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ORAU/ORNL COMMITTEE ON HUMAN STUDIES
ORAU INACTIVE PROTOCOLS
AND RELATED DOCUMENTS
(FILE 4)

1049159

708208

REPOSITORY Oak Ridge Institute for Science and Education, Medical Sciences Division

COLLECTION ORAU/ORNL Committee of Human Studies

BOX No.

FOLDER

1049160

Ident No._____

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities

Date: January 22, 1975

Principal Investigator: R. L. Hayes, Ph.D.
Co-Investigators: C. L. Edwards, M.D.
G. A. Andrews, M.D.
K. F. Hubner, M.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CLINICAL USE OF ^{11}C-LABELED DL-TRYPTOPHAN FOR PANCREAS IMAGING

I. Objectives of Experiment:

The goal of this proposed research is to carry out in humans a Phase I investigation of the use of carbon-11 carboxyl-labeled DL-tryptophan as a potential pancreas-imaging agent. This work is being supported by NIH Grant 1 R01 CA 14669-01.

II. Methods of Procedure:

The labeled tryptophan will be synthesized in a hot cell adjacent to the ORNL 86-inch cyclotron where ^{11}C will be generated by a p,n interaction with ^{11}B (B_2O_3 target). The ^{11}C is evolved from the molten target in the form of $^{11}CO_2/^{11}CO$ which is removed by a stream of helium. The $^{11}CO_2/^{11}CO$ is converted catalytically to $^{11}CH_4$ and then to $H^{11}CN$. Subsequently the $H^{11}CN$ is absorbed in a basic solution containing $(NH_4)_2CO_3$, NH_4Cl, KCN, and 1-acetyl-3-indoleacetaldehyde semicarbazone. This solution is then heated at 210°C in a sealed stainless steel reaction vessel for 7 minutes after which NaOH is added under pressure to achieve hydrolysis of the intermediate hydantoin during an additional heating period of 10 minutes. The reaction mixture is then filtered through a combination filter composed of a glass fiber filter and a paper prefilter into another stainless steel reaction vessel where the filtrate is first heated at 120°C to expel excess ammonia and then acidified with HCl and again heated to expel carbon dioxide and $HCN/H^{11}CN$. The HCl solution (pH ∿3) is then fed onto a 1x3 cm cation exchange resin (Bio-Rad Laboratories, AG50W-X4, 20-50 mesh) to which the amino acid adheres. Following washing with 0.1N HCl, distilled water, ethyl alcohol, and distilled water again, the product is eluted with 0.1N NaOH. The amino acid (1 mg) will be contained in a volume of 5-10 ml which will be brought to pH 7.0 ± 0.2 with 0.1N HCl and then filtered through a sterile 0.22 μ Millipore filter into a capped presterilized bottle. A portion of the solution will be removed for pyrogen testing using the limulus technique (E-Toxate, Sigma Chemical Co.). (The short half life of ^{11}C [20.5m] precludes testing with rabbits in the conventional USP manner.)

The chemical yield of this set of reactions and purification steps is estimated to be 20%. The time required for the synthesis and processing should be ∿1 hr. At present we are able to generate ∿5000 mCi of usable ^{11}C in the 86-inch cyclotron. Thus the overall activity yield at the time of patient use should be in the neighborhood of 100 mCi. We propose to administer intravenously no more than 25 mCi per 70 kg patient. (Maximum tumor to nontumor ratios are achieved in animal models at ∿30m after intravenous administration.) Thus the amount of tryptophan (as the chemical) will be approximately 0.25 mg or 0.004 mg/kg in a 70 kg patient.

Following administration to patients, multiple rectilinear and positron camera images will be obtained during a period of approximately 1-1/2 hours. (Should we obtain approval of a supplemental NIH grant, that is to be submitted by February 1, 1975, we will also at a later date make use of a positron transaxial tomographic instrument for detailed studies.)

Appropriate samples of blood and urine will be collected. Occasionally, linear scans will be made. Patients will be adults with known cancer. We plan to use 20 subjects in this Phase I study.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Labeled DL-tryptophan, which is proposed as a pancreas-scanning agent, is the racemic mixture corresponding to L-tryptophan, a naturally occurring amino acid which is essential in man's diet. Little toxicity data is available for the racemate, but the toxicity in the rat after intraperitoneal administration is less for the unnatural D-isomer than for the naturally occurring L-isomer (LD_{50} of 1664 mg/kg for the L-isomer and 4368 mg/kg for the D-isomer [Gullino et al., Arch. Biochem. Biophys. 58:253, 1955; 64:319, 1956]). Thus the racemic mixture too should be less toxic than L-tryptophan itself.

The toxicity of intravenous tryptophan is considerably greater than that by the intraperitoneal route. The LD_{50} of L-tryptophan for intravenous injection in female white mice has been reported as 225 mg/kg (Kubistová, Pracovní Lekařství 8:260, 1956).

In humans L-tryptophan has been administered intravenously as an agent for the stimulation of prolactin secretion and it has been also tested orally as a natural hypnotic substance. The amino acid has been infused intravenously over a 20-minute period in total doses of 5-10 grams (approximately 100 mg/kg) without evidence of serious toxicity. Some patients complained of lightheadedness, flushing, or slight pain at the site of injection, but these effects were transient and often controlled by decreasing the rate of flow of the intravenous solution (MacIndoe et al., J. Clin. Invest. 52:1972, 1973). L-tryptophan has been given orally in doses of up to 15 grams (approximately 200 mg/kg) with no report of toxic symptoms (Hartmann, JAMA 230:1680, 1974).

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Starting Date: April-July 1975.

Signatures: R. J. Hayes — Principal Investigator
Paul Edwards — Co-Investigator
Donald Cardwell — Co-Investigator
Karl F. Hubner — Co-Investigator
Lee C. Washburn — Co-Investigator
Bruce W. Wieland — Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Offical signing for the Institution:

Signature Donald Cardwell

Title Chairman, Medical Division

Institution Medical Division, ORAU

Date 24 January 1975

1049163

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator R. L. Hayes, Ident. No. 39

Project Title Clinical Use of ^{11}C - Labeled Dl-Tryptophan for Pancreas Imaging

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

See 4 and 5

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:

See 4 and 5

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

See 4 and 5

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

The committee expects to have the proposal presented again, with additional data, before any patients are treated.

5. Other committee comments:

The committee unanimously agrees that on the basis of data available so far, the project is well worth pursuing. The committee wants to insure that the identity of the compound is verified, and that the question of incidental inclusion of an extraneous toxic material be considered. They foresee the likelihood that with the later data, the material will be approved for human use.

Approve X

Disapprove

Robert D. Lange, M.D.

Chairman of Committee
Robert D. Lange, M.D.

25 January 75
Date

1049164

(Revised January 1972)

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 3, 1976

Dr. Robert Lange
Assistant Director
University of Tennessee
Memorial Research Center and Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Dear Bob:

I talked with Dr. Joan Woods in Murfreesboro, and she said that she could be listed as approving the tryptophan protocol.

Sincerely,

Gould A. Andrews, M.D.

GAA:dgb

cc: Dr. Ray Hayes

1049165

1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920

THE UNIVERSITY OF TENNESSEE
MEMORIAL RESEARCH CENTER

November 4, 1976

Dr. C. C. Lushbaugh
Chairman, Medical and Health Division
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, TN 37830

Dear Dr. Lushbaugh:

The project entitled "Clinical Use of DL-Tryptophane [Side Chain-3-^{11}Cl (^{11}C-DL-Tryptophan)," a proposal of Drs. Hübner, Andrews, Collmann, Hayes, Washburn, and Wieland, has been approved by seven of the nine members of the ORAU/ORNL Committee on Human Studies. Replies have not been received from the other two members.

Sincerely yours,

Robert D. Lange, M.D.
Chairman, ORAU/ORNL
Committee on Human Studies

mse

CC: GAA
Hübner
Hayes
11/12/76

1049166

1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920

THE UNIVERSITY OF TENNESSEE
MEMORIAL RESEARCH CENTER

November 9, 1976

Gould A. Andrews, M.D.
Oak Ridge Associated Universities
Medical and Health Sciences Div.
P.O. Box 117
Oak Ridge, TN 37830

Dear Andy:

Enclosed is the form that Ray Hayes sent me regarding the tryptophan study.

Re. Dr. Slaga's proposal -- apparently from Lush's conversation this does not need to be taken up with the committee. However, I would agree with you that John Storer should sign it, we should have a letter from Dr. Carabia and a copy of the consent form.

Re. change in committee rules for proposals -- I think this is fine but should be taken up at the next committee meeting.

Re. new business -- believe it is time for Randy Brill to take his turn as chairman.

Sincerely,

Robert D. Lange, M.D.
Acting Director and
Research Professor

mse

1049161

NOV 1 1 1976

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Drs. Gould A. Andrews, Karl F. Hübner Ident. No. 39

Project Title Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C](^{11}C-DL-Tryptophan

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

   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:~~

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

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

5. ~~Other committee~~ comments:

Approve ✓

Disapprove_____

Robert W. Lange, MD
Chairman of Committee

9 Nov. 1976
Date

1049168

Tryptophan

Dr. Lushbaugh
Dr. Lushbaugh
Co

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 12,967

NOV 2 2 1976

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

Dear Dr. Lushbaugh:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 12,967

Sponsor: C. C. Lushbaugh, Ph.D., M.D.

Name of Drug: DL-Tryptophan [side chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Date of Submission: November 9, 1976

Date of Receipt: November 11, 1976

As sponsor of the clinical study proposed in this IND you are now free to obtain supplies of the investigational drug, but it is understood that studies in humans will not be initiated prior to 30 days after the date of receipt shown above. If, within the 30 day period, we notify you of serious deficiencies which require correction before human studies can begin or which require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

1049169

All future communications concerning this IND should be forwarded in triplicate, identified with the IND number assigned, and addressed as follows:

Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM 17B-34
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely yours,

William J. Gyarfas

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 28, 1977

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 12,967 (Progress Report)

Clinical Studies. This progress report covers a period from November, 1976, through November 23, 1977, during which time carbon-11 labeled tryptophan was used as a pancreas scanning agent in a total of seven patients. Five of these patients were male, and two were female between 39 and 40 years of age. Doses between 17.5 mCi and 35 mCi per study were used. All of the scans were obtained with the new emission computerized axial tomographic (ECAT) scanner at ORAU. The first clinical results indicate that carbon-11 labeled tryptophan showed good visualization of the pancreas in all cases studied and useful diagnostic information.

None of the patients experienced any unpleasant or uncomfortable side effects.

Laboratory Studies. Whole body counts were performed to determine the whole body retention of the radionuclide approximately 60 minutes after the injection of the dose and immediately after emptying of the urinary bladder. This assay showed that approximately 10 percent (average) of the total dose is excreted in the urine during the first 60 minutes. The radioassay of the urine showed an average excretion of 14.3 percent during the first 60 minutes.

Blood levels of the radioactivity were determined at 5, 10, 15, 20, 30, and 60 minutes. This assay showed a fairly rapid disappearance of the radiopharmaceutical during the first 5 minutes at which time only 23.9 percent of the injected dose were present in the blood. At 15 minutes the blood activity was 13.4 percent of the dose, and after 30 minutes it ranged between 11.2 percent at 30 minutes and 9.2 percent at 60 minutes.

Laboratory studies included hemogram, urinalysis, and plasma hemoglobin before dose injection and 24 hours later. None of these parameters has showed any change during the period of observation.

1049171

Summary. Carbon-11 labeled tryptophan appears to be a safe and extremely useful scanning agent for the diagnosis of pancreatic disease. Additional clinical studies will emphasize a comparison of carbon-11 labeled tryptophan with carbon-11 labeled valine to be used with the ECAT scanner.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Division

CCL:dgb

1049172

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

October 20, 1978

Dr. William J. Gyarfas
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 12,967

This is the second progress report on the clinical use of ^{11}C-labeled DL-tryptophan. The total number of studies has now reached 26 of which two were done with a rectilinear scanner and 24 with the emission computerized axial tomographic (ECAT) scanner.

In the previous report, dated November 28, 1977, we indicated that based on seven studies pancreas scanning with this ^{11}C-labeled amino acid holds the promise to become a useful diagnostic modality. We have not seen any evidence of toxicity of ^{11}C-DL-tryptophan in any of the additional patients. The results obtained thus far confirm our initial impression that ECAT scanning with ^{11}C-DL-tryptophan not only delineates the normal pancreas but also has a definite value in the diagnosis of pancreatic disease.

We have summarized our preliminary results in two articles which have been submitted for publication in the "Journal of Nuclear Medicine" and in "Radiology," respectively. As soon as we receive reprints of these publications, we will supply your office with some reprints as an addendum to this report.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Division

CCL:dg

1049173

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner

FROM Dianne Gresham

DATE April 6, 1982

COPIES TO File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049174

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 R01 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

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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. Hilmas, M.D. Principal Investigator

Donald G. Andrews M.D. Co-Investigator

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

Title Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date 9/29/76

1049176

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

September 28, 1976

TO: Members of the ORAU/ORNL Committee on Human Studies

G. A. Andrews, Secretary
A. B. Brill
D. W. Goodwin
K. F. Hübner
M. E. Koons
R. D. Lange, Chairman
M. S. Lawyer
T. A. Lincoln
J. B. Storer
J. B. Woods
C. C. Lushbaugh, ex officio

SUBJECT: CLINICAL USE OF DL-TRYPTOPHAN[SIDE CHAIN-3-^{11}C]
(^{11}C-DL-TRYPTOPHAN)

This proposal has been submitted by Drs. Karl Hübner, Gould Andrews, R. T. Collmann, Ray Hayes, Lee Washburn, and Bruce Wieland. I would like to have your opinion of it at your earliest possible convenience.

Approve _____

Disapprove _____

Believe meeting is necessary for consideration _____

Comment _____

_____

Please send your reply directly to Dr. Lange in the enclosed self-addressed and stamped envelope.

Gould A. Andrews, M.D.
Secretary

GAA:dgb

Enclosure

1049177

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Drs. Gould A. Andrews, Karl F. Hübner Ident. No. 39

Project Title Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C](^{11}C-DL-Tryptophan

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

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:~~

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

4. ~~The committee seeks continuing communication with the investigator(s) on this project along the following lines:~~

5. ~~Other committee comments:~~

Approve ✓

Disapprove

Robert W. Lange, MD
Chairman of Committee

9 Nov. 1976
Date

1049178

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Karl F. Hübner, M.D.

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 25, 1980

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 4/4/80.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Tryptophan[Side Chain-3-^{11}-C] (^{11}C-DL-Tryptophan) for Pancreas Imaging

Proposal No.: 39 Date Approved: 1976

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Since the last progress report we have used ^{11}C-DL-tryptophan in 23 more patients for ECAT pancreas scanning. Progress has been published in J. Nucl. Med. 20: 507-513, 1979, J. Comput. Asst. Tomogr. 3(6): 825-828, 1979; and Radiology 133: 195-201, 1979.
(See attached reprints or copies of papers). In addition, progress has been reported at # national respective meetings.
Last progress report to FDA submitted ------ 1979.

2. Report any complications.

None.

1049179

3. Are there any planned changes? None

4. Do you wish the project to be continued? Yes. We are projecting to do more "C-DL-tryptophan scans, especially if a recently submitted proposal, entitled C-11-amino acids/Positron ECT for pancreatic studies should get funded by the National Pancreatic Cancer Project.

5. Comments. None.

1049180

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 2/27/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of Dl-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Proposal No.: 39 Date Approved: 11/9/76

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Based on the results of data obtained with ^{11}C DL-Tryptophan a grant proposal entitled "^{11}C-11-amino acids/Positron Scan for pancreatic Studies" was submitted to the National Pancreatic Cancer Project.

2. Report any complications.

No complications

1049181

3. Are there any planned changes?

~~Selected patients will be scanned both with "C DL-tryptophan and "C-L-tryptophan according~~

If we succeed to develop a rapid resolution procedure for DL-Tryptophan, selected patients with pancreatic tumors will be scanned both with "C-DL, and C-L-tryptophan. An amendment to this IND would have to be prepared.

4. Do you wish the project to be continued?

Yes.

5. Comments. none

1049182

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C](^{11}C-DL-Tryptophan

Proposal No.: 39 Date Approved: November, 1976

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only one clinical pancreas study was done using ^{11}C - DL - tryptophan.

2. Report any complications. None

1049183

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

This project ~~has~~ recently has received grant support from the National Pancreatic Cancer Project (243,000 K for 3 years.

5. Comments. None

1049184

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C](^{11}C-DL-Tryptophan)

Proposal No.: 39 Date Approved: 11/9/76

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Fifteen pancreatic studies were done.

DL-tryptophan is the best pancreas scanning agent

2. Report any complications.

No side effects were noted.

1049185

3. Are there any planned changes?

No changes planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

1049186

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049187

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Tryptophan[Side Chain-3](^{11}C-DL-Tryptophan)

Proposal No.: 39 Date Approved: 11/9/76

Karl F. Hubner 4/24/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done.

2. Report any complications.

N.A.

1049188

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

We are planning to continue some of the ^{11}C-DL-tryptophan work in collaboration with Brookhaven National Laboratory.

1049189

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049190

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Proposal No.: 39 Date Approved: 1976

Signature of Principal Investigator — Date Signed: 4/19/85

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1049191

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049192

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

39 Clinical Use of DL-Tryptophan[Side Chain-3-11C] (11C-DL-Tryptophan) (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39 Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Proposal No. 39 DATE APPROVED: 1976

J R Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049194

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049195

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39 Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Date Approved: 1976

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 meV cyclotron to produce clinically useful amounts of carbon-11

1049196

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39 Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Proposal No. 39 DATE APPROVED: 1976

James E Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049197

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049198

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 39 "Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049199

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39 Clinical Use of DL-Tryptophan[Side Chain-3-^{11}C] (^{11}C-DL-Tryptophan)

Date Approved: 1976

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049200

Ident No. 38

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities

Date: January 22, 1975

Principal Investigator: R. L. Hayes, Ph.D.

Co-Investigators: C. L. Edwards, M.D.
G. A. Andrews, M.D.
K. F. Hubner, M.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CLINICAL USE OF ^{11}C-LABELED 1-AMINOCYCLOPENTANE-CARBOXYLIC ACID FOR TUMOR DETECTION.

I. Objectives of Experiment:

The goal of this proposed research is to carry out in humans a Phase I investigation of the use of carbon-11 carboxyl-labeled 1-aminocyclopentane-carboxylic acid (ACPC) as a potential tumor-imaging agent. This work is being supported by NIH Grant 1 R01 CA 14669-01. Our original observations on the concentration of ACPC in animal tumors are contained in ORAU-122, p. 79.

II. Methods of Procedure:

The labeled ACPC will be synthesized in a hot cell adjacent to the ORNL 86-inch cyclotron where ^{11}C will be generated by a p,n interaction with ^{11}B (B_2O_3 target). The ^{11}C is evolved from the molten target in the form of $^{11}CO_2/^{11}CO$ which is removed by a stream of helium. The $^{11}CO_2/^{11}CO$ is converted catalytically to $^{11}CH_4$ and then to $H^{11}CN$. Subsequently the $H^{11}CN$ is absorbed in a basic solution containing $(NH_4)_2CO_3$, NH_4Cl, KCN, and cyclopentanone. This solution is then heated at 210°C in a sealed stainless steel reaction vessel for 4 minutes after which $Ba(OH)_2$ is added under pressure to achieve hydrolysis of the intermediate hydantoin during an additional heating period of 10 minutes. After first adding sufficient Na_2CO_3 to precipitate soluble Ba^{++} as $BaCO_3$, the reaction mixture is then filtered through a combination filter composed of a glass fiber filter and a paper prefilter into another stainless steel reaction vessel where the

filtrate is first heated at 120°C to expel excess ammonia and then acidified with HCl and again heated to expel carbon dioxide and HCN/$H^{11}CN$. The HCl solution (pH ∿3) is then fed onto a 1x3 cm cation exchange resin (Bio-Rad Laboratories, AG50W-X4, 20-50 mesh) to which the amino acid adheres. Following washing with 0.1N HCl and distilled water the product is eluted with 0.1N NaOH. The amino acid (∿4 mg) will be contained in a volume of 5-10 ml which will be brought to pH 7.0 ± 0.2 with 0.1N HCl and then filtered through a sterile 0.22 μ Millipore filter into a capped presterilized bottle. A portion of the solution will be removed for pyrogen testing using the limulus technique (E-Toxate, Sigma Chemical Co.). (The short half life of ^{11}C [20.5m] precludes testing with rabbits in the conventional USP manner.)

The chemical yield of this set of reactions and purification steps is estimated to be ∿50%. The time required for the synthesis and processing should be ∿1 hr. At present we are able to generate ∿5000 mCi of usable ^{11}C in the 86-inch cyclotron. Thus the overall activity yield at the time of patient use should be in the neighborhood of 250 mCi. We propose to administer intravenously no more than 25 mCi per 70 kg patient. (Maximum tumor-to-nontumor ratios are achieved in animal models at ∿30m after intravenous administration.) Thus the amount of ACPC (as the chemical)will be approximately 0.4 mg or 0.006 mg/kg in a 70 kg patient.

Following administration to patients, multiple rectilinear and positron camera images will be obtained during a period of approximately 1-1/2 hours. (Should we obtain approval of a supplemental NIH grant, which is to be submitted by February 1, 1975, we will also at a later date make use of a positron transaxial tomographic instrument for detailed studies.)

Appropriate samples of blood and urine will be collected. Occasionally, linear scans will be made. Patients will be adults with known cancer. We plan to use 20 subjects in this Phase I study.

III. Possible Hazards and Their Evaluation:

1. Chemical:

1-Aminocyclopentanecarboxylic acid (ACPC) is an agent with anti-tumor activity which was discovered through the screening program of the Cancer Chemotherapy Service Center of the National Cancer Institute (Ross et al., J. Med. Pharm. Chem. 3:1, 1961). 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.

Clinical 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 Chemotherapy Fact Sheet 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.

1049202

Much the same is true of the human toxicity for which a large amount of data exists as the result of the clinical trials that have been carried out (see Chemotherapy Fact Sheet attached). 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 (TSP) are seen. The drug is obviously less toxic in man than in small animals, such as mice and rats, apparently because of the faster excretion rate in man.

At the chemical dose level of the drug which we would use for tumor scanning (∿0.006 mg/kg), we would expect no toxicity, since we will be below the threshold of toxicity by a factor of approximately 10,000.

2. Radiation Dose:

Carbon-11 has a 20.5 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 Radiation Physics section 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 0.25 rads per 25 mCi as proposed. The attached tables give details of the expected radiation dose to various organs in the human estimated from animal data.

IV. Radionuclides and New Drugs:

Carbon-11 will be present in amounts up to 25 mCi. The toxicity of 1-aminocyclopentanecarboxylic acid and the radiation dose from the contained ^{11}C is discussed in III above. The initial runs of the ^{11}C-labeled compound will first be tested in animals and the ORAU Medical Radionuclide Committee will then pass on the results of these preclinical tests before the agent is considered for administration to patients. FDA approval will be obtained before clinical trials are initiated.

This project is being presented to the Committee on Human Studies at this time in order to seek preliminary authorization required by NIH. It will be brought up again after animal work is reported and before clinical trials are started.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from among our patients and from patients in the Oak Ridge Hospital and surrounding hospitals. An informed consent will be obtained from each patient (minor 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.

Starting Date: April-July 1975

Signatures: R. L. Hayes, Jr. Principal Investigator

O. Powell Edwards Co-Investigator

Ernest Andrews Co-Investigator

Karl F. Hubner 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 Ernest Andrews

Title Chairman, Medical Division

Institution Medical Division, ORAU

Date 24 January 1975

1049204

ESTIMATED RADIATION DOSE TO SPECIFIC TISSUES 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.

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator R. L. Hayes Ident. No. 38

Project Title Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

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

   See 4 and 5

   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:

   See 4 and 5

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

   See 4 and 5

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

The committee expects to have the proposal presented again, with additional data, before any patients are treated.

5. Other committee comments:

The committee unanimously agrees that on the basis of data available so far, the project is well worth pursuing. The committee wants to insure that the identity of the compound be verified, and that the question of incidental inclusion of an extraneous toxic material be considered. They also want more data on distribution in animal tumors. They foresee the likelihood that with the later data, the material will be approved for human use.

Approve X

Disapprove

Robert D Lange MD

Chairman of Committee
Robert D. Lange, M.D.

Jan. 25, 1975

Date

1049206

(Revised January 1972)

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Karl F. Hübner, M.D.

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 25, 1980

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 4, 1980.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of Carboxyl-labeled ^{11}C-1-Amino cyclopentane-Carboxylic Acid for Tumor Detection

Proposal No.: 38 Date Approved: 1975

Karl F. Hübner, M.D.

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

[illegible] ^{11}C-ACBC [illegible]

We have [illegible] a series of comparative [illegible] studies [illegible] ^{11}C-ACBC [illegible] ECG [illegible] to [illegible] [illegible] is the [illegible] of the [illegible] [illegible] brain [illegible].

Our initial experience [illegible] was reported in the 1979 Year Book of Cancer, p. 227-234.

The last progress report to FDA is dated [illegible] 1979.

2. Report any complications.

[illegible]

1049207

3. **Are there any planned changes?**

There are no planned changes.

4. **Do you wish the project to be continued?**

Yes, we wish to continue to use ^{11}C-ACBC and compare it to ^{11}C-ACBC in patients with neoplastic lesions other than pancreatic tumors, and use it in selected cases that will be examined with ^{11}C-DL-tryptophane or ^{11}C-DL-valine before during and after treatment

5. **Comments.**

None

1049208

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Proposal No.: 38 Date Approved: 1972

Signature of Principal Investigator: 4/19/85
Date Signed

1. Report progress made in past year:

Administered to 15 patients.

2. Report any complications:

None

1049209

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049210

file

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

38 Clinical Use of 11C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection (Crook)

Progress

Administered to 15 patients.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049211

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5, 1986~~. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Proposal No. 38 Date 1972

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

No pts studied

2. Report any complications. NN

1049212

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments.

1049213

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 38 Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Proposal No. 38 Date Approved: 1972

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. —

2. Report any complications. NA

1049214

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049215

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 38 Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Proposal No. 38 DATE APPROVED: 1972

Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049216

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049217

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 38 Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Date Approved: 1972

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049218

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 38 Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Proposal No. 38 DATE APPROVED: 1972

James E Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed.

2. Report any complications. None.

1049219

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments. None

1049220

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 38 Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection

Date Approved: 1972

32 Inactive
27 Active

1. Report progress made in the past year.

   No studies performed.

2. Report any complications.

   None

6

3. Are there any planned changes:

   No

27
LIST

4. Do you wish the project to be continued?

   Yes

87
Form
28 Process
58 memos

5. Comments.

   None

1049221

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 38 "Clinical Use of ^{11}C-Labeled 1-Aminocyclopentane-Carboxylic Acid for Tumor Detection" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049222

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 576-3098

Medical and
Health Sciences
Division

October 25, 1979

Dr. William J. Gyarfas
Director, Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 12,967

This is the third progress report on the clinical use of ^{11}C-DL-tryptophan in the diagnosis of pancreatic diseases. Since our last report which was sent a year ago on October 20, 1978, we have used ^{11}C-DL-tryptophan in 16 more patients. There were no untoward subjective or objective side effects or toxic manifestations during and after the studies.

Preliminary clinical results with the amino acids and other amino acids have been described and summarized in two publications. For your information I am enclosing reprints of a paper entitled "Carbon-11-Labeled Amino Acids for the Rectilinear and Positron Tomographic Imaging of the Human Pancreas" (Journal of Nuclear Medicine, Vol. 20, 507-514, 1979) and a copy of a paper entitled "Positron-Emission Computed Tomography of the Pancreas: A Preliminary Study" (Radiology, 133: 195-201, October, 1979).

We would like to request FDA's permission to keep this IND on an active status.

Sincerely,

Clarence C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:dg

Enclosures (4)

1049223

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615-576-3098

Medical and
Health Sciences
Division

November 1, 1979

Mr. Richard Podliska
Bureau of Drugs HDF-150
Document Control Room 17B-34
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Podliska:

IND'S 12,459 and 12,967

Enclosed are amendments for our IND's 12,459 and 12,967. We request permission to use the amino acids DL-valine and DL-tryptophan in patients with brain tumors.

As indicated in the amendments, the study will be conducted in collaboration with the University of North Carolina. The amendments and the respective consent forms are currently reviewed by the ORAU-ORNL Committee on Human Studies.

I shall inform you about the decision of the Committee as soon as we have received the votes.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:dg

Enclosures

1049224

DRAFT - FOR REVIEW BY HUMAN USE COMMITTEE

Dear Dr. Gyarfas:

IND 11,848

On February 5, 1981, we submitted an amendment to IND 12,459 requesting permission to use L-valine-1-^{11}C to study the rate of protein synthesis in patients with Huntington's Disease, Phenylketonuria, cerebral palsy, brain tumors, and pancreas disease.

Recent investigations in Dr. Agranoff's laboratory have shown that at least in animal brain (rat), the distribution of ^{14}C-1-aminocyclopentane-carboxylic acid (ACPC, IND #11,848) is very similar to the distribution of L-valine-1-^{14}C. Since ACPC is non-metabolizable, it appears to be an excellent choice for measuring amino acid extraction by the brain in order to get a "valine utilization map," if indeed ACPC mimics valine in humans also. Based on this rationale we request permission to use ^{11}C-ACPC in patients with non-neoplastic brain disease.

So far, we have used ^{11}C-ACPC in 62 patients with various neoplastic disease. We have not observed any untoward side effects or experienced any complications from the application of ^{11}C-ACPC.

Please let us know if you need further information to support this request.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

1049225

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title #38b Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Principal Investigator Karl F. Hübner, M.D.

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.	Howard Ross	✓			4/1/81
2.	Donald U Goodwin	✓			"
3.	[illegible]	✓			4/1/81
4.	Shirley A Fry				
5.	[illegible]	✓			4/1/81
6.	[illegible]	✓			"
7.	[illegible] Miller	✓			4/1/81
8.	L. C. M. [illegible]	✓			4/1/81
9.					
10.					
11.					
12.					
13.					
14.	OK. Robert N Lange				

Chairman's statement of Committee consensus:

4/1/81
DATE

[illegible]

1049226

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 38b

Project Title Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve X

Disapprove ____

Robert W. Tarver MD
Chairman of Committee
4/1/81
Date

1049227

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection use in metabolic brain disease

Proposal No.: 38b Date Approved: 4/1/81

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only one patient with the diagnosis of Phenylketonuria was studied. ^{11}C-ACPC which seems to mimic valine biologically only concentrated very little in the brain of this patient just like ^{11}C-L-valine in another P.K.U. patient.

2. Report any complications. N. A.

1049228

MEMORAN

Dr . F.

DATE Ap

SUBJECT AP

Th
an
an
as

dg

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes

5. Comments. Reason for slow progress is long time of cyclotron.

1049229

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Proposal No.: 38b Date Approved: 4/1/81

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

One patient with proven and one with suspected neoplasm were studied.
The study was positive in the proven case.

2. Report any complications.

No side effects were observed.

1049230

3. Are there any planned changes?

No changes planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

1049231

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049232

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Proposal No.: 38b Date Approved: 4/1/81

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done.

2. Report any complications.

N.A.

1049233

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

Although ^{11}C is not likely to be available to us for some time, we still would like to keep the project active as a collaborative activity with Brookhaven National Laboratory.

1049234

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049235

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amednment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Proposal No.: 38b Date Approved: 1981

Signature of Principal Investigator

4/19/85
Date Signed

1. Report progress made in past year:

Administered to 15 patients.

2. Report any complications:

None

1049236

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049237

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

38b Amendment to Clinical Use of Carboxyl Labeled 11C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection (Crook)

Progress

Administered to 15 patients.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049238

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Proposal No. 38b

Date 1981

Signature of Principal Investigator

Date Signed 5/14/86

1. Report progress made in the past year.

No pt. studied

2. Report any complications. NNE

1049239

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049240

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 38b Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Proposal No. 38b Date Approved: 1975

J R Cook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. —

2. Report any complications. N/A.

1049241

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049242

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.

1049243

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. Hübner, 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

1049244

Medical and Health Sciences Division
OAK RIDGE ASSOCIATED UNIVERSITIES

Adult ____ Patient ____

Guardian ____ Parent ____

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

1049245

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Amino Acid (tryptophan) Utilization Pancreatic Disease

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 head 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 tryptophan 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 tryptohan 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)

1049246

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 tryptophan 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 tryptophan 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 tryptophan, 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)

1049247

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal 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 tryptophan 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 tryptophan 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)

1049248

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 tryptophan 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 tryptophan 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)

1049249

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

November 3, 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.

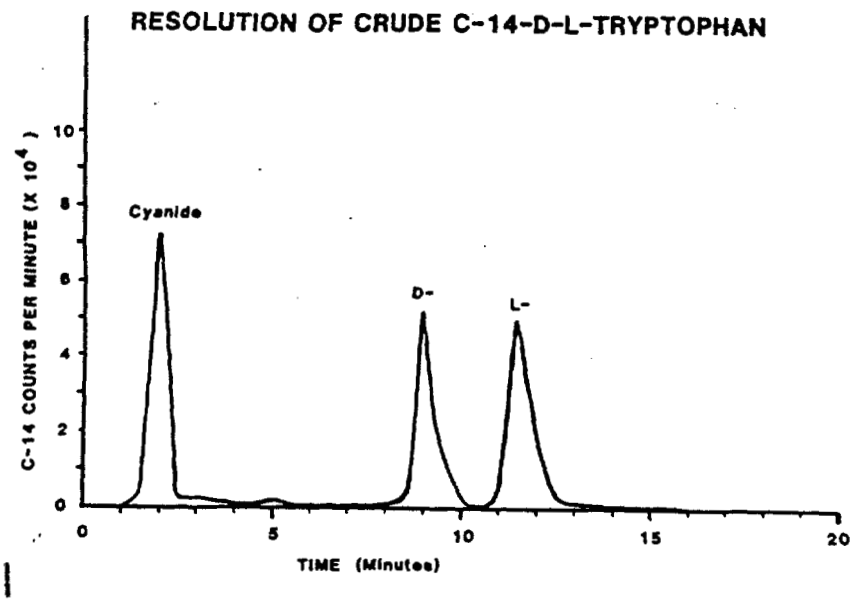
Tamemasa and co-workers (3) have found that D-amino acids are concentrated selectively by tumor tissue. Therefore, it appears that the uptake of ^{11}C-DL-tryptophan by pancreatic carcinoma may be due to the presence of ^{11}C-D-tryptophan in the mixture. We anticipate that use of ^{11}C-L-tryptophan 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.

1049250

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.



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.

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.

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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,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:bbc

1049259

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.

1049260

TO: Deanna Gresham

SUBJECT: Proposal # 39b. and 67

DATE: 10/27/81

Reply Message

FOLD

MESSAGE

#39b appears to be okay. I've suggested some editorial changes on the consent forms.

#67. I don't think this proposal needs committee action. If the majority think otherwise, then I have no objection. There is no need for consent forms.

M E Kons

SIGNED

DATE OF REPLY

REPLY TO

REPLY

SIGNED

1049261

39-f

Medical and Health Sciences Division
Oak Ridge Associated Universities

102

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. tryptophan 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 tryptophan 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)

1049262

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title #39b - AMENDMENT TO EXISTING IND 12,967: PHYSIOLOGICAL STUDIES OF THE PANCREAS AND BRAIN USING ^{11}C-L-TRYPTOPHAN

Principal Investigator Karl F. Hübner, M.D.

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.	Donald Goodwin	✓			10-29-81
2.	Richard Gruesemer	✓			10-29-81
3.	John B. Storer	✓			10-29-81
4.	Leatra Garrett	✓			10/29/81
5.	Steve Lawrence	✓			10/29/81
6.	Ruby A. Miller	✓			10/29/81
7.	William M. Gilbert	✓			10/29/81
8.	J. Clifford Hall	✓			10/29/81
9.	Howard Friedman				10/29/81
10.	Robert W. Langs	✓			10/29/81
11.					
12.					
13.					
14.					

Chairman's statement of Committee consensus:

Approved with changes in consent form typographical errors

DATE

1049263

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 39b

Project Title AMENDMENT TO EXISTING IND 12,967: PHYSIOLOGICAL STUDIES OF THE PANCREAS AND BRAIN USING ^{11}C-L-TRYPTOPHAN

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approved with minor changes in consent form (typographical errors). Changes made (11/20/81)

Approve ✓

Disapprove ____

Robert W Lange, M.D.
Chairman of Committee

10/29/81

1049264

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

Title of Proposal: AMENDMENT TO EXISTING IND 11,967: PHYSIOLOGICAL STUDIES OF THE PANCREAS AND BRAIN USING ^{11}C-L-TRYPTOPHAN

Proposal No.: 39b Principal Investigator: Karl F. Hübner, M.D.

Date of Approval: 10/29/81 Date of Disapproval: _____

Acknowledgment of Principal Investigator:

_____

Signature

12/2/8[illegible]

Date

1049265

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No.: 39b Date Approved: 10/29/81

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Project has not been started since ^{11}C-L-Tryptophan not yet available in clinically useful quantities.

2. Report any complications. N.A.

1049266

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments. None

1049267

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner

FROM Dianne Gresham

DATE April 6, 1982

COPIES TO File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049268

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No.: 39b Date Approved: 10/29/81

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Eight patients with pancreatic disease and two patients having brain disease were studied.

2. Report any complications.

No complications

1049269

3. Are there any planned changes?

No changes are planned

4. Do you wish the project to be continued?

Project to be continued

5. Comments.

No comments

1049270

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049271

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,967; ^{11}C-L-Tryptophan Physiological Studies of the Pancreas and Brain Using

Proposal No.: 39b Date Approved: 10/29/81

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done during the past 12 months.

2. Report any complications.

N.A.

1049272

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

Continuation of work in collaboration with Brookhaven National Laboratory is planned.

1049273

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049274

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,967; Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No.: 39b Date Approved: 1981

Signature of Principal Investigator 4/19/85 Date Signed

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1049275

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049276

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using 11C-L-Tryptophan (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049277

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No. 39b Date 1981

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

No pt studied

2. Report any complications.

1049278

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments.

1049279

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No. 39b Date Approved: 1981

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

One pt c̄ Ca pancreas studied

2. Report any complications. None

1049280

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049281

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No. 39b DATE APPROVED: 1981

J. S. Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049282

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049283

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Date Approved: 1981

1. Report progress made in the past year.

   No patient doses administered.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049284

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Proposal No. 39b DATE APPROVED: 1981

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049285

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049286

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39b Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan

Date Approved: 1981

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049287

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 39b "Amendment to Existing IND 12,967: Physiological Studies of the Pancreas and Brain Using ^{11}C-L-Tryptophan" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049288

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 38b Amendment to Clinical Use of Carboxyl Labeled ^{11}C-1-Aminocyclopentane Carboxylic Acid for Tumor Detection

Date Approved: 1975

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049289

Dr. William J. Gyarfas, Director
Division of Oncology and Radio-
pharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas: Re: IND 12,967

This letter constitutes a request for approval of an amendment to IND 12,967. The original IND for the clinical use of ^{11}C-DL-tryptophan was amended once before on November 3, 1981, at which time we proposed to use the levo active form of ^{11}C-tryptophan for physiological studies of the pancreas and brain. In this amendment we propose the use of ^{11}C-D-tryptophan for similar studies.

Background:

The rationale for the first amendment was to have the racemic mixture and the L-isomer of ^{11}C-tryptophan available for double radiotracer studies in the differential diagnosis of cancer of the pancreas. Based on results of animal studies obtained by Tamemasa and co-workers (1), pancreatic cancer would be expected to concentrate the D-form of the amino acid to a much higher degree than the L-form. In radionuclide imaging of pancreatic cancer the ^{11}C-DL-tryptophan would tend to give a positive ("hot spot") image of the tumor and the ^{11}C-L-tryptophan would concentrate more in the normal pancreatic tissue and show the tumor as a cold spot. This seems to be the case, as we have seen in a few clinical studies. But a direct quantitative comparison of the distribution pattern of ^{11}C-D-tryptophan and ^{11}C-L-tryptophan is not possible if the D isomer has to be injected with an equal amount of the L isomer as is present in the DL-form. We, therefore, propose to use ^{11}C-D-tryptophan for this purpose in an attempt to develop an improved imaging agent for the diagnosis and metabolic studies of pancreatic cancer. Also, ^{11}C-D-tryptophan may be advantageous in localizing brain tumors and in studying metabolic brain diseases.

Production of ^{11}C-D-tryptophan.

In the first amendment for IND 12,967, the procedure for the production of ^{11}C-L-tryptophan by high-performance liquid chromatography (HPLC) has been described in detail. The production method of ^{11}C-D-tryptophan is exactly the same with the exception of the time of recovery or collection of the ^{11}C-D-tryptophan which comes off the column before the L-form. A copy of the procedure is attached as Appendix A.

Toxicity.

In Appendix B the toxicity as it relates to the HPLC procedure and the chemicals involved in it is described for the production of ^{11}C-L-tryptophan. The same information applies for ^{11}C-D-tryptophan since it is produced by exactly the same technique.

/p

The chemical toxicity (LD_{50}) of unlabeled L-tryptophan in rats after intraperitoneal injection is 1632 mg/kg and the D-isomer is reported as being even less toxic (2). The amount of D-tryptophan we are proposing to use in humans (0.1 mg/kg or less) is 16,000 times below the LD_{50} dose for rats for L-tryptophan and even less than that of D-tryptophan. In our experience with ^{11}C-DL-tryptophan (81 doses) there has been no observable toxic effect in humans at these dose levels. Accordingly, ^{11}C-D-tryptophan by itself should not be toxic either, as has been shown in animal experiments. The original IND 12,967 and the amendments (^{11}C-L-tryptophan and ^{11}C-D-tryptophan) have been approved by the ORAU/ORNL Committee on Human Studies.

Radiation Dosimetry:

The radiation dose to the patient from ^{11}C-D-tryptophan will be essentially no different from the dose when using ^{11}C-DL-tryptophan. This dose has been approved by the FDA under the current IND 12,967 and by the M&HSD ORAU Medical Radionuclide Committee. The radiation dose is relatively small because of the short half life of carbon-11 (20.4 min). The estimated radiation dose from ^{11}C-D-tryptophan was calculated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center making the assumption that none of the injected ^{11}C-D-tryptophan is excreted and that complete decay of the ^{11}C-label occurs in situ after initial uniform distribution in a 70 kg human. The table below gives the expected radiation dose to the various organs in the human estimated from animal data. ^{11}C-D-tryptophan was approved for human use by the M&HSD, ORAU Medical Radionuclide Committee.

Estimated Radiation Dose from ^{11}C-D-Tryptophan to Organs in Man*

Tissue	Radiation Dose (rads/mCi)
Total body	
Pancreas	
Liver	
Spleen	
Kidney	
Bone marrow	
Lung	
Small intestine	
Ovary	
Testis	

* Based on the 30-minute tissue distribution in male and female rats following intravenous administration of ^{11}C-carboxyl-labeled D-tryptophan (0.2 mg/kg) assuming immediate uptake and no further change in distribution.

Clinical Studies:

In this amendment we request permission from the FDA to use the diagnostic radiopharmaceutical ^{11}C-D-tryptophan in patients with the

/p

following proven or suspected diseases: pancreatic cancer, other neoplasms,and non-neoplastic pancreatic or neurological diseases.

Patient Selection Criteria:

During the first year the investigational use of ^{11}C-D-tryptophan will be restricted to three clinical problems: cancer of the pancreas (suspected or proven), brain tumors (suspected or proven), and non-neoplastic focal or diffuse brain disease. In patients having these conditions ^{11}C-D-tryptophan will be compared to ^{11}C-L-tryptophan or ^{11}C-ACBC (IND No. 13,867) to determine whether the combination of the two forms of tryptophan improves the differential diagnostic approach (especially to pancreatic cancer) and whether the D-form of tryptophan is a better tumor imaging agent than ^{11}C-ACBC.

In patients with non-malignant focal or diffuse brain disease, the objective of the study is to determine to what extent the two forms of the amino acids localize in intracerebral focal abnormalities and whether ^{11}C-D-tryptophan is a suitable agent to measure amino acid transport in the brain.

The number of patients in each of these categories is not expected to be any higher than 5 (total of 20).

Protocol/Procedures for Patients with Pancreatic Diseases:

1. Patients will be instructed to have nothing by mouth after breakfast except water. They will be encouraged to drink one milkshake 30 minutes before the ^{11}C-D-tryptophan 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 15-20 mCi of ^{11}C D-tryptophan 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 D-tryptophan concentration in plasma by HPLC.

6. ECAT scanning of the abdomen (pancreas) will be started one minute after injection and carried out for 30-60 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.

/p

Protocol/procedures for patients with brain diseases (neoplastic and non-neoplastic).

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. The 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 15-20 mCi of ^{11}C-D-tryptophan 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 tryptophan 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. ECAT 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.

Non-malignant neurological disorders. Patients to be included in this study are epileptics (focal epilepsy) and patients with Huntington's Disease or phenylketonuria (PKU) as discussed in the first amendment to this IND. The total number of patients to be studied should not exceed 10/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 ^{11}C-D-tryptophan 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

/p

venous blood.

5. Following the transmission scans the patient will remain on the scanning table. A dose of 15-20 mCi of ^{11}C-D-tryptophan 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. 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 D-tryptophan concentration by HPLC..

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 head will be scanned a second time using the same four planes. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time.

General Considerations

General considerations for human subjects participating in this study will be the following: 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 C) have been approved by the ORAU/ORNL Committee on Human Studies. Consent will 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 take place in the presence of a nurse, and the patient will be encouraged to ask questions and will be 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 15-20 mCi which is less than 50% of the doses of ^{11}C-DL-tryptophan and ^{11}C-ACBC approved by FDA for a 70 kg person.

Potential benefits include information on the extent of the disease, and possible useful metabolic information on tumor growth for therapeutic decisions. The risk as related to the potential benefits is minimal.

/p

Please consider the proposed application of ^{11}C-D-tryptophan in clinical investigations for approval as an amendment for IND 12,967. If you need additional information, please contact me or Dr. K. F. Hubner, the principal investigator.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:bbc

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan)

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 other non-malignant brain diseases.

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 D-tryptophan 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 tryptophan 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 tryptophan 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 tryptophan, 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 or the metabolic aspects of other, non-malignant, brain diseases.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1049296

Dr. Gyarfas

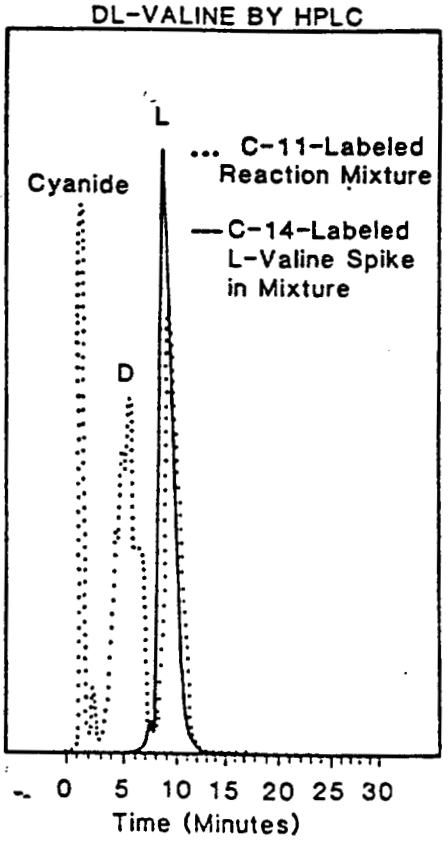
APPENDIX A

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.

RESOLUTION OF CRUDE C-11-LABELED DL-VALINE BY HPLC



1049297

Dr. Gyarfas

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 pre-washed 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.

1049298

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.

Effect of Added L-Proline on the Tissue Distribution of L-Valine-1-^{14}C in the Rat at 30 Minutes Postinjection

	Percent Administered Dose/g	
Tissue	L-Valine-1-^{14}C (0.01 mg/kg)	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.

VOTING FORM FOR PROPOSAL 39C

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

8/12/83

(Date)

1049300

VOTING FORM FOR PROPOSAL 39C

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Melvin E. Koon

(Signature)

July 26, 1983

(Date)

1049301

VOTING FORM FOR PROPOSAL 39C

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____

_____

E C M K

(Signature)

1/23/83

(Date)

1049302

Oak Ridge Associated Universities

Memorandum

To Dianne Gresham

From Dr. Hubner KFH

Date July 14, 1983

Copies to Drs. Hayes, Lange, Lushbaugh, file

Subject AMENDMENT FOR IND's 12,967 and 12,459

Attached are two drafted letters to Dr. Gyarfas in which we request approval of an amendment to IND's 12,967 and 12,459. These IND's have been amended once before for ^{11}C-L-tryptophan and ^{11}C-L-valine. Now we are proposing to use the D-forms of these two amino acids. Of course, before we can send the letters to FDA our human use committee has to approve the amendments first.

I am submitting the amendments to the committee with a request for an expedited review.

NOTE TO THE REVIEWERS: The table on dosimetry is not completed as yet. We anticipate no significant differences between the doses from the L-forms and the D-forms. We are in the process of doing tissue distribution studies involving ^{14}C-D-valine and ^{14}C-D-tryptophan for the requested dose calculations for review and approval by the ORAU/MHSD Radionuclide Committee. I shall notify the Human Use Committee of the decision of the Radionuclide Committee and present the completed dose table. For the purpose of saving time, the information on the dosimetry in the letter has been written prae factum.

bbc

1049303

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division
(615) 576-3480

TO: ORAU/ORNL Committee on Human Studies
Expedited Review Committee (Garrett, McKee, Koons)

FROM: Dianne Gresham

RE: Amendments to Proposals 39C and 45C

DATE: July 21, 1983

Please review the enclosed amendments for Proposals 39C and 45C submitted by Dr. Karl Hübner. The attached cover memo is an explanation by Dr. Hübner of his intentions.

A self-addressed envelope is enclosed for your convenience. Please return the voting form to me by August 4, 1983.

dg

Enclosures

cc: Dr. Robert Lange
Committee Chairman

1049304

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

Title of Proposal: Amendment to IND 12,967 - Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No.: 39C Principal Investigator: Karl F. Hübner, M.D.

Date of Approval: 8/12/83 Date of Disapproval: _____

Acknowledgment of Principal Investigator:

Karl F. Hübner

Signature

3/25/83

Date

The Expedited Review Committee (Garrett, Koons, and McKee) unanimously approved the study.

1049305

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 39C

Project Title Amendment to IND 12,967 - Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

The Expedited Review Committee (Garrett, Koons, and McKee) unanimously approved the amendment.

Approve X

Disapprove ____

104930b

Robert D. Lange, M.D.
Chairman of Committee

8/22/83

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and 11C-D-Tryptophan Studies in Brain Diseases (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No.: 39c Date Approved: 1983

Signature of Principal Investigator 4/19/85 Date Signed

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1049308

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049309

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

4-28

Title of Project: Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No. 39c Date 1983

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

No pt. studied

2. Report any complications.

1049310

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments.

1049311

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No. 39c Date Approved: 1983

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

One pt c̄ Ca pancreas studied.

2. Report any complications. None

1049312

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049313

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No. 39c DATE APPROVED: 1983

J E Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049314

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

Oak Ridge
Associated
Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Proposal No. 39c DATE APPROVED: 1983

James C Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None

1049316

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049317

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Date Approved: 1983

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049318

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 39c "Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049319

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 39c Amendment to IND 12,967: Amino Acid (tryptophan) Utilization Pancreatic Disease (D-tryptophan) and ^{11}C-D-Tryptophan Studies in Brain Diseases

Date Approved: 1983

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049320

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor C. C. Lushbaugh, Ph.D., M.D.

Address Medical & Health Sciences Division, Oak Ridge Associated Universities,
P. O. Box 117, Oak Ridge, Tennessee 37830

Date

Name of Investigational Drug DL-Valine-1-^{11}C

Commissioner
Food and Drug Administration
Bureau of Drugs (BD-26)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, C. C. Lushbaugh, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of 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.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of three copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug it is received from the investigators, together with a ment that the sponsor has obtained from each investor a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man--only animal and in vitro data are available--with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be ted only in the progress reports on these early phases, the development of the plan for the clinical trial, 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be and criteria proposed for subject selection by age, nd condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

c. Institutional review committee. If the phases of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations: that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their

resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD 1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD 1571. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

11. It is understood that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. It is understood that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, an additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

Very truly yours,

SPONSOR	PER
C. C. Lushbaugh, Ph.D., M.D.	Oak Ridge Associated Universities
	INDICATE AUTHORITY
	Chairman, Medical & Health Sciences Division

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

1049323

Ident. No.: 45

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

DATE: April 8, 1976

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigators: G. A. Andrews, M.D.
J. R. ~~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-VALINE-1-^{11}C FOR PANCREAS VISUALIZATION

I. Objectives of Experiment:

The goal of this proposed research is to determine in humans, by a Phase I investigation, whether DL-Valine-1-^{11}C has promise as a potential pancreas-imaging agent. This work is being supported by NIH Grant 1 R01 CA 14669- and USERDA.

II. Methods of Procedure:

An amino acid DL-valine will be rapidly synthesized using a ^{11}C label produced on the 86 in. cyclotron at Oak Ridge National Laboratory. Doses not exceeding 0.714 mC per kilo body weight will be given intravenously to patients with known or suspected disease of the pancreas. The total weight of valine (stable plus radioactive) will not exceed 7 mgm for a 70 kilo subject. This is far below the minimal dietary requirement for L-valine. DL-valine has been shown to be at least as safe as L-valine. The method of synthesis has been developed and is satisfactory in terms of purity and absence of contaminants. Each dose will be tested by radioassay, and the Pyrotest limulus lysate test will be used to rule out pyrogenicity.

The radiation dose of 1 millicurie of this preparation, assuming uniform whole body distribution, is about 0.01 rad per millicurie or a total of 0.5 rad for a 50 millicurie dose.

Suitable laboratory tests to look for possible harmful effects, including hematologic and biochemical blood and urine studies will be done.

Patients will be selected from willing volunteers and will be given an explanation of the nature and details of the study.

Appropriate methods will be used to protect personnel from ^{11}C labeled gas that will be exhaled by the patient.

1049324

II. (continued)

Scans of the abdomen will be done promptly to attempt to visualize the pancreas. Animal studies suggest that a 30-minute interval after administration may give optimal results.

If the human pancreas is visualized, suitable correlations with other diagnostic tests and surgical findings will be made.

Animal studies already done at ORAU suggest possible useful results.

III. Possible Hazards and Their Evaluation:

The hazards are believed to be minimal. The normal person has in his blood stream at any one time about 120 mgm of L-valine, and we propose to add about 7 mgm of labeled DL-valine. Since valine is a normal amino acid in the body, no chemical toxicity is expected. We have given experimental animals relatively large doses without untoward effects. The radiation dose, see above, will be quite small. Thus, we consider the appearance of any harmful effects to be highly unlikely. However, careful clinical and laboratory surveillance will be done on the first.

IV. Radionuclides and New Drugs:

The ^{11}C labels a familiar naturally occurring amino acid. The ^{11}C has a half life of approximately 20 minutes and leaves the bloodstream quite rapidly.

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 offered to obtain voluntary consent. Patients will be recruited specifically for the test with no promise of medical care beyond the period of this specific test. Patients will have known or potential 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: May, 1976

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Signatures: Karl T. Adams Principal Investigator

Raymond L. Dalgard Co-Investigator

Daniel Andrews Co-Investigator

Lee C. Washburn Co-Investigator

Bruce W. Wieland Co-Investigator

Alan C. Wilcox Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the Institution:

Signature P. B. Gustafson

Title Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date April 8, 1976

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RESEARCH WAIVER FORM

The following waiver form shall be used.

Patient: _____ Age: _____

Date: _____ Time: _____ AM/PM

I hereby request and authorize _____ M.D. to perform

upon _____ the following diagnostic procedure:
(myself)

Pancreas visualization with the ^{11}C labeled amino acid DL-valine

I have been fully informed of the possible risks and understand that the results of this diagnostic procedure may not be necessarily of benefit to me. I understand that these tests are part of a research program, and I do not object if any information relating to my case, is published and republished 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 ~~or~~ in any other way.

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.

Witness _____

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NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Medical and Health Sciences Division (MHSD), Oak Ridge

Associated Universities (ORAU), Oak Ridge, Tennessee

April 8, 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).

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4. SOURCE OF NEW DRUG SUBSTANCE:

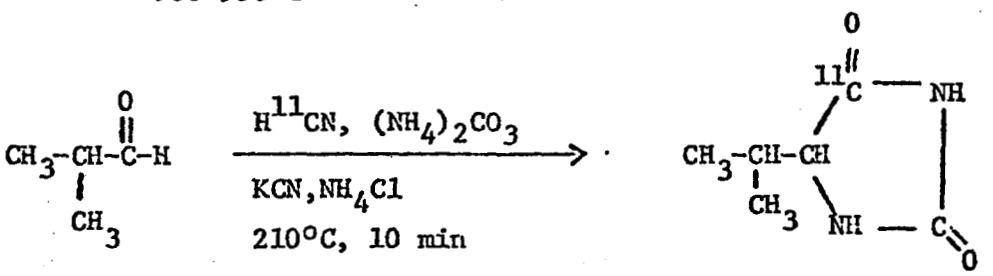
Reference should be made to the details of synthesis and purification of ^{11}C-ACPC in our IND 11848 (dated 16 September 1975) application for a similarly prepared radiopharmaceutical. (^{11}C-ACPC has been under clinical investigation at MHSD, ORAU, since November 1975.)

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:

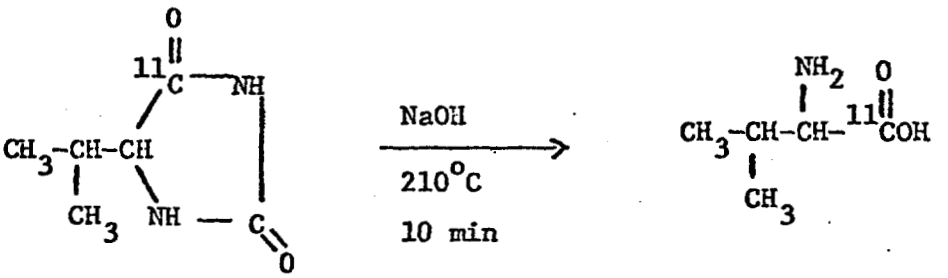
$$B_2O_3 \xrightarrow{^{11}B(p,n)^{11}C} {}^{11}CO_2/{}^{11}CO \qquad \text{Step I}$$

$$^{11}CO_2/{}^{11}CO \xrightarrow[\text{Ni, } 370^\circ C]{H_2} {}^{11}CH_4 \qquad \text{Step II}$$

$$^{11}CH_4 \xrightarrow[900\text{-}950^\circ C]{\text{Pt, } NH_3} H{}^{11}CN \qquad \text{Step III}$$



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 $^{11}CO_2/^{11}CC$ 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 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°C, 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.

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-other-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 ± 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). Each DL-valine-1-^{11}C dose will be assayed for activity content just prior to administration.

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.

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-life (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 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 (non-radioactive area) in the normal pancreatic image produced with 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.

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 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).

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.

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.

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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.

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.

1049340

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.

1049341

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.

1049342

Table [illegible]

Tissue Distribution of [illegible] in the Hamster at [illegible] Minutes [illegible]

Tissue	[illegible]
Liver	[illegible]
Spleen	[illegible]
Kidney	[illegible]
Lung	[illegible]
Muscle	[illegible]
Marrow	[illegible]
Blood	[illegible]
Small intestine	[illegible]

[a] Average of 4 animals [illegible]

1049343

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.

1049344

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.

1049345

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.

1049346

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

1049347

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.

1049348

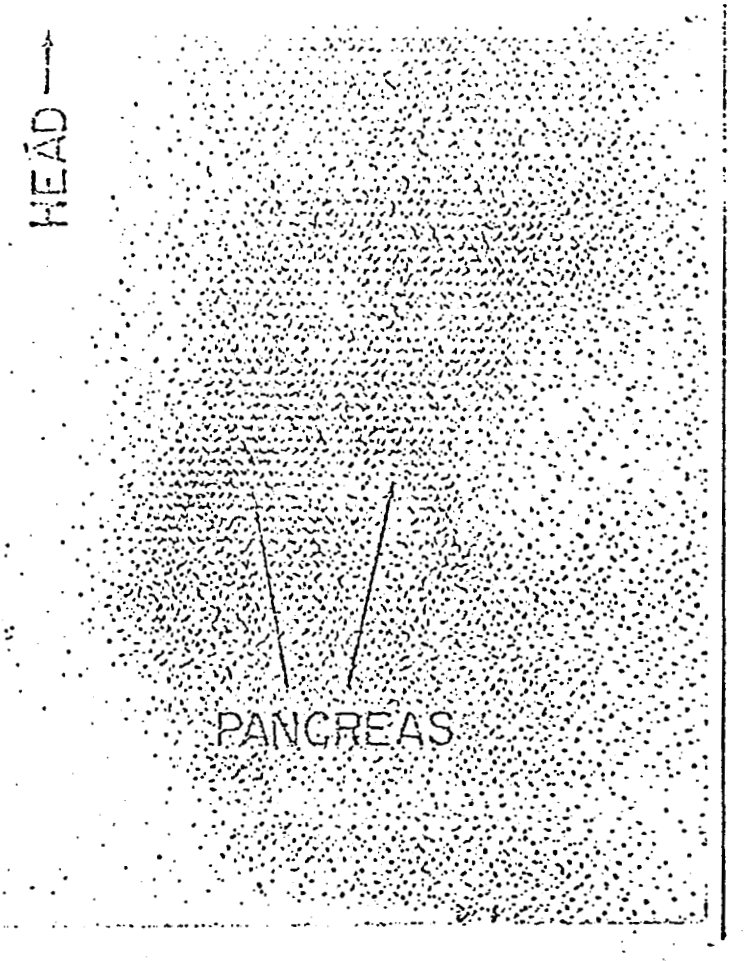

Fig. 1 Scan of a normal mongrel dog started 40 min after I.V. injection of DL-valine-1-^{11}C. Note visualization of pancreas that was obtained.

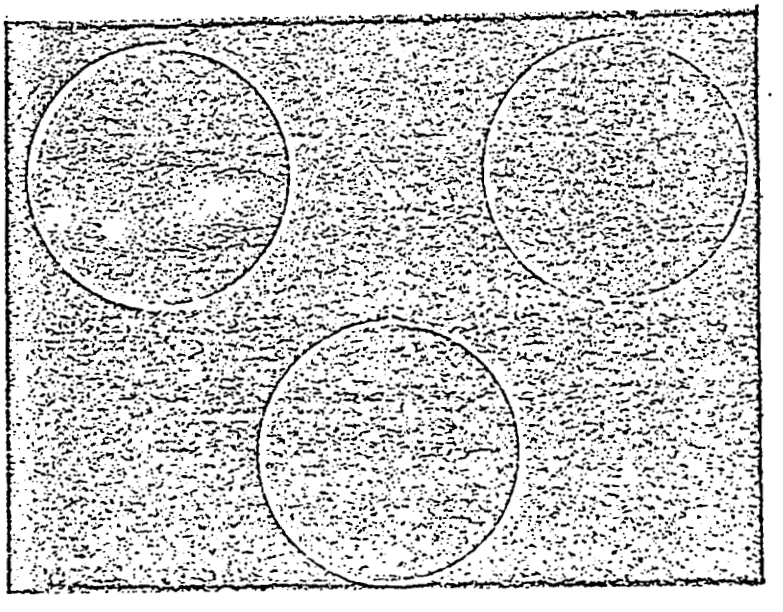

Fig. 2 Anger camera positron image of rat 30 min after administration of DL-valine-1-^{11}C.

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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.

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Division of Nuclear Medicine & Physics
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Minister, United Church
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1049350

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John B. Storer, M.D.
Director, Biology Division
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Joan B. Woods, M.D.
Psychiatrist
Oak Ridge Mental Health Center
Oak Ridge, Tennessee 37830

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Palo Alto Medical Clinic
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Palo Alto, California 94301

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Madison, Wisconsin 53706

Joseph F. Volker, Ph.D. (Ex officio member from the ORAU Board of Directors)
President
University of Alabama
Birmingham, Alabama

1049351

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:	Crinnell, 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

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.

1049353

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

1049354

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.

1049355

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

1049356

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

1049357

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 with a conventional and possibly with an experimental scanning device will be made over a two-hour period.

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

DATE: _____ _____
Investigator

Revised May, 1977

1049358

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 45

Project Title Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approved without special comments.

Approve X

Disapprove ____

Robert D Lang MD

Chairman of Committee

May 11, 1976

1049359

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Dr Hirnel

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 12,459

MAY 2 6 1976

C. C. Lushbaugh, Ph.D., M.D.
Medical & Health Sciences Division
Oakridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 12,459

Sponsor: C. C. Lushbaugh, Ph.D., M.D.

Name of Drug: DL Valine-1-11-C for Injection

Date of Submission: May 12, 1976

Date of Receipt: May 13, 1976

As sponsor of the clinical study proposed in this IND you are now free to obtain supplies of the investigational drug, but it is understood that studies in humans will not be initiated prior to 30 days after the date of receipt shown above. It is further understood that you will continue to withhold or restrict such studies should we so request within that 30 day period.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

1049360

JUN 0 2 1976

All future communications concerning this IND should be forwarded in triplicate, identified with the IND number assigned, and addressed as follows:

Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM 17B-34
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely yours,

William J. Gyarfas

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

OAK RIDGE NATIONAL LABORATORY
OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION

POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

May 26, 1976

Gould A. Andrews, M.D., Secretary
Committee on Human Studies
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Gould:

I approve of Project Number 45 (Use of ^{11}C-valine for studies of the pancreas).

I approve of the consent form to be used when individuals have been internally exposed to radionuclides and DTPA treatment is recommended.

I give informal approval of Project Number 47, but would like to see the minutes of the UTHRCH Committee on Human Experimentation before I give final approval.

Sincerely,

Tom

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

TAL:ph

1049362

MAY 28 1976

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 5, 1976

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education, and Welfare
Rockville, Maryland 20852

Dear Dr. Gyarfas:

I have received your letter dated November 2, 1976, in which you request additional information concerning our Notice of Claimed Investigational Exemption for a New Drug for ^{11}C-dl-Valine for pancreas imaging (IND 12,459), and I submit to you the following information:

1. The explanation to the patient in relation to Item 3 of the consent form will be changed as follows:

   The radiation dose will average approximately 0.25 - 0.5 rad to the whole body. This is less than would be received from a widely accepted nuclear medical procedure for study of the pancreas (radioactive selenomethionine) and much less than would be received to the abdominal region from a gastrointestinal x-ray diagnostic study.

2. The criteria for evaluating results include (a) surgical exploration (with biopsies) shortly before or after the experimental scans; (b) scan results, when available, to be compared to ultrasound tracings; (c) relating general clinical and biochemical evaluation of the patient to the scans; and (d) comparing the results of ^{75}Se-selenomethionine scans to ^{11}C-Valine scans in selected patients with proven cancer. In addition, autopsy data are expected to become available eventually in some cases.

3. The curriculum vita of Dr. Hübner, the principal nuclear medical investigator, is included.

You may be interested in learning that we have given ^{11}C-Valine to eight patients so far. We did not observe any untoward reactions or clinical biochemical changes in any of these patients.

1049363

Please let me know if you need any other information with regard to IND 12,459.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and
Health Sciences Division

CCL:dgb

Enclosure

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.

1049365

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.

1049366

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.

1049367

Rec 11-4-76

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 12,459

NOV 2 1976

C. C. Lushbaugh, Ph.D., M.D.
Medical and Health Sciences Division
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for dl-Valine-1-11-C for Injection.

We have completed our review and have no objection to initiation of your proposed clinical investigation as originally planned, but we request that you submit the following information:

MEDICAL

1. The informed consent form should contain specific information in lay language concerning radiation exposure.

2. The criteria used for evaluating the efficacy of the procedure should be specified.

3. A curriculum vitae should be submitted for the person who is responsible for the nuclear medicine aspects of this IND.

You may use a copy of this letter to inform the appropriate licensing agency that the FDA has permitted your clinical investigation of dl-Valine-1-11-C for Injection.

Please submit the requested information promptly.

Sincerely yours,

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

1049368 Hubner should comply

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 5, 1976

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education, and Welfare
Rockville, Maryland 20852

Dear Dr. Gyarfas:

I have received your letter dated November 2, 1976, in which you request additional information concerning our Notice of Claimed Investigational Exemption for a New Drug for ^{11}C-dl-Valine for pancreas imaging (IND 12,459), and I submit to you the following information:

1. The explanation to the patient in relation to Item 3 of the consent form will be changed as follows:

   The radiation dose will average approximately 0.25 - 0.5 rad to the whole body. This is less than would be received from a widely accepted nuclear medical procedure for study of the pancreas (radioactive selenomethionine) and much less than would be received to the abdominal region from a gastrointestinal x-ray diagnostic study.

2. The criteria for evaluating results include (a) surgical exploration (with biopsies) shortly before or after the experimental scans; (b) scan results, when available, to be compared to ultrasound tracings; (c) relating general clinical and biochemical evaluation of the patient to the scans; and (d) comparing the results of ^{75}Se-selenomethionine scans to ^{11}C-Valine scans in selected patients with proven cancer. In addition, autopsy data are expected to become available eventually in some cases.

3. The curriculum vita of Dr. Hübner, the principal nuclear medical investigator, is included.

You may be interested in learning that we have given ^{11}C-Valine to eight patients so far. We did not observe any untoward reactions or clinical biochemical changes in any of these patients.

1049369

Please let me know if you need any other information with regard to IND 12,459.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and
Health Sciences Division

CCL:dgb

Enclosure

1049370

Oak Ridge Associated Universities

MEMORANDUM

Dr. Richter

FROM R. L. Hayes RLH

DATE March 25, 1977

COPIES TO Drs. Andrews and Hubner

SUBJECT PURCHASE AND MAINTENANCE OF DOGS FOR ACBC AND ECAT STUDIES

Our present plans are to proceed with hematological and biochemical tests of ACBC in a marmoset from the marmoset colony as authorized by the Marmoset Committee on March 23. We also plan to carry out similar studies in 4 dogs. However, we will use the 4 pound dogs that are presently on hand for tissue distribution studies of ^{11}C-DL-valine. Therefore, we will require 4 additional dogs in the near future for the ACBC studies. These animals should be in good health at the time they are purchased, and accordingly, they probably should not be pound dogs. The preclinical radiopharmaceutical development program will cover the purchase cost of these dogs. We expect that, in addition to tests of the effects of ACBC, they will also be used for an extended period of time in ECAT studies of various positron radiopharmaceutical preparations.

^{11}C - Valine file

MAR 2 1976

1049371

ORAU-A-001

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 28, 1977

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 12,459 (Progress Report)

Clinical Studies. This progress report covers the total number of clinical studies done with dl-valine-1-11 since November of 1976. Since that time, the total number of patient studies, i.e., pancreas scans with dl-Valine-1-11, has risen to 11. The doses given to these patients ranged from 13.5 mCi to a total of 45 mCi. Four of these patients had cancer of the pancreas, and one is suspected of having an insulinoma. Three patients had pancreatitis, and three had Hodgkin's and non-Hodgkin's lymphoma involving the mesenteric lymph nodes. Nine of these studies were done with the Ohio Nuclear Total Body Scanner, and one patient was scanned with the new ECAT scanner. Our preliminary impression about the usefulness of carbon-11 labeled valine is that it appears to be a better pancreas scanning agent than 75-selenomethionine.

Laboratory Observations. Whole body retention of the radionuclide was determined by whole body counting, approximately one hour after injection of the dose and immediately after emptying of the urinary bladder. The results show that less than 10 percent (average) of the total dose is excreted within the first 60 minutes after dose application. The radioassay of the urine showed an average excretion of 12.9 percent approximately 60 minutes after the dose. This value corresponds fairly well with the value which was obtained by whole body counting.

The blood levels of the radioactivity were measured at 5, 10, 15, 30, and 60 minutes. The 100 percent blood level was calculated by dividing the dose given by the estimated blood volume of a particular patient. On this basis the blood level fell to 26 percent of the dose at five minutes, 19.6 percent at 15 minutes, and to a plateau between 13.6 percent and 11.1 percent between 30 and 60 minutes after dose application.

1049372

Hemograms, urinalysis, and plasma hemoglobin levels were determined before the injection of the radiopharmaceutical and 24 hours after the scan and remained unchanged.

Reactions and/or Side Effects. None of the patients experienced any discomfort or unusual symptoms that would indicate any kind of toxicity.

Summary. On the basis of 11 patient studies carbon-11 labeled dl-valine was found to be nontoxic and well tolerated. The compound is well localized in the pancreas. Initial data were obtained with conventional scanning equipment. In the future, carbon-11 labeled valine will be used in conjunction with the ECAT scanner and compared to the quality of scans obtained with another pancreas imaging agent, namely, carbon-11 labeled tryptophan.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Division

CCL:dgb

1049373

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

October 20, 1978

Dr. William J. Gyarfas
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Gyarfas:

IND 12,459

This is the second progress report on the use of ^{11}C-DL-Valine as a pancreas scanning agent. Our last report, dated November 28, 1978, was based on 11 patient studies. We have not used ^{11}C-DL-Valine since that time and consequently have no reportable information at this time.

There are several reasons for the temporary halt in this project. Our program in emission positron tomography depends on cyclotron produced positron emitters such as ^{11}C as used in ^{11}C-DL-Valine. Due to downtime and for priority reasons, we had very little cyclotron time during the past 12 months, and we had to make a choice between ^{11}C-DL-Valine and ^{11}C-DL-Tryptophan as well as ^{11}C-ACBC on the other hand.

We still plan to go ahead with a comparison of ^{11}C-labeled valine and tryptophan as we have indicated in the past progress report and would, therefore, like to keep IND 12,459 on an active status.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Division

CCL:dg

1049374

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Karl F. Hübner, M.D.

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 25, 1980

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 4/4/80.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: 1976

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

We have started an ECAT comparison between ^{11}C-DL-Valine and ^{11}C-DL-tryptophan. The total number of patients studied with ^{11}C-DL-Valine is now 18.
Progress was reported in J. Nucl. Med. 20: 507-513, 1979.
^{11}C-DL-tryptophan appears to be superior to ^{11}C-DL-Valine as a pancreas scanning agent
Last progress report to FDA dated 1979

2. Report any complications.

No complications or side effects were observed.

1049375

3. Are there any planned changes? There are no plans to make any changes.

4. Do you wish the project to be continued? Yes, this project will remain active as part of the comparative study proposed in the Grant Request to the National Pancreatic Cancer Project on April 1, 1980.

5. Comments. None

1049376

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 2/27/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: 5/11/76

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only 2 pancreatic studies were done with "C-DL-valine during the past year. The last progress report to FDA was sent on Oct 29 1980.

2. Report any complications. No complications.

1049377

3. Are there any planned changes?

A few selected patients will be examined both with "C-DL-Valine and "C-L-Valine under the recently submitted amendment to this IND.

4. Do you wish the project to be continued? yes.

5. Comments. None

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: May 11, 1976

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only two pancreatic studies were done with ^{11}C-DL-valine. In one patient a comparison study was done using the L-form of ^{11}C-valine. Preliminary results indicate higher concentration of the natural L-form in pancreas. The DL-/L- concentration ratios were found to be @ 1:2!

2. Report any complications. None

1049379

3. Are there any planned changes? none

4. Do you wish the project to be continued? yes

5. Comments. ~~no~~ none

1049380

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner

FROM Dianne Gresham DG

DATE April 6, 1982

COPIES TO File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049381

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: 5/11/76

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

We studied four pancreas patients with DL-valine.

2. Report any complications.

There were no complications

1049382

3. Are there any planned changes?

No changes are planned

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

1049383

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049384

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: 5/11/76

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done during the past 12 months.

2. Report any complications.

N.A.

1049385

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

Work is to be continued in collaboration with Brookhaven National Laboratory.

1049386

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049387

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No.: 45 Date Approved: 1976

Signature of Principal Investigator: R Crook Date Signed: 4/19/85

1. Report progress made in past year:

Administered to 3 patients.

2. Report any complications:

None

1049388

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049389

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

45 Clinical Use of DL-Valine-1-11C for Pancreas Visualization (Crook)

Progress

Administered to 3 patients.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of DL-Valine-1-^{11}C for Pancreas Visualization

Proposal No. 45 Date 1976

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

No pt Studied

2. Report any complications. None

1049391

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes

5. Comments.

1049392

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45 Clinical Use of DL-Valine-^{11}C for Pancreas Visualization

Proposal No. 45 Date Approved: 1976

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

One pt c̄ Ca pancreas studied

2. Report any complications. None

1049393

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049394

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45 Clinical Use of DL-Valine-^{11}C for Pancreas Visualization

Proposal No. 45 DATE APPROVED: 1976

J R Crook
Signature of Principal Investigator

6/25/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049395

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049396

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45 Clinical Use of DL-Valine-^{11}C for Pancreas Visualization

Date Approved: 1976

1. Report progress made in the past year.

   No patient doses administered.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049397

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45 Clinical Use of DL-Valine-^{11}C for Pancreas Visualization

Proposal No. 45 DATE APPROVED: 1976

James E Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049398

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None

1049399

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 45 "Clinical Use of DL-Valine-^{11}C for Pancreas Visualization" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049400

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45 Clinical Use of DL-Valine-^{11}C for Pancreas Visualization

Date Approved: 1976

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049401

Oak Ridge
Associated
Universities

======= 576-3098

M E M O R A N D U M

TO: ORAU/ORNL Committee on Human Studies

FROM: Dianne Gresham dg

DATE: October 31, 1979

RE: Amendments 39a and 45a

Amendments for proposals 39 and 45 (IND 12,967 and 12,459, respectively) are enclosed for your review. Proposal 39 was originally submitted and approved by the Committee in November, 1976; proposal 45 was submitted and approved in May, 1976. FDA now requires all amendments to be reviewed and approved by the Committee. A voting form is attached to each amendment; please study the amendment carefully and return the voting form to me by November 14, 1979 in the enclosed self-addressed envelope.

Also enclosed is a copy of an HEW publication "Comparison of the HEW and FDA Proposed Regulations for IRBs and Informed Consent Published on August 14, 1979." It should be useful to the Committee as you meet and discuss changing guidelines and new consent forms to be used by investigators.

The minutes of the last meeting will be sent to you as soon as possible. Due to changing priorities in this office, I have been unable to work with the Committee files. I apologize for the delay.

dg

Enclosures: Amendments 39a and 45a
Self-Addressed Envelope
HEW Publication

1049402

MEDICAL AND HEALTH SCIENCES DIVISION

OAK RIDGE ASSOCIATED UNIVERSITIES, OAK RIDGE, TN

AMENDMENT TO IND 12,459

Use of ^{11}C-DL-Valine for Localization of Brain Tumors
By Positron Emission Computed Tomography

In the original IND 12,459 we have proposed to evaluate ^{11}C-DL-valine in conjunction with positron emission computerized tomography in patients with proven or suspected pancreatic disease.

We would like to expand the spectrum of clinical applications of ^{11}C-DL-valine to include patients with brain tumors. This study will consist of observations of the metabolism of ^{11}C-DL-valine as evidenced by the localizing properties of the radiopharmaceutical in brain tumors (gliomas and meningiomas) and the relative specificity of valine in certain brain tumor cell types. This hypothesis is supported by recent data from Robertson (in press, Journal of Neurosurgery).

Patients (approxiamtely 30) for this study will be mainly referred by Dr. M. S. Mahaley, Chief, Neurosurgery, University of North Carolina and North Carolina Memorial Hospital, Chapel Hill.

The study is expected to cover a period of 1-1/2 to two 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 3.6 rads to the pancreas, 1.2 rads to the small intestine, 1.0 rads to the liver, and 0.3 rads to the whole body when 30 mci is administered. No 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. The proposed diagnostic doses appear well below any that could cause medical toxicity from the DL-valine or detrimental radiation effects from the ^{11}C present. We will start our studies with the full diagnostic dose (0.43 mCi/kg) in patients with known or strongly suspected of brain tumor who are, however, considered to be in good general condition. Careful observations of pulse and blood pressure will be made during the study. At least two physicians will be present during the first clinical trials.

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. Can gliomas and meningiomas be specifically imaged with ^{11}C-DL-Valine?

2. Will the uptake of ^{11}C-DL-valine in human brain tumors be sufficient to permit brain tumor imaging?

3. What is the optimum dose and scanning time for brain tumor visualization?

The criteria for evaluating results include (a)* surgical exploration (with biopsies) shortly before or after the experimental scans; (b) scan results, when available, to be compared to conventional CT, and (c) relating general clinical and biochemical evaluation of the patient to the scans. In addition, autopsy data are expected to become available eventually in some cases.

*Surgical procedures are not done for the purpose of explaining scan results but rather for routine diagnostic and clinical management of the patients. Any surgical procedure will be performed at the University of North Carolina or any other hospital with approved neurosurgery service; patients will be asked to consent to surgical procedures at those particular institutions.

MEDICAL AND HEALTH SCIENCES DIVISION

OAK RIDGE ASSOCIATED UNIVERSITIES, OAK RIDGE, TN

AMENDMENT TO IND 12,459

Use of ^{11}C-DL-Valine for Localization of Brain Tumors
By Positron Emission Computed Tomography

In the original IND 12,459 we have proposed to evaluate ^{11}C-DL-valine in conjunction with positron emission computerized tomography in patients with proven or suspected pancreatic disease.

We would like to expand the spectrum of clinical applications of ^{11}C-DL-valine to include patients with brain tumors. This study will consist of observations of the metabolism of ^{11}C-DL-valine as evidenced by the localizing properties of the radiopharmaceutical in brain tumors (gliomas and meningiomas) and the relative specificity of valine in certain brain tumor cell types. This hypothesis is supported by recent data from Robertson (in press, Journal of Neurosurgery).

Patients (approxiamtely 30) for this study will be mainly referred by Dr. M. S. Mahaley, Chief, Neurosurgery, University of North Carolina and North Carolina Memorial Hospital, Chapel Hill.

The study is expected to cover a period of 1-1/2 to two 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 3.6 rads to the pancreas, 1.2 rads to the small intestine, 1.0 rads to the liver, and 0.3 rads to the whole body when 30 mci is administered. No 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. The proposed diagnostic doses appear well below any that could cause medical toxicity from the DL-valine or detrimental radiation effects from the ^{11}C present. We will start our studies with the full diagnostic dose (0.43 mCi/kg) in patients with known or strongly suspected of brain tumor who are, however, considered to be in good general condition. Careful observations of pulse and blood pressure will be made during the study. At least two physicians will be present during the first clinical trials.

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. Can gliomas and meningiomas be specifically imaged with ^{11}C-DL-Valine?

2. Will the uptake of ^{11}C-DL-valine in human brain tumors be sufficient to permit brain tumor imaging?

1049405

3. What is the optimum dose and scanning time for brain tumor visualization?

The criteria for evaluating results include (a)* surgical exploration (with biopsies) shortly before or after the experimental scans; (b) scan results, when available, to be compared to conventional CT, and (c) relating general clinical and biochemical evaluation of the patient to the scans. In addition, autopsy data are expected to become available eventually in some cases.

*Surgical procedures are not done for the purpose of explaining scan results but rather for routine diagnostic and clinical management of the patients. Any surgical procedure will be performed at the University of North Carolina or any other hospital with approved neurosurgery service; patients will be asked to consent to surgical procedures at those particular institutions.

1049406

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 brain and brain tumor 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 five times during a period of 60 minutes after administration.

5. Scans with an emission computerized tomograph will be made over a two-hour period.

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

DATE: _____ _____
Investigator

October 30, 1979

1049407

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 576-3098

Medical and
Health Sciences
Division

October 25, 1979

Dr. William J. Gyarfas
Director, Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM #17-B34
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Gyarfas:

IND 12,459

Since our last progress report on ^{11}C-DL-Valine as a diagnostic agent for the detection of diseases of the pancreas (October 20, 1978), we have had the opportunity to study six more patients with this amino acid in conjunction with positron emission computerized tomography.

In three of the patients ^{11}C-DL-tryptophan was also used for comparison. Based on this small number of cases, ^{11}C-DL-tryptophan seems to give better results. But we need more cases to support this very preliminary conclusion. Therefore, we would like to maintain this IND 12,459 on active status.

In support of this progress report, I am enclosing two reprints of our article "Carbon-11-Labeled Amino Acids for the Rectilinear and Positron Tomographic Imaging of the Human Pancreas" (Journal of Nuclear Medicine, 20: 507-514, June, 1979).

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:dg

Enclosures (2)

1049408

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615-576-3098

Medical and
Health Sciences
Division

November 1, 1979

Mr. Richard Podliska
Bureau of Drugs HDF-150
Document Control Room 17B-34
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Podliska:

IND'S 12,459 and 12,967

Enclosed are amendments for our IND's 12,459 and 12,967. We request permission to use the amino acids DL-valine and DL-tryptophan in patients with brain tumors.

As indicated in the amendments, the study will be conducted in collaboration with the University of North Carolina. The amendments and the respective consent forms are currently reviewed by the ORAU-ORNL Committee on Human Studies.

I shall inform you about the decision of the Committee as soon as we have received the votes.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:dg

Enclosures

1049409

VOTING FORM FOR AMENDMENT 45a

APPROVE _____

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____

_____

_____

(Signature)

_____

(Date)

1049410

VOTING FORM FOR AMENDMENT 45a

APPROVE See Comment

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT

Approved subject to inclusion in consent form an explanation of the ..." surgical exploration (with biopsies)..."

M. E. Koons

(Signature)

November 14, 1979

(Date)

When I have called institutions, doctors and explained to them that no surgical procedures will be done at OuA, and that any surgical procedures outside the study will be coincidental to the screening protocol although it may contribute valuable information to our research. Accordingly, I have added an explanatory note to

1044011

VOTING FORM FOR AMENDMENT 45a

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____

_____

William H Lackey

(Signature)

Nov 19, 1979

(Date)

1049412

VOTING FORM FOR AMENDMENT 45a

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT The expansion of this research should not be expected to have harmful effects on the mental status of these patients.

Howard Fine

(Signature)

11/9/79

(Date)

1049413

VOTING FORM FOR AMENDMENT 45a

APPROVE XX

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION No

COMMENT _____

A. Seaton Garrett, Jr., M.D.
(Signature)

November 12, 1979

(Date)

1049414

VOTING FORM FOR AMENDMENT 45a

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Donald H. Goodman

(Signature)

Nov. 2, 1978

(Date)

1049415

VOTING FORM FOR AMENDMENT 45a

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Robert W Tangy, MD
(Signature)

6 November 1979
(Date)

1049416

VOTING FORM FOR AMENDMENT 45a

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

11/5/79

(Date)

1049417

VOTING FORM FOR AMENDMENT 45a

APPROVE x

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

L. Clifford McKay Jr.
(Signature)

11/1/79
(Date)

1049418

VOTING FORM FOR AMENDMENT 45a

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Ruby A. Miller

(Signature)

Nov. 9, 1979

(Date)

1049419

VOTING FORM FOR AMENDMENT 45a

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

11/9/79

(Date)

1049420

VOTING FORM FOR AMENDMENT 45a

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Martha S. Hansard

(Signature)

12/31/29

(Date)

1049421

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner Ident. No. 45a

Project Title USE OF ^{11}C-DL-VALINE FOR LOCALIZATION OF BRAIN TUMORS BY POSITRON EMISSION COMPUTED TOMOGRAPHY

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve X (by mail vote 11/79)

Disapprove ____

1049422

Robert D. Lange M.D.
Chairman of Committee

2/21/80
Date

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45a Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography

Proposal No. 45a DATE APPROVED: 1980

J E Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049423

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049424

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45a Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography

Date Approved: 1980

1. Report progress made in the past year.

   No patient doses administered.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049425

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45a Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography

Proposal No. 45a DATE APPROVED: 1980

James E Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049426

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049427

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45a Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography

Date Approved: 1980

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049428

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 45a "Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049429

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 2/27/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 45a Date Approved: 2/21/80

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Nine patients were studied with ^{11}C-DL-valine using the EMI scanner. The results show a fairly selective distribution of this amino acid in various structures of the brain and a more intense uptake in brain tumors than ^{18}F-2-deoxyglucose (tumor to normal brain concentration ratio ≥ 2:1). The [illegible] FDG [illegible]

2. Report any complications.

None of the patients experienced any reactions or [illegible] from the iv injection of ^{11}C-DL-valine

1049430

3. Are there any planned changes?

Planned changes are a comparison between "C-2L-yellow" and "C-L-white" under the recently submitted amendment to this IND.

4. Do you wish the project to be continued?

Yes

5. Comments. None

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 45a Date Approved: 2/21/80

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No Studies been done

2. Report any complications. N. A.

1049432

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. ~~None~~ long cyclotron down time!

1049433

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner — FROM Dianne Gresham

DATE April 6, 1982 — COPIES TO File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 45a Date Approved: 2/21/80

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

We studied 12 patients with proven or suspected brain tumors with DL-valine. DL-valine appears to be a good brain scanning agent, probably more useful than L-valine.

2. Report any complications.

No complications

1049435

3. Are there any planned changes?

No changes planned

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

1049436

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049437

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. K. F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 45a Date Approved: 2/21/80

Kenneth F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done during the past 12 months.

2. Report any complications.

N.A.

1049438

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.

1049439

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049440

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors Position Emission Computed Tomography

Proposal No.: 45a Date Approved: 1980

Signature of Principal Investigator — Date Signed: 4/19/85

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1049441

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049442

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

45a Use of 11C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049443

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No. 45a Date 1980

Signature of Principal Investigator 5/14/86
Date Signed

1. Report progress made in the past year.

NO pts. studied

2. Report any complications. None

1049444

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049445

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45a Use of ^{11}C-DL-Valine for Localization of Brain Tumors by Positron Emission Computer Tomography

Proposal No. 45a Date Approved: 1980

Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. —

2. Report any complications. N.A.

1049446

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments.

1049447

Ident. No. 45b

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 1/21/81

Principal Investigator: K. F. Hübner

Co-Investigators: Lee Washburn

R. L. Hayes

Title of Project: Amendment to existing IND 12,459: physiological studies of the pancreas and brain using L-valine 1-^{11}C

I. Objectives of Experiment:

1. To determine whether the L-valine localizes to a higher degree in normal pancreatic tissue than in neoplastic or inflammatory lesions, and whether L-valine-1-^{11}C in conjunction with ^{11}C-1-aminocyclobutanecarboxylic 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 tomograpy.

2. To study the metabolic activity of the brain or specific structures of the brain in patients with post CVA hypertonia, Phenylketonuria (PKU), Huntington's Disease (HD), possibly Cerebral Palsy, and brain tumors by measuring the rate of protein synthesis using L-valine-1-^{11}C 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-valine) 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.

1049448

III. Possible Hazards and Their Evaluation

There are no chemical risks from injecting L-valine in the amounts proposed in this investigation. Adherence to quality control procedures (sterility, pyrogenicity testing) prior to i.v. injection of L-valine-1-^{11}C should eliminate any side effects.

IV. Radioisotopes and New Drugs

L-valine, a natural essential amino acid, will be labeled with carbon-11. The whole body radiation doses from the injection of carbon-11 labeled L-valine 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 March 1, 1981

Signatures: Karl F. Hubner, M.D. Principal Investigator

Co-Investigator

R. L. Hayes "

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

1049449

Medical and Health Sciences Division
OAK RIDGE ASSOCIATED UNIVERSITIES

Adult ____ Patient ____

Guardian ____ Parent ____

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

1049450

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 valine (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)

1049451

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal 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 valine (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)

1049452

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 valine (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)

1049453

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Local Brain Metabolism in Hypertonic Humans

The purpose of this study: is to measure the rate of protein formation (synthesis) in the brain of stroke patients in order to gain a better understanding about the nature of their brain damage and possibly find an improved treatment.

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 valine (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 my (her/his) whole body is equivalent to the dose I (she/he) would receive from an ordinary brain scan in my (her/his) home town 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 my (her/his) 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)

1049454

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 valine (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)

1049455

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Local Brain Metabolism in Cerebral Palsy

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 cerebral palsy and possibly find an improved treatment for patients with that disease.

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. 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 valine (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. Blood samples will be taken and a series of scans of her/his brain will be made.

Duration of this study: The entire examination should take approximately 1-1/2 to 2 hours.

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.

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 cerebral palsy 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)

1049456

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator K. F. Hübner, M.D. Ident. No. 45b

Project Title Amendment to existing IND 12,459: physiological studies of the pancreas and brain using L-valine 1-^{11}C

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

This proposal was mailed to the members in January of 1981 with voting forms. All members responded approving the proposal. Dr. Fry suggested some changes in the consent form which were incorporated into the form on February 5, 1981.

Approve X

Robert W Tangy M.D.
Chairman of Committee

Disapprove ____ 1049457

2/5/81
Date

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

2/5 or 6/81

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.

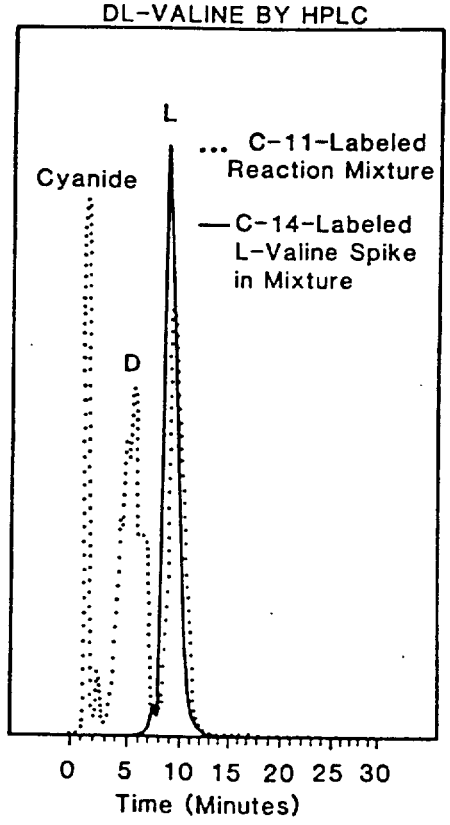
1049458

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.

RESOLUTION OF CRUDE C-11-LABELED DL-VALINE BY HPLC



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 pre-washed 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.

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)	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 January 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.

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>

Nonmalignant 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 animals with hemiplegia from cerebrocortical ablations demonstrate marked changes in the metabolic activity of the basal ganglia and thalamus. These studies indicate that similar changes will be found in patients who develop hypertonic hemiplegia from cerebral infarction. 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.

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.

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 may 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

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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

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1049471

Ident. No. 45b

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 1/21/81

Principal Investigator: K. F. Hübner

Co-Investigators: Lee Washburn

R. L. Hayes

Title of Project: Amendment to existing IND 12,459: physiological studies of the pancreas and brain using L-valine 1-^{11}C

I. Objectives of Experiment:

1. To determine whether the L-valine localizes to a higher degree in normal pancreatic tissue than in neoplastic or inflammatory lesions, and whether L-valine-1-^{11}C in conjunction with ^{11}C-1-aminocyclobutanecarboxylic 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 tomograpy.

2. To study the metabolic activity of the brain or specific structures of the brain in patients with post CVA hypertonia, Phenylketonuria (PKU), Huntington's Disease (HD), possibly Cerebral Palsy, and brain tumors by measuring the rate of protein synthesis using L-valine-1-^{11}C 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-valine) 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.

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III. Possible Hazards and Their Evaluation

There are no chemical risks from injecting L-valine in the amounts proposed in this investigation. Adherence to quality control procedures (sterility, pyrogenicity testing) prior to i.v. injection of L-valine-1-^{11}C should eliminate any side effects.

IV. Radioisotopes and New Drugs

L-valine, a natural essential amino acid, will be labeled with carbon-11. The whole body radiation doses from the injection of carbon-11 labeled L-valine 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 March 1, 1981

Signatures: Karl F. Hubner, M.D. Principal Investigator

Lee C. Washburn Co-Investigator

R. L. Hayes "

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

1049473

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
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Medical and
Health Sciences
Division

May 15, 1981

Dr. William J. Gyarfas, Director
Division of Oncology and Radio-
pharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education, and Welfare
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Gyarfas:

Amendment to IND #11,848 - ^{11}C-ACPC

In February of this year we submitted an amendment to IND #12,459 in which we proposed to study patients with various metabolic brain diseases or pancreatic disease using positron tomography and carbon-11-labeled-L-valine. One of the neurological diseases included in the proposal is phenylketonuria (PKU). PKU patients are referred to us from the Medical Center of the University of Michigan, specifically by Dr. Richard J. Allen, Professor of Pediatrics and Director of Pediatric Neurology. The collaborative scientists (Drs. B. Agranoff, S. Gilman, Anne B. Young, and R. J. Allen) are now interested in comparing cerebral uptake and distribution of ^{11}C-L-valine and ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC) in patients with PKU.

We have an IND for ^{11}C-ACPC (11,848), and the internal review board of the University of Michigan Medical Center (Ann Arbor) has approved the use of ^{11}C-ACPC for patients who have PKU. The basis for this request is that ^{11}C-ACPC appears to be valine analog which has several advantages; it is easier to synthesize, and it is easier to measure its rate of utilization in metabolic processes. I have informed Dr. R. Lange, Chairman of the ORAU/ORNL Committee on Human Studies and other members of our internal review board of this expansion in ^{11}C-ACPC patient studies and request FDA approval of this change.

Please let me know if you need additional information to support this request for amending IND #11,848.

Sincerely,

Original signed by CCL

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:KFH:dg

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VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

R. W. Carey
(Signature)

1/29/8.
(Date)

1049475

VOTING FORM FOR PROPOSAL 45b

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

L. Clifford McKee
(Signature)

1/28/81
(Date)

1049476

VOTING FORM FOR PROPOSAL 45b

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

1/26/81

(Date)

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VOTING FORM FOR PROPOSAL 45b

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

William M Lachman

(Signature)

Feb 3, 1981

(Date)

1049478

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓ with consideration of suggestions 1 & 3 below.

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION No.

COMMENT (1) corrected Consent for Research Study: would prefer use of 'control' instead of 'normal'. (2) ok as is Re. application 45b. page 1. para 1, item 1 – I assume "L-value-1-"C with ("C-ACB or L-value-1-"C with ("C-ACPC)" is understood? (3) corrected Protocol page 11 # 8: suggest 'may have' instead of 'will have'

S. J. Fry

(Signature)

1 23. 81

(Date)

corrections made 2/5/81

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VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

1/30/81

(Date)

1049480

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Donald W Goodwin
(Signature)

Jan. 27, 1981
(Date)

1049481

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Ruby A. Miller
(Signature)

Jan. 26, 1981
(Date)

1049482

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Steve Lemm
(Signature)

1/26/81
(Date)

1049483

VOTING FORM FOR PROPOSAL 45b

APPROVE _____

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Principle investigator — not voting

Karl F. Hirsch

(Signature)

1/22/81

(Date)

1049484

VOTING FORM FOR PROPOSAL 45b

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Richard A. Gruesemer
(Signature)

2/4/~~82~~ 81
(Date)

1049485

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

2/12/81

(Date)

1049486

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Martha S. Hansard

(Signature)

4/5/81

(Date)

1049487

VOTING FORM FOR PROPOSAL 45b

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT It would be nice if, on the "Consent for Research Study" form, the first paragraph would read "... on the attached form has been given and explained to me ...."

Howard Fine MD

(Signature)

2/5/81

(Date)

1049488

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-Valine 1-^{11}C

Proposal No.: 45b Date Approved: 2/5/81

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Eight patients (5 Huntington's disease, 2 cerebral palsy and 1 PKU) received ^{11}C-L-valine for P.E.T. brain studies. We have demonstrated that amino acid uptake in the brain can be measured. As expected L-Valine uptake in the patient with PKU was extremely low.
Three patients with pancreatic disease have been given ^{11}C-L-valine for tomographic studies.

2. Report any complications. none

1049489

3. Are there any planned changes? no

4. Do you wish the project to be continued? yes

5. Comments. none

1049490

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner

FROM Dianne Gresham

DATE April 6, 1982

COPIES TO File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049491

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine-1-^{11}C

Proposal No.: 45b Date Approved: 2/5/81

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

L-valine was used in two patients with pancreatic disease and 14 patients with brain disease.

L-valine is useful in conjunction with DL-valine for distinguishing neoplastic from non-neoplastic processes.

2. Report any complications.

No side effects.

1049492

3. Are there any planned changes?

No changes are planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

1049493

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049494

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,349: Physiological Studies of the Pancreas and Brain Using L-Valine-1-^{11}C

Proposal No.: 45b Date Approved: 2/5/81

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No studies were done.

2. Report any complications.

N.A.

1049495

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

Brookhaven National Laboratory has filed an IND for collaborative studies.

1049496

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049497

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Proposal No.: 45b Date Approved: 1976

Signature of Principal Investigator 4/19/85 Date Signed

1. Report progress made in past year:

Administered to 1 patient.

2. Report any complications:

None

1049498

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049499

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-11C (Crook)

Progress

Administered to one patient.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049500

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 28 ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Proposal No. 45b Date 1976

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

One pt studied

2. Report any complications. None

1049501

3. Are there any planned changes? NO

4. Do you wish the project to be continued? Yes

5. Comments.

1049502

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Proposal No. 45b Date Approved: 1976

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

One pt ē Ca pancreas studied

2. Report any complications. None-

1049503

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049504

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Proposal No. 45b DATE APPROVED: 1976

J R Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049505

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049506

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Date Approved: 1976

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049507

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Proposal No. 45b DATE APPROVED: 1976

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049508

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None

1049509

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45b Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C

Date Approved: 1976

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049510

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies

RE: Committee Action on Active Proposals KH

DATE: June 28, 1990

Your project number 45b "Amendment to Existing IND 12,459: Physiological Studies of the Pancreas and Brain Using L-valine 1-^{11}C" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049511

Dr. Gyarfas

PROPOSALS 34C AND 45C

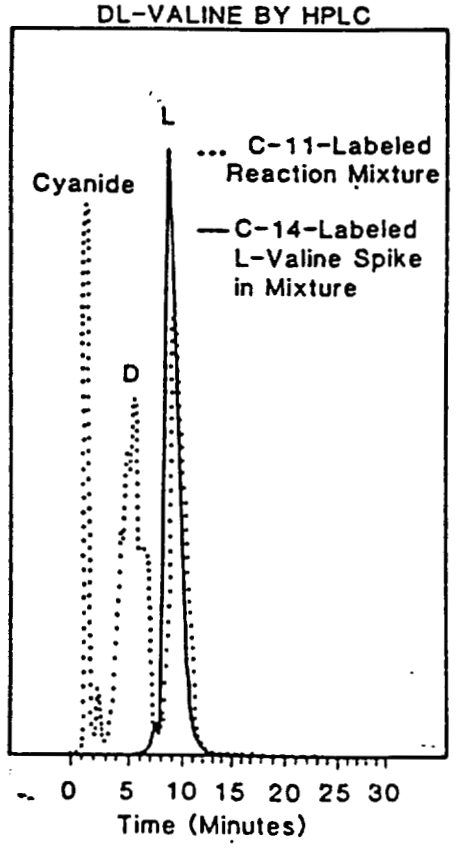
APPENDIX A

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.

RESOLUTION OF CRUDE C-11-LABELED DL-VALINE BY HPLC



1049512

Dr. Gyarfas

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 pre-washed 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.

Effect of Added L-Proline on the Tissue Distribution of L-Valine-1-^{14}C in the Rat at 30 Minutes Postinjection

	Percent Administered Dose/g	
Tissue	L-Valine-1-^{14}C (0.01 mg/kg)	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.

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Amino Acid (valine) Utilization in Pancreatic Diseases (D-valine)

The purpose of this study: is to measure the rate of protein formation (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 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 D-valine 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, and I (she/he) understand(s) that I (she/he) may have to return for one or 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)

1049515

Medical and Health Sciences Division
OAK RIDGE ASSOCIATED UNIVERSITIES

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

1049516

Medical and Health Sciences Division
Oak Ridge Associated Universities

Principal Investigator: _____

Title of Project: Local Brain Metabolism in Brain Tumors and other Non-malignant, brain diseases (D-valine)

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 other non-malignant brain diseases.

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 carbon-11-labeled D-valine 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 or the metabolic aspects of other, non-malignant, brain diseases.

Date _____

_____
Signature of Volunteer

_____
Signature of Parent or Guardian
(when applicable)

1049517

Medical and Health Sciences Division
OAK RIDGE ASSOCIATED UNIVERSITIES

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

1049518

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 45C

Project Title Amendment to IND 12,459 - Amino Acid (valine) Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and other Non-malignant, brain diseases (D-valine)

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

The Expedited Review Committee (Garrett, Koons, and McKee) unanimously approved the amendment.

Approve X

Disapprove ____

1049519

Robert D. Langer, MD
Chairman of Committee

8/22/83

VOTING FORM FOR PROPOSAL 45C

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

8/12/83

(Date)

1049520

VOTING FORM FOR PROPOSAL 45C

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

Melvin E. Koons

(Signature)

July 26, 1983

(Date)

1049521

JUL 27 1983

VOTING FORM FOR PROPOSAL 45C

APPROVE ____X____

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____

_____

E. C. M. R.

(Signature)

7/23/83

(Date)

1049522

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

Title of Proposal: Amendment to IND 12,459 - Amino Acid (valine) Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and other Non-malignant, brain diseases (D-valine)

Proposal No.: 45C Principal Investigator: Karl F. Hübner, M.D.

Date of Approval: 8/12/83 Date of Disapproval: _____

Acknowledgment of Principal Investigator:

Karl F. Hübner

Signature

8/25/83

Date

The Expedited Review Committee (Garrett, Koons, and McKee) unanimously approved the study.

1049523

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45c Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)

Date Approved: 1983

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049524

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by **May 17**. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45c Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)

Proposal No. 45c DATE APPROVED: 1983

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049525

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None

1049526

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 45c Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)

Date Approved: 1983

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049527

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 45c "Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049528

Oak Ridge Associated Universities

Memorandum

To Dianne Gresham

From Dr. Hubner KFH

Date July 14, 1983

Copies to Drs. Hayes, Lange, Lushbaugh, file

Subject AMENDMENT FOR IND's 12,967 and 12,459

Attached are two drafted letters to Dr. Gyarfas in which we request approval of an amendment to IND's 12,967 and 12,459. These IND's have been amended once before for ^{11}C-L-tryptophan and ^{11}C-L-valine. Now we are proposing to use the D-forms of these two amino acids. Of course, before we can send the letters to FDA our human use committee has to approve the amendments first.

I am submitting the amendments to the committee with a request for an expedited review.

NOTE TO THE REVIEWERS: The table on dosimetry is not completed as yet. We anticipate no significant differences between the doses from the L-forms and the D-forms. We are in the process of doing tissue distribution studies involving ^{14}C-D-valine and ^{14}C-D-tryptophan for the requested dose calculations for review and approval by the ORAU/MHSD Radionuclide Committee. I shall notify the Human Use Committee of the decision of the Radionuclide Committee and present the completed dose table. For the purpose of saving time, the information on the dosimetry in the letter has been written prae factum.

bbc

1049529

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division
(615) 576-3480

TO: ORAU/ORNL Committee on Human Studies
Expedited Review Committee (Garrett, McKee, Koons)

FROM: Dianne Gresham

RE: Amendments to Proposals 39C and 45C

DATE: July 21, 1983

Please review the enclosed amendments for Proposals 39C and 45C submitted by Dr. Karl Hübner. The attached cover memo is an explanation by Dr. Hübner of his intentions.

A self-addressed envelope is enclosed for your convenience. Please return the voting form to me by August 4, 1983.

dg

Enclosures

cc: Dr. Robert Lange
Committee Chairman

1049530

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and Health Sciences Division
615/576-3090

August 15, 1983

Dr. William J. Gyarfas, Director
Division of Oncology and Radio-
pharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas: Re: IND 12,459

This letter constitutes a request for approval of an amendment to IND 12,459. The original IND for the clinical use of 11C-DL-valine was amended once before on November 6, 1981, at which time we proposed to use the levo active form of 11C-valine for physiological studies of the pancreas and brain. In this amendment we propose the use of 11C-D-valine for similar studies.

Background:

The rationale for the first amendment was to have the racemic mixture and the L-isomer of 11C-valine available for double radiotracer studies in the differential diagnosis of cancer of the pancreas. Based on results of animal studies obtained by Tamemasa and co-workers (Gann. 73:147-152, 1982) pancreatic cancer would be expected to concentrate the D-form of the amino acid to a much higher degree than the L-form. In radionuclide imaging of pancreatic cancer the 11C-D-valine would tend to give a positive ("hot spot") image of the tumor and the 11C-L-valine would concentrate more in the normal pancreatic tissue and show the tumor as a cold spot. This seems to be the case, as we have seen in a few clinical studies. But a direct quantitative comparison of the distribution pattern of 11C-D-valine and 11C-L-valine is not possible if the D isomer has to be injected with an equal amount of the L isomer as is present in the DL-form. We, therefore, propose to use 11C-D-valine for this purpose in an attempt to develop an improved imaging agent for the diagnosis and metabolic studies of pancreatic cancer. Also, 11C-D-valine may be advantageous in localizing brain tumors and in studying metabolic brain diseases.

1049531

Production of ^{11}C-D-valine:

In the first amendment for IND 12,459, the procedure for the production of ^{11}C-L-valine by high-performance liquid chromatography (HPLC) has been described in detail. The production method of ^{11}C-D-valine is exactly the same with the exception of the time of recovery or collection of the ^{11}C-D-valine which comes off the column before the L-form. A copy of the procedure is attached as Appendix A.

Toxicity.

In Appendix B the toxicity as it relates to the HPLC procedure and the chemicals involved in it is described for the production of ^{11}C-L-valine. The same information applies for ^{11}C-D-valine since it is produced by exactly the same technique.

The chemical toxicity (LD_{50}) of unlabeled L-valine in rats after intraperitoneal injection is 5380 mg/kg and the D-isomer is reported as being even less toxic (Gullino, P, et al, Arch. Biochem. Biophys. 58:253, 1955). The amount of D-valine we are proposing to use in humans (0.1 mg/kg or less) is approximately 50,000 times below the LD_{50} dose for rats for L-valine and even less than that of D-valine. In our experience with ^{11}C-DL-valine (47 doses) there has been no observable toxic effect in humans at these dose levels. Accordingly, ^{11}C-D-valine by itself should not be toxic either, as has been shown in animal experiments. The original IND 12,459 and the amendments (^{11}C-L-valine and ^{11}C-D-valine) have been approved by the ORAU/ORNL Committee on Human Studies.

Radiation Dosimetry:

The radiation dose to the patient from ^{11}C-D-valine will be essentially no different from that obtained with ^{11}C-DL-valine. This dose has been approved by the FDA under the current IND 12,459 and by the M&HSD ORAU Medical Radionuclide Committee. The radiation dose is relatively small because of the short half life of carbon-11 (20.4 min). The estimated radiation dose from ^{11}C-D-valine was calculated by the ORAU Radiopharmaceutical Internal Dosimetry Information Center making the assumption that none of the injected ^{11}C-D-valine is excreted and that complete decay of the ^{11}C-label occurs in situ after initial distribution in a 70 kg human. The table below gives the expected radiation dose to the various organs in the human estimated from animal data. ^{11}C-D-valine was approved for human use by the M&HSD, ORAU Medical Radionuclide Committee.

Estimated Radiation Dose from ^{11}C-D-valine to Organs in Man*

Tissue	Radiation Dose (rads/mCi)
Total body	0.011
Pancreas	0.046
Liver	0.008
Spleen	0.012
Kidney	0.016
Bone marrow	0.012
Lung	0.012
Small intestine	0.013
Ovary	0.011
Testis	0.009

* Based on the 30-minute tissue distribution in male and female rats following intravenous administration of ^{11}C-carboxyl-labeled D-valine (0.2 mg/kg) assuming immediate uptake and no further change in distribution.

Clinical Studies:

In this amendment we request permission from the FDA to use the diagnostic radiopharmaceutical ^{11}C-D-valine in patients with the following proven or suspected diseases: pancreatic cancer, other neoplasms, and non-neoplastic pancreatic or neurological diseases.

Patient Selection Criteria:

During the first year the investigational use of ^{11}C-D-valine will be restricted to three clinical problems: cancer of the pancreas (suspected or proven), brain tumors (suspected or proven), and non-neoplastic focal or diffuse brain disease. In patients having these conditions ^{11}C-D-valine will be compared to ^{11}C-valine or ^{11}C-ACBC (IND No. 13,867) to determine whether the combination of the two forms of valine improves the differential diagnostic approach (especially to pancreatic cancer) and whether the D-form of valine is a better tumor imaging agent than ^{11}C-ACBC.

In patients with non-malignant focal or diffuse brain disease, the objective of the study is to determine to what extent the two forms of the amino acids localize in intracerebral focal abnormalities and whether ^{11}C-D-valine is a suitable agent to measure amino acid transport in the brain.

The number of patients in each of these categories is not expected to be any higher than 5 (total of 20).

Protocol/Procedures for Patients with Pancreatic Diseases:

1. Patients will be instructed to have nothing by mouth after breakfast except water. They will be encouraged to drink one milkshake 30 minutes before the ^{11}C-D-valine 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 15-20 mCi of ^{11}C D-valine 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 D-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.

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.

Protocol/procedures for patients with brain diseases (neoplastic and non-neoplastic).

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. The 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 15-20 mCi of ^{11}C-D-valine 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. ECAT 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.

Non-malignant neurological disorders. Patients to be included in this study are epileptics (focal epilepsy) and patients with Huntington's Disease or phenylketonuria (PKU) as discussed in the first amendment to this IND. The total number of patients to be studied should not exceed 10/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 ^{11}C-D-valine 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.

5. Following the transmission scans the patient will remain on the scanning table. A dose of 15-20 mCi of ^{11}C-D-valine 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. 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 D-valine concentration by HPLC..

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 head will be scanned a second time using the same four planes. The procedure should not exceed 90 to 120 minutes, and the study may be repeated at some later time.

General Considerations

General considerations for human subjects participating in this study will be the following: 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 C) have been approved by the ORAU/ORNL Committee on Human Studies. Consent will 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 take place in the presence of a nurse, and the patient will be encouraged to ask questions and will be 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 15-20 mCi which is less than 50% of the doses of ^{11}C-DL-valine and ^{11}C-ACBC approved by FDA for a 70 kg person.

Potential benefits include information on the extent of the disease, and possible useful metabolic information on tumor growth for therapeutic decisions. The risk as related to the potential benefits is minimal.

Please consider the proposed application of ^{11}C-D-valine in clinical investigations for approval as an amendment for IND 12,459. If you need additional information, please contact me or Dr. K. F. Hubner, the principal investigator.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

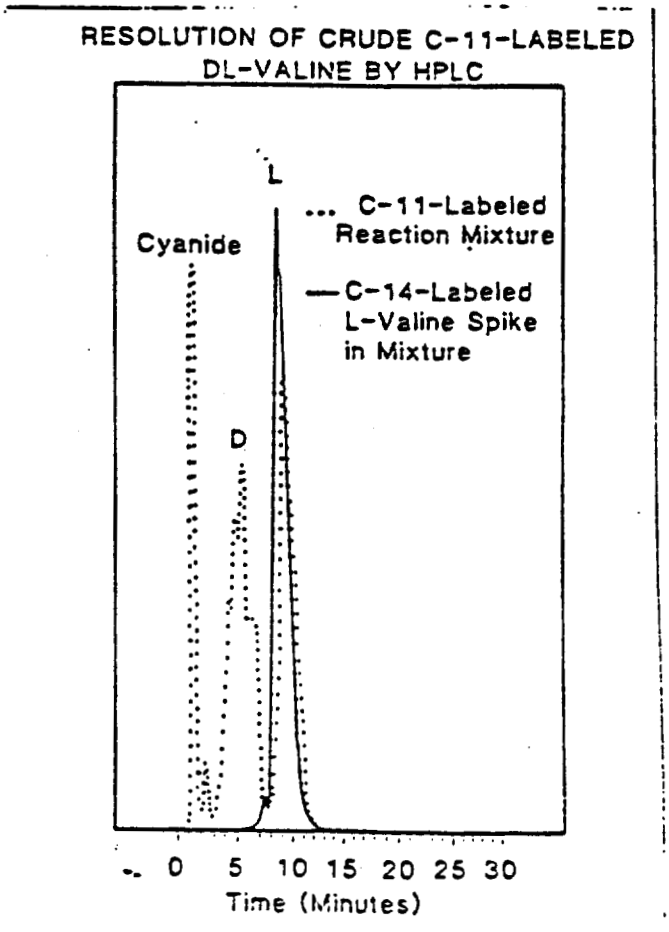
CCL:bbc

1049536

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.



1049537

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Amino Acid (Valine) Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-malignant, Brain Diseases (D-valine)

Proposal No.: 45c Date Approved: 1983

Signature of Principal Investigator

4/19/85
Date Signed

1. Report progress made in past year:

Administered to 2 patients.

2. Report any complications:

None

1049538

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049539

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to Existing IND 12,459: Amino Acid (Valine) Utilization in Pancreatic Disease (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-malignant, Brain Diseases (D-valine)

Proposal No. 45c Date 1983

Signature of Principal Investigator Date Signed 5/14/86.

1. Report progress made in the past year.

one pt. studied

2. Report any complications. None

1049540

3. Are there any planned changes? no

4. Do you wish the project to be continued? yes

5. Comments. —

1049541

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

45c Amendment to Existing IND 12,459: Amino Acid (Valine) Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-malignant, Brain Diseases (D-valine) (Crook)

Progress

Administered to 2 patients

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049542

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45c Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)

Proposal No. 45c Date Approved: 1983

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

One pt c̄ Ca pancreas studied

2. Report any complications. None.

1049543

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049544

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 45c Amendment to Existing IND 12,459: Amino Acid (Valine Utilization in Pancreatic Diseases (D-valine) and Local Brain Metabolism in Brain Tumors and Other Non-Malignant, Brain Diseases (D-valine)

Proposal No. 45c DATE APPROVED: 1983

JE Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049545

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049546

68 Ga - EDTA file

48

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor C. C. Lushbaugh, Ph.D., M.D.

Address Medical & Health Sciences Division, Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, Tennessee 37830

Date April 5, 1977

Name of Investigational Drug Gallium-68 ethylenediamine-NNN'N'-tetraacetic acid (^{68}Ga EDTA)

To the Secretary of Health, Education and Welfare
For the Commissioner of Food and Drugs
Bureau of Drugs (HFD-106)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, C. C. Lushbaugh, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of 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.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested

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by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable ts to investigate the safety of the drug, bearing in mind what own about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will dertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

The specific nature of the investigations to be conducted, er with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review committee. If the phases of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations: that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD-1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same

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procedures, this is acceptable in lieu of the above assurances and a statement to this effect should be provided with the signed FD-1571. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, an additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 6.1 of this chapter.

Very truly yours,

SPONSOR	PER
C. C. Lushbaugh, Ph.D., M.D.	Oak Ridge Associated Universities
	INDICATE AUTHORITY Chairman, Medical & Health Sciences Division

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

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Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

TO: Members of the ORAU/ORNL Committee on Human Studies

FROM: Gould A. Andrews, M.D., Secretary GAA

RE: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

DATE: March 16, 1977

This revised proposal has been submitted by Drs. Gould A. Andrews, Karl F. Hübner, Ray Hayes, and John Purvis, and we would like to have your opinion on it. Please return this form to Dr. Lange in the enclosed self-addressed, stamped envelope.

APPROVE _____

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____
Signature

GAA;dgb

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FORM P-4

MEMORANDUM

TO Bill Byrd

DATE February 11, 1977

SUBJECT DOSE TO BLADDER WALL FROM ^{68}Ga-EDTA

COPIES TO File

When we use your retention data, the radiation dose to the bladder wall from ^{68}Ga-EDTA is 0.98 rad/mCi if we assume a voiding interval of 0.5 hr. If we assume a 1.5 hr. voiding interval, the dose would be 2.6 rad/mCi.

Concerning the radiosensitivity of the bladder wall, I have enclosed a page from Radiation Biology by Alison Casarett. The bladder is not considered to be very radiosensitive but rarely is detailed information found on this. Some of the radiation biologists at the Medical Division may be able to tell you more about this.

Jack L. Coffey

Jack L. Coffey

JLC:np

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from: S.P. Casarett: Radiation Biology 1968 Prentice Hall

frequently occurs in the lungs following exposure of the chest to large doses of radiation. This is characterized by edema (fluid accumulation), followed by hyalinization and fibrosis (thickening of connective tissue) of the alveolar walls. Resulting impairment of ventilatory and diffusion capacities of the lung may be significant in terms of the long-term effects on the animal. Hemorrhage in the lung may occur, also, as a result of changes in the blood vessels. Inhaled radioactive materials deposit in the lung and may produce carcinogenic or other changes.

URINARY SYSTEM

The urinary system is composed of the kidney, in which urine is formed, and the bladder and excretory ducts, through which the urine is removed from the body. The latter are radioresistant structures.

The parenchymal cells of the kidney are radioresistant as far as short-term changes are concerned. Months or years after exposure, however, secondary kidney effects may occur which are due, at least in part, to changes in the blood vessels. For example, a decrease in blood supply (ischemia) will produce hypertension, an increase in blood pressure. This causes a thickening of the walls of renal vessels and, therefore, a decrease in the size of the capillary lumen. The ischemia which follows results in a further increase in blood pressure, and so on. A diminished excretory function, retention of nitrogen, proteinuria (protein in the urine), hematuria (blood in the urine), and diuresis have all been observed in dogs several months after kidney irradiation with moderate to large doses.

MUSCLE AND CONNECTIVE TISSUE

Muscle is among the most radioresistant tissues of the body. Only slight muscular atrophy in rats is produced by localized irradiation with massive doses. Total necrosis may appear if the dose is as high as 72,000 rads. Intermediate doses produce a range of changes from atrophy to necrosis. Greater than 50,000 rads results in early fatigue and decrease in the amplitude of contraction in frog muscles, according to some authors.

Connective tissue has been described as morphologically radioresistant. However, low doses have apparently increased the permeability of dermal connective tissue, as indicated by an increased rate of absorption of intracutaneous saline, glucose, or dyes. It has been suggested that this effect is due to a depolymerization of the mucopolysaccharides which form the ground substance of the connective tissue.

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^{68}Ga-EDTA

Radiation Dose (Rads) from IV Injection of 1 mCi of ^{68}Ga-EDTA

in Man Extrapolated from Rat Data[1]

Bladder Wall Voiding Time (hr)				Total Body	Kidney	Liver	Spleen	Lung	Ovary	Testes
4.8	1.5	1.0	0.5							
5.1	2.6	2.0	1.0	0.051	0.063	0.022	0.028	0.017	0.083	0.076

[1] Dose to all organs except bladder wall was calculated assuming a 4.8 hour voiding interval. Volume of urine in bladder was assumed to be 200 ml.

ORAU Radiopharmaceutical Internal Dosimetry
Information Center

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Oak Ridge Associated Universities

MEMORANDUM

Dr. Ray Hayes — FROM Jack Coffey

DATE February 8, 1977 — COPIES TO Files

SUBJECT RADIATION DOSIMETRY OF ^{68}GA-EDTA

We have calculated the radiation dose from ^{68}Ga-EDTA using the data you supplied. The dose to the total body would be 0.054 rad/mCi if we assumed uniform distribution and no excretion. As you can see from the attached table, this value is not significantly different from the value obtained using your data.

If you have any question, please let me know.

Jack Coffey

Jack Coffey

pr

Attachment

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Radiation Dose from IV Injection of 1 mCi of ^{68}Ga-EDTA

Total Body	Bladder Wall 4.8 hr. voiding interval	Bladder Wall 1.0 hr. voiding interval	Kidneys	Liver	Spleen	Lungs	Ovaries	Testes
0.051	5.1	2.0	0.063	0.022	0.028	0.017	0.083	0.076

1. Based on animal data of Hayes et al.
2. Dose to all organs except bladder wall was calculated assuming a 4.8 hour voiding interval.

Radiopharmaceutical Internal Dosimetry
Information Center

February 8, 1977

1049555

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.

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).

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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.

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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.

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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.

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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.

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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 Body	Kidney	Liver	Spleen	Lung	Ovary	Testes
4.8	1.0	0.5							
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.

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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.

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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 pati[illegible] will be expected to drink several glasses of water before and during the pr[illegible]e.

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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.

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Palo Alto, California 94301

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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

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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

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

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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

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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.

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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

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Oak Ridge
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Medical and
Health Sciences
Division

April 7, 1977

Dr. Robert Lange
Assistant Director
The University of Tennessee Memorial
Research Center and Hospital
1924 Alcoa Highway
Knoxville, Tennessee 37920

Dear Bob:

It turned out that your five responses on the gallium-68 EDTA proposal make up a majority of the Committee; and thus, we felt we could go forward with the IND. Therefore, I did not make calls to the other members of the Committee that have not been heard from. Perhaps, you and I can get in touch in another week or two if there are still some who have not responded.

Sincerely,

Andy

Gould A. Andrews, M.D.

GAA:dgb

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REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. (9/29/77 Minutes) ~~Gould A. Andrews, M.D.~~ Ident. No. 48

Project Title ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

The first five patients are to be studied with special attention to the bladder dose and further investigations will depend upon the outcome of this study.

4. Other committee comments:

Approve ✓

Disapprove ____ 1049581

Robert W. Lang, M.D.
Chairman of Committee

27 April, 1977

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

MAY 2 1977

IND 13,383

Date 5/7/77

Copies to R. Hayes
Dr Hirhus

C. C. Lushbaugh, Ph.D., M.D.
Medical & Health Sciences Division
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 13,383

Sponsor: C. C. Lushbaugh, Ph.D., M.D.

Name of Drug: Gallium 68 EDTA Injection

Date of Submission: April 5, 1977

Date of Receipt: April 7, 1977

As sponsor of the clinical study proposed in this IND you are now free to obtain supplies of the investigational drug, but it is understood that studies in humans will not be initiated prior to 30 days after the date of receipt shown above. If, within the 30 day period, we notify you of serious deficiencies which require correction before human studies can begin or which require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

1049582

MAY 0 5 1976

All future communications concerning this IND should be forwarded in triplicate, identified with the IND number assigned, and addressed as follows:

Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM 17B-34
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

William J. Gyarfas

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

044

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).

1049584

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 $\pm$ 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.

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.

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.

1049590

April, 1976

New England Nuclear
Atomlight Place
North Billerica, Mass. 01862

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	Castrointestinal 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.

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.

1049593

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)

1049594

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
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1049595

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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

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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

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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.

1049601

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

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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.

1049603

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.

1049604

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. I., 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.

1049605

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.

1049606

Ident. No. 48

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: Karl F. Hübner, M.D. (9/29/77 Minutes) ~~Gould A. Andrews, M.D.~~

Co-Investigators: Karl F. Hübner, M.D.

Ray Hayes, Ph.D.

John Purvis, M.D.

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

I. Objectives of Experiment:

To evaluate ^{68}Ga EDTA in three clinical applications (1) as a detector of brain tumors and other brain lesions, (2) as a detector of soft tissue neoplasms in various parts of the body, and (3) as an agent for evaluating kidney structure and function. We plan to evaluate the agent in conjunction with a new instrument that will give multiple two dimensional patterns of distribution in various sampled cross-sections of the body. This is the emission computerized axial tomograph (ECAT) designed to detect and localize the annihilation radiations from positron emitting nuclides. ^{68}Ga is a positron emitter with a 68 minute half-life; it is readily available from a germanium-68 generator.

Whenever possible, other tests to confirm (or not confirm) the results of the new procedure will be obtained, so that a correct diagnosis can ultimately be arrived at, and an assessment made of the results. These additional tests will consist of a variety of radiologic and laboratory tests, as well as the results of surgery and autopsy when available.

II. Methods of Procedure:

Projects: (1) Detection and localization of brain lesions.
(2) Detection of obscure soft tissue tumors.
(3) Imaging of kidneys and urinary bladder.

1049607

Patient selection criteria are as follows:

Project 1 - Suspected or proven brain tumors and other lesions with a breakdown of the blood-brain barrier.

Project 2 - Only patients with a known diagnosis of malignant disease are acceptable.

Project 3 - Suspected or proven renal lesions, tumors, cysts, or extrinsic lesions.

In each project, a total of 30 patients will be studied over a one to two year period.

Procedures for projects are as follows:

Project 1:

(a) Two glasses of water 30 minutes before injection of scanning agent.

(b) Intravenous injection of 0.23 mCi ^{68}Ga-EDTA/kg body weight or less.

(c) Blood samples (2 ml each) will be drawn through "Heparin lock" from an arm vein 2 min, 10 min, 30 min, and 60 min. after injection for determination of blood disappearance by radioassay.

(d) Transaxial tomographic scans (ECAT) of the head will be obtained. Scanning starts 20 to 30 min. after the dose.

(e) ECAT scanning results will be compared with results obtained with "conventional" nuclear-medical or roentgenographic techniques.

(f) Radioassay of blood samples and urine samples will provide new information for radiation dosimetry estimates for this scanning agent.

Project 2:

(a) Demonstration of presence of tumor by ^{67}Ga-citrate rectilinear scan and by biopsy is required.

(b) Obtain blood and total body background radioactivity before injection of dose.

(c) Two glasses of water 30 minutes before injection of scanning agent.

(d) Intravenous injection of 0.23 mCi ^{68}Ga-EDTA/kg body weight or less at time 0.

(e) Blood and urine samples will be collected as outlined for Project 1.

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(f) Transaxial tomographic images will be made with the ECAT. The level for the tomographic sections required will depend on the known location of the tumor. Scanning will be started 30 min. after injection.

(g) Results of scans will be compared with results of other diagnostic images.

(h) Blood and urinary activity will be used for dosimetry purposes.

Project 3:

(a) Two glasses of water 30 min. before injection of scanning agent.

(b) Intravenous injection of 0.23 mCi ^{68}Ga-EDTA/kg body weight or less at time 0.

(c) Blood samples and urine samples as mentioned for Project 1.

(d) Transaxial tomographic images will be made of several sections of the abdomen including the entire renal area. Scans will be made with the ECAT, starting 30 min. after injection.

(e) Scan results will be compared with IVP, ultrasound, or CT images.

(f) Blood and urinary activities will be used to upgrade dose estimates to the patients.

III. Possible Hazards and their Evaluation

Chemical Hazards

(a) Since the gallium-68 is carrier free, the amounts given will be exceedingly small. Previous experience with radiogallium studies in which added carrier was given have shown little or no toxicity even when the amounts were hundreds of times as large as will be used here.[1]

(b) The vehicle, the chelating agent disodium ethylenediamine - NNN'N' - Tetraacetic acid has been used in doses of 1 gram daily up to 50 mg/kilo of body weight in treatment of hypercalcemia. We propose to give a maximum dose of 17 mgm, which is far below toxic levels.[2]

(c) A very small amount of NaCl (not more than 1 mgm/kilo) and water are known to be safe.

Radiation Hazards

(a) The gallium-68 will give a whole body average radiation dose of 0.8 rad for the maximum administered dose proposed. Most doses will be smaller. We will use the minimal adequate dose for each

purpose. The organ receiving the highest dose will be the urinary bladder, which may receive as much as 30 rads. We will attempt to minimize this by hastening excretion through high water intake and frequent voiding. Doses of the radiopharmaceutical that we will give to young patients with a possible good prognosis will be very carefully considered, and an absolute minimum will be used. No doses will be given to persons under 18 years of age or to pregnant women.

We plan to start with a dose of 0.07 mCi per kilo in five patients and will calculate bladder dose on the basis of excreted urine radioactivity and adjust the final dose to be given to subsequent patients so that the bladder radiation dose will be kept generally below 30 rads.

The above procedures and radiation dose exposures were considered and approved by the ORAU Medical Radionuclide Committee at a meeting held on March 14, 1977.

(b) There may be a small amount of germanium-68 that escapes from the generator. This will be carefully monitored and kept within less than 0.05% of the gallium dose, which would contribute less than 0.06 rad total body radiation exposure.

IV. Radioisotopes and New Drugs

This material has been used clinically in the past and reported in the literature[3,4,5,6] without any untoward effects described. Many of these patients were given smaller doses than we may require for the new instrument, however. The preparation has been administered to over 200 patients altogether.

V. Responsibility of Principal Investigator:

The clinical investigators responsible for the safety of the patients to be studied under this proposal assure safe administration of the radioactive scanning agent at the lowest possible dose, close observation of the patients for undesirable side effects. Each patient (none younger than 18 years) will be properly informed about possible (although unlikely) side effects and the scientific and potential diagnostic value of the procedure before he is asked to sign a consent form. A copy of the consent form to be used is attached.

The investigators are obligated to stop the project if unexpected untoward effects should occur in any of the patients.

1049610

REFERENCES

1. Brucer, M., et al. "A Study of Gallium^{72}." Radiology 61: 534-613, 1953.

2. AMA Drug Evaluations. American Medical Association, Chicago, Illinois, 1971, p. 661.

3. 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.

4. 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.

5. 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.

6. Anger, H. O., and Gottschalk, A. "Localization of Brain Tumors with the Positron Scintillation Camera." J. Nucl. Med. 4: 326-330, 1963.

1049611

Starting Date: _____

Signatures: Donald Andrews Principal Investigator

Raymond J. Hayes Co-Investigator

_____ "

_____ "

Division Review:

The application described above has been reviewed and approved.

Official signing for the Institution:

Signature _____

Title _____

Institution _____

Date _____

1049612

Ident. No. 48

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.

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7. Scans will be made with a special tomographic scanner.
8. The patient may withdraw from the test at any time.

Date: _____ _____
Investigator

Rec. 11-30-77
cc: Dr. Hayes
Dr. Hitner

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

IND 13,383

NOV 21 1977

C. C. Lushbaugh, Ph.D., M.D.
Medical & Health Services Division
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Gallium Ga 68 EDTA Injection.

We have completed our review and have no objection to initiation of your proposed clinical investigation as originally planned, but we request that you submit the following information:

Medical

Protocols should be amended to state prospectively the criteria by which the efficacy of these studies will be evaluated.

Chemical

1. The list of components should be expanded to include ^{68}Ge as the parent nuclide of the investigational drug to be eluted from the nuclide generator. Further, the adsorbant should be in this list.

2. Qualifications of the technical personnel who are responsible for the integrity and uniformity of the drug batch to batch.

3. The positron-photon cow with shield and collecting apparatus should appear in a cutaway diagram to clarify preparation of the ^{68}Ga.

1049615

4. A copy of the gamma ray spectrum from 0-2 MeV should be made part of the Notice.

5. The following additional information on the packaging system:

   a. Type of glass used to fabricate the final drug container. We suggest you refer to the U.S.P. XIX (1975), page 644.

   b. The size of the glass vial and the volume of the drug filled into the vial.

   c. Identification of the manufacturer of the rubber closure, and its formulation. Your supplier may aid you in this regard.

6. We are uncertain whether you measure hydrogen ion concentration or particulate matter in the finished dosage form. Please clarify.

7. An information brochure for clinical investigators should be developed.

You may use a copy of this letter to inform the appropriate licensing agency that the FDA has permitted your clinical investigation of Gallium Ga 68 EDTA Injection.

Please submit the requested information promptly.

Sincerely yours,

for

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

1049616

New England Nuclear

December 12, 1977

Food and Drug Administration
Department of Health, Education, and Welfare
5600 Fishers Lane
Rockville, Maryland 20852

Attention: Ms. Rita Pessotti

Re: DMF 2583

Dear Ms. Pessotti:

This letter will serve as authorization for Dr. R. L. Hayes, Oak Ridge Associated Universities, Medical and Health Sciences Division, to refer to the above Drug Master File Procedure for the preparation of the Gallium-68 Generator. This procedure was submitted by the Nuclide and Source Division of the New England Nuclear Corporation on December 16, 1975.

Dr. Hayes and his associates are authorized to cite this protocol in support of their IND covering the use of this product in their investigations.

Sincerely,

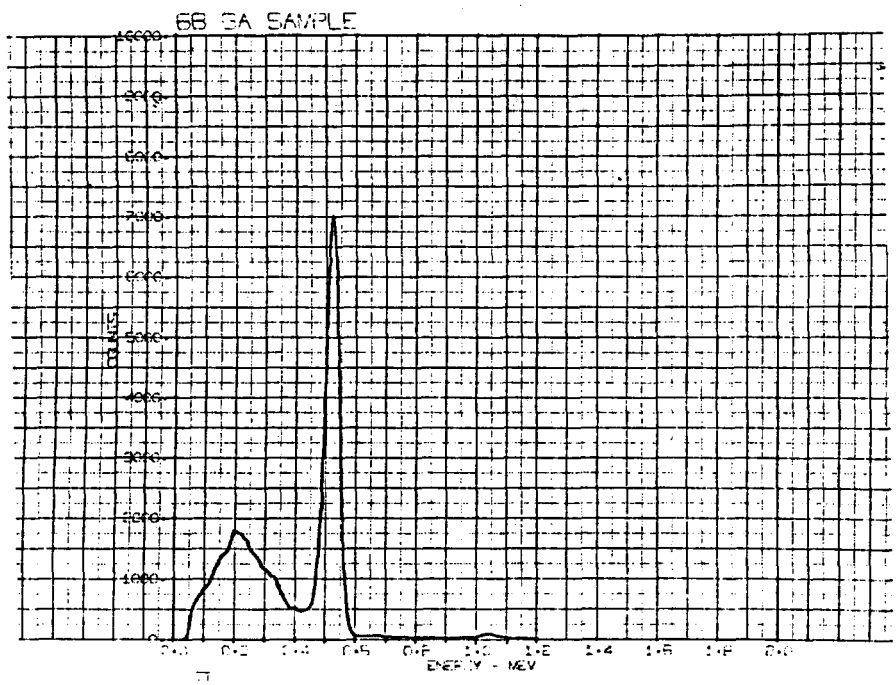
NEW ENGLAND NUCLEAR

Gerald P. Tercho

Gerald P. Tercho
Section Leader, Radionuclides
Nuclide and Source Division

GPT:sm
cc: Dr. R. L. Hayes

1049617



Spectrum of Gallium-68 from 0-2 MeV

AMENDMENT TO CLINICAL PROTOCOL OF IND #13,383
(GALLIUM ^{68}EDTA INJECTION)

The Phase II clinical studies proposed on page 7 and 8 (Section 10 of the original IND) include:

a. Imaging of kidney and bladder

b. Detection and localization of brain lesions

c. Detection of obscure soft tissue tumors

The efficacy of ^{68}Ga-EDTA in conjunction with the Emission Computerized Axial Tomograph (ECAT) will be evaluated by comparing its diagnostic information with the diagnostic value of other radiological methods and agents and/or surgery and autopsy.

For project (a) intravenous pyelograms, echograms, and CT scans will be the conventional diagnostic procedures used for comparison with the experimental approach. However, a patient may or may not have undergone all of these tests before being referred to us. Histologic confirmation of the diagnosis will be sought whenever possible.

Project (b) involves comparing ^{68}EDTA-ECAT scans of the brain with ^{99m}Tc-pertechnetate brain scans and CT-transmission scans. In addition, ^{68}Ga-EDTA will be evaluated especially for its potential to detect strokes earlier than "routine brain scans." Biopsy information will be obtained for neoplastic lesions if possible.

In project (c) the criterion to evaluate ^{68}Ga-EDTA as a potential tumor scanning agent (especially of highly vascular tumors) is diagnostic information obtained by conventional ^{68}Ga-citrate scintigraphy and biopsy or autopsy.

1049619

file under 68Ga-EDTA IND Dr. Hübner

Oak Ridge Associated Universities

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

Medical and Health Sciences Division

December 15, 1977

William J. Gyarfas, M.D.
Director, Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Re: IND 13,383

Dear Dr. Gyarfas:

This letter will act as an answer to the questions raised in your letter of November 2, 1977, regarding our IND 13,383 on Gallium-68 EDTA Injection.

Medical

The clinical studies proposed on page 7 and 8 (Section 10 of the original IND) include:

a. Imaging of kidney and bladder
b. Detection and localization of brain lesions
c. Detection of obscure soft tissue tumors

The efficacy of ^{68}Ga-EDTA when used in conjunction with the Emission Computerized Axial Tomograph (ECAT) will be evaluated by comparing the diagnostic information so obtained with conventional diagnostic methods and/or surgery and autopsy as follows:

For project (a) conventional intravenous pyelograms, echograms, and CT scans will be used for comparison with the ^{68}Ga-EDTA-ECAT approach. A patient may or may not have undergone all of these tests before being referred to us. Histologic confirmation of the diagnosis will be sought whenever possible.

Project (b) will involve a comparison of ^{68}Ga-EDTA-ECAT scans of the brain with ^{99m}Tc-pertechnetate brain scans and CT-transmission scans. In addition, ^{68}Ga EDTA will be evaluated especially for its potential for detection of strokes at earlier times than "routine brain scans." Biopsy information will be obtained for neoplastic lesions when possible.

In project (c) the criteria for evaluating ^{68}Ga EDTA as a potential tumor scanning agent (especially with highly vascular tumors) will be the use of conventional ^{67}Ga-citrate scintigraphy and biopsy or autopsy.

1049620

Chemical

1. In Section 2, the following additions should be made:

e. Gallium-68 Germanium-68 generator (as source of Ga-68).
f. Aluminum oxide (as support for Ge-68).

2. The preparation of this radiopharmaceutical is under the supervision of R. L. Hayes, Ph.D. (see p. 20 of the IND application for biographical material). James E. Carlton, B.S., Chemistry, 1961, Tennessee Wesleyan College, Athens, Tn., has technical responsibility for the preparation and quality control of Gallium-68 EDTA. He has had extensive experience in the preparation of radiopharmaceuticals for human use, both with routine NDA kit preparations and with our institution's investigational preparations and has handled the radiopharmacy involved with eleven IND's. Billy L. Byrd, B.S., Chemistry, 1956, Austin Peay University, Clarksville, Tn., and John J. Rafter, B.S., Biology, 1953, Tennessee Technological University, Cookeville, Tn., act as backups for Carlton in the preparation of Gallium-68 EDTA.

3. A drawing of the NEN Ga-68 generator, as modified by us for maintenance of sterility, is attached. This generator is stored behind a lead brick shield in a laminar flow hood. New England Nuclear has given permission for us to cite their Drug Master File (DMF 2583). See the attached copy of their letter to the Food and Drug Administration.

4. A copy of the annihilation and gamma ray spectrum of Ga-68 from 0-2 MeV is attached.

5. We are using the packaging system supplied by E. R. Squibb and Sons Inc., Princeton, J.J. This is their Evacuated Sterile Collecting Vial, List 08868, intended for use with Squibb's Minitec (Tc-99m) Generator. In answer to your detailed questions concerning this packaging system, the following is pertinent:

a. The glass used is USP Type I. The container is supplied to Squibb by Wheaton Glass Co., Millville, N.J.
b. The capacity of the container system is 20 ml. The final volume of the drug solution is 10 ml.
c. Squibb informs us that the manufacturer of the container closure is Tompkins (list number B0848). It is fabricated from gray butyl rubber by Tompkins.

6. We do not make any measurements for particulate matter in the final drug solution, since as indicated on page 2 of our IND we microfilter the solution during its introduction into the final drug container. However, as a check against the inadvertent use of a ruptured microfilter membrane, the filter is bubble tested immediately after the filtration process. We have not been testing the pH of the Ga-68 generator eluate, since the eluent has in each case been previously adjusted to pH 7.0 (page 2 of our IND).

However, we plan in the future to check the pH of the final saline-Ga-68 mixture using a pH meter and a combination electrode. We, therefore, request that IND 13,383 be changed in section 5 on page 2 of our IND to substitute for the sixth sentence the following statement: "After mixing and testing the pH (7.0 + 0.5) using a pH meter and a combination electrode, the solution will be filtered through a sterile, nonpyrogenic 0.22 μ microfilter (Millipore Corp., Bedford, Mass.) into a precapped, presterilized evacuated vial (E. R. Squibb and Sons Inc., Princeton, J.J., list 08868)."

7. As indicated on page 6 in section 7 of our IND, this radiopharmaceutical will not be used outside of our institution. All investigators involved in this study have received a copy of the original IND application. They will also receive a copy of this correspondence. We feel that preparation of a formal brochure above and beyond the IND material already made available would be redundant, and by its nature probably less informative than the material that has been and will be distributed to our staff.

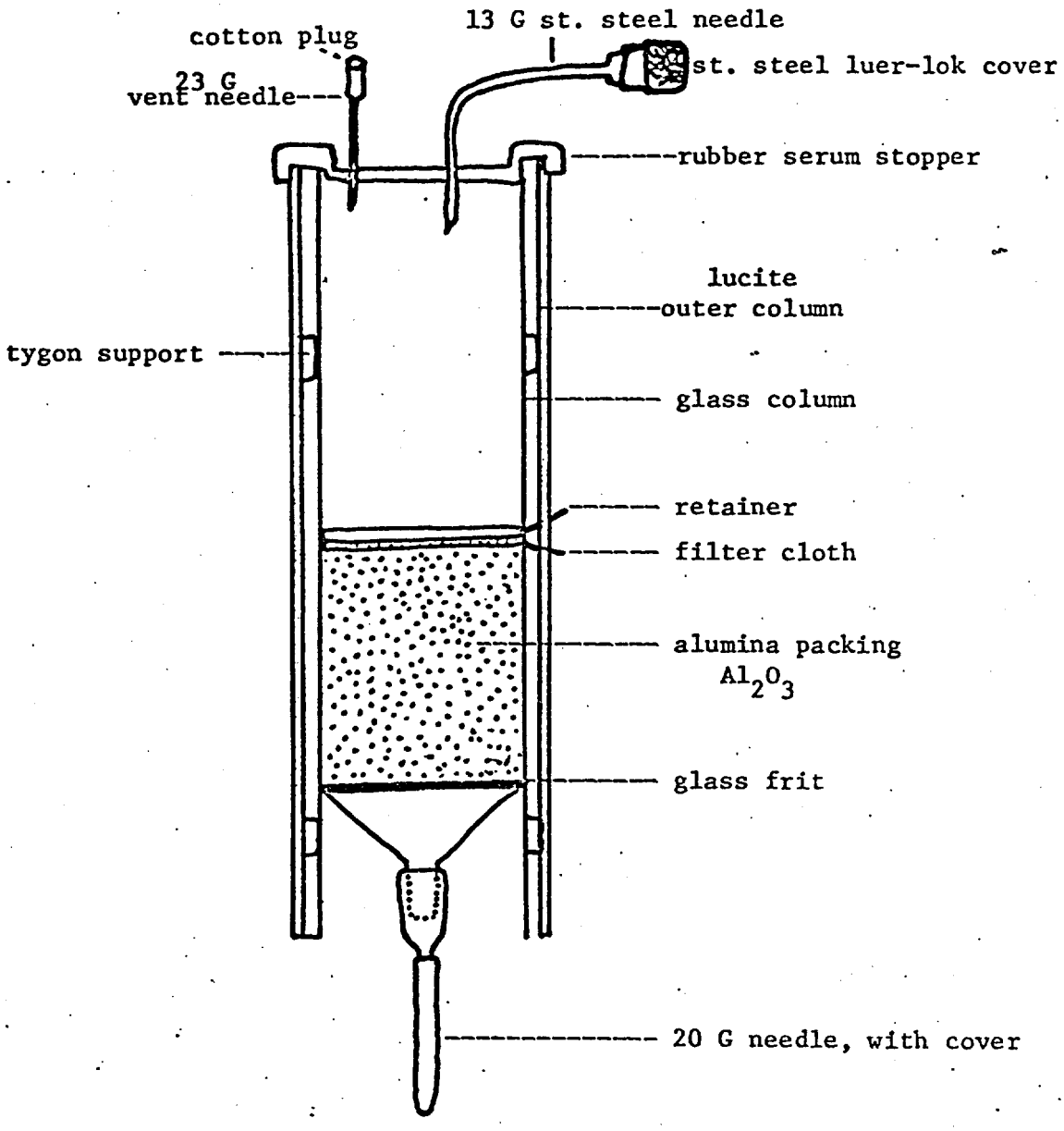
We trust that these answers to your questions concerning our IND 13,383 will meet with your approval.

Sincerely yours,

C. C. Lushbaugh, Ph.D., M.D.

CCL:bbc

1049622


cotton plug
13 G st. steel needle
st. steel luer-lok cover
23 G
vent needle
rubber serum stopper
lucite
outer column
tygon support
glass column
retainer
filter cloth
alumina packing
Al_2O_3
glass frit
20 G needle, with cover

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

August 7, 1978

William J. Gyarfas, M.D.
Director, Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 13,383

This is a progress report on our clinical studies with gallium-68 EDTA (IND 13,383), for (a) imaging of kidney and bladder, (b) detection and localization of brain lesions, and (c) detection of obscure soft tissue tumors.

The gallium-68 EDTA was given to eight patients with proven or suspected brain lesions. Scans were made with an emission computerized axial tomograph (ECAT). The radiopharmaceutical and the procedure is well tolerated; there were no side effects. Initial evaluation of urinary excretion and whole body retention studies indicate that our estimation of maximally 30 rads to the urinary bladder 60 minutes after a 15 mCi dose to a 70 kg person is roughly correct as discussed on page 5 of the IND submitted to your office.

We have found that strokes can easily be visualized with positron emission tomography and this radiopharmaceutical. The number of cases studied is still too small for an adequate comparison with conventional brain imaging with ^{99m}Tc-pertechnetate. We have not had an opportunity yet to look at soft tissue or renal malignancies. Our ORAU/ORNL Committee on Human Studies was informed on July 10, 1978, that this research project continues to be on active status.

Please let me know if you need further information.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman

CCL:dg

1049624

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049625

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hubner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 3/2/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}GA-EDTA FOR STUDIES OF BRAIN LESIONS, SOFT TISSUE MALIGNANCIES, AND KIDNEYS

Proposal No.: 48 Date Approved: 4/27/77

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

No ^{68}Ga-EDTA studies were done since April 1980

2. Report any complications. N.A.

1049626

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes

5. Comments. None

1049627

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No.: 48 Date Approved: April 27, 1977

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

One brain study was done. Brake down of BBB, caused by intracerebral hemorrhage, could be demonstrated in the right occipital lobe.

2. Report any complications. None

1049628

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes

5. Comments. None

1049629

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner **FROM** Dianne Gresham

DATE April 6, 1982 **COPIES TO** File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049630

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No.: 48 Date Approved: 4/27/77

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Ten clinical studies were done with ^{68}Ga-EDTA, all in patients having proven or suspected focal neoplastic cerebral lesions. ^{68}Ga-EDTA is a useful imaging agent for examining the integrity of the blood brain barrier. Also useful in differential diagnosis of tumor versus stroke.

2. Report any complications.

No complications were observed.

1049631

3. Are there any planned changes?

No changes planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

None

1049632

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049633

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No.: 48 Date Approved: 4/27/77

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only two patients were studied during the last 12 months.

2. Report any complications.

No complications.

1049634

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.

1049635

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049636

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

November 14, 1984

M E M O R A N D U M

To: Expedited Review Committee

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: AMENDMENT TO IND 13,383 FOR CLINICAL USE OF ^{68}GA-EDTA
(COMMITTEE IDENT. NO. 48)

Dr. Hübner has requested that I send a copy of this letter from Dr. Crook to you for your information and any comments you wish to make.

1049637

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No.: 48 Date Approved: 1977

Signature of Principal Investigator 4/19/85 Date Signed

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1049638

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049639

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~ 28, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No. 48 Date 1977

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

Six pt. studied

2. Report any complications. None

1049640

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. —

1049641

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No. 48 Date Approved: 1977

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

9 patients studied.

2. Report any complications. None

1049642

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes.

5. Comments.

1049643

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No. 48 DATE APPROVED: 1977

J. R. Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049644

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   None.

1049645

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Date Approved: 1977

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049646

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Proposal No. 48 DATE APPROVED: 1977

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None

1049647

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049648

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48 ^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys

Date Approved: 1977

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049649

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 48 "^{68}Ga-EDTA for Studies of Brain Lesions, Soft Tissue Malignancies, and Kidneys" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049650

Ident No. 48c

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and Health Sciences Division

November 8, 1984

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Gyarfas:

Your attention is called to our original Investigational New Drug Application, IND 13,383 and the amendment of March 9, 1983 to allow us to use the closed-bed ionic ^{68}Ge-^{68}Ga generator obtained from New England Nuclear (NEN), Boston, Massachusetts, as a source of ^{68}Ga for the preparation of ^{68}Ga EDTA for clinical studies.

The radioactivity level of the ^{68}Ge has now decayed to the point where we can no longer obtain quantities of ^{68}Ga adequate for clinical studies. Rather than purchase an entire new generator, we would like to recharge our present one with approximately 10 mCi of ^{68}Ge. Since the ^{68}Ge adsorbs readily to the SnO_2 bed, this can readily and easily be done by passing the ^{68}Ge through the present generator in a 1N hydrochloric acid solution. After the addition of the ^{68}Ge, the column will be thoroughly washed with certified 1N HCl (Fisher Scientific, Fair Lawn, New Jersey) and the eluant measured for ^{68}Ge leakage. The material will not be used unless it conforms to the contamination levels of ^{68}Ge breakthrough from the original generator. In addition, pyrogen and sterility tests will be performed on the eluted solution to assure no contamination has been introduced onto the column. It is felt that since there is no physical alteration of the existing generator, there should be no reason the eluant would contain any products other than these eluted from the generator now in use.

We, therefore, request approval for the use of the ^{68}Ge-^{68}Ga generator system with the modification listed above. Please contact us if you have any questions relative to this request.

Sincerely,

James E. Crook, M.D., Ph.D.
Director, Radiopharmaceutical Development
and Preclinical Nuclear Medicine and
Assistant Director, Clinical Nuclear
Medicine

EC:lmp
bcc: Dr. Lushbaugh

1049651

DIVISION REVIEW:

The above application has been reviewed and approved.

Official signing for the institution:

Signature: Clarence C. Lushbaugh
signing for William W. Burr, Jr.

Title: Chairman, Medical & Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: November 14, 1984

VOTING FORM FOR PROPOSAL IDENT NO. 48c

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

(Signature)

Jan. 19, 1981

(Date)

1049653

VOTING FORM FOR PROPOSAL IDENT NO. 48c

APPROVE ✓

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT Are there any established standards or certifications for this procedure?

(Signature)

3/11/85

(Date)

1049654

VOTING FORM FOR PROPOSAL IDENT NO. 48c

APPROVE X

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

L. C. M.

(Signature)

4/28/85

(Date)

1049655

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Dr. James E. Crook Ident. No. 48c

Project Title AMENDMENT TO IND 13,383 FOR CLINICAL USE OF ^{68}Ga-EDTA

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve ✓

Disapprove _____

1049656

Karl F. Hubner

Chairman of Committee

May 28, 1985

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

February 27, 1985

M E M O R A N D U M

To: Dr. L. Clifford McKee, Jr.

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROPOSAL NO. 48c
AMENDMENT TO IND 13,383 FOR
CLINICAL USE OF ^{68}GA-EDTA

I have not received your voting form on the above proposal. I called your office but had trouble reaching you.

I am enclosing a copy of Dr. James Crook's request (in letter form) and a voting form. For your convenience a stamped, self-addressed envelope is also included.

Enclosures 3

1049657

f up
3/14

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

February 27, 1985

M E M O R A N D U M

To: Dr. A. Seaton Garrett

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROPOSAL NO. 48c
AMENDMENT TO IND 13,383 FOR CLINICAL USE
OF ^{68}GA-EDTA

I have not received your voting form on the above-referenced proposal. I called your office but had trouble reaching you.

I am enclosing a copy of Dr. James Crook's request (in letter form) and a voting form. For your convenience a stamped, self-addressed envelope is also included.

Enclosures 3

1049658

VOTING FORM FOR PROPOSAL IDENT NO. 48c

APPROVE _____

DISAPPROVE _____

BELIEVE MEETING IS NECESSARY FOR CONSIDERATION _____

COMMENT _____

_____

_____

_____

_____

_____

(Signature)

_____

(Date)

1049659

f-up

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. A. Seaton Garrett

From: Dr. Karl F. Hübner, Chairman K. F. Hübner/lmr
ORAU/ORNL Committee on Human Studies

Subject: PROPOSAL NO. 48c
AMENDMENT TO IND 13,383 FOR CLINICAL
USE OF ^{68}Ga-EDTA

In reply to your question about establishing standards, there are three criteria which must be met:

bacterial free

sterile

no significant breakthrough (germanium 68 must be less than .05% of the galium 68 dose)

Dr. Crook's letter request was submitted to FDA over 60 days ago and they have not objected to the amendment.

LMR:slb

1049660

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

April 1, 1985

M E M O R A N D U M

To: Dr. A. Seaton Garrett

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROPOSAL NO. 48c
AMENDMENT TO IND 13,383 FOR CLINICAL USE
OF ^{68}Ga-EDTA

Do you have further questions concerning this proposal?

Dr. Hübner asked me to contact you to make sure his March 20th response to your request concerning established standards satisfied your needs.

Please contact me at 6-3087 if I can be of some service to you.

lmr

1049661

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~ 28, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Proposal No. 48c Date 1985

Signature of Principal Investigator Date Signed

1. Report progress made in the past year.
6 pts studied

2. Report any complications. None

1049662

3. Are there any planned changes? NO

4. Do you wish the project to be continued? Yes

5. Comments.

1049663

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48c Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Proposal No. 48c Date Approved: 1985

Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

5 pts studied

2. Report any complications. None -

1049664

3. Are there any planned changes? NO

4. Do you wish the project to be continued? Yes

5. Comments.

1049665

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48c Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Proposal No. 48c DATE APPROVED: 1985

J E Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049666

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   None.

1049667

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48c Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Date Approved: 1985

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049668

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48c Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Proposal No. 48c DATE APPROVED: 1985

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed.

2. Report any complications. None.

1049669

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None

1049670

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 48c "Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049671

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48c Amendment to IND 13,383 for Clinical Use of ^{68}Ga-EDTA

Date Approved: 1985

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049672

Oak Ridge Associated Universities
(615) 576-3105
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

October 24, 1985

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas:

Your attention is called to our original Investigational New Drug Application IND 13,383 for ^{68}Ga ethylenediaminetetraacetic acid (^{68}Ga EDTA) and the amendments of April 15, 1983, and November 8, 1984. The original IND specified that the source of the ^{68}Ga EDTA would be from elution of an open-bed alumina ^{68}Ge/^{68}Ga generator obtained from New England Nuclear (NEN), Boston, MA, with a 0.005 M solution of EDTA to produce ^{68}Ga EDTA directly. The first amendment (dated April 15, 1983) changed the source of ^{68}Ga to a closed-bed SnO_2 ^{68}Ge/^{68}Ga generator (also obtained from NEN) eluted with 1 N HCI, which must then be evaporated to dryness and reconstituted in 0.005 M EDTA. The second amendment (dated November 8, 1984) provided for the regeneration of the closed-bed SnO_2 ^{68}Ge/^{68}Ga generator by adding approximately 10 mCi of ^{68}Ge to the generator bed.

We now request approval to leave these two amendments in effect and to amend the original IND a third time. We propose to regenerate the original open-bed alumina ^{68}Ge/^{68}Ga generator by passing through the column 10-20 mCi of ^{68}Ge dissolved in 10 ml of 0.005 M EDTA solution, pH 7. A generator that has been recharged in this manner has given a breakthrough of ^{68}Ge well within the requirements stated in the original IND, ~0.02% of the ^{68}Ga eluted. Because the ^{68}Ge contamination level does tend to increase on standing between "milkings," we will wash the generator with 10 ml of sterile EDTA solution, pH 7, on the day before a planned ^{68}Ga EDTA patient administration. For a patient dose preparation, the recharged generator will be eluted with 10 ml of sterile 0.005 M EDTA, pH 7, into a sterile beaker containing 1 ml of sterile 9% aqueous saline. The resulting solution will be adjusted to a final pH of 7.0 ± 0.2, if necessary, and filtered through a 0.22μ microfilter. Sterility and pyrogenicity tests on the recharged generator have been negative, and a pyrogenicity test (using the Limulus Lysate technique) will be carried out on each batch of ^{68}Ga EDTA before administration to patients, as stated in the original IND application.

We have found that having the capability of obtaining ^{68}Ga EDTA directly from the open-bed alumina generator is much more convenient than having to boil down and reconstitute the $^{68}GaCl_3$ from the closed-bed SnO_2 generator. However, being able to use either of the two generator systems for production of ^{68}Ga EDTA, both

of which have proven quite satisfactory, will add a tremendous amount of flexibility to our program in ^{68}Ga-labeled radiopharmaceuticals.

Furthermore, we propose to continue to recharge each of the two generator systems with ^{68}Ge as required to maintain a useable quantity of ^{68}Ga eluate for patient studies. Such recharging has proven to be technically satisfactory and provides a much more cost effective source of ^{68}Ga than having to purchase a new generator each time the ^{68}Ge has decayed to a nonuseable level.

Our Committee on Human Studies has approved this action. Please contact me if you have any questions relative to this request.

Sincerely,

William W. Burr, Jr., M.D.
Chairman, Medical and Health
Sciences Division

WWB:JEC:jal

1049674

DIVISION REVIEW:

The above application has been reviewed and approved.

Official signing for the institution:

Signature: William W. Burr, Jr.
William W. Burr, Jr.

Title: Chairman, Medical & Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: October 24, 1985

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5,~~ 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND 13,383 to allow use of aluminum or tin-based generator

Proposal No. 48d Date 1985

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

Six pt. studied

2. Report any complications. None

1049676

3. Are there any planned changes? No

4. Do you wish the project to be continued? yes

5. Comments.

1049677

ORAU-48D

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title ORAU-48D AMENDMENT TO IND 13, 383 FOR CLINICAL USE OF ^{68}GA-EDTA

Principal Investigator _____

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.	R A Greenwer	✓			
2.	W. E. Kornd	✓			
3.	R. A. Miller	✓			
4.	Kenneth Flatt	✓			
5.	John B. Stern	✓			
6.	William M Cochran	✓			
7.	[illegible]	✓			
8.	Robert W Conger	✓			
9.	Howard Friedman	✓			
10.	Karl F. Hubner	✓			
11.					
12.					
13.					
14.					

Chairman's statement of Committee consensus:

_____

_____

_____
DATE

1049678

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Dr. James Crook Ident. No. 48d

Project Title AMENDMENT TO IND 13,383 FOR CLINICAL USE OF ^{68}Ga-EDTA

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve ✓

Disapprove ____

Karl F. Hubner

Chairman of Committee

October 24, 1985

1049679

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48d Amendments to IND 13,383 to allow use of aluminum or tin-based generator

Proposal No. 48d Date Approved: 1977

Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year.

9 pts studied

2. Report any complications. None

1049680

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments.

1049681

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48d Amendments to IND 13,383 to allow use of aluminum or tin-based generator

Proposal No. 48d DATE APPROVED: 1977

J. R. Crook
Signature of Principal Investigator

6/20/88
Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049682

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   None.

1049683

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48d Amendments to IND 13,383 to allow use of aluminum or tin-based generator

Date Approved: 1977

1. Report progress made in the past year.

   No patient doses administered.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049684

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 48d Amendments to IND 13,383 to allow use of aluminum or tin-based generator

Proposal No. 48d DATE APPROVED: 1977

James E. Crook
Signature of Principal Investigator

6/8/90
Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049685

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes

5. Comments. None.

1049686

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48d Amendments to IND 13,383 to allow use of aluminum or tin-based generator

Date Approved: 1977

1. Report progress made in the past year.

   No studies performed.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049687

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 48d "Amendments to IND 13,383 to allow use of aluminum or tin-based generator" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049688

Ident No. 51

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

Date: September 29, 1977

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigators: R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CLINICAL USE OF ^{11}C-CARBOXYL-LABELED 1-AMINOCYCLOBUTANE-CARBOXYLIC ACID (^{11}C-ACBC) FOR TUMOR DETECTION.

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-carboxyl-labeled 1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) as a potential tumor-imaging agent for positron computerized axial tomography. Whenever possible, the utility of ^{11}C-ACBC will be compared to that of the analogous ^{11}C-ACPC, which has previously been approved by the ORAU/ORNL Committee on Human Studies (Identification Number 38A) and by the FDA as an Investigational New Drug, and to ^{67}Ga-citrate, the most widely-used tumor-imaging agent which, unlike the two ^{11}C-labeled amino acids, can only be studied using single-photon detection.

II. Methods of Procedure:

Patients with known or suspected malignancy will be referred from the Oak Ridge Hospital, East Tennessee Chest Disease Hospital, the University of Tennessee Memorial Research Hospital, and practicing physicians in the East Tennessee area. 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. An informed consent will be obtained from each patient, and minors or 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 offered to obtain voluntary consent. Patients will be recruited specifically for the test with no promise of medical care.

1049689

The unnatural alicyclic amino acid ^{11}C-ACBC will be rapidly synthesized and purified in a hot cell at the Oak Ridge National Laboratory 86-Inch Cyclotron complex. Techniques for the synthesis and purification are exactly analogous to those used for two other ^{11}C-labeled amino acids, ^{11}C-ACPC and DL-valine-1-^{11}C, which have received previous human use approval both from the ORAU/ORNL Committee on Human Studies and the FDA.

The purified ^{11}C-ACBC will be adjusted to pH 7.0 $\pm$ 0.2 and then filtered through a 0.22 μ microfilter into a precapped, presterilized vial. Each dose will be tested by radioassay, and the Pyrotest limulus lysate test will be used to rule out pyrogenicity. The vial containing the ^{11}C-ACBC will finally be labeled as to its content and assay.

Doses not exceeding 0.714 mCi per kg body weight (50 mCi for a 70 kg subject) will be given intravenously. The total weight of ACBC (stable plus radioactive) will not exceed 7 mg for a 70 kg subject, which is far below the toxic level (see Section III).

At short intervals after drug administration (∿15 minutes), scanning will begin using the ECAT (Emission Computerized Axial Tomographic) instrument. 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 previously been approved for that agent. Also, whenever it is feasible, a conventional nuclear medical scan will be obtained using ^{67}Ga-citrate, so that a direct comparison of the three tumor-imaging agents can be made.

If a tumor is visualized, suitable correlations with other diagnostic tests and surgical findings will be made.

III. Possible Hazards and Their Evaluation:

The potential hazards are believed to be minimal. ACBC has been shown in test animals to be extremely nontoxic. An intravenous dose of 2000 mg/kg (20,000 times higher than we propose to use in humans) was well tolerated in mice, and an intravenous dose of 200 mg/kg (2000 times higher) was likewise well tolerated in both the dog and the marmoset, producing no significant gross toxicity or alterations in hematology and clinical chemistry values.

The radiation dose for ^{11}C-ACBC will also be quite small, about 0.01 rad per millicurie or a total of 0.5 rad for a 50-millicurie dose (assuming uniform whole-body distribution).

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 so as to alleviate the problem of radiation dose.

Suitable laboratory tests to look for possible harmful effects, including hematologic and biochemical blood and urine studies, will be done.

1049690

IV. Radionuclides and New Drugs:

In ^{11}C-ACBC, the ^{11}C labels an unnatural, alicyclic amino acid which is analogous to ^{11}C-ACPC, an agent which is currently being used clinically at ORAU. However, ^{11}C-ACBC has been shown in animal tumor systems to have a somewhat greater tumor specificity than ^{11}C-ACPC. The ^{11}C has a half-life of 20.4 minutes and leaves the blood stream quite rapidly.

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 safeguarding 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: October 1977

Signatures: Karl F. Hubner, MD Principal Investigator

R. 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

Title Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date

1049691

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 made available to the US Food and Drug Administration or 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 1049692

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 November, 1977

1049693

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 November, 1977

1049694

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title 51 Clinical Use of ^{11}C-Carboxyl-labeled 1-aminocyclobutane carboxylic acid (^{11}C-ACBC) for Tumor Detection

Principal Investigator Karl Hubner

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.	M. C. Koons	✓		with modifications to consent form as agreed on meeting	9/29/77
2.	M. Goodman	✓		"	9-29-77
3.	T. Thomas	✓		"	9/29/77
4.	William Mahon	✓		with modification of consent for 9/29/77,	
5.	R. D. Lange	✓		" "	
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					

Chairman's statement of Committee consensus:

Committee agrees with the proposal with a modification of the consent form

29 Sept. 1977
DATE

Acknowledgment of submitter:

Karl F. Hubner

1049695

10/13/77
DATE

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 51

Project Title CLINICAL USE OF ^{11}C-CARBOXYL-LABELED 1-AMINOCYCLOBUTANE-CARBOXYLIC ACID (^{11}C-ACBC) FOR TUMOR DETECTION

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve ✓

Disapprove ____

Robert D Lange MD

Chairman of Committee

19 / Oct. / 1977

1049696

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

June 29, 1978

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas:

This letter is in answer to the questions raised in your letter of May 25, 1978, regarding our IND 13,867 for Carboxyl-Labeled ^{11}C-1-Aminocyclobutanecarboxylic Acid (^{11}C-ACBC).

CHEMICAL

1. Section 4 of the Notice (pages 2 and 3) contains complete information on the ingredients used in the synthesis and purification of the investigative drug substance. These ingredients are not, of course, components in the drug solution administered to patients. The purification techniques employed serve to very effectively remove unreacted starting material as well as other impurities.

2. The preparation of this radiopharmaceutical is under the supervision of L. C. Washburn, Ph.D. (see p. 25 of the IND application for biographical material). Tan Tan Sun, B.S., Pharmacy, National Taiwan University, Taipei, M.S., Chemistry, St. Joseph's College, Philadelphia, Pa., has technical responsibility for the synthesis and purification of ^{11}C-ACBC. She has had extensive experience in the preparation of radiopharmaceuticals for human use, having acted in a similar capacity for three other investigative new drugs. James E. Carlton, B.S., Chemistry, 1961, Tennessee Wesleyan College, Athens, TN., has technical responsibility for the final radiopharmaceutical processing and quality control techniques. Washburn is responsible for the pyrogen testing and also acts as a backup for Mrs. Sun. John J. Rafter, B.S., Biology, 1953, Tennessee Technological University, Cookeville, TN., acts as a backup for both Carlton and Washburn in their areas of primary responsibility.

3. Full information on the reaction times and temperature are stated in Section 4 of the IND (p. 3). The pressure is not measured but is simply the vapor pressure of the aqueous solution at 230°C, approximately 400 psi. The pH of the initial reaction mixture is not adjusted; the reagents are simply combined.

1049697

4. Unlabeled ACBC was synthesized by the Bücherer-Strecker technique under conditions similar to those used for synthesis of ^{11}C-ACBC, but on a larger scale. The purified ACBC was submitted to Galbraith Laboratories, Inc., Knoxville, TN., for elemental analysis. Calculated for $C_5H_9NO_2$: C, 52.16%; H, 7.88%; N, 12.17%. Found: C, 52.29%; H, 7.92%; N, 12.20%.

5. The statement in the Notice to which you refer was not intended to imply that TLC is used routinely for determining the purity of ^{11}C-ACBC. The lengthy development time for TLC precludes such determination for short-lived radiopharmaceuticals such as ^{11}C-ACBC ($T_{1/2}$ = 20.4 min). Rather TLC was used to demonstrate that the techniques employed for synthesis and purification of ^{11}C-ACBC did indeed yield a pure product. The TLC chromatograms may be visualized either by ninhydrin development or, when a ^{14}C tracer is used, by means of a spark chamber. A single spot is observed by either method.

a. A drawing of the finished ninhydrin-developed chromatogram which is obtained by spotting ^{11}C-ACBC and ^{14}C-ACBC side-by-side is enclosed. Of course, no difference can be distinguished between the two agents.

b. The R_f value which is obtained for ACBC using Eastman silica gel, Chromagram Sheet 13179 TLC plates and a solvent system of n-butanol: water: acetic acid (100:10:5 v/v) is 0.23.

c. No other detectable zones on the chromatogram are observed.

d. As stated above, it is not feasible to use TLC to detect batch-to-batch differences in the purity of ^{11}C-ACBC. However, a number of batches of drug produced using the standard synthesis and purification techniques were tested by TLC prior to initiation of the human studies. None showed any detectable impurities. In fact, in order for an agent to be eluted properly from both the anion-exchange and cation-exchange columns (p. 3), it must be zwitterionic, and ACBC is the only conceivable product of this type.

6. All inorganic starting materials (ammonium carbonate, ammonium chloride, and potassium cyanide) are used as supplied by the individual manufacturers, as stated on p. 3 of the IND application, and all meet American Chemical Society (A.C.S.) purity specifications. The cyclobutanone used has a boiling point of 99°C and a freezing point of 10°C and is also used as supplied by the manufacturer, Aldrich Chemical Co., Milwaukee, Wis. All reagents used in the synthesis and purification are made up with commercially obtained distilled water (Grand Island Biological Co., Grand Island, N.Y.).

7. The statement to which you refer was not intended to imply that preparations containing pyrogenic contamination are intentionally administered to humans at our institution. In fact, we exercise all feasible precautions to prevent this from happening. The actual meaning of our statement concerning gross pyrogenic contamination is this: Because of the 20.4-minute half-life of carbon-11, it is not feasible to test for pyrogens by the standard U.S.P. procedure using preconditioned rabbits. The alternative Pyrotest Limulus Lysate technique requires one hour for development as described by the manufacturer (Difco Laboratories, Detroit, Mich.) and is thus also not practical. However, we have found that use of a 15-minute development time for the Limulus Lysate test provides a quite sensitive pyrogen test. In fact, our preliminary results indicate that this 15-minute test may be even more sensitive than the U.S.P.-approved procedure using preconditioned rabbits.

8. As stated on p. 4 of the IND, each ^{11}C-ACBC dose is assayed for radioactivity content just prior to administration by means of a pre-calibrated Capintec CRC-10 radioisotope calibrator (Capintec, Inc., Montvale, N.J.). 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 presence of any peaks other than those resulting from the decay of carbon-11 will form the basis for rejection of the preparation.

9. We are using the packaging system supplied by E. R. Squibb and Sons Inc., Princeton, N. J. This is their Evacuated Sterile Collecting Vial, List 08868, intended for use with Squibb's Minitec (Tc-99m) Generator. In answer to your detailed questions concerning this packaging system, the following is pertinent.

a. The glass used is USP Type I. The container is supplied to Squibb by Wheaton Glass Co., Millville, N.J.

b. The capacity of the container system is 20 ml. The final volume of the drug solution is $\sim$ 15 ml.

c. Squibb informs us that the manufacturer of the container closure is Tompkins (list number B0848). It is fabricated from gray butyl rubber by Tompkins.

10. TLC determinations of completely decayed solutions of ^{11}C-ACBC (done 24 hours after preparation of the agent) have shown no radiolytic or other decomposition products present in the preparation. Because of the 20.4-minute half-life, the radiopharmaceutical decays to unusable levels within two hours of its preparation.

11. In accordance with your suggestions, the label to be used with ^{11}C-ACBC will be revised to read:

^{11}C-1-AMINOCYCLOBUTANECARBOXYLIC ACID
(FOR INTRAVENOUS INJECTION)

Assay _____mCi/ml as of _____

Volume_____ml: Batch No._____

Expiration Time_____

CAUTION - NEW DRUG - LIMITED BY FEDERAL LAW
TO INVESTIGATIONAL USE
Oak Ridge Associated Universities, Oak Ridge, TN.

The expiration time will be 2 hours after the vial is filled. In addition, the radioactivity symbol will appear on the vial label.

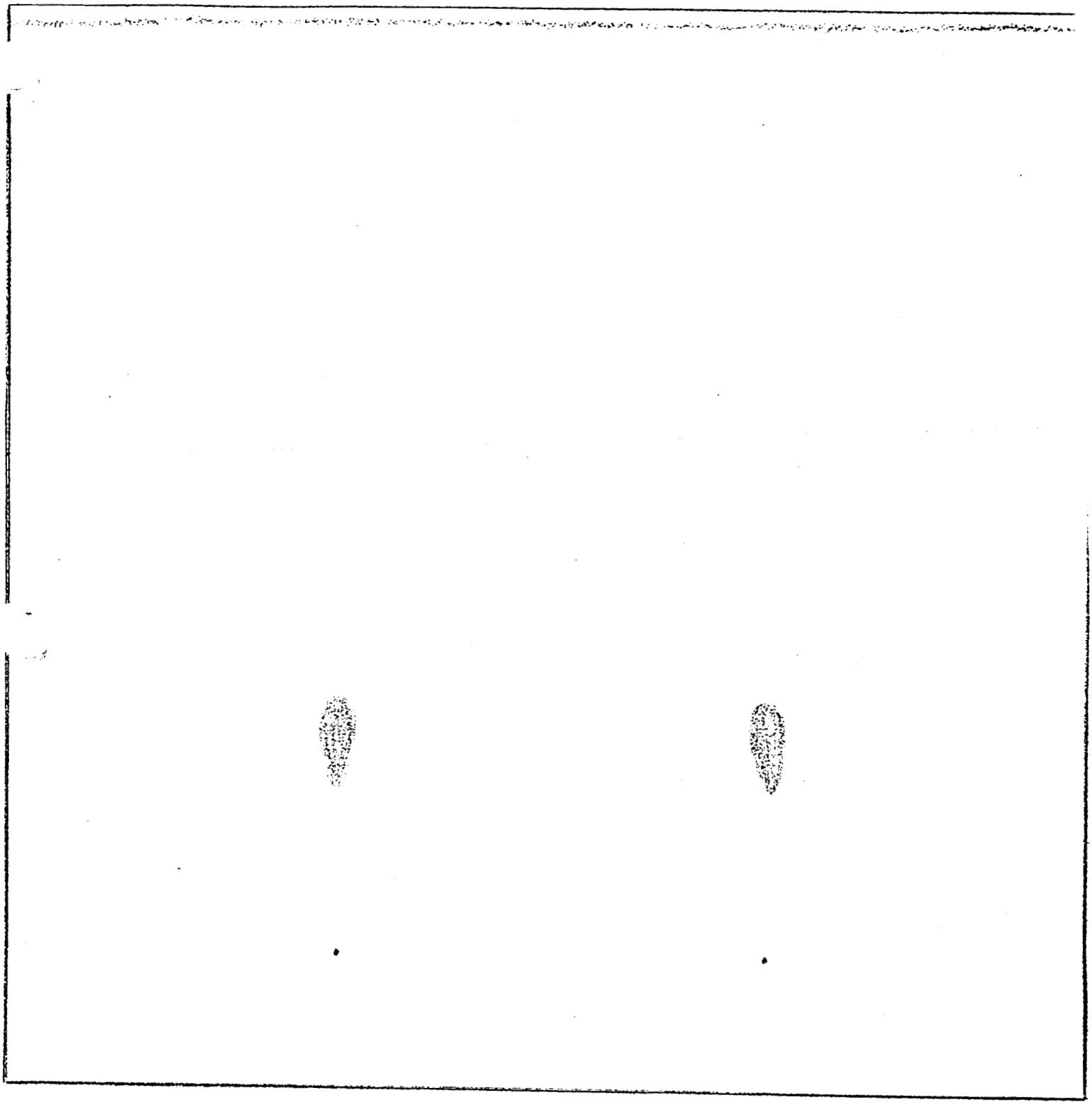
We trust that these answers to your questions concerning our IND 13,867 will meet with your approval.

Sincerely yours,

C. C. Lushbaugh, Ph.D., M.D.
Chairman, Medical and Health
Sciences Division

CCL:bbc

Enclosure



Drawing of the finished ninhydrin-developed TLC plate obtained by spotting ^{11}C-ACBC and ^{14}C-ACBC side-by-side. Dots near bottom of plate are the respective origins and blue line near the top is the solvent front.

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

October 24, 1978

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM 17B-34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 13,867

This is the first progress report on the use of carboxyl-labeled ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) for which an IND had been activated on November 11, 1977.

^{11}C-ACBC has been tested in conjunction with the ECAT scanner in 11 patients with the following diagnosis: bronchogenic carcinoma (3), pulmonary metastasis from primary breast cancer (1), proven or suspected cancer of the pancreas (4), metastatic epidermoid cancer to the liver (1), mesenteric lymphoma (1), and mediastinal tumor (1). The results were of diagnostic value in nine cases and equivocal in two. We have found ^{11}C-ACBC to be valuable as a "dual" scanning agent together with ^{11}C-tryptophan for the diagnosis of cancer of the pancreas or tumors around the pancreas.

We have not observed any evidence for toxicity or other side effects in these eleven patients. ^{11}C-ACBC was used in a dose range of between 10 and 45 mCi. With more experience in emission positron tomography, we now know that doses between 10 to 15 mCi are sufficient for an adequate study. Blood clearance is rapid (90% at 15-20 min) and urinary excretion minimal (1.4% in 1 hr).

Our limited clinical experience with ^{11}C-ACBC in patients with cancer of the pancreas has been included in a paper which will be published in the journal "Radiology." We shall send you reprints of that report as soon as we have them.

Please let us know if you need additional information on the status of this IND.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman, Medical and Health
Sciences Divison

CCL:dg

1049702

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615-576-3098

Medical and
Health Sciences
Division

November 27, 1979

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
Attention: DOCUMENT CONTROL ROOM 17B-34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 13,867

This is the second annual progress report for IND 13,867. Since initiation and approval of this IND, we have used the alicyclic aminoacid ^{11}C-ACBC for 27 studies. The subsequent table lists the different diagnosis on the patient population. I should mention, though, that in a few instances the same patient was examined more than one time. The table lists the total number of studies done in 24 patients.

Diagnosis	No. of Studies with ^{11}C-ACBC
Bronchogenic Ca	3
Pulmonary metastasis (Ca-Breast)	1
Bone metastasis (Ca-Breast)	1
Proven or suspected Ca of pancreas	11
Metastatic epidermoid cancer to the liver	1
Mesenteric lymphoma	1
Mediastinal tumor	3
Pancreatitis	2
Pheochromocytoma	1
Poorly differentiated adeno Ca-metastatic	2
Retroperitoneal tumor	1

The data collected in these studies and the first clinical results are being prepared for publication.

1049703

Some of the results with ^{11}C-ACBC in selected cases have been published recently.

1. Buonocore, E., and Hübner, K. F. Positron-emission computed tomography of the pancreas: A preliminary study. Radiology 133:195-201, October, 1979.

2. Buonocore, E., Hübner, Karl F., and Collmann, I. Reid. Differentiation of retroperitoneal tumor using positron emission computed tomography: A case report. Journal of Computer Assisted Tomography 3(6):825-828, December, 1979.

Copies of the articles are enclosed for your information.

Please let us know if you need more information on the status of IND 13,867.

Sincerely,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:dg

Enclosures (2)

1049704

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Karl F. Hübner, M.D.

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 25, 1980

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 4/4/80.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-labeled 1-aminocyclobutane-carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No.: 51 Date Approved: 1977

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

The total number of patients studied with this compound is 37 as of March 31, 1980. "C-ACBC is an excellent tumor localizing agent and continues to be used diagnostically for pancreatic cancer and other cancers.

Progress has been reported in national and international meetings during 1979 and in publications such as: J. Comput. Asst. Tomogr. 3(6) 825 - 828 1979 and Radiol. 133 195-201, 1979.

2. Report any complications. Last report to FDA 1979

None

1049705

3. Are there any planned changes? none

4. Do you wish the project to be continued?

Yes, we wish to continue the project. With updated SCAT equipment and software we anticipate to use ^{11}C-ACBC as a non-metabolized amino acid analog to measure amino acid extraction of malignant tumors before, during and after treatment courses.

5. Comments. None

1049706

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 3/2/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: CLINICAL USE OF ^{11}C-CARBOXYL-LABELED 1-AMINOCYCLOBUTANE-CARBOXYLIC ACID (^{11}C-ACBC) FOR TUMOR DETECTION

Proposal No.: 51 Date Approved: 10/19/77

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Since April 1980 we have done 15 PCAT studies using ^{11}C-ACBC as scanning agent. ^{11}C-ACBC is an excellent tumor ~~scanner~~ localizer. Preliminary results will be published in the Proceedings of the 1980 IAEA Symposium on Medical Imaging. The last progress report to FDA was prepared on Nov 5, 1980.

2. Report any complications. ~~None observed.~~

There have been no toxic reactions or other untoward effects in any of the patients after i.v. injection of ^{11}C-ACBC

1049707

3. Are there any planned changes?

Essentially no changes ~~except~~ in procedures, except a few selected patients will be studied more than once.

4. Do you wish the project to be continued?

Yes.

5. Comments. None

1049708

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Hübner

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-Labeled 1-Aminocyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No.: 51 Date Approved: October 19, 1977

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Two clinical studies were performed using ^{11}C-ACBC. In ~~two~~ one case cancer of the pancreas could be identified.

2. Report any complications. None

1049709

3. Are there any planned changes? None

4. Do you wish the project to be continued? yes

5. Comments. Slow program because of ECAT-II and system down time

1049710

Oak Ridge Associated Universities

MEMORANDUM

Dr. K. F. Hübner **FROM** Dianne Gresham

DATE April 6, 1982 **COPIES TO** File, Committee on Human Studies

SUBJECT APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE

The Committee on Human Studies approved for continuation Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, 57, and 68. Please report any changes or problems to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1049711

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hübner, ORAU, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-Labeled 1-Aminocyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No.: 51 Date Approved: 10/19/77

Karl F. Hübner 4/6/83

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Three patients were studied during the reporting period: one for detection of a pancreas tumor and two for detection of a brain tumor.
In one case ACBC helped to rule out a neoplasm; patient had arterial venous malformation.

2. Report any complications.

No complications

1049712

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments.

None

1049713

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 ~~483-8411~~ 576-3102

Medical and
Health Sciences
Division

April 15, 1983

William J. Gyarfas, M.D.
Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Re: IND 13,383

Dear Dr. Gyarfas:

Your attention is called to our Investigational New Drug Application IND 13,383 under which we are currently carrying out clinical studies of the use of ^{68}Ga ethylenediamine-NNN'N'-tetraacetic acid (^{68}Ga EDTA). We now wish to amend this IND by substituting for section 4 (Source of New Drug Substance) the following statement: "The ^{68}Ga will be separated as needed from its parent, ^{68}Ge, by elution of a closed-bed ionic ^{68}Ge, ^{68}Ga generator (catalog #IGG-100) obtained from New England Nuclear (NEN), Boston, MA. The eluant will be certified 1 N hydrochloric acid (Fisher Scientific, Fair Lawn, N.J.)."

In our original IND 13,383 it was stipulated that an open-bed alumina-^{68}Ge generator system from NEN would be used as the source of the ^{68}Ga for the proposed ^{68}Ga EDTA studies. This open-bed generator system yields the desired ^{68}Ga-EDTA directly, following elution with a 0.005 M solution of EDTA. The ^{68}Ga EDTA preparation obtained is, however, contaminated with a small amount of ^{68}Ge ($\sim 2\times10^{-3}$% of the ^{68}Ga present). A recently developed closed-bed SnO_2-^{68}Ge generator system (also available from NEN) provides ^{68}Ga in the chloride form with a ^{68}Ge contamination level that is approximately one-tenth that of the alumina-^{68}Ge system, i.e., $1\text{-}2\times10^{-4}$% of the ^{68}Ga present (our verification). Also with this generator system the ^{68}Ge contamination level is not affected by the frequency of generator elution as it is with the alumina-^{68}Ge system. (The ^{68}Ge contamination level in the eluant from the alumina generator tends to increase on standing between "milkings".) For these reasons it is felt that it would now be advisable to use the NEN SnO_2-^{68}Ge generator system as the source for the ^{68}Ga used in the studies involved in IND 13,383. Approval is therefore requested for use of this new generator system as the source of ^{68}Ga for the preparation of ^{68}Ga EDTA (IND 13,383).

1049714

The microfiltered 1 N HCl solution of ^{68}Ga obtained from the NEN SnO_2-^{68}Ge generator system will be evaporated to dryness. After the residual $^{68}GaCl_3$ has first been taken up in 1 ml of 0.005 N HCl, 9 ml of 0.005 M EDTA will then be added. The resulting ^{68}Ga EDTA solution will then be processed as originally outlined in IND 13,383 (see section 5, Methods, Facilities and Controls). We have found this preparation to be sterile and nonpyrogenic. Its biodistribution in rats is the same as that of the original IND 13,383 drug. A low level of stannic tin is present in the 1 N hydrochloric acid eluant ($\leq$ 1 ppm). This we feel, however, is acceptable (see attached pages from the pharmacology manual by Sollmann). Our Committee on Human Studies has approved this action. Please contact us if you have any questions relative to this request.

Sincerely yours,

C. C. Lushbaugh, Ph.D., M.D.
Chairman, Medical and Health Sciences Division

CCL:bbc

Enclosures

1049715

A Manual of Pharmacology, T. Sollmann, M.D., 7th edition W.B. Saunders Co. 1948.

but its mechanism is not understood (C. O. Warren *et al.*, 1944). It occurs when the marrow is denervated (Q. D. Schubmehl *et al.*, 1948). It is preceded by a significant rise in the proportion of reticulocytes. The bilirubin concentration of the serum is slightly increased. Splenectomy may delay the increase of blood cells (Orten, 1935, 1936) and may prevent it (Berwald *et al.*, 1934). In rabbits, the addition of manganese heightens the action (Kleinberg, 1934). It does not occur if the diet is deficient in copper (J. M. Orten, Underhill *et al.*, 1932). In four dogs rendered anemic by milk diet, the feeding of 0.1 mg. of cobalt daily enhanced materially the utilization of added iron and copper (D. V. Frost *et al.*, 1941; review, M. O. Schultz, 1940).

Cutaneous Vasodilatation.—LeGoff, 1930, 1934, reported that hypodermic injection of 10 to 50 mg. of cobalt chloride, citrate or salicylate, in man dilates the vessels of the face and ear, beginning in three minutes and persisting for fifty minutes. The blood pressure falls about 10 mm. No toxic symptoms were observed. The effect occurs also on oral administration; it is not produced by similar doses of nickel.

Blood Sugar.—Bertrand and Macheboeuf reported that cobalt enhances the hypoglycemic action of insulin. Others have failed to confirm this on dogs (Magenta, 1927) and on standardized rabbits (Blatherwick and Sahyun, 1927).

Toxic Actions.—Intravenous injection of 0.5 mg. of cobalt salts into rabbits produces considerable fall of blood pressure (LeGoff, 1930). Canjolle *et al.*, 1944, report prolonged vasodilatation, chiefly by the diminished excitability and tone of the vasomotor center supported by direct action on arterial muscle. Respiration is increased by direct action and reflex stimulation of the center. Peristalsis is increased after transient inhibition. A. Stuart, 1884, reported that intravenous or hypodermic injection of cobalt or nickel salts affects the central nervous system directly, in addition to the usual metal action on capillaries, heart and kidneys. There are tremors, chorea and convulsions, followed by paresis. In frogs the medulla is stimulated before the spinal cord (A. Stuart, 1884). Some tolerance is acquired.

The urine is increased, and always contains sugar, often proteins. Cobalt salts act as antidotes to HCN poisoning, through the formation of cobalt cyanides. To be effective they must be introduced subcutaneously in doses which are not devoid of danger. They are therefore not used in man.

The toxicity of cobalt (and nickel) for rats is diminished by the sulfur aminoacids, especially by cysteine, but not by choline. This suggests that the cobalt produces its toxic effects by fixing the sulfhydryl group, analogous to arsenic (W. H. Griffith *et al.*, 1942).

NICKEL

The pharmacologic significance of this metal appears slight. The metal is extensively used, but is not easily soluble, and the salts are not easily absorbed. They are astringent and irritant on local application. Nickel salts have been used as emetics, but are not to be recommended. Nickel cooking vessels give up a harmless trace of the metal to the food (Dzerzgowski and Schumoff-Sieber, 1906, 1908; Lehmann, 1909). Nickel platers are subject to eczema.

Du Bois, 1932, reported 80 per cent of the workers in nickel plants affected. Gaul and Stand, 1934, found 0.01 to 0.09 mg. of nickel per 25 mg. of fresh tissue in psoriasis lesions, in persons not especially exposed to nickel, and never more than 0.01 mg. in normal skin.

Intravenous injection of nickel salts produces fall of blood pressure and the usual flocculation phenomena. The nickel is *excreted* slowly, chiefly by the urine. The urine contains about two-thirds of the nickel of food (N. L. Kent and McCance, 1941). *Hypodermic* injection into mice and frogs is followed by paralyses (Yamagami, 1928). A. Stuart, 1884, described the same effects that he observed with cobalt salts.

With *excised intestine*, dilute solutions of nickel salts produce primary depression, which may be followed by stimulation. Higher concentrations abolish the movements. Nickel is much less toxic than zinc (Salant and Mitchell, 1916).

Nickel Carbonyl.—This gas—$Ni(CO)_4$—is formed by passing CO over finely divided nickel, as in the Mond process of obtaining pure nickel. The phenomena following its inhalation are serious. There is transient malaise, with quick recovery in fresh air; but after twelve to thirty-six hours the patient becomes dyspneic, cyanotic, febrile and delirious, with a blood-stained cough. Death occurs in four to eleven days, with hemorrhages (due to fatty degeneration of the vessel walls) in the lungs, brain and suprarenal glands, and pulmonary edema (Mond, Langer and Quincke, 1890; Armit, 1907, 1908; Brandes, 1934). It is not absorbed as such, but is decomposed by moisture and deposits absorbable colloidal metallic nickel on the respiratory epithelium.

Metal carbonyls in general are volatile liquids that may be absorbed from the skin. *Iron carbonyl* damages the liver severely.

TIN

Absorption and Fate.—When soluble salts of tin are fed, a small quantity is absorbed and accumulates in the tissues. Of the normal tin income, 50 to 80 per cent is excreted by the urine. After intravenous injection the excretion is also largely by the urine (N. L. Kent and McCance, 1941). When soluble salts are injected hypodermically, elimination occurs slowly, mainly by the alimentary tract, but somewhat by the urine, producing marked injury of the kidneys. Considerable quantities are retained: 20 to 25 per cent in the skin, 5 per cent in the liver (Salant and co-workers, 1940).

The *acute toxicity* of the nonprecipitant stannic or stannous sodium citrate by intravenous injection into rabbits is of the order of sodium citrate, so that the tin salts as such are not acutely toxic. Animals with 25 per cent of the fatal dose recover completely. The tin leaves the blood rapidly. The organ distribution is similar to that of bismuth; the kidneys retain it longest (J. Seifter and Rambousek, 1948). Older observers reported *chronic effects* ranging from gastro-enteritis to ataxia and motor

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A Manual of Pharmacology, T. Sollmann, M.D., 7th edition, W. B. Saunders Co, 1948.

paralyses resembling chronic lead poisoning (White, 1880). Salzer, 1918, reports chronic poisoning resulting from a dental plate of "*Watt's metal.*" There were nervous symptoms and anemia. "*Stannoxyl,*" a proprietary compound advertised for oral and intramuscular administration in boils and styes, was found worthless by J. A. Kolmer *et al.*, 1931.

Tetramethyl tin, when inhaled, causes immediate aliphatic narcosis, followed by temporary paralysis and delayed encephalopathy. Tetra-ethyl tin has similar actions, but is less potent (J. Seifter, 1939).

Tin hydride, SnH_4, is highly toxic to mice and guinea pigs, producing pulmonary irritation and convulsions (F. Paneth and Joachimoglu, 1924).

MERCURY

Mercury, particularly in the mercuric salts, has a strongly toxic action on protoplasm. Mercurial compounds are therefore potent antiseptic agents, but their usefulness is limited by precipitation, irritation and toxic systemic effects. The local actions depend on the mercury ions, and are absent in organic compounds that hold the mercury in molecular form. Intravenous injection of the mercury-fluorescein dyes (mercurochrome, and so forth) produces colloidal "reactions." The water-insoluble mercury compounds are fairly rapidly converted into soluble compounds, and these are absorbed, distributed through all the tissues and excreted by all channels, but mainly by the urine and feces. Traces remain in the body for many months. Acute poisoning presents chiefly the phenomena of local corrosion, followed later by the characteristic features of systemic poisoning, stomatitis, dysentery and nephritis. In chronic poisoning, nervous symptoms and cachexia appear. Calomel is comparatively insoluble, so that it may be employed as a cathartic and diuretic. The relatively nontoxic organic compounds, such as mercurophylline (mercupurin) and mersabyl (salyrgan), are injected intramuscularly or intravenously as active diuretics; this effect is also produced by small doses of inorganic mercurials. Mercury was the earliest and for centuries the only effective agent for the treatment of syphilis.

Local Actions and Uses of Mercurials.—The application of soluble mercury compounds produces antiseptic, stimulant, irritant and escharotic effects. These depend on the concentration of mercuric ions in the solution, and on the precipitation of proteins. The latter is not a simple function of the ionization, for the protein precipitates redissolve in excess of protein and in a variety of other substances, such as the halide salts of alkalis, especially the iodides; and in alkalis, amides, and so on. When these are present in or added to the mercuric salts, the precipitation of protein is diminished or prevented. Solutions that ionize weakly also fail to precipitate proteins, presumably because they always leave a sufficient excess of protein to prevent precipitation. Absence of protein precipitation diminishes local irritation and favors the penetration of the mercury. In the presence of proteins and in complex culture fluids, the *antiseptic action* of such nonprecipitant compounds may therefore appear equal to or greater than that of more highly ionized but more precipitant compounds. From the standpoint of local and antiseptic actions, the mercury compounds fall into three broad groups: (1) the soluble inorganic mercuric salts; (2) the water-insoluble mercury compounds, mostly mercurous, which are dissolved slowly on contact with the tissues; and (3) organic mercury compounds, mercury of which is attached to a benzene ring, and held more or less firmly, so that it ionizes but little.

Ionization of Mercury Compounds.—The following classification is similar to that of F. Mueller, Schoeller and Schraut, 1911, but also takes into account the antiseptic action on yeast cultures, as determined by J. Peterson, 1926. These also give a convenient index of ionization, the restraining effect for equivalent mercury content being expressed in terms of $HgCl_2$ as unit; for instance, "yeast restraint 0.1" signifies that the anti-yeast activity is one-tenth that of mercuric chloride, after making allowance for the difference in mercury content. The individual compounds are arranged according to this coefficient, in descending order. Those in square brackets were not investigated by Peterson, so that their position is conjectural.

Simple Highly Ionizable Inorganic Mercuric Salts.—Yeast restraint, 1.7 to 1; precipitate proteins, but redissolve in excess; greatest local irritation; rust metals; readily precipitated by H_2S = Mercuric chloride ($HgCl_2$). It should be added that the actual ionization of mercuric chloride is not high, but that it can apparently replace the ions readily, so that it behaves chemically as if it were highly ionized.

Moderately Ionizable Mercuric Compounds.—Yeast restraint, 0.6 to 0.35; protein precipitation, slight or absent; irritation relatively slight; rusting of metals slight; precipitated by H_2S = Potassium-mercuric iodide (K_2HgI_4) [or bromide]; mercuric succinimide; sublamine (mercuric sulfate-ethylenediamine); metaphen (aceto-oxymercuri-nitrocresol), requires alkali for solution [Mercurophen (sodium oxymercury-nitrophenolate), Schamberg *et al.*, 1917, 1919].

1049717

Oak Ridge Associated Universities

Memorandum

To Karl F. Hübner, M.D.

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Lange
File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 38a and 38b, 39-39b, 45-45b, 48 and 48a, 51, 54, and 68 at its May 6 meeting. Please report any changes or problems to the Committee Chairman should they occur.

Approval for Proposal No. 57 was postponed until the Committee meets again; in the interim additional information was requested from the University of New Mexico regarding their Human Use Committee's decision on the use of Ytterbium. Since the meeting a copy of your letter dated May 10 to Dr. Lange has been received. It will be circulated with the minutes of the Committee meeting on May 6. Dr. Lange has not sent to me a copy of his reply to your letter. This proposal should be discussed again at the next meeting of the Committee.

Thank you for your assistance and cooperation.

dg

1049718

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-Labeled 1-Aminocyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No.: 51 Date Approved: 10/19/77

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Only one clinical study was done in a patient from the Sloan-Kettering Institute. The study was done at Brookhaven National Laboratory.

2. Report any complications.

There were no side effects or other complications associated with the procedure.

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3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.

1049720

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049721

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No.: 51 Date Approved: 1977

Signature of Principal Investigator

4/19/85
Date Signed

1. Report progress made in past year:

Administered to 15 patients.

2. Report any complications:

None

1049722

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049723

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

51 Clinical Use of 11C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (11C-ACBC) for Tumor Detection (Crook)

Progress

Administered to 15 patients.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1049724

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5~~ 28, 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Clinical Use of ^{11}C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection)

Proposal No. 51 Date 1977

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year. No pts. studied

2. Report any complications. ND

1049725

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments. —

1049726

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 51 Clinical Use of ^{11}C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Proposal No. 51 Date Approved: 1985

J R Crook
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. ——

2. Report any complications. N.A.

1049727

3. Are there any planned changes? NO

4. Do you wish the project to be continued? Yes.

5. Comments.

1049728

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 51 Clinical Use of ^{11}C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Date Approved: 1985

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049729

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 51 Clinical Use of ^{11}C-Carboxyl-Labeled 1-Amino-Cyclobutane-Carboxylic Acid (^{11}C-ACBC) for Tumor Detection

Date Approved: 1985

1. Report progress made in the past year.

   No patient doses administered.

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   Currently evaluating the capability of an in-house 8 MeV cyclotron to produce clinically useful amounts of carbon-11.

1049730

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: October 31, 1983

Principal Investigator: Karl F. Hübner, M.D.

Co-Investigators: Raymond L. Hayes, Ph.D.
Lee C. Washburn, Ph.D.

Title of Project: COPPER-64 CITRATE FOR THE DETECTION OF MALIGNANT LESIONS

1. Objective of Experiment:

The objective of this study is to determine the effectiveness of ^{64}Cu for use in the positron tomographic detection of cancer in humans. Table 1 indicates the specificity that ^{64}Cu citrate has for rodent tumors. Of particular interest will be whether ^{64}Cu can be used to detect malignant processes during the first few hours after administration (see Table 2). Tumor scans with ^{67}Ga citrate normally require 24 h or longer.

II. Methods of Procedure:

Reactor-produced high-specific-activity ^{64}Cu chloride (1 μg Cu/mCi^{64}Cu) will be obtained from Oak Ridge National Laboratory. Following tests for radiochemical purity, the ^{64}Cu will be converted into 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 which will in turn be steam sterilized. The contents of each vial will be tested for pyrogenicity before it is administered. All details of the preparation, quality control and dispensing of each particular ^{64}Cu citrate batch will be kept in a master log book.

The preparation (7 mCi ^{64}Cu/70 kg) will be injected intravenously in a volume of 5 ml or less. The administered dose will contain stable copper at a level of no more than 1 μg Cu/kg and the amount of citrate administered will not exceed 0.1 mg/kg. Scans will be made at 2-6 h and 24 h after ^{64}Cu citrate administration.

1049731

A total of 15 ambulatory patients 18 years or older having known or strongly suspected malignant 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. No pregnant patients will be studied.

III. Possible Hazards and Their Evaluation:

1. Toxicity

There should be no chemical hazard involved with the use of ^{64}Cu citrate, since the maximum level of stable copper administered will not exceed 1 μg/kg. Human blood normally contains copper at a level of 100 μg% (E.J Underwood, Trace Elements in Human and Animal Nutrition, Academic Press, 1971, pp.69).

2. Radiation Dose

This proposal was approved by the ORAU Medical Isotopes Committee on October 31, 1983. Table 3 indicates the human radiation dose estimates that have been made for ^{64}Cu citrate based on ^{64}Cu tissue distribution data in rodents.

IV. 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 Appendix A). The investigator recognizes that he retains the primary responsibility for safeguarding the interests of the participants under study. Any significant changes in methods of procedure or the development of any unexpected risks will be immediately brought to the attention of the Committee on Human Studies.

Starting Date December 19, 1983

Signatures: Kenneth F. Hubner Principal Investigator

R. L. Hayes Co-Investigator

Lee C. Washburn Co-Investigator

1049732

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, Medical and Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: 10-31-83

1049733

TABLE 1.

TISSUE DISTRIBUTION (24 HRS) CU-64 IN RATS BEARING VARIOUS

TRANSPLANTED TUMORS

TISSUES	MORRIS 5123C HEPATOMA	REUBER H-35 HEPATOMA	R-4047 COLON CANCER
Tumor conc. (%/g)*	2.0	3.0	1.1
Ratio tumor conc. to that in:			
Liver	1.0	1.8	0.7
Spleen	3.3	3.2	3.0
Kidney	0.4	0.8	0.3
Lung	3.6	6.3	2.4
Muscle	25.0	61.0	18.0
Femur	11.0	12.0	6.9
Marrow	1.6	2.3	1.0
Blood	3.5	6.8	2.5

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

1049734

TABLE 2.

TISSUE DISTRIBUTION OF CU-64 IN RATS BEARING MORRIS 5123C HEPATOMAS AT VARIOUS TIMES AFTER I.V. ADMINISTRATION OF CU-64 CITRATE

Tissues	Time (hrs) 2	4	6	12	24
Tumor conc. (%/g)*	1.6	1.8	1.6	1.7	2.0
Ratio tumor conc. to that in:					
Liver	0.8	1.1	0.9	0.8	1.0
Spleen	3.7	3.5	2.5	2.9	3.3
Kidney	0.1	0.2	0.3	0.2	0.4
Lung	3.1	3.8	3.1	3.4	3.6
Muscle	13.0	24.0	23.0	21.0	26.0
Femur	7.3	8.3	9.1	8.8	10.6
Marrow	2.1	2.1	1.6	1.3	1.6
Blood	2.4	2.3	2.5	2.0	3.5

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

1049735

TABLE 3.

RADIATION DOSE ESTIMATES FOR THE ADMINISTRATION OF CU-64 CITRATE TO THE STANDARD MAN*

Organ	Rads/mCi	mGy/MBg
Total Body	0.13	0.04
Liver	0.48	0.13
Kidney	1.50	0.40
Bone	0.08	0.02
Bone Marrow	0.17	0.05
Lungs	0.15	0.04
Spleen	0.20	0.05
Muscle	0.10	0.03

*Based on tissue distribution of Cu-64 citrate in the rat.

APPENDIX A

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

CONSENT FOR RESEARCH WAIVER FORM

Patient: _____ Age: _____

Date: _____ Time: _____ AM/PM

I hereby request and authorize _____ M.D.

to perform upon _____ the following
(myself)

diagnostic procedure:

POSITRON TOMOGRAPHIC (ECAT II) SCAN USING COPPER-64 CITRATE.

The purpose of this study is to find out whether copper-64 citrate can be used effectively for the detection of malignant processes using positron tomographic procedures. The study will consist of an intravenous injection of the radioactive scanning agent copper-64 citrate which will be followed by ECAT scanning procedures at approximately 4 and 24 hours after administration.

This test is not a treatment for my disorder nor is it being done primarily for my benefit; it is a test for experimental purposes. ~~I am also aware that no children or~~ pregnant women will be involved in these studies.

Revised for Nov. 16, 1983 committee meeting

A radiation risk from the use of copper-64 is involved in this investigational procedure, particularly to the kidneys, bone marrow and liver. The radiation dose to the bone marrow from the radioactive copper-64 is about 3 times as high as that from x-ray examination of the large bowel. It was explained to me that I may withdraw from the test at any time.

Dr._____ has explained the procedure, possible risks, and complications to me and has given me an opportunity to ask questions.

Since these tests are part of a research program, I do not object if information relating to my case is published in scientific 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.

APPENDIX A

I understand further that, in the event of physical injury resulting from the research procedure described above, only essential medical treatment is available, including hospitalization if required. I also understand that monetary compensation is not available from either Oak Ridge Associated Universities or Oak Ridge National Laboratory for wages lost because of my participation.

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 _____

1049738

MEDICAL RADIONUCLIDE COMMITTEE
Medical Division
Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Dr. Ray Hayes PROPOSAL NO. 83-02

DESCRIPTION: Copper-64 citrate for the detection of malignant lesions.

☒ 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 patient:

Other: Administered Activity ≤ 7 mCi

☐ The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
Jack L. Cossey	✓			10/31/83
Evelyn E. Whatson	✓			10/31/83
Russell D. Vik Jr.	✓			10/31/83
Edgar B. Dardenne	✓			10/31/83

Acknowledgement of Submitter _____ Date_____

- -

Proposal does ✓ does not ___ require approval of Committee on Human Studies.

1049739

Final version

APPENDIX A

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

CONSENT FOR RESEARCH WAIVER FORM

Patient: _____ Age: _____

Date: _____ Time: _____ AM/PM

I hereby request and authorize _____ M.D.

to perform upon _____ the following
(myself)

diagnostic procedure:

POSITRON TOMOGRAPHIC (ECAT II) SCAN USING COPPER-64 CITRATE.

The purpose of this study is to find out whether copper-64 citrate can be used effectively for the detection of malignant processes using positron tomographic procedures. The study will consist of an intravenous injection of the radioactive scanning agent copper-64 citrate which will be followed by ECAT scanning procedures at approximately 4 and 24 hours after administration.

This test is not a treatment for my disorder nor is it being done primarily for my benefit; it is a test for experimental purposes.

I understand that copper-64 used in this investigational procedure is radioactive. The radiation dose to the bone marrow from the radioactive copper-64 is approximately the same as that from x-ray examination of the large bowel.

Dr._____ has explained the procedure, possible risks, and complications to me and has given me an opportunity to ask questions. It was explained to me that I may withdraw from the test at any time.

Since these tests are part of a research program, I do not object if information relating to my case is published in scientific 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.

1049740

APPENDIX A

I understand further that, in the event of physical injury resulting from the research procedure described above, only essential medical treatment is available, including hospitalization if required. I also understand that monetary compensation is not available from either Oak Ridge Associated Universities or Oak Ridge National Laboratory for wages lost because of my participation.

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 _____

1049741

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title PROPOSAL NO. 69 "Copper-64 Citrate for the Detection of Malignant Lesions."

Principal Investigator Karl F. Hübner, M.D.

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.					
2.	John B. Stone per				11/16/83
3.	[illegible]	approve			11/16/83
4.	[illegible]	approve			11/16/83
5.	Kenneth E. Fleet	approve			11/16/83
6.	[illegible]	"			11/16/83
7.	[illegible]	approve			11-16-83
8.	[illegible]	approve			11/16/83
9.					
10.					
11.					
12.					
13.					
14.					

Chairman's statement of Committee consensus:

November 16, 1983
DATE

1049742

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 69

Project Title "Copper-64 Citrate for the Detection of Malignant Lesions."

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:

Approve ✓

Disapprove ____ 1049743

Robert D Tangy MD

Chairman of Committee

November 16, 1983

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

Title of Proposal: COPPER-64 CITRATE FOR THE DETECTION OF MALIGNANT LESIONS

Proposal No.: 69 Principal Investigator: Karl F. Hübner, M.D.

Date of Approval: 11/16/83 Date of Disapproval: _____

Acknowledgment of Principal Investigator:

Karl F. Hübner

Signature

Dec 21, 1983

Date

1049744

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner **From** Blanche Carden B Carden

Date December 13, 1983 **Copies to** Dr. Lange and file

Subject APPROVAL OF PROPOSAL 69 REVIEWED BY COMMITTEE ON HUMAN STUDIES

On November 16, 1983, the Committee on Human Studies approved Proposal 69 with a suggestion that the consent form be modified. These changes have been made, and a copy of the form is attached. Please report any other changes or problems to the Committee Chairman should they occur.

bbc

1049745

APPENDIX A

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

CONSENT FOR RESEARCH WAIVER FORM

Patient: _____ Age: _____

Date: _____ Time: _____ AM/PM

I hereby request and authorize _____ M.D.

to perform upon _____ the following
(myself)

diagnostic procedure:

POSITRON TOMOGRAPHIC (ECAT II) SCAN USING COPPER-64 CITRATE.

The purpose of this study is to find out whether copper-64 citrate can be used effectively for the detection of malignant processes using positron tomographic procedures. The study will consist of an intravenous injection of the radioactive scanning agent copper-64 citrate which will be followed by ECAT scanning procedures at approximately 4 and 24 hours after administration.

This test is not a treatment for my disorder nor is it being done primarily for my benefit; it is a test for experimental purposes.

I understand that copper-64 used in this investigational procedure is radioactive. The radiation dose to the bone marrow from the radioactive copper-64 is approximately the same as that from x-ray examination of the large bowel.

Dr._____ has explained the procedure, possible risks, and complications to me and has given me an opportunity to ask questions. It was explained to me that I may withdraw from the test at any time.

Since these tests are part of a research program, I do not object if information relating to my case is published in scientific 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.

1049746

APPENDIX A

I understand further that, in the event of physical injury resulting from the research procedure described above, only essential medical treatment is available, including hospitalization if required. I also understand that monetary compensation is not available from either Oak Ridge Associated Universities or Oak Ridge National Laboratory for wages lost because of my participation.

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 _____

1049747

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. Hubner, ORAU, M&HSD

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No.: 69 Date Approved: 11/16/83

Karl F. Hubner 4/25/84

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Preliminary testing of reactor-produced ^{64}Cu-citrate done. Pyrogen test (X1) negative; ready for clinical investigations.

2. Report any complications.

N.A.

1049748

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.

1049749

Oak Ridge Associated Universities

Memorandum

To Dr. Karl F. Hubner

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 38a, 38b, 39, 39a, 39b, 45, 45a, 45b, 48, 48a, 48b, 51, 54, 54a, 68, 68a and 69 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1049750

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Crook

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No.: 69 Date Approved: 1983

Signature of Principal Investigator — Date Signed: 4/19/85

1. Report progress made in past year:

Has been utilized exclusively in animal studies.

2. Report any complications:

None

1049751

3. Are there any planned changes?

Yes. Considering expanding its proposed use for detection of soft tissue tumors to include cardiac imaging.

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1049752

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

69 Copper-64 Citrate for the Detection of Malignant Lesions (Crook)

Progress

Has been utilized exclusively in animal studies.

Complications

None.

Changes

Considering expanding its proposed use for detection of soft tissue tumors to include cardiac imaging.

Continuation

Keep active.

Comments

None.

1049753

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5,~~ 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No. 69 Date 1983

Signature of Principal Investigator Date Signed 5/14/86

1. Report progress made in the past year.

New protocol in progress form

— No pt. studied under this proposal

2. Report any complications. None

1049754

3. Are there any planned changes?

4. Do you wish the project to be continued?

5. Comments.

1049755

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 69 Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No. 69 Date Approved: 1983

Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. —

2. Report any complications. N/A.

1049756

3. Are there any planned changes? NO

4. Do you wish the project to be continued? Yes.

5. Comments.

1049757

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and
Health Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 69 Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No. 69 DATE APPROVED: 1983

JE Cro 6/20/88

Signature of Principal Investigator Date Signed

1. Report progress made in the past year.
   No patient doses administered.

2. Report any complications.
   None.

1049758

3. Are there any planned changes?
   No.

4. Do you wish the project to be continued?
   Yes.

5. Comments.
   None.

1049759

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 69 Copper-64 Citrate for the Detection of Malignant Lesions

Date Approved: 1983

1. Report progress made in the past year.

   No patient doses administered

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   yes

5. Comments.

   None

1049760

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 69 Copper-64 Citrate for the Detection of Malignant Lesions

Proposal No. 69 DATE APPROVED: 1983

James E. Crook — Signature of Principal Investigator

6/8/90 — Date Signed

1. Report progress made in the past year. No studies performed

2. Report any complications. None.

1049761

3. Are there any planned changes? No

4. Do you wish the project to be continued? Yes.

5. Comments. None.

1049762

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 69 Copper-64 Citrate for the Detection of Malignant Lesions

Date Approved: 1983

1. Report progress made in the past year.

   No studies performed

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None

1049763

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. James Crook

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 69 "Copper-64 Citrate for the Detection of Malignant Lesions" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1049764