenously administered DL-valine-1-^{11}C. The animal was anesthetized with pentobarbital at 30 min postinjection of DL-valine-1-^{11}C and scanned from 40-60 minutes postinjection. Table 1 shows the tissue distribution (based on ^{11}C counts) in this animal after being sacrificed and autopsied at 2 hr postinjection.

Table 1 also shows tissue distribution data at 30 min postinjection for a series of four dogs given commercial DL-valine-1-^{14}C. Even though the valine appears to have cleared somewhat from all tissues by 2 hr postinjection, the pancreas-to-tissue concentration ratios are similar for the two sets of data. Figure 2 shows an image of a rat killed 30 min after intravenous administration of DL-valine-1-^{11}C. Table 2 shows the tissue distribution based on ^{11}C counts from this animal and also includes tissue concentration data at 30 min for a series of four rats given commercial DL-valine-1-^{14}C. (See section 6 for more animal data.)

5. METHODS, FACILITIES AND CONTROLS:

The solution containing the purified DL-valine-1-^{11}C will be transported from the ORNL cyclotron complex to MHSD, ORAU located on Vance Road in Oak Ridge (trip time, 6-8 min). After being transferred to a magnetically stirred conical beaker, the pH of the solution will be adjusted to 7.0 $\pm$ 0.2 with 1 N HCl using a combination electrode and pH meter. (The stem of the electrode, when not in use, will be stored in 0.9% benzyl alcohol and will be rinsed repeatedly with sterile water before each preparative use.) The solution will then be filtered through a sterile nonpyrogenic 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (multipuncture type, Wheaton Glass Co., Millville, N.J.). A portion of the solution will be removed for final radioassay using a sodium iodide crystal calibrated with NBS standards (a previous preliminary ion chamber assay will have been made at the cyclotron facility). A portion of this solution will also be tested for pyrogens using the Pyrotest Limulus Lysate technique (Difco Laboratories, Detroit, Mich.). The short half-life of ^{11}C (20.4 min) precludes testing with rabbits in the conventional USP manner, and, although this particular limulus technique normally requires an hour for completion, it should act as a test for gross pyrogen contamination during the period of time required for radioassay and transport of the preparation to the site of administration (~15 min). The full test will become part of the record as will the standard USP sterility test. The vial containing the DL-valine-1-^{11}C will finally be labeled as to its assay and total content (see section 7). ~~A final ion chamber assay will be made of each DL-valine-1-^{11}C syringe dose just before administration to each patient~~.
EACH DL-VALINE-1-^{11}C dose will be assayed for activity content just prior to administration.

1048955

Preparation of each batch of DL-valine-1-^{11}C for clinical use will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized by steam. Each batch of DL-valine-1-^{11}C will be given a batch number and all particulars relative to its preparation and use will be entered into a master log book.

6. STATEMENT OF INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations

1. Animal studies

All animal studies of DL-valine-1-^{14}C and DL-valine-1-^{11}C have been directly supervised by L. C. Washburn and R. L. Hayes. G. A. Andrews and K. F. Hübner have participated in the evaluation of the data (see Appendix on Biographical Material).

The insertion of radioisotopic labels into the intrinsic structure of organic compounds and biological substances that have high affinities for specific tissues is an ideal method of labeling, since structures are not altered. The radionuclides ^{11}C, ^{13}N, and ^{15}O are all candidates for use in labeling such agents for nuclear medical diagnosis by scanning. Their decay is accomplished by photon emission in the form of positron annihilation radiation which can be utilized for conventional rectilinear scanning or for coincidence detection techniques such as positron emission transaxial tomography utilizing computer reconstruction. This latter method is an instrumentation technique that may shortly come into its own in nuclear medical technology (1). Of these three radionuclides, ^{11}C is the obvious choice as a label because of its longer half-life (20.4 min), although, even with this radionuclide, rapid tissue distribution is necessarily required of any radiopharmaceutical agent that is labeled with it.

One of the most important diagnostic problems in nuclear medicine is the need for a more suitable agent for pancreas imaging (2). Carcinoma of the pancreas is the fourth leading cause of cancer deaths in the United States (3,4), being responsible for the death of approximately 7000 persons each year (5). Very little progress has been made in combatting this disease, as evidenced by the present 5-year survival rate of 1.5% for patients diagnosed as having pancreatic carcinoma, compared to 1.0% in 1940 (6). This poor survival rate seems to be due more to the lack of reliable diagnostic techniques than to the non-availability of adequate treatment procedures (5).

The most reliable procedure for diagnosing pancreatic carcinoma at the present time involves imaging the pancreas with the radiopharmaceutical ^{75}Se-selenomethionine coupled with a ^{99m}Tc-sulfur colloid scan to permit subtraction of interfering radiation from the liver (7). However, ^{75}Se-selenomethionine has a number of disadvantages associated with its use (8). One problem is the high radiation dose to the patient. Selenium-75 has a long physical half-life (120 days) and ^{75}Se-selenomethionine in turn has a long biological half-life (20 days). This results in the

1048956

exposure of the patient to radiation for a much longer time than is required for the diagnostic procedure (8). The most acute problem, however, is the inability of the agent to clearly delineate neoplasms associated with the pancreas. Uptake of ^{75}Se-selenomethionine even by a normal pancreas is not uniform from patient to patient and often nonspecific. Significant percentages of both false positives and false negatives are observed (9, 10).

A number of labeled amino acid preparations have been investigated as potential radiopharmaceuticals for pancreas scanning (11-13), but the biochemical behavior of the radioactive label generally differs greatly from that of the natural amino acid. This makes ^{11}C an obvious choice for labeling amino acids for pancreatic imaging, since the biochemical utilization of the labeled compound should be similar in magnitude to that of the natural amino acid.

Studies in the mouse using DL-valine-1-^{14}C (14) showed this amino acid to be one of the best natural amino acids with regard to pancreas uptake and pancreas specificity, and we have adapted the high temperature, high pressure Strecker synthesis developed for carboxyl-labeled ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC) (15) to the synthesis of DL-valine-1-^{11}C.

The uptake of DL-valine-1-^{14}C by the pancreas is almost complete at 15 min postinjection but does increase somewhat between 15 and 60 min postinjection while the concentration in most other tissues declines (Table 3); therefore, in view of the 20.4 min half-life of ^{11}C, 20-30 min postinjection is perhaps the optimum time to begin a scan. Added carrier DL-valine, up to 5 mg/kg, has no effect on the tissue distribution in the rat (Table 4).

We have carried out studies of the tissue distribution of DL-valine in a wide variety of animal species in order to assess the importance of species differences in the distribution. These species included the hamster (see Table 5), rat (Table 2, 3, and 4, and Fig. 2), rabbit (Table 6), and dog (Table 1 and Fig. 1). All of these species showed good pancreas uptake, although the pancreas specificity varied in the following order: hamster > rat > dog > rabbit.

A Morris 5123C hepatoma showed no preferential uptake of DL-valine-1-^{14}C (Table 7). Pancreatic cancer would thus be expected to be diagnosed by a defect (negative scan) in the normal pancreatic uptake of DL-valine-1-^{11}C.

One potential problem in the use of DL-valine-1-^{11}C arises from the significant decarboxylation encountered in administration of DL-valine-1-^{14}C (or L-valine-1-^{14}C). The amino acid is decarboxylated (with exhalation of radioactive $^{14}CO_2$) to the extent of 18% in 30 min and 33% in 120 min (Table 8) in the rat. This will necessitate the venting or isolation of the $^{11}CO_2$ present in a patient's breath during scanning in order to protect the personnel performing the scan. The results of a total body retention study of DL-valine-1-^{11}C in rats are shown in Table 9. The total loss of label through the exhaled breath and urine (and feces) measured 27% in 30 min and 48% in 120 min.

1048957

2. Toxicity

L-Valine, of course, is one of the essential, naturally occurring amino acids, and, as such, it is present to the extent of 2.4 (2.0-2.9) mg per 100 ml of normal human blood (16). Assuming that blood comprises 7% of total human body weight, there is, therefore, ~118 mg of L-valine in the blood stream of a normal 70 kg human. (We propose to administer no more than a total of 7 mg DL-valine per 70 kg subject.)

The LD_{50} of intraperitoneally administered L-valine in rats is reported as 5.38 g/kg and the D-isomer is reported as being even less toxic (17).

At the dose level of the drug which we would use for pancreas imaging (0.1 mg/kg or less), we would expect no toxicity, since we will be below the LD_{50} value by a factor of approximately 50,000.* The ORAU/ORNL Committee on Human Studies has approved the use of DL-valine-1-^{11}C as outlined in this application (see Appendix for membership of committee and biographical material).

3. Radiation Dosimetry

Carbon-11 has a 20.4 min half-life decaying by positron emission (99+%) to stable ^{11}B. Because of its short half-life the radiation dose to patients will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center (headed by R. J. Cloutier) that the complete decay of 1 mCi of DL-valine-1-^{11}C uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.01 rads or a total of 0.50 rads per 50 mCi (the maximum proposed administered dose of DL-valine-1-^{11}C). Table 10 gives details of the expected radiation dose to various organs in the human estimated from animal data. The MHSD, ORAU Medical Radionuclide Committee has approved the use of DL-valine-1-^{11}C from a ~~dosimetry~~ PATIENT SAFETY standpoint.

b. Previous Marketing:

This ^{11}C-labeled drug has not been marketed before.

c. Drug Combination:

DL-Valine-1-^{11}C is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with DL-valine-1-^{11}C will have the following form:

DL-VALINE-1-^{11}C (FOR I.V. INJECTION)

Assay_____mCi/ml as of_____
Volume_____ml: Batch No._____
Expiration Time _____
CAUTION: INVESTIGATIONAL NEW DRUG
CAUTION: RADIOACTIVE MATERIAL
Oak Ridge Assoc. Univ., Oak Ridge, Tn.

* The daily minimum dietary requirement for L-valine in man is 800 mg. This amount of L-valine is given intravenously to patients on total parenteral alimentation (Aminosol 5%, page 502-503, PDR 1976).

1048958

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal information material will be prepared; however, each participant will of course be issued a copy of this application.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See bibliographical material in the appendix about Drs. Andrews, Hayes, Hübner, Washburn, and Wieland.

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by G. A. Andrews, R. L. Hayes, K. F. Hübner, and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Chairman of the ORAU Medical and Health Sciences Division, with advice from the ORAU Medical Advisory Committee and the ORAU/ORNL Committee on Human Studies (see attached lists and biographies in the Appendix).

10. CLINICAL STUDIES

Phases I and II, clinical pharmacology, in this study will consist of observations on the metabolism and toxicity of DL-valine-1-^{11}C together with preliminary observations on the radiopharmaceutical's pancreas-localizing properties.

Patients (30) for this study will be mainly those referred by Dr. Reid Collmann, a gastroenterologist from Knoxville, Tennessee. Other patient volunteers will be recruited from patients in the Oak Ridge Hospital and surrounding hospitals. They will be selected for evidence of possible pancreatic disease, i.e., symptoms and laboratory findings suggestive of pancreatic carcinoma and/or having a diagnosis of chronic alcoholic pancreatitis. This latter group of pancreatitis patients should provide a sufficient number of negative subjects for us to develop reasonable criteria for the characteristics of the normal pancreatic scan without resorting to normal volunteers. The DL-valine-1-^{11}C study is expected to cover a period of 1-1/2 to 2 years. Only adult subjects will be studied. Each patient will be fully informed that this is an experimental procedure, that it might have some toxic effect (although we know of no specific toxicity that is at all likely) and that the procedure will cause a radiation dose of approximately 1.6 to 4 rads to the pancreas and approximately 0.2 to 0.5 rads to the whole body when between 20 and 50 mCi of DL-valine-1-^{11}C are administered. No DL-valine-1-^{11}C doses will be given without the informed consent of the patient. Subjects incapable of giving an informed consent will be excluded from the study. A copy of the informed consent form is attached.

For dosimetry purposes and to determine optimal timing of scanning, blood levels of radioactivity will be determined at frequent intervals during the first 1 to 1-1/2 hours after injection of the radiopharmaceutical. Additional information for radiation dose estimates will be gathered by whole body counting and determination of the radioactivity excreted in the urine.

1048959

Since the proposed diagnostic doses appear well below any that could cause chemical toxicity from the DL-valine or detrimental radiation effects from the ^{11}C present, we will start our studies using the full diagnostic dose (0.71 mCi/kg), but using patients strongly suspected of pancreatic disease who are, however, considered to be in good general condition. Careful observations of pulse and blood pressure will be made during the first 5 doses given. At least two physicians will be present during the first clinical trials.

The following laboratory tests will be done both before and 24 hours after injection of the radiopharmaceutical: complete blood count, urinalysis and plasma hemoglobin.

If any abnormality in clinical or laboratory observations is seen, appropriate follow-up studies will be carried out. If the abnormality appears serious, we will stop all further clinical trials and immediately notify the Food and Drug Administration.

Expired $^{11}CO_2$ from patients receiving DL-valine-1-^{11}C (see Table 8) will be trapped in a shielded CO_2 adsorbant container to protect the scanning personnel. At the termination of the study the percent expired $^{11}CO_2$ will be determined by comparing the activity in the CO_2 adsorbent container with an aliquot of the DL-valine-1-^{11}C dose given the patient.

The principal questions to be answered are:

1. Are there any unsuspected toxic effects of DL-valine-1-^{11}C on humans at the dose levels proposed?
2. Will the uptake of DL-valine-1-^{11}C in the human pancreas be sufficient to permit pancreatic imaging?
3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for DL-valine-1-^{11}C in humans?
4. What is the optimum dose and scanning time for pancreas visualization?

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of DL-valine-1-^{11}C prior to 30 days after the date of receipt of notice of this application by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

References

1. M. M. Ter-Pogossian, M. E. Phelps, E. J. Hoffman, and N. A. Mullani. Radiol. 114, 89 (1975).

2. J. G. McAfee in "Radiopharmaceuticals", G. Subramanian, B. A. Rhodes, J. F. Cooper, and V. J. Sodd, eds., p. 6, The Society of Nuclear Medicine, Inc., New York, 1975.

3. L. Ernst, K. Wynder, K. Mabuchi, N. Maruchi, and J. G. Fortner. J. Nat'l. Cancer Inst., 50, 645 (1973).

4. D. L. Levin and R. R. Connelly. Cancer, 31, 1231 (1973).

5. M. Blau and R. F. Manske. J. Nucl. Med., 2, 102 (1961).

6. S. Kaplan. Oncology Address before Society of Nuclear Medicine, Annual Meeting, San Diego, California, 1974.

7. G. R. Youngs, J. E. Agnew, G. E. Levin and I.A.D. Bouchler. Q. J. Med., 42, 576 (1973).

8. M. Blau and J. F. Holland. U.S. Atomic Energy Comm. Symp. Ser. No. 6, 409-21 (1966).

9. J. A. Burdine and T. P. Haynie. J.A.M.A., 194, 979 (1965).

10. A. Rodriguez-Antunes, E. J. Filson, B. H. Sullivan, Jr., and C. H. Brown. Ann. Int. Med., 65, 730 (1966).

11. H. L. Adkins, D. R. Christman, J. S. Fowler, W. Hauser, R. M. Hoyte, J. F. Klopper, S. S. Lin, and A. P. Wolf. J. Nucl. Med., 13, 713 (1972).

12. R. M. Lambrecht, H. Adkins, H. Elias, J. S. Fowler, S. S. Lin, and A. P. Wolf. J. Nucl. Med., 15, 863 (1974).

13. D. M. Taylor and M. F. Cottrall. In "Radiopharmaceuticals and Labeled Compounds," Vol. 1, p. 433. International Atomic Energy Agency, Vienna, 1973.

14. O. Tamemasa, R. Goto, M. Tezuka, and S. Okada in "Recent Advances in Nuclear Medicine", pp. 875-877, Japan Radioisotope Association, Tokyo, Japan, 1974.

1048961

15. R. L. Hayes, L. C. Washburn, B. W. Wieland, T. T. Sun, R. R. Turtle, and T. A. Butler. J. Nucl. Med. (in press)

16. "Blood and Other Body Fluids," D. S. Ditner, ed., p. 73, Federation of American Societies for Experimental Biology, Washington, D.C., 1961.

17. P. Gullino, M. Winitz, S. M. Birnbaum, J. Cornfield, M. C. Otey, and J. P. Greenstein. Arch. Biochem. Biophys., 58, 253 (1955).

1048962

Table 1

Tissue Distribution of DL-Valine-1-^{11}C and DL-Valine-1-^{14}C in the Dog After Intravenous Administration.

Tissue	Commercial DL-Valine-1-^{14}C[a] (30 min postinjection)	DL-Valine-1-^{11}C Preparation (2 hr postinjection)
	Percent Administered Dose/g[b]	
Pancreas	0.100 ± 0.015	0.087
	Pancreas-to-Tissue Conc. Ratio	
Liver	6.36 ± 1.11	7.80
Spleen	8.64 ± 1.18	12.04
Kidney	4.65 ± 0.43	-
Lung	7.97 ± 0.75	-
Muscle	12.89 ± 1.56	-
Small intestine	4.39 ± 0.85	4.78
Marrow	11.99 ± 3.49	-
Blood	9.64 ± 0.42	14.79
Thymus	8.09 ± 1.18	-
Adrenal	5.73 ± 0.72	-
Urine	0.39 ± 0.14	-
Heart	8.80 ± 1.08	-
Lymph node	4.62 ± 0.89	-

[a] Average of 4 animals ± S.E.

[b] Normalized to a body weight of 10 kg.

1048963

Table 2

Tissue Distribution of DL-Valine-1-^{14}C and DL-Valine-1-^{11}C in the Rat at 30 Minutes Postinjection.

Tissue	Commercial DL-Valine-1-^{14}C[a]	DL-Valine-1-^{11}C Preparation
	Percent Administered Dose/g[b]	
Pancreas	6.47 ± 0.64	5.61
	Pancreas-to-Tissue Conc. Ratio	
Liver	9.8 ± 0.2	9.1
Spleen	12.5 ± 1.9	10.2
Kidney	12.0 ± 1.3	9.8
Lung	15.3 ± 1.8	14.7
Muscle	33.2 ± 5.2	26.8
Marrow	7.8 ± 0.6	9.2
Small intestine	5.7 ± 0.5	7.5
Blood	20.3 ± 4.0	29.1

[a] Average of 4 animals ± S.E.

[b] Normalized to a body weight of 250 g.

1048964

Table 3

Effect of Time on the Tissue Distribution of DL-Valine-1-^{14}C (0.021 mg/kg) in the Rat.

Tissue	Percent Administered Dose/g[a]		
	15 Min	30 min	60 min
Pancreas	5.84 ± 0.34	6.47 ± 0.64	6.86 ± 0.10
Liver	0.67 ± 0.02	0.66 ± 0.06	0.55 ± 0.01
Spleen	0.68 ± 0.03	0.54 ± 0.05	0.58 ± 0.03
Kidney	0.68 ± 0.03	0.54 ± 0.01	0.55 ± 0.01
Lung	0.54 ± 0.03	0.43 ± 0.01	0.35 ± 0.01
Muscle	0.24 ± 0.01	0.21 ± 0.03	0.16 ± 0.00
Marrow	0.77 ± 0.04	0.82 ± 0.03	0.81 ± 0.02
Small intestine	1.14 ± 0.04	1.14 ± 0.06	1.03 ± 0.07
Blood	0.46 ± 0.06	0.34 ± 0.03	0.27 ± 0.01

[a] Average of 4 animals ± S.E.; normalized to a body weight of 250 g.

1048965

Table 4

Effect of Carrier DL-Valine on the Tissue Distribution of DL-Valine-1-^{14}C in the Rat at 30 Minutes Postinjection.

Tissue	Pancreas/Tissue Conc. Ratio[a]		
	0.021 mg/kg	1.0 mg/kg	5.0 mg/kg
Liver	9.8 ± 0.2	9.7 ± 0.4	9.6 ± 0.6
Spleen	12.5 ± 1.9	10.1 ± 0.3	10.3 ± 0.6
Kidney	12.0 ± 1.3	9.7 ± 0.3	11.0 ± 0.6
Lung	15.3 ± 1.8	13.8 ± 0.6	15.3 ± 0.6
Muscle	33.2 ± 5.2	29.5 ± 2.0	27.9 ± 2.3
Marrow	7.8 ± 0.6	8.2 ± 0.6	8.1 ± 0.4
Small intestine	5.7 ± 0.5	4.5 ± 0.3	6.6 ± 1.6
Blood	20.3 ± 4.0	24.5 ± 1.2	24.5 ± 1.7

[a] Average of 4 animals ± S.E.

1048966

Table 5

Tissue Distribution of DL-Valine-1-^{14}C (0.027 mg/kg) in the Hamster at 30 Minutes Postinjection.

Tissue	Pancreas/Tissue Conc. Ratio[a]
Liver	13.0 ± 1.3
Spleen	10.6 ± 1.4
Kidney	6.8 ± 1.7
Lung	17.6 ± 2.2
Muscle	33.8 ± 4.3
Marrow	6.2 ± 0.2
Blood	23.3 ± 2.8
Small intestine	8.7 ± 1.6

[a] Average of 4 animals ± S.E.

1048967

Table 6

Tissue Distribution of DL-Valine-1-^{14}C (0.027 mg/kg) in the Rabbit at 30 Minutes Postinjection.

Tissue	Pancreas/Tissue Conc. Ratio[a]
Liver	4.7 ± 0.8
Spleen	3.1 ± 0.4
Kidney	3.2 ± 0.5
Lung	4.3 ± 0.7
Muscle	14.7 ± 1.8
Small intestine	2.3 ± 0.2
Marrow	6.0 ± 1.5
Blood	4.8 ± 0.7
Thymus	5.1 ± 1.0
Adrenal	4.3 ± 0.8
Heart	5.5 ± 0.8
Lymph node	3.6 ± 0.4

[a] Average of 4 animals ± S.E.

1048968

Table 7

Tissue Distribution of DL-Valine-1-^{14}C (0.021 mg/kg) at 30 Minutes Postinjection in Rats Bearing the Morris 5123C Hepatoma.

Tissue	Percent Administered Dose/g[a]
Tumor	0.79 ± 0.05
Pancreas	3.92 ± 0.40
Liver	0.65 ± 0.05
Spleen	0.88 ± 0.08
Kidney	0.67 ± 0.02
Lung	0.62 ± 0.06
Muscle	0.19 ± 0.01
Marrow	0.97 ± 0.05
Small intestine	1.28 ± 0.09
Blood	0.33 ± 0.01

[a] Average of 4 animals ± S.E.; normalized to a body weight of 250 g.

1048969

Table 8

Rate of Decarboxylation of DL-Valine-1-^{14}C and L-Valine-1-^{14}C by Male Buffalo Rats.

Time (min)	Cumulative Percent Exhaled as $^{14}CO_2$ [a]	
	DL-Valine-1-^{14}C	L-Valine-1-^{14}C
5	2.5	2.7
10	6.3	6.3
15	9.8	9.7
30	18.2	17.7
45	24.1	23.0
60	28.1	25.8
90	31.74	29.8
120	34.1	31.4

[a] Average of two animals.

1048970

Table 9

Total Metabolic Loss of DL-Valine-1-^{11}C by Male Fischer Rats as $^{11}CO_2$

Time (min)	% Administered ^{11}C Lost + S.E.
15	12.6 ± 1.2
30	27.1 ± 0.8
60	41.3 ± 1.1
90	44.5 ± 0.5
120	48.1 ± 1.0

1048971

Table 10

Estimated Radiation Dose From DL-Valine-1-^{11}C to Organs in Man.[a]

Tissue	Radiation Dose (rads)/50 mCi
Pancreas	4.00
Liver	1.10
Spleen	0.95
Kidney	1.20
Lung	0.85
Muscle	0.65
Small intestine	1.60
Bone marrow	0.65
Adrenal	1.15
Ovary	0.50
Testis	0.42

[a] Based on 30-minute tissue distribution in the dog following intravenous administration of DL-valine-1-^{14}C (0.027 mg DL-valine/kg) assuming no further change in distribution.

1048972

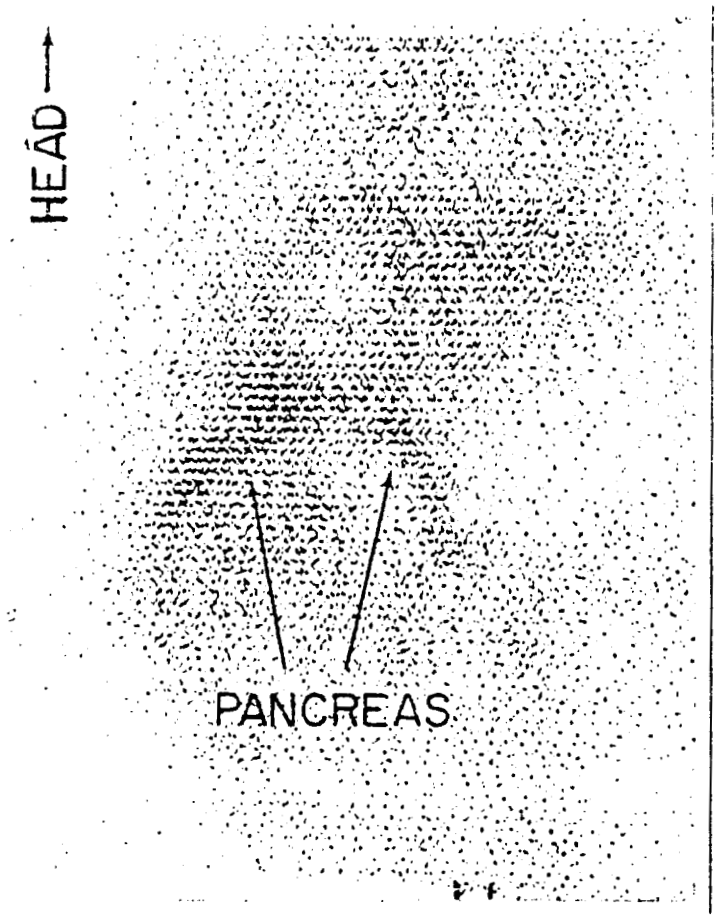


Fig. 1 Scan of a normal mongrel dog started 40 min after I.V. injection of DL-valine-1-^{11}C. Note visualization of pancreas that was obtained.

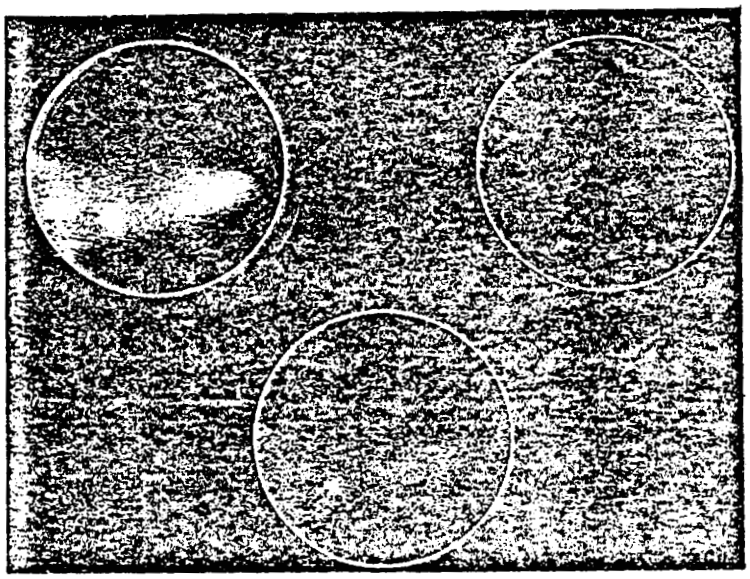


Fig. 2 Anger camera positron image of rat 30 min after administration of DL-valine-1-^{11}C.

1048973

APPENDIX

Chief Investigators:

G. A. Andrews, M.D.
R. L. Hayes, Ph.D.
K. F. Hübner, M.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

ORAU/ORNL Committee on Human Studies:

Gould A. Andrews, M.D. (Secretary)
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Donald W. Goodwin, Ph.D.
Minister, United Church
Chapel-on-the-Hill
Oak Ridge, Tennessee 37830

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Y-12 Area, Building 9704-2
Union Carbide Nuclear Company
P. O. Box Y
Oak Ridge, Tennessee 37830

Robert D. Lange, M.D. (Chairman)
Assistant Director
University of Tennessee
Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

1048974

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

Clarence C. Lushbaugh, Ph.D., M.D. (Ex officio)
Chairman, Medical & Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Joan B. Woods, M.D.
Psychiatrist
Oak Ridge Mental Health Center
Oak Ridge, Tennessee 37830

ORAU Medical Advisory Committee:

George B. Hutchison, M.D.
Professor of Epidemiology
Harvard University School of Public Health
55 Shattuck
Boston, Massachusetts 02115

John M. Johnston, Ph.D.
Department of Biochemistry
University of Texas Medical School
(Southwestern)
Dallas, Texas 75235

Leonard A. Sagan, Ph.D.
Internal Medicine, Research Administration
Associate Director, Dept. of Environmental Medicine
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Professor of Genetics
University of Wisconsin
Madison, Wisconsin 53706

Joseph F. Volker, Ph.D. (Ex officio member from the ORAU Board of Directors)
President
University of Alabama
Birmingham, Alabama

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews
Position:	Internist, Director of Clinical Applications
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association
Other Indication of Experience and Competence:	Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name:	Donald W. Goodwin
Position:	Minister, United Church, Chapel-on-the-Hill
School:	Bangor Theological Seminary, Bachelor of Divinity, 1959 Brown University, Ph.D., 1965
Memberships:	Ministerial Standing, United Church of Christ
Additional Information:	Member of various boards which change from time to time

Name:	R. L. Hayes
Position:	Director of Radiopharmaceutical Development, Chief Scientist
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U.S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

1048976

Name:	George B. Hutchison
Position:	Epidemiologist, Michael Reese Hospital, Chicago, 66-present
Schools:	Harvard University, A.B., 1943 Harvard University, M.D., 1951 Harvard University, M.P.H., 1960
Positions:	Fel. med. Lahey Clin., 52-55; asst. med. dir. Equitable Life Assurance Soc., U.S., 55-56; Health Ins. Plan Greater New York, 56-57; dir. res. City Health Dept., New York, 57-59; asst. prof. epidemiol. sch. pub. health, Harvard, 60-61; assoc. prof. 61-66; consult, Health Ins. Plan Greater New York, 57-present.
Memberships:	Fel. Am. Pub. Health Asn; Am. Statist. Asn; World Med. Asn.; Asn. Teachers Prev. Med.

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name:	John Marshall Johnston
Position:	Professor of Biochemistry, University of Texas (Southwest) Med. School, Dallas, 1966-present
Schools:	B.A., Hastings Colorado, 1949; Ph.D., Colorado, 1953
Postions:	Res. Assoc., Walter Reed Inst. Res. 53-55; Asst. Prof., Univ. of Texas (Southwest) Medical School, Dallas, 55-57; Assoc. Prof. 57-60; Professor 60-66; Nat. Sci. Found. Sr. Res. Fel., Univ. Lund, 62-63; U.S.A.R. 53-55
Memberships:	AAAS; Am. Chem. Soc.; Soc. Exp. Biol. & Med.; Am. Soc. Biol. Chem.

1048977

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961. Admitted to practice of law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A., 1941 Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association for the Advancement of Science; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry), 1946; University of Minnesota, Minneapolis, Minnesota, B.S., 1949; M.D., 1950 Rotating Internship, Ancker Hospital, St. Paul, Minnesota, 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination, June 5, 1963
Memberships:	Fellow Industrial Medical Association; Past President, Tennessee Industrial Medical Association; American Academy of Occupational Medicine; American Medical Association; Past President, Roan-Anderson County Medical Society; Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Chairman, Medical and Health Sciences Division, ORAU Director, Radiation Emergency Assistance Center/Training Site (REAC/TS)
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; American Society for Experimental Pathology; Associated Researchers and Clinicians in Cancer; Society for Experimental Biology and Medicine; Health Physics Society; Radiation Research Society; Society of Nuclear Medicine; American Medical Association; Tennessee State Medical Society

1048978

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fellow American College of Physicians
Interests:	Late effects of radiation

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; American Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name:	John B. Storer
Position:	Director, Biology Division, Oak Ridge National Laboratory
School:	University of Chicago, M.D., 1947
Memberships:	American Association for Cancer Research; American Society for Experimental Pathology; Radiation Research Society; Society for Experimental Biology and Medicine; National Council on Radiation Protection and Measurements

Name:	Joseph F. Volker
Position:	President, University of Alabama, Birmingham, Alabama
Schools:	Indiana University, D.D.S., 1936 University of Rochester, A.B., 1938 University of Rochester, M.S., 1939 University of Rochester, Ph.D., 1942 Univ. Med. Sci., Bankok, hon. D.Sc., 1967 Univ. Lund, hon. Dr. Ontol., 1968 University of Alabama, hon. D.Sci., 1970 Indiana Univ., hon. D. Sci., 1970 Louis Pasteur Univ., hon. Dr., 1972
Memberships:	Mem. Unitarian Med. Teaching Mission, Czech., 1946, Ger., 1948 Specialist, U. S. Dept. State, Thailand, 1951-. Dir. Arizona Med. Sch. Study, 1960-1961 Mem. Inst. Med. Nat. Acad. Sci., 1971 Mem. Order of White Lion, Czech, 1946 Comdr., Order of Crown, 1959 Fel. Royal Col. Surg., 1961 Comdr., Order of Falcon, Repub. Iceland, 1969 AAAS; Soc. Expl. Biol. and Med.; Int. Assn. Dent. Res.

1048979

Name:	Lee Cross Washburn
Position:	Associate Scientist, Medical and Health Sciences Division Oak Ridge Associated Universities
Schools:	Murray State University, B.A., 1968 Vanderbilt University, 1972
Membership:	American Chemical Society
Interests:	Synthetic organic chemistry; chromatography, radiopharmaceutical tissue distribution studies; radioprotective drugs

Name:	Bruce W. Wieland
Position:	Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools:	Iowa State University, B.S., 1960 Ohio State University, Ph.D., 1973
Membership:	Society of Nuclear Medicine
Interests:	Production and utilization of short-lived positron-emitting isotopes for nuclear medical applications. Development of hot cell equipment for the synthesis of labeled compounds. Isotope imaging instrumentation, including coincidence detection and computer reconstruction techniques for tomography.

Name:	Joan B. Woods
Position:	Psychiatrist, Oak Ridge Mental Health Center
School:	University of Chicago School of Medicine, B.S. and M.D., 1960
Licensure:	Tennessee
Boards:	American Board of Psychiatry and Neurology
Memberships:	American Psychiatric Association American Medical Association and Subsidiaries

1048980

MEDICAL AND HEALTH SCIENCES DIVISION
OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon _____
(myself or name of patient)
of the following test: Phase I radiopharmaceutical tests of DL-valine-1-^{11}C for pancreas visualization.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes. Further, I understand that any information gained from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Medical and Health Sciences Division, Oak Ridge Associated Universities.

DATE_____ _____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: DL-Valine-1-^{11}C.
2. The drug contains the radioactive isotope ^{11}C and an organic chemical in quantities much less than those required to produce any measurable chemical effect in the body. Patient should feel no effect from the drug.
3. The radiation dose will be approximately 0.25-0.5 rad to the whole body.
4. Blood samples (2 ml) will be drawn at intervals during a period of 1-1/2 hours after administration.
5. Whole body counts and scans will be made over a 2-hr period.
6. The patient may withdraw from the test at any time.

DATE:_____ _____
Investigator

1048981

FORM P-4

MEMORANDUM

TO Mr. Jim Berger, Dr. Ray Hayes
Dr. Karl Hübner, Dr. Don Swartzendruber

DATE March 10, 1976

SUBJECT Meeting of Medical Radionuclide Committee

COPIES TO File

Attached you will find three proposals for consideration by the Medical Radionuclide Committee. Please look them over and let me know if you have any questions.

I will call a meeting of the Committee during the week of March 15, 1976, for formal consideration of these proposals.

William D. Gibbs

William D. Gibbs

WDG:dgb

CALL EVELYN ABOUT FDA APPROVAL FOR ORAL IF IF 75 52 PACKAGE INSERT FROM EVELYN.

NOT APPROVED
NEEDS IND

1048982

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. Karl Hübner PROPOSAL NO. 76-4

DESCRIPTION: Flourine-18 as flouride ion in saline solution. Oral administration for skeletal imaging. The dose will not exceed 4 millicuries in accordance with the attached package insert.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patient.

Other: Radiopharmaceutical to be administered in accordance with package insert supplied with the radiopharmaceutical. ~~Physicians may not administer more than twice the normally recommended activity without specific approval of the Medical Radionuclide Committee.~~

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William R. Bibbo	✓			April 9, 1976
[illegible]	✓			4/9/76
[illegible]	✓			4/9/76
KARL HUBNER	NOT	VOTING		
RAYMOND HAYES			✓	

Acknowledgement of Submitter Karl F. Hübner Date 4/9/76

- -

Proposal does ___ does not ___ require approval of Committee on Human Studies.

1048983

Fluorine 18

^{18}F) as Fluoride Ion in Saline Solution

Package Insert Information

Description

This solution contains no-carrier-added fluorine-18 as the fluoride ion in isotonic sodium chloride solution. The ^{18}F is produced by bombardment of neon gas by deuterium particles accelerated in a cyclotron. The nuclear reaction is ^{20}Ne(d, α) ^{18}F. The product is essentially carrier free; the only known source of nonradioactive fluoride ion present is that found in the distilled water and saline solutions used in preparing this product.

Actions (Clinical Pharmacology)

Following its intravenous administration ^{18}F fluoride rapidly equilibrates, primarily within the extracellular fluid space, from where it is rapidly cleared by deposition in bone and excretion into urine. Deposition of ^{18}F fluoride in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the ^{18}F from the blood perfusing the bone.[1]

Fluoride ions do not appear to be bound to serum proteins, and the clearance of ^{18}F from the blood is rapid.[2]

In patients with normal renal function, 20% or more of the ^{18}F is cleared from the body in the urine within the first two hours after its intravenous administration.[2] Subsequently, small amounts of ^{18}F continue to be excreted in the urine further diminishing ^{18}F activity in soft tissues of the body.

^{18}F normally accumulates in the skeleton in a symmetrical fashion, and with greater deposition in the axial skeleton (e.g., vertebrae and pelvis) than in the appendicular skeleton and in bones around joints than in the shafts of long bones. Increased deposition around joints can occur in arthritis and following trauma and increased deposition in bone has been noted around fracture sites, in osteomyelitis, fibrous dysplasia, spondylitis tuberculosa, Paget's disease, hyperostosis frontalis interna, myositis ossificans and in rapidly growing epiphyses. The tendency for ^{18}F to accumulate in the vicinity of primary and metastatic malignancy in bone has proven clinically useful in detection of such lesions.[3-10]

Indications

^{18}F is used as a bone imaging agent to define areas of altered osteogenic activity.

Contraindications

None.

Warnings

^{18}F should not be administered to pregnant women, those liable to be pregnant, in lactation, or in patients under 18 years of age unless the benefits to be gained outweigh the risks. Radiopharmaceuticals produced in a nuclear reactor or particle accelerator should be used only by physicians who are qualified by specific training in the safe use in handling of radioisotopes and whose experience and training has been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Precautions

The patient should be encouraged to drink fluids immediately before and following administration of the ^{18}F preparation. To minimize radiation dose to the bladder, the patient should void one-half hour after administration of the ^{18}F and as often thereafter as is possible. Voiding immediately prior to imaging ^{18}F distribution in the pelvis is recommended. In the use of any radiopharmaceutical care should be taken to insure minimum radiation exposure to patient and all personnel involved in the procedure by using the smallest dose of radioactivity consistent with safety and relative value of diagnostic information.

Adverse Reactions

No adverse reactions were noted in over 400 patient studies reported in the medical literature.

For the skeleton absorbed radiation dose may be calculated assuming uniform distribution of activity within the skeleton, that the skeleton is a 7000 gram ellipsoid and that 100% of administered radioactivity is retained in this organ. For gamma rays $\Delta_i = (2.13)(1.94)(0.511) =$

$$2.11 \frac{\text{gram-rad}}{\mu\text{Ci-hrs.}}$$

$\phi_i = 0.130$ (assuming 5% backscatter)

$\tilde{A}_i = 10.56 \times 10^3\ \mu$Ci-hr. (for 4 mCi)

$$D_\gamma(v \leftarrow v) = \left(\frac{10.56 \times 10^3\ \mu\text{Ci-hr}}{7000\ \text{gram}}\right)\left(0.274 \frac{\text{gram-rad}}{\mu\text{Ci-hr.}}\right)$$

$D_\gamma(v \leftarrow v) = 0.41$ rad to skeleton

For positrons, $\Delta_i = (2.13)(0.97)(0.250) = 0.517 \frac{\text{gram-rad}}{\mu\text{Ci-hr.}}$

$\phi_i = 1$ and $\Delta_i\phi_i = 0.517 \frac{\text{gram-rad}}{\mu\text{Ci-hr.}}$

(since w_K and w_L are very small, K-radiation, L-radiation and Auger electrons from L and M shells are negligible).

$$\bar{D}_\beta(v \leftarrow v) = \left(\frac{10.56 \times 10^3}{7000}\right)(0.517)$$

$$= 0.79 \text{ rad to skeleton}$$

$\bar{D}_{\beta+\gamma}$ (skeleton) $= 0.41 + 0.79 = 1.20$ rads for 4 mCi of ^{18}F.

Assuming 100% retention and uniform distribution of activity in the whole body (assuming whole body is a 70,000 gram ellipsoid) the whole body radiation dose from 4 mCi of ^{18}F can be calculated as follows:

For gamma rays:

$$\Delta_i\phi_i = (2.11)(0.341) = 0.720 \frac{\text{gram-rad}}{\mu\text{Ci-hr}}$$

$$\bar{D}_\gamma(v \leftarrow v) = \left(\frac{10.56 \times 10^3}{70{,}000}\right)(0.720) = 0.11 \text{ rads}$$

$$\bar{D}_\beta(v \leftarrow v) = \left(\frac{10.56 \times 10^3}{70{,}000}\right)(0.517) = 0.08 \text{ rads}$$

$\bar{D}_{\beta+\gamma}$ (whole body) $= 0.11 + 0.08 = 0.19$ rads for 4 mCi of ^{18}F.

How Supplied

^{18}F as the fluoride ion in isotonic saline solution at ph 6-8, prepared by appropriate manufacturing procedures to be sterile and pyrogen free.

Calibration Chart

Time	Specific Concentration of ^{18}F (mCi/ml)
2 hours before calibration	4.20
1½ hours before calibration	3.49
1 hour before calibration	2.90
½ hour before calibration	2.41
Calibration Time	2.00
½ hour after calibration	1.66
1 hour after calibration	1.38
1½ hours after calibration	1.15
2 hours after calibration	.95
2½ hours after calibration	.79
3 hours after calibration	.66
3½ hours after calibration	.55
4 hours after calibration	.45
4½ hours after calibration	.36
5 hours after calibration	.31
5½ hours after calibration	.26
6 hours after calibration	.22

1048984

1048985

Dosage

The dose of ^{18}F used in a given patient should be minimized consistent with the objectives of the study, and the nature of the radiation detection devices employed. Satisfactory studies have been reported following administration of between 0.5 and 2.0 mCi of ^{18}F activity administered intravenously. However, it has been estimated that use of even 4.0 mCi of ^{18}F results in a calculated whole body radiation dose one-sixth of that associated with the use of approximately 100 μCi of ^{85}Sr. It is recommended that the dose of ^{18}F used in a given study not exceed 4 mCi. The patient should be instructed to ingest copious amounts of fluid immediately prior and subsequent to the administration of ^{18}F. The patient should void one-half hour after administration of ^{18}F and as frequently thereafter as possible. Imaging of the ^{18}F can begin one to two hours after administration of the ^{18}F, however, the longer the imaging procedure is delayed, the greater will be the ratio of activity in bone to that in soft tissue. The patient should be instructed to void immediately prior to imaging the ^{18}F activity in the lumbar spine or bony pelvis.

In the past, ^{18}F has been most commonly administered intravenously. However, some investigators have reported satisfactory results following oral administration.

Dosimetry

^{18}F decays with a physical half-life of 109.7 minutes (1.828 hrs.). 97% of the decay results in emission of a positron with a maximum energy of 0.635 MeV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The bone and bone marrow are considered the target and critical organs and the absorbed radiation dose to these organs and the whole body can be calculated using the absorbed fraction method using the following equation:

$$\bar{D}(v \leftarrow v) = \frac{\bar{A}_v}{m_v} \sum_i D_i \phi_i (v \leftarrow v)$$

References

1. D. Van Dyke, H. O. Anger, Y. Yano and C. Bozzini, "Bone Blood Flow Shown with ^{18}F and the Positron Camera." Am. J. Physiology, 209, 64 (1965).

2. D. A. Weber, E. J. Greenberg, A. Dimich, P. J. Kenny, E. O. Rothschild, W. P. L. Myers and J. S. Laughlin, "Kinetics of Radionuclides used for Bone Studies," J. Nuclear Med. 10, 8 (1969).

3. C. L. Harmer, J. E. Burns, A. Sams and M. Spittle, "The Value of ^{18}F for Scanning Bone Tumors," Clin. Radio., 20, 204 (1969).

4. H. J. Dworkin and E. V. Filmanowicz, "Radiofluorine Photoscanning of Bone for Reticulum Cell Sarcoma: Early Detection of Bone Involvement." J. Amer. Med. Assoc. 198, 985 (1966).

5. H. G. Kampffmeyer, H. Dworkin, E. A. Carr, and F. E. Bull, "Effect of Drug Therapy on the Uptake of Radioactive Fluorine by Osseous Metastases." Clin. Pharmacol. Ther., 8, 657 (1967).

6. R. Spencer, R. Herbert, M. W. Rish, and W. A. Little, "Bone Scanning with ^{85}Sr, ^{87m}Sr and ^{18}F. Physical and Radiopharmaceutical Considerations and Clinical Experience in 50 Cases." Brit. J. Radiol. 40, 641 (1967).

7. L. R. Holsti and L. K. Patomaka, "^{18}F Scanning of Primary and Metastatic Bone Tumors." Ann. Med. Intern. Fenn. 56, 131 (1967).

8. R. J. French and V. R. McReady, "Use of ^{18}F for Bone Scanning," Brit. J. Radiol. 40, 655 (1967).

9. N. F. Moon, H. J. Dworkin and P. D. La Fleur, "The Clinical Use of Sodium Fluoride ^{18}F in Bone Photoscanning," J. Amer. Med. Assoc. 204, 974 (1968).

10. P. Ronai, H. S. Winchell and H. O. Anger, "Skeletal Survey for Metastatic Tumors of Bone Using ^{18}F and ^{85}Sr with Scintillation Camera and Whole Body Scanner," J. Nuclear Med. 9, 517 (1968).

medi-physics

5855 Christie Avenue
Emeryville
California 94106

Radiation Dose from ^{18}F- oral administration

rad/millicurie administered

total body	stomach	small intestine	upper large intestine	lower large intestine	bone	marrow	ovaries	tes
.047	1.0	0.35	0.37	0.082	0.15	0.063	0.056	0.0

2-24-76

Radiopharmaceutical Internal Dosimetry Center

1048986

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. Karl Hübner PROPOSAL NO. 76-4

DESCRIPTION:
^{131}I sodium rose bengal in sterile solution for injection for determination of liver function and liver imaging. The usual dose will range from 25 to 200 microcuries; not to exceed 3 microcuries per kilogram of body weight.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William D. Bible	✓			4 June, 1976
[illegible]	✓			4 June, 1976
[illegible]	✓			June 4, 1976
Karl Hubner	NOT VOTING			
R. HAYES			✓	

Acknowledgement of submitter Karl F. Hübner Date June 4 1976

Proposal does____ does not ✓ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048987

Mallinckrodt NUCLEAR

TECHNICAL PRODUCT DATA

MALLINCKRODT, INC. • ST. LOUIS, MO. 63147

This radiopharmaceutical is licensed by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to Sections 35.14 and 35.100 Groups I and II of 10 CFR Part 35 or under equivalent licenses of Agreement States.

SODIUM ROSE BENGAL I 131 INJECTION

DESCRIPTION

Sodium Rose Bengal I 131 Injection is a sterile, pyrogen-free aqueous solution containing 0.03% sodium chloride, 0.9% benzyl alcohol as a preservative, and approximately 0.1% sodium biphosphate and 0.4% sodium phosphate as buffers. Sodium hydroxide or hydrochloric acid may be present for pH adjustment.

ACTIONS

Following parenteral administration, sodium rose bengal I-131 accumulates in the polygonal cells of the liver and is excreted via the biliary system primarily into the intestines. With marked impairment of liver function sodium rose bengal I-131 is excreted via the kidneys.

INDICATIONS

Sodium Rose Bengal I 131 Injection is indicated as a diagnostic aid in determination of the liver function and liver imaging.

CONTRAINDICATIONS

None.

WARNINGS

This radiopharmaceutical agent should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs the potential hazards.

1048988

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 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.

PRECAUTIONS

Administration of a laxative after the procedure will minimize the radiation absorbed dose.

As in the use of any other 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.

ADVERSE REACTIONS

To prevent possible photosensitivity, patients who have received large doses of rose bengal, particularly "blocking doses" for imaging should be instructed to avoid direct sunlight or ultraviolet light for 24 hours. Patients should also be aware of the possibility of coloration of their stools from the dye. The use of this type of preparation should be carefully considered in patients known to be sensitive to iodides, although no acute allergic reactions have been reported.

DOSAGE AND ADMINISTRATION

Sodium Rose Bengal I 131 Injection is administered intravenously for both liver function tests and liver imaging.

For liver function test, the usual dose is 10-25 microcuries.

For liver imaging, the usual dose for the average patient (70 kg) is 1.0-3.0 microcuries per kilogram of body weight. To retard the excretion rate, a blocking dose (100 mg) of non-radioactive rose bengal may be given intravenously about 10 minutes prior to starting the procedure.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Iodine-131 decays by beta and gamma emissions with a physical half-life of 8.05 days.[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. 26, 1969.

Table I. Principal Radiation Emission Data

Radiation	*Mean Percent Per Disintegration*	*Mean Energy (keV)*
Beta-1	1.6	70.1
Beta-2	6.9	95.5
Beta-4	90.4	191.7
Gamma-6	83.3	364.5

The specific gamma ray constant for iodine-131 is 2.2 R/mCi-hr at 1 cm. The half-value layer is 3 mm of Pb.

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

Table II. Physical Decay Chart; Iodine-131, half-life 8.05 days

Days	*Percent Remaining*	*Days*	*Percent Remaining*	*Days*	*Percent Remaining*
-7	182.	7	54.8	19	19.5
-5	153.	8	50.2	20	17.9
-3	129.	9	46.1	21	16.4
-2	118.	10	42.3	22	15.0
-1	108.	11	38.9	23	13.8
0*	100.	12	35.6	24	12.7
1	91.8	13	32.6	25	11.6
2	84.2	14	29.9	26	10.7
3	77.2	15	27.5	27	9.8
4	70.8	16	25.2	28	9.0
5	65.0	17	23.1	29	8.2
6	59.6	18	21.2	30	7.6

* *Calibration day*

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to an average patient (70 kg) from an intravenous injection of a maximum dose of 210 microcuries of sodium rose bengal I-131 are shown in Table III.

[2] Method of Calculation: A Schema for Absorbed Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, *J. Nucl. Med.*, p. 7, 1968.

1048989

Table III. Radiation Doses

Tissue	*Absorbed Radiation Dose (rads/210 μCi)*
Liver	0.25
Testes	0.044
Ovaries	0.045
Whole-body	0.08

HOW SUPPLIED

Catalog Number

110 Sodium Rose Bengal I 131 Injection is available at a concentration of approximately 100 microcuries/milliliter and a specific activity of approximately 300 microcuries/milligram as of the time of standardization.

1048990

```
RADIONUCLIDE? I-125
SHIELDING MATERIAL? LEAD
DENSITY? 11.35
INPUT ENERGY,FRACT/DECAY,U(LEAD)? .0355,.0678,18.7
FOR .0355 MEV, U(A) IS? 11.4
INPUT ENERGY,FRACT/DECAY,U(LEAD)? .0275,.738,37
FOR .0275 MEV, U(A) IS? 28
INPUT ENERGY,FRACT/DECAY,U(LEAD)? .03-F7----
MORE? .0272,.378,37
FOR .0272 MEV, U(A) IS? 28
INPUT ENERGY,FRACT/DECAY,U(LEAD)? .031,.199,29
FOR .031 MEV, U(A) IS? 18
INPUT ENERGY,FRACT/DECAY,U(LEAD)? .0318,.0413,28
FOR .0318 MEV, U(A) IS? 17
INPUT ENERGY,FRACT/DECAY,U(LEAD)? -1,0,0

SPEC. GAMMA CONSTANT FOR I-125 IS .1586445 MR/HR-MCI AT 1 METER

EXP. RATE          CM LEAD
 .1317245          5.000000E-4
 .126546           6.000000E-4
 .1215737          7.000000E-4
 .1167993          8.000000E-4
 .1122149          9.000000E-4
 .1078127          1.000000E-3
 .1035856          1.100000E-3
 .09952639         1.200000E-3
 .09562847         1.300000E-3
 .09188533         1.400000E-3
 .08829077         1.500000E-3
 .08483884         1.600000E-3
 .08152381         1.700000E-3
 .07834022         1.800000E-3
 .07528279         1.900000E-3
 .07234648         2.000000E-3
 .06952644         2.100000E-3
 .06681802         2.200000E-3
 .06421676         2.300000E-3
 .06171837         2.400000E-3
 .05931873         2.500000E-3
 .05701392         2.600000E-3
 .05480013         2.700000E-3
 .05267374         2.800000E-3
 .05063125         2.900000E-3
 .04866931         3.000000E-3
 .04678472         3.100000E-3
 .04497439         3.200000E-3
 .04323536         3.300000E-3
```

0.00175 cm or 0.0175 mm 1st

1048991

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 76-5

DESCRIPTION:

Selenium-75 Selenomethionine in sterile solution for injection for pancreas imaging. Dose will be not more than 3.5 microcuries per kilogram of body weight (not to exceed 250 microcuries). Administration will be by intravenous injecton.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Fitts	✓			4 June, 1976
W. C. Swartzendruber	✓			4 June, 1976
[illegible]	✓			June 4, 1976
Karl Hubner	NOT VOTING			
R. Hayes			✓	

Acknowledgement of submitter Karl F. Hubner Date June 4, 1976

Proposal does___ does not ✓ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1048992

Mallinckrodt® NUCLEAR

TECHNICAL PRODUCT DATA

MALLINCKRODT, INC. ● ST. LOUIS, MO. 63147

160

This radiopharmaceutical is licensed by the U.S. Atomic Energy Commission for distribution to persons licensed pursuant to Sections 35.14 and 35.100 Group II of 10 CFR Part 35 or under equivalent licenses of Agreement States. B

4/74

SELENOMETHIONINE Se 75 INJECTION

DESCRIPTION

Selenomethionine Se 75 Injection is supplied as a sterile non-pyrogenic aqueous solution containing 0.9% benzyl alcohol as a preservative. The solution is made isotonic with sodium chloride and may contain hydrochloric acid or sodium hydroxide for pH adjustment.

ACTIONS

Selenomethionine is an analog of the essential amino acid, methionine, in which the sulfur atom is replaced by a selenium atom. After intravenous administration, Selenomethionine Se 75 is localized in all organs involved in active protein synthesis and is incorporated into newly synthesized proteins. A relatively high degree of uptake is found in the pancreas and is related to rapid rate of synthesis of digestive enzymes in this organ. The peak of pancreatic activity is observed within the first half hour after intravenous administration. Significant uptake also occurs in the liver and proximal small intestine, as well as several other tissues.

INDICATIONS

Selenomethionine Se 75 is indicated for pancreas scanning as an aid in the diagnosis of suspected pancreatic disease.

CONTRAINDICATIONS

None.

1048993

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or during lactation unless the information to be gained outweighs 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.

The transplacental transport and long biologic half-time of this agent may result in significant radiation exposure to the fetus. Since Selenomethionine Se 75 is secreted in milk during lactation, formula feeding should be substituted.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by 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.

PRECAUTIONS

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

Fasting prior to administration of Selenomethionine Se 75 may enhance hepatic uptake of the agent which may result in degradation of pancreatic image quality.

ADVERSE REACTIONS

Adverse reactions have not been reported following the administration of Selenomethionine Se 75 Injection.

DOSAGE AND ADMINISTRATION

The suggested dose range of Selenomethionine Se 75 for imaging of the pancreas is 125 to 250 microcuries (1.8 to 3.5 μCi/kg of body weight) administered intravenously.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Selenium-75 decays by electron capture with a physical half-life of 120 days [1] The primary gamma energy is 265 keV.

[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. 20. 1969

Table I. Principal Radiation Emission Data

Radiation	*Mean percent per disintegration*	*Mean Energy (keV)*
Gamma-4	16.4	121.1
Gamma-5	55.5	135.9
Gamma-7	58.6	264.5
Gamma-8	25.2	279.5
Gamma-10	13.0	400.5
Kax-rays	47.5	10.5

The specific gamma ray constant for selenium-75 is 2.0 R/mCi-hr at 1 cm. The half-value layer is 3 mm of Pb.

To correct for radioactive decay of selenium-75, the percentages that remain at selected time intervals before and after the date of calibration are shown in Table II.

Table II. Physical Decay Chart; selenium-75, half-life 120 days.

Days	*% Remaining*	*Days*	*% Remaining*
-10	105.9	60	70.7
- 5	102.9	65	68.7
0*	100.0	70	66.8
5	97.2	75	64.9
10	94.4	80	63.0
15	91.7	85	61.2
20	89.1	90	59.5
25	86.6	95	57.8
30	84.1	100	56.2
35	81.7	105	54.5
40	79.4	110	53.0
45	77.1	115	51.5
50	74.9	120	50.0
55	72.8	125	48.6

* *Calibration Day*

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to an average 70 kg patient from an intravenous injection of a maximum dose of 250 microcuries of Selenomethionine Se-75 are shown in Table III.

[2] Modified from: Summary of Current Radiation Dose Estimates to Humans from ^{75}Se-L-Selenomethionine. *J. Nucl. Med.*, *14*, No. 1, p. 19, January 1973.

1048994

Table III. Radiation Doses

Tissue	*Absorbed Radiation Dose ±s.d.*
	(rads/250 μCi)
Blood	2.25 ± 0.25
Kidney (l)	5.25 ± 0.75
Kidney (r)	5.75 ± 0.75
Liver	6.25 ± 1.0
Ovaries	1.25 ± 0.25
Pancreas	3.00 ± 0.5
Spleen	4.00 ± 0.5
Testes	2.75 ± 0.5
Thyroid	1.50 ± 0.25
Whole-body	2.00 ± 0.25

HOW SUPPLIED

Catalog
Number

160 Selenomethionine Se 75 Injection. Available at a concentration of approximately 100 microcuries per milliliter in vials containing 250 microcuries and 1000 microcuries (1 millicurie).

Mallinckrodt NUCLEAR

MALLINCKRODT, INC. • ST. LOUIS, MO. 63147

1048995

mird / DOSE ESTIMATE REPORT NO. 1

SUMMARY OF CURRENT RADIATION DOSE ESTIMATES TO HUMANS FROM ^{75}Se-L-SELENOMETHIONINE

January 1973

SUMMARY OF ESTIMATED ABSORBED DOSES FROM A SINGLE INTRAVENOUS ADMINISTRATION OF ^{75}Se-L-SELENOMETHIONINE (*1*)

Tissue	Absorbed dose* (mrad/μCi ^{75}Se injected)
Blood (whole)	9 ± 1
Kidney (left)	21 ± 3
Kidney (right)	23 ± 3
Liver	25 ± 4
Ovaries	5 ± 1
Pancreas	12 ± 2
Spleen	16 ± 2
Testes	11 ± 2
Thyroid	6 ± 1
Total body	8 ± 1

* Calculated value ±1 s.d. The standard deviation was computed from standard deviations of the cumulated activities and the coefficients of variation of the absorbed fractions.

This report summarizes the contents of MIRD Pamphlet 9 entitled "Radiation Dose to Humans from ^{75}Se-L-Selenomethionine" (*1*).

RADIOPHARMACEUTICAL

Selenium-75-L-selenomethionine can be produced by chemical or biological synthesis. When intravenously administered, the method of preparing the compound does not influence the total-body retention of ^{75}Se administered as L-selenomethionine.

NUCLEAR DATA

The nuclear data are given in Table 1.

TABLE 1. NUCLEAR DATA

Radionuclide	^{75}Se	
Physical half-life	120 days	
Decay constant	0.000240 hr^{-1}	
Mode of decay	Electron capture	
Principal photons:	E_i (MeV)	n_i
E_i, energy	0.0106	0.541
n_i, mean number/dis	0.1211	0.164
	0.1359	0.555
	0.2645	0.586
	0.2795	0.252
	0.4005	0.130

* Photons with a mean number of photons per disintegration of greater than 0.05 are listed. See Ref. 2, p. 20 for complete compilation.

BIOLOGICAL DATA

Six institutions contributed data collected from 40 subjects of whom ten were normal controls, seven had parathyroid adenoma, twelve had various types of carcinoma, and eleven had miscellaneous or unspecified diseases.

Of the total administered ^{75}Se, corrected for radioactive decay, the excretion is estimated to be 80% in the urine, 15% in the feces, 4% via hair, nails, and skin, and 1% via expired air. These estimates are based on measurements of these substances as well as on total-body counting measurements. Quantitative urinary and fecal excretion recoveries were obtained in five patients for periods up to 12 days. Total-body retention data obtained from measurements of 24 patients in total-body counters were supplied by four institutions. Three of the 24 subjects were counted for less than 3 days, and the

TABLE 2. BIOLOGICAL PARAMETERS DESCRIBING THE DISTRIBUTION FOR ^{75}Se FROM A SINGLE INTRAVENOUS ADMINISTRATION OF ^{75}Se-L-SELENOMETHIONINE*

	Biological disappearance constants, λ_j (hr^{-1})		
	$\lambda_1 = 0.0523$	$\lambda_2 = 0.00063$	$\lambda_3 = 0.00013$
	Fraction of administered ^{75}Se activity per organ†		
Tissue	f_1	f_2	f_3
Blood‡	0.065	0.086	0.035
Fat	0.	0.020	0.024
Renal cortices (2)	0.	0.021	0.00078
Renal medullae (2)	0.010	0.0054	0.00074
Liver	0.092	0.14	0.0099
Lungs (2)	0.0040	0.029	0.0027
Muscle	0.20	0.	0.25
Ovaries (2)	0.	0.00018	0.00004
Pancreas	0.0060	0.00067	0.00021
Skin	0.031	0.055	0.0067
Spleen	0.0048	0.0093	0.00048
Testes (2)	0.	0.00076	0.00016
Thyroid	0.	0.00040	0.00026
Total body	0.14	0.44	0.42

* Adapted from Table B-1, p. 25 of Ref. 1.
† The organ masses of MIRD Pamphlet No. 5 were used (3).
‡ Two additional components are required to describe the distribution of ^{75}Se in blood. These components are $f_4 = 0.211$, $\lambda_4 = 5.64$ hr^{-1}, and $f_5 = -0.205$, $\lambda_5 = 0.636$ hr^{-1}; p. 14, Ref. 1.

Reprinted from the JOURNAL OF NUCLEAR MEDICINE, January, 1973, Volume 14, Number 1, Pages 49 - 50 and October, 1973, Volume 14, Number 10, Pages 755 - 756.

1048996

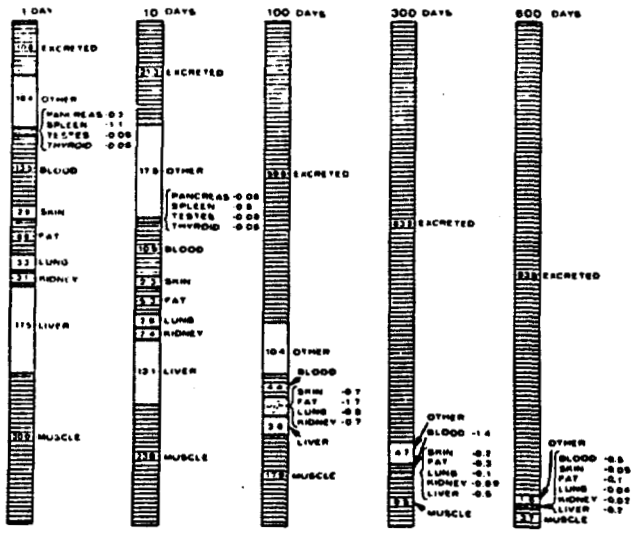


FIG. 1. Estimated percent of injected ^{75}Se, corrected for radioactive decay, in organs of body at various times after single intravenous injection of ^{75}Se-L-selenomethionine (*1*).

remaining subjects had the last count made between 64 and 923 days. Based on the total-body retention and excretion measurements, 13.1 ± 2% ("best fit" parameter ± standard deviation) of the injected ^{75}Se has a biological half-time of 0.55 ± 0.12 days, 44.3 ± 7% has a biological half-time of 46 ± 11 days, and 41.9 ± 8% has a biological half-time of 220 ± 31 days.

Calculations based on ^{75}Se in whole blood, plasma, and red blood cells were made using data obtained from three patients studied up to 466 days which agreed well with previously published reports from several investigators. The concentration of ^{75}Se was determined in 128 specimens of tissues from 23 patients collected at four laboratories either at surgery or autopsy over an interval between 0.02 and 361 days. All tissue data were normalized to 70-kg body weight. Figure 1 summarizes the estimated distribution of ^{75}Se in various organs of the body at 1, 10, 100, 300, and 600 days after the intravenous injection of ^{75}Se-L-selenomethionine. The "other" category indicated in Fig. 1 represents approximately 20% of the body mass and consists of organs for which tissue samples were not taken.

ABSORBED-DOSE ESTIMATES

The cumulated activity used to calculate the doses to specific organs is based on the fraction of the administered ^{75}Se deposited in the organ, f_j, and the biological disappearance constants, λ_j, for the tissues listed in Table 2. The same three biological elimination constants were used for all tissues except blood. The organ masses of MIRD Pamphlet No. 5 were used (*3*).

The absorbed fractions used in these calculations were obtained for the complete ^{75}Se photon spectrum instead of from interpolated values derived from *MIRD Pamphlet No. 5*. These are tabulated in Table B-3 of Ref. *1*.

In Appendix B of Ref. *1*, the calculations of the absorbed dose to the liver from different source tissues are given to illustrate the methods of calculation used by the MIRD Committee. In Appendix C of Ref. *1*, the error considerations are given for these dose estimates.

REFERENCES

1. LATHROP KA, JOHNSTON RE, BLAU M, et al: Radiation dose to humans from ^{75}Se-L-selenomethionine. MIRD Pamphlet No 9, *J Nucl Med* 13: Suppl No 6, 1972

2. DILLMAN LT: Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation. MIRD Pamphlet No 4, *J Nucl Med* 10: Suppl No 2, p 20, 1969

3. SNYDER WS, FORD MR, WARNER GG, et al: Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogenous phantom. MIRD Pamphlet No 5, *J Nucl Med* 10: Suppl No 3, p 8, 1969

ACKNOWLEDGMENTS

The MIRD Committee wishes to acknowledge the use of published and unpublished data from the following individuals:

1. M. Ben-Porath, Hines V.A. Hospital, Hines, Ill.
2. M. Blau, Roswell Park Memorial Institute, Buffalo, N.Y.
3. N. E. Herrera, Danbury Hospital, Danbury, Conn.
4. K. A. Lathrop, Argonne Cancer Research Hospital*, University of Chicago, Chicago, Ill.
5. E. O. Rothschild, Sloan-Kettering Institute for Cancer Research, New York, N.Y.
6. H. N. Wellman, National Cancer for Radiological Health and the Radioisotope Laboratory, University of Cincinnati, Cincinnati, Ohio.

The Committee wishes to acknowledge the contributions of W. S. Snyder, Oak Ridge National Laboratory, for the calculation of absorbed fractions for ^{75}Se and those of Karin R. Corey who initiated the compilation of these data and prepared the first report to the MIRD Committee.

The work of the MIRD Committee is supported in part by Grant RL-00029 from the Bureau of Radiological Health, FDA, USPHS.

TASK GROUP

K. A. Lathrop, The Univ. of Chicago and the Argonne Cancer Research Hospital*, Chicago, Ill.

R. E. Johnston, Veterans Administration Hospital and Vanderbilt University, Nashville, Tenn.

M. Blau, Roswell Park Memorial Institute, Buffalo, N.Y.

E. O. Rothschild, Sloan-Kettering Institute for Cancer Research and Memorial Hospital for Cancer and Allied Disease, N.Y., N.Y.

E. M. Smith, Editor of Dose Estimate Reports, Univ. of Miami School of Medicine, Miami, Fla.

* Operated by the Univ. of Chicago for the USAEC.

1048997

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 76-6

DESCRIPTION: DL-TRYPTOPHAN[side chain-3-^{11}C](^{11}C-DL-TRYPTOPHAN)

We propose to use this new radiopharmaceutical agent in clinical studies for visualization of the pancreas. The IND we have submitted to FDA is attached. Maximum dose proposed is 0.429 mCi per kilogram of body weight. (See Table 10 for radiation dosimetry)

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
James A. Berger	✓			10/22/76
William D. Eable	✓			10/22/76
R. L. Hayes	✓			10/22/76
[illegible]	✓			10/22/76
Karl F. Hübner	not voting			

Acknowledgement of submitter_____ Date_____

Proposal does ✓ does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on Nov. 9, 1976

8b8b4b01

Ident No. 39

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: ORAU/ORNL COMMITTEE ON HUMAN STUDIES
Medical and Health Sciences Division
Oak Ridge Associated Universities

September 24, 1976

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigators: G. A. Andrews, M.D.
R. T. Collmann, M.D.
R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CLINICAL USE OF DL-TRYPTOPHAN[SIDE CHAIN-3-^{11}C] (^{11}C-DL-TRYPTOPHAN)

I. Objectives of Experiment:

The goal of this proposed research is to carry out in humans a Phase I investigation of the use of ^{11}C-DL-Tryptophan as a potential pancreas-imaging agent. This work is being supported by NIH Grant 1 RO1 CA 14669.

II. Methods of Procedure:

See 3, 4 and 5 in attached IND application.

III. Possible Hazards and Their Evaluation:

See 6-a-2 and 6-a-3 in attached IND application.

IV. Radionuclides and New Drugs:

See 3 and 6-a-1 in attached IND application.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from patients in the Oak Ridge Hospital and surrounding hospitals. An informed consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). The consent form to be used is attached as an appendix to this application. No inducement will be

1048999

offered to obtain voluntary consent. Patients will be recruited specifically for the test with no promise of medical care. Patients will have known or strongly suspected pancreatic disease, so that they stand to benefit if procedure is successful, but this will not be used as an inducement to participate.

Starting Date: October 1976

Signatures: Karl T. Holmes, M.D. Principal Investigator

Donald G. Anderson M.D. Co-Investigator

Paul Altmann Co-Investigator

Raymond L. Hayes Co-Investigator

Lee C. Washburn Co-Investigator

Bruce W. Wieland Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the Institution:

Signature [illegible]

Title Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date 9/29/76

1049000

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division (MHSD), Oak Ridge

Associated Universities (ORAU), Oak Ridge, Tennessee

1. NAME OF DRUG: DL-TRYPTOPHAN[SIDE CHAIN-3-^{11}C](^{11}C-DL-TRYPTOPHAN). This drug will be administered intravenously, dissolved in a sterile, nonpyrogenic saline solution.

2. COMPONENTS:

   a. ^{11}C-DL-Tryptophan (active radioactive drug).

   b. DL-Tryptophan [nonradioactive carrier (stable) drug].

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION: Since the ^{11}C present in labeled ^{11}C-DL-tryptophan is radioactive ($T_{1/2}$ ^{11}C = 20.4 min), we cannot state a completely exact relationship between the components of this preparation at the time of administration. From radiation dosimetry considerations, however, we have determined that the maximum ^{11}C activity that will be administered will not exceed 0.429 mCi per kilogram of body weight (a 30 mCi dose for a 70 kg subject). The actual amount of stable DL-tryptophan that will be administered will be determined by the amount of ^{11}C used in labeling DL-tryptophan and also the time that elapses from the time of ^{11}C-DL-tryptophan preparation to the time of its administration to the patient. The composition stated below, therefore, represents the dosage limits that will be adhered to for the components in this radiopharmaceutical preparation:

   a. ^{11}C-DL-Tryptophan: maximum of 0.429 mCi per kilogram of body weight (30 mCi total for a 70 kg subject).

   b. DL-Tryptophan: maximum of 0.1 mg per kilogram of body weight (7 mg total for a 70 kg subject). The weight of ^{11}C-DL-tryptophan administered (a, above) will be negligible compared to that of stable DL-tryptophan.

   c. Sodium chloride: maximum of 3 mg per kilogram of body weight (210 mg total for a 70 kg subject).

   d. Water: maximum of 0.5 ml per kilogram of body weight (35 ml total for a 70 kg subject).

1049001

4. SOURCE OF NEW DRUG SUBSTANCE:

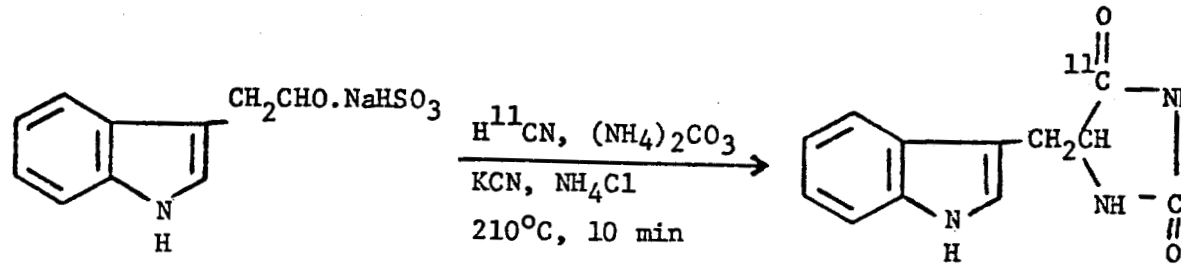
Reference should be made to the details of synthesis and purification of ^{11}C-ACPC (IND 11848 dated 16 September 1975) and DL-valine-1-^{11}C (IND 12459 dated 12 May 1976) which are similarly prepared radiopharmaceuticals. (^{11}C-ACPC and DL-valine-1-^{11}C have been under clinical investigation at MHSD, ORAU, since November 1975 and July 1976, respectively.)

^{11}C-DL-Tryptophan will be synthesized in the preparatory hot cell at the 86-Inch Oak Ridge National Laboratory (ORNL)'s 22 Mev proton cyclotron complex using the following series of reactions:

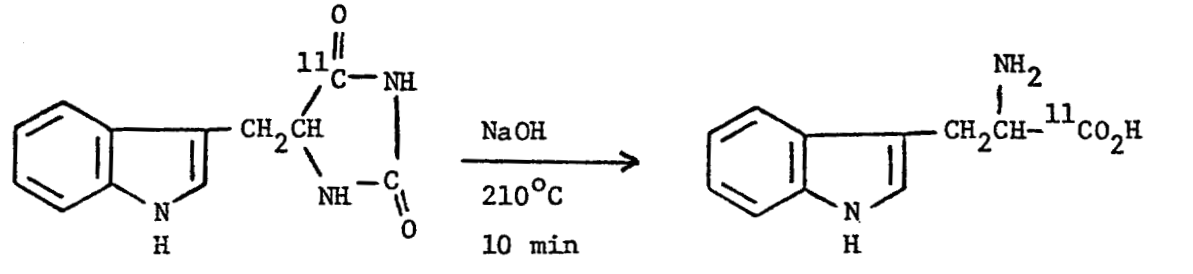
$$B_2O_3 \xrightarrow{^{11}B(p,n)^{11}C} {}^{11}CO_2/{}^{11}CO \qquad \text{Step I}$$

$$^{11}CO_2/{}^{11}CO \xrightarrow[\text{Ni, } 370^\circ C]{H_2} {}^{11}CH_4 \qquad \text{Step II}$$

$$^{11}CH_4 \xrightarrow[900\text{-}950^\circ C]{\text{Pt, } NH_3} H^{11}CN \qquad \text{Step III}$$



Step



Step V

1049002

Targetry and Production of $^{11}CO_2/^{11}CO$ (Step I): B_2O_3, prepared by heating H_3BO_3 (Fisher Scientific Co., Fair Lawn, N.J.), is fused onto a graphite substrate, which is mounted in an aluminum annulus-type header. The annulus provides a water coolant flow of 15 liters/min. The header assembly is connected in turn to a gas flow loop that has provisions for on-line gas purge or recirculation. The outlet of the loop is located in the remote control preparatory hot cell that is adjacent to the cyclotron. During bombardment, when He (Lif-O-Gen Inc., Cambridge, Md.) is used as the carrier gas in the loop, a $^{11}CO_2/^{11}CO$ ratio of approximately 4 is obtained. Outgassing of target ^{11}C activity into the gas flow loop during bombardment is approximately 50% complete. With a beam current of 150-175 μA approximately 3 Ci of usable $^{11}CO_2/^{11}Co$ activity are produced.

Production of $^{11}CH_4$ and $H^{11}CN$ (Steps II and III): Both $^{11}CH_4$ and $H^{11}CN$ are produced by contact catalysis. A 100 ml/min He stream introduced into the cyclotron gas flow loop is mixed at the loop outlet with a 50 ml/min H_2 (Lif-O-Gen Inc.) stream and fed through a quartz tube containing Ni catalyst on kieselguhr (Ventron Alpha Products, Beverly, Mass.) held at a temperature of 370°C. The output gas flow from this conversion (containing $^{11}CH_4$) is passed through a $CaSO_4/NaOH$ trap and then mixed with a 50 ml/min stream of anhydrous NH_3 (Lif-O-Gen Inc.). This mixture is then passed through another quartz tube containing Pt catalyst on alumina (Ventron Alpha Products) heated to 900-950°C to complete the conversion of $^{11}CH_4$ to $H^{11}CN$.

Synthesis of ^{11}C-DL-Tryptophan (Steps IV and V): Prior to the start of a ^{11}C-DL-tryptophan production run, a stainless steel (type 316) pressure vessel having an internal volume of 3 ml and fitted with a needle valve is charged with a mixture of 26.3 mg 3-indoleacetaldehyde bisulfite addition compound (ICN Life Sciences Group, Plainview, N.Y.), 57.6 mg $(NH_4)_2CO_3$ (certified A.C.S., Fisher Scientific Co.), 5.4 mg NH_4Cl and 6.5 mg KCN (both Baker Analyzed Reagents, J. T. Baker Chemical Co., Phillipsburg, N.J.). The gas stream from Step III, containing $H^{11}CN$ is bubbled into a gas absorption column containing 1 ml of 0.005 N NaOH. This solution is then introduced into the charged reaction vessel and the closed vessel then rapidly heated to 210°C and maintained at that temperature for 10 min, after which it is rapidly cooled. One ml of 6.25 N NaOH (Fisher Scientific Co.) is then introduced and the vessel again heated at 210°C for another period of 10 min.

Purification of ^{11}C-DL Tryptophan: After completion of Step V, the cooled reaction mixture is withdrawn remotely by means of a syringe, filtered, acidified with 2 ml of 6N HCl, and then loaded onto a 1.0 cm (dia.) x 10 cm (length) column containing Porapak Q, 150-200 mesh (Waters Associates, Inc., Milford, Mass.). (The column is prepared beforehand by soaking the Porapak Q in acetone, loading the column, rinsing with 40 ml H_2O/gram of Porapak Q, and finally rinsing well with 0.1 N HCl.) After loading, the column is washed twice with 0.1 N HCl (∿ 30 ml), once with H_2O (∿ 30 ml), and eluted with 50% aqueous ethanol, the process being monitored by means of a shielded gamma probe. The eluate is acidified with 2 cc of 6 N HCl

1.0 cm (dia.) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydrogen form. Cationic ^{11}C-DL-tryptophan is retained while anionic material passes through the column. After washing repeatedly with distilled water (∿ 30 ml), the column is finally eluted with 0.2 N NaOH, the process again being monitored with a shielded gamma probe to minimize the volume of eluate containing the product (∿ 10 ml). This solution is collected in a sterile bottle for transport to MHSD, ORAU for final processing.

Assessment of Purity. The purity of the ^{11}C-DL-tryptophan product has been assessed by thin layer chromatography (tlc) (Eastman Chromogram Sheet 13181, silica gel with fluorescent indicator) using an n-butanol: water:acetic acid (94:6:1, v/v) solvent system and also by comparison of its tissue distribution in animals with those that have previously been obtained with commercially available DL-tryptophan-[3-side chain-^{14}C] (New England Nuclear Corp., Boston, Mass.). Pyrogenicity tests of the ^{11}C-DL-tryptophan product by standard USP techniques have been negative. There has also been no indication of decomposition of ^{11}C-DL-tryptophan as the result of radiolysis.

^{11}C-DL-Tryptophan (from a run spiked with K^{14}CN prior to synthesis) gave a tlc pattern that was similar to that of standard ^{14}C-DL-tryptophan with no indication of any impurities when the two tlc patterns were viewed with a spark chamber (Burchover Instruments, Ltd., Bancroft, England). Ninhydrin development of the tlc chromatograms also gave single amino acid spots with the same Rf values. Similar results were obtained upon examination of the fluorescence on the chromatograms under ultraviolet light.

Table 1 shows the tissue distribution at 30 min postinjection in a series of four male Buffalo rats given ^{11}C-carboxyl-labeled DL-tryptophan. This may be compared with an analogous tissue distribution study done using commercial ^{14}C-carboxyl-labeled DL-tryptophan. The results of the two studies agree within experimental error. (See Section 6 for more animal data.)

5. METHODS, FACILITIES AND CONTROLS:

The solution containing the purified ^{11}C-DL-tryptophan will be transported from the ORNL cyclotron complex to MHSD, ORAU located on Vance Road in Oak Ridge (trip time, 6-8 min). After being transferred to a magnetically stirred conical beaker, the pH of the solution will be adjusted to 7.0 + 0.2 with 1 N HCl using a combination electrode and pH meter. (The stem of the electrode, when not in use, will be stored in 0.9% benzyl alcohol and will be rinsed repeatedly with sterile water before each preparative use.) The solution will then be filtered through a sterile, nonpyrogenic 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (multipuncture type, Wheaton Glass Co., Millville, N.J.). A portion of this solution will be tested for pyrogens using the Pyrotest Limulus Lysate technique (Difco Laboratories, Detroit, Mich.). The short half-life of ^{11}C (20.4 min) precludes testing with rabbits in the conventional USP manner, and, although this particular limulus technique normally requires an hour for completion, it acts as

a test for gross pyrogenic contamination during the period of time required for transport of the preparation to the site of administration (∿ 15 min). The test will become part of the record. Each ^{11}C-DL-tryptophan dose will be assayed for radioactivity content just prior to administration by means of a Capintec CRC-10 radioisotope calibrator (Capintec, Inc., Montvale, N.J.). (A previous preliminary ion chamber assay will have been made at the cyclotron facility.) Each dose will also be assayed for isotopic contamination using a sodium iodide detector and a multichannel analyzer. A photograph of the spectrum from 0-2 Mev will be made a part of the permanent record. The vial containing the ^{11}C-DL-tryptophan will finally be labeled as to its assay and total content (see Section 7).

Preparation of each batch of ^{11}C-DL-tryptophan for clinical use will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized by steam. Each batch of ^{11}C-DL-tryptophan will be given a batch number and all particulars relative to its preparation and use will be entered into a master log book.

6. STATEMENT OF INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations

1. Animal studies

All animal studies with ^{14}C- and ^{11}C-carboxyl-labeled DL-tryptophan have been directly supervised by L. C. Washburn and R. L. Hayes. G. A. Andrews and K. F. Hübner have participated in the evaluation of the data (see Appendix on Biographical Material).

The insertion of radioisotopic labels into the intrinsic structure of organic compounds and biological substances that have high affinities for specific tissues is an ideal method of labeling, since structures are not altered. The radionuclides ^{11}C, ^{13}N, and ^{15}O are all candidates for use in labeling such agents for nuclear medical diagnosis by scanning. Their decay is accomplished by photon emission in the form of positron annihilation radiation which can be utilized for conventional rectilinear scanning or for coincidence detection techniques such as positron emission transaxial tomography utilizing computer reconstruction. This latter method is an instrumentation technique that may shortly come into its own in nuclear medical technology (1). Of these three radionuclides, ^{11}C is the obvious choice as a label because of its longer half-life (20.4 min), although, even with this radionuclide, rapid tissue distribution is necessarily required of any radiopharmaceutical agent that is labeled with it.

One of the most important diagnostic problems in nuclear medicine is the need for a suitable agent for pancreas imaging (2). Carcinoma of the pancreas is the fourth leading cause of cancer deaths in the United States (3, 4). Approximately 22,000 new cases of cancer of the pancreas will be diagnosed in the United States, and 19,600 persons are expected to die of the disease, in 1976 (5). Very little progress has been made in combatting this disease, as evidenced by the present 5-year survival rate of 1.5% for patients diagnosed as having pancreatic

carcinoma, compared to 1.0% in 1940 (6). This poor survival rate seems to be due more to the lack of reliable diagnostic techniques than to the nonavailability of adequate treatment procedures.

The most reliable non-surgical diagnosis of pancreatic carcinoma at the present time involves imaging the pancreas with the radiopharmaceutical ^{75}Se-selenomethionine coupled with a ^{99m}Tc colloid liver scan to permit subtraction of interfering radiation from the liver (7). However, ^{75}Se-selenomethionine has a number of disadvantages associated with its use (8). One problem is the high radiation dose to the patient. Selenium-75 has a long physical half-life (120 days) and ^{75}Se-selenomethionine in turn has a long biological half-time (20 days). This results in the exposure of the patient to radiation for a much longer time than is required for the diagnostic procedure (8). The most acute problem, however, is the inability of the agent to clearly delineate neoplasms associated with the pancreas. Uptake of ^{75}Se-selenomethionine even by a normal pancreas is not uniform from patient to patient and is often nonspecific. Significant percentages of both false positives and false negatives are observed (9, 10).

A number of labeled amino acid preparations have been investigated as potential radiopharmaceuticals for pancreas scanning (11-13), but the biochemical behavior of the radioactive label generally differs greatly from that of the natural amino acid. This makes ^{11}C an obvious choice for labeling amino acids for pancreatic imaging, since the biochemical utilization of the labeled compound should be similar in magnitude to that of the natural amino acid.

Studies in the mouse (14) and rat (13, 15) with ^{14}C-carboxyl-labeled DL-tryptophan have shown this amino acid to be superior to all other naturally occurring amino acids with regard to pancreas uptake and pancreas specificity. We have compared the tissue distribution of ^{14}C-labeled DL-tryptophan with that of ^{14}C-labeled DL-valine and DL-leucine, two other amino acids with high pancreas specificity, and DL-tryptophan was found to be the most selective for the pancreas (Table 2). Taylor and Cottrall (13) suggested the potential value of ^{11}C-labeled DL-tryptophan as a pancreas-imaging agent, but the synthesis of the agent presented problems. We have adapted the high-temperature, high-pressure modification of the Strecker amino acid synthesis developed for ^{11}C-carboxyl-labeled 1-aminocyclopentanecarboxylic acid (16) and other amino acids (17) to the synthesis of ^{11}C-carboxyl-labeled DL-tryptophan.

The tissue distribution of ^{14}C-labeled DL-tryptophan is complete in the rat at 30 min postinjection (Table 3), and, therefore, if the human behaves similarly, this appears to be approximately the optimum time for scanning. This is quite compatible with the short (20.4 min) half-life of ^{11}C.

The effect of added carrier DL-tryptophan on the tissue distribution of ^{14}C-labeled DL-tryptophan was studied in the rat. The presence of small amounts of carrier DL-tryptophan appear to aid the pancreas specificity, but larger amounts of carrier decrease the selective uptake by the pancreas (Table 4). The optimum carrier level appears to be approximately 0.4 mg/kg, very near the level which we propose to use.

1049006

We have carried out studies of the tissue distribution of DL-tryptophan in a wide variety of animal species in order to assess the importance of species differences in the distribution. These species included the rat (Tables 1, 3, and 4), rabbit (Table 5), and dog (Table 6 and Fig. 1). All of these species showed good pancreas uptake, although the pancreas specificity varied in the following order: rat > dog > rabbit.

Busch and co-workers (15) found that ^{14}C-labeled DL-tryptophan was not incorporated selectively by a Walker 256 carcinosarcoma. This suggests that pancreatic cancer may be diagnosed by a defect (non-radioactive area) in the normal pancreatic image produced with ^{11}C-DL-tryptophan.

The blood clearance of intravenously administered ^{14}C-labeled DL-tryptophan in the rat is very rapid (Table 7), with only 10.3% of the injected activity remaining in the blood at 15 min postinjection and 7.6% at 30 min postinjection. The rates of decarboxylation (Table 8) and total metabolic loss (decarboxylation plus urinary excretion) (Table 9) are much slower for DL-tryptophan than for DL-valine, another ^{11}C-labeled amino acid being studied for pancreas imaging (see IND 12459 dated 12 May 1976). For example, at one hour postinjection in the rat, decarboxylation and total metabolic losses for DL-tryptophan measure 3.7% and 11.7% respectively, compared to 28.1% and 41.3% respectively for DL-valine. Although decarboxylation has apparently not been a problem in clinical studies with DL-valine-1-^{11}C, the high rate of urinary excretion at early time periods has resulted in the pancreas being obscured by kidney activity which does not clear until approximately one hour postinjection. The lesser rate of urinary excretion with DL-tryptophan should help to decrease this problem associated with DL-valine-1-^{11}C.

Figure 1 shows a rectilinear scan of a normal dog that was started 40 min after intravenous administration of ^{11}C-DL-tryptophan. The pancreas is delineated much more clearly than in similar scans of the same dog done with DL-valine-1-^{11}C (Fig. 2).

2. Toxicity

L-Tryptophan, of course, is one of the essential, naturally occurring amino acids, and, as such, it is present to the extent of 0.274 (0.269-0.289) mg per 100 ml of normal human blood (18). Assuming that blood comprises 7% of total human body weight, there is, therefore, ∿ 13.4 mg of L-tryptophan in the blood stream of a normal 70 kg human. (We propose to administer no more than a total of 7 mg DL-tryptophan per 70 kg subject.)

Oral doses of L-tryptophan of up to 15 grams have been administered to humans with no toxic effects in studies of the amino acid as a possible natural hypnotic substance (19).

The LD_{50} of intraperitoneally administered L-tryptophan in rats is reported as 1632 mg/kg and the D-isomer is reported as being even less toxic (20).

At the dose level of the drug which we would use for pancreas imaging (0.1 mg/kg or less), we would expect no toxicity, since we will be below the LD_{50} value by a factor of approximately 16,000*. The ORAU/ORNL Committee on Human Studies has approved the use of ^{11}C-DL-tryptophan as outlined in this application (see Appendix for membership of committee and biographical material).

3. Radiation Dosimetry

Carbon-11 has a 20.4 min half-life decaying by positron emission (99+%) to stable ^{11}B. Because of its short half-life the radiation dose to patients will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center (headed by R. J. Cloutier) that the complete decay of 1 mCi of ^{11}C-DL-tryptophan uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.01 rads or a total of 0.30 rads per 30 mCi (the maximum proposed administered dose of ^{11}C-DL-tryptophan). Table 10 gives details of the expected radiation dose to various organs in the human estimated from animal data. The MHSD, ORAU Medical Radionuclide Committee has approved the use of ^{11}C-DL-tryptophan from a patient safety standpoint.

b. Previous Marketing:

This ^{11}C-labeled drug has not been marketed before.

c. Drug Combination:

^{11}C-DL-Tryptophan is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with ^{11}C-DL-tryptophan will have the following form:

^{11}C-DL-TRYPTOPHAN (FOR I.V. INJECTION)

Assay_____mCi/ml as of _____

Volume_____ml: Batch No._____

Expiration Time_____

CAUTION: INVESTIGATIONAL NEW DRUG

CAUTION: RADIOACTIVE MATERIAL

Oak Ridge Assoc. Univ., Oak Ridge, Tn.

---

* Suggested average minimal daily dietary requirements for L-tryptophan are 2.9 mg/kg for men and 2.1 mg/kg for women.

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal information material will be prepared; however, each participant will of course be issued a copy of this application.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See bibliographical material in the appendix about Drs. Andrews, Hayes, Hübner, Washburn, and Wieland.

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by G. A. Andrews, R. L. Hayes, K. F. Hübner, and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Chairman of the ORAU Medical and Health Sciences Division, with advice from the ORAU Medical Advisory Committee and the ORAU/ORNL Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phases I and II, clinical pharmacology, in this study will consist of observations on the metabolism and toxicity of ^{11}C-DL-tryptophan together with preliminary observations on the radiopharmaceutical's pancreas-localizing properties.

Patients (30) for this study will be mainly those referred by Dr. Reid Collmann, a gastroenterologist from Knoxville, Tennessee. Other patient volunteers will be recruited from patients in the Oak Ridge Hospital and surrounding hospitals. They will be selected for evidence of possible pancreatic disease, i.e., symptoms and laboratory findings suggestive of pancreatic carcinoma and/or having a diagnosis of chronic alcoholic pancreatitis. This latter group of pancreatitis patients should provide a sufficient number of negative subjects for us to develop reasonable criteria for the characteristics of the normal pancreatic scan without resorting to normal volunteers. The ^{11}C-DL-tryptophan study is expected to cover a period of 1-1/2 to 2 years. Only adult subjects will be studied. Each patient will be fully informed that this is an experimental procedure, that it might have some toxic effect (although we know of no specific toxicity that is at all likely) and that the procedure will cause a radiation dose of approximately 3.3 to 6.0 rads to the pancreas, approximately 0.9 to 1.0 rads to the liver, and 0.3 rads to the whole body when 30 mCi of ^{11}C-Dl-tryptophan is administered. No ^{11}C-DL-tryptophan doses will be given without the informed consent of the patient. Subjects incapable of giving an informed consent will be excluded from the study. A copy of the informed consent form is attached.

For dosimetry purposes and to determine optimal timing of scanning, blood levels of radioactivity will be determined at frequent intervals during the first 1 to 1-1/2 hours after injection of the radiopharmaceutical. Additional information for radiation dose estimates will be gathered by whole body counting and determination of the radioactivity excreted in the urine.

1049009

Since the proposed diagnostic doses appear well below any that could cause chemical toxicity from the DL-tryptophan or detrimental radiation effects from the ^{11}C present, we will start our studies using the full diagnostic dose (0.43 mCi/kg), but using patients strongly suspected of pancreatic disease who are, however, considered to be in good general condition. Careful observations of pulse and blood pressure will be made during the first 5 doses given. At least two physicians will be present during the first clinical trials.

The following laboratory tests will be done both before and 24 hours after injection of the radiopharmaceutical: complete blood count, urinalysis and plasma hemoglobin.

If any abnormality in clinical or laboratory observations is seen, appropriate follow-up studies will be carried out. If the abnormality appears serious, we will stop all further clinical trials and immediately notify the Food and Drug Administration.

The principal questions to be answered are:

1. Are there any unsuspected toxic effects of ^{11}C-DL-tryptophan on humans at the dose levels proposed?
2. Will the uptake of ^{11}C-DL-tryptophan in the human pancreas be sufficient to permit pancreatic imaging?
3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{11}C-DL-tryptophan in humans?
4. What is the optimum dose and scanning time for pancreas visualization?

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{11}C-DL-tryptophan prior to 30 days after the date of receipt of notice of this application by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

REFERENCES

1. Ter-Pogossian, M.M., Phelps, M.E., Hoffman, E.J., and Mullani, N.A. Radiol. 114:89, 1975.

2. McAfee, J.G. In "Radiopharmaceuticals", G. Subramanian, B. A. Rhodes, J. F. Cooper, and V.J. Sodd, eds., p. 6, The Society of Nuclear Medicine, Inc., New York, 1975.

3. Ernst, L., Wynder, K., Mabuchi, K., Maruchi, N., and Fortner, J.G. J. Nat'l. Cancer Inst., 50:645, 1973.

4. Levin, D.L. and Connelly, R.R. Cancer 31:1231, 1973.

5. Seidman, H., Silverberg, E., and Hollab, A.E. CA - A Cancer Journal for Clinicans 26:2, 1976.

6. Kaplan, S. Oncology Address before Society of Nuclear Medicine, Annual Meeting, San Diego, California, 1974.

7. Youngs, G.R., Agnew, J.E., Levin, G.E., and Bouchler, I.A.D. Q. J. Med. 42:576, 1973.

8. Blau, M. and Holland, J.F. U. S. Atomic Energy Comm. Symp. Series No. 6, 409-421, 1966.

9. Burdine, J.A. and Haynie, T.P. JAMA 194:979, 1965.

10. Rodriguez-Antunes, A., Filson, E.J., Sullivan, Jr., B.H., and Brown, C.H. Ann. Int. Med. 65:730, 1966.

11. Adkins,H.L., Christman, D.R., Fowler, J.S., Hauser, W., Hoyte, R.M., Klopper, J.F., Lin, S.S., and Wolf, A.P. J. Nucl. Med. 13:713, 1972.

12. Lambrecht,R.M., Adkins, H., Elias, H., Fowler, J.S., Lin, S.S., and Wolf, A.P. J. Nucl. Med. 15:863, 1974.

13. Taylor, D.M. and Cottrall, M.F. In "Radiopharmaceuticals and Labeled Compounds", Vol. 1, p. 433. International Atomic Energy Agency, Vienna, 1973.

14. Tamemasa, O., Goto, R., Tezuka, M., and Okada, S. In "Recent Advances in Nuclear Medicine", pp. 875-877, Japan Radioisotope Association, Tokyo, Japan, 1974.

15. Busch, H., Fujiwara, E., and Keer, L.M. Cancer Res. 20:50-57, 1960.

16. Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. J. Nucl. Med. 17:748, 1976.

17. Washburn, L.C., Sun, T.T., Rafter, J.J., and Hayes, R.L. J. Nucl. Med. 17:557, 1976.

1049011

18. "Blood and Other Body Fluids", D. S. Ditner, ed., p. 73, Federation of American Societies for Experimental Biology, Washington, D.C., 1961.

19. Hartmann, E. JAMA 230:1680, 1974.

20. Gullino, P., Winitz, M., Birnbaum, S.M., Cornfield, J., Otey, M.C., and Greenstein, J.P. Arch. Biochem. Biophys. 58:253, 1955.

1049012

Table 1

Tissue Distribution of ^{14}C- and ^{11}C-Carboxyl-Labeled DL-Tryptophan in Male Buffalo Rats at 30 Minutes Postinjection

Tissue	DL-Tryptophan[side chain-3-^{14}C]	DL-Tryptophan[side chain-3-^{11}C] Preparation
	Percent Administered Dose/g[a]	
Pancreas	12.4 ± 0.3	12.1 ± 0.3
	Pancreas-to-tissue Conc. Ratios	
Liver	11.4 ± 0.2	9.3 ± 0.3
Spleen	16.2 ± 0.7	14.8 ± 0.9
Kidney	8.4 ± 0.2	7.7 ± 0.4
Lung	25.6 ± 0.8	19.0 ± 2.1
Muscle	51.8 ± 1.0	54.5 ± 2.5
Marrow	7.4 ± 1.0	-
Small intestine	8.4 ± 0.3	7.6 ± 0.8
Blood	43.8 ± 1.0	32.3 ± 1.4

[a] Average of 4 animals ± S.E.; normalized to a body weight of 250 g.

1049013

Table 2

Comparison of the Tissue Distribution of ^{14}C-Carboxyl-Labeled Amino Acids (0.02 mg/kg) in Male Buffalo Rats at 30 Minutes Postinjection

Tissue	Pancreas/Tissue Concentration Ratio		
	DL-Tryptophan	DL-Valine	DL-Leucine
Liver	11.4	9.8	6.4
Small intestine	8.4	5.7	4.0
Blood	43.7	20.3	20.2
Muscle	51.7	33.2	20.6

1049014

Table 3

Effect of Time on the Tissue Distribution of DL-Tryptophan[side chain-3-^{14}C] in the Rat

Tissue	Percent Administered Dose/g[a]		
	15 min	30 min	60 min
Pancreas	8.88 ± 0.03	12.37 ± 0.25	11.84 ± 0.64
Liver	1.05 ± 0.04	1.08 ± 0.02	0.96 ± 0.03
Spleen	0.69 ± 0.04	0.77 ± 0.03	0.66 ± 0.01
Kidney	1.63 ± 0.09	1.50 ± 0.04	1.36 ± 0.14
Lung	0.52 ± 0.01	0.49 ± 0.01	0.42 ± 0.01
Muscle	0.25 ± 0.01	0.24 ± 0.00	0.20 ± 0.01
Marrow	1.64 ± 0.03	1.75 ± 0.30	1.68 ± 0.34
Small intestine	1.22 ± 0.04	1.47 ± 0.03	1.33 ± 0.07
Blood	0.50 ± 0.05	0.28 ± 0.01	0.26 ± 0.02

[a] Average of 4 animals ± S.E.; normalized to a body weight of 250 g.

1049015

Table 4

Effect of Carrier DL-Tryptophan on the Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] in the Rat at 30 Minutes Postinjection

Tissue	Pancreas/Tissue Conc. Ratio[a]			
	0.0004 mg/kg[b]	0.04 mg/kg	1.0 mg/kg	5.0 mg/kg
Liver	9.3 ± 0.6	11.4 ± 0.2	9.4 ± 0.5	8.7 ± 0.2
Spleen	13.2 ± 1.3	16.2 ± 0.7	14.0 ± 0.8	12.8 ± 0.6
Kidney	6.4 ± 1.6	8.4 ± 0.2	8.2 ± 0.5	8.5 ± 0.6
Lung	16.9 ± 3.5	25.6 ± 0.8	16.1 ± 0.7	14.0 ± 0.7
Muscle	37.9 ± 3.2	51.8 ± 1.0	46.5 ± 2.1	35.3 ± 1.9
Small intestine	8.9 ± 0.5	8.4 ± 0.3	7.4 ± 0.6	7.3 ± 0.2
Marrow	10.3 ± 0.6	7.4 ± 1.0	5.0 ± 0.8	4.5 ± 0.6
Blood	21.2 ± 2.1	43.8 ± 1.0	38.2 ± 1.4	28.9 ± 1.4
Heart	22.9 ± 2.3	-	-	-

[a] Average of 4 animals ± S.E.

[b] DL-Tryptophan[side chain-2,3-^{3}H (N)] was used to attain the high specific activity.

1049016

Table 5

Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] (0.02 mg/kg) in the Rabbit at 30 Minutes Postinjection

Tissue	%/g/2.5 kg ± S.E.	Pancreas/Tissue
Pancreas	0.58 ± 0.03	-
Liver	0.11 ± 0.00	5.4
Spleen	0.12 ± 0.01	4.7
Kidney	0.19 ± 0.01	3.1
Lung	0.09 ± 0.01	6.5
Muscle	0.04 ± 0.00	16.0
S. intestine	0.16 ± 0.01	3.6
Marrow	0.08 ± 0.00	7.4
Blood	0.06 ± 0.00	9.3
Thymus	0.07 ± 0.01	8.9
Adrenals	0.10 ± 0.01	5.6
Urine	0.36 ± 0.12	1.6

1049017

Table 6

Effect of Time on the Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] (0.04 mg/kg) in the Dog

Tissue	30 minutes		60 minutes	
	%/g/10 kg ± S.E.	Pancreas/Tissue	%/g/10 kg ± S.E.	Pancreas/Tissue
Pancreas	0.155 ± 0.004	-	0.148 ± 0.026	-
Liver	0.033 ± 0.003	4.6	0.028 ± 0.002	5.3
Spleen	0.017 ± 0.002	9.2	0.013 ± 0.002	12.7
Kidney	0.030 ± 0.001	5.2	0.032 ± 0.001	4.7
Lung	0.014 ± 0.001	11.1	0.010 ± 0.000	14.3
Muscle	0.007 ± 0.000	21.8	0.007 ± 0.001	24.4
S. intestine	0.032 ± 0.007	4.9	0.030 ± 0.006	5.5
Marrow	0.019 ± 0.004	8.1	0.026 ± 0.008	8.4
Blood	0.012 ± 0.002	13.5	0.008 ± 0.000	18.8
Thymus	0.022 ± 0.010	7.2	0.009 ± 0.001	17.2
Adrenal	0.021 ± 0.003	7.4	0.019 ± 0.002	7.8
Urine	0.283 ± 0.163	0.5	0.146 ± 0.060	1.0
Heart	0.012 ± 0.001	12.9	0.009 ± 0.000	16.4
L. node	0.035 ± 0.004	4.4	0.025 ± 0.002	6.1

1049018

Table 7

Blood Clearance of DL-Tryptophan[side chain-3-^{14}C] in Male Fischer Rats

Time (min)	Percent of Administered Dose Remaining in Blood[a]
2	24.6 ± 1.8
5	17.3 ± 2.1
10	12.0 ± 0.9
15	10.3 ± 0.8
30	7.6 ± 0.5
60	5.1 ± 0.2
120	4.3 ± 0.3

[a] Average of 4 animals ± S.E.

1049019

Table 8

Rate of Decarboxylation of DL-Tryptophan[side chain-3-^{14}C]

by Male Buffalo Rats

Time (min)	Cumulative Percent Exhaled as $^{14}CO_2$[a]
5	0.0
10	0.2
15	0.5
30	1.7
45	2.8
60	3.7
90	5.4
120	6.7

[a] Average of two animals.

1049020

Table 9

Total Metabolic Loss of DL-Tryptophan[side chain-3-^{11}C] by Male Fischer Rats

Time (min)	Percent Administered Dose Lost[a]
20	4.9 ± 0.6
40	9.4 ± 0.6
60	11.7 ± 0.5
90	15.5 ± 0.6
120	17.3 ± 1.2

[a] Average of 5 animals ± S.E.

1049021

Table 10

Estimated Radiation Dose to Reference Man From Intravenous Administration of DL-Tryptophan [side chain-3-^{11}C]

Organ	Radiation Dose[a] (rads/mCi)		
	Rat	Rabbit	Dog
Total body	0.011	0.011	0.011
Pancreas	0.200	0.110	0.120
Liver	0.029	0.030	0.034
Spleen	0.011	0.0096	0.010
Kidney	0.037	0.042	0.032
Lung	0.016	0.022	0.016
Muscle	0.011	0.013	0.012
Small intestine	0.040	0.047	0.039
Marrow	0.027	0.017	0.019
Adrenals	0.012[b]	0.027	0.024

[a] Based on 30-min tissue distribution of ^{14}C-labeled DL-tryptophan in the rat, rabbit, and dog, respectively, following intravenous administration (0.04 mg/kg), assuming immediate uptake by the organs followed by complete decay in situ.

[b] Adrenal dose using rat data calculated on the basis of radiation from the surrounding organs only.

1049022

Fig. 1. Rectilinear scan of a normal mongrel dog started 40 min after intravenous administration of ^{11}C-DL-tryptophan.

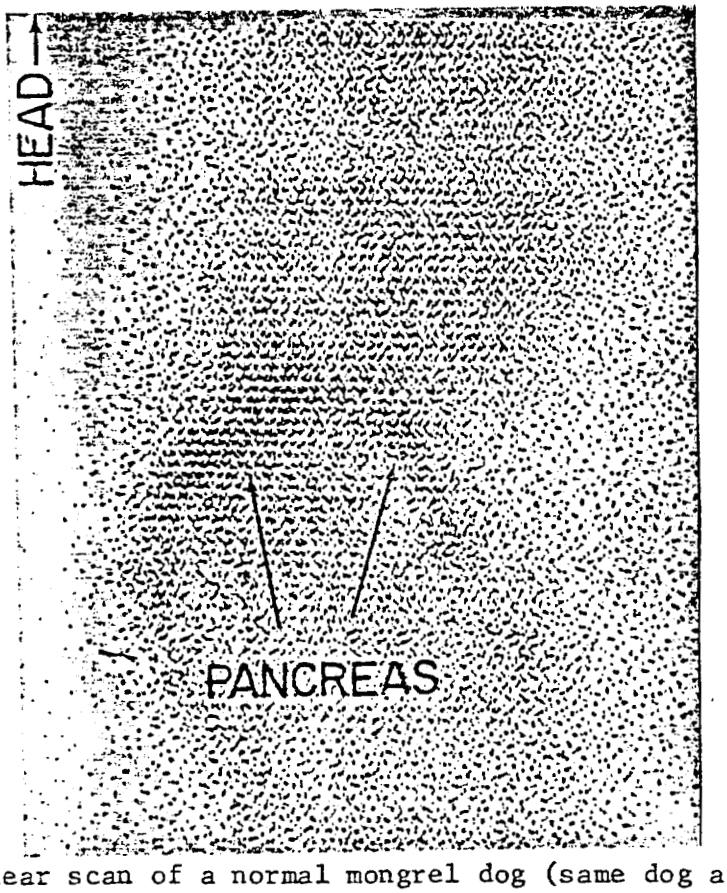


Fig. 2. Rectilinear scan of a normal mongrel dog (same dog as in Fig. 1) started 40 min after intravenous administration of DL-valine-1-^{11}C (included for comparison).

APPENDIX

Chief Investigators:

G. A. Andrews, M.D.
R. L. Hayes, Ph.D.
K. F. Hübner, M.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

ORAU/ORNL Committee on Human Studies:

Gould A. Andrews, M.D. (Secretary)
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Donald W. Goodwin, Ph.D.
Minister, United Church
Chapel-on-the-Hill
Oak Ridge, Tennessee 37830

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Y-12 Area, Building 9704-2
Union Carbide Nuclear Company
P. O. Box Y
Oak Ridge, Tennessee 37830

Robert D. Lange, M.D. (Chairman)
Assistant Director
University of Tennessee
Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

1049024

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

Clarence C. Lushbaugh, Ph.D., M.D. (Ex officio)
Chairman, Medical & Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Joan B. Woods, M.D.
Psychiatrist
Oak Ridge Mental Health Center
Oak Ridge, Tennessee 37830

ORAU Medical Advisory Committee:

George B. Hutchison, M.D.
Professor of Epidemiology
Harvard University School of Public Health
55 Shattuck
Boston, Massachusetts 02115

John M. Johnston, Ph.D.
Department of Biochemistry
University of Texas Medical School
(Southwestern)
Dallas, Texas 75235

Leonard A. Sagan, Ph.D.
Internal Medicine, Research Administration
Associate Director, Dept. of Environmental Medicine
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Professor of Genetics
University of Wisconsin
Madison, Wisconsin 53706

Joseph F. Volker, Ph.D.(Ex officio member from the ORAU Board of Directors
President
University of Alabama
Birmingham, Alabama

1049025

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews
Position:	Internist, Director of Clinical Applications
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society for Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Science; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society; American Thyroid Association

Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name:	Donald W. Goodwin
Position:	Minister, United Church, Chapel-on-the-Hill
School:	Bangor Theological Seminary, Bachelor of Divinity, 1959 Brown University, Ph.D., 1965
Memberships:	Ministerial Standing, United Church of Christ
Additional Information:	Member of various boards which change from time to time

Name:	R. L. Hayes
Position:	Director of Radiopharmaceutical Development, Chief Scientist
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U.S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

1049026

Name:	George B. Hutchison
Position:	Epidemiologist, Michael Reese Hospital, Chicago, 66-present
Schools:	Harvard University, A.B., 1943 Harvard University, M.D., 1951 Harvard University, M.P.H., 1960
Positions:	Fel. med. Lahey Clin., 52-55; asst. med. dir. Equitable Life Assurance Soc., U.S., 55-56; Health Ins. Plan Greater New York, 56-57; dir. res. City Health Dept., New York, 57-59; asst. prof. epidemiol. sch. pub. health, Harvard, 60-61; assoc. prof. 61-66; consult, Health Ins. Plan Greater New York, 57-present.
Memberships:	Fel. Am. Pub. Health Asn; Am. Statist. Asn; World Med. Asn.; Asn. Teachers Prev. Med.

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Licensure:	Tennessee
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), 1962-64 Internship (rotating) at 2nd General Hospital of the U.S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Memberships:	AMA, Tenn. Med. Association
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology.

Name:	John Marshall Johnston
Position:	Professor of Biochemistry, University of Texas (Southwest) Med. School, Dallas, 1966-present
Schools:	B.A., Hastings Colorado, 1949; Ph.D., Colorado, 1953
Positions:	Res. Assoc., Walter Reed Inst. Res. 53-55; Asst. Prof., Univ. of Texas (Southwest) Medical School, Dallas, 55-57; Assoc. Prof. 57-60; Professor 60-66; Nat. Sci. Found. Sr. Res. Fel., Univ. Lund, 62-63; U.S.A.R. 53-55
Memberships:	AAAS; Am. Chem. Soc.; Soc. Exp. Biol. & Med.; Am. Soc. Biol. Chem.

1049027

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961. Admitted to practice of law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A., 1941 Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association for the Advancement of Science; AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry), 1946; University of Minnesota, Minneapolis, Minnesota, B.S., 1949; M.D., 1950 Rotating Internship, Ancker Hospital, St. Paul, Minnesota, 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination, June 5, 1963
Memberships:	Fellow Industrial Medical Association; Past President, Tennessee Industrial Medical Association; American Academy of Occupational Medicine; American Medical Association; Past President, Roan-Anderson County Medical Society; Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Chairman, Medical and Health Sciences Division, ORAU Director, Radiation Emergency Assistance Center/Training Site (REAC/TS)
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; American Society for Experimental Pathology; Associated Researchers and Clinicians in Cancer; Society for Experimental Biology and Medicine; Health Physics Society; Radiation Research Society; Society of Nuclear Medicine; American Medical Association; Tennessee State Medical Society

1049028

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fellow American College of Physicians
Interests:	Late effects of radiation

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; American Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name:	John B. Storer
Position:	Director, Biology Division, Oak Ridge National Laboratory
School:	University of Chicago, M.D., 1947
Memberships:	American Association for Cancer Research; American Society for Experimental Pathology; Radiation Research Society; Society for Experimental Biology and Medicine; National Council on Radiation Protection and Measurements

Name:	Joseph F. Volker
Position:	President, University of Alabama, Birmingham, Alabama
Schools:	Indiana University, D.D.S., 1936 University of Rochester, A.B., 1938 University of Rochester, M.S., 1939 University of Rochester, Ph.D., 1942 Univ. Med. Sci., Bankok, hon. D.Sc., 1967 Univ. Lund, hon. Dr. Ontol., 1968 University of Alabama, hon. D.Sci., 1970 Indiana Univ., hon. D. Sci., 1970 Louis Pasteur Univ., hon. Dr., 1972
Memberships:	Mem. Unitarian Med. Teaching Mission, Czech., 1946, Ger., 1948 Specialist, U. S. Dept. State, Thailand, 1951-. Dir. Arizona Med. Sch. Study, 1960-1961 Mem. Inst. Med. Nat. Acad. Sci., 1971 Mem. Order of White Lion, Czech, 1946 Comdr., Order of Crown, 1959 Fel. Royal Col. Surg., 1961 Comdr., Order of Falcon, Repub. Iceland, 1969 AAAS; Soc. Expl. Biol. and Med.; Int. Assn. Dent. Res.

1049029

Name:	Lee Cross Washburn
Position:	Associate Scientist, Medical and Health Sciences Division Oak Ridge Associated Universities
Schools:	Murray State University, B.A., 1968 Vanderbilt University, Ph.D., 1972
Membership:	American Chemical Society
Interests:	Synthetic organic chemistry; chromatography, radiopharmaceutical tissue distribution studies; radioprotective drugs

Name:	Bruce W. Wieland
Position:	Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools:	Iowa State University, B.S., 1960 Ohio State University, Ph.D., 1973
Membership:	Society of Nuclear Medicine
Interests:	Production and utilization of short-lived positron-emitting isotopes for nuclear medical applications. Development of hot cell equipment for the synthesis of labeled compounds. Isotope imaging instrumentation, including coincidence detection and computer reconstruction techniques for tomography.

Name:	Joan B. Woods
Position:	Psychiatrist, Oak Ridge Mental Health Center
School:	University of Chicago School of Medicine, B.S. and M.D., 1960
Licensure:	Tennessee
Boards:	American Board of Psychiatry and Neurology
Memberships:	American Psychiatric Association American Medical Association and Subsidiaries

1049030

MEDICAL AND HEALTH SCIENCES DIVISION
OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon_____
(myself or name of patient)
of the following test: Phase I radiopharmaceutical tests of ^{11}C-DL-tryptophan for pancreas visualization.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes. Further, I understand that any information gained from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Medical and Health Sciences Division, Oak Ridge Associated Universities.

DATE_____ _____
(Patient or person authorized to consent for patient)

WITNESS:_____

_____

I have talked with _____about the proposed test to be given including the following:

1. This is a new radioactive drug: ^{11}C-DL-Tryptophan.
2. The drug contains the radioactive isotope ^{11}C and an organic chemical in quantities much less than those required to produce any measurable chemical effect in the body. Patient should feel no effect from the drug.
3. The radiation dose will be approximately 0.3 rad to the whole body.
4. Blood samples (2 ml) will be drawn at intervals during a period of 1-1/2 hours after administration.
5. Whole body counts and scans will be made over a 2-hr period.
6. The patient may withdraw from the test at any time.

DATE:_____ _____
Investigator

1049031

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 76-7

DESCRIPTION: Technetium 99m - Iron - Ascorbate - DTPA
(Renotec R)
For renal scanning. Dose will be 3-5 millicuries. For radiation dosimetry see attached copy of pages from PDR

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not X be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not X be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Bebb	✓			Nov. 12, 1976
[illegible]	✓			11/12/76
[illegible]	✓			11/15/76
R. L. Hayes	✓			11/15/76
Karl Hubner	NOT	VOTING		

Acknowledgement of submitter_____ Date_____

Proposal does____ does not X require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049032

PDR — 1976/7

Squibb & Sons—Cont.

c. Insert the vial containing the ^{99m}Tc sample into the lead shield and cover with the ring and top lids.

d. Record the net count rate (cpm) of the ^{99m}Tc sample (gross cpm minus background cpm).

e. Calculate the ^{99}Mo activity as follows: ^{99}Mo activity = ^{99}Mo factor (from step 1) × net count rate (cpm) of ^{99m}Tc sample.

Example: If net count rate of ^{99m}Tc sample (as determined in step 2d) = 1700 cpm and the ^{99}Mo factor = 0.003 μCi/cpm, then the ^{99}Mo activity = 0.003 μCi/cpm × 1700 cpm, which equals 5.1 μCi.

f. Calculate the concentration of ^{99}Mo per millicurie of ^{99m}Tc sample by dividing the ^{99}Mo activity (from step 2e) by the total ^{99m}Tc activity. *Example:* ^{99}Mo activity (in μCi) ÷ ^{99m}Tc activity (in mCi) = 5.1 ÷ 51, which equals 0.1 μCi Molybdenum 99 per mCi Technetium 99m.

B. Alternate Method

1. Place the Collecting Vial containing the total ^{99m}Tc eluate in a ¼-inch lead container and set this on the surface of a well-type scintillation detector or scintillation probe. (The lead container is provided on request with the Cesium 137 Standard mentioned below.)
2. Determine the activity in the 0.6–1.0 mev range. Record net counts per minute (cpm).
3. Remove the vial of ^{99m}Tc from the lead container and replace it with a Cesium 137 Standard. Determine the activity in the 0.6–1.0 mev range, maintaining constant geometry with previous count. Record net counts per minute (cpm). (The Cesium 137 Standard is provided on request in a Collecting Vial with a total volume of 5 ml. If the Squibb Standard is not used, be certain that the substitute ^{137}Cs standard is used in a container having the same geometry as the Collecting Vial.)
4. Calculate ^{99}Mo activity using the following formula: ^{99}Mo Activity (μCi/ml.) = (A × B × 4.5) ÷ C; where: A = net cpm of ^{99m}Tc sample, B = activity (in microcuries per ml.) of ^{137}Cs Standard, C = net cpm of ^{137}Cs Standard, and 4.5 = factor for converting ^{137}Cs activity to equivalent ^{99}Mo activity (see Table V below).

This generator is licensed for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Sec. 35.14 and Sec. 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

How Supplied

Available in potencies of 220 mCi, 440 mCi, 880 mCi, 1330 mCi, 1770 mCi, or 2220 mCi ^{99}Mo respectively, at calibration time. Complete assay data for each generator are provided on the label; directions for determining the activity of material eluted from the generator are provided in this monograph.

Supplied with the generator are vials of sterile, non-pyrogenic eluent, and suitable equipment for eluting, collecting, and assaying the Technetium 99m.

A 1½" lead shield, MAXI-SHIELD™, is also available for use with Minitec (Technetium 99m) Generator. Maxi-Shield consists of a base, cap, and interlocking half rings and is easily assembled on the site.

RENOTEC® (Technetium 99m-Iron-Ascorbate-DTPA Kit) B

Description

Renotec (Technetium 99m-Iron-Ascorbate-DTPA Kit) provides all the nonradioactive reagents needed to prepare a sterile, nonpyrogenic solution of technetium 99m-iron-ascorbate-diethylenetriamine pentaacetic acid. NOTE: The sterile ^{99m}Tc-sodium pertechnetate to be used in the reaction is obtained by elution from a Squibb Technetium 99m Generator.

Actions

The ^{99m}Tc-iron-ascorbate-DTPA prepared from Renotec is not a true chelate. It has been theorized that the radioactive component which localizes in the kidneys is a hydrolyzed form of technetium similar to that formed by the ^{99m}Tc-iron-ascorbic acid complex; both are alike in biological behavior.

The ^{99m}Tc-iron-ascorbate-DTPA is not excreted purely by glomerular filtration as are the chelates ^{99m}Tc-DTPA (Ferrous) and ^{99m}Tc-DTPA (Sn), and is retained in higher amounts in the kidney.

After intravenous administration, the ^{99m}Tc-iron-ascorbate-DTPA is uniformly distributed throughout most of the extracellular fluid but does not pass the blood-brain barrier. It does not localize in the choroid plexus, sali glands, stomach, or thyroid, thus reducin radiation dose and eliminating interferin calization of radioactivity. Most of the iso clears rapidly through the urinary tract w out entering into metabolic processes.

Indications

The ^{99m}Tc-iron-ascorbate-DTPA, prep from the Renotec (Technetium 99m-Iro corbate-DTPA Kit) reagents, is used as agent for imaging the kidneys.

Contraindications

At present, there are no known contraind tions to the use of ^{99m}Tc-iron-ascorbate-DT

Warnings

The contents of the two Unimatic® dispos syringes provided in the kit are intended o for use in the preparation of the ^{99m}Tc-i ascorbate-DTPA and are NOT to be direc injected into a patient.

Renotec (Technetium 99m-Iron-Ascrob DTPA Kit) is not radioactive. However, a ^{99m}Tc-sodium pertechnetate is added, adequ shielding of the resulting preparation must maintained.

This radiopharmaceutical should not be ministered to patients who are pregnant who may become pregnant or during lactat unless the information to be gained outwei the possible potential risks from the radiat exposure involved.

Since ^{99m}Tc is excreted in milk during lac tion, formula-feedings should be substitu for breast-feedings.

Ideally, examinations using radiopharmac ticals, especially those elective in nature, o woman of childbearing capability, should performed during the first few (approximat 10) days following the onset of menses.

Radiopharmaceuticals should be used only physicians who are qualified by specific tra ing in the safe use and safe handling of dionuclides, produced by nuclear reactor cyclotron, and whose experience and traini have been approved by the appropriate fede or state agency authorized to license the use radionuclides.

Precautions

The components of the kit are sterile and no pyrogenic. It is essential that the user foll the directions carefully and adhere to str aseptic procedures during preparation of t product.

To assure adequate urinary flow, the patie should be sufficiently hydrated. To minimi radiation dose to the bladder, the patie should be encouraged to void when the exam nation is completed and as often thereafter possible for the next four to six hours.

As in the use of any other radioactive materia care should be taken to insure minimum radi tion exposure to the patient consistent wit proper patient management and to insure mi imum radiation exposure to occupation workers.

Use the preparation within six hours after l beling with ^{99m}Tc.

Adverse Reactions

At present, adverse reactions have not bee reported following the administration of ^{99m}T iron-ascorbate-DTPA prepared with Renote (Technetium 99m-Iron-Ascorbate-DTPA Kit)

Preparation of ^{99m}Tc-Iron-Ascorbat DTPA

The directions outlined below must be car fully followed for optimum preparation of th technetium 99m-iron-ascorbate-DTPA. Th ^{99m}Tc-sodium pertechnetate used should b obtained by eluting a Squibb Technetium 99m Generator. See the package insert provide with the generator for complete directions o eluting and assaying ^{99m}Tc. Do not use the elu ate if there is any evidence of foreign matter. I ^{99m}Tc-sodium pertechnetate solutions must b diluted for use with Renotec (Technetium 99m Iron-Ascorbate-DTPA Kit), only Squibb Tech netium 99m Generator sterile eluent ...

TABLE V

Decay Chart: Molybdenum 99 half-life, 66.7 hr.

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
−48	1.647	36	0.688	120	0.287	204	0.120
−44	1.580	40	0.660	124	0.276	208	0.115
−40	1.515	44	0.633	128	0.264	212	0.111
−36	1.454	48	0.607	132	0.254	216	0.106
−32	1.395	52	0.583	136	0.243	220	0.102
−28	1.338	56	0.559	140	0.233	224	0.098
−24	1.283	60	0.536	144	0.224	228	0.094
−20	1.231	64	0.514	148	0.215	232	0.090
−16	1.181	68	0.493	152	0.206	236	0.086
−12	1.133	72	0.473	156	0.198	240	0.083
−8	1.087	76	0.454	160	0.190	244	0.079
−4	1.042	80	0.436	164	0.182	248	0.076
0*	1.000	84	0.418	168	0.175	252	0.073
4	0.959	88	0.401	172	0.167	256	0.070
8	0.920	92	0.384	176	0.161	260	0.067
12	0.883	96	0.369	180	0.154	264	0.064
16	0.847	100	0.354	184	0.148	268	0.062
20	0.812	104	0.339	188	0.142	272	0.059
24	0.779	108	0.326	192	0.136	276	0.057
28	0.748	112	0.312	196	0.130	280	0.055
32	0.717	116	0.300	200	0.125	284	0.052
						288	0.050

*Calibration time

1049033

TABLE I
Technetium 99m

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (kev)
M [illegible] electron, γ-1	98.6	1.7
[illegible]	88.3	140.5
K [illegible] 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 α x-rays	6.5	18.4

Dillman LT: Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, MIRD Pamphlet No. 4. J Nucl Med Suppl 2:22, 1969

Specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr. at 1 cm. The half value layer is 0.25 mm. of Pb. To facilitate control of the radiation exposure from millicurie amounts of the radionuclide, the use of a 4 mm. thickness of lead will attenuate the radiation emitted by a factor of about 0,000.

TABLE II
Decay Chart: Technetium 99m half-life, 6.0 hr.

Hours	Fraction Remaining	Hours	Fraction Remaining
−5	1.779	5	.562
−4	1.587	6	.500
−3	1.414	7	.446
−2	1.260	8	.397
−1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

reparation of ^{99m}Tc-iron-ascorbate-DTPA the solution will undergo color changes ranging from brown to yellow.

Procedure:

Swab the rubber closure of the Sterile Reaction Solution vial with germicide. Place the [illegible] a suitable radiation shield; keep [illegible] shielded at all times during the [illegible] aration.

Aseptically inject the proper volume (1 to 5 ml.) of sterile ^{99m}Tc eluate into the Sterile Reaction Solution vial. The volume is determined by the required dosage (in millicuries) and the activity of the eluate at the time of administration (see Step No. 5). **Relieve the excess pressure in the vial by withdrawing a volume of air from the vial approximately equal to the volume of the eluate injected.** Shake the vial gently to mix the contents.

Assemble Syringe 1, containing sterile 0.07N sodium hydroxide (see Directions for Assembly of Unimatic Syringe on Carton), and aseptically inject the entire contents into the Sterile Reaction Solution vial. **Relieve the excess pressure in the vial by withdrawing approximately 2 ml. of air.** Shake the vial gently to mix the contents.

Assemble Syringe 2, containing sterile DTPA solution, and aseptically inject its entire contents into the Sterile Reaction Solution vial. **Relieve excess pressure by withdrawing approximately 2 ml. of air.** Shake the vial gently to mix the contents.

Calculate the radioconcentration of the ^{99m}Tc-iron-ascorbate-DTPA solution by using the following formula: C = A ÷ (6 + V), where C = radioconcentration of the ^{99m}Tc-iron-ascorbate-DTPA solution (mCi/ml.), A = ^{99m}Tc activity added to Sterile Reaction Solution vial (mCi), and V = volume of ^{99m}Tc-eluate added to Sterile Reaction Solution vial (ml.).

6. Record the time and date of preparation and the radioactivity and volume of the ^{99m}Tc-iron-ascorbate-DTPA solution on the pressure-sensitive label supplied for each kit. Place the label on the radiation shield.
7. The prepared solution may be stored at room temperature; use within six hours after preparation.

Dosage and Administration

The suggested dose range for the average patient (70 kg.) for kidney imaging is 3 to 5 millicuries of ^{99m}Tc-iron-ascorbate-DTPA administered intravenously.

Withdrawals from the Sterile Reaction Solution vial should be made with a 22–26 gauge needle.

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. Photons that are useful for imaging studies are listed in Table I.

To correct for radioactive decay, multiply the assay value stated on the label by the fraction remaining at the time of administration. The fraction remaining at selected time intervals before and after the calibration time is shown in Table II.

Radiation Dosimetry

A summary of estimated absorbed radiation doses to an average 70 kg. patient from an intravenous injection of a maximum dose of 20 millicuries of ^{99m}Tc-iron-ascorbate-DTPA is shown in Table III.

TABLE III
Technetium 99m

Radiation Doses for 70 kg. Man

Tissue	Absorbed Dose (rads) 20 mCi ^{99m}Tc
Kidneys	0.84
Bladder	11.1
Testes	0.32
Ovaries	0.38
Whole-body	0.32

Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides. MIRD Pamphlet No. 1. J Nucl Med Suppl 1:7, 1968

This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Sec. 35.14 and Sec. 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

Storage

Store in refrigerator; protect from light.

How Supplied

In cartons containing 5 Kits. Each Kit includes the following components: one Sterile Reaction Solution vial providing 2 ml. of a sterile aqueous solution containing 10 mg. ferric chloride (5 mg./ml.), 5 to 10 mg. ascorbic acid (2.5 to 5 mg./ml.), and sodium hydroxide to adjust the pH to 2.0–4.0 (the solution contains no preservative); one 2 ml. Unimatic® disposable syringe—Syringe 1—Sterile 0.07N Sodium Hydroxide Solution—each 2 ml. provides 5.6 mg. sodium hydroxide (2.8 mg./ml.) in aqueous solution; one 2 ml. Unimatic disposable syringe—Syringe 2—Sterile Diethylenetriamine Pentaacetic Acid Solution—each 2 ml. provides 5 mg. DTPA (2.5 mg./ml.) in aqueous solution; and an adequate supply of pressure-sensitive labels.

SETHOTOPE® R

Selenomethionine Se 75 Injection

Description

Sethotope (Selenomethionine Se 75 Injection) is a sterile, nonpyrogenic, aqueous solution, for intravenous use, of L-selenomethionine ^{75}Se providing a specific activity of not less than 25 microcuries per microgram of selenium at the time of manufacture. The preparation also contains, in each ml., not more than 3 mg. L-methionine as a carrier, not more than 12 mg. 2-aminoethanethiol as an antioxidant, sodium chloride for isotonicity, and 0.9% (w/v) benzyl alcohol as a preservative; the pH has been adjusted to 3.5–6.0 with sodium hydroxide or hydrochloric acid.

Actions

Selenomethionine is an analog of the essential amino acid, methionine, in which the sulfur atom is replaced by a selenium atom. After intravenous administration, selenomethionine ^{75}Se is localized in all organs involved in active protein synthesis and is incorporated into newly synthesized proteins. A relatively high degree of uptake is found in the pancreas which is related to rapid rate of synthesis of digestive enzymes in this organ. The peak of pancreatic activity is observed within the first half-hour after intravenous administration. Significant uptake also occurs in the liver and proximal small intestine, as well as several other tissues.

Indications

Sethotope (Selenomethionine Se 75 Injection) is indicated for pancreas imaging as an aid in the diagnosis of suspected pancreatic disease.

Contraindications

At present, there are no known contraindications to the use of Selenomethionine Se 75 Injection.

Warnings

This radiopharmaceutical should not be administered to patients who are pregnant or who may become pregnant or during lactation unless the information to be gained outweighs

Continued on next page

1049034

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Gould A. Andrews, M.D. PROPOSAL NO. 77-1

DESCRIPTION: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys. SEE ATTACHED IND. MAXIMUM DOSE NOT TO EXCEED 15 mCi.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other: FIRST 5 PATIENTS TO RECEIVE NO MORE THAN 5 mCi FOR ~~purpo~~ VERIFICATION OF ESTIMATED DOSE TO BRAIN. THIS COMMITTEE WILL RE-EVALUATE THIS PROPOSAL AFTER 5 PATIENTS.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Fitts	✓			14 March, 1977
R. J. Hayes	not voting			14 Mar 1977
D. C. Swartzendruber	✓			14 Mar 1977
J. Bergan	✓			3/14/77
KARL F. HUBNER	ABSENT			

Acknowledgement of submitter Gould A. Andrews Date 16 March '77

Proposal does ✓ does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on 27 APRIL, 1977

1049035

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division (MHSD), Oak Ridge

Associated Universities (ORAU), Oak Ridge, Tennessee

April 5, 1977

1. NAME OF DRUG: ^{68}GA EDTA. This drug will be dissolved in a sterile, nonpyrogenic saline solution and administered intravenously.

2. COMPONENTS:

   a. Gallium-68 ethylenediamine-NNN'N'-tetraacetic acid (^{68}Ga EDTA).

   b. Disodium ethylenediamine - NNN'N' - tetraacetic acid (Na_2 EDTA).

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION:

   Since the ^{68}Ga present in ^{68}Ga EDTA is radioactive ($T_{1/2}$ = 68 min.), we cannot state an exact relationship between the components of this preparation at the time of administration. From radiation dosimetry considerations, however, we have determined that the maximum ^{68}Ga activity administered will not exceed 0.23 mCi per kilogram of body weight (a 15 mCi dose for a 70 kg subject). The quantitative relationship between ^{68}Ga and the other components in the preparation will be determined by the time that elapses from the elution of ^{68}Ga from its generator and the administration of the agent to the patient. Also there will be a gradual decrease in the ^{68}Ga yield of the generator as parent ^{68}Ge decays while the amount of eluting Na_2 EDTA will remain the same. The composition stated below, therefore, represents the dose limits that will be adhered to for the components in this radiopharmaceutical preparation:

   a. ^{68}Ga EDTA: maximum of 0.23 mCi per kilogram of body weight (15 mCi total for a 70 kg subject).

   b. Disodium EDTA: maximum of 0.5 mg per kilogram of body weight (35 mg total for a 70 kg subject). The weight of ^{68}Ga EDTA administered (a, above) will be negligible compared to that of Na_2 EDTA.

1049036

c. Sodium chloride: maximum of 1 mg per kilogram of body weight (70 mg total for a 70 kg subject).

d. Water: maximum of 0.15 ml per kilogram of body weight (10 ml total for a 70 kg subject).

4. SOURCE OF NEW DRUG SUBSTANCE:

The ^{68}Ga will be separated as needed from its parent, ^{68}Ge, by elution of a ^{68}Ge, ^{68}Ga generator obtained from New England Nuclear (NEN), Boston, Mass. The eluent will be a 0.005 M solution of sterile Na_2 EDTA adjusted to pH 7.0.

5. METHODS, FACILITIES AND CONTROLS:

Gallium-68 will be eluted from an NEN generator using 10 ml portions of a pH 7.0, 0.005 M Na_2 EDTA solution. These portions of eluting solution will be contained in individual vials (Wheaton Glass Co., Millville, N.J.) that have previously been filled, capped and steam sterilized. Each batch of vials will have been checked before use for sterility and absence of pyrogens using standard USP techniques. The 0.005 M EDTA solution will be prepared by dilution of a 0.5 M EDTA stock solution supplied by NEN. The eluate from the ^{68}Ga generator will be collected in a sterile beaker containing 1 ml of sterile 9% aqueous saline. After mixing, the solution will be filtered through a sterile, nonpyrogenic 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (Wheaton Glass). A portion of this filtered solution will be removed for radioassay, USP sterility testing and pyrogen testing (using the Pyrotest Limulus Lysate technique [Difco Laboratories, Detroit, Mich.]). The short half-life of ^{68}Ga (68 min) precludes pyrogen testing with rabbits in the conventional USP manner. The radioassay and other test results will become part of the record. Radioassay and verification of radioisotopic purity will be carried out using a sodium iodide detector (calibrated with NBS standards) and a multichannel analyzer. (A photograph of the gamma ray spectrum from 0-2 MeV will be made a part of the permanent record.) The vial containing the ^{68}Ga EDTA will then be labeled as to its assay and total content (see section 7). After removal from the vial, each ^{68}Ga EDTA dose will again be assayed for radioactivity content just prior to administration using a Capintec CRC-10 radioisotope calibrator (Capintec Inc., Montvale, N.J.).

Preparation of each batch of ^{68}Ga EDTA for clinical use will be carried out in a positive-pressure clean room equipped with a vertical laminar flow hood with an air curtain (Envirco, Albuquerque, N.M.). All glassware used will be presterilized by steam. Each batch of ^{68}Ga EDTA will be given a batch number and all particulars relative to its preparation and use will be entered into a master logbook.

6. STATEMENT OF INFORMATION AVAILABLE TO THE SPONSOR:

a. Preclinical and Clinical Investigations

1. Animal studies

Animal studies of ^{68}Ga EDTA have been carried out under the supervision of R. L. Hayes (appendix). When administered intravenously in rats, ^{68}Ga EDTA is excreted rapidly through the kidneys with an initial blood half disappearance time of ∿ 10 min (1). Foreman (2) has reported a blood clearance half time in the rat of 1 hr over a 1-6 hr period using ^{14}C-labeled EDTA. He also reported over 90% urinary excretion of EDTA in the rat during a 3-hr period (3). Tissue concentrations of ^{68}Ga activity in the rat through 2 hrs are shown in Table 1 (our data). Table 2 shows the whole body retention (corrected for decay) of ^{68}Ga (EDTA) through 2 hrs in the rat as determined in a geometry-independent small animal whole body counter following removal of ^{68}Ga activity from the urinary bladder before assay (our data also). The data in Tables 1 and 2 have been used to calculate the radiation doses expected to occur in man (see section 6-a-4). Little dissociation of ^{68}Ga EDTA would be expected to occur at physiological pH and consequently ^{68}Ga would be expected to be excreted almost completely in the EDTA form (4). This has been verified biologically in the rat (1). It is, however, of interest that, although ^{68}Ga given in the EDTA form is excreted rapidly and almost completely, the ^{68}Ga activity that does remain is proportioned between transplanted tumors and nontumor tissues in much the same way that ^{67}Ga citrate is (see Table 3). This suggests that ^{68}Ga EDTA may also be of use in the detection of extracranial tumors at the same time a search is being made for intracranial tumors.

2. Human studies

Our research group has had extensive experience with the use of the radioisotopes of gallium. Between 1949 and 1952, we made an extensive study of ^{72}Ga (containing stable carrier gallium) as a potential diagnostic and therapeutic agent (5), and toward the end of that study our observations were extended to carrier-free ^{67}Ga (6).

In 1966, we resumed studies on the radionuclides of this element; this work involved initially ^{68}Ga citrate with various doses of added stable gallium carrier for use as a bone-scanning agent (1, 7). Somewhat later, as the result of improvements in instrumentation, we resumed studies with ^{67}Ga citrate and out of this work grew the discovery that ^{67}Ga citrate in carrier-free form was a valuable agent for scanning soft tissue tumors (8).

Clinical studies with ^{68}Ga EDTA, the radionuclide and drug form that is the subject of this IND application,have been carried out by a number of workers. In an early report on ^{68}Ga in 1964, Shealy et al. (9) used ^{68}Ga versenate (EDTA) to perform 47 brain scans in 35 patients. They used an extraction technique to separate ^{68}Ga from parent ^{68}Ge rather than the NEN alumina-type generator (10) and also

employed stable carrier gallium in the separation procedure. The dose of ^{68}Ga was not stated, but the largest amount of stable gallium administered per patient was about 1 mg. No toxic reactions were reported. Results were considered promising. Gottschalk et al., took advantage of the annihilation photons from ^{68}Ga to use ^{68}Ga EDTA in scanning for brain tumors with the use of an Anger positron scintillation camera. They studied 20 patients with doses of 700 to 750 μCi per patient with moderately good localization of brain tumors, and no untoward reactions (11). A later report by Schaer et al. (12), which may have included some of the same cases in the preceding report, described results in 96 patients. In addition, 41 patients were studied but not included in the report because of inadequate follow-up. The dosage was usually 400 to 450 μCi. No untoward effects were recorded. Success in localizing brain tumors was considered generally good.

The blood clearance and urinary excretion of ^{14}C-labeled EDTA in man has been reported by Foreman to be similar to that found in the rat (2). Anger and Gottschalk (13) have reported that they found the tissue distribution and urinary excretion of ^{68}Ga EDTA in the rat to be similar to that reported by Foreman, although they gave no data in their paper. They also found that the urinary excretion of ^{68}Ga EDTA in humans was similar to that reported for man by Foreman (14) who used ^{14}C-labeled EDTA.

3. Toxicity

The toxicity of ^{68}Ga, when administered as proposed, should be nil from a chemical standpoint, since the ^{68}Ga will be carrier-free and hence present in the preparation at only the nanogram level.

As previously stated, the maximum Na_2 EDTA to be administered will be 0.5 mg/kg (35 mg for a 70 kg subject) which is far below any level that should produce any toxic symptoms (see 6-a-2 above for reports on absence of human reactions to the administration of ^{68}Ga EDTA).

Prolonged EDTA administration at high dose levels in the rat does produce a nephrotic syndrome, consisting of severe hydropic degeneration of the proximal tubules (15). The ED_{50} (the amount of EDTA required to produce the first histological evidence of damage in 50% of the animals treated daily for 16 days) was 203 mg/kg/day. Prolonged administration of large doses was required to produce lesions and the lesions were reversible. Since the Na_2 EDTA to be administered in the proposed ^{68}Ga EDTA preparation will be no more than 0.5 mg/kg, adverse effects in patients are considered to be highly unlikely.

The ORAU-ORNL Committee on Human Studies has approved these studies (see appendix for membership).

4. Radiation Dosimetry

Gallium-68 has a 68 min half-life decaying by positron emission to stable ^{68}Zn. Because of its short half-life and rapid urinary excretion, the radiation dose to patients will be acceptable. It has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center (headed by R. J. Cloutier) that the complete decay of 1 mCi of ^{68}Ga EDTA uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.054 rads or a total of 0.8 rads per 15 mCi (the maximum proposed administered dose of ^{68}Ga EDTA).

Table 4 gives details of the expected radiation dose to various organs in the human estimated from the animal data shown in Tables 1 and 2 using MIRD methods of dosimetric calculation. The only normal tissue receiving a large dose of radiation from the maximum dose of ^{68}Ga EDTA to be administered (15 mCi) will be the wall of the urinary bladder. It is estimated that this particular radiation dose will be between 15 and 30 rads, depending on the time interval between urinary bladder emptying (0.5 to 1.0 hr intervals). This frequency of urination will be obtained by thoroughly hydrating the patient with water by mouth prior to administration of ^{68}Ga EDTA and encouraging the patients to urinate at least once during each hourly interval after ^{68}Ga EDTA administration through 3 hours. Each urination would be followed by consumption of more water by the patient (see attached patient consent form). Before the maximum dose of ^{68}Ga EDTA (0.23 mCi/kg) is administered, a series of 5 patients will be studied at a level of 1/3 the maximum dose to determine from the timing and amounts of ^{68}Ga excreted whether the estimates in Table 3 for the dose to the urinary bladder wall are essentially correct. If the study indicates that higher bladder wall doses will probably be incurred, the maximum dose of ^{68}Ga EDTA will be adjusted downward accordingly. Since the bladder and excretory ducts are considered to be radioresistant structures (16), we do not consider that a dose of 30 rads to the wall of the urinary bladder is excessive.

A small amount of parent ^{68}Ge ($T_{1/2}$ = 287 d) leaches from the NEN generator when it is eluted with EDTA and ^{68}Ge will necessarily be present as a contaminant in the ^{68}Ga EDTA preparation. This ^{68}Ge contamination amounts, in our experience, to $\sim$ 0.02% of the ^{68}Ga eluted on an activity basis. In the rat germanium is almost quantitatively excreted through the kidney within 24 hours, even when administered intramuscularly (17). The ^{68}Ge present in the preparation would, therefore, act only as a transient additive source of ^{68}Ga. Assuming that the biological half time of ^{68}Ge is 0.93 days (ICRP value for ^{71}Ge) and that a half-life period of 68 minutes elapses after ^{68}Ga elution before the ^{68}Ga EDTA preparation is administered, it is estimated that the additional total body radiation dose produced by the ^{68}Ge in a 15 mCi dose of ^{68}Ga would be approximately 0.06 rads.

The ORAU Medical Radionuclide Committee has reviewed our protocol, and approved of the use of ^{68}Ga EDTA from a radiation dosimetry standpoint.

1049040

b. Previous Marketing

Gallium-68 EDTA has not been marketed before.

c. Drug Combination

Gallium-68 EDTA is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with ^{68}Ga EDTA will have the following form:

GA-68 EDTA (FOR I.V. INJECTION)

Assay _____mCi/ml as of_____

Volume_____ml: Batch No._____

Expiration Time_____

CAUTION: INVESTIGATIONAL NEW DRUG

CAUTION: RADIOACTIVE MATERIAL

Oak Ridge Assoc. Univ., Oak Ridge, Tn.

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal information material will be prepared; however, each participant will of course be issued a copy of this application.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the investigators, all of whom are supported by competent associates, to be well qualified for this type of research. See bibliographical material in the appendix about Drs. Andrews, Hayes, Hübner, and Purvis.

9. PROGRESS OF THE INVESTIGATION:

The principal investigator will be Dr. G. A. Andrews. The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by G. A. Andrews, M.D., R. L. Hayes, Ph.D., K. F. Hübner, M.D. and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Chairman of the ORAU Medical and Health Sciences Division, with advice from the ORAU Medical Advisory Committee and the ORAU/ORNL Committee on Human Studies (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

Phase I studies are deemed unnecessary, since ^{68}Ga EDTA has already had considerable use in patients without evidence of toxicity (9, 11, 12). The carrier-free ^{68}Ga present in the preparation is minute in weight, far below any chemically toxic level and at the activity level planned will deliver a radiation dose generally well within acceptable limits for a nuclear medical diagnostic study (0.8 rads to the whole body).

The radiation dose to the wall of the urinary bladder (15-30 rads) will, however, be much higher but the protocol to be used will act to minimize the dose to this radioresistant tissue (see section 6-a-4). The amount of EDTA present in the preparation will also be well below any known toxic level.

All Phase II studies of ^{68}Ga EDTA will take advantage of tomographic techniques made possible by the positron emission of ^{68}Ga. A positron emission computerized axial tomograph (ECAT, available from ORTEC Inc., Oak Ridge, Tenn.) will be used in all studies. This instrument is a refined version of the St. Louis PETT III (18). Only nonpregnant adult patients capable of giving informed consent will be studied and each will be fully informed concerning the extent of radiation exposure involved and that the study is experimental. A written document of consent (copy attached) will be obtained from each patient. Blood samples will be taken and quantitative measurements of whole body retention and urinary excretion will be made in order to select optimum doses of ^{68}Ga EDTA and the timing for best imaging. Estimates of radiation dosimetry will be revised on the basis of the data collected.

The following Phase II studies will be carried out using ^{68}Ga EDTA:

a. Imaging of Kidney and Bladder

The main objective is to visualize the kidneys which concentrate ^{68}Ga EDTA and excrete it into the urine. This excretion, although rapid, is slow enough to permit imaging the kidneys as has been demonstrated by earlier work (1). Transverse section ECAT images of the body through the kidneys should show tumors and cysts as areas of decreased concentration. Intrinsic and extrinsic lesions may also be shown due to anatomical distortions.

Patients will all have suspected or proven renal lesions, and will be referred from physicians in the Oak Ridge-Knoxville area and possibly from the East Tennessee Chest Disease Hospital located in Knoxville. The ^{68}Ga EDTA will be given intravenously in doses of 0.23 mCi/kg or less. Imaging will start immediately after administration in the first patients studied. Optimal results are expected within 1 hour. Depending upon the promise shown by initial results, we expect to study up to 30 patients in this fashion. Bladder images will be made in the same group of patients at the completion of the renal study. This research project is expected to be completed within a period of 1 to 2 years.

The principal question to be answered is whether this test is superior to intravenous pyelography with contrast media as a method of studying the kidneys for anatomical lesions.

b. Detection and Localization of Brain Lesions

It is known that ^{68}Ga EDTA localizes in some brain tumors and other (vascular) lesions because of disturbances in the blood-brain-barrier, and possibly by other mechanisms (11). Because of its positron emission

and the resulting improved anatomic localization by new tomographic instrumentation, ^{68}Ga EDTA may possibly be superior to ^{99m}Tc pertechnetate in some clinical situations. This superiority might be in terms of better localization or better differentiation of the type of lesion; the latter would eventuate if there is some unknown chemical behavior unique to ^{68}Ga EDTA and certain types of lesions.

Patients will be those with known or strongly suspected brain lesions. Most of them will be referred by Dr. John T. Purvis, a neurosurgeon practicing in Knoxville. ^{68}Ga EDTA will be administered at a dose level of 0.23 mCi/kg or less. Imaging of the brain will be started immediately after the intravenous dose is given, and in the initial patients will be continued for as long as statistically valid images can be obtained. Optimum results are expected to occur between 30 minutes and 2 hours. Images will be compared with those obtained with other standard techniques, such as routine ^{99m}Tc brain scans, pneumoencephalograms, and surgical results. A specific comparison will be made in as many cases as possible between positron computerized transaxial tomography (ECAT) and X-ray transmission computerized axial tomography. The latter type studies are available at the Presbyterian Hospital in Knoxville where Dr. Purvis practices. A total of up to 30 patients will be studied over a 1- to 2-year period using this protocol.

The principal question to be answered by this study is whether the proposed new technique will give superior diagnostic information in certain clinical situations.

c. Detection of Obscure Soft Tissue Tumors

Gallium-67 citrate is of known value in visualizing cancers and abscesses. Imaging is usually delayed for 48 hours to allow clearance of the isotope from surrounding normal tissues. Uptake in the lesions is known to be quite rapid (see Table 5), but high ^{67}Ga levels bound by plasma proteins dictate delay of scanning until 48 hours after administration to permit clearance of ^{67}Ga from the blood. As was pointed out in section 6-a-1, ^{68}Ga EDTA shows a tumor-to-nontumor distribution pattern similar to that of ^{67}Ga citrate although absolute tissue concentrations for the EDTA form are much lower than they are with the citrate form. Thus it is possible, considering the rapid clearance of ^{68}Ga EDTA from the blood and the essentially uniform detection of positron emitters with respect to depth, that, using positron tomography, ^{68}Ga EDTA could also be effective in detecting extracranial tumors, i.e., following or during a ^{68}Ga EDTA brain study.

Patients with a known diagnosis of malignant disease will be used. Gallium-68 EDTA will be given intravenously at a dose of 0.23 mCi/kg. Imaging will be started within 30 minutes after administration. The results will be compared in as many instances as possible with ^{67}Ga citrate scans, and also with all other available data from diagnostic tests, surgery and autopsy.

The main question to be answered is whether this diagnostic procedure has clinical value and is possibly equal or superior to ^{67}Ga scanning.

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{68}Ga EDTA prior to 30 days after the date of receipt of notice of this application by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

1049044

REFERENCES

1. Hayes, R.L. Radioisotopes of Gallium. In: Radioactive Pharmaceuticals, edited by G. A. Andrews, R. M. Kniseley, and H. N. Wagner, Jr. AEC Symposium Series No. 6, CONF-651111, April 1966, pp. 603-618.

2. Foreman, H. The pharmacology of some useful chelating agents. In: Metal-Binding in Medicine, 1960, pp. 82-94.

3. Foreman, H., Vier, M., and Magee, M. The metabolism of C^{14}-labeled ethylenediaminetetraacetic acid in the rat. J. Biol. Chem. 203:1045-1053, 1953.

4. Saito, K. and Tsuchimoto, M. A kinetic study of the isotopic exchange of gallium between the gallium ion and gallium ethylenediamine-N,N,N',N'-tetraacetate and N-2-hydroxyethyl ethylenediamine-N,N',N'-triacetate in water. J. Inorg. Nucl. Chem. 23:71-79, 1961.

5. Brucer, M., et al. A study of $gallium^{72}$. Radiology 61:534-613, 1953.

6. Bruner, H.D., Hayes, R.L., and Perkinson, J.D., Jr. X. Preliminary data on $gallium^{67}$. Radiology 61:602-612, 1953.

7. Kniseley, R.M., Andrews, G.A., Edwards, C.L., and Hayes, R.L. Bone-marrow and skeletal scanning. Radiologic Clinics of North America 7:265-280, 1969.

8. Edwards, C.L. and Hayes, R.L. Scanning malignant neoplasms with gallium 67. JAMA 212:1182-1190, 1970.

9. Shealy, C.N., Aronow, S., and Brownell, G.L. Gallium-68 as a scanning agent for intracranial lesions. J. Nucl. Med. 5:161-167, 1964.

10. Greene, M.W. and Tucker, W.D. An improved gallium-68 cow. Int. J. Appl. Radiat. Isotopes 12:62-63, 1961.

11. Gottschalk, A., McCormack, K.R., Adams, J.E., and Anger, H.O. A comparison of results of brain scanning using Ga^{68}-EDTA and the positron scintillation camera, with Hg^{203}-neohydrin and the conventional focused collimator scanner. Radiology 84:502-506, 1965.

12. Schaer, L.R., Anger, H.O., and Gottschalk, A. Gallium edetate ^{68}Ga experiences in brain-lesion detection with the positron camera. JAMA 198:139-141, 1966.

13. Anger, H.O. and Gottschalk, A. Localization of brain tumors with the positron scintillation camera. J. Nucl. Med. 4:326-330, 1963.

14. Foreman, H. and Trujillo, T.T. The metabolism of C^{14} labeled ethylenediaminetetraacetic acid in human beings. J. Lab. Clin. Med. 43:566-571, 1963.

15. Foreman, H., Finnegan, C., and Lushbaugh, C.C. Nephrotoxic hazard from uncontrolled edathamil calcium disodium therapy. JAMA 160: 1042, 1956.

104045

16. Casarett, A.P. In: Radiation Biology, Prentice Hall, 1968, p. 198.

17. Durbin, P.W. Metabolic characteristics within a chemical family. Health Physics 2:225-238, 1960 (see p. 230).

18. Hoffman, E.J., et al. Design and performance characteristics of a whole body positron transaxial tomograph. J. Nucl. Med. 17:493-502, 1976.

1049046

Table 1

Tissue Distribution of ^{68}GaEDTA in COBS Rats*

Tissue	Percent of injected dose/gram**		
	30 min.	60 min.	120 min.
Liver	0.096 ± 0.009***	0.11 ± 0.019	0.08 ± 0.008
Spleen	0.165 ± 0.014	0.18 ± 0.032	0.30 ± 0.028
Kidney	1.143 ± 0.167	0.68 ± 0.040	0.36 ± 0.003
Muscle	0.042 ± 0.003	0.03 ± 0.003	0.02 ± 0.000
Femur	0.091 ± 0.013	0.05 ± 0.003	0.05 ± 0.005
Blood	0.189 ± 0.014	0.11 ± 0.004	0.04 ± 0.004

* 5 or more animals per group.

** Normalized to body weight of 250 g.

*** Standard error.

Table 2

Whole Body Retention of ^{68}GaEDTA in COBS Rats*

Time (min)	Percent Retention
5	92.7 ± 1.80**
10	60.6 ± 1.51
15	63.6 ± 5.45
30	40.1 ± 6.01
45	23.6 ± 2.54
60	19.4 ± 2.26
90	9.6 ± 0.75
120	13.7 ± 0.53
180	9.4 ± 1.46

* 5 animals per group.

** Standard error.

1049047

Table 3

Comparison of the Tissue Distribution of ^{67}Ga Citrate with that of ^{67}Ga EDTA in Fischer 344 Rats Bearing RFT Tumors

Tissue	Citrate	EDTA
Tumor (%/g)*	4.2	0.071
Ratio tumor to:		
Liver	4.3	2.8
Spleen	3.0	0.4
Kidney	4.6	1.2
Lung	13.0	8.9
Muscle	21.0	18.0
Femur	2.9	2.1
Blood	19.0	12.0

* Normalized to body weight of 250 g; 4 animals per group.

Table 4

Radiation Dose (Rads) from I.V. Injection of 1 mCi of ^{68}Ga EDTA in Man Extrapolated from Rat Data*

Bladder Wall Voiding Time (hr)			Total						
4.8	1.0	0.5	Body	Kidney	Liver	Spleen	Lung	Ovary	Testes
5.1	2.0	1.0	0.051	0.063	0.022	0.028	0.017	0.083	0.076

* Dose to all organs except bladder wall was calculated by MIRD method assuming a 4.8 hour voiding interval. Volume of urine in bladder was assumed to be 200 ml.

1049048

Table 5

Uptake of ^{67}Ga in RFT Tumor Tissue with Time

Time (hr)	% Administered $^{67}Ga/g$
2	1.11 ± 0.15*
4	1.93 ± 0.33
12	3.15 ± 0.37
24	3.59 ± 0.17

*Standard error; 4 animals per group.

1049049

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon _____
(myself or name of patient)

of the following test: Phase II Radiopharmaceutical Tests of ^{68}Ga-labeled ethylenediamine-N,N,N'N'-tetraacetic acid (^{68}Ga-EDTA) as an agent to detect brain, soft tissue or kidney tumors, and/or non-tumorous lesions in brain or kidneys.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes and is being done only for gathering information related to my disease, treatment or both. Further, I understand that any information learned from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Oak Ridge Associated Universities Medical Division.

Date: _____ _____
(Patient or person authorized to consent for patient)

Witness: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a modified radioactive drug: [^{68}Ga-ethylenediamine-N,N,N'N'-tetraacetic acid (a chelating agent)] which differs from the previously known and medically approved form of this drug only by the fact that it is labeled with ^{68}Ga.
2. The drug contains the isotope ^{68}Ga and a chelating agent in quantities much less than those required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. However, untoward effects are remotely possible with any new drug.
4. The radiation dose will be no more than 0.8 rad to the whole body, and probably less. The bladder will receive a higher dose, possibly as much as 30 rads (approximately twice the yearly approved occupational dose.) All radiation used in a diagnostic test such as this has some possibility of contributing to an increased incidence of cancer or leukemia. This possibility has been considered by the ORAU Medical Radionuclide Committee and is believed so low as to make the possible benefits of the test far outweight the possible risks.
5. Blood samples (2 ml) will be drawn at frequent intervals during a period 1-1/2 hours after administration for research purposes, and urine samples will also be collected for a period of 2-3 hours. The venipunctures will inevitably cause some discomfort. We hope to limit them to two - one for administering the isotope and one for an inlying sample collecting tube.
6. The patient will be expected to drink several glasses of water before and during the procedure.

7. Scans will be made with a special tomographic scanner.
8. The patient may withdraw from the test at any time.

Date: _____ _____
Investigator

1049051

7. Scans will be made with a special tomographic scanner.
8. The patient may withdraw from the test at any time.

Date: _____ _____
Investigator

APPENDIX

Investigators:

G. A. Andrews, M.D., Principal Investigator
R. L. Hayes, Ph.D.
K. F. Hübner, M.D.
J. T. Purvis, M.D.

ORAU/ORNL Committee on Human Studies:

Gould A. Andrews, M.D. (Secretary)
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Donald W. Goodwin, Ph.D.
Minister, United Church
Chapel-on-the-Hill
Oak Ridge, Tennessee 37830

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Y-12 Area, Building 9704-2
Union Carbide Nuclear Company
P. O. Box Y
Oak Ridge, Tennessee 37830

Robert D. Lange, M.D. (Chairman)
Assistant Director
University of Tennessee
Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

1049053

Michael Scott Lawyer, J.D.
Staff Attorney
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

Clarence C. Lushbaugh, Ph.D., M.D. (Ex officio)
Chairman, Medical & Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Joan B. Woods, M.D.
Psychiatrist
Veterans Administration Hospital
Murfreesboro, Tennessee 37130

ORAU Medical Advisory Committee:

George B. Hutchison, M.D.
Professor of Epidemiology
Harvard University School of Public Health
55 Shattuck
Boston, Massachusetts 02115

John M. Johnston, Ph.D.
Department of Biochemistry
University of Texas Medical School
(Southwestern)
Dallas, Texas 75235

David Kuhl, M.D.
Division of Nuclear Medicine
Room B2-128
Center for the Health Sciences
University of California
Los Angeles, California 90024

Leonard A. Sagan, Ph.D.
Internal Medicine, Research Administration
Associate Director, Dept. of Environmental Medicine
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

William H. Stone, Ph.D.
Professor of Genetics
University of Wisconsin
Madison, Wisconsin 53706

Joseph F. Volker, Ph.D. (Ex officio member from the ORAU Board of Directors)
President
University of Alabama
Birmingham, Alabama

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews (see additional material at end of Appendix)
Position:	Internist, Director of Clinical Applications
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society of Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Sciences; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society, American Thyroid Association

Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name:	Donald W. Goodwin
Position:	Minister, United Church, Chapel-on-the-Hill
School:	Bangor Theological Seminary, Bachelor of Divinity, 1959 Brown University, Ph.D., 1965
Memberships:	Ministerial Standing, United Church of Christ
Additional Information:	Member of various boards which change from time to time

1049055

Name:	R. L. Hayes
Position:	Director of Radiopharmaceutical Development, Chief Scientist
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U. S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

Name:	George B. Hutchison
Position:	Epidemiologist, Michael Reese Hospital, Chicago, 66-present
Schools:	Harvard University, A.B., 1943 Harvard University, M.D., 1951 Harvard University, M.P.H., 1960
Positions:	Fel. med. Lahey Clin., 52-55; asst. med. dir. Equitable Life Assurance Soc., U.S., 55-56; Health Ins. Plan Greater New York, 56-57; dir. res. City Health Dept., New York, 57-59; asst. prof. epidemiol. sch. pub. health, Harvard, 60-61; assoc. prof. 61-66; Consult, Health Ins. Plan Greater New York, 57-present
Memberships:	Fel. Am. Pub. Health Asn; Am. Statist. Asn; World Med. Asn.; Asn. Teachers Prev. Med.

Name:	Karl F. Hübner
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Licensure:	Tennessee
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Memberships:	AMA, Tenn. Med. Association
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology

1049056

Name:	John Marshall Johnston
Position:	Professor of Biochemistry, University of Texas (Southwest) Med. School, Dallas, 1966-present
Schools:	B.A., Hastings Colorado, 1949; Ph.D., Colorado, 1953
Positions:	Res. Assoc. Walter Reed Inst. Res. 53-55; Asst. Prof., Univ. of Texas (Southwest) Medical School, Dallas, 55-57; Assoc. Prof. 57-60; Professor 60-66; Nat. Sci. Found. Sr. Res. Fel., Univ. Lung, 62-63; U.S.A.R. 53-55
Memberships:	AAAS; Am. Chem. Soc.; Soc. Exp. Biol. & Med.; Am. Soc. Biol. Chem.

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961; admitted to practice of Law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	David E. Kuhl
Position:	Chief, Division of Nuclear Medicine Professor of Radiological Sciences University of California, Los Angeles
School:	Temple University, A.B., 1951 University of Pennsylvania School of Medicine, M.D., 1955
Positions:	Intern, Hosp., Univ. Pa., 55-56; resident radiol, 58-62; Prof. Radiol. & Dir. Div. Nuclear Med. (until fall of 1976 moved to California)
Licensure:	Pennsylvania, California
Memberships:	American College of Nuclear Physicians; Society of Nuclear Medicine; Fellow American College of Radiologists; Radiological Society of North America; Association of University Radiologists
Boards:	Founding Member American Board of Nuclear Medicine American Board of Radiology
Interest:	Radionuclide computed tomography

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A., 1941 Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association for the Advancement of Science: AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology

1049057

Name:	Michael Scott Lawyer
Position:	Staff Attorney, Oak Ridge Associated Universities
School:	University of Mississippi, B.P.A., 1968; Juris Doctor, 1970
Admissions:	Mississippi, 1970; U. S. District Court, Northern District of Mississippi, 1970; U. S. Court of Military Appeals, 1971; U. S. Tax Court, 1975; U. S. Court of Claims, 1975; U. S. Supreme Court, 1975
Memberships:	Federal Bar Association; Government Contracts and Administrative Law Committees; Mississippi Bar Association

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry), 1946; University of Minnesota, Minneapolis, Minnesota, M.S., 1949; M. D. 1950 Rotating Internship, Ancker Hospital, St. Paul,Minnesota, 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination, June 5, 1963
Memberships:	Fellow Industrial Medical Association; Past President, Tennessee Industrial Medical Association; American Academy of Occupational Medicine; American Medical Association; Past President, Roane-Anderson County Medical Society; Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Chairman, Medical and Health Sciences Division, Oak Ridge Associated Universities; Director, Radiation Emergency Assistance Center/Training Site (REAC/TS)
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Sciences; American Society for Experimental Pathology; Associated Researchers and Clinicians in Cancer; Society for Experimental Biology and Medicine; Health Physics Society; Radiation Research Society; Society of Nuclear Medicine; American Medical Association; Tennessee State Medical Society

Name:	John T. Purvis
Position:	Neurosurgeon, Fort Sanders Presbyterian Hospital, Knoxville, Tennessee
School:	University of Tennessee College of Medicine, Memphis, Tennessee
Licensure:	Tennessee
Board:	American Board of Neurological Surgey

1049058

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fellow American College of Physicians
Interest:	Late effects of radiation

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; American Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name:	John B. Storer
Position:	Director, Biology Division, Oak Ridge National Laboratory
School:	University of Chicago, M.D., 1947
Memberships:	American Association for Cancer Research; American Society for Experimental Pathology; Radiation Research Society; Society for Experimental Biology and Medicine; National Council on Radiation Protection and Measurements

Name:	Joseph F. Volker
Position:	President, University of Alabama, Birmingham, Alabama
Schools:	Indiana University, D.D.S., 1936 University of Rochester, A.B., 1938 University of Rochester, M.S., 1939 University of Rochester, Ph.D., 1942 Univ. Med. Sci., Bangkok, hon. D. Sc., 1967 Univ. Lund, hon. Dr. Ontol., 1968 University of Alabama, hon. D. Sci., 1970 Indiana Univ., hon. D. Sci., 1970 Louis Pasteur Univ., hon. Dr., 1972
Memberships:	Mem. Unitarian Med. Teaching Mission, Czech., 1946, Ger., 1948 Specialist, U. S. Dept. State, Thailand, 1951- Dir. Arizona Med. Sch. Study, 1960-1961 Mem. Inst. Med. Nat. Acad. Sci., 1971 Mem. Order of White Lion, Czech, 1946 Comdr., Order of Crown, 1959 Fel. Royal Col. Surg., 1961 Comdr., Order of Falcon, Repub. Iceland, 1969 AAAS; Soc. Expl. Biol. and Med.; Int. Assn. Dent. Res.

1049059

Name:	Joan B. Woods
Position:	Psychiatrist, Veterans Administration Hospital, Murfreesboro, Tennessee
School:	University of Chicago School of Medicine, B.S. and M.D., 1960
Licensure:	Tennessee
Boards:	American Board of Psychiatry and Neurology
Memberships:	American Psychiatric Association American Medical Association and Subsidiaries

1049060

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 77-2

DESCRIPTION:

ECAT Studies of Gallium-68 Citrate. DOSE NOT TO EXCEED 15 MILLICURIES PER 70KG PATIENT.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William R. Hibbs	✓			20 May, 1977
Karl Hubner	NOT	VOTING		
Raymond Hayes	NOT	VOTING		
O C Strategeler	✓			20 May 1977
[illegible]				

Acknowledgement of submitter_____ Date_____

Proposal does ✓ does not _____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049061

TABLE 1

Estimated Radiation Dose to Humans from Intravenously Administered Gallium-~~67~~ 68 Citrate*

Tissue	Rads/mCi	Rads/15 mCi
Gastrointestinal tract		
Stomach	0.042	0.63
Small intestine	0.21	3.15
Upper large intestine	0.23	3.45
Lower large intestine	0.094	1.41
Gonads		
Ovaries	0.048	0.72
Testes	0.039	0.59
Kidneys	0.089	1.34
Liver	0.096	1.44
Marrow	0.10	1.50
Skeleton†	0.094	1.41
Spleen	0.13	1.95
Total body‡	0.052	0.78

* From ref. 6. All dose calculations assume a uniform distribution of activity in an organ.

† Skeleton = bone + marrow.

‡ Dose calculated assuming a uniform distribution of radioactivity in total body.

OK - J. D. Wenger 5/20/77

1049062

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division (MHSD), Oak Ridge

Associated Universities (ORAU), Oak Ridge, Tennessee

Date: May 31, 1977

1. NAME OF DRUG: GALLIUM-68 CITRATE. This drug will be dissolved in a sterile, nonpyrogenic saline solution and administered intravenously.

2. COMPONENTS:

   a. Gallium-68 citrate.

   b. Sodium citrate.

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION:

   Since the ^{68}Ga present in ^{68}Ga citrate is radioactive ($T_{1/2}$ = 68 min.), we cannot state an exact relationship between the components of this preparation at the time of administration. From radiation dosimetry considerations, however, we have determined that the maximum ^{68}Ga activity to be administered will not exceed 0.23 mCi per kilogram of body weight (a 15 mCi dose for a 70 kg subject). The quantitative relationship between ^{68}Ga and the other components in the preparation will be determined by the time that elapses from the elution and preparation of ^{68}Ga in the citrate form and its administration to the patient. The composition stated below, therefore, represents the dose limits that will be adhered to for the components in this radiopharmaceutical preparation:

   a. Gallium-68 citrate: maximum of 0.23 mCi per kilogram of body weight (15 mCi total for a 70 kg subject).

   b. Sodium citrate: maximum of 0.5 mg per kilogram of body weight (35 mg total for a 70 kg subject).

   c. Sodium chloride: maximum of 1.5 mg per kilogram of body weight (105 mg total for a 70 kg subject).

   d. Water: maximum of 0.15 ml per kilogram of body weight (10 ml total for a 70 kg subject).

4. SOURCE OF NEW DRUG SUBSTANCE:

The ^{68}Ga will be separated as needed from its parent, ^{68}Ge, by elution of a ^{68}Ge-^{68}Ga generator obtained from New England Nuclear (NEN), Boston, Mass. The eluent used will be a 0.005 M solution of sterile disodium ethylenediaminetetraacetate (Na_2EDTA) adjusted to pH 7.0.

5. METHODS, FACILITIES AND CONTROLS:

Gallium-68 will be eluted from an NEN generator using 10 ml portions of a pH 7.0, 0.005 M Na_2 EDTA solution. These portions of eluting solution will be contained in individual vials (Wheaton Glass Co., Millville, N.J.) that have previously been filled, capped and steam sterilized. Each batch of vials will have been checked before use for sterility and absence of pyrogens using standard USP techniques. The 0.005 M EDTA solution will be prepared by dilution of a 0.5 M EDTA stock solution supplied by NEN.

The eluate from the ^{68}Ga generator will be collected in a beaker and mixed with an equal volume of reagent grade concentrated hydrochloric acid. The ^{68}Ga contained in this $\sim$ 6 N HCl solution of ^{68}Ga EDTA will be freed of EDTA and traces of aluminum and ^{68}Ge by the anion exchange technique of Carlton and Hayes (1) as modified by Hnatowich (2), and the resulting solution of ^{68}Ga chloride will then be converted to the citrate form by the combined procedures outlined below.

The $\sim$ 6 N HCl solution of ^{68}Ga EDTA from above will be run rapidly through a Bio-Rad AG 1-X2, 50-100 mesh, 0.4 cm x 2.5 cm anion exchange column (chloride form) that has previously been washed thoroughly, first with pyrogen-free distilled water (water for injection, bacteriostatic, U.S.P., Parke-Davis, Detroit, Mich.) and then with 6 N HCL. The Bio-Rad AG 1-X2 resin will be obtained from Bio-Rad Laboratories, Richmond, Cal. It will be washed free of fines and stored in 0.1 N HCl prior to use in conversion of ^{68}Ga EDTA to ^{68}Ga chloride. Columns for ^{68}Ga EDTA conversion will be constructed as needed from the barrel of a sterile 1 ml glass syringe (containing a plug of glass wool to support the resin). A sterile disposable plastic stopcock (MX401, Medex Inc., Hilliard, Ohio) will be attached to the tip of the syringe. The flow through the exchange column will be controlled by setting the flow control on a special addition funnel (1) so that the level of the ^{68}Ga EDTA - HCl in the column is held just above the top of the resin bed. Following the passage of all the ^{68}Ga EDTA-HCl solution into the ion-exchange column, the column will then be washed with four portions of 6 N HCl (the volume of each wash being larger than the previous wash to insure complete rinsing of all surfaces previously in contact with the ^{68}Ga EDTA-HCl solution). A final wash with a 0.4 ml (one void volume) portion of pyrogen-free distilled water will then be made. (The solutions passing through the column,containing the EDTA as well as traces of aluminum and ^{68}Ge,will be discarded.)

The elution of the ^{68}Ga retained by the column will then be made with a 1.0 ml portion of pyrogen-free distilled water. This solution will be allowed to run into a sterile beaker containing a sterile magnetic stirring bar, 1.5 ml of 2.5% sodium citrate solution (Eli Lilly and Co., Indianapolis, Ind.), 4 ml of pyrogen-free distilled water and 4 ml of sterile, nonpyrogenic 0.9% sodium chloride solution (sodium chloride inj.,

bacteriostatic, U.S.P., Abbott Laboratories, North Chicago, Ill.). The resulting stirred solution will be brought to a pH of 7.0 ± 0.4 with 1.0 N NaOH using a pH meter and a combination electrode. (The tip of the electrode will be stored in aqueous 0.9% benzyl alcohol between uses.) The final solution of ^{68}Ga citrate will then be filtered through a sterile, nonpyrogenic 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (Wheaton Glass). A portion of this filtered solution will be removed for radioassay, USP sterility testing and pyrogen testing (using the Pyrotest limulus lysate technique [Difco Laboratories, Detroit, Mich.]). The short half-life of ^{68}Ga (68 min) precludes pyrogen testing with rabbits in the conventional USP manner.

Radioassay and verification of radioisotopic purity will be carried out by means of a sodium iodide detector (calibrated with NBS standards) and a multichannel analyzer. (A photograph of the gamma ray spectrum from 0-2 MeV will be made a part of the permanent record.) The vial containing the ^{68}Ga citrate will then be labeled as to its assay and total content (see section 7). After removal from the vial and just prior to administration, each ^{68}Ga citrate dose will again be assayed for radioactivity content using a Capintec CRC-10 radioisotope calibrator (Capintec Inc., Montvale, N.J.).

Preparation of each batch of ^{68}Ga citrate for clinical use will be carried out in a positive-pressure clean room equipped with a vertical laminar flow hood with an air curtain (Envirco, Albuquerque, N.M.). All glassware used will be presterilized by steam. Each batch of ^{68}Ga citrate will be given a batch number and all particulars relative to its preparation and use will be entered into a master logbook.

6. STATEMENT OF INFORMATION AVAILABLE TO THE SPONSOR:

a. Preclinical and Clinical Investigations.

1. Animal and human studies

Gallium-67 citrate, as supplied by New England Nuclear (NEN), North Billerica, Mass., is an approved new drug for diagnostic use in the demonstration of certain malignancies such as Hodgkin's disease, lymphomas and bronchogenic carcinoma. This NDA classification by FDA of NEN's ^{67}Ga citrate preparation was based at least in part on our institution's pioneering work using IND 5489 (^{67}Ga citrate). The scientific literature is now replete with documentation of the effectiveness of ^{67}Ga citrate as an agent for detection of malignancies in humans. It has also been shown to be of use in the detection of abscesses, particularly those in the abdomen.

The drug preparation involved in this application (Gallium-68 citrate) is essentially the same as NEN's NDA Gallium-67 citrate except that ^{67}Ga will be replaced with carrier-free ^{68}Ga, a positron emitter having a half-life of 68 minutes. Because of this fact it is felt that there is sufficient information generally available in the literature on the use of carrier-free gallium radionuclides in both animals and humans to preclude our submission of detailed information in this application on the expected tissue distribution of gallium-68 citrate and the lack of any possible toxic effects that might result from the use of it. An NEN gallium-67 citrate package insert is attached for informational purposes.

Our clinical investigation of gallium-68 citrate will be carried out with the use of a positron tomograph (ECAT, manufactured by ORTEC Inc., Oak Ridge, Tn.). The ECAT is a modified version of the positron emission transaxial tomograph (PETT) developed at Washington University, St. Louis, Mo. (3). Because of the exceptional resolution and three dimensional imaging capabilities that are available with the ECAT, it is considered highly likely that malignant lesions can be visualized as well with positron emitting ^{68}Ga (and possibly even better) than they can be with gamma emitting ^{67}Ga, even though the half life of ^{68}Ga (68 min.) will limit the time interval over which imaging can be carried out ($\sim$ 4 hr). Animal studies have indicated that tumor uptake of ^{67}Ga reaches approximately 50% of its maximum level within 2-4 hours after administration (4). Inflammatory processes are well visualized with ^{67}Ga within 2 hours after administration (5). The ORAU-ORNL Committee on Human Studies (see appendix for membership) is now in the process of reviewing this application. Gallium-68 citrate will not be used clinically until the approval of both this committee and the FDA have been obtained.

2. Radiation dosimetry

The radiation dose to the whole body and various organs from the intravenous administration of ^{68}Ga citrate has been estimated by the MIRD Committee of the Society of Nuclear Medicine (6). Data from this MIRD report on ^{68}Ga citrate is shown in Table 1. The ORAU Medical Radionuclide Committee has approved the use of ^{68}Ga citrate from a radiation dosimetry standpoint.

b. Previous Marketing

Gallium-68 citrate has not been marketed before.

c. Drug Combination

Gallium-68 citrate is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with ^{68}Ga citrate will have the following form:

GA-68 CITRATE (FOR I.V. INJECTION)

Assay_____mCi/ml as of _____

Volume_____ml Batch No._____

Expiration Time_____

CAUTION: INVESTIGATIONAL NEW DRUG
CAUTION: RADIOACTIVE MATERIAL

Oak Ridge Assoc. Univ., Oak Ridge, Tn.

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal information material will be prepared; however, each participant will be issued a copy of this application.

1049066

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the investigators, all of whom are supported by competent associates, to be well qualified to carry out this research. See bibliographical material in the appendix about Drs. Andrews, Hayes, Hübner, Purvis, Washburn, and Wieland.

9. PROGRESS OF THE INVESTIGATION:

The principal investigator will be Dr. Karl F. Hübner. The progress of of the investigation and evidence of safety and effectiveness of the drug will be evaluated with advice from the ORAU Medical Advisory Committee and the ORAU/ORNL Committee on Human Studies, by G. A. Andrews, M.D., R. L. Hayes, Ph.D., K. F. Hübner, M.D. and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Chairman of the ORAU Medical and Health Sciences Division (see attached lists and biographies in the appendix).

10. CLINICAL STUDIES:

a. Objectives - To determine, using positron tomography, whether ^{68}Ga (a positron emitter with a half life of 68 minutes) can in the citrate form provide diagnostic information superior to that that can be obtained with ^{67}Ga citrate.

b. Source of patients - Patients will come from the East Tennessee Chest Disease Hospital, Fort Sanders Hospital, University of Tennessee Memorial Research Center and Hospital, and from private physicians. All patients will have the research nature of the procedure explained by the referring physician, and, after further discussion, an informed consent form will be signed by each patient at ORAU (see attached consent form).

c. Categories of patients - Five different categories of patients will be studied: (1) patients with known malignancies in whom it is desirable to determine the size of the lesion(s) and the presence of metastases (20 to 30 patients), (2) patients with known or strongly suspected brain tumors primary or metastatic (10 to 20 patients), (3) patients with known or strongly suspected abscesses, especially abdominal, mediastinal, and brain (15 to 30 patients), (4) patients with systemic symptoms, i.e., fever, weight loss and unexplained anemia, who are suspected of having occult cancer (15 to 30 patients), and (5) patients suspected of having inflammatory processes such as pancreatitis (10 to 20 patients). (In most instances ^{68}Ga citrate studies will be preceded by a standard ^{67}Ga scan.)

d. Dose - The dose of ^{68}Ga will be not more than 0.23 mCi/kg. Since it is a carrier-free nuclide, the chemical dose will be exceedingly small. We will not use the agent in pregnant women, any patients under 18 years of age, or persons incapable of giving informed consent.

e. Blood levels, excretion, chemical toxicity - All of these problems have been worked out for ^{67}Ga, and it is known that ^{68}Ga will behave in a fasion identical to that of ^{67}Ga.

f. Protocol - The ^{68}Ga citrate doses, after a final assay recheck, will be injected intravenously. Scanning will be started 1 to 2 hours after administration. This will be done with the new ECAT positron tomograph. Use of this machine, built by ORTEC Inc., of Oak Ridge, Tn., will not involve any conceivable mechanical hazard to the patient. Scanning may continue for an hour or slightly more, depending on results. The scan study will include rectilinear whole body scans and sectional scans through the body.

g. Evaluation of results - All other relevant clinical and diagnostic information will be correlated with the scan data, especially subsequent gross anatomical and histologic data obtained at surgery or autopsy. Eventually it should be possible to determine for general tumor scanning whether the tomographic data will more than compensate for the loss of contrast resulting from inability to delay the scanning to allow for excretion and decreased blood levels, as is possible with ^{67}Ga because of its longer half-life. It is expected, on the basis of data now available, however, that abscesses and brain lesions may be well seen relatively early after administration of the agent.

h. Significance - This technique may prove to be a significant advance in the diagnosis and localization of certain inflammatory and neoplastic lesions. The shortening of the time required, as compared with ^{67}Ga, is one advantage. Improved data on depth and extent of neoplastic lesions may improve staging and planning of radiotherapy.

i. Duration of study - We anticipate completion of the investigation of patients with malignant diseases within 1 to 2 years, and for the less common cases with abscesses, pancreatitis and other poorly defined inflammatory processes, the study should not exceed a period of 3 years.

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{68}Ga citrate prior to 30 days after the date of receipt of notice of this application by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

1049068

References:

1. Carlton, J.E. and Hayes, R.L. Rapid separation of generator-produced gallium-68 from EDTA eluate. Int. J. Appl. Rad. Isotopes 22:44-45, 1971.

2. Hnatowich, D.J. A method for the preparation and quality control of ^{68}Ga radiopharmaceuticals. J. Nucl. Med. 16:764-768, 1975.

3. Hoffman, E.J., Phelps, M.E., Mullani, N.A., et al.: Design and performance characteristics of a whole-body positron transaxial tomograph. J. Nucl. Med. 17:493-502, 1976.

4. Hayes, R.L. and Brown, D.H. Biokinetics of radiogallium. In Nuklearmedizin: Fortschritte der Nuklearmedizin in klinischer und technologischer Sicht, 12th Annual Meeting, Gesellschaft fur Nuclearmidizin, München, September 11-14, 1974, eds. H.W. Pabst, G. Hor, and H.A.E. Schmidt, F. K. Schattauer Verlag, Stuttgart-New York, 1975, pp 837-847.

5. Gelrud, L.G., Arseneau, J.C., Milder, M.S., et al.: The kinetics of ^{67}gallium incorporation into inflammatory lesions: experimental and clinical studies. J. Lab. Clin. Med. 83:489-495, 1974.

6. Cloutier, R.J., Watson, E.E., Hayes, R.L., Nelson, B., and Smith, E.M. MIRD/Dose Estimate Report No. 2 - Summary of current radiation dose estimates to humans from ^{66}Ga-, ^{67}Ga-, ^{68}Ga-, and ^{72}Ga-citrate. J. Nucl. Med. 14: 755-756, 1973.

1049069

April, 1976

New England Nuclear
Atomlight Place
North Billerica, Mass. C1862

GALLIUM CITRATE Ga 67

FOR DIAGNOSTIC USE

DESCRIPTION: Gallium Citrate Ga 67 is supplied in isotonic solution as a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous administration. Each milliliter of the isotonic solution contains 2mCi of Gallium Ga 67 on the calibration date, as a complex formed from 9ng gallium chloride Ga 67, 2mg of sodium citrate, 6.8mg sodium chloride, and 0.9% benzyl alcohol w/v as preservative. The pH is adjusted to between 4.5-7.5 with hydrochloric acid and/or sodium hydroxide solution. Gallium Ga 67, with a half-life of 78 hours, is cyclotron produced by the proton irradiation of enriched zinc oxide, is essentially carrier-free and contains negligible concentrations of other radioactive isotopes.

PHYSICAL CHARACTERISTICS

Gallium Ga 67 decays to stable Zinc Zn 67 by electron capture with a physical half-life of 78 hours.

TABLE 1. Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	38.0	93.3
Gamma-3	23.9	184.6
Gamma-5	16.1	300.2
Gamma-6	4.3	393.6

TABLE 2. Gallium Ga 67 Decay Chart Half-Life 78 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-48	1.53	30	0.77	90	0.45
-36	1.38	36	0.73	96	0.43
-24	1.24	42	0.69	108	0.38
-12	1.11	48	0.65	120	0.35
- 6	1.05	54	0.62	132	0.31
0*	1.00	60	0.59	144	0.28
6	0.95	66	0.56	156	0.25
12	0.90	72	0.53	168	0.23
18	0.85	78	0.50		
24	0.81	84	0.47		

*Calibration Time.

EXTERNAL RADIATION

The specific gamma ray constant for Gallium Ga 67 is 1.6R/mCi-hr. at 1cm. The first half value thickness of lead is 0.04mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 3. For example, the use of 8mm of Pb will decrease the external radiation exposure by a factor of 61.

TABLE 3. Radiation Attenuation by Lead Shielding

mm of Pb	Radiation Attenuation Factor	mm of Pb	Radiation Attenuation Factor
1	4.2	5	22
2	7.0	6	31
3	11	7	44
4	15	8	61

CLINICAL PHARMACOLOGY: Carrier-free Gallium Citrate Ga 67 has been found to concentrate in certain viable primary and metastatic tumors. The mechanism of concentration is unknown, but investigational studies have shown that Gallium Ga 67 accumulates in lysosomes and is bound to a soluble intracellular protein.

It has been reported in the scientific literature that following intravenous injection, the highest tissue concentration of Gallium Ga 67 — other than tumors — is in the renal cortex. After the first day, the maximum concentration shifts to bone and lymph nodes, and after the first week, to liver and spleen. Gallium is excreted relatively slowly from the body. The average whole body retention is 65% after 7 days, with 26% having been excreted in the urine and 9% in the stools.

INDICATIONS AND USAGE: Gallium Citrate Ga 67 may be useful to demonstrate the presence and extent of certain malignancies such as Hodgkin's disease, lymphomas, and bronchogenic carcinoma. Positive Ga 67 uptake in the absence of prior symptoms warrants follow-up as an indication of a potential disease state.

CONTRAINDICATIONS: None known.

WARNINGS: Gallium Citrate Ga 67 should not be administered to children or to patients who are pregnant or to nursing mothers unless the information to be gained outweighs the potential hazards. Ideally, examinations using radiopharmaceutical drug products, especially those elective in nature of a woman of childbearing capability should be performed during the first few (approximately ten) days following the onset of menses.

PRECAUTIONS:

GENERAL

A thorough knowledge of the normal distribution of intravenously administered Gallium Citrate Ga 67 is essential in order to

accurately interpret pathologic studies.

The finding of an abnormal gallium concentration usually implies the existence of underlying pathology, but further diagnostic studies should be done to distinguish benign from malignant lesions. Gallium Citrate Ga 67 is intended for use as an adjunct in the diagnosis of certain neoplasms. Certain pathologic conditions may yield up to 40% false negative gallium studies. Therefore a negative study cannot be definitively interpreted as ruling out the presence of disease.

Lymphocytic lymphoma frequently does not accumulate Gallium Ga 67 sufficiently for unequivocal imaging; and the use of gallium with this histologic type of lymphoma is not recommended at this time.

Gallium Citrate Ga 67, as well as other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize external radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to patients consistent with proper patient management.

CARCINOGENESIS

No long term animal studies have been performed to evaluate carcinogenic potential.

PREGNANCY CATEGORY C

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Gallium Citrate Ga 67 should be used in pregnant women only when clearly needed.

NURSING MOTHERS

Gallium Citrate Ga 67 has been found to accumulate in breast milk and should not be used in nursing mothers.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Severe itching, erythema and rash were observed in one patient of 300 studied.

DOSAGE AND ADMINISTRATION: The recommended adult (70kg) dose of Gallium Citrate Ga 67 is 2-5mCi. Gallium Citrate Ga 67 is intended for intravenous administration only.

Approximately 10% of the administered dose is excreted in the feces during the first week after injection. Daily laxatives and/or enemas are recommended from the day of injection until the final images are obtained in order to cleanse the bowel of radioactive material and minimize the possibility of false positive studies.

Studies indicate the optimal tumor to background concentration of ratios are often obtained about 48 hours post-injection. However, considerable biological variability may occur in individuals, and acceptable images may be obtained as early as 6 hours and as late as 120 hours after injection.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

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

RADIATION DOSIMETRY

The dosimetry values listed in Table 4 for Gallium Citrate Ga 67 are those of the MIRD Committee.*

TABLE 4. Dosimetry of Gallium Citrate Ga 67 for Maximal Dose of 5mCi

	Rads/5mCi		Rads/5mCi
Whole Body	1.30	Testes	1.20
Skeleton	2.20	Gastrointestinal Tract	
Liver	2.30	Stomach	1.10
Bone Marrow	2.90	Small Intestine	1.80
Spleen	2.65	Upper Large Intestine	2.80
Kidney	2.05	Lower Large Intestine	4.50
Ovaries	1.40		

*MIRD Dose Estimate Report No. 2. J. Nucl. Med. 14: 755-6. (1973).

HOW SUPPLIED: Gallium Citrate Ga 67 is supplied sterile and non-pyrogenic for intravenous use. Each ml contains 2mCi of Gallium Ga 67 on the calibration date, as a complex formed from 9ng gallium chloride Ga 67, 2mg of sodium citrate, 6.8mg sodium chloride, and 0.9% benzyl alcohol w/v as preservative. The pH is adjusted to between 4.5-7.5 with hydrochloric acid and/or sodium hydroxide solution.

Vials are available from 3mCi to 18mCi in increments of 3mCi on calibration date.

The contents of the vial are radioactive and adequate shielding and handling precautions must be maintained.

Catalog Number NRP-121

New England Nuclear
Radiopharmaceutical Division
Atomlight Place, North Billerica, Mass. 01862
Telephone 617-667-9531

511161 S-1065 PRINTED IN U.S.A.

1049071

TABLE 1

Estimated Radiation Dose to Humans from Intravenously Administered Gallium-68 Citrate*

Tissue	Rads/mCi	Rads/15 mCi
Gastrointestinal tract		
Stomach	0.042	0.63
Small intestine	0.21	3.15
Upper large intestine	0.23	3.45
Lower large intestine	0.094	1.41
Gonads		
Ovaries	0.048	0.72
Testes	0.039	0.59
Kidneys	0.089	1.34
Liver	0.096	1.44
Marrow	0.10	1.50
Skeleton†	0.094	1.41
Spleen	0.13	1.95
Total body‡	0.052	0.78

* From ref. 6. All dose calculations assume a uniform distribution of activity in an organ.

† Skeleton = bone + marrow.

‡ Dose calculated assuming a uniform distribution of radioactivity in total body.

1049072

Ident. No._____

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

I authorize the performance upon_____
(myself or name of patient)
of the following test: Phase II radiopharmaceutical tests of gallium-68 citrate as an agent to detect inflammatory processes and tumors of the brain and other soft tissues.

The nature and purpose of the test, the risks involved, and the possibilities of any complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes and is being done only for gathering information related to my disease, its treatment, or both. Further, I understand that any information learned from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Oak Ridge Associated Universities Medical and Health Sciences Division.

Date:_____ _____
(Patient or person authorized to consent for patient)

Witness:_____

_____

I have talked with _____about the proposed test to be given luding the following:

1. This is a modified form of gallium-67 citrate, a radiopharmaceutical that has been approved by the Food and Drug Administration as a new drug. In the gallium-68 citrate that the patient will receive the gallium-67 has been replaced by gallium-68, a positron emitter.
2. The drug also contains citric acid, a normal constituent of the body, in quantities much less than those required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. However, untoward effects are remotely possible with any experimental drug.
4. The radiation dose will be approximately 0.8 rad to the whole body. The intestinal tract will receive a higher dose, approximately 4 rads (roughly one third the yearly permitted occupational radiation dose). All radiation used in a diagnostic test such as this has some possibility of contributing to an increased incidence of cancer or leukemia. This possibility has been considered by the ORAU Medical Radionuclide Committee and is believed so low as to make the possible benefits of the test far outweigh the possible risks.
5. The patient will be expected to drink several glasses of water before the gallium-68 citrate is administered.
6. Scans will be made with a special tomographic scanner that makes use of the positrons emitted by gallium-68.
7. The patient may withdraw from the test at any time.

Date:_____ _____
(Investigator)

1049073

APPENDIX

Investigators:

K. F. Hubner, M.D., Principal Investigator
G. A. Andrews, M.D.
R. L. Hayes, Ph.D.
J. T. Purvis, M.D.

ORAU/ORNL Committee on Human Studies:

Gould A. Andrews, M.D. (Secretary)
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor, Dept. of Medicine
Division of Nuclear Medicine & Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Donald W. Goodwin, Ph.D.
Minister, United Church
Chapel-on-the-Hill
Oak Ridge, Tennessee 37830

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Y-12 Area, Building 9704-2
Union Carbide Nuclear Company
P. O. Box Y
Oak Ridge, Tennessee 37830

Robert D. Lange, M.D. (Chairman)
Assistant Director
University of Tennessee
Memorial Research Center & Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

1049074

Michael Scott Lawyer, J.D.
Staff Attorney
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

Clarence C. Lushbaugh, Ph.D., M.D. (Ex officio)
Chairman, Medical & Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Joan B. Woods, M.D.
Psychiatrist
Veterans Administration Hospital
Murfreesboro, Tennessee 37130

ORAU Medical Advisory Committee:

George B. Hutchison, M.D.
Professor of Epidemiology
Harvard University School of Public Health
55 Shattuck
Boston, Massachusetts 02115

John M. Johnston, Ph.D.
Department of Biochemistry
University of Texas Medical School
(Southwestern)
Dallas, Texas 75235

David Kuhl, M.D.
Division of Nuclear Medicine
Room B2-128
Center for the Health Sciences
University of California
Los Angeles, California 90024

Leonard A. Sagan, Ph.D.
Internal Medicine, Research Administration
Associate Director, Dept. of Environmental Medicine
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

1049075

William H. Stone, Ph.D.
Professor of Genetics
University of Wisconsin
Madison, Wisconsin 53706

Joseph F. Volker, Ph.D. (Ex officio member from the ORAU Board of Directors)
President
University of Alabama
Birmingham, Alabama

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews
Position:	Internist, Director of Clinical Applications
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society of Experimental Biology and Medicine; American Association for Cancer Research; American Thyroid Association; Society of Nuclear Medicine; Southern Society for Clinical Research; American Medical Association; American Association for the Advancement of Sciences; American Federation for Clinical Research; Fellow, American College of Physicians; American Society of Hematology (1968); Health Physics Society, East Tennessee Chapter; Tennessee Academy of Science; Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology, Vanderbilt School of Medicine
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science; Society of Nuclear Medicine; Radiation Research Society, American Thyroid Association

Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Maryland

Name:	Donald W. Goodwin
Position:	Minister, United Church, Chapel-on-the-Hill
School:	Bangor Theological Seminary, Bachelor of Divinity, 1959 Brown University, Ph.D., 1965
Memberships:	Ministerial Standing, United Church of Christ
Additional Information:	Member of various boards which change from time to time

1049076

Name:	R. L. Hayes
Position:	Director of Radiopharmaceutical Development, Chief Scientist
Schools:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U. S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society, Society of Nuclear Medicine, Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

Name:	George B. Hutchison
Position:	Epidemiologist, Michael Reese Hospital, Chicago, 66-present
Schools:	Harvard University, A.B., 1943 Harvard University, M.D., 1951 Harvard University, M.P.H., 1960
Positions:	Fel. med. Lahey Clin., 52-55; asst. med. dir. Equitable Life Assurance Soc., U.S., 55-56; Health Ins. Plan Greater New York, 56-57; dir. res. City Health Dept., New York, 57-59; asst. prof. epidemiol. sch. pub. health, Harvard, 60-61; assoc. prof. 61-66; Consult, Health Ins. Plan Greater New York, 57-present
Memberships:	Fel. Am. Pub. Health Asn; Am. Statist. Asn; World Med. Asn.; Asn. Teachers Prev. Med.

Name:	Karl F. Hübner (see additional material at end of appendix)
Schools:	2 years of college (last 2 years of German "high school") 1952-54 University of Heidelberg, Germany, M.D., 1959
Licensure:	Tennessee
Positions:	Senior Staff Member with clinical staff of the ORAU Medical Division, 1971 to present Research Associate in Experimental Immunology, ORAU Medical Division, 1967-70 Resident in Pediatrics, University of Tübingen, Germany, Medical School, 1964-67 Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), 1962-64 Internship (rotating) at 2nd General Hospital of the U. S. Army, and the 86th Tactical Hospital of the U. S. Air Force, 1960-61
Memberships:	AMA, Tenn. Med. Association
Interests:	Clinical immunology, treatment of neoplastic diseases of the bone marrow and lymphatic system, with special interest in immunotherapy and transplantation immunology

Name:	John Marshall Johnston
Position:	Professor of Biochemistry, University of Texas (Southwest) Med. School, Dallas, 1966-present
Schools:	B.A., Hastings Colorado, 1949; Ph.D., Colorado, 1953
Positions:	Res. Assoc. Walter Reed Inst. Res. 53-55; Asst. Prof., Univ. of Texas (Southwest) Medical School, Dallas, 55-57; Assoc. Prof. 57-60; Professor 60-66; Nat. Sci. Found. Sr. Res. Fel., Univ. Lung, 62-63; U.S.A.R. 53-55
Memberships:	AAAS; Am. Chem. Soc.; Soc. Exp. Biol. & Med.; Am. Soc. Biol. Chem.

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris doctor, 1961; admitted to practice of Law: North Dakota, 1961; Tennessee, 1964; Federal District Court, North Dakota, 1961; East Tennessee, 1964; U. S. Supreme Court, 1966
Memberships:	American Bar Association, Public Contracts Section; Federal Bar Association, Government Contracts Committee, R & D Contracts Subcommittee; Tennessee Bar Association; North Dakota Bar Association, Ward County, North Dakota, Bar Association

Name:	David E. Kuhl
Position:	Chief, Division of Nuclear Medicine Professor of Radiological Sciences University of California, Los Angeles
School:	Temple University, A.B., 1951 University of Pennsylvania School of Medicine, M.D., 1955
Positions:	Intern, Hosp., Univ. Pa., 55-56; resident radiol, 58-62; Prof. Radiol. & Dir. Div. Nuclear Med. (until fall of 1976 moved to California)
Licensure:	Pennsylvania, California
Memberships:	American College of Nuclear Physicians; Society of Nuclear Medicine; Fellow American College of Radiologists; Radiological Society of North America; Association of University Radiologists
Boards:	Founding Member American Board of Nuclear Medicine American Board of Radiology
Interest:	Radionuclide computed tomography

Name:	Robert Lange
Position:	Research Professor; Assistant Director, University of Tennessee Memorial Research Center
Schools:	Macalester College, B.A., 1941 Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association for the Advancement of Science: AMA; Knoxville Acad. Med.; Southern Soc. Res.; Central Soc. Clin. Res.; Amer. Coll. Physicians; International Soc. of Hematology

1049078

Name:	Michael Scott Lawyer
Position:	Staff Attorney, Oak Ridge Associated Universities
School:	University of Mississippi, B.P.A., 1968; Juris Doctor, 1970
Admissions:	Mississippi, 1970; U. S. District Court, Northern District of Mississippi, 1970; U. S. Court of Military Appeals, 1971; U. S. Tax Court, 1975; U. S. Court of Claims, 1975; U. S. Supreme Court, 1975
Memberships:	Federal Bar Association; Government Contracts and Administrative Law Committees; Mississippi Bar Association

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry), 1946; University of Minnesota, Minneapolis, Minnesota, M.S., 1949; M. D. 1950 Rotating Internship, Ancker Hospital, St. Paul,Minnesota, 1949-50
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination, June 5, 1963
Memberships:	Fellow Industrial Medical Association; Past President, Tennessee Industrial Medical Association; American Academy of Occupational Medicine; American Medical Association; Past President, Roane-Anderson County Medical Society; Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Chairman, Medical and Health Sciences Division, Oak Ridge Associated Universities; Director, Radiation Emergency Assistance Center/Training Site (REAC/TS)
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Sciences; American Society for Experimental Pathology; Associated Researchers and Clinicians in Cancer; Society for Experimental Biology and Medicine; Health Physics Society; Radiation Research Society; Society of Nuclear Medicine; American Medical Association; Tennessee State Medical Society

Name:	John T. Purvis
Position:	Neurosurgeon, Fort Sanders Presbyterian Hospital, Knoxville, Tennessee
School:	University of Tennessee College of Medicine, Memphis, Tennessee
Licensure:	Tennessee
Board:	American Board of Neurological Surgey

Name:	Leonard A. Sagan
Position:	Internal Medicine, Research Administration
Schools:	Stanford, A.B., 1950 University of Chicago, M.D., 1955 Harvard, M.P.H., 1965
Memberships:	Dipl. Amer. Board Internal Medicine; Fellow American College of Physicians
Interest:	Late effects of radiation

Name:	William Harold Stone
Position:	Genetics, Immunology
Schools:	Brown University, A.B., 1948 Maine, M.S., 1949 Wisconsin, Ph.D., 1953
Memberships:	Genetics Soc.; Soc. Human Genetics; American Assoc. Immunology; Transplantation Society; Science Research Society Amer. Animal Science
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name:	John B. Storer
Position:	Director, Biology Division, Oak Ridge National Laboratory
School:	University of Chicago, M.D., 1947
Memberships:	American Association for Cancer Research; American Society for Experimental Pathology; Radiation Research Society; Society for Experimental Biology and Medicine; National Council on Radiation Protection and Measurements

Name:	Joseph F. Volker
Position:	President, University of Alabama, Birmingham, Alabama
Schools:	Indiana University, D.D.S., 1936 University of Rochester, A.B., 1938 University of Rochester, M.S., 1939 University of Rochester, Ph.D., 1942 Univ. Med. Sci., Bangkok, hon. D. Sc., 1967 Univ. Lund, hon. Dr. Ontol., 1968 University of Alabama, hon. D. Sci., 1970 Indiana Univ., hon. D. Sci., 1970 Louis Pasteur Univ., hon. Dr., 1972
Memberships:	Mem. Unitarian Med. Teaching Mission, Czech., 1946, Ger., 1948 Specialist, U. S. Dept. State, Thailand, 1951- Dir. Arizona Med. Sch. Study, 1960-1961 Mem. Inst. Med. Nat. Acad. Sci., 1971 Mem. Order of White Lion, Czech, 1946 Comdr., Order of Crown, 1959 Fel. Royal Col. Surg., 1961 Comdr., Order of Falcon, Repub. Iceland, 1969 AAAS; Soc. Expl. Biol. and Med.; Int. Assn. Dent. Res.

1049080

Name:	Joan B. Woods
Position:	Psychiatrist, Veterans Administration Hospital, Murfreesboro, Tennessee
School:	University of Chicago School of Medicine, B.S. and M.D., 1960
Licensure:	Tennessee
Boards:	American Board of Psychiatry and Neurology
Memberships:	American Psychiatric Association American Medical Association and Subsidiaries

1049081

Curriculum Vitae

HUBNER, Karl F., M.D.

109 Ditman Lane
Oak Ridge, Tennessee 37830

Telephone No. (615) 483-1218

Born: Striegau, Germany, January 20, 1934

Citizenship: German; (American Immigration Visa)

Married, two children

Schools: 2 years of college (last 2 years of German "high school") 1952-1954

Basic Sciences and Medical School, University of Heidelberg, Germany, 1954-1959

Positions:

October 1973 to present:	Senior Research Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
1971 - Oct. 1973	Senior Staff Member with Clinical staff of the Medical Division, ORAU
1967 - 1970:	Research Associate in Experimental Immunology, ORAU Medical Division
1964 - 1967:	Resident in Pediatrics, University of Tübingen, Germany, Medical School
1962 - 1964:	Resident in Clinical Investigation, Oak Ridge Institute of Nuclear Studies Oak Ridge, Tennessee, (now Oak Ridge Associated Universities).
1960 - 1961:	Internship (rotating) at 2nd General Hospital of the U. S. Army, and at the 86th Tactical Hospital of the U. S. Air Force

Special Interests: Nuclear medicine, clinical immunology, treatment and diagnosis of neoplastic diseases with special interest in immunological methods.

Publications: Please see appended list.

1049082

List of Publications

1959

Thom, H-J. and Hübner, K. F. Milzzellsuspension bei strahlenbedingter knochenmarkschädigung. Strahlentherapie, Band 108, Heft 3: 371-382, 1959.

1965

Gengozian, N., Edwards, C. L., and Hübner, K. Clinical and experimental studies on the effect of penicillamine on antibody formation. Clin. Res. 13: 68, 1965, Abstract.

Hübner, K. and Brown, D. W. Scanning of the spinal subarachnoid space after intrathecal injection of ^{131}I labeled human serum albumin. J. Nucl. Med. 6: 465-472, 1965.

Hübner, K. F. and Gengozian, N. Depression of the primary immune response by dl-penicillamine. Proc. Soc. Exp. Biol. Med. 118: 561-565, 1965.

1966

Hübner, K. F. and Brown, D. L. Scanning of subarachnoid space after intrathecal injection of ^{131}I labeled human serum albumin. The Year Book of Nuclear Medical Publishers, Vol. 1, Chicago, 1966.

1967

Gengozian, N. and Hübner, K. F. Effect of phytohemagglutinin (PHA) on an antibody-forming system. J. Immunol. 99: 1:184-190, 1967.

1969

Hübner, K. F. and Gengozian, N. Critical variables of the Jerne plaque technique as applied to rodent antibody-forming systems responding to heterologous red cell antigens. J. Immunol. 102: 1:155-167, 1969.

1970

Hübner, K. F. and Gengozian, N. Graft-versus-host reactivity in spleens of mouse radiation chimeras. In IVe Congres international de Radiobiologie et de Physico-Chimie des Rayonnements, Evian, 1970. Abstract of papers, p. 104, 1970, Abstract 399.

1971

Gengozian, N. and Hübner, K. F. "In situ" visualization of a graft-vs-host reaction. J. Immunol. 106: 5:1159-1165, 1971.

1049083

Swartzendruber, D. C. and Hübner, K. F. Effect of irradiation on ^{67}Ga distribution in mouse tissues. In American Society for Cell Biology. Eleventh Annual Meeting, New Orleans, 1971. Abstract of papers, p. 296, 1971, Abstract 583.

1972

Littlefield, L. G., Hübner, K. F., and Steinman, M. Cytogenetic studies in an American girl with Burkitt's lymphoma. Mammalian Chromosome Newsletter, Vol. 13: 2, April 1972.

1973

Gengozian, N., Edwards, C. L., Vodopick, H. A., and Hübner, K. F. Bone marrow transplantation in a leukemic patient following immunosuppression with antithymocyte globulin and total body irradiation. Transplantation 15: 446-454, 1973.

Swartzendruber, D. C. and Hübner, K. F. Effect of external whole-body X-irradiation on gallium-67 retention in mouse tissues. Radiat. Res. 55: 457-468, 1973.

Swartzendruber, D. C., Wolfe, G., and Hübner, K. F. Gallium-67 localization in mouse peritoneal cells. J. Reticuloendothel. Soc. 13: 379-380, 1973, Abstract 72.

1974

Swartzendruber, D. C., Idoyaga-Vargas, N. L., Hübner, K. F., and Urso, P. Effect of antigenic stimulation of ^{67}Ga uptake in mouse lymphoreticular tissues. J. Reticuloendothel. Soc. 16: 30a, Abstract Supplement, 1974.

1975

Hübner, K. F. The current use of BCG in active immunotherapy of cancer. Professional Education Newsletter, American Cancer Society, January 1975.

Hübner, K. F. and Littlefield, L. G. Burkitt's lymphoma in three American children. Clinical and cytogenetic observations. Am. J. Dis. Child. 129: 1219-1223, October, 1975.

Hübner, K. F., Gengozian, N., and Gilman, T. A. Suppression and recovery of the immune response of mice during and after chronic exposure to low-dose-rate gamma (^{60}Co) irradiation. Int. J. Radiat. Biol. 28: 301-312, 1975.

1976

Lushbaugh, C. C., Cloutier, R. J., Andrews, G. A., Beck, W. L., Hubner, K. F., and Berger, J. D. "REACTS": A pragmatic approach for providing medical care and physician education for radiation emergencies. In: Proceedings of the International Atomic Energy Agency Symposium on Diagnosis and Treatment of Incorporated Radionuclides, Vienna, 1975, pp. 565-577, 1976.

1040804

1977

Hübner, K. F., Andrews, G. A., Lushbaugh, C. C., and Tompkins, E. A Follow-Up Study Program for Persons Irradiated in Radiation Accidents. Presented at the International Symposium on the Handling of Radiation Accidents, February 28-March 2, 1977, Vienna, Austria. To be published.

Johnston, Gerald S., Go, Mae F., Benua, Richard S., Larson, Steven M., Andrews, Gould A., and Hübner, Karl F. ^{67}Ga-Citrate Imaging in Hodgkin Disease: Final Report of Cooperative Group. Accepted for publication J. Nuc. Med., 1977.

Hübner, Karl F., Andrews, Gould A., Hayes, R. L., Poggenburg, J. K., and Solomon, Alan. Use of Rare Earth Radionuclides and Other Bone-Seekers in Evaluating Bone Lesions in Patients with Multiple Myeloma and Solitary Plasmacytoma. Accepted for publication in Radiology, 1977.

1049085

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 77-3

DESCRIPTION: ^{11}C-Carboxyl-labeled 1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) We propose to investigate this new radiopharmaceutical agent for the positron tomographic (ECAT) detection of tumors in humans and to compare its efficacy in this regard with that of ^{11}C-ACPC (ECAT studies also) and ^{67}Ga citrate (single-photon detection). A table of radiation dose estimates, as calculated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center, is attached. The maximum dose of ^{11}C-ACBC proposed is 0.714 mCi per kilogram of body weight (50 mCi for a 70 kg subject)

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Bibbs	✓			28 Sept., 1977
L. C. Scientific Member	✓			28 Sept, 1977
R. J. Hayes	Not	voting		9/28/77
KARL HUBNER	NOT	VOTING		

Acknowledgement of submitter_____ Date_____

Proposal does ✓ does not _____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049086

Radiation Dose (rad) from IV Injection
of 1 mCi of ^{11}C-ACBC*

Total Body	Liver	Spleen	Kidneys	Lungs	Muscle
0.011	0.015	0.019	0.019	0.016	0.011

Red Marrow	Pancreas	Small Intestine	Testes	Ovaries
0.020	0.078	0.022	0.0094	0.021

*Using animal data from Washburn

Radiopharmaceutical Internal Dosimetry
Information Center

September 23, 1977

1049087

Radiation Dose (rad) from IV Injection
of 1 mCi of ^{11}C-ACBC*

Total Body	Liver	Spleen	Kidneys	Lungs	Muscle
0.011	0.015	0.019	0.019	0.016	0.011

Red Marrow	Pancreas	Small Intestine	Testes	Ovaries
0.020	0.078	0.022	0.0094	0.021

*Using animal data from Washburn

Radiopharmaceutical Internal Dosimetry
Information Center

September 23, 1977

1049088

APPLICATION FOR INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee

October 7, 1977

1. NAME OF DRUG: CARBOXYL-LABELED ^{11}C-1-AMINOCYCLOBUTANECARBOXYLIC ACID. This drug, dissolved in saline solution, will be administered intravenously.

2. COMPONENTS:

   a. Carboxyl-labeled ^{11}C-1-Aminocyclobutanecarboxylic acid (^{11}C-ACBC).

   b. 1-Aminocyclobutanecarboxylic acid (ACBC).

   c. Sodium chloride.

   d. Water.

3. QUANTITATIVE COMPOSITION: Since the ^{11}C present in the labeled 1-aminocyclobutanecarboxylic acid is radioactive ($T_{1/2}$ = 20.4 min), we cannot state an exact relationship between the components of this preparation. From radiation dosimetry considerations, however, we have determined that the maximum ^{11}C activity administered will not exceed 0.714 mCi per kilogram of body weight (a 50 mCi dose for a 70 kg subject). The actual amount of stable ACBC that will be administered will be determined by the amount of ^{11}C used in labeling ACBC and also the time that elapses from the time of ^{11}C-ACBC preparation to the time of its administration. The composition stated below, therefore, represents the dosage limits that will be adhered to for the components in this radiopharmaceutical preparation.

   a. Carboxyl-labeled ^{11}C-1-aminocyclobutanecarboxylic acid: maximum of 0.714 mCi per kilogram of body weight (50 mCi for a 70 kg subject).

   b. 1-Aminocyclobutanecarboxylic acid: maximum of 0.1 mg per kilogram of body weight (7 mg for a 70 kg subject).

   c. Sodium chloride: maximum of 3 mg per kilogram of body weight (210 mg for a 70 kg subject).

   d. Water: maximum of 0.5 ml per kilogram of body weight (35 ml for a 70 kg subject).

1049089

4. SOURCE OF NEW DRUG SUBSTANCE:

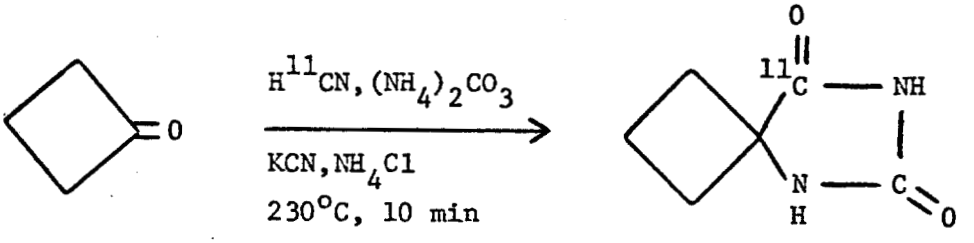
Reference should be made to the details of synthesis and purification of ^{11}C-ACPC (IND 11848 dated 16 September 1975), ^{11}C-DL-valine (IND 12459 dated 12 May 1976), and ^{11}C-DL-tryptophan (IND 12967 dated 9 November 1976), which are similarly prepared radiopharmaceutical agents. ^{11}C-ACPC, ^{11}C-DL-valine, and ^{11}C-DL-tryptophan have been in clinical use at the Medical and Health Sciences Division of ORAU since November 1975, July 1976, and August 1977, respectively.

Carboxyl-labeled ^{11}C-1-aminocyclobutanecarboxylic acid will be synthesized in the preparatory hot cell at the 86-Inch Oak Ridge National Laboratory's (ORNL) 22 Mev proton cyclotron complex using the following series of reactions:

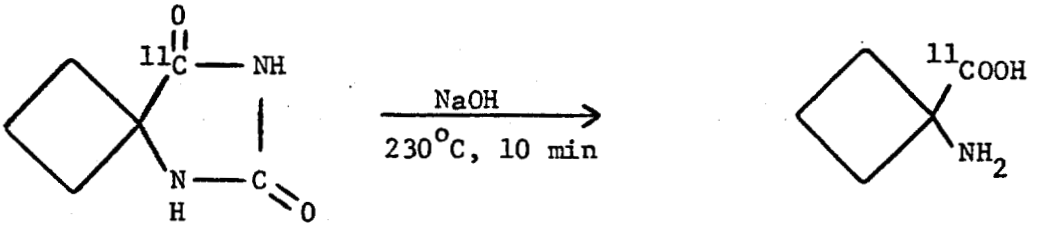
$$B_2O_3 \xrightarrow{^{11}B(p,n)^{11}C} {}^{11}CO_2/{}^{11}CO \qquad \text{STEP I}$$

$$^{11}CO_2/{}^{11}CO \xrightarrow[\text{Ni, } 370^\circ C]{H_2} {}^{11}CH_4 \qquad \text{Step II}$$

$$^{11}CH_4 \xrightarrow[900\text{-}950^\circ C]{Pt, NH_3} H^{11}CN \qquad \text{Step III}$$



Step IV



Step V

Targetry and Production of $^{11}CO_2/^{11}CO$ (Step I): B_2O_3 (Ultrex, J. T. Baker Chemical Co., Phillipsburg, N.J.) is fused onto a graphite substrate which is mounted in an aluminum annulus-type header. The annulus provides a water coolant flow of 15 liters/min. The header assembly is connected in turn to a gas flow loop which has provisions for on-line gas purge or

recirculation. The outlet of the loop is located in the remote control preparatory hot cell adjacent to the cyclotron. During bombardment, when He (Lif-O-Gen Inc., Cambridge, Md.) is used as the carrier gas in the loop, a $^{11}CO_2/^{11}CO$ ratio of approximately 4 is obtained. With a beam current of 150-175 μA approximately 5 Ci of usable $^{11}CO_2/^{11}CO$ is produced.

Production of $^{11}CH_4$ and $H^{11}CN$ (Steps II and III): Both $^{11}CH_4$ and $H^{11}CN$ are produced by contact catalysis. A 100 ml/min He stream introduced into the cyclotron gas flow loop is mixed at the loop outlet with a 50 ml/min H_2 (Lif-O-Gen Inc.) stream and fed through a quartz tube containing Ni catalyst on kieselguhr (Ventron Alpha Products, Beverly, Mass.) held at a temperature of 370°C. The output gas flow from this conversion (containing $^{11}CH_4$) is passed through a $CaSO_4$/NaOH trap and then mixed with a 50 ml/min stream of anhydrous NH_3 (Lif-O-Gen Inc.). This mixture is then passed through another quartz tube containing Pt catalyst (Ventron Alpha Products) heated to 900-950°C to complete the conversion of $^{11}CH_4$ to $H^{11}CN$.

Synthesis of ^{11}C-ACBC (Steps IV and V): Prior to the start of a ^{11}C-ACBC production run a stainless steel (type 316) pressure vessel having an internal volume of 3 ml and fitted with a needle valve is charged with a mixture of 35 μl (32.8 mg) cyclobutanone (b.p. 99°C, Aldrich Chemical Co., Inc., Milwaukee, Wis.), 72 mg $(NH_4)_2CO_3$ (certified A.C.S., Mallinckrodt, Inc., St. Louis, Mo.), 6.7 mg NH_4Cl and 8.2 mg KCN (both Baker Analyzed Reagents, J. T. Baker Chemical Co., Phillipsburg, N.J.). The gas stream from Step III, containing $H^{11}CN$, is bubbled into a gas absorption column containing 1 ml of 0.005 N NaOH. This solution is then introduced into the charged reaction vessel and the closed vessel then rapidly heated to a temperature of 230°C and maintained at that temperature for 10 min, after which it is rapidly cooled. The valve is then opened, 1.0 ml of 6.25 N NaOH (Fisher Scientific Co., Fair Lawn, N.J.) is introduced, and the closed vessel is again heated at 230°C for another period of 10 min.

Purification of ^{11}C-ACBC: After completion of Step V the cooled reaction mixture is withdrawn remotely by means of a syringe and then loaded directly onto a 1.5 cm (diameter) x 5 cm (length) prewashed AG 1-X2, 100-200 mesh, anion exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydroxide form. Anionic components, including ^{11}C-ACBC, are retained by the column while cationic and nonionic components pass through. After washing repeatedly with distilled water (∿ 50 ml) the column is then eluted with 1 N HCl, the process being monitored by means of a shielded gamma probe. The acidic eluate is loaded onto a prewashed 1.0 cm (diameter) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation exchange bed (Bio Rad Laboratories) in the hydrogen form. Cationic ^{11}C-ACBC is retained while anionic material passes through the column. After washing repeatedly with distilled water (∿ 30 ml), the column is finally eluted with 0.2 N NaOH, the process again being monitored with a shielded gamma probe to minimize the volume of eluate containing the product (∿ 15 ml). This solution is collected in a sterile bottle for transport to the Medical and Health Sciences Division of Oak Ridge Associated Universities (ORAU) for final processing.

1049091

In developmental studies prior to actual production of ^{11}C-ACBC, it had previously been determined by elemental analysis (carbon, hydrogen and nitrogen) that the synthesis and purification processes which are used did indeed yield pure ACBC.

The purity of the ^{11}C-ACBC product has been assessed by thin layer chromatography (tlc) (Eastman silica gel, Chromagram Sheet 13179) using an n-butanol: water: acetic acid (100:10:5 v/v) solvent system. ^{11}C-ACBC (from a run spiked with $K^{14}CN$ prior to synthesis) gave a tlc pattern that was similar to that of ^{14}C-labeled ACBC with no indication of any impurities when the two tlc patterns were viewed with a spark chamber. Ninhydrin development of the tlc chromatograms also gave similar results.

Pyrogenicity tests of the ^{11}C-ACBC product by standard USP techniques have been negative. There has also been no indication of decomposition of ^{11}C-ACBC as the result of radiolysis.

5. METHODS, FACILITIES AND CONTROLS:

The solution containing the purified ^{11}C-ACBC will be transported from the ORNL cyclotron complex to the ORAU Medical and Health Sciences Division located on Vance Road in Oak Ridge (trip time, 6-8 min). After being transferred to a magnetically stirred conical beaker, the pH of the solution will be adjusted to 7.0 $\pm$ 0.2 with 1 N HCl using a combination electrode and pH meter. (The stem of the electrode will be stored in 0.9% benzyl alcohol and will be rinsed repeatedly with sterile water before each preparative use.) The solution will then be filtered through a sterile 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized vial (multipuncture type, Wheaton Glass Co., Millville, N.J.). A portion of the solution will be tested for pyrogens using the Pyrotest Limulus Lysate technique (Difco Laboratories, Detroit, Mich.). The short half-life of ^{11}C (20.4 min) precludes testing with rabbits in the conventional USP manner, and, although this particular limulus technique normally requires an hour for completion, it acts as a test for gross pyrogenic contamination during the period of time ($\sim$ 15 min) required for transport of the preparation to the site of administration (1). The test will become part of the record. Each ^{11}C-ACBC dose will be assayed for radioactivity content just prior to administration by means of a Capintec CRC-10 radioisotope calibrator (Capintec, Inc., Montvale, N.J.). (A previous preliminary ion chamber assay will have been made at the cyclotron facility.) The vial containing the ^{11}C-ACBC will finally be labeled as to its assay and total content (see Section 7).

Preparation of each batch of ^{11}C-ACBC for clinical use will be carried out in a positive pressure clean room equipped with vertical laminar flow hoods having air curtains (Envirco, Albuquerque, N.M.). All glassware used will be presterilized by steam. Each batch of ^{11}C-ACBC will be given a batch number and all particulars relative to its preparation and use will be entered into a master log book.

6. STATEMENT OF INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Investigations

1. Animal studies

All animal studies with ^{14}C- and ^{11}C-carboxyl-labeled ACBC were directly supervised by L. C. Washburn and R. L. Hayes. K. F. Hübner participated in the evaluation of the data (see Appendix on Biographical Material).

The insertion of radioisotopic labels into the intrinsic structure of organic compounds and biological substances that have high affinities for specific tissues is an ideal method of labeling, since structures are not altered. The radionuclides ^{11}C, ^{13}N, and ^{15}O are all candidates for use in labeling such agents for nuclear medical diagnosis by scanning. Their decay is accomplished by photon emission in the form of positron annihilation radiation which can be utilized for conventional rectilinear scanning or for coincidence detection techniques such as positron emission computerized axial tomography. This latter method is an instrumentation technique which has recently come into its own in nuclear medical technology (2,3). Of these three radionuclides, ^{11}C is the obvious choice as a label because of its longer half-life (20.4 min), although, even with this radionuclide, rapid tissue distribution is necessarily required of any radiopharmaceutical agent that is labeled with it.

The unnatural, alicyclic amino acid, 1-aminocyclopentanecarboxylic acid (ACPC, also referred to as "cycloleucine") was reported by Berlinguet et al. (4) to concentrate rapidly at high levels in the tumor tissue of mice bearing sarcoma-180 tumors. Their investigation was carried out autoradiographically with ^{14}C-labeled ACPC and was prompted by the fact that this compound had shown chemotherapeutic potential against animal tumors (5,6). We synthesized ^{11}C-carboxyl-labeled ACPC and found it to have significant potential as an agent for imaging soft-tissue tumors (7). Clinical trials of ^{11}C-ACPC for tumor imaging have been in progress at our institution since November 1975, and the agent has been shown to localize in a variety of human tumor types (8,9). In addition, the method which we developed for synthesizing ^{11}C-ACPC, a rapid, high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis, has been found to be applicable to the synthesis of a variety of ^{11}C-labeled amino acids (7,10), including three which we are now studying clinically - ^{11}C-DL-valine and ^{11}C-DL-tryptophan in addition to ^{11}C-ACPC.

In order to assess the importance of structural modification on the tumor specificity of alicyclic amino acids, a series of ^{14}C-labeled amino acids containing 3-, 4-, 5-, and 6-membered alicyclic ring systems (ACPRC, ACBC, ACPC, and ACHC, respectively) (Fig. 1) was synthesized, and their tissue distributions were compared at 30 minutes postinjection in rats bearing Morris 5123C hepatomas (Fig. 2). ^{14}C-ACBC clearly had the greatest tumor specificity of the four agents studied. This suggests the potential superiority of ^{11}C-ACBC over ^{11}C-ACPC as a tumor-imaging agent.

The tissue distribution of ^{14}C-ACBC in rats bearing Morris 5123C hepatomas was complete at 30 minutes postinjection (Fig. 3), which is compatible with the short half-life of ^{11}C (20.4 minutes). The presence of stable ACBC (through 5 mg/kg) had no effect on the tissue distribution of ^{14}C-ACBC (Table 1). Total excretion of ^{11}C-ACBC in the rat was low, 3.6% in 2 hours (Table 2).

^{11}C-ACBC was used for rectilinear scanning of rats bearing transplanted hepatomas, and all three tumor types studied showed positive uptakes of the agent (Fig. 4). Tissue distribution comparisons of the same three tumor types with ^{14}C-ACBC gave data consistent with the scan images (Table 3). In earlier studies the Morris 7777 hepatoma had shown no tumor specificity with ^{14}C- and ^{11}C-ACPC (7).

2. Toxicity

ACBC is an unnatural, alicyclic amino acid which is very similar structurally to ACPC, an agent which has been studied quite extensively in humans as a chemotherapeutic drug and which, when labeled with ^{11}C, is being used as a radiopharmaceutical agent for tumor imaging. However, ACBC is considerably less toxic than ACPC. In 1960, Connors and co-workers (11) reported the tumor growth inhibitory activity and toxicity of a number of alicyclic α-amino acids and related compounds in the rat; included were both ACBC and ACPC. ACPC showed extreme toxicity at an intraperitoneal dose of 500 mg/kg, killing all three animals studied and only at lower doses (75 to 125 mg/kg) was significant tumor growth inhibitory activity seen. On the other hand ACBC showed no tumor growth inhibitory activity and also no toxicity at an intraperitoneal dose of 500 mg/kg, causing no deaths in the three animals studied.

A similar lack of toxicity of ACBC was observed in our studies using mice and dogs, as well as in a study involving one marmoset. A group of 10 mice were each administered an intravenous dose of 2000 mg/kg (20,000 times higher than the proposed human dose), and no deaths were observed within 60 days. In fact, the dose was very well tolerated. One mouse was given 2900 mg/kg and this too was well tolerated. The one mouse which was administered 4000 mg/kg intravenously (40,000 times higher than the proposed human dose) died immediately after the completion of injection, perhaps in part because of hypervolemia. (The 27 g mouse was given 0.86 ml of solution intravenously.)

A study of four laboratory-grade beagle dogs (Ridglan Research Farms, Inc., Mt. Horeb, Wis.) and one marmoset (from the ORAU marmoset colony) at intravenous dosage levels of 200 mg/kg (2000 times higher than the proposed dose) produced a similar lack of toxicity. In both cases complete hematology and clinical chemistry determinations were done.

In the study using dogs, two complete baseline determinations were done during the week prior to administration, and similar determinations were done on days 1, 7, 14, and 28 postadministration. There was no change in either the hematologic or enzyme values, and clinical evaluation of the animals remained normal throughout the test.

In the study with a single marmoset, one complete baseline determination was done at 7 days prior to administration of ACBC, and similar determinations were done on days 1, 14, 28, and 42 postadministration. There was no change in the hematologic values, but it was not possible to evaluate the enzyme values in this case. However, the clinical evaluation remained normal throughout the test.

At the dosage level which we propose to use for tumor scanning (0.1 mg/kg or less), we would expect no toxicity, since we will be below the threshold of toxicity by a factor of at least 2000. The ORAU/ORNL Committee on Human Studies has approved these studies (see Appendix for membership).

3. Radiation Dose

Carbon-11 has a 20.4-minute half-life decaying by positron emission (99+ %) to stable ^{11}B. Because of its short half-life the radiation dose to patients will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center (headed by R. J. Cloutier) that the complete decay of 1 mCi of ^{11}C-ACBC uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.011 rads or a total of 0.55 rads per 50 mCi (the maximum administered dose of ^{11}C-ACBC). Table 4 gives details of the expected radiation dose to various organs in the human estimated from animal data. (The selective uptake of alicyclic amino acids by the pancreas appears to be rodent specific, and the actual radiation dose to the human pancreas is expected to be much lower than that calculated from the rat data.) The MHSD, ORAU Medical Radionuclide Committee has approved the use of ^{11}C-ACBC from a patient safety standpoint.

b. Previous Marketing:

This ^{11}C-labeled drug has not been marketed before.

c. Drug Combination:

^{11}C-ACBC is not a combination of previously marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

The label to be used with ^{11}C-ACBC will have the following form:

^{11}C-1-AMINOCYCLOBUTANECARBOXYLIC ACID
(FOR I.V. INJECTION)

Assay_____mCi/ml as of _____

Volume_____ml: Batch No._____

Expiration Time_____

CAUTION: INVESTIGATIONAL NEW DRUG

CAUTION: RADIOACTIVE MATERIAL

Oak Ridge Assoc. Univ., Oak Ridge, Tn.

The investigators preparing and administering this drug are working in close collaboration in the same institution. Therefore, no formal informational material will be prepared; however, each participant will be issued a copy of this application.

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The sponsor considers the chief investigators, all of whom are supported by competent associates, to be exceedingly well qualified for this research. See biographical material in the Appendix about Drs. Hayes, Hübner, Washburn, and Wieland.

9. PROGRESS OF THE INVESTIGATION:

The progress of the investigation and evidence of safety and effectiveness of the drug will be evaluated by K. F. Hübner, R. L. Hayes, and the sponsor, C. C. Lushbaugh, Ph.D., M.D., Chairman of the ORAU Medical and Health Sciences Division, with advice from the ORAU Medical Advisory Committee and the ORAU/ORNL Committee on Human Studies (see attached lists and biographies in the Appendix).

10. CLINICAL STUDIES:

Phases I and II, clinical pharmacology, in this study will consist of observations on the metabolism and toxicity of ^{11}C-ACBC together with preliminary observations on its tumor-localizing properties. K. F. Hübner, M.D., will be in charge of the initial phase of the clinical investigation which will be done on an out-patient basis at the ORAU Medical and Health Sciences Division, Vance Road, Oak Ridge, Tennessee.

A total of 30 patients with known or suspected cancer will be studied. They will be adult patients referred for tumor scans by physicians in the Oak Ridge Hospital, East Tennessee Chest Disease Hospital (Knoxville), and the University of Tennessee Memorial Hospital (Knoxville), and by other practicing physicians in the East Tennessee area. The ^{11}C-ACBC study is expected to cover a period of 1-1/2 to 2 years. Each patient will be fully informed that this is an experimental procedure, that it might have some toxic effect (although none is expected at the dosage level to be used), and that the procedure will cause a radiation dose (for the maximum 50 mCi dose) of approximately 0.55 rad to the whole body, 1.1 rads to the small intestine, and 1.0 rad to the bone marrow. No ^{11}C-ACBC doses will be given without the informed consent of the patient. Subjects incapable of giving an informed consent will be excluded from the study. No inducement will be offered to obtain voluntary consent. Patients will be recruited specifically for the test with no promise of medical care. A copy of the informed consent form is attached as an Appendix.

For patients without known malignancy, careful selection will be made to avoid giving unnecessary radiation exposure to patients in the younger age group, particularly early in the study before the diagnostic value of the procedure is established. Pregnant women will not be used.

1049096

While it is not anticipated that there will be any toxic effect of ^{11}C-ACBC at the doses to be used in this study (see sections 3 and 6-a-2), the first four patients studied will receive reduced doses of stable ACBC as a precautionary measure. The first two patients will receive a maximum of 0.01 mg/kg and the next two patients will receive a maximum of 0.05 mg/kg. This will be done by decreasing the level of stable KCN used in the synthesis of ^{11}C-ACBC by factors of 10 and 2, respectively. This procedure does not in any way compromise the quality of the pharmaceutical preparation; rather it simply produces a preparation of higher specific activity at the expense of a somewhat lower chemical yield. Since animal studies (see section 6-a-1) have shown that the level of carrier ACBC does not affect the tumor specificity of the agent, this alteration in procedure is not expected to have any effect upon the quality of the images obtained in these four patients.

At short time intervals after drug administration (∿ 15 minutes), scanning will begin using the ECAT (Emission Computerized Axial Tomographic) instrument or other appropriate nuclear medical instrumentation. Due to the short half-life of ^{11}C (20.4 minutes), other studies are feasible after short time intervals (2-3 hours). Whenever possible, the same patient will be studied on the same day using ^{11}C-ACPC by the protocol which has been previously approved for that agent (IND 11848, dated 16 September 1975). Also, whenever it is feasible, a conventional nuclear medical scan will be obtained using NDA ^{67}Ga-citrate, so that a direct comparison of the three tumor-imaging agents can be made. It is realized that, for the comparative study of ^{11}C-ACBC, ^{11}C-ACPC, and ^{67}Ga-citrate, the radiation dose will become of greater concern. Therefore, in these cases, the dose of each radiopharmaceutical will be adjusted downward by a factor adequate to alleviate problems of radiation dose.

For dosimetry purposes and to determine optimal timing of scanning, blood levels of radioactivity will be determined at frequent intervals during the first 1 to 1-1/2 hours after injection of the radiopharmaceutical. Additional information for radiation dose estimates will be gathered by whole body counting and determination of the radioactivity excreted in the urine.

The following laboratory tests will be done both before and 24 hours after injection of the radiopharmaceutical: complete blood count, urinalysis and plasma hemoglobin. Careful observation of the pulse rate will be made during the first 6 doses given.

If any abnormality in clinical or laboratory observations is seen, appropriate follow-up studies will be carried out. If the abnormality appears serious, we will stop all further clinical trials and immediately notify the Food and Drug Administration.

The principal questions to be answered are:

1. Is there any unsuspected toxic effect of ACBC on humans at the chemical dose levels proposed?

2. Will the uptake of ^{11}C-ACBC in human tumors be sufficient to permit tumor detection by scanning?

3. For purposes of radiation dosimetry, what is the blood clearance rate and excretion pattern for ^{11}C-ACBC in humans?

4. What is the optimum dose and scanning time for tumor imaging?

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.

12. The sponsor will notify the investigators if a new drug application is approved.

13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic and introductory clinical research phase of this work.

14. The sponsor will not permit initiation of clinical studies of ^{11}C-ACBC prior to 30 days after the date of receipt of notice of this application by the Food and Drug Administration. He also will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

1049098

References

1. J. F. Cooper, J. Levin, and H. N. Wagner, Jr. J. Lab. Clin. Med. 78:138, 1971.

2. R. A. Brooks and G. Di Chiro. Phys. Med. Biol. 21:689, 1976.

3. M. P. Cronin. Appl. Radiol. 5:220, 1976.

4. L. Berlinguet, N. Begin, and L. M. Babineau. Can. J. Biochem. Phys. 40: 1111, 1962.

5. T. A. Connors, L. A. Elson, and W. C. J. Ross. Biochem. Pharmacol. 1:239, 1958.

6. R. B. Ross, C. I. Noll, W.C.J. Ross, M. V. Nadkarni, B. H. Morrison, and H. W. Bond. J. Med. Pharm. Chem. 3:1, 1961.

7. R. L. Hayes, L. C. Washburn, B.W. Wieland, T. T. Sun, R. R. Turtle, and T. A. Butler. J. Nucl. Med. 17:748, 1976.

8. G. A. Andrews, K. F. Hübner, L. C. Washburn, B. W. Wieland, W. D. Gibbs, R. L. Hayes, T. A. Butler, and I. R. Collmann. J. Nucl. Med. 18:638, 1977.

9. K. F. Hübner, G. A. Andrews, L. C. Washburn, B. W. Wieland, W. D. Gibbs, and R. L. Hayes. J. Nucl. Med. (in press).

10. R. L. Hayes, L. C. Washburn, B. W. Wieland, T. T. Sun, J. B. Anon, T. A. Butler, and A.P. Callahan. Int. J. Appl. Radiat. Isotopes (in press).

11. T. A. Connors, L. A. Elson, A. Haddow, and W.C.J. Ross. Biochem. Pharmacol. 5:108, 1960.

1049099

TABLE 1

Effect of Carrier ACBC on the Tissue Distribution of ^{14}C-ACBC in Male Buffalo Rats Bearing Morris 5123C Hepatomas at 30 Minutes Postinjection.

Tissue	Tumor/Tissue Conc. Ratio[a]		
	0.09 mg/kg	1.0 mg/kg	5.0 mg/kg
Liver	9.5 ± 0.5	8.9 ± 1.3	10.8 ± 1.4
Spleen	5.8 ± 0.2	6.4 ± 0.7	7.3 ± 0.9
Kidney	6.2 ± 0.2	6.5 ± 0.6	7.5 ± 0.9
Lung	5.4 ± 0.7	6.9 ± 1.1	5.4 ± 1.0
Muscle	12.7 ± 0.1	17.5 ± 2.4	16.6 ± 2.2
Marrow	4.7 ± 0.2	5.5 ± 0.3	5.7 ± 0.3
Small intestine	3.9 ± 0.2	4.0 ± 0.4	4.8 ± 0.2
Blood	13.2 ± 0.3	13.3 ± 1.7	15.4 ± 2.2
Pancreas	1.3 ± 0.1	1.3 ± 0.2	1.4 ± 0.2

[a] Average of 4 animals ± S.E.

TABLE 2

Total Excretion of ^{11}C-ACBC by Male Fischer Rats

Time (min)	% Administered ^{11}C Lost[a]
20	1.6 ± 0.4
40	2.3 ± 0.7
60	2.5 ± 0.6
90	3.3 ± 0.6
120	3.6 ± 0.5

[a] Average of 5 animals ± S.E.

1049100

TABLE 3

Effect of Tumor Type on the Tissue Distribution of ^{14}C-ACBC (0.09 mg/kg) at 30 Minutes Postinjection.

Tissue	Tumor/Tissue Conc. Ratio[a]		
	Morris 5123C	Morris 7777	Reuber H-35
Liver	9.6 ± 1.0	1.7 ± 0.1	6.3 ± 0.5
Spleen	7.6 ± 0.6	1.4 ± 0.1	3.9 ± 0.2
Kidney	6.8 ± 0.1	1.5 ± 0.1	5.1 ± 0.2
Lung	8.0 ± 0.2	1.6 ± 0.2	5.8 ± 0.4
Muscle	16.3 ± 1.0	3.7 ± 0.1	10.3 ± 0.5
Marrow	7.3 ± 0.6	1.2 ± 0.2	4.2 ± 0.4
Small intestine	4.3 ± 0.3	0.9 ± 0.0	3.9 ± 0.3
Blood	15.1 ± 1.7	2.6 ± 0.2	11.5 ± 0.7
Pancreas	1.3 ± 0.1	0.3 ± 0.0	0.8 ± 0.1

[a] Average of 4 animals ± S.E.

TABLE 4

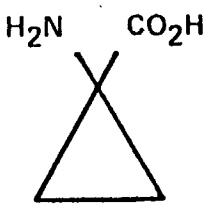
Estimated Radiation Dose from ^{11}C-ACBC to Organs in Man[a]

Tissue	Radiation dose (rads/mCi)
Total body	0.011
Liver	0.015
Spleen	0.019
Kidney	0.019
Lung	0.016
Muscle	0.011
Marrow	0.020
Small intestine	0.022
Pancreas	0.078
Testis	0.009
Ovary	0.021

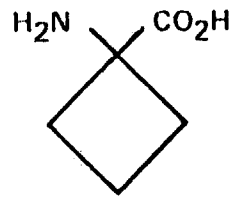
[a] Based on 30-minute tissue distribution of ^{14}C-ACBC (2.3 mg/kg) in the rat following intravenous administration, assuming immediate uptake by the organs followed by complete decay in situ.

1049101

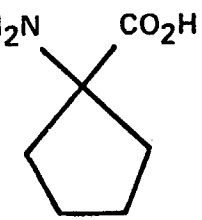
STRUCTURES OF ALICYCLIC AMINO ACIDS



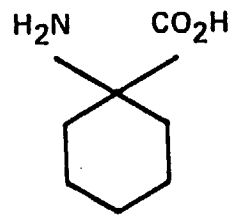
1-Aminocyclopropane-carboxylic acid (ACPRC)



1-Aminocyclobutane-carboxylic acid (ACBC)



1-Aminocyclopentane-carboxylic acid (ACPC)



1-Aminocyclohexane-carboxylic acid (ACHC)

Fig. 1. Chemical structures of a series of unnatural, alicyclic amino acids.

1049102

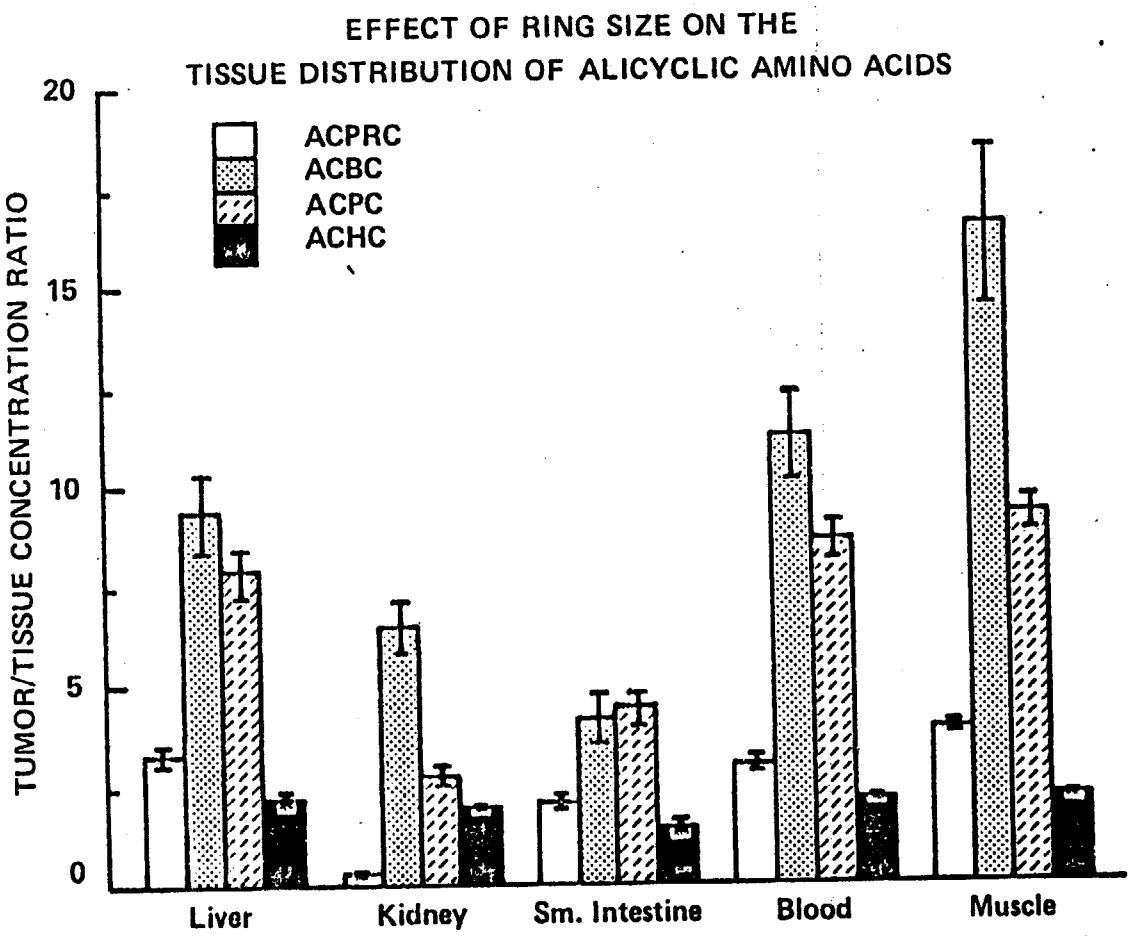


Fig. 2. Effect of ring size on the tissue distribution of alicyclic amino acids (0.02 mmoles/kg) in male Buffalo rats bearing Morris 5123C hepatomas (30 minutes postinjection).

1049103

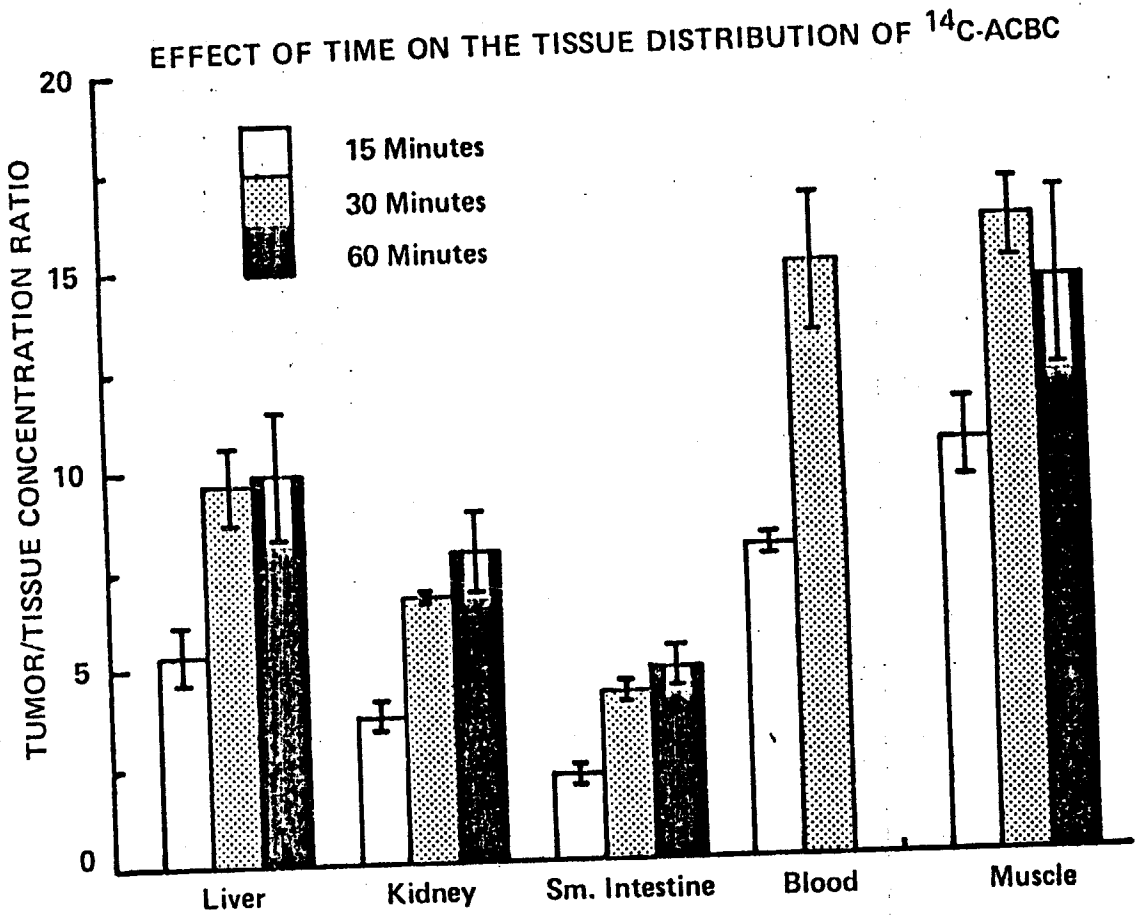


Fig. 3. Effect of time on the tissue distribution of ^{14}C-ACBC (0.09 mg/kg) in male Buffalo rats bearing Morris 5123C hepatomas.

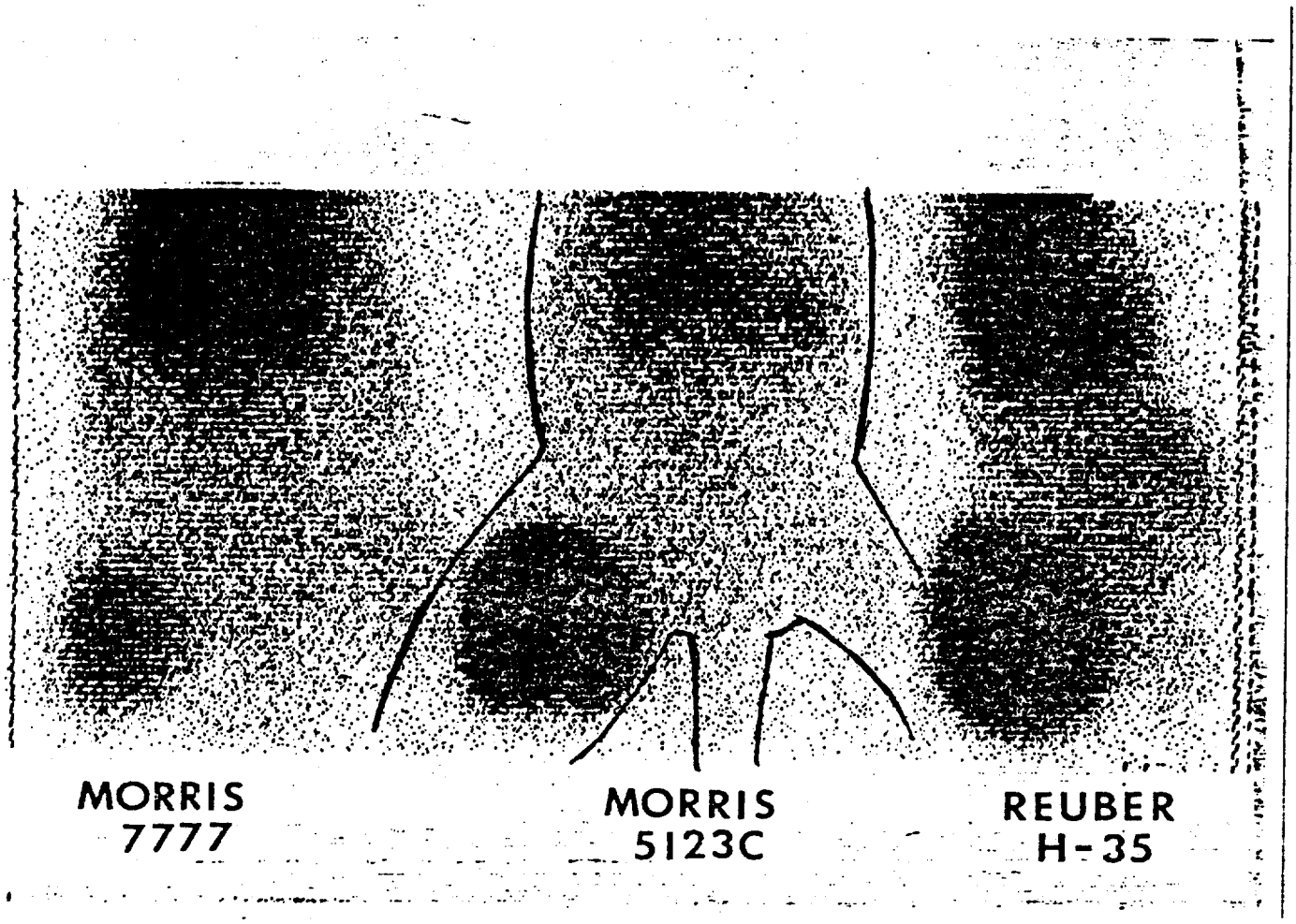


Fig. 4. Rectilinear scan of rats bearing three types of transplanted hepatomas.

1049105

APPENDIX

Chief Investigators:

K. F. Hübner, Principal Investigator
R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

ORAU/ORNL Committee on Human Studies:

Gould A. Andrews, M.D.
Director of Clinical Applications
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

A. Bertrand Brill, M.D., Ph.D.
Associate Professor of Medicine and Radiology
Division of Nuclear Medicine and Physics
Vanderbilt University School of Medicine
Nashville, Tennessee 37235

William H. Calhoun, Ph.D.
Professor and Head, Department of Psychology
University of Tennessee
1400 Cumberland Avenue SW
Knoxville, Tennessee 37916

Donald W. Goodwin, Ph.D.
Minister, United Church, Chapel-on-the-Hill
85 Kentucky Avenue
Oak Ridge, Tennessee 37830

Karl F. Hübner, M.D.
Chief of Outpatient Clinical Studies
Director of REAC/TS Facility
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Melvin E. Koons, J.D.
Executive Assistant to President
Union Carbide Corporation, Nuclear Division
P. O. Box Y, Building 9704-2
Oak Ridge, Tennessee 37830

1049106

Robert D. Lange, M.D.
Director, University of Tennessee
Memorial Research Center and Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Thomas A. Lincoln, M.D.
Director, Health Division
Oak Ridge National Laboratory
Building 4500-N, Room K-122
Oak Ridge, Tennessee 37830

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

Ruby L. Anderson-Miller, B.S.
Public Relations Representative
Union Carbide Corporation, Nuclear Division
Oak Ridge National Laboratory
Building 4500-N, Room K-250
Oak Ridge, Tennessee 37830

John B. Storer, M.D.
Director, Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Edythalena Tompkins, A.B.
Chief Epidemiologist
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Joan B. Woods, M.D.
Psychiatrist
Veterans Administration Hospital
Murfreesboro, Tennessee 37130

ORAU Biomedical Advisory Committee:

William H. Stone, Ph.D. (Immunobiology)
Department of Genetics
University of Wisconsin
Madison, Wisconsin 53706

George B. Hutchison, M.D. (Epidemiology)
Harvard University School of Public Health
677 Huntington Avenue
Boston, Massachusetts 02115

John M. Johnston, Ph.D. (Biochemistry)
Department of Biochemistry
University of Texas Southwestern Medical School
Dallas, Texas 75235

David E. Kuhl, M.D. (Nuclear Medicine)
Center for the Health Sciences
UCLA
Los Angeles, California 90024

Norman C. Telles, M.D. (Radiation Health)
Associate Director of Medical Affairs
Bureau of Radiological Health
Rockville, Maryland 20857

BIOGRAPHICAL MATERIAL

Name:	Gould A. Andrews
Position:	Internist, Director of Clinical Applications, Medical and Health Sciences Division Oak Ridge Associated Universities
School:	University of Michigan, A.B., 1940 University of Michigan, M.D., 1943
Licensure:	Tennessee, Florida
Boards:	Internal Medicine, Nuclear Medicine
Memberships:	Society for Experimental Biology and Medicine American Association for Cancer Research American Thyroid Association Society of Nuclear Medicine Southern Society for Clinical Research American Medical Association American Association for the Advancement of Science American Federation for Clinical Research Fellow, American College of Physicians American Society of Hematology (1968) Health Physics Society, East Tennessee Chapter Tennessee Academy of Science Tennessee Blood Club

Name:	A. Bertrand Brill
Position:	Associate Professor of Medicine and Radiology Vanderbilt School of Medicine, Nashville, Tennessee
School:	Grinnell, A.B., 1949 University of Utah, M.D., 1956 University of California, Berkeley, Ph.D., 1961
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science Society of Nuclear Medicine Radiation Research Society American Thyroid Association

Other Indication of Experience and Competence:
Medical Director, Division of Radiological Health, U. S. Public Health Service, 1957-1964, Rockville, Md.

1049108

Name:	William H. Calhoun
Position:	Professor and Head, Department of Psychology, The University of Tennessee, Knoxville, Tennessee
School:	Santa Rosa Junior College, A.A., 1952 Stanford University, B.A., 1959 University of California, Berkeley, Ph.D., 1964
Memberships:	American Psychological Association, Division 1, 2, 3, 6, 25, and 28 American Association of University Professors American Association for the Advancement of Science Behavioral Pharmacological Society Southeastern Psychological Association Tennessee Psychological Association Sigma Xi Southern Society of Philosophy and Psychology Psychonomic Society

Name:	Donald W. Goodwin
Position:	Minister, United Church, Chapel-on-the-Hill Oak Ridge, Tennessee
School:	Bangor Theological Seminary, Bachelor of Divinity, 1959 Brown University, Ph.D., 1965
Memberships:	Ministerial Standing, United Church of Christ
Additional information:	Member of various boards which change from time to time

Name:	R. L. Hayes
Position:	Chief Scientist (in charge of medical radioisotope development), Medical and Health Sciences Division, Oak Ridge Associated Universities
School:	University of North Carolina, B.S., 1944 University of North Carolina, Ph.D., 1952
Positions:	Senior Chemist, U. S. Rubber Co., North Carolina, 1944 U. S. Army, 1944-46 ORAU Medical Division, 1950 - present
Memberships:	American Chemical Society Society of Nuclear Medicine Reticuloendothelial Society
Interests:	Development of medical radioisotopic agents; radiation dosimetry

Name:	Karl F. Hübner
Position:	Internist, Chief of Outpatient Clinical Studies and Director of REAC/TS Facility, Medical and Health Sciences Division, Oak Ridge Associated Universities
School:	University of Heidelberg, M.D., 1959
Licensure:	Tennessee
Board:	Nuclear Medicine
Memberships:	Roane-Anderson County Medical Society Tennessee Medical Association American Medical Association Society of Nuclear Medicine

Name:	George B. Hutchison
Position:	Professor of Epidemiology, Harvard University School of Public Health, Boston, Massachusetts
School:	Harvard University, A.B., 1943; M.D., 1951; M.P.H., 1960
Memberships:	Fellow, American Public Health Association American Statistical Association World Medical Association Association of Teachers of Preventive Medicine

Name:	John M. Johnston
Position:	Professor of Biochemistry, University of Texas, Southwestern Medical School, Dallas, Texas
School:	Hastings College, B.A., 1949 University of Colorado, Ph.D., 1953
Memberships:	AAAS American Chemical Society Society for Experimental Biology and Medicine American Society for Biology
Interests:	Chemical mechanism of lipid absorption; membrane enzymology

Name:	Melvin E. Koons
Position:	Executive Assistant to President, Union Carbide Corporation, Nuclear Division, Oak Ridge, Tennessee
School:	University of North Dakota, B.A., 1955; Juris Doctor, 1961
Admitted to Practice of Law:	North Dakota 1961; Tennessee 1964; Federal District Court, North Dakota 1961; East Tennessee 1964, U. S. Supreme Court, 1966
Memberships:	American Bar Association Public Contracts Section Federal Bar Association Government Contracts Committee R & D Contracts Subcommittee Tennessee Bar Association North Dakota Bar Association, Ward County

Name:	David E. Kuhl
Position:	Chief, Division of Nuclear Medicine, Center for the Health Sciences, UCLA, Los Angeles, California
School:	Temple University, A.B., 1951 University of Pennsylvania, M.D., 1955
Memberships:	Society of Nuclear Medicine Fellow, American College of Radiology Radiological Society of North America Association of University Radiologists
Interest:	Radionuclide imaging

Name:	Robert Lange
Position:	Research Professor; Director, The University of Tennessee Memorial Research Center, Knoxville, Tennessee
School:	Macalester College, B.A. Washington University, M.D., 1944
Licensure:	Tennessee, Minnesota, Missouri, Georgia
Board:	Internal Medicine
Memberships:	American Association for the Advancement of Science American Medical Association Knoxville Academy of Medicine Southern Society of Research Central Society of Clinical Research American College of Physicians International Society of Hematology

Name:	Thomas A. Lincoln
Position:	Director, Health Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee
School:	Macalester College, St. Paul, Minnesota, B.A. (Chemistry), 1946; University of Minnesota, Minneapolis, B.S., 1947; B.M., 1949; and M.D., 1950
Licensure:	Tennessee, Minnesota
Board:	American Board of Preventive Medicine, by examination June 5, 1963
Memberships:	Fellow Industrial Medical Association Past President, Tennessee Industrial Medical Association American Academy of Occupational Medicine American Medical Association Past President, Roane-Anderson County Medical Society Treasurer, Board of Directors, Oak Ridge Regional Mental Health Center

Name:	Clarence C. Lushbaugh
Position:	Chairman, Medical and Health Sciences Division Oak Ridge Associated Universities
School:	University of Chicago, B.S., 1938 (Anatomy) University of Chicago, Ph.D., 1942 (Pathology) University of Chicago, M.D., 1948 (Pathology)
Licensure:	Tennessee
Memberships:	American Association for the Advancement of Science American Society for Experimental Pathology Associated Researchers and Clinicians in Cancer Society for Experimental Biology and Medicine Health Physics Society Radiation Research Society Society of Nuclear Medicine American Medical Society Tennessee State Medical Society American Occupational Medical Association

Name:	Ruby L. Anderson Miller
Position:	Public Relations Representative, UCCND, ORNL, Oak Ridge, Tennessee
School:	Livingstone College, Salisbury, N.D., B.S., 1968 Union Carbide Management Training Program and Professional Development Course at New York University
Memberships:	Chairman, Personnel Advisory Board, Oak Ridge School System Member of ERDA's Personnel Security Board Oak Ridge Chamber of Commerce Committee on Community Affairs Member, Board of Directors of Knoxville Area Urban League Member, Oak Ridge Branch, NAACP Member of Volunteer Chapter, Public Relations Society of America

Name:	William H. Stone
Position:	Professor of Genetics, University of Wisconsin, Madison, Wisconsin
School:	Brown University, A.B., 1948 University of Maine, M.S., 1949 University of Wisconsin,Ph.D., 1953
Memberships:	AAAS Genetics Society Society of Human Genetics American Association of Immunology Transplantation Society Scientific Research Society of American Animal Sciences
Interests:	Immunogenetics and immunochemical studies of blood groups; immunology of fertility and sterility; transplantation and tolerance

Name:	John B. Storer
Position:	Director, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee
School:	University of Chicago, M.D., 1947
Memberships:	American Association for Cancer Research American Society for Experimental Pathology Radiation Research Society Society for Experimental Biology and Medicine National Council on Radiation Protection and Measurements

Name:	Norman C. Telles
Position:	Assistant Director, Bureau of Radiation Health, Rockville, Md.
School:	Boston University, M.D., 1956
Primary Specialty:	Pathology
Secondary Specialty:	Radiology

Name:	Edythalena Tompkins
Position:	Chief Epidemiologist, Medical and Health Sciences Division, Oak Ridge Associated Universities
School:	Stanford University, A.B., 1939 Graduate School, 1940-1955 University of Minnesota, Graduate Summer Sessions in Epidemiology 1969 and 1970
Memberships:	American Public Health Association Society for Epidemiological Research Society for Occupational and Environmental Health American Thyroid Society

Name:	Lee C. Washburn
Position:	Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools:	Murray State University, B.A., 1968 Vanderbilt University, Ph.D., 1972
Interests:	Synthetic organic chemistry; chromatography, radiopharmaceutical tissue distribution studies; radioprotective drugs

Name:	Bruce W. Wieland
Position:	Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities
Schools:	Iowa State University, B.S., 1960 Ohio State University, Ph.D., 1973
Membership:	Society of Nuclear Medicine
Interests:	Production and utilization of short-lived positron-emitting isotopes for nuclear medical applications. Development of hot cell equipment for the synthesis of labeled compounds. Isotope imaging instrumentation, including coincidence detection and computer reconstruction techniques for tomography.

Name:	Joan B. Woods
Position:	Psychiatrist, Veterans Administration Hospital, Murfreesboro, Tennessee
School:	University of Chicago School of Medicine, B.S. and M.D., 1960
Licensure:	Tennessee
Boards:	American Board of Psychiatry and Neurology
Memberships:	American Psychiatric Association American Medical Association and Subsidiaries

1049113

MEDICAL AND HEALTH SCIENCES DIVISION
OAK RIDGE ASSOCIATED UNIVERSITIES
OAK RIDGE, TENNESSEE

I authorize the performance upon _____
myself or name of patient
the following test: Phase I and II radiopharmaceutical tests of carboxyl-labeled ^{11}C-1-aminocyclobutanecarboxylic acid for tumor detection.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. It has been made clear to me that I may ask questions about it, and I have no unanswered questions. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes, to evaluate the efficiency and safety of the procedure, and that it may benefit others. Further I understand that any information from the test becomes the property of ORAU and may be published in the scientific literature, without use of my name, at the discretion of the staff of ORAU.

Date _____ _____
(patient or person authorized to consent for patient)

Witness: _____

_____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: Carboxyl-labeled ^{11}C-1-aminocyclobutane-carboxylic acid.
2. The drug contains the radioactive isotope ^{11}C and an organic chemical in quantities much less than those required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. The radiation dose will be not more than approximately 0.5 rad to the whole body.
4. Whole body counts and scans with a conventional and possibly with an experimental scanning device will be made over a two-hour period.
5. The patient may withdraw from the test at any time.
6. I have offered to answer any questions the patient may have.

Date: _____ _____
Investigator

Revised September, 1977

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 78-1

DESCRIPTION:

A ^{68}GA-LABELED MICROSPHERE PREPARATION FOR THE STUDY OF LUNG PERFUSION IN SUBJECTS WITH PNEUMOCONIOSIS. Dose not to exceed 1 millicurie per 70 kg body weight.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

SUPERSEDED BY 78-1A 22 MARCH, 1979

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William R. Fitz	✓			10 July 1978
Lloyd Swartzendruber	✓			10 July, 1978
James D. Geiger	✓			10 July 1978
Karl F. Hübner	not voting			10 July 1978
R. J. Hayes	Not voting			10 July 1978

Acknowledgement of submitter Karl F. Hübner Date 10 July 1978

Proposal does ✓ does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049115

78-1

Ident No. 54

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: June 26, 1978

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigator: Raymond L. Hayes, Ph.D.

Title of Project: A ^{68}GA-LABELED MICROSPHERE PREPARATION FOR THE STUDY OF LUNG PERFUSION IN SUBJECTS WITH PNEUMOCONIOSIS

I. Objectives of Experiment:

The basic objective of this study is to determine the benefits that may be derived from the use of ^{68}Ga-labeled 3M Microspheres in the quantitative assessment of the degree of perfusion impairment in patients afflicted with different stages of pneumoconiosis.

Gallium-68 is a positron emitter with a 68-min half life that is available from a long-lived ($T_{1/2}$ = 287 d) ^{68}Ge generator. Tin-treated albumin Microspheres (3M Company, St. Paul, Minn.) can be labeled with ^{68}Ga by a suitable adjustment of the pH of Microsphere suspensions containing $^{68}GaCl_3$. This preparation has been shown in animals to localize preferentially in the lungs (see Appendix). By using the ORTEC ECAT positron tomograph, it will be possible to obtain cross-sectional images of the lungs which can then be evaluated quantitatively for perfusion defects.

II. Methods of Procedure:

3M Microspheres (obtained in kit form) will be labeled with ^{68}Ga by incubation of suspended Microspheres in the presence of $^{68}GaCl_3$ at pH 4.5. The $^{68}GaCl_3$ will be produced from ^{68}GaEDTA which in turn will be obtained from a ^{68}Ge generator (procedure covered in IND 13,533 for ^{68}Ga citrate).

1049116

The intravenously injected volume of the preparation will not exceed 5 ml nor contain more than 2 mg of albumin (360,000 particles). The size range of the particles will be checked with a hemocytometer and the preparation rejected if clumping or particles exceeding 100 μ are present. The amount of ^{68}Ga injected will not exceed 1 mCi/70 kg.

A total of 20 patients will be studied. Half of these patients will have chronic obstructive lung disease or pneumoconiosis (black lung). The other half will be patients who have had radiation therapy for treatment of breast cancer with potential complications from radiation-induced pneumonitis or pulmonary fibrosis. The latter conditions will act as a model for pneumoconiosis in its earliest stage. These subjects will be periodically examined with ^{68}Ga-labeled Microspheres during and following conventional fractionated radiotherapy.

The schedule for scanning the radiotherapy patients with ^{68}Ga-labeled Microspheres will be the following: (1) before therapy, (2) at 4 weeks or 2/3 of the way through the treatment period, (3) at the end of therapy, and (4) at monthly intervals for a period of 9 months following completion of radiotherapy. All patients will receive, in addition to the ^{68}Ga Microsphere scans, ^{133}Xe ventilation studies, ^{99m}Tc 3M Microsphere perfusion studies, and conventional pulmonary function studies.

Patients will be referred to the Medical and Health Sciences Division by Drs. Spencer Bell (Knoxville) and Frank Comas and Thomas Sullivan of the University of Tennessee Memorial Hospital.

III. Possible Hazards and their Evaluation:

1. Toxicity of albumin Microspheres.

It has been shown that the toxicity of macroaggregated albumin (MAA) increases with increasing particle size. Taplin et al., found no change in systemic or pulmonary arterial blood pressure of dogs when suspensions of MAA smaller than 35 μ in diameter were administered in doses as high as 40 mg/kg.

Abrupt increases in pulmonary arterial pressure, followed by decreases in systemic arterial pressure, were found with suspensions of particles up to 80, 150 and 300 μ in diameter at doses of 20-25, 10 and 5 mg/kg respectively. Use of suspensions with significant numbers of particles exceeding 100 μ in diameter should be avoided. We will not use suspensions that contain any particles >100 μ in diameter. Each preparation will be checked before injection. Furthermore, the total dose of albumin will not exceed 2 mg/70 kg.

2. Hazards in patients with pulmonary arterial hypertension or left to right shunt.

A typical dose of 100,000 to 500,000 particles obstructs well under 1/1,000 of the cross-section of the pulmonary vasculature of a normal individual (Roger H. Secker-Walker, Lung Scanning. In Diagnostic Nuclear Medicine, A. Gottschalf and E.J. Potchen, eds., The Williams & Wilkins Company, Baltimore, 1976, pp. 341-398).

1049117

The control of particle size is particularly important in patients with pulmonary arterial hypertension. The diameter of the lumen of the small muscular pulmonary arteries of these individuals may be reduced to 10-20% of the normal. Particles thus will lodge more proximally in the pulmonary arterial tree than in normal lungs and obstruct a larger fraction of the cross-sectional area of the pulmonary vasculature, which already has been reduced by disease.

In patients with right to left shunts, peripheral arterial embolism could be a problem especially with large particles. Attention to the patients history and diagnosis and again strict control of particle size should avoid any complications such as iatrogenic pulmonary embolism.

IV. Radioisotopes and New Drugs:

This proposal will be submitted to the ORAU Medical Isotopes Committee on July 5, 1978. The Committee on Human Studies will be notified of their action when the Committee meets on July 10, 1978. The ORAU Internal Dose Information Center estimates the radiation dose from ^{68}Ga Microspheres to be 2.8 rads/mCi, assuming complete deposition in the lungs with no loss from that organ during decay.

The drug used in this ^{68}Ga preparation will be 3M Company's Instant Microspheres produced from human serum albumin and dispensed in kit form for labeling with ^{99m}Tc. The manufacturer claims a particle size range of 95% 10-45 μ with all particles having a diameter of less than 50 μ. Our procedure using ^{68}Ga rather than ^{99m}Tc results in a ^{68}Ga labeling efficiency of greater than 95%.

V. Responsibility of Principal Investigator:

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be immediately brought to the attention of the Committee on Human Studies.

Starting Date August 20, 1978

Signatures: Karl F. Holmes, M.D. Principal Investigator

R. L. Hayes Co-Investigator

1049118

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

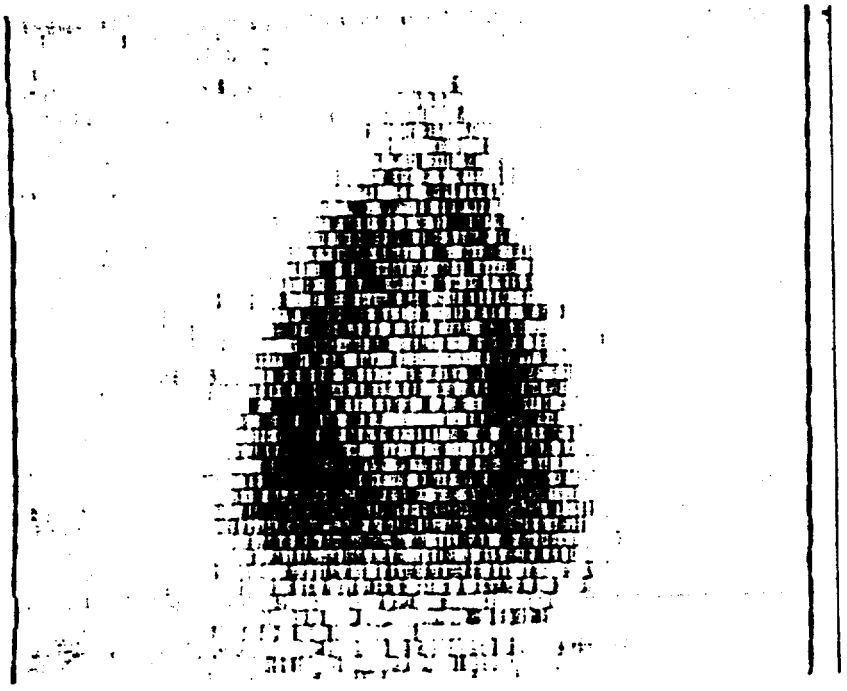
Signature

Title: Chairman, Medical and Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: June 26, 1978

1049119



Anterior rectilinear lung scan of a dog that had received ^{68}Ga-labeled Microspheres ∿45 minutes previously.

Posterior rectilinear scan from study shown above.

1C-1

R.L. Hayes

March 16, 1978

RADIATION DOSE FROM ^{68}GA

Evelyn E. Watson

File

As you requested, I have calculated the radiation dose to a patient from one millicurie of ^{68}Ga. If we assume that 100% of the administered activity goes to the lungs and remains there until decay is complete, the dose to the lungs would be 2.8 rads/millicurie administered and the dose to the total body would be 0.054 rads/millicurie administered.

EEW:np

1049121

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 78-1A

DESCRIPTION:

GA-68-LABELED 3M MICROSPHERES

Change previous approved level of ^{68}Ga from 1 mCi per 70 kg to 1.4 mCi per 70 kg (20 μCi/kg) based on new assessment of radiation dose (see attached table).

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
J. Bergan	✓			3/22/79
[illegible]	✓			3/22/79
R. L. Hayes	✓			3/22/79
William H. Sebb	✓			3/22/79
Karl F. Hübner	not	voting		

Acknowledgement of submitter Karl F. Hübner Date 3/19/79

Proposal does___ does not ✓ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049122

Oak Ridge Associated Universities

MEMORANDUM

Dr. Ray Hayes **FROM** Jack Coffey Jack

DATE March 1, 1979 **COPIES TO** File

SUBJECT RADIATION DOSE FROM Ga-68 MICROSPHERES

Below is a table of dose estimates for Ga-68 microspheres based on the information you gave me by phone. If you have any questions, just give me a call.

Radiation Dose (rad/mCi) from IV Injection
of Ga-68 microspheres

Organ	Radiation Dose
Kidneys	0.062
Liver	0.068
Lungs	2.1
Ovaries	0.014
Spleen	0.037
Testes	0.014
Total Body	0.054

1049123

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 79-1

DESCRIPTION:
^{68}Ga-EDTA aerosol for lung ventilation studies by positron tomography. Dose per study not to exceed 1.5 mCi. The chemical quantity of Na_2-EDTA will not exceed 3 mg.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not X be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not X be administered to pregnant patients.

Other:

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
James O'Keeffe	✓			5/21/79
William D. Bibbo	✓			5/21/79
H. B. Swartzendruber	✓			5/21/79
R. L. Hayes	✓			5/21/79

Acknowledgement of submitter Karl F. Hübner Date 5/30/79

Proposal does ✓ does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on 2 July, 1979

1049124

DOSE ESTIMATES FOR ^{68}GA AEROSOL

Organ	Radiation Dose (Rads) Per 1.5 mCi
Kidneys	0.066
Liver	0.073
Lungs	3.15
Ovaries	0.015
Spleen	0.040
Testes	0.015
Total Body	0.058

AMENDMENT TO IND 13,383

Use of ^{68}Ga-EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)

We propose to test the use of ^{68}Ga-EDTA for diagnostic evaluation of lung air spaces by positron emission computed tomography (ECT). One distinct advantage of any ^{68}Ga labeled radiopharmaceutical (unlike ^{13}N and ^{11}C agents), if proven useful, is that ^{68}Ga (T-1/2 68 min) is readily available from a ^{68}Ge-generator with a 287 day half life. Clinical diagnostic applications of ^{68}Ga-EDTA aerosol ECT would complement perfusion studies with ^{68}Ga-labeled microspheres (3M) as described in our IND

Preparation and Administration of ^{68}Ga-EDTA Aerosol

Gallium will be prepared by the procedure described in IND #13,383.

Aerosol production and inhalation is done according to the method of Taplan and Chopra (Ref. 1, 2). A copy of the most recent version of Dr. G. Taplan's procedure is attached to this amendment.

The ^{68}Ga-EDTA will be of high specific activity (0.5 to 1 mCi/ml) so that small volumes may be nebulized in a relatively short time for fairly rapid administration of the dose. The dose ^{68}Ga-EDTA aerosol proposed in this study is not to exceed 1.5 mCi per study. The chemical quantity of Na_2EDTA will not exceed 3 mg.

Patient Population of the Study

Patients to be included in this study are patients with one of three pulmonary disease states:

(a) Sarcoidosis

(b) Radiation fibrosis or pneumonitis

(c) Chronic obstructive pulmonary disease (COPD)

The patients are going to be studied on an outpatient basis referred by the UT-Memorial Hospital Radiology Department, Radiation Oncology Department, and the Knoxville Pulmonary Group.

Control subjects are not included. Test results will be compared to diagnostic findings and values obtained with conventional diagnostic modalities. In addition, patients who are scheduled to receive radiation therapy to the chest (patients with mammary carcinoma, and patients with Hodgkin's Disease) offer the opportunity to compare "normal" test results collected before the start of treatment or from areas of the lung not directly affected by the treatment with results obtained with ^{68}Ga-EDTA aerosol.

A sample of the "Informed Consent Form" for this study is attached to this amendment.

Summary of Research Protocol

Ten to 20 patients are scheduled for each disease category.

1049126

(a) Sarcoidosis patients are scheduled to have physiologic pulmonary function studies and a chest radiogram and tomographic ECT scans with ^{68}Ga-EDTA aerosol and ^{68}Ga-microspheres at the time of diagnosis and at 3 months intervals as the course of the disease may indicate.

(b) Patient selected for radiation therapy (to the axillae, the cervical and mediastinal regions) will have the same studies as indicated for patients under (a) before beginning radiation therapy, at 4 weeks or 2/3 of the way through the treatment period, at the end of therapy, and at monthly intervals for a period of 9 months following completion of radiotherapy.

(c) Patients with COPD will only have one set of studies, since changes of pulmonary function are likely to occur only slowly in this type of disease. However, changed pulmonary function due to COPD could provide a good test for the sensitivity and specificity offered by the different diagnostic methods to be compared in this study.

It is anticipated that the study will be completed within two years after approval of the amendment to IND #13,383.

Risks from ^{68}Ga-EDTA Aerosol Lung Studies

No chemical or pharmaceutical risks can be foreseen with the chemical amounts of ^{67}Ga and EDTA as proposed for this clinical investigation. The risk from the radiation associated with the use of ^{68}Ga-EDTA by inhalation is exceedingly small. The ORAU Internal Dose Information Center estimates the radiation dose from ^{68}Ga-EDTA aerosol to be 2.8 rad/mCi, assuming complete deposition in the lungs with no loss from that organ during decay.

Internal Approval of this Amendment Was Obtained

Internal Approval of this amendment was obtained by the ORAU Medical Isotopes Committee on _____, 1979 and by the ORAU/ORNL Committee on Human Studies on _____, 1979.

Reference

Taplin, George V., and Chopra, Sawtantra K. Inhalation lung imaging with radioactive aerosols and gases. Prog. nucl. Med., 5, 119-143, 1978.

Taplin, George V., and Chopra, Sawtantra K. Lung perfusion-inhalation scintigraphy in obstructive airway disease and pulmonary embolism. Rad. Clin. of N. Amer., 16, 491-513, 1978.

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL DR. KARL HUBNER PROPOSAL NO. 79-2

DESCRIPTION: ^{99m}Tc PERTECHNETATE FOR PERIPHERAL VASCULAR IMAGING AND BLOOD POOL IMAGING IN PATIENTS WITH PROBABLE RADIATION INJURY. DOSE: 10-30 mCi I.V. PER 70 Kg. BODY WEIGHT. PACKAGE INSERT ATTACHED.

[✓] The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other: IN PATIENTS UNDER 18 YEARS OF AGE CASE BY CASE APPROVAL OF THE MEDICAL RADIONUCLIDE COMMITTEE IS REQUIRED.

[ ] The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Gibbs	✓			3 Dec., 1979
James D. Geyer	✓			12/3/79
R. J. Hayes	✓			12/3/79
D. Chwastyndzka	✓			12/3/79
KARL HUBNER			✓	

Acknowledgement of submitter Karl F. Hubner Date 12/3/79

Proposal does____ does not ✓ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049128

Revised January 1979

MINITEC®
Technetium Tc 99m GENERATOR

DESCRIPTION

Minitec (Technetium Tc 99m) Generator consists of a specially designed lead-shielded column containing fission product-produced Molybdenum Mo 99 adsorbed on alumina which releases ^{99m}Tc upon elution. The lead shield has access ports at the top of the column, allowing aseptic elution and storage under conditions of constant shielding.

Elution of the generator provides a means of obtaining a sterile, nonpyrogenic supply of Technetium Tc 99m, as sodium (^{99m}Tc) pertechnetate. ^{99m}Tc, the short-lived daughter (T½ = 6.03 hours) of Molybdenum Mo 99 (^{99}Mo, T ½ = 66.0 hours), is obtained from the generator by periodic elution. The amount (in millicuries) of ^{99m}Tc obtained in the initial elution will depend on the original potency of the generator, while the activity obtained from subsequent elutions will depend on the time interval between elutions.

The fission product Molybdenum Mo 99 used in the generator meets or exceeds the purity requirements of the US Nuclear Regulatory Commission with respect to allowable levels of contaminants. The aluminum concentration is not more than 10μg per ml of generator eluate. The eluate meets the USNRC limits for ^{99}Mo contamination, that is, not more than 1 microcurie ^{99}Mo per millicurie of ^{99m}Tc or 5 microcuries per dose of ^{99m}Tc administered. Each elution from the generator should be assayed before use for ^{99m}Tc activity and for the possible presence of ^{99}Mo. Directions for both assays are provided in this monograph. Material containing more than 5 microcuries of ^{99}Mo per dose of ^{99m}Tc pertechnetate exceeds US Nuclear Regulatory Commission limits and should not be administered.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.03 hours.[1] The principal photon that is useful for detection and imaging studies is shown in Table I.

TABLE I

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma	90.7[2]	140.5

[1]Dillman LT, Von der Lage FC: Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, MIRD Pamphlet No 10, p 62. Soc Nucl Med, Sept 1975

[2]From the Evaluated Nuclear Structure Data File (ENSDF), Atomic Industrial Forum Steering Committee on Standards, May 1977

External Radiation

The specific gamma ray constant for ^{99m}Tc is 0.8 R/millicurie-hour at 1 cm. The first half value layer is 0.2 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 2.7 mm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

TABLE II

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) mm	Attenuation Factor
0.2	0.5
0.95	10^{-1}
1.8	10^{-2}
2.7	10^{-3}
3.6	10^{-4}
4.5	10^{-5}

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

TABLE III

Physical Decay Chart: ^{99m}Tc, half-life 6.03 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
−5	1.777	5	0.563
−4	1.584	6	0.502
−3	1.412	7	0.447
−2	1.258	8	0.399
−1	1.122	9	0.355
*0	1.000	10	0.317
1	0.891	11	0.282
2	0.795	12	0.252
3	0.708	18	0.126
4	0.631	24	0.063

*Calibration Time

CLINICAL PHARMACOLOGY

The biological distribution of pertechnetate ^{99m}Tc is similar to that of the iodide ion, concentrating in the thyroid gland, salivary glands, choroid plexus, and gastric mucosa. However, in contrast to the iodide ion, the pertechnetate ion is released unchanged from the thyroid gland. Pertechnetate tends to accumulate in areas of high vascularity such as in intracranial lesions with excessive neovascularity or an altered blood-brain barrier.

Following intravenous administration, the pertechnetate ion remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies; then it gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

INDICATIONS AND USAGE

Adults

Sodium pertechnetate ^{99m}Tc is indicated in adults for brain imaging including cerebral radionuclide angiography, thyroid gland imag-

ing, salivary gland imaging, placenta localization, and blood pool imaging including radionuclide angiography.

Pediatric Patients

Sodium pertechnetate ^{99m}Tc is indicated in pediatric patients for brain imaging including cerebral radionuclide angiography, thyroid gland imaging, and blood pool imaging including radionuclide angiography.

CONTRAINDICATIONS

None known.

WARNINGS

Radiopharmaceuticals should not be administered to patients who are pregnant or to nursing mothers unless the expected benefit to be gained outweighs the potential hazards.

Since ^{99m}Tc is excreted in human milk during lactation, formula-feedings should be substituted for breast-feedings.

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.

Radiation risks associated with the use of sodium pertechnetate ^{99m}Tc are greater in children than in adults and, in general, the younger the child the greater the risk owing to greater absorbed radiation doses and longer life expectancy. These greater risks should be taken firmly into account in all benefit-risk assessments involving children.

IMPORTANT

Since material obtained from the generator may be intended for intravenous administration, aseptic technique must be strictly observed in all handling. Only the eluent provided should be used to elute the generator. Do not administer material eluted from the generator if there is any evidence of foreign matter.

PRECAUTIONS

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

At the time of administration the solution should be crystal clear.

ADVERSE REACTIONS

No adverse reactions specifically attributable to the use of ^{99m}Tc have been reported.

DOSAGE AND ADMINISTRATION

Sodium pertechnetate ^{99m}Tc is usually administered by intravenous injection but can be given orally; the dosage employed varies with each diagnostic procedure.

Adults

The suggested dose ranges in the average adult (70 kg) for various diagnostic indications are:

Brain imaging: 10 to 20 millicuries
Thyroid gland imaging: 1 to 10 millicuries
Salivary gland imaging: 1 to 5 millicuries
Blood pool imaging: 10 to 30 millicuries
Placenta localization: 1 to 3 millicuries

Pediatric Patients

The suggested dose ranges in pediatric patients for various diagnostic indications are:

Brain imaging: 140 to 280 microcuries/kg body weight
(A minimum dose of 3 to 5 millicuries should be employed if cerebral radionuclide angiography is performed as part of the brain imaging procedure.)
Thyroid gland imaging: 60 to 80 microcuries/kg body weight
Blood pool imaging: 140 to 280 microcuries/kg body weight
(A minimum dose of 3 to 5 millicuries should be employed if radionuclide angiography is performed as part of the blood pool imaging procedure.)

NOTE: Up to 1 g of reagent grade potassium perchlorate in a suitable base or capsule may be given orally prior to administration of sodium pertechnetate ^{99m}Tc for brain imaging, blood pool imaging, and placenta localization. When sodium pertechnetate ^{99m}Tc is used in children for brain or blood pool imaging, administration of potassium perchlorate is especially important to minimize the absorbed radiation dose to the thyroid gland.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Radiation Dosimetry

Adults

The estimated absorbed radiation doses to an average adult (70 kg) from an intravenous injection of a maximum dose of 30 millicuries of sodium pertechnetate ^{99m}Tc distributed uniformly in the total body of subjects not pretreated with a blocking agent such as reagent grade potassium perchlorate are shown in Table IV. For placental localization studies when a maximum dose of 3 millicuries is used it is assumed to be uniformly equilibrated between maternal and fetal tissues.

TABLE IV

Estimated Absorbed Radiation Doses to Average Adult (70 kg)

	rads/30 millicuries		rads/3 millicuries
Tissue	Resting Population	Active Population	
Bladder wall	1.59	2.55	
Gastrointestinal tract			
Stomach wall	7.50	1.53	
Upper large intestine wall	2.04	3.60	
Lower large intestine wall	1.83	3.30	
Red marrow	0.57	0.51	
Testes	0.27	0.27	
Ovaries	0.66	0.90	
Thyroid	3.90	3.90	
Brain	0.42	0.36	
Whole-body	0.42	0.33	
Placenta			0.05
Fetus			0.05

Summary of Current Radiation Dose Estimates to Normal Humans from ^{99m}Tc as Sodium Pertechnetate, MIRD Dose Estimate Report No. 8. J Nucl Med 17:1, 1976

Pediatric Patients

The maximum absorbed radiation doses will be obtained when a dose of 5 millicuries of sodium pertechnetate ^{99m}Tc is administered to a neonate (3.5 kg) for brain or blood pool imaging with radionuclide angiography. The absorbed radiation doses under these circumstances are shown in Table V.

TABLE V

Estimated Absorbed Radiation Doses to a Neonate (3.5 kg)

Tissue	rads/5 millicuries
Thyroid (without perchlorate)	23.0
Thyroid (with perchlorate)	4.85
Large bowel (with perchlorate)	9.55
Testes	0.51
Ovaries	1.10
Whole-body	0.76

HOW SUPPLIED

Minitec (Technetium Tc 99m) Generator is available in potencies of 220, 440, 880, 1330, 1770, or 2220 millicuries ^{99}Mo at calibration time. Complete assay data for each generator are provided on the label; directions for determining the activity of material eluted from the generator are provided in this monograph.

Supplied with the generator are vials of sterile, nonpyrogenic eluent, and suitable equipment for eluting, collecting, and assaying the Technetium Tc 99m.

DIRECTIONS FOR ELUTING ^{99m}Tc

Eluting the generator every 24 hours will provide optimal amounts

of ^{99m}Tc. Most laboratories will therefore find it convenient to elute the generator each day at a specific time. However, the generator may be eluted whenever sufficient amounts of ^{99m}Tc have accumulated within the column.

Read entire procedure before beginning elution. Carefully follow each step in the order described.

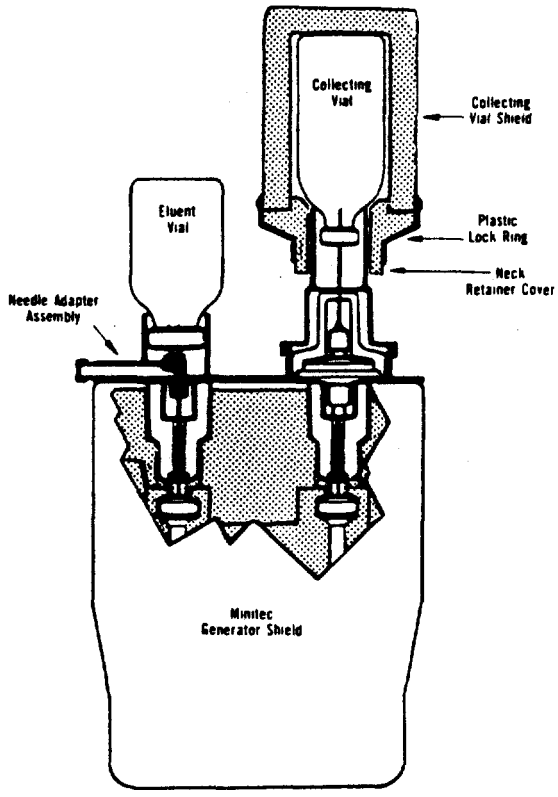
IMPORTANT: Do NOT remove the white plastic needle covers when inserting Needle Adapter Assembly into generator.

1. To attach sterile Needle Adapter Assembly to the lead generator shield:
   (a) Remove the two port plugs from top of the shield.
   (b) Using a sterile cotton-tipped applicator, swab the exposed rubber closures inside the port holes with a suitable germicide.
   (c) Position Assembly so that the guide pin on underside of Assembly will align with hole in shield; the needle ends will then align with port holes. (Assembly can only be mounted one way.)
   (d) Press Assembly into port holes so that it is firmly seated. The needles have now pierced the rubber closures. Be certain that Assembly is securely attached to the shield. Once seated, the Assembly should not be removed.
2. **Using only the Sterile Eluent Vial provided with the Minitec (*Technetium* Tc 99m) Generator,** insert the vial into the short compartment on Needle Adapter Assembly as follows:
   (a) Swab rubber closure of Eluent Vial with germicide.
   (b) Remove cap from the short compartment on Assembly and firmly position Eluent Vial on the needles.

NOTE: THE ELUENT VIAL MUST BE ATTACHED TO THE NEEDLE ADAPTER ASSEMBLY BEFORE ATTACHING THE EVACUATED VIAL OR THE VACUUM IN THE EVACUATED VIAL WILL BE LOST.

3. Attach Sterile Evacuated Collecting Vial:
   (Fits into the tall compartment on Needle Adapter Assembly)
   (a) Place Collecting Vial into the Collecting Vial lead shield; cover with the lead neck retainer cover and firmly secure cover to shield with the plastic lock ring.
   (b) Swab rubber closure of the lead-shielded Collecting Vial with germicide.

The following illustration shows generator assembled for elution.



   (c) Remove cap from the tall compartment on Assembly and firmly position Collecting Vial on the needle. This will start the elution. Elution should be complete three minutes after Eluent Vial has emptied.
4. When elution is complete, replace Collecting Vial with the Minitec Needle Cover Vial.
   (a) Swab rubber closure of Needle Cover Vial with germicide.
   (b) Remove lead-shielded Collecting Vial (which now contains the radioactive eluate) from the needle and immediately position Needle Cover Vial on the needle. Push Needle Cover Vial on needle as far as it will go.
   (c) For added shielding of eluate, place lead cap over the lead-shielded Collecting Vial.
5. To maintain sterility of the system, after each milking, leave the empty Sterile Eluent Vial (Step 2) in position and replace the Collecting Vial with the same Needle Cover Vial (Step 4) until the generator is to be eluted again.

DIRECTIONS FOR ASSAYING ^{99m}Tc ACTIVITY

The ^{99m}Tc activity of the Minitec (*Technetium* Tc 99m) Generator eluate may be conveniently assayed by using an ionization chamber-type dose calibrator such as the Squibb Radioisotope Calibrator, if such equipment is available in the laboratory. The directions accompanying the Radioisotope Calibrator should be followed for measurement of ^{99m}Tc activity, and also for checking for the possible presence of ^{99}Mo activity in the generator eluate.

The ^{99m}Tc activity of the Minitec Generator eluate may also be assayed by the Whole Vial Assay Method described below. (Note: The Minitec Whole Vial Assay Kit is available upon request only.)

A ^{99m}Tc standard contained in a 5 ml volume should be used to establish the ^{99m}Tc factor. A container having the same geometry as the Collecting Vial should be used to contain the 5 ml ^{99m}Tc standard.

The Whole Vial Assay Method can be performed with any scintillation detector used in conjunction with a pulse height analyzer (well-type scintillation spectrometer or an upright scintillation probe). The Whole Vial Assay components are: (A) top lid, (B) ring lid, (C) shield, (D) Cobaltous Chloride Co 57 Solution (check source) (from 5 to 15 microcuries), (E) platform, and (F) lead absorbers.

1. Place the shield (C) on top of the well of a scintillation spectrometer; if the well aperture is too large for support, place the shield in the middle of the platform (E) and center over the well.
2. Set the discriminator to the 100 to 200 keV range. Record the background counting rate.
3. Insert a ^{99m}Tc standard* in the shield (C) and cover it with ring lid (B) and the top lid (A).
4. Count and record the ^{99m}Tc standard activity. (NOTE: If the count rate is too high, place lead absorbers (F) into the shield (C) until an acceptable count rate is obtained. To prevent errors, the lead absorbers should then be glued to the bottom of the shield.)
5. Replace the ^{99m}Tc standard with the ^{99m}Tc sample, cover as in Step 3, and record the count rate of the ^{99m}Tc sample. (NOTE: The volume of the standard solution and the sample solution must be equal and in a container of the same geometry.)
6. Replace the shield (C) with the Cobalt 57 check source (D) and record count rate. [NOTE: Once the count rate of the Cobalt 57 check source has been determined, the continued use of the ^{99m}Tc standard is unnecessary provided the count rate of the check source does not vary more than ± 10 percent from the expected count rate (after correction for radioactive decay).]
7. For subsequent assays only Steps 5 and 6 need be followed.
8. Calculate the ^{99m}Tc factor as follows:

$$^{99m}\text{Tc factor} = \frac{\text{activity (millicuries) of } ^{99m}\text{Tc standard}}{\text{net count rate (cpm) of } ^{99m}\text{Tc standard}}$$

Example:
activity of ^{99m}Tc standard = 10 millicuries
count rate as determined in Step 4 = 20,000 cpm

$$^{99m}\text{Tc factor} = \frac{10 \text{ millicuries}}{20{,}000 \text{ cpm}} = 0.0005$$

*A ^{99m}Tc sample calibrated by existing methods, such as the dilution method, can be used as the initial standard.

1049131

9. The ^{99m}Tc factor (Step 8) is used to determine the ^{99m}Tc activity in 5 ml of eluate from the sterile generator provided the count rate of the Cobalt 57 check source is within ± 10 percent of the expected count rate. Calculate as follows.

^{99m}Tc activity (millicuries/5 ml) = ^{99m}Tc factor × net count rate (cpm) of ^{99m}Tc sample

Example:
^{99m}Tc factor = 0.0005
net count rate from unknown sample = 38,000 cpm
^{99m}Tc activity (millicuries/5 ml) = 0.0005 × 38,000 = 19 millicuries/5 ml

Note: If assay for ^{99m}Tc activity indicates that the radioconcentration of the eluate requires dilution, use only *Sodium* Chloride Injection USP as diluent.

COBALT 57 DECAY FACTORS

To determine the activity of ^{57}Co for the calculation of ^{99m}Tc activity, multiply the assay value stated on the label of the Cobalt 57 (^{57}Co, T ½ = 270 days) Standard by the appropriate factor in Table VI.

TABLE VI

Weeks	Factor	Weeks	Factor	Weeks	Factor	Weeks	Factor
1	0.982	14	0.778	27	0.616	40	0.487
2	0.965	15	0.764	28	0.605	41	0.479
3	0.948	16	0.750	29	0.594	42	0.470
4	0.931	17	0.737	30	0.583	43	0.462
5	0.914	18	0.724	31	0.573	44	0.454
6	0.898	19	0.711	32	0.563	45	0.445
7	0.882	20	0.698	33	0.553	46	0.438
8	0.866	21	0.686	34	0.543	47	0.430
9	0.851	22	0.673	35	0.533	48	0.422
10	0.836	23	0.661	36	0.524	49	0.415
11	0.821	24	0.650	37	0.514	50	0.407
12	0.806	25	0.638	38	0.505	51	0.400
13	0.792	26	0.627	39	0.496	52	0.393

TEST FOR INSTRUMENT LINEARITY

The use of ^{99m}Tc generators has resulted in the assay of considerably larger quantities of activity (up to 1 curie of ^{99m}Tc) than previously encountered. It would appear worthwhile, therefore, to check the accuracy of the assay methods for these larger quantities of activity. This is especially important since most instruments are calibrated with standards containing approximately 10 millicuries of ^{99m}Tc while the initial eluates contain up to 900 millicuries of ^{99m}Tc. It is not unlikely that spectrometers used in the Whole Vial Assay procedure are not linear up to the count rates being encountered in initial assays, and that dose calibrators standardized on the lower scale are not accurate on the higher scales.

To check the assay procedures where yield problems are encountered with the high activity generators, the following is recommended:

1. Assay the entire ^{99m}Tc eluate on the first day of generator use by the procedure normally used. Record assay in millicuries/ml.
2. Aseptically withdraw 1 ml of the eluate and transfer to an empty Collecting Vial. Add 4 ml of water and mix thoroughly.
3. Assay the Collecting Vial containing the eluate-water solution. Record assay, corrected for decay, in total millicuries present in the vial.
4. If the calibration of the assay procedure is linear for the higher activities, the values obtained in Steps 1 and 3 should be identical. If the instrument is losing counts at the higher activities, the value obtained in Step 3 will be higher than that obtained in Step 1.

NOTE: DO NOT USE SOLUTION PREPARED FOR LINEARITY TEST FOR PARENTERAL ADMINISTRATION.

For example:

(a) The assay value in Step 1 is 660 millicuries in 5 ml; therefore, the eluate contains 132 millicuries/ml.
(b) The assay value in Step 3 is 169 millicuries.
(c) Assuming that the 169 millicurie value is correct, since the instrument was calibrated in this range of activity, the assay would be off (on the low side) by approximately 22 percent, calculated as follows:

$$\% \text{ error} = \frac{\text{True activity—Observed activity}}{\text{True activity}} \times 100$$

$$= \frac{169 - 132}{169} \times 100$$

$$= 22\%$$

If an error of greater than 5 percent is observed in conducting the above assay check, it will be necessary in routine assays to either assay an aliquot of the eluate that can be accurately measured, or construct a curve to correct for counting losses at higher counting rates. Such a curve can be constructed by assaying various aliquots of a high activity milking—e.g., 1,2,3,4, and 5 ml—and plotting the activity assayed versus the true activity (calculated for assay of 1 ml aliquot).

DIRECTIONS FOR ASSAYING ^{99}Mo ACTIVITY

A. Whole Vial Assay Method

1. Determination of the ^{99}Mo factor:
Use the Whole Vial Assay components previously described and set the discriminator to the 0.6 to 1.0 meV range. Calculate the ^{99}Mo factor by dividing the activity (in microcuries) of the Cesium Chloride (^{137}Cs) Reference Standard Solution by the net count rate (gross cpm minus background cpm) of the Cesium Chloride (^{137}Cs) Reference Standard Solution and multiplying by a factor of 4.5 to convert ^{137}Cs activity to equivalent ^{99}Mo activity. (NOTE: The Cesium Chloride (^{137}Cs) Reference Standard Solution is provided on request in a Collecting Vial with a total volume of 5 ml. If the Squibb Standard is not used, be certain that the substitute ^{137}Cs standard is used in a container having the same geometry as the Collecting Vial.)
Calculate as follows:

$$^{99}\text{Mo factor} = \frac{\text{Cesium Cs 137 activity (total microcuries)} \times 4.5}{\text{net count rate of Cesium Chloride } (^{137}\text{Cs}) \text{ Reference Standard Solution (cpm)}}$$

NOTE: The ^{99}Mo factor remains the same for each assay if the instrument calibration is not altered; if there is change in calibration, a new factor must be determined.

2. For each assay:
   a. Place the lead shield on top of the well of a scintillation spectrometer; if the well aperture is too large for support, place the shield in the middle of the Whole Vial Assay platform and center over the well.
   b. Set the discriminator to the 0.6 to 1.0 meV range. Record the background activity (cpm).
   c. Insert the vial containing the ^{99m}Tc sample into the lead shield and cover with the ring and top lids.
   d. Record the net count rate (cpm) of the ^{99m}Tc sample (gross cpm minus background cpm).
   e. Calculate the ^{99}Mo activity as follows:

^{99}Mo activity = ^{99}Mo factor (from Step 1) × net count rate (cpm) of ^{99m}Tc sample

Example:
net count rate of ^{99m}Tc sample
(as determined in Step 2 d) = 1700 cpm
^{99}Mo factor = 0.003 microcurie/cpm
^{99}Mo activity = 0.003 microcurie/cpm × 1700 cpm
= 5.1 microcuries

   f. Calculate the concentration of ^{99}Mo per millicurie of ^{99m}Tc sample by dividing the ^{99}Mo activity (From Step 2 e) by the total ^{99m}Tc activity.

Example:

$$\frac{^{99}\text{Mo activity (in microcuries)}}{^{99m}\text{Tc activity (in millicuries)}} = \frac{5.1}{51}$$

0.1 microcurie Molybdenum Mo 99 per millicurie Technetium Tc 99m

B. Alternate Method

1. Place the Collecting Vial containing the total ^{99m}Tc eluate in a ¼-inch lead container and set this on the surface of a well-type scintillation detector or scintillation probe. (The lead container is provided on request with the Cesium Chloride (^{137}Cs) Reference Standard Solution mentioned below.)
2. Determine the activity in the 0.6 to 1.0 meV range. Record net counts per minute (cpm).
3. Remove the vial of ^{99m}Tc from the lead container and replace it with a Cesium Chloride (^{137}Cs) Reference Standard Solution. Determine the activity in the 0.6 to 1.0 meV range, maintaining constant geometry with previous count. Record net counts per minute (cpm). (The Cesium Chloride (^{137}Cs) Reference Standard Solution is provided on request in a Collecting Vial with a total volume of 5 ml. If the Squibb Standard is not used, be certain that the substitute ^{137}Cs standard is used in a container having the same geometry as the Collecting Vial.)
4. Calculate ^{99}Mo activity using the following formula:

$$^{99}\text{Mo activity (microcuries/ml)} = \frac{A \times B \times 4.5}{C}$$

Where:

A = net cpm of ^{99m}Tc sample
B = activity (in microcuries per ml) of ^{137}Cs standard
C = net cpm of ^{137}Cs standard
4.5 = factor for converting ^{137}Cs activity to equivalent ^{99}Mo activity

TABLE VII

Physical Decay Chart: ^{99}Mo, half-life, 66.0 hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
−48	1.656	36	0.685	120	0.284	204	0.117
−44	1.587	40	0.657	124	0.272	208	0.113
−40	1.522	44	0.630	128	0.261	212	0.108
−36	1.459	48	0.604	132	0.250	216	0.103
−32	1.399	52	0.579	136	0.240	220	0.099
−28	1.342	56	0.555	140	0.230	224	0.095
−24	1.287	60	0.533	144	0.220	228	0.091
−20	1.234	64	0.511	148	0.211	232	0.087
−16	1.183	68	0.490	152	0.203	236	0.084
−12	1.134	72	0.469	156	0.194	240	0.080
− 8	1.088	76	0.450	160	0.186	244	0.077
− 4	1.043	80	0.432	164	0.179	248	0.074
− 0*	1.000	84	0.414	168	0.171	252	0.071
4	0.959	88	0.397	172	0.164	256	0.068
8	0.919	92	0.381	176	0.157	260	0.065
12	0.882	96	0.365	180	0.151	264	0.062
16	0.845	100	0.350	184	0.145	268	0.060
20	0.811	104	0.335	188	0.139	272	0.057
24	0.777	108	0.322	192	0.133	276	0.055
28	0.745	112	0.308	196	0.128	280	0.053
32	0.715	116	0.296	200	0.122	284	0.051
						288	0.049

*Calibration time

This generator is licensed for use by persons licensed by the US Nuclear Regulatory Commission pursuant to § 35.14 and § 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

E.R. Squibb & Sons Inc.
Princeton, NJ 08540

Canadian License No. 7

Printed in USA Revised January 1979 J3-389L

1049133

Ident. No._____

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: April 4, 1980

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigator: Raymond L. Hayes, Ph.D.

Title of Project: YTTERBIUM-169 CITRATE FOR THE DETECTION OF INFLAMMATORY LESIONS

I. Objective of Experiment:

The objective of this study is to determine whether ^{169}Yb citrate can be used as an effective substitute for ^{67}Ga citrate in the detection of inflammatory lesions. Of particular interest is whether ^{169}Yb citrate can be used to detect inflammatory processes during the first few hours after administration. Tests with ^{67}Ga citrate normally require approximately 24 hrs. Appendix A contains an abstract summary of our comparison of ^{169}Yb citrate with ^{67}Ga citrate using an experimental abscess in the rat.

II. Methods of Procedure:

Reactor-produced high-specific-activity ^{169}Yb chloride will be obtained from Union Carbide Corp., Tuxedo, N.Y. Following tests for radiochemical purity, the ^{169}Yb will be converted to the citrate form. The resulting solution will then be adjusted to isotonicity and physiologic pH and filtered through a sterile microfilter into capped sterile evacuated vials. These vials will then be steam sterilized. The contents of representative vials from each batch will be tested for pyrogenicity and sterility using the methods prescribed by the U.S. Pharmacopeia. All details of the preparation, quality control and dispensing of the ^{169}Yb citrate preparation will be kept in a master log book.

The preparation (0.5 mCi ^{169}Yb/70 kg) will be injected intravenously in a volume of 2 ml or less. The administered dose will contain stable ytterbium at a level of no more than 10 μg Yb/kg and the amount of citrate administered will not exceed 0.1 mg/kg. Scans will be made at 4 h and 24 h after ^{169}Yb citrate administration. Following the 24 h scan the instrument scan settings will be changed to those for ^{67}Ga and the patient re-scanned to obtain a data file for later scan subtraction. The patient will then be administered

^{67}Ga citrate (5.0 mCi/70 kg) and scanned for ^{67}Ga at 4 h and 24 h after the administration. These ^{67}Ga scans will then be corrected for ^{169}Yb contribution by computer subtraction techniques.

A total of 15 ambulatory patients having chronic inflammatory processes will be studied. They will be referred to the Medical and Health Sciences Division by consulting physicians in Oak Ridge and the surrounding area.

III. Possible Hazards and Their Evaluation:

1. Toxicity

There should be no chemical hazard involved with the use of ^{169}Yb citrate, since the maximum level of stable ytterbium administered will not exceed 10 μg/kg. The LD_{50} i.p. dose for ytterbium nitrate has been determined to be 250 mg/kg in the mouse and 255 mg/kg in the rat. (T.J. Haley, J. Pharm. Sciences 54:663, 1965.) We have had no difficulties in the past with the clinical use of ^{171}Er and ^{157}Dy citrates using chemical levels that were similar to that proposed for ^{169}Yb.

2. Radiation Dose

This proposal will be submitted to the ORAU Medical Isotopes Committee on April 7, 1980. The Committee on Human Studies will be notified of their action when the committee meets April 18, 1980. Appendix B indicates the radiation dose estimates that have been made by the ORAU Radiopharmaceutical Internal Dosimetry Information Center for both ^{169}Yb and ^{67}Ga citrates.

IV. Radioisotopes and New Drugs:

No new nonradioactive drugs are involved. ^{169}Yb citrate has been used as a scanning agent for tumor (K. Hisada et al., Radiolanthanides as Tumour-Localizing Agents in Tumor Localization with Radioactive Agents, IAEA, Vienna, 1976, p. 113).

V. Responsibility of Principal Investigator:

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be immediately brought to the attention of the Committee on Human Studies.

Starting Date June 1, 1980

Signatures: _____ Principal Investigator

_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature_____

Title: Chairman, Medical and Health Sciences Divison

Institution: Oak Ridge Associated Universities

Date:_____

1049136

Use of Yb-169 Citrate for Detection of Inflammatory Lesions

R. L. HAYES, B. L. BYRD, J. J. RAFTER, J. E. CARLTON, AND J. L. COFFEY
Medical and Health Sciences Division, Oak Ridge Associated Universities*,
Oak Ridge, TN., USA

Ga-67 citrate is now widely used for the detection of inflammatory processes, particularly postsurgical abscesses. We previously observed that 24 hr after the administration of Yb-169 citrate, Yb-169 showed a relative uptake in an experimental abscess that was similar to that observed with Ga-67 (1). Since the binding of Ga-67 by plasma protein delays the clearance of Ga-67 from blood, whereas the clearance of Yb-169 from blood is rapid, we compared in detail the tissue distribution of Yb-169 with that of Ga-67 at both 4 and 24 hr in rats bearing experimental abscesses (produced with S. aureus 6339) to determine whether Yb-169 citrate might be a suitable substitute for Ga-67 as an agent for detecting inflammatory processes. At 4 hr the absolute uptakes (%/g) of Yb-169 and Ga-67 in viable abscess tissue were nearly the same, but at 24 hr the uptake of Ga-67 in the abscess was much higher than that of Yb-169. At 4 hr, except for the blood, the tissue distribution of Yb-169 was nearly complete, while with Ga-67 the distribution process was still actively proceeding. At both 4 and 24 hr kidney and bone uptakes were higher for Yb-169, but with all other tissues Ga-67 uptakes were considerably higher than those of Yb-169.

Because of the basic differences observed in the tissue distributions of these two agents, a more appropriate method of assessing their relative worth in abscess detection is through a comparison of abscess-to-nonabscess concentration ratios. The table below shows this type of comparison for a portion of the tissues studied.

Abscess-to-Nonabscess Concentration Ratios Obtained with Yb-169 Citrate and Ga-67 Citrate in the Rat at 4 and 24 hr After Administration

Ratio of Abscess Conc. to:	Yb-169 4 hr	Ga-67 4 hr	Yb-169 24 hr	Ga-67 24 hr
Necrotic abscess	26.0	11.0	10.0	27.0
Liver	1.8	1.7	1.7	1.8
Spleen	2.0	1.9	1.8	1.8
Kidney	1.2	2.4	1.7	4.4
Lung	3.0	2.1	8.4	8.9
Muscle	18.0	10.0	58.0	26.0
Bone	0.6	2.0	0.5	3.1
Bone marrow	2.8	1.9	3.0	2.9
Blood	2.5	1.3	70.0	15.0
Skin	11.0	5.3	33.0	23.0
Fat	30.0	17.0	130.0	120.0

* Oak Ridge Associated Universities operates under contract number DE-AC05-76OR00033 with the U. S. Department of Energy, Office of Health and Environmental Research.

At 4 hr the lung, muscle, bone marrow, blood and skin ratios were significantly better with Yb-169, while with Ga-67 the ratios were higher for only kidney and bone, suggesting that Yb-169 might be somewhat better than Ga-67 for detecting inflammatory processes at early time periods. At 24 hr the two agents were approximately equal with better ratios again being obtained for kidney and bone with Ga-67 but only the ratios for muscle and blood being superior for Yb-169. A comparison of the tissue concentrations of Yb-169 and Ga-67 found in the gastrointestinal tract (both walls and contents) at 4 and 24 hr indicated that no great differences existed between the two agents with respect to their relative uptakes in the experimental abscess and the G.I. tract. One drawback to the possible clinical use of Yb-169 citrate is the long $T_{1/2}$ of this radionuclide (31 d). Extrapolated radiation doses in humans for Yb-169 and Ga-67 have been calculated from the data generated in this study using MIRD techniques. If one assumes the administration of 0.5 mCi of Yb-169 citrate and compares the predicted Yb-169 radiation doses with those for a standard dose of Ga-67 (3.5 mCi), the Yb-169 doses for various tissues are between 1 and 2 times that of Ga-67 except for the kidney and bone (3 and 8 times Ga-67, respectively). Although the dose is rather high for bone, the estimated Yb-169 dose to bone marrow (including crossfire from bone) was only 1.4 times that of the dose for Ga-67.

Yb-169, unlike Ga-67, can be reactor-produced. It has suitable photon emissions, and, although its $T_{1/2}$ of 31 d limits the nuclide dose that could be administered, that particular property in turn would provide for a long shelf life for the agent. We conclude that Yb-169 citrate may be useful clinically for detecting inflammatory lesions.

REFERENCES

[1] HAYES, R.L. In "Tumour Localization with Radioactive Agents", IAEA, Vienna, Austria, 1976, pp. 29-40.

1049138

Radiation Dose to Various Human Tissues From Administration of Proposed Maximum Doses of Yb-169 and Ga-67*

Organ	0.5 mCi Yb-169/70 kg	5.0 mCi Ga-67/70 kg
	Rads	
Bone	13.5	2.5
Bone marrow	3.0	3.6
Kidneys	4.4	1.9
Stomach	7.5	4.8
Small intestine	5.0	4.0
Upper large intestine	6.0	4.0
Lower large intestine	3.8	2.6
Liver	4.5	5.5
Spleen	3.4	4.5
Lungs	1.5	1.9
Ovaries	1.9	-
Testes	1.4	1.0
Heart	5.5	3.2
Total body	2.6	1.3

* Estimated by ORAU Radiopharmaceutical Internal Dosimetry Information Center from tissue distribution data obtained in the rat.

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

CONSENT FOR RESEARCH WAIVER FORM

(Inflammatory Lesions)

Patient:_____ Age:_____

Date:_____ Time:_____AM/PM

I hereby request and authorize_____M.D.

to perform upon_____the following diagnostic
(myself)

procedure:

(a) A scan study with ytterbium-169 citrate for detecting inflammatory lesions.
(b) A scan study with gallium-67 citrate for purposes of comparison.

I have been informed that procedure (b) is a routine diagnostic procedure for the detection of abscesses. The (a) study with ytterbium-169 is experimental and is expected to show the same thing as gallium-67 but at an earlier time period.

I also understand that the risks involved in these procedures are minimal. The radiation dose from the radioactive portion of these two scanning agents will be the same except with ytterbium the dose to the bone will be higher.

I understand that these tests are part of a research program and do not object if any information relating to my case may be published in professional journals or medical books, or used for any other purpose which my physician may deem proper 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 by name.

I understand further that in the event of physical injury resulting from the research procedures described above, only essential medical treatment is available, including hospitalization if required. I also understand that monetary compensation is not available from either ORAU or Union Carbide Corporation/ORNL for wages lost because of injury, but medical treatment is provided free of charge.

Signed_____

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.

Date:_____ Witness:_____

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Karl F. Hübner, M.D. PROPOSAL NO. 80-1

DESCRIPTION: ^{169}Yb citrate for the detection of inflammatory lesions. Administered dose will not exceed 0.5 mCi ^{169}Yb/70 Kg. Dosimetry and application to Committee on Human Studies is attached.

☑ The Committee approves with the following limitations:

Radiopharmaceutical may___ may not ✓ be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not ✓ be administered to pregnant patients.

Other: SHALL NOT BE ADMINISTERED TO LACTATING MOTHERS.

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
William H. Gibbs	✓			14 April, 1980
[illegible]	✓			4/14/80
[illegible]	✓			4/14/80
[illegible]	✓			4/14/80
R. J. Hayes	✓			4/14/80

Acknowledgement of submitter Karl F. Hübner Date 4/14/80

Proposal does ✓ does not _____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049141

Radiation Dose to Various Human Tissues From Administration of Proposed Maximum Doses of Yb-169 and Ga-67*

Organ	0.5 mCi Yb-169/70 kg	5.0 mCi Ga-67/70 kg
	Rads	
Bone	13.5	2.5
Bone marrow	3.0	3.6
Kidneys	4.4	1.9
Stomach	7.5	4.8
Small intestine	5.0	4.0
Upper large intestine	6.0	4.0
Lower large intestine	3.8	2.6
Liver	4.5	5.5
Spleen	3.4	4.5
Lungs	1.5	1.9
Ovaries	1.9	-
Testes	1.4	1.0
Heart	5.5	3.2
Total body	2.6	1.3

* Estimated by ORAU Radiopharmaceutical Internal Dosimetry Information Center from tissue distribution date obtained in the rat.

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

William J. Gyarfas, M.D., Director
Division of Oncology and Radio-
pharmaceutical Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: IND 12,459

Dear Dr. Gyarfas:

The following information, submitted in triplicate, constitutes an amendment to IND 12,459. The proposed amendment involves the resolution of DL-valine-1-^{11}C, the previously approved drug, by high-performance liquid chromatography and the intravenous administration of an optically active form of the approved drug, L-valine-1-^{11}C, for physiological studies of the pancreas and brain.

Background

DL-Valine-1-^{11}C was shown in animal studies (1) to be potentially useful as a pancreas-imaging agent and was subsequently approved for human studies. Clinical trials with DL-valine-1-^{11}C and a similar agent, ^{11}C-DL-tryptophan (IND 12,967), have shown that both agents concentrate very selectively in the pancreas (2); however, differential diagnosis of pancreatic carcinoma has not been feasible, apparently because of similarly high uptakes in the pancreas and tumor.

Tamemasa and co-workers (3) have found that D-amino acids are concentrated selectively by tumor tissue. Therefore, it appears that the uptake of DL-valine-1-^{11}C by pancreatic carcinoma may be due to the presence of D-valine-1-^{11}C in the mixture. We anticipate that use of L-valine-1-^{11}C may overcome these difficulties and permit detection of pancreatic carcinoma as a defect rather than a "hot spot" in pancreas scans.

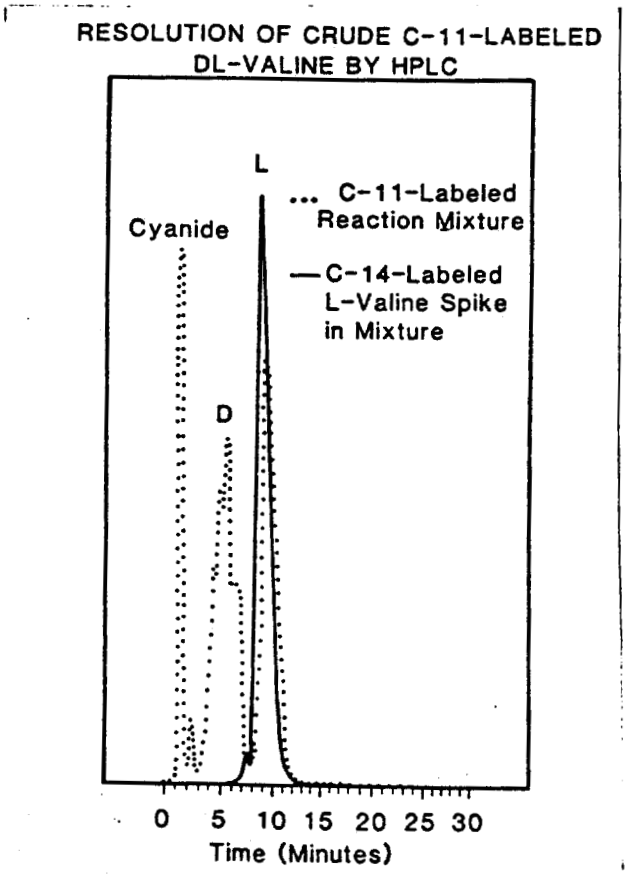
In addition, DL-valine-1-^{11}C has been shown to localize quite selectively in malignant gliomas, a type of brain tumor with an unusually high nutritional requirement for valine (4). However, for truly physiological studies, L-valine-1-^{11}C is required. Availability of this agent should not only permit better detection of tumors which have high amino acid requirements but also allow studies of L-valine metabolism in various neurological diseases, such as those proposed for study in this amendment.

1049143

Production of L-valine-1-^{11}C

L-Valine-1-^{11}C is produced by separation of the two optical isomers of ^{11}C-carboxyl-labeled DL-valine by high-performance liquid chromatography (HPLC) using a chiral mobile phase. Crude DL-valine-1-^{11}C is prepared as previously described (5, IND 12,459) with the exception that measures are taken to minimize the volume of the reaction mixture: (1) The gas absorption column is not rinsed with water; and (2) 0.5 ml of 12 N NaOH (Fisher Scientific Co., Fair Lawn, N.J.) is used in place of 1.0 ml of 6.25 N NaOH for hydrolysis of the hydantoin.

The HPLC (LC/System Support Unit I, Laboratory Data Control, Riviera Beach, FL) is fitted with a preparative [10 mm (i.d.) x 25 cm (length)] ultrasphere ODS, 5 μ column (Altex Scientific Inc., Berkeley, CA). The column is equilibrated with the mobile phase [0.008 M cupric acetate (Fisher Scientific Co.), 0.017 M L-proline (Sigma Chemical Co., St. Louis, MO), and 0.03 M sodium acetate (J. T. Baker Chemical Co., Phillipsburg, N.J.) in distilled water (Grand Island Biological Co., Grand Island, N.Y.)]. The flow rate is adjusted to 7.2 ml/minute, giving a pressure of 3600-3800 psi. The crude DL-valine-1-^{11}C reaction mixture (1.5 ml) is neutralized with 500 μl of concentrated HCl (Fisher Scientific Co.), 3.2 mg cupric acetate and 3.9 mg L-proline are added, and the solution is microfiltered and loaded onto the HPLC column using a 3-ml disposable syringe. The elution of the ^{11}C-labeled mixture is monitored using a shielded gamma probe. The figure below shows the elution pattern which is typically obtained. In this case, a ^{14}C-labeled L-valine spike was added to the mixture to be separated. The elution time for L-valine-1-^{11}C corresponds very well with that of the L-valine-1-^{14}C spike.



1049144

Before clinical use the copper must be removed. The L-valine-1-^{11}C fraction (∿ 20 ml) is acidified and 5 ml of saturated aqueous hydrogen sulfide [made fresh that day by dissolving hydrogen sulfide (MG Scientific Gases, Somerville, N.J.) in distilled water] is added to precipitate the copper as cupric sulfide. The precipitate is removed by filtration using a coarse prefilter over a 0.22 μ microfilter (Millipore Corp., Millville, N.J.).

The final purification is by cation-exchange chromatography, as in the production of DL-valine-1-^{11}C. The acidic filtrate is loaded onto a prewashed 1.0 cm (dia.) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation-exchange bed (Bio Rad Laboratories, Rockville Center, N.Y.) in the hydrogen form. Cationic L-valine-1-^{11}C is retained while neutral and anionic materials, including hydrogen sulfide, pass through the column. After washing repeatedly with distilled water (∿ 30 ml), the column is finally eluted with 0.2 N NaOH, the process being monitored using a shielded gamma probe to minimize the volume of eluate containing the product (∿ 15 ml). This solution is collected in a sterile bottle for transport to M&HSD, ORAU for final processing. Final radiopharmaceutical processing (neutralization, microfiltration, and Limulus Lysate pyrogen testing) is done as detailed in the original IND 12,459.

Toxicity

The final solution has been checked for the presence of cupric and sulfide ions - the former by the ferric thiocyanate spot test (6) and the latter by means of lead acetate test strips. The copper level is below the sensitivity of the test, i.e., < 0.4 μg Cu/ml (< 6 μg Cu total). The sulfide level is negligible.

The purification method, however, does not remove the L-proline which was present in the HPLC mobile phase. Assuming 20 ml of HPLC eluate, this amounts to 39 mg of L-proline. Assuming that blood comprises 7% of the total human body weight and a hematocrit of 40, there is an average of 69.4 mg of L-proline in the blood stream of a normal 70 kg human (7). Administration of 39 mg of L-proline to a 70 kg human would give a level of 0.56 mg/kg. The LD_{50} of intraperitoneally administered L-proline in mice is reported to be 8.06 g/kg (8). Thus we will be below the LD_{50} value by a factor of 14,400.

The presence of L-proline in the injection solution does not affect the tissue distribution of labeled L-valine, as shown in the following table (p. 4).

Chemical toxicity from unlabeled L-valine will likewise be negligible. We propose to administer no more than 4 mg of L-valine per 70 kg subject. L-Valine is present to the extent of 2.4 (2.0-2.9) mg per 100 ml of normal human blood (7). Assuming that blood comprises 7% of total human body weight, there is, therefore, ∿ 118 mg of L-valine in the blood stream of a normal 70 kg human. The LD_{50} of intraperitoneally administered L-valine in rats is reported as 5.38 g/kg (9). Thus we will be below the LD_{50} value by a factor of approximately 95,000. This amendment has been approved by ORAU/ORNL Committee on Human Studies.

1049145

Effect of Added L-Proline on the Tissue Distribution of L-Valine-1-^{14}C in the Rat at 30 Minutes Postinjection

Tissue	Percent Administered Dose/g: L-Valine-1-^{14}C (0.01 mg/kg)	Percent Administered Dose/g: L-Valine-1-^{14}C (0.01 mg/kg) + L-Proline (1 mg/kg)
Pancreas	10.87 ± 0.47*	11.10 ± 0.31
Liver	1.11 ± 0.05	1.20 ± 0.02
Spleen	0.84 ± 0.07	0.82 ± 0.03
Kidney	0.75 ± 0.05	0.76 ± 0.03
Lung	0.58 ± 0.08	0.52 ± 0.03
Muscle	0.23 ± 0.02	0.23 ± 0.01
Marrow	1.45 ± 0.04	1.42 ± 0.04
Blood	0.16 ± 0.01	0.16 ± 0.01
Small intestine	1.77 ± 0.09	1.72 ± 0.04
Urine	0.28 ± 0.06	0.23 ± 0.03
Brain	0.12 ± 0.01	0.11 ± 0.00

* Mean of 5 animals ± S.E.; normalized to body weight of 250 g.

Radiation Dosimetry

Because of the short half-life of carbon-11 (20.4 minutes), the radiation dose to patients from L-valine-1-^{11}C will be minimal. As a guide it has been estimated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center that the complete decay of 1 mCi of L-valine-1-^{11}C uniformly distributed in a 70 kg human, assuming no excretion, would produce a whole body radiation dose of 0.01 rads or a total of 0.20 rads per 20 mCi (the maximum proposed administered dose of L-valine-1-^{11}C). The table below gives the expected radiation dose to various organs in the human estimated from animal data. Use of L-valine-1-^{11}C was approved by the M&HSD, ORAU Medical Radionuclide Committee on ~~April 9, 1976~~. Feb. 23, 1981

Estimated Radiation Dose from L-Valine-1-^{11}C to Organs in Man*

Tissue	Radiation Dose (rads/mCi)
Pancreas	0.19
Liver	0.028
Spleen	0.022
Kidney	0.019
Bone marrow	0.021
Ovary	0.011
Testis	0.0073

* Based on 30-minute tissue distribution in male and female rats following intravenous administration of L-valine-1-^{14}C (0.01 mg/kg) assuming no further change in distribution.

Clinical Studies

This amendment is being submitted for the purpose of obtaining FDA approval to use L-valine-1-^{11}C in patients with different diseases or suspected diseases. Essentially patients to be included in these clinical investigations are grouped in two categories: patients with pancreas disease, notably pancreatic cancer, and patients with neurological diseases which will be mentioned subsequently.

Selection criteria and study protocol for patients with pancreatic disease. The aim of this study is to determine whether in man L-valine-1-^{11}C localizes to a higher degree in normal pancreatic tissue than in neoplastic and inflammatory lesions of the pancreas (pancreatitis, pancreatic cysts, and benign tumors) and whether L-valine-1-^{11}C in conjunction with ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC) or ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) can be used for the differential diagnosis of pancreatic disease by positron tomography.

According to the general aim of this investigation, approximately 10 patients with suspected pancreatic carcinoma will be studied during the first year. Each patient is to have one tomographic pancreas scan with L-valine-1-^{11}C and a tumor scan with ^{11}C-ACPC or ^{11}C-ACBC. In addition, 10 patients with proven pancreatic carcinoma undergoing chemotherapy and/or radiation therapy will be examined by positron emission computerized tomography (PETT) using L-valine-1-^{11}C and ^{11}C-ACPC or ^{11}C-ACBC. The latter group of patients will be studied three times: before, during and after the first course of treatment (this study will probably take 1 to 2 years). Criteria for suspicion of pancreatic carcinoma are pain, weight loss, steatorrhea, jaundice, and existing metastatic disease with suspected primary carcinoma of pancreas. The patients are expected to be referred to us from the hospitals of the Oak Ridge-Knoxville area and possibly from Nashville (Vanderbilt University).

Depending on the condition of the patients, some of them will be asked to volunteer for a brain scan after completion of the pancreas scan with L-valine-1-^{11}C. This information (L-valine distribution in normal human brain) could be valuable in interpreting abnormal findings expected in brains of persons with certain neurological diseases that will be discussed below.

Protocol/Procedures

1. Patients will be instructed to have nothing by mouth after breakfast except water, and will be encouraged to drink one milkshake 30 minutes before the L-valine-1-^{11}C dose for the pancreas scan.

2. A series of transmission ECAT scans of the abdomen (and head) will be done prior to the injection of the dose. The patient will be asked to be quiet but to stay awake.

3. Intracatheters will be placed into a vein in each hand and both hands will be kept in a thermostatically controlled water bath (44°C) during the transmission scans and for an additional 30 minutes after injection of the dose.

4. A dose of 20 mCi of L-valine-1-^{11}C in a volume of 10 to 20 ml physiological saline will be injected by slow push (30 to 60 seconds) into one hand.

5. Blood samples from the hand opposite to that injected (2 ml, heparinized) will be drawn at 1, 5, 10, 20 and 30 minutes for radioassay. The last sample will also be used to determine the absolute L-valine concentration in plasma by HPLC.

6. ECAT scanning of the abdomen (pancreas) will be started one minute after injection and carried out for 30 minutes. Thereafter, tomographic scans of the head (brain) will be made over another period of 20 to 30 minutes.

1049147

7. The entire procedure should not exceed 2 hours. Some of the patients will be asked to be examined 3 times during the course of their disease.

8. General considerations for human subjects participating in this study. Pregnant women and patients under 18 years of age will not be included. Only patients capable of giving informed consent will be accepted for participation.

   After initial discussion with their primary physician, the patients will be informed about the procedures and tests about 1 to 2 hours prior to the examination. The consent forms (see Attachment A) have been approved by the ORAU/ORNL Committee on Human Studies. Consent will usually be obtained by a physician involved in the project. The purpose of the procedure, the chemical aspects with regard to the amino acids and the radiological aspects with regard to the ^{11}C-label of the radiopharmaceuticals as well as the scanning procedure will always be discussed with the patient. The discussion will usually take place in the presence of a nurse, and the patient will be encouraged to ask questions and reminded that she/he can withdraw from the study at any time. The signed consent forms are to be kept in the patient's record.

   There are no physical risks other than the radiation dose; there are no psychological, social or legal risks. There are no alternative methods for the in vivo metabolic studies proposed in this amendment.

   The activity level will be kept at 20 mCi which is less than 50% of the doses approved by FDA (^{11}C-DL-valine, ^{11}C-ACPC and ^{11}C-ACBC) for a 70 kg person.

   Potential benefits include information on the extent of the disease, possible useful metabolic information on tumor growth for therapeutic decisions, and valuable data on protein synthesis in normal brain. The risk as related to the potential benefits is minimal.

<u>Selection criteria and scanning protocols for patients with non-malignant neurological diseases and for patients with brain tumors.</u>

Non-malignant neurological diseases to be studied under the amended IND are: post CVA hypertonia, phenylketonuria, Huntington's disease and possibly cerebral palsy. The principle rationale is to study the metabolic activity of the brain or specific structures of the brain in such patients by measuring protein synthesis using L-valine-1-^{11}C as a precursor.

Studies in patients with <u>hypertonia</u> indicate that the metabolic activity in the basal ganglia or vestibular nuclei changes in those patients who become hypertonic as a consequence of cerebral infarctions. In vivo measurement of metabolic activity as based on amino acid (L-valine) utilization should provide a better insight into the nature of the brain injury and might form the basis for new information needed for improved treatment of this disease. The patients will be selected by Dr. Sid Gilman, Professor and Chairman of Neurology, The University of Michigan. Only patients with unilateral non-hemorrhagic disease, limited to the cortical branches of the middle cerebral artery or within the internal capsule, will be included in the study.

1049148

Phenylketonuria (PKU), a metabolic disease in which abnormally high blood levels of phenylalanine interfere with uptake and utilization of other amino acids by the brain, especially the developing brain, can serve as a unique model for a number of human diseases in which protein metabolism of the brain is disturbed. This observation and rationalization forms the basis for using patients with PKU in this study. The patients will be selected by Dr. Richard J. Allen, Professor of Pediatrics and Director of Pediatric Neurology at The University of Michigan. The patients will be over 18 years of age and untreated at the time of study.

Huntington's Disease (HD) is an autosomal dominant disorder associated with progressive dementia and involuntary movements, usually beginning in midlife. The underlying metabolic defect is poorly understood and there is no predictive test that could identify asymptomatic gene carriers. This disease in which abnormalities of cerebral glucose metabolism have been demonstrated may also have an abnormal protein synthesis (especially in the caudate nucleus) that most likely antedate the onset of symptoms. Positron emission computerized tomographic scans using L-valine-1-^{11}C in patients with established HD and patients at risk appears to offer the opportunity to gain a better understanding of this disease and inspires the hope that carriers of HD may be detectable. The patients to be studied will be selected by Dr. Anne B. Young, Assistant Professor at the Department of Neurology at The University of Michigan.

"Cerebral Palsy" a neurological disorder (100 to 600 per 100,000) which expresses itself in different forms and degrees of severity of disturbed motor function is caused prenatally, during birth or at some later time before the brain is fully developed. The accompanying metabolic abnormalities are poorly understood. In vivo analysis of protein synthesis using PETT and L-valine-1-^{11}C might aid to identify focal defects for possible neurosurgical intervention and also form the basis for possible pharmacologic intervention studies. This disease is tentatively included in this IND although a commitment to go ahead with PETT/L-valine-1-^{11}C studies has not been made at this time by The University of Michigan staff who would select and refer such patients for these clinical investigations.

Brain tumors, notably malignant gliomas seem to express a preference for some essential amino acids as has been demonstrated by in vitro analysis, and dietary elimination of these preferentially utilized amino acids has shown a favorable effect on the survival of patients with malignant gliomas. PETT studies (done under the existing IND) have confirmed high uptake of DL-valine-1-^{11}C in several glioma patients.

To use the natural L-form of valine as a scanning agent would be highly desirable for the obvious reason that the natural form would more closely reflect amino acid utilization and protein synthesis of neoplastic lesions in the brain. For this study patients with brain tumors or strongly suspected brain tumors will be selected and referred by Dr. J. Purvis, neurosurgeon (Knoxville), Dr. J. Robertson, neurosurgeon at UT Memphis, and Dr. N. S. Mahaley, The University of North Carolina.

Protocols/Procedures

Hypertonia (no more than 10 patients are expected to be studied at Oak Ridge during the first year).

1. The patients will be asked to remain fasting (except for water) after breakfast. All essential medications will be continued.

2. Approximately 30 minutes prior to the injection of L-valine-1-^{11}C a series of tomographic transmission scans will be made to obtain data for attenuation correction of the final images.

3. The eyes of the subjects will be covered and a stethoscope headset will be placed in the ears. The patient will be instructed to remain quiet but awake and not to move his/her head if at all possible.

4. An intracatheter will be placed into a vein of each hand for injection of the radiopharmaceutical in one hand (hemiplegic arm) and blood samples from the other. Each hand will be kept in a "water bath" (44°C) to arterialize the venous blood. Samples will be taken several times during the first 30 minutes postinjection (for radioassay) and at time 0 and at the end of the 30-minute period for determination of plasma L-valine concentration by HPLC.

5. Following the transmission scans the patient will remain on the scanning table. A dose of 20 mCi of L-valine-1-^{11}C will be injected by i.v. push, and time-activity data (counts per 10 seconds) will be collected for plane 1 using the ECAT as a count rate meter.

6. Blood samples (2 ml each) are to be drawn at time 0, 1, 5, 10, 20, 25 and 30 minutes after injection of the dose.

7. Positron emission computerized tomographic scans of the head will be started 30 minutes after the dose. Four consecutive "slices", each 18 mm thick will be obtained, starting with "plane 1" approximately 7.5 cm above the OM line with subsequent slices in a caudad direction.

8. Depending on remaining activity and the count rate from the brain/head, the same four planes of the head will be scanned a second time. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time to establish "longitudinal" information on protein synthesis in hypertonia.

9. General considerations for human subjects participating in this study:

   Pregnant women and patients under 18 years of age will not be studied. The ECAT - L-valine-1-^{11}C scans will not be done during the acute phase of cerebral infarction. It is planned to repeat the scans between 8 and 20 weeks later for followup information.

   Patients will be informed about the scanning and other procedures first by the referring physician(s) at The University of Michigan, and again within 2 to 3 hours prior to the start of the clinical investigation with L-valine-1-^{11}C.

1049150

The consent forms will be signed by the patient or his/her rightful guardian. A copy of the general consent form and the detailed information is attached. This is the essential information to be given to the patient in obtaining "informed consent". This discussion will take place in the presence of a nurse or a nuclear medicine technologist, and the patient will be encouraged to raise questions and will be reminded that he/she may withdraw from the study at any time. The signed consent form is to be kept in the patient's file.

There are no physical or chemical risks other than the radiation dose from the radiopharmaceutical provided the quality control steps indicated in the original IND and in this amendment are taken. There are no psychological, social or legal risks. Alternative methods to study in vivo protein synthesis in stroke patients are not available.

Phenylketonuria. Only 4 patients with PKU will be studied under this IND at Oak Ridge during the first year. If funds permit, these patients, all older than 18 years, will be examined at least twice, once while on an uncontrolled diet and again while on a controlled diet, i.e., a diet low in phenylalanine and supplemented with isoleucine.

1. The patients will be kept fasting after a light breakfast (according to their previously determined diet), if the L-valine-1-^{11}C injection is to be given at around noon. Water will be allowed ad libitum.

2. Approximately 30 minutes prior to the injection of the dose, 4 transmission scans for attenuation correction purposes are to be performed.

3. Pads will be placed over both eyes and a stethoscope headset (with sound control) will be put into the ears.

4. The subject will be instructed to remain quiet and not to move for the rest of the examination, but to stay awake.

5. An intracatheter will be inserted in a vein of each hand. Hands will be kept in a 44°C water bath prior to injection and for about 30 additional minutes. One 2 ml blood sample will be taken for plasma phenylalanine determination.

6. At the completion of the transmission scans a dose of 20 mCi of L-valine-1-^{11}C will be injected by i.v. push into one hand. Blood samples are to be taken from the catheter of the other hand at 1, 5, 10, 20 and 25 minutes for radioassay and at 30 minutes for phenylalanine and valine determination in the plasma.

7. Thirty minutes after the L-valine-1-^{11}C injection, four PETT scans each with 18 mm thickness starting 7.5 cm above to the O.M. line will be started.

8. Four more scans may be obtained if remaining activity permits. The entire scanning procedure should not exceed 90 to 120 minutes (including transmission scans).

9. General considerations for human subjects included in this study:

Informed consent is to be obtained from the patient's parents or legal guardians. There are no known risks from chemical toxicity of L-valine and the overall risk continues to be limited to an acceptably small radiation dose. At the age of 18 or above, a PKU patient is not at a disadvantage when taken off a controlled diet for a short period of time as suggested in this study.

Huntington's Disease. In a preliminary study, the rate of protein synthesis in the brain and especially in the basal ganglia will be studied in 4 patients with HD during the first year following approval of this amendment. The scanning and blood sampling protocol is as follows:

1. The patients will be asked to remain fasting (except for water) after breakfast. All essential medications will be continued.

2. Approximately 30 minutes prior to the injection of L-valine-1-^{11}C a series of tomographic transmission scans will be made to obtain data for attenuation correction of the final images.

3. The eyes of the subjects will be covered and a stethoscope headset will be placed in the ears. The patient will be instructed to remain quiet but awake and not to move his/her head if at all possible.

4. An intracatheter will be placed into a vein of each hand for injection of the radiopharmaceutical in one hand (hemiplegic arm) and blood samples from the other. Each hand will be kept in a "water bath" (44°C) to arterialize the venous blood. Samples will be taken several times during the first 30 minutes postinjection (for radioassay) and at time 0 and at the end of the 30-minute period for determination of plasma L-valine concentration by HPLC.

5. Following the transmission scans the patient will remain on the scanning table. A dose of 20 mCi of L-valine-1-^{11}C will be injected by i.v. push, and time-activity data (counts per 10 seconds) will be collected for plane 1 using the ECAT as a count rate meter.

6. Blood samples (2 ml each) are to be drawn at time 0, 1, 5, 10, 20, 25 and 30 minutes after injection of the dose.

7. Positron emission computerized tomographic scans of the head will be started 30 minutes after the dose. Four consecutive "slices", each 18 mm thick will be obtained, starting with "plane 1" approximately 7.5 cm above the OM line with subsequent slices in a caudad direction.

8. Depending on remaining activity and the count rate from the brain/head, the same four planes of the head will be scanned a second time. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time to establish "longitudinal" information on protein synthesis in hypertonia.

9. General considerations for human subjects selected for this research project:

Informed consent will be obtained from the patient's parents or legal guardians. The risk from the radiation associated with the procedure will be explained and discussed. There may be a psychological risk, especially for subjects who have no signs of the disease but could conceivably be found to be a carrier of HD. The results of psychological counseling in conjunction with genetic advice should, however, outweigh this risk.

Cerebral Palsy. As indicated above, only patients who have lived to be 18 years or older will be selected for PETT using L-valine-1-^{11}C. The development of a definite study protocol will depend on the findings in the proposed preliminary study which is designed to detect focal alterations of the rate of cerebral protein synthesis. Only 4 patients will be studied in Oak Ridge.

1. Patients will be kept on all essential medications. They will be kept on clear protein-free liquids following their usual breakfast.

2. Approximately 30 minutes prior to the injection of L-valine-1-^{11}C a series of tomographic transmission scans will be made to obtain data for attenuation correction of the final images.

3. An intracatheter will be placed into a vein of each hand for injection of the radiopharmaceutical in one hand (hemiplegic arm) and withdrawal of blood samples from the other. Each hand will be kept in a "water bath" (44°C) to arterialize the venous blood. Samples will be taken several times during the first 30 minutes postinjection (for radioassay) and at time 0 and at the end of the 30-minute period for determination of plasma L-valine concentration by HPLC.

4. Following the transmission scans the patient will remain on the scanning table. A dose of 20 mCi of L-valine-1-^{11}C will be injected by i.v. push, and time-activity data (counts per 10 seconds) will be collected for plane 1 using the ECAT as a count rate meter.

5. Blood samples (2 ml each) will be drawn at time 0, 1, 5, 10, 20, 25 and 30 minutes after injection of the dose.

6. Positron emission computerized tomographic scans of the head will be started 30 minutes after the dose. Four consecutive "slices", each 18 mm thick will be obtained, starting with "plane 1" approximately 7.5 cm above the OM line.

7. Depending on remaining activity and the count rate from the brain/head, the same four planes of the head will be scanned a second time. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time to establish "longitudinal" information on protein synthesis in hypertonia.

8. General considerations for human subjects selected for this study:

Parents or guardians will have to give informed consent. The radiation risk, especially in view of the extremely poor prognosis of these patients quoad vitam, has to be considered extremely low. It should be mentioned

that this study may be aborted if it should become difficult to keep these patients still during the study period. Any significant movement during transmission or emission scanning would make the results invalid, at least for an accurate quantitative analysis.

Brain Tumors. During the first year 5 patients with brain tumors will be selected for this test prior to surgical removal of the tumor (surgery will not be delayed because of the ECAT studies).

1. The patients will be N.P.O. after a light breakfast.

2. Tomographic transmission scans will be made starting about 30 minutes before dose application.

3. Subject will remain on the scanning table, eyes will be covered and a stethoscope type headphone music system with volume control will be put in the ears. The patients will be instructed to remain quiet but to stay awake.

4. Intracatheters are to be placed, one in each hand for the same purpose as for the patients with non-malignant neurological diseases.

5. A dose of 20 mCi of L-valine-1-^{11}C will be injected by i.v. push when transmission scans are completed.

6. Blood samples (2 ml each) will be drawn at 1, 5, 10, 20, 25 and 30 minutes for radioassays and plasma valine determination. During the first 30 minutes a time-activity curve - using the ECAT as a count rate meter - will be obtained for one "slice".

7. PETT scans of the head will be started 30 minutes after injection of the dose. Four slices, each 18 mm thick, will be scanned; slice level will depend on location of the tumor. Scans will be repeated if enough activity is left after the first 4 scans.

8. General considerations for human subjects selected for this study:

   Informed consent to be obtained from the patients will be based on discussion of this protocol and the points mentioned in the attached consent form and material. Each patient will be scanned also with DL-valine-1-^{11}C on the same day.

   We are not aware of any chemical toxicity from either the DL- or L-form of valine in the amounts to be used in this proposed study. The risk from radiation exposure involved in the diagnostic procedure will be discussed and explained.

The data analysis, in addition to image interpretation, will include a calculation of the rate of protein synthesis of specific regions of interest in the brain. Calculations will be based on an equation derived by Sokoloff et al. The protocols outlined above indicate that all the information required

to calculate the rate of protein synthesis can be obtained using the ECAT/L-valine-1-^{11}C approach. The necessary input data are: the integral value for blood amino acid radioactivity from time 0 - 30 minutes, blood amino acid level at time 0 and at 30 minutes, and the brain radioactive uptake at 30 minutes as based on the scan data.

As mentioned above, all of the protocols have been approved by our Institutional Review Board and the ORAU Medical Radionuclide Committee.

Please consider each of the applications and protocols for approval as an amendment for IND 12,459. If you need additional information, do not hesitate to contact me.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:bbc

References

1. L. C. Washburn, B. W. Wieland, T. T. Sun, R. L. Hayes, and T. A. Butler. J. Nucl. Med. 19, 77 (1978).
2. K. F. Hubner, G. A. Andrews, E. Buonocore, R. L. Hayes, L. C. Washburn, I. R. Collmann, and W. D. Gibbs. J. Nucl. Med. 20, 507-513 (1979).
3. O. Tamemasa, R. Goto, and T. Suzuki. Gann 69, 517 (1978).
4. C. L. Partain, K. F. Hubner, N. S. Mahaley, F. D. Rollo, R. R. Price, and J. H. Scatliff. J. Comput. Asst. Tomog. 4, 702 (1980).
5. L. C. Washburn, T. T. Sun, B. L. Byrd, R. L. Hayes, T. A. Butler, and A. P. Callahan. In Radiopharmaceuticals II, Soc. Nucl. Med., New York, 1979, p. 767-777.
6. F. Feigl, "Laboratory Manual of Spot Tests," Academic Press, Inc., New York, N. Y., 1943, p. 161.
7. "Blood and Other Body Fluids," D. S. Ditner, ed., Federation of American Societies for Experimental Biology, Washington, D.C., 1961, p. 73.
8. J. W. Madden, M. Chvapil, E. C. Carlson, and J. N. Ryan. Toxicol. Appl. Pharmacol. 26, 426 (1973).
9. P. Gullino, N. Winitz, S. M. Birnbaum, J. Cornfield, M. C. Otey, and J. P. Greenstein, Arch. Biochem. Biophys. 58, 253 (1955).

1049156

MEDICAL RADIONUCLIDE COMMITTEE
Medical and Health Sciences Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL K. F. Hübner PROPOSAL NO. 81-1

DESCRIPTION: L-Valine-1-^{11}C in doses of approximately 20 mCi and not more than 50 mCi will be injected i.v. for the purpose of studying the rate of protein synthesis by Positron Emission Computerized Tomography in neoplastic lesions and in the brain as outlined in the attached amendment for IND 12,459.

[✓] The Committee approves with the following limitations:

Radiopharmaceutical may___ may not X be administered to patients under 18 years of age.

Radiopharmaceutical may___ may not X be administered to pregnant patients.

Other:

[ ] The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
C C Christenbury	X			1-23-81
William H. Gibbs	X			1-23-81
Russell J. DeFrenn	✓			1-23-81
K. F. Hayes	X			1/23/81
James C Bergen	X			1/23/81

Acknowledgement of submitter Karl F. Hübner Date 1/23/81

Proposal does X does not ____ require approval of Committee on Human Studies.

Human Studies approval granted on _____

1049157

Oak Ridge Associated Universities

MEMORANDUM

Medical Radionuclide Committee Members

FROM Secretary - Medical
Jim Berger, Radionuclide Committee

DATE February 2, 1981

COPIES TO file

SUBJECT MINUTES OF MEDICAL RADIONUCLIDE COMMITTEE MEETING - JANUARY 23, 1981

A meeting of the Medical Radionuclide Committee was held January 23, 1981, at 1:30 p.m. Members present were D. Swartzendruber, R. Hayes, R. DuFrain, B. Gibbs, and J. Berger. The purpose of the meeting was to review a proposal from Dr. K. Hubner for the use of L-Valine-1-^{11}C for positron emission tomographic imaging of the brain and neoplastic lesions. Several typing errors in the proposal were pointed out. A change (page 4) in maximum activity from 20 millicuries to 50 millicuries was made. The proposal was approved with the above changes and with the provisions that patients shall not be under 18 years of age or pregnant. Approval by the Committee on Human Studies is also required. The meeting adjourned at approximately 1:50 p.m.

1049158