

707754

ORAU/ORNL COMMITTEE ON HUMAN STUDIES
ORAU PROTOCOLS AND RELATED DOCUMENTS
INACTIVE PROPOSALS (FILE 2)

REPOSITORY OAK RIDGE INSTITUTE FOR SCIENCE
EDUCATION, MEDICAL SCIENCE DIV.
COLLECTION OAK RIDGE ASSN. UNIVERSITIES/OAK
RIDGE NATL LAB (ORAU/ORNL)

BOX No. VANCE ROAD FACILITY, Rm. 202A

FOLDER ORAU-30517 FILE 2

1030520

REPOSITORY Oak Ridge Institute for Sciences & Education, Medical Research Div.
COLLECTION Oak Ridge Associated Univ, Oak Ridge Hall Lab (ORAU, ORNL) Comm. on Human Studies
BOX No. Vance Road Facility, Room 202A
FOLDER No file title. Document #
ORAU-30017. File 2

1030521

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

Principal Investigator: R. C. Ricks, Ph. D.

Co-investigators: C. C. Lushbaugh, M. D.
C. L. Edwards, M. D.

Title of Project: Feasibility of Measuring Cognitive and Psychomotor
Functions after Total-Body Irradiation in Man

I. Objective of Study

The objective of this study is to determine the feasibility of using existing cognitive and psychomotor function tests, or procedures adapted from them, to study these functions in consenting in- and outpatients and control volunteers at the ORAU Medical Division.

II. Methods of Procedure

Participating patients (inpatient and outpatient pools) and non-patient volunteers will be selected on the basis of their willingness and availability. Participants will include male and female subjects with age ranging from 15 to 75 years. No patient will be included without prior permission of his attending physician. No patient will be urged to participate and the availability or type of treatment will not depend on participating. Participating patients and ORAU-employed control volunteers will not be paid for participating in these studies. Control volunteers obtained from other sources will receive compensation of at least minimum wage per hour, and transportation costs to and from the ORAU Medical Division.

All subjects will be given, initially and periodically, a simple psychological written test (Multiple Affect Adjective Check List*) to measure their current level of anxiety, depression, and hostility. These negative affects of anxiety, depression, and hostility may bias human performance ability and it is therefore important to obtain a quantitative measure of them prior to psychomotor and cognitive testing. All psychological data obtained will be strictly confidential. Administration of the MAACL is possible only after a consulting psychologist, who is a member of the American Psychological Society, has reviewed the experimental design, how and when the check list is to be used, and is satisfied that the privacy of the test subject has not been invaded. The consulting psychologist, after this review, must sign the purchase order form before the E & I Testing Service will sell check list sheets to non-psychologists. Dr. John Byrne, Oak Ridge Mental Health Center, will serve in this capacity of consulting psychologist.

* Educational and Industrial Testing Service, San Diego, California 92107.

1030522

The feasibility of measuring psychomotor or cognitive performance will be determined using several new, but well-defined, testing procedures. These tests were chosen after a thorough search for well-established background data to determine what functions and mental processes are known to be required of aircrews in the performance of their duties and what means and methods are presently available for measuring capabilities of performing these functions. Those anticipated testing methods for human psychomotor function are:

1. Sternberg critical letter recognition - this test requires a subject to respond with a yes or no to a series of letters in which one to five letters are defined as his critical letter and measure the response time for this recognition.
2. Simple mathematical tests - e.g., adding a column of two-digit numbers.

Any or all of these tasks can be administered over a 1 hour period of time. It is anticipated that daily or three times/week testing periods of <1 hr duration will be used in this experiment. All the above described tasks are simple and require little physical or mental effort on the part of the test subject. Rather, the tasks are designed to present day-to-day real world situations to the test subject. All participating patients will be required to sign consent forms after it is thoroughly understood that this study is not a part of their clinical treatment.

III. Possible Hazards and Their Evaluation:

The possibility exists that a small percentage of the subjects may become frustrated with the tests. Any test subject will, of course, be allowed to drop out of the program at any time. Otherwise, no foreseeable detriment to the test subject is anticipated.

IV. Radiation, Radioisotopes, and New Drugs:

Since this is only a feasibility study for administration of these tests to the described sample population no studies will be done on irradiated patients. No isotopes or drugs will be administered.

If the feasibility can be established, a new proposal will be submitted for evaluation of the effects of total-body irradiation on human cognitive and psychomotor performance.

(For Dr. Ricks' proposal, "Feasibility of Measuring Cognitive and Psychomotor Functions after Total-Body Irradiation in Man")

CONSENT FORM FOR PARTICIPATION IN PSYCHOLOGICAL
EVALUATION AND PSYCHOMOTOR TESTING

I _____, of my own free
will, agree to participate ^(name) in a psychomotor testing program at the Oak
Ridge Associated Universities Medical Division. I understand that these
psychomotor testing procedures (e.g., tests of vigilance, tracking,
coordination, logic, reaction time, mathematics) present little physical
or mental stress and that I may withdraw from the program at any time.

I further agree to a psychological evaluation test (the MAACL
written test) that has been explained to me. I understand that any
information obtained through any psychological evaluation test is
completely confidential.

Data obtained through these studies become the property of the
ORAU Medical Division and may be published in report form.

Date

Signature

Witnesses:

Patients Only: After having read and signed the above statements, I understand
that participation in the psychomotor testing study is not
used as treatment for my disease nor does my participation,
or lack of participation, determine my form of treatment.

(initials)

1030525

(For Dr. Ricks' proposal, "Feasibility of Measuring Cognitive and Psychomotor Functions after Total-Body Irradiation in Man")

CONSENT FORM FOR PARTICIPATION IN PSYCHOLOGICAL
EVALUATION AND PSYCHOMOTOR TESTING

I _____, of my own free
will, agree to participate in a psychomotor testing program at the Oak
Ridge Associated Universities Medical Division. I understand that these
psychomotor testing procedures (e.g., tests of vigilance, tracking,
coordination, logic, reaction time, mathematics) present little physical
or mental stress and that I may withdraw from the program at any time.

I further agree to a psychological evaluation test (the MAACL
written test) that has been explained to me. I understand that any
information obtained through any psychological evaluation test is
completely confidential.

Data obtained through these studies become the property of the
ORAU Medical Division and may be published in report form.

Date

Signature

Witnesses:

Patients Only: After having read and signed the above statements, I understand
that participation in the psychomotor testing study is not
used as treatment for my disease nor does my participation,
or lack of participation, determine my form of treatment.

(initials)

1030526

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator R. C. Ricks, Ph.D. Ident. No. 31

Project Title Feasibility of Measuring Cognitive and Psychomotor Functions
after Total-Body Irradiation in Man

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

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: Risks are small and the information is worthwhile.

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

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

5. Other committee comments: The committee asked that the application be rewritten. This has been done.

Approve

Disapprove

Gerald Andrews
Chairman of Committee

11 December 73

Date

1030527

25 Jan 1974: Cancelled - no patient studies allowed by funding agency

ABSTRACT

Data concerning the effects of irradiation on human cognitive and psychomotor function are limited in scope. Information extrapolated to man from lower animals is questionable due to variation in extrapolation factors among several investigators. The purpose of this current study was to determine what methods were currently available to measure human cognitive and psychomotor functions, and to determine the feasibility of using such methods, to study these functions in consenting, therapeutically irradiated humans. Unfortunately, due to USAF internal restrictions, we were only able to study the effect of sex and age on human psychomotor function in non-patient volunteers (ages 22-60) using a complex (4-limb) coordinator designed by Dr. Randall Chambers, Georgia Institute of Technology, Atlanta, Georgia. During repetitive daily testing over one month's duration each of 18 subjects showed a characteristic initial rapid decrease in performance time as the task was learned and mastered. This phase was followed sooner or later by a second phase characterized by no further decrease in performance time which we have defined as the point of maximal performance capacity. Statistical analysis of learning rates, and maximal performance capacity revealed the following:

1. There was no significant difference in learning and maximum performance capacity with regard to sex, independent of age.
2. Age was the determining factor in task learning and performance capacity with males >45 years showing the poorest performance.
3. Native ability was significantly different when females >45 years vs. females <45 years and males >45 years vs. females >45 years were compared.

1030528

Although not statistically significant, these data demonstrate that females generally learn faster than males and that young males out-performed all other groups. The data further demonstrated that performance errors and anxiety levels in the test subjects were not determining factors in total performance times. We are confident that chronically ill patients would perform in a manner similar to normal volunteers but our confidence does not extend to the acutely ill subject. Finally, we anticipate that this feasibility study might eventually help design an ethical study protocol whereby additional human radiobiologic experience would result.

1030529

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, 1973

Principal Investigator: Melvin M. Ketchel

Co-Investigators: _____

Title of Project: Female Reaction to Sperm Histocompatibility
Antigens

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

Title of Project: Female Reaction to Sperm Histocompatibility Antigens

Ident. No. 32

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date May 1, 1974 if approved and funded.

Signatures: M. M. Kebede Principal Investigator

_____ Co-Investigator

_____ "

_____ "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Bonnie Andrews

Title Chm. Medical Division

Institution Oak Ridge Associated Universities

Date 11 Dec 73

1030531

APPLICATION FOR THE USE OF
HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

October 31, 1973

Principal Investigator: Melvin M. Ketchel

Title of Project: Female Reaction to Sperm Histocompatibility
AntigensI. Objectives of Experiment:

It is now established that female animals may become sensitized to foreign proteins introduced into their reproductive tracts. Our laboratory has previously worked out a reasonable explanation for why women do not become sensitized to seminal plasma proteins. Many laboratories are currently engaged in evaluating the consequences of sensitization to sperm-specific antigens. The goal of the present experiments is to try to find a rational explanation for the fact that female animals (and women) do not seem to become sensitized to the histocompatibility antigens which are now known to occur on sperm. Our hypotheses are that (1) the seminal plasma "masks" these antigens or (2) that women are sensitized to these antigens, but that "blocking antibodies" similar to those which protect the female during pregnancy are also formed.

Most of these experiments will be done on inbred strains of mice. However, if evidence of "blocking antibodies" is found as a result of sensitization with histoincompatible sperm in female mice, we would want to obtain evidence that women also utilize the same protective mechanism. We are suspicious that the extended period of childlessness among women who use contraceptives which, unlike the condom and withdrawal, expose them repeatedly to semen, might lead to lowered fertility when these women attempt to begin their families.

We therefore wish to obtain blood and semen samples from

young couples who have been married for at least 2 years and in which the wife has never been pregnant and has been using the pill or IUD as a contraceptive. We will require 20 ml samples of venous blood from the wife and the husband, and an ejaculate from the husband. Tests on these samples will include MLC's as follows: wife's leucocytes and husband's leucocytes in wife's serum, wife's leucocytes and husband's leucocytes in control serum. In addition, cultures of wife's leucocytes and husband's sperm will be set up with wife's and control serum. If blocking antibodies against histocompatibility antigens do occur in the wife's serum, these tests should demonstrate their action.

It should be emphasized that the experiments proposed for the human will only be done to verify the existence of the system in the human if we can establish its presence in mice. While it is possible that certain cases of unexplained infertility may be explained as a breakdown of the "blocking antibody" system in certain individuals, no evidence for this now exists. Our primary goal in proposing these experiments in humans is to further understand the reproductive process, though we would be prepared to exploit any "fallout" of information in terms of controlling fertility and infertility.

II. Methods of Procedure:

No medication would be given. Twenty ml of blood from the antecubital vein would be taken in a syringe, and the husband requested to provide a fresh ejaculate by masturbation.

We expect to enlist 10 couples to provide us with this material. The experiments might be repeated in those couples in which there was a method failure, or in which the results were inconsistent or provocative.

III. Possible Hazards:

Only the very small risk involved in drawing venous blood is present. Although I am not a physician, I have had extensive experience in taking blood samples. I would like the committee to decide whether I should take the samples, or whether it should be done by a physician.

IV. Radioisotopes and New Drugs:

None.

OAK RIDGE ASSOCIATED UNIVERSITIES

BLOOD AND/OR SEMEN SAMPLE PROCUREMENT,
RELEASE AND PAYMENT AUTHORIZATION

I, the undersigned, do hereby acknowledge that I have on this day, of my own free will and accord, delivered and sold to the Oak Ridge Associated Universities (hereinafter referred to as "Association") twenty cc's of my own blood, by direct vein aspiration, and/or a sample of my own semen.

It is understood that I am to be paid the specified sum by the Association in consideration of which I do hereby release and discharge the Association, its successors and assigns, from all claims, actions and causes of action, at law or in equity, which I do now or may hereafter have against the Association, resulting from or growing out of the sale of said blood and/or semen and its removal from my body. It is further understood and agreed that I am to retain no control whatsoever over the said blood and/or semen or the use thereof.

_____ Blood sample (\$5.00)

_____ Semen sample (\$5.00)

This _____ day of _____, 19__.

Name of donor (please print)

Signature of donor

Mail check to

City

State

ZIP

Witnesses:

Account to charge: _____

Samples received by

Division approval

1030534

CONSENT FORM FOR PARTICIPATION IN PSYCHOLOGICAL
EVALUATION AND PSYCHOMOTOR TESTING

I _____, of my own free
will, agree to participate in a psychomotor testing program at the Oak
Ridge Associated Universities Medical Division. I understand that these
psychomotor testing procedures (e.g., tests of vigilance, tracking,
coordination, logic, reaction time, mathematics) present little physical
or mental stress and that I may withdraw from the program at any time.

I further agree to a psychological evaluation test (the MAACL
written test) that has been explained to me. I understand that any
information obtained through any psychological evaluation test is
completely confidential.

Data obtained through these studies become the property of the
ORAU Medical Division and may be published in report form.

Date

Signature

Witnesses:

Patients Only: After having read and signed the above statements, I understand
that participation in the psychomotor testing study is not
used as treatment for my disease nor does my participation,
or lack of participation, determine my form of treatment.

(initials)

1030535

MEMORANDUM

TO Dr. Andrews

DATE 23 January 1975

SUBJECT Dr. Ketchel

COPIES TO _____

Dr. Ketchel called to say that because of lack of funds they were not able to activate the proposal, "Female Reaction to Sperm Histocompatibility Antigens," (our No. 32), and that it should be put in our inactive file.

Polly E.

PAH

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8111

Medical and
Health Sciences
Division

August 30, 1977

Dr. Melvin M. Ketchel
138 Morningside Drive
Oak Ridge, TN 37839

Dear Dr. Ketchel:

We are updating our list of human studies projects. Your proposal entitled "Female Reaction to Sperm Histocompatibility Antigens" (No. 32) is included on this list.

We assume that you would like to have this removed from the active list, and we will remove it unless we hear something to the contrary from you.

Sincerely,



Gould A. Andrews, M.D.

GAA:dgb

1030537

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Melvin M. Ketchel, Ph.D Ident. No. 32

Project Title Female Reaction to Sperm Histocompatibility Antigens

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

Only those of drawing blood samples.

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:

Worthwhile research

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

As submitted

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

None special

5. Other committee comments:

Additional information requested purely for the interest of committee members .

Approve X

Disapprove _____

Gould A. Andrews
Chairman of Committee
Gould A. Andrews

11 December 73

Date

25 January 1975: Noted !. No funds

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: December 10, 1973

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

Co-Investigator: R. L. Hayes, Ph.D.

J. K. Poggenburg, Ph.D. (ORNL)

Title of Project: ERBIUM-171 AS A CLINICAL SCANNING AGENT FOR THE DETECTION
OF OSSEOUS AND NONOSSEOUS TUMORS

I. Objectives of Experiment:

To determine whether ^{171}Er can be used as an effective tumor-localizing agent in humans. Animal experiments indicate that the higher-atomic-number rare-earth radionuclides show unusual affinities for tumor tissue (Fig. 1, appendix), clear rapidly from normal tissue (Table 1, appendix), and may have the same or better tumor-localizing properties as ^{67}Ga in certain tumor types (Table 2, appendix). This radionuclide also has better bone-seeking properties than do technetium phosphate agents. The half-life of ^{171}Er is sufficiently short so that it may be an effective bone scanning agent. It has good decay photons for scanning (Table 3, appendix).

II. Methods of Procedure:

^{171}Er will be obtained from Isotopes Development, ORNL, as the chloride in dilute hydrochloric acid solution. After conversion to the citrate form, sterilization by Millipore filtration (0.22 micron) and testing for pyrogenicity, 0.15 mCi/kg or less will be administered intravenously (1.0-0.1 mg citrate/kg). A group of 20 adult patients with known cancer will initially be used to evaluate this radionuclide. When possible, comparisons will be made with ^{67}Ga and ^{111}In in the same patient. When bone is involved scans with $^{99\text{m}}\text{Tc}$ Osteoscan will also be made. Further studies with patient volunteers will then be determined after a review by the committee.

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose and at 12-hr intervals thereafter through 42 hours.
2. Individual urine specimens will be collected through the first 2 days.
3. Fecal excreta will be collected through 2 days.
4. Linear scans will be obtained immediately after the dose, at 3-4 hours, and then daily thereafter through 2 days.
5. Whole body and area scans will be made at 3-4 hours after administration (or as soon as practical) and at 24 hours and 48 hours.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Since ^{171}Er will be produced by neutron activation of ^{170}Er (HIFR), stable erbium will be present in this radionuclide preparation (although at only microgram levels).

We propose to administer no more than 10 $\mu\text{g}/\text{kg}$ of stable erbium (and generally much less), since stable rare earths in excess of this amount tend to decrease the relative specificity of rare earth nuclides for tumor tissue (see Table 4, appendix). At a level of 10 $\mu\text{g}/\text{kg}$ or less there should be no toxic effects from the I.V. administration of erbium, since the I.V. LD_{50} in rats for the nitrate is reported to be 36 mg/kg in the female and 52 mg/kg in the male (T. J. Haley, J. Pharmaceutical Sciences 54: 663, 1965).

2. Radiation Dose:

The proposed maximum activity dose as stated in II (Methods of Procedure) is based on a calculated whole body radiation dose of 2 rads (assuming uniform distribution and no excretion) and is thought to be acceptable for the proposed study. Radiation Physics supplied the radiation dose estimates .

^{171}Er decays to ^{171}Tm which has a 1.9 y half life. ^{171}Tm is, however, a weak beta emitter (0.1 Mev) and dose estimates by E. Watson indicate that the whole body radiation dose to be expected from the ^{171}Tm generated by the decay of 1 mCi of ^{171}Er would be only 8.5×10^{-3} rads. If we assume neutron activation of ^{170}Er for 3 half lives of ^{171}Er (87.5% saturation) and the resultant production of ^{171}Tm during this period and also a further decay period of 1 day before administration, the radiation dose from the ^{171}Tm associated with and generated by the decay of 1 mCi of ^{171}Er would be ~ 6 times that produced by the complete decay of 1 mCi of pure ^{171}Er . This would give a radiation dose of ~ 0.5 rads for the maximum activity dose proposed for ^{171}Er . Accordingly, no ^{171}Er will be administered after an individual preparation has decayed for more than 1 day following removal from the pile.

IV. Radionuclides and New Drugs:

¹⁷¹Er will be a new radionuclide in our clinical program. Following approval of this application by the Committee on Human Studies and the ORAU Medical Radionuclide Committee an IND will be filed with the Food and Drug Administration.

V. Responsibility of Principal Investigator:

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

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

Starting Date: February 1, 1974

Signatures: *C. L. Edwards* Principal Investigator
R. L. Hayes Co-Investigator
Kenneth Poggendorf, Jr. Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature: *Donald C. Edwards*
Title *Chm. The Medical Division*
Institution *Oak Ridge Associated Universities*
Date *11- Dec - 73*

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Consent for Experimental Test

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

of the following test: Phase I Radiopharmaceutical Test of Erbium-171.

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

DATE: _____

(Patient or person authorized to consent
for patient)

WITNESS: _____

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

1. This is a new radioactive drug: ^{171}Er - Erbium citrate.
2. The drug contains the element erbium in quantities much less than that required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. The radiation dose will be approximately 2 rads to the whole body.
4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hr, and 42 hrs.
5. All urine and feces will be saved for 2 days.
6. Whole body counts and scans will be made at frequent intervals for 2 days.
7. The patient may withdraw from the test at anytime.

DATE: _____

Investigator

1030542

	160 yb	67 ob								
	6.20	2.00	3.30	2.30	1.20	1.20	3.30	0.63		
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38		
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67		
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20		
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27		
Marrow	5.20	5.10	-	-	-	-	-	-		
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62		
Fluid	-	-	-	-	-	-	3.60	0.36		

1030543

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

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

TABLE 4

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

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

1030544

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

November 30, 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:

In answer to your letter concerning IND 10,680, I can give you the following information.

- (1) The clinical investigators involved in this study have been notified of the discontinuance of the IND.
- (2) The Erbium-171 Citrate was compounded as needed and used promptly because of its limited half-life. Therefore, none is on hand. The stable isotope from which it was made, Erbium-170, was withdrawn only as needed from the Oak Ridge National Laboratory's store of stable isotopes.

We hope that this is the information that is needed.

Sincerely,



Gould A. Andrews, M.D.

GAA:dgb

cc: ✓ Dr. Ray Hayes
Dr. Karl Hübner
Dr. C. C. Lushbaugh

1030545



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

IND 10,680

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated University
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

We acknowledge receipt of your October 12, 1976 communication regarding your discontinued Notice of Claimed Investigational Exemption for Erbium-171 Citrate.

The submission notifies us that clinical investigation has been discontinued because "We are concluding the study at this time."

It is not clear that all clinical investigators have been notified of the discontinuance of your IND. Please verify that all clinical investigators have been notified.

Your communication fails to state the steps taken with regard to the final disposition of any unused drug. The steps taken must be reported before this file may be closed.

We accept your report contained in the above communication as the final report.

If this drug is again subjected to clinical investigation, it is required that we be notified. This may be done by submitting a new IND. Information in this discontinued IND may also be included by specific reference.

Sincerely yours,

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

1030546

NOV 29 1976

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 33

Project Title Erbium-171 as a Clinical Scanning Agent for the Detection of Osseous and Nonosseous Tumors

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

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

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

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

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

5. Other committee comments: None

Approve X

Disapprove _____

Gerald Andrews
Chairman of Committee

11 December 73

Date

25 January 1975: Action, see report

1030547

No. 33 ^{171}Er as a Clinical Scanning Agent for Detection of Osseous and Nonosseous Tumors

Only one patient has received ^{171}Er as yet. The results on this patient were not encouraging.

1030548

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

October 12, 1976

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Dear Dr. Gyarfas:

This is to respond to your recent letter concerning the Notice of Claimed Investigational Exemption for Erbium-171 Citrate.

This preparation has been given to 25 patients without any untoward reactions of any type. It has shown some ability to localize in malignant tissue, but the degree of concentration is not as satisfactory as that of Gallium-67. We are concluding the study at this time, and we're sending you two manuscripts that give further details about the information obtained.

At a later date we will submit a new request for investigational exemption for another radioisotope, Erbium-165, which has different radiation characteristics and which we believe can be studied advantageously with positron emitting equipment. Suitable documentation will be sent when we are ready to start this new investigation.

Sincerely,

Gould A. Andrews

Gould A. Andrews, M.D.

GAA:dgb

Enclosures

"Use of Rare Earth Radioisotopes and Other Bone-Seekers in Evaluating Bone Lesions in Patients with Multiple Myeloma"

"Use of ¹⁵⁷Dy and ¹⁷¹Er as Diagnostic Agents in Cancer"

1030549



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

IND 10,680

OCT 7 1976

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Erbium-171 Citrate.

It is required that a sponsor of an Exemption forward a progress report of clinical investigation at reasonable intervals not exceeding one year. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the proposed plan of study. We have not received a report since your May 5, 1975 submission. We are requesting, therefore, that you promptly report at this time.

In the event clinical study was not initiated or was discontinued during trial, we should be notified promptly. Notification of discontinuance should include the reason therefor, assurance that investigators have been informed, and any steps taken with respect to unused supplies of the drug. Such information should be forwarded in triplicate and directed to the assigned IND number, 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, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

OCT 11 1976

1030550

5 May 1975

Philip G. Walters, Acting Director
Division of Oncology & Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Public Health Service
Rockville, Maryland 20852

Dear Doctor Walters:

RE: IND 10,680

We mailed to you, earlier today, via air, the original of the copies of the letter enclosed regarding the Erbium-171 Citrate. We failed to notice that you required this information in triplicate, and we are enclosing with this note two additional complete copies to fulfill your requirement.

We are sorry for this oversight.

Sincerely,

Gould A. Andrews, M.D.

Enclosures

Sincerely,

Gould A. Andrews, M.D.

1030551

GTA file

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

5 May 1975

Philip G. Walters, Acting Director
Division of Oncology & Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
Public Health Service
Rockville, Maryland 20852

Dear Doctor Walters:

RE: IND 10, 680

I am sorry to be slow in replying to your inquiry about our Notice of Claimed Investigational Exemption for the new drug, Erbium-171 Citrate. Although we made application for exemption on this drug some time ago, we are just now beginning to initiate this investigation. The following will, we trust, satisfy your requirements for the further details requested in your July 10, 1974 letter.

The following relates to questions 1, 4, and 5 in your letter: As indicated in the original IND 10, 680, the maximum amount of ^{171}Er that will be administered will be 0.1 millicurie per kilogram of body weight (7.0 mCi per a 70 kg. subject). Since radioactive decay will dictate the exact weight relationship of the other constituents to the ^{171}Er content in the preparation after its formulation (see p. 2 section 5), the maximum amount of the other constituents per millicurie of ^{171}Er will be as follows: stable erbium citrate 0.1 mg., sodium citrate 10 mg., and sodium chloride 2 mg. The volume of intravenously injected solution containing the maximum dose of ^{171}Er (7 mCi/70 kg. subject) will vary from approximately 0.5 ml to 3.5 ml. The preparation will become out-dated 24 hours after removal of the target ^{170}Er from the reactor (see page 5, section 6, 3 radiation dosimetry and also Table 10 in the original IND 10, 680). The attached memo from E. E. Watson also included dosimetry figures for the ovaries and testes (question 2). In answer to question 3, we do not expect to make a comparison of ^{171}Er with ^{157}Dy and ^{167}Tm in individual patients; however, since ^{67}Ga is at present generally accepted to be the agent of choice in scanning tumors in general, we do plan comparison of ^{171}Er and ^{67}Ga in individual patients.

Sincerely yours,

Gould A. Andrews, M.D.

RLH/pe
Attachment

1030552

MEMORANDUM

TO Dr. R. L. Hayes

DATE July 30, 1974

SUBJECT SUPPLEMENTAL INFORMATION FOR ER-171 IND APPLICATION 10.680

COPIES TO file

The following information should answer the additional requests of FDA concerning the dosimetry for Er-171.

1. Details of dosimetry calculations

The MIRD technique was used for calculating the dose (MIRD Pamphlet No. 1, Supplement No. 1, J. Nucl. Med., 1968) with Cloutier's modification (Cloutier et al., J. Nucl. Med. 14, 53-55, 1973). The decay scheme for Er-171 was calculated by Dillman's procedure. Uptake in the different organs was extrapolated from animal data, and the effective half-time was assumed to be equal to the physical half-life. The total-body dose was based on uniform distribution of the Er-171 throughout the body.

2. Maximum doses to gonads and other organs

We had no values for the concentration of Er-171 in the gonads; however, concentrations should be no higher than that in muscle. For this reason we based the dose to the ovaries and testes on the muscle concentrations.

Dose from Er-171 and Tm-171*

	rad/mCi Er-171 adm.	rad/10.5 mCi Er-171 adm.
Ovaries	0.078	0.82
Testes	0.073	0.77
Total body	0.36	3.8

*¹⁷¹Tm concentration if ¹⁷¹Er given 24-hr after 20-hr irradiation

The maximum doses for the other organs are listed on the table I prepared April 17, 1974.

If you have further questions, call me..


Evelyn E. Watson

EEW:ras 1030553



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

IND 10,680

JUL 10 1974

Gould A. Andrews, M.D.
 Medical Division
 Oak Ridge Associated Universities
 Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

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: 10,680

Sponsor: Gould A. Andrews, M.D.

Name of Drug: Erbium-171 Citrate

Date of Submission: May 21, 1974

Date of Receipt: May 24, 1974

We have completed our preliminary review of your Notice and you are permitted to begin investigations as proposed in the study. The following information or corrections should be submitted to this Administration:

1. Details of the proposed dosage are required. The method is noted as intravenous but the quantity has not been clearly specified.
2. The estimated radiation exposure doses for the ovaries and testes to supplement the already submitted radiation dosimetry.
3. A comparison of this drug with Thulium-167 and Dysprosium-157 and perhaps Gallium-67 is provided for. Indicate if this is between patients or if a patient is to receive each of the drugs for comparison within that same patient and dosage interval.
4. The formula for a representative batch should be stated, this should represent the exact composition of the finished dosage form of the drug.

MC; ?

10,629

other conditions

12 July 74
Dr. Hayes
Dr. Edwards

REC'D. MEDICAL DIVISION *12 July 74*

1030554

5. The Notice should be amended to include a statement which represents the composition of the finished dosage form of the drug and a proposed outdating period. The Notice should also include some information on the method of assay employed and the standards that will be used.

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.

All future communications concerning this IND should be forwarded in triplicate and identified with the IND number assigned.

Sincerely yours,

Philip G. Walters, M.D.

Philip G. Walters, M.D.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs

Proposal 513

File 513

*(copy to
C. L. Andrews
R. L. Hayes
31 May 74)*



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

Your submission has been received by the Bureau of Drugs on the date stamped on the enclosed photocopy of the first page or cover letter. It has been forwarded to the division marked below for review and evaluation.

For all drugs except methadone and certain psychotomimetic agents, it is understood that this submission includes your assurance that clinical studies in humans will not be initiated prior to 30 days after the date of receipt shown on the enclosed photocopy, and that you will continue to withhold or to restrict clinical studies if requested to do so by this Administration prior to the expiration of such 30 days.

Division of Surgical and Dental Drug Products - 301-443-3560

~~Division of Oncology and Radiopharmaceutical Drug Products - 301-443-4250~~

Division of Anti-infective Drug Products - 301-443-4310

Division of Cardiacpulmonary and Renal Drug Products - 301-443-4730

Division of Neuropharmacological Drug Products - 301-443-4020

Division of Metabolic and Endocrine Drug Products - 301-443-3490

2 Submissions Rec'd 24 May
1 letter Rec'd 28 May

1038556

REC'D. MEDICAL DIVISION 31 May 74

OAK RIDGE ASSOCIATED UNIVERSITIES

INCORPORATED

P. O. BOX 117

OAK RIDGE, TENNESSEE 37830

May 24, 1974

AREA CODE 615
TELEPHONE 483-4411

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

Attn: Division of Oncology and
Radiopharmaceutical Drug
Products 301-443-4250

Gentlemen:

On May 21, we sent you our application for investigational exemption for a new drug on ERBIUM-171 CITRATE. It has been called to my attention that there were several small errors in the text. On page 5, paragraph 5, the first sentence should read "Erbium-171 decays to ^{171}Tm ..." and in paragraph 6 the first sentence should read "... small amounts of 49 hour ^{172}Er (producing daughter ^{172}Tm , $T_{1/2} = 64 \text{ h}$)...." Would you please make these corrections on your copies of the application.

Thank you for your attention to this matter.

Sincerely yours,

G. A. Andrews

G. A. Andrews, M.D.
Chairman, Medical Division

GAA:bbc

1030557

will
ADD
To submission
Rec'd 24
MAY 24



NOTICE OF
CLAIMED INVESTIGATIONAL EXEMPTION
FOR A NEW DRUG

AND

Name of Sponsor Gould A. Andrews, M.D.
Address Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn. 37830
Date May 21, 1974
Name of Investigational Drug Erbium-171 citrate

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



Dear Sir:

The sponsor, Gould A. Andrews, M.D. submits this notice of claimed investigational exemption for a new drug under the provisions of section 509 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 the 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 shall 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 pre-existing information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness of 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 information 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 pre-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.

RECEIVED COPY
PHOTOSTATS OF
COVER LETTER MADE
FOR DISTRIBUTION TO TRIP

1030558

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 investiga-

tions 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 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. 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

Gerald A. Andrews M.D.

PER

Oak Ridge Associated Universities

INDICATE AUTHORITY

Chairman, Medical 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.

1030559

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: December 10, 1973

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

Co-Investigators: R. L. Hayes, Ph. D.
L. C. Brown, Ph. D. (ORNL)

Title of Project: THULIUM-167 AS A CLINICAL SCANNING AGENT FOR DETECTING
OSSEOUS AND NONOSSEOUS TUMORS.

I. Objectives of Experiment:

To determine whether ^{167}Tm can be used as an effective tumor-localizing agent in humans. Animal experiments indicate that the higher-atomic-number rare-earth radionuclides show unusual affinities for tumor tissue (Fig. 1, appendix), clear rapidly from normal tissue (Table 1, appendix), and may have the same or better tumor-localizing properties as ^{67}Ga in certain tumor types (Table 2, appendix). It has good decay photons for scanning (Table 3, appendix).

II. Methods of Procedure:

^{167}Tm will be obtained from Isotopes Development, ORNL, as the chloride in dilute hydrochloric acid solution. After conversion to the citrate form, sterilization by Millipore filtration (0.22 micron) and testing for pyrogenicity, 0.015 mCi/kg or less will be administered intravenously (1.0-0.1 mg citrate/kg). A group of 20 adult patients with known cancer will initially be used to evaluate this radionuclide. When possible, comparisons will be made with ^{67}Ga and ^{111}In in the same patient. When skeletal lesions are present bone scans with $^{99\text{m}}\text{Tc}$ Osteoscan will also be made. Further studies with patient volunteers will then be determined after a review by the committee.

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose and at 12-hr intervals thereafter through 42 hours and then daily through 7 days.
2. Individual urine specimens will be collected through the first 24 hr and pooled 24-hr samples thereafter for 7 days.
3. Fecal excreta will be collected through 7 days.
4. Linear scans will be obtained immediately after the dose, at 3-4 hours, and then daily thereafter through 7 days.

1030560

5. Whole body and area scans will be made at 3-4 hours after administration (or as soon as practical), at 24 hours, 48 hours, and at later times as called for by the physician in charge.

III. Possible Hazards and Their Evaluation:

1. Chemical:

Since ^{167}Tm will be produced by a p,2n interaction on ^{168}Er and then separated from the erbium target material, it will be carrier free with respect to thulium; however, a small amount of erbium (micrograms) will be present as a contaminant from an ion exchange separation procedure.

We propose to administer no more than 10 $\mu\text{g}/\text{kg}$ of stable erbium (and generally much less) since stable rare earths in excess of this amount tend to decrease the relative specificity of these nuclides for tumor tissue (see Table 4, appendix). At a level of 10 $\mu\text{g}/\text{kg}$ or less there should be no toxic effects from the I.V. administration of erbium, since the I.V. LD_{50} in rats for the nitrate is reported to be 36 mg/kg in the female and 52 mg/kg in the male (T. J. Haley, J. Pharmaceutical Sciences 54: 663, 1965).

2. Radiation Dose:

The proposed maximum activity dose for ^{167}Tm as stated in II (Methods of Procedure) is based on a calculated whole body radiation dose of 2 rads (assuming uniform distribution and no excretion) and is thought to be acceptable for the proposed study. Radiation Physics supplied the radiation dose estimates.

IV. Radionuclides and New Drugs:

^{167}Tm will be a new radionuclide in our clinical program. It decays by electron capture with a $T_{1/2}$ of 9 days giving off a 208 KeV photon in 43% of its disintegrations (Table 3, appendix). Following approval of this application by the Committee on Human Studies and the ORAU Medical Radionuclide Committee, an IND will be filed with the Food and Drug Administration.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from among our clinic patients and from patients in the Oak Ridge Hospital and surrounding hospitals. An informed consent will be obtained from each patient (minors and adults incapable of giving an informed consent will be excluded from the study). No inducement will be offered to obtain voluntary consent. The latter group of patients will be recruited specifically for the test with no promise of continued medical care at ORAU and the ORAU patients will be assured that their participation is not a prerequisite to their continuing to receive treatment at ORAU. Attached is a copy of the proposed consent form (appendix A).

Starting Date: February 1, 1974

Signatures: C. Paul Edwards Principal Investigator
R. F. Hayes Co-Investigator
Kenneth Fogelson, Jr. Co-Investigator
...

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Donald C. ...
Title Chm. The Medical Division
Institution Cape Ridge Associated Univ
Date 11 Dec 73

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

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

of the following test: Phase I Radiopharmaceutical Test of Thulium-167.

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

DATE: _____
(Patient or person authorized to consent for patient)

WITNESS: _____

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

1. This is a new radioactive drug: ^{167}Tm - Thulium citrate.
2. The drug contains the element thulium in quantities much less than that required to produce any measurable chemical effect in the body. Patients should feel no effect from the drug.
3. The radiation dose will be approximately 2 rads to the whole body.
4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hr, 42 hr, and then daily for a total of 12 samples.
5. All urine and feces will be saved for one week.
6. Whole body counts and scans will be made at frequent intervals for one week.
7. The patient may withdraw from the test at any time.

DATE: _____
Investigator

1030563

#94

ORAU-ORNL HUMAN STUDIES COMMITTEE

Project Title: Thulium-167 as a Clinical Scanning Agent for Detecting
Osseous and Nonosseous Tumors

Investigators: C. L. Edwards (at another institution now)
Karl F. Hübner, M.D. (signing)

This project was placed on concluded or inactive status on
July 10, 1978. The documentation will be kept
(date)

on file in the Committee's records for at least three years.

If you should wish to reactivate the project, the Committee's approval must be obtained; but if still appropriate, the original written proposal may suffice.

Please return the following form to the secretary of the Committee.

I am aware that the project _____

Thulium-167 as a Clinical Scanning Agent for Detecting Osseous
and Nonosseous Tumors

is no longer on the approved list of the ORAU-ORNL Human Studies Committee, and I have informed all coinvestigators (if any were originally listed) of this fact.

Karl F. Hübner
Senior Investigator

1030564

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 34

Project Title Thulium-167 as a Clinical Scanning Agent for Detecting Osseous
and Nonosseous Tumors

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

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

2. In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons: Possible better diagnostic agent.
3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate: as submitted.
4. The committee seeks continuing communication with the investigator(s) on this project along the following lines: None.
5. Other committee comments: None.

Approve X

Gordon Andrews
Chairman of Committee

Disapprove _____

Date 11 Dec. 73

25 Jan 1975 - Review, see report

1030565

No. 34 ^{167}Tm as a Clinical Scanning Agent for Detection of Osseous
and Nonosseous Tumors

One patient received a scanning dose of ^{167}Tm and a second patient received a dose prior to surgical excision of the tumor. The results were not encouraging although neither patient experienced any adverse effects.

1030566

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

August 3, 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 10,681

This is the final progress report on our studies with Thulium-167 citrate (IND 10,681).

Only seven patients have been given this radiopharmaceutical since the study was initiated in 1973. There were no untoward reactions in any of the patients, and no significant changes were noted in the hemogram, clotting status, and liver enzymes of these patients.

Thulium-167 citrate localized in a patient with bronchogenic carcinoma. No clear tumor localization was seen in patients with cancer of the colon, ovarian cancer, chronic lymphocytic leukemia, or three patients with multiple myeloma. The limited clinical experience with Thulium-167 citrate in the multiple myeloma cases is included in a publication "The Use of Rare-Earth Radionuclides and Other Bone Seekers in the Evaluation of Bone Lesions in Patients with Multiple Myeloma or Solitary Plasmacytoma," Karl F. Hübner, et. al., Radiology, 125, 1, 171-176, October, 1977. A reprint of this paper is attached.

We have discontinued this project and notified the ORAU/ORNL Committee on Human Studies of this action on July 10, 1978. In addition to the not very impressive results obtained with Thulium-167, the investigators felt this radionuclide (being accelerator produced) is expensive and has a dose limitation which does not seem to make it a very practical radiopharmaceutical at the present time.

Sincerely,

C. C. Lushbaugh, M.D.
Chairman

CCL:dg

1030567

Enclosure

Dr. Hübner

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8111

Medical and
Health Sciences
Division

July 11, 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:

I am responding to your letter written to Dr. Andrews recently concerning studies of Thulium-167 Citrate. This radionuclide is of interest to us because it is one of the rare earth elements that might show promise in localizing skeletal lesions.

In March, 1976, two patients received Thulium-167 Citrate in the amount of 0.015 mCi/kg. Both patients had multiple myeloma with known active disease, and in neither case was the Thulium effective in showing areas of disease. There were no untoward reactions to the injection of the radioisotope.

Because of the expense of the radionuclide and the urgency of other ongoing investigations, we have held this study in abeyance. However, the members of our staff would like to continue to keep the Thulium-167 IND active until we can make a more adequate assessment of the material.

Thank you for calling our attention to this matter.

Sincerely,

ORIGINAL SIGNED BY:
C. C. LUSHBAUGH, M. D.

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

CCL:dgb

cc: Dr. Andrews
Dr. Hayes
Dr. Hübner

1030568



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

JUL 1 1977

IND 10,681

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37380

Dear Dr. Andrews:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Thulium-167 Citrate.

It is required that a sponsor of an IND forward a progress report of clinical investigation at reasonable intervals not exceeding a year. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. Your IND does not contain this information. We request that you report within 30 days.

In the event study was not initiated or was discontinued during trial, we should be notified promptly. Notification of discontinuance should include the reason; assurance that investigators have been informed; and the steps taken with respect to the unused supplies of the drug. This information and your final progress report should be in triplicate and directed to the assigned IND number, 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, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

1030569

JUL 6 1977

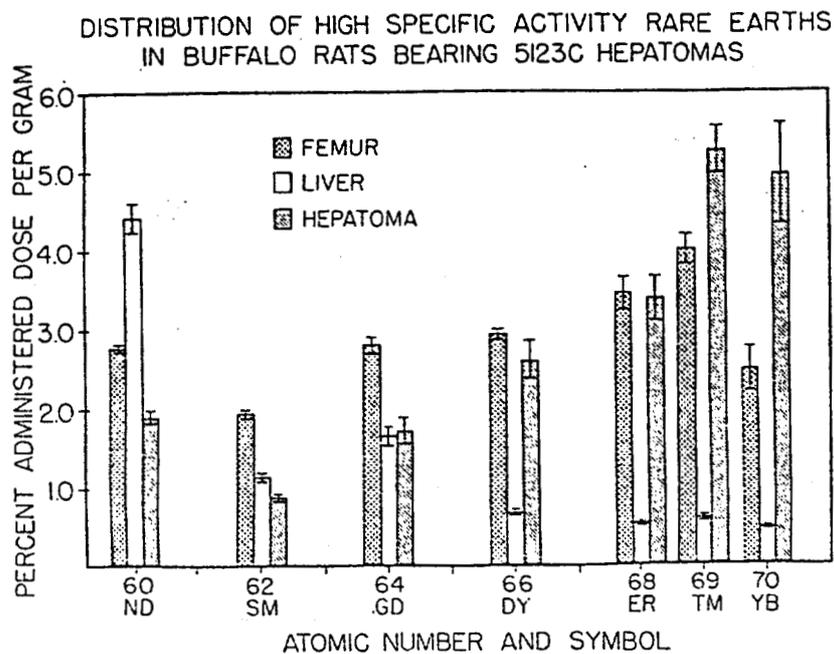
TABLE 1

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

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

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

** Not significantly different from 4 hour value.



1030570

Fig. 1

TABLE 2

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

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

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

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

TABLE 4

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

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

1030512

Proposal no. 34



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

Your submission has been received by the Bureau of Drugs on the date stamped on the enclosed photocopy of the first page or cover letter. It has been forwarded to the division marked below for review and evaluation.

For all drugs except methadone and certain psychotomimetic agents, it is understood that this submission includes your assurance that clinical studies in humans will not be initiated prior to 30 days after the date of receipt shown on the enclosed photocopy, and that you will continue to withhold or to restrict clinical studies if requested to do so by this Administration prior to the expiration of such 30 days.

- Division of Surgical and Dental Drug Products - 301-443-3550
- ~~Division of Oncology and Radiopharmaceutical Drug Products - 301-443-4250~~
- Division of Anti-infective Drug Products - 301-443-4310
- Division of Cardiacpulmonary and Renal Drug Products - 301-443-4730
- Division of Neuropharmacological Drug Products - 301-443-4020
- Division of Metabolic and Endocrine Drug Products - 301-443-3490

2 Submissions Rec'd 24 May
1 letter Rec'd 28 May

1030573

U.S. GOVERNMENT PRINTING OFFICE: 1969 O 344-100

NOTICE OF
CLAIMED INVESTIGATIONAL EXEMPTION
FOR A NEW DRUG

Name of Sponsor Gould A. Andrews, M.D.
Address Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee 37830
Date May 21, 1974
Name of Investigational Drug Thulium-167 citrate

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



Dear Sir:
The sponsor, Gould A. Andrews, M.D., 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 individual investigators; a summary of the results and a conclusion that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted; and 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 pre-existing 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.

A total of three copies of all informational material, including label and labeling, which is to be supplied to the 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 be stated that the safety or usefulness of the drug has not 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.

3. 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.

RECEIVED
STATS OF
COVER LETTER MADE
TRIP

1030574

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 investiga-

tions 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 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. 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

Donald Andrews

PER

Oak Ridge Associated Universities

INDICATE AUTHORITY

Chairman, Medical 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.

May 4, 1976

TO: ORAU/ORNL COMMITTEE ON HUMAN STUDIES

This is to remind you of the scheduled meeting (Tuesday, May 11, 10 a.m., Second Floor Conference Room, ORAU, Medical and Health Sciences Division). We anticipate that the meeting can be concluded by noon unless some unusual problems arise.

New Proposals:

1. Use of ^{11}C -DL-Valine as a potential scanning agent (Dr. Hübner and Dr. Hayes). Relevant dates are included in this mailing. The rather bulky IND (Investigational New Drug) permit is to be sent to the Food and Drug Administration. It is not expected that you read all of it, but for those members of the committee not familiar with these forms, it might be of interest.
2. Discussion of use of chelating agents in radiation accidents involving accidental internal presence of radionuclides (Dr. Lushbaugh). (See attached manuscript by Dr. T. A. Lincoln).
3. Discussion of WR-2721 for human use (Dr. Hayes).

Progress on Previously Approved Proposals:

4. Projects 33, 34, and 35: These rare earth elements have been injected intravenously in the planned doses. Numbers of patients studied so far are Erbium-171, 22 patients; Dysprosium-157, 24 patients; and Thulium-167, 3 patients. We have noted no reactions to these materials. Clinical usefulness is still in doubt. Malignant lesions have some avidity for all of these materials but in most instances the visualization was not as good as was obtained with Gallium-67 in the same patient. It does appear that the newly tried isotopes have little or no localization in the colon and thus might prove superior to Gallium-67 in patients with suspected abdominal lesions. Unfortunately, we have not yet had a chance to study patients with abdominal lesions. It was also observed that Dysprosium-157 shows up bone lesions quite well, including some missed by gallium. However, the dysprosium visualization is not as good as that usually obtained with technetium phosphate preparations.
5. Project 38 was started in November, 1975. Since then we have administered 15 doses of ^{11}C -ACPC ranging from 10 mCi to 40 mCi per patient with the largest volume being 12 ml per dose. To the first ten patients the radiopharmaceutical was given through the tubing of an intravenous infusion of 5%D/0.45%S. There has been no reaction of any type to the injections. There was no discomfort nor any subjective side effects in any of the patients.

Laboratory tests showed an average excretion of 2.1 percent of the dose between 45 minutes to 2 hours after injection. Radioassays of blood samples showed that 85-90 percent of the activity has left the blood within 5 minutes. Standard hemograms and serum chemistry studies failed

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to show any significant changes. In the future the multiple early laboratory tests will be discontinued. Instead, a pretreatment and 24-hour survey will be made.

So far we have observed some tumor localization of this compound in approximately two-thirds of the patients studied. Concentration of the ^{111}C -ACPC in tumors is not as high as seen with ^{67}Ga -citrate. Most of the patients included in the study had cancer of the lung. In the future patients with other malignancies may have different results with ^{111}C -ACPC as a tumor scanning agent. Almost all of the scans in this project have been done in conventional gamma mode. We anticipate greatly improved resolution of ^{111}C -ACPC when positron emission transaxial tomography will be available for the evaluation of ^{111}C -ACPC and other positron emitters.

6. Project 41 - Trials of the Line Scanner Developed at ORNL. Approximately 100 patients have been studied, but unfortunately very few of them had thyroid nodules. The techniques for using the new instrument were greatly improved by adjustments made after the clinical trials were started.

At present the instrument gives results that, on the average, equal those from a standard scanner. In individual cases one or the other techniques may prove superior. The radiation from the ^{125}I used for this new procedure is within accepted limits but is higher than would be obtained with ^{123}I or $^{99\text{m}}\text{Tc}$.

We are attempting to study ¹³¹a group of patients with palpable thyroid nodules to make a more useful evaluation.

Prepared by G. A. Andrews, M.D., and
Karl F. Hübner, M.D.

May 4, 1976

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: December 10, 1973

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

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

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

I. Objectives of Experiment:

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

II. Methods of Procedure:

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

The following data will be collected:

1. Blood concentrations at 1/2 hr, 1 hr, 3 hr, and 6 hr after the dose and then at 12-hr intervals thereafter through 42 hours.
2. Individual urine specimens will be collected through 2 days.
3. Fecal excreta will be collected through 2 days.

1030578

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

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

Starting Date: February 1, 1974

Signatures: *O. Paul Edwards, Sr.* Principal Investigator
F. R. L. Hayes Co-Investigator
Kenneth Toggerson, Jr. Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature *Donald C. Andrews*
Title *Chm. The Medical Division*
Institution *Oak Ridge Associated Univ.*
Date *11 Dec 73*

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

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

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

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

DATE: _____

(Patient or person authorized to
consent for patient)

WITNESS: _____

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

1. This is a new radioactive drug: ¹⁵⁷Dy - Dysprosium citrate.
2. The drug contains the element dysprosium in quantities much less than that required to produce any measurable chemical effect in the body. The patients should feel no effects from the drug.
3. The radiation dose will be from approximately 1 rad to the whole body.
4. Blood samples (3 ml) will be drawn at 1/2 hr, 1 hr, 3 hr, 6 hr, 18 hr, 30 hrs and 42 hrs.
5. All urine and feces will be saved for two days.
6. Whole body counts and scans will be made at frequent intervals for two days.
7. The patient may withdraw from the test at any time.

DATE: _____

Investigator

1030580

TABLE 1

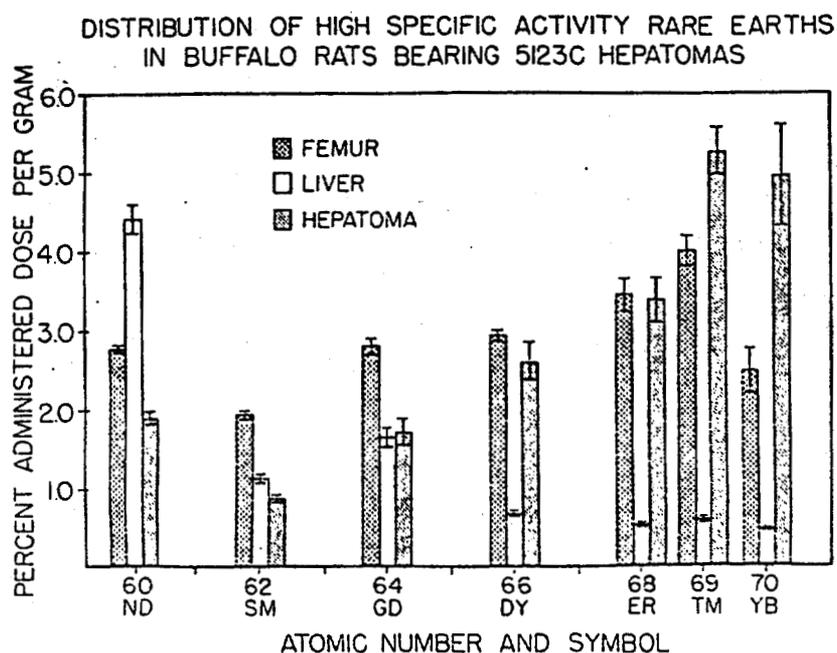
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BEARING 5123C HEPATOMAS

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Ratio tumor conc. to:					
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Spleen	5.5	7.9	6.4	4.6	6.3
Kidney	1.3	1.7	2.0	3.4	4.7
Lung	6.3	12.0	19.0	11.0	25.0
Muscle	43.0	87.0	180.0	66.0	160.0
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** Not significantly different from 4 hour value.



1030581

Fig. 1

TABLE 2

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

	7777 Hepatoma		CA-755		P-1798		EA Cells	
	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga	^{169}Yb	^{67}Ga
Tumor conc. (%/g)	3.20	5.80	4.70	7.90	3.10	6.00	4.30	1.50
Ratio tumor conc. to:								
Liver	9.50	7.30	1.50	1.20	0.80	1.20	1.90	0.46
Spleen	6.90	5.00	3.30	2.30	1.90	1.40	3.30	0.63
Kidney	4.10	8.00	0.33	2.40	0.22	1.10	0.40	0.38
Lung	4.00	19.00	2.10	4.00	1.10	1.80	4.10	0.67
Muscle	210.00	34.00	23.00	57.10	5.40	11.00	6.30	1.20
Femur	1.60	4.60	0.30	0.80	0.20	0.70	0.30	0.27
Marrow	5.20	5.10	-	-	-	-	-	-
Blood	190.00	33.0	28.00	4.70	14.00	6.60	14.00	0.62
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1030582

TABLE 3

RARE EARTH RADIONUCLIDES FOR TUMOR SCANNING

Isotope	Decay Mode	T _{1/2}	γ Energy (%)	Comments
¹⁶⁷ Tm	EC	9d	208 Kev _γ (43%)	¹⁶⁸ Er p, 2n
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¹⁵⁷ Dy	EC	8.2h	326 Kev (91%)	σ ¹⁵⁶ Dy (0.05%) = 3

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

1030583

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

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

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

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

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

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

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

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

5. Other committee comments: None.

Approve x

Disapprove _____

Gould Andrews
Chairman of Committee

11 December 73

Date _____

25 Jan 75: update, See Report

1030584

No. 35 ^{157}Dy as a Clinical Scanning Agent for Detection of Osseous and Nonosseous Tumors

Six patients were scanned after received ^{157}Dy . Blood clearance of this nuclide, as predicted from animal experiments was much more rapid than ^{67}Ga . However the anticipated localization in tumors has not been seen. No patient experienced any untoward effects of the study.

1030585



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

Your submission has been received by the Bureau of Drugs on the date stamped on the enclosed photocopy of the first page or cover letter. It has been forwarded to the division marked below for review and evaluation.

For all drugs except methadone and certain psychotomimetic agents, it is understood that this submission includes your assurance that clinical studies in humans will not be initiated prior to 30 days after the date of receipt shown on the enclosed photocopy, and that you will continue to withhold or to restrict clinical studies if requested to do so by this Administration prior to the expiration of such 30 days.

Division of Surgical and Dental Drug Products - 301-443-3560

Division of Oncology and Radiopharmaceutical Drug Products - 301-443-4250

Division of Anti-infective Drug Products - 301-443-4310

Division of Cardiopulmonary and Renal Drug Products - 301-443-4730

Division of Neuropharmacological Drug Products - 301-443-4020

Division of Metabolic and Endocrine Drug Products - 301-443-3490

50

1030586

REC'D. MEDICAL DIVISION 9/25/74

Copy to Dr. H...
" " Dr. S...

NOTICE OF
CLAIMED INVESTIGATIONAL EXEMPTION
FOR A NEW DRUG

112

Name of Sponsor Gould A. Andrews, M.D.
Address Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn. 37830
Date May 3, 1974
Name of Investigational Drug Dysprosium-157 citrate

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

Dear Sir: Gould A. Andrews, M.D.

The sponsor, Gould A. Andrews, M.D., 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 pre-existing 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 of the investigation. It shall describe all relevant hazards, including side-effects, and precautions suggested by prior investigations and experience with the drug under investigation or related drugs for the information of clinical investigators.

8. The scientific training and experience of the sponsor to qualify the investigator to investigate the safety of the drug, taking in mind what is known about the pharmacological action of the drug and the phases of the investigation program that is to be undertaken.

1030587

RECEIVED
MAY 6 1974
FEDERAL BUREAU OF INVESTIGATION
U.S. DEPARTMENT OF JUSTICE

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8111

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 #17B-34
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

IND 10,624

This letter is a response to your letter sent to Dr. Andrews in October, 1978, in which you request a progress report or a final progress report on the investigational use of Dysprosium-157-citrate.

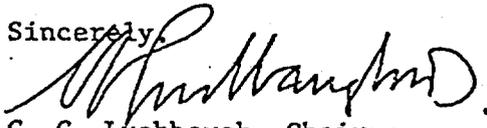
Dr. Andrews no longer works here; he left this institution in November, 1977. It is due to an oversight that a final report has not been submitted to your office. The project was discontinued on September 22, 1977, at which time the ORAU/ORNL Committee on Human Studies was notified of this action.

The reason for discontinuing the clinical investigation with Dysprosium-157-citrate was the conclusion that Dysprosium-157-citrate does not appear to be better than the conventionally used ^{99m}Tc -phosphate compounds for bone scanning and definitely not superior to ^{67}Ga -citrate as used for the detection of the soft tissue tumors. All investigators associated with the project have been notified. There is no supply of the unused "drug" remaining since the radioactive tracer had to be produced in a reactor; and because of the short physical half-life (8.2 hrs.), the drug had to be used within 24 hours after production of the radio-pharmaceutical.

In lieu of a formal progress report, I am enclosing three copies of a paper published in "Radiology" (V. 25, 171-176, October, 1977) and three copies of a manuscript submitted for publication in the journal "Clinical Nuclear Medicine." Both articles include information on numbers of cases in which Dysprosium-157-citrate was used and a discussion of the potential diagnostic value of this diagnostic agent.

If you need additional information, please let me know.

Sincerely,


C. C. Lushbaugh, Chairman
Medical & Health Sciences Division

CCL:dg

cc: IND Files

Committee on Human Studies File

1030588

Oak Ridge
Associated
Universities

Office of the
Chief Executive Officer
of the University of Maryland

Medical and
Health Sciences
Division

March 18, 1977

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

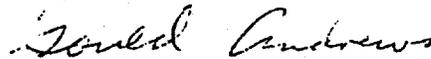
Dear Dr. Gyarfas:

We are writing to report on our Notice of Claimed Investigational Exemption for the New Drug Dysprosium-157 Citrate, IND 10,624.

We have given 29 doses of this nuclide to patients with neoplastic disease. No untoward reaction of any type have been encountered. The localizations of the nuclide appears generally inferior to that of gallium-67 citrate, although the dysprosium has the advantage of not concentrating in the colon and feces, thus allowing a better examination of the abdominal regions. The dysprosium shows a distinct uptake in several types of neoplasms and has been of some value in evaluating multiple myeloma.

We wish to maintain the research project as an active one until further evaluation and consideration of the results has been made.

Sincerely,



Gould A. Andrews, M.D.

GAA:dgb

1030589



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

IND 10,624

MAR 11 1977

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Dysprosium-157 Citrate.

It is required that a sponsor of an IND forward a progress report of clinical investigation at reasonable intervals not exceeding a year. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. Your IND does not contain this information. We request that you report within 30 days.

In the event study was not initiated or was discontinued during trial, we should be notified promptly. Notification of discontinuance should include the reason; assurance that investigators have been informed; and the steps taken with respect to the unused supplies of the drug. This information and your final progress report should be in triplicate and directed to the assigned IND number, 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

1030590

MAR 16 1976

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

September 2, 1975

Dr. William J. Gyarfas
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs HFD-150
5600 Fishers Lane
Rockville, Maryland 20852

Attention: DOCUMENT CONTROL ROOM #17B-34

Dear Dr. Gyarfas:

This is in response to your recent letter reminding us that we had not sent in recent information concerning our Notice of Claimed Investigational Exemption for the drug Dysprosium-157 Citrate.

We have given 13 doses of this radionuclide preparation to patients with known cancer and have found no unfavorable responses of any sort. On the other hand, this initial small series does not show a very promising uptake in tumors. We plan to continue the study until we have at least 20 patients so that we will have a more adequate evaluation of Dysprosium-157 Citrate as a possible tumor localizing agent. This should be accomplished within the next few months.

Please let us know if there is further information that you need.

Sincerely,

Gould A. Andrews, M.D.

GAA:dgb

1030591



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

AUG 25 1975

IND 10,624

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Dysprosium-157 Citrate.

It is required that a sponsor of an Exemption forward a progress report of clinical investigation at reasonable intervals not exceeding one year. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the proposed plan of study. We have not received a report since your May 3, 1974 submission. We are requesting, therefore, that you promptly report at this time.

In the event clinical study was not initiated or was discontinued during trial, we should be notified promptly. Notification of discontinuance should include the reason therefor, assurance that investigators have been informed, and any steps taken with respect to unused supplies of the drug. Such information should be forwarded in triplicate and directed to the assigned IND number, 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.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

1030592

AUG 29 1975



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

JUN 6 1974

IND 10,624

Gould A. Andrews, M.D.
Medical Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug as follows:

Sponsor: Gould A. Andrews, M.D.

Name of Drug: Dysprosium-157 citrate

Date of Notice: May 3, 1974

Date of Receipt: May 6, 1974

IND Number Assigned: 10,624

Assignment of this number is for record keeping purposes only. All submissions must be made in triplicate and identified with this number.

On the basis of our preliminary review, we have no objection to initiation of your proposed clinical investigation as originally planned, but we request that you submit the following information or corrections:

1. In order to complete your application, submit details of dosimetry calculations, including equations used and assumptions made.
2. A statement on the expected duration of the study.
3. The maximum dose of the drug to be administered should be stated.

*Revised by R. Hayes
L. Edwards
11 June 74*

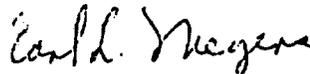
1030593

4. A statement of the composition of the finished dosage form of the drug.
5. Please indicate the maximum radiation doses to the gonads and other organs for the maximum amount of the drug to be administered.

We may communicate with you further should any questions arise as a result of a comprehensive review of your proposal.

You are responsible for compliance with the applicable provisions of 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.

Sincerely yours,



Earl L. Meyers, Ph.D., Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs

May 4, 1976

TO: ORAU/ORNL COMMITTEE ON HUMAN STUDIES

This is to remind you of the scheduled meeting (Tuesday, May 11, 10 a.m., Second Floor Conference Room, ORAU, Medical and Health Sciences Division). We anticipate that the meeting can be concluded by noon unless some unusual problems arise.

New Proposals:

1. Use of ^{11}C -DL-Valine as a potential scanning agent (Dr. Hübner and Dr. Hayes). Relevant dates are included in this mailing. The rather bulky IND (Investigational New Drug) permit is to be sent to the Food and Drug Administration. It is not expected that you read all of it, but for those members of the committee not familiar with these forms, it might be of interest.
2. Discussion of use of chelating agents in radiation accidents involving accidental internal presence of radionuclides (Dr. Lushbaugh). (See attached manuscript by Dr. T. A. Lincoln).
3. Discussion of WR-2721 for human use (Dr. Hayes).

Progress on Previously Approved Proposals:

4. Projects 33, 34, and 35: These rare earth elements have been injected intravenously in the planned doses. Numbers of patients studied so far are Erbium-171, 22 patients; Dysprosium-157, 24 patients; and Thulium-167, 3 patients. We have noted no reactions to these materials. Clinical usefulness is still in doubt. Malignant lesions have some avidity for all of these materials but in most instances the visualization was not as good as was obtained with Gallium-67 in the same patient. It does appear that the newly tried isotopes have little or no localization in the colon and thus might prove superior to Gallium-67 in patients with suspected abdominal lesions. Unfortunately, we have not yet had a chance to study patients with abdominal lesions. It was also observed that Dysprosium-157 shows up bone lesions quite well, including some missed by gallium. However, the dysprosium visualization is not as good as that usually obtained with technetium phosphate preparations.
5. Project 38 was started in November, 1975. Since then we have administered 15 doses of ^{11}C -ACPC ranging from 10 mCi to 40 mCi per patient with the largest volume being 12 ml per dose. To the first ten patients the radiopharmaceutical was given through the tubing of an intravenous infusion of 5%D/0.45%S. There has been no reaction of any type to the injections. There was no discomfort nor any subjective side effects in any of the patients.

Laboratory tests showed an average excretion of 2.1 percent of the dose between 45 minutes to 2 hours after injection. Radioassays of blood samples showed that 85-90 percent of the activity has left the blood within 5 minutes. Standard hemograms and serum chemistry studies failed

1030595

to show any significant changes. In the future the multiple early laboratory tests will be discontinued. Instead, a pretreatment and 24-hour survey will be made.

So far we have observed some tumor localization of this compound in approximately two-thirds of the patients studied. Concentration of the ^{111}C -ACPC in tumors is not as high as seen with $^{67}\text{Gallium}$ -citrate. Most of the patients included in the study had cancer of the lung. In the future patients with other malignancies may have different results with ^{111}C -ACPC as a tumor scanning agent. Almost all of the scans in this project have been done in conventional gamma mode. We anticipate greatly improved resolution of ^{111}C -ACPC when positron emission transaxial tomography will be available for the evaluation of ^{111}C -ACPC and other positron emitters.

6. Project 41 - Trials of the Line Scanner Developed at ORNL. Approximately 100 patients have been studied, but unfortunately very few of them had thyroid nodules. The techniques for using the new instrument were greatly improved by adjustments made after the clinical trials were started.

At present the instrument gives results that, on the average, equal those from a standard scanner. In individual cases one or the other techniques may prove superior. The radiation from the $^{125}\text{Iodine}$ used for this new procedure is within accepted limits but is higher than would be obtained with $^{123}\text{Iodine}$ or $^{99\text{m}}\text{Technetium}$.

We are attempting to study a group of patients with palpable thyroid nodules to make a more useful evaluation.

Prepared by G. A. Andrews, M.D., and
Karl F. Hübner, M.D.

May 4, 1976

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

February 26, 1974

Principal Investigator: R. L. Tyndall

Co-Investigators: J. C. Daniel, Jr.
M. Ketchel

Title of Project: ESTERASE ACTIVITY AND MAMMALIAN REPRODUCTION

I. Objectives of Experiment:

Analysis of serum and tissue esterases from a variety of mammals shows that these enzymes are often excellent indicators of both differentiation and hormonal action. Little is known, however, of the role esterases play in hormonal regulation and developmental processes. Here we propose studies designed to improve our understanding of these interactions primarily as they concern the preimplantation period of pregnancy in mammals. Additionally, we will test the applicability of such knowledge in the detection of ovulation and early pregnancy and possibly the cessation of the latter.

The predictable coincidence between heightened esterase activity in serum and uterine fluid when a female mammal is host to an embryo generates questions of origin, function, and control of the enzyme(s). As altered activity is also demonstrable in the sera of cancer bearing animals, we hypothesize that esterases are critical to, or in some way reflective of, the conditions that support dynamic growth of tissues, whether they be embryonic or neoplastic. Because of the ease of manipulating pregnancy, pseudopregnancy and preimplantation embryonic growth in laboratory mammals, we have elected to use the rabbit reproductive system as primary subject for studies designed to seek answers to these questions. To apply this information to detection of early pregnancy in women we have to look at human samples of sequentially collected serum throughout, and coordinated with different stages in the cycle to determine whether the same kinds of general patterns seen in the rabbit may be detected in women. (A single preliminary check confirms the presence of esterase activity in human serum but the electrophoretic mobility differs from the rabbit.) These findings will be coordinated with esterase changes that may be found in uterine fluids from these same individuals and ultimately in other body fluids, particularly saliva.

II. Methods of Procedure:

Specimens of serum, saliva, and uterine washings will be collected from five paid volunteers during the first, third, and fourth week of their menstrual cycle. The serum and saliva samples will be obtained by standard methods of collection. Serum samples will be 5 ml and saliva 5 ml. Uterine washings will be obtained by a qualified physician, either an ORAU staff physician or consultant, using the disposable Gravlee Jet Washer (see description in section III below).

The specimens will then be analyzed for their esterase content. In our own and other studies esterase profiles of tissues have been shown to be excellent indicators of both the degree of differentiation and of hormone action. Likewise some serum esterases have also been excellent indicators of hormone action. We have recently described the activation of multiple esterases in rabbit endometrium following coitus. The esterase activation was also associated with a marked increase in ^{67}Ca localization in such tissue. Esterase profiles are determined by acrylamide electrophoresis of tissue extracts or plasma with subsequent reaction of the gels with α -naphthyl acetate and Fast Blue RR. The resultant esterase bands can be quantitated by microdensitometry.

Volunteers will be compensated at the rate of \$35 for each set of specimens, viz., 5 ml whole blood, 5 ml of saliva, and one uterine washing.

III. Possible Hazards and their Evaluation:

The experimental procedure is believed to be free of significant risk to the volunteers and experimentalists. The risks associated with collecting the blood and saliva samples are so small or non-existent as to be well accepted.

The uterine washings will be obtained by using a sterile disposable Gravlee Jet Washer sold by the Upjohn Corporation for the routine collection of uterine washings for cytology as a screening test for endometrial cancer. Use of the device involves insertion of a sterile double lumen catheter through the cervical os into the uterine cavity. Sterile saline is then aspirated from a sterile container through one lumen of the catheter into the uterine cavity then back out the other lumen into a syringe. Thus the saline enters the uterine cavity under negative pressure avoiding any tendency to pass through the fallopian tubes into the peritoneal cavity.

A review of the literature reveals no reports of complications to its use. The clinical staff at Upjohn state they have received no reports of complications, and a survey of local gynecologists revealed no serious complications although 6 of 13 physicians responding to our inquiry indicate that patients occasionally have some discomfort described as mild to moderate, especially where there is stenosis of the cervical os as often develops postmenopausally.

IV. Radioisotopes and New Drugs:

None.

1030598

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 appended consent form will be used for each specimen collection.

Starting Date 9.1.74

Signatures:

[Signature] Principal Investigator
William M. Keefe Co-Investigator
Joseph C. Daniel J. Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Donald A. Andrews M.D.
Chairman
ONAU Medical Division

11 Dec. 1974
Date

OAK RIDGE ASSOCIATED UNIVERSITIES

Whole Blood, Saliva, and Uterine Washings Procurement, Release and
Payment Authorization

I, the undersigned, do hereby acknowledge that I have on this day, of my own free will and accord, delivered and sold to the Oak Ridge Associated Universities (hereinafter referred to as "Association" _____ cc's of my own blood, by direct vein aspiration, _____ cc of my saliva, and the uterine washings obtained by aspiration. I further consent to the pelvic (vaginal) examination and the uterine aspiration by Dr _____ using the Gravlee Jet Washer, which has been described to me. The hazards and risks of these procedures have been explained to me as being limited to mild to moderate discomfort during the pelvic examination, the insertion of the aspirator through the cervix and the actual aspiration.

It is understood that I am to be paid the below specified sum by the association in consideration of which I do hereby release and discharge the Association, its successors and assigns, from all claims, actions, and causes of action, at law or in equity, which I do now or may hereafter have against the Association, resulting from or growing out of the sale of said specimens or their removal from my body. It is further understood and agreed that I am to retain no control whatsoever over the said specimens or the use thereof.

Amount to be paid \$ _____

This _____ day of _____

Name (Please Print)

Signature of Donor

Mail Check To

WITNESSES:

City State

Zip

Account to Charge: _____

BLOOD RECEIVED BY

SALIVA RECEIVED BY

UTERINE WASHINGS RECEIVED

DIVISION APPROVAL

1030600

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Tyndall, R. L. Ident. No. 36

Project Title Esterase Activity and Mammalian Reproduction

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

No significant risks; attention has been given to the use of the Gravlee Jet Washer and no hazards are known.

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:

No immediate significant benefits or hazards to patient; advancement of knowledge sought.

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

Routine forms.

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

Interested in results.

5. Other committee comments:

Approve

Disapprove

Gould Andrews
Chairman of Committee

2 May 1974

Date

After Dec. 11, 1973 meeting this proposal was considered; a memo to members of the Committee, plus a telephone poll, resulted in its acceptance.

1030601

(Revised January 1972)

MEMORANDUM

TO Dr. Dick TyndallDATE 8 March 1974SUBJECT Research Proposal to Committee on Human StudiesCOPIES TO File

no 36

Mr. Melvin Koons sent the following comment regarding your proposal.

"From a reading of Dr. Tindall's project, I find it hard to see where there is an "experimental procedure" involved. As I understand Paragraph 111, the uterine washing procedure using the Gravelee Jet Washer is not per se experimental. Nor of course is the taking of blood and saliva samples. Therefore, I do not see a need for a consent form. On the other hand, if you feel that such is necessary, I have no objections."

MEK

Gould A. Andrews

pe

1030602

MEMORANDUM

TO Dr. Gould AndrewsDATE April 10, 1974SUBJECT Two New Proposals to ORAU-ORNL Committee on Human Studies

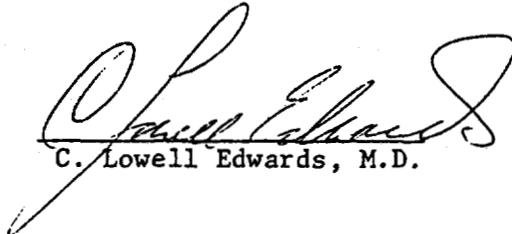
COPIES TO _____

During the week of March 4-8 I contacted each of the six other members of the ORAU-ORNL Committee on Human Studies regarding two proposals circulated to them by mail on February 18, 1974. These proposals were

no. 36 (1) Esterase Activity and Mammalian Reproduction with Dr. R. L. Tyndall as principal investigator and (2) the one to cover animal studies designed to lead up to subsequent proposals for human use of carbon 11 with Dr. R. L. Hayes as principal investigator. (no. 37)

In my phone and personal contact with the members of the committee none raised any objection, and it was agreed to approve these proposals without a meeting.

I suggest that these proposals be entered in our book and circulated for signatures as necessary.


C. Lowell Edwards, M.D.

gd

cc: Committee on Human Studies:

A. B. Brill
M. E. Koons
R. D. Lange
T. A. Lincoln
B. M. Nelson
J. B. Storer

Dr. R. L. Hayes
Dr. R. L. Tyndall

1030603

OAK RIDGE ASSOCIATED UNIVERSITIES

INCORPORATED

P. O. BOX 117

OAK RIDGE, TENNESSEE 37830

February 27, 1974

AREA CODE 615
TELEPHONE 483-8411

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

A. B. Brill
C. L. Edwards
M. E. Koons
R. D. Lange
T. A. Lincoln
B. Nelson
J. B. Storer

Subject: Esterase Activity and Mammalian Reproduction
R. L. Tyndall, J. C. Daniel, Jr., and M. Ketchel

no. 36

This material from Dr. Tyndall involves a new proposal to study esterase activity in uterine fluids which is thought to be of importance in support of growth of neoplasms as well as embryos. We are anxious for an early answer on this, and Dr. Edwards will telephone you about it the latter part of next week.

Gould A. Andrews

Gould A. Andrews

fb

Enc.

1030604

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities

Date: February 28, 1974

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

Co-Investigators: R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CARBON-11 LABELED COMPOUNDS FOR ORGAN AND TUMOR
LOCALIZATION.

I. Objectives of Experiment:

The major goal of this proposed research is to investigate the value of certain organic compounds labeled with carbon-11 ($T_{1/2} = 20$ min) in the detection of malignant neoplasms, with the ultimate objective the development of radiopharmaceutical agents and methods for the early diagnosis of cancer in man. Another objective is to develop new and better agents for visualizing and assessing the structure of specific organs, such as the pancreas.

This general proposal for the use of carbon-11 labeled compounds is generated by the need for review certification to satisfy the funding requirements of the National Cancer Institute (NCI) for grants involving research in human subjects. The grant entitled "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine" (RO1 CA14669-01) is presently in funding review by NCI. According to NCI regulations, certification must be within the twelve-month period prior to the beginning date of the grant. Note that each labeled compound will be submitted individually for review by the Committee on Human Studies following necessary synthetic and pre-clinical work.

II. Methods of Procedure:

In general the carbon-11 labeled compounds (examples listed in III-1) will be synthesized at the 86" cyclotron at the ORNL Y-12 Plant. After preliminary separation and purification, the labeled material will be transferred to the Medical Division where the final purification and sterilization will be made in the new clean room facility (laminar flow hoods). The exact methods used will depend on the individual compound involved. Following administration to patients multiple rectilinear and positron camera images will be obtained during a period of approximately

1-1/2 hours. Appropriate samples of blood and urine will be obtained for assay. Occasionally linear scans will be obtained. Patients will be adults with known cancer.

III. Possible Hazards and Their Evaluation:

1. Chemical:

The carbon-11 labeled compounds will be either carrier-free or in a state of very high specific activity. Consequently toxicity considerations will be minimal. Nevertheless each compound will be evaluated on its own for possible toxic effects following the adoption of a final synthetic scheme and testing in animals. As previously stated this information will be relayed to the Committee for their evaluation. Carbon-11 labeled compounds now under consideration are the following:

- a. 1-aminocyclopentanecarboxylic acid.
- b. tryptophan
- c. estradiol
- d. thymidine
- e. hyaluronidase
- f. ethidium bromide

These compounds have been established (from literature citations or ^{14}C tracer work at the Medical Division) as having potential as rapid organ and tumor localizing agents. There will be a continuing search in the course of this project for other agents as candidates for carbon-11 labeling.

2. Radiation Dose:

Carbon-11 has a 20.3 min half life decaying by positron emission (99+%). Because of its short half life the radiation dose to patients will be minimal. Each labeled compound will necessarily have to be evaluated on its own following distribution studies in animals at the specific activity levels planned for human administration. However, 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.

IV. Radionuclides and New Drugs:

Carbon-11 will be present in each of the agents to be tested clinically. The radiation dose from carbon-11 is discussed in III-2 above. The initial drugs to be tested are listed in III-1. As previously stated, each drug will receive thorough preclinical testing in animals and each will then be referred individually to the Committee for their evaluation. The ORAU

1030606

-3-

Medical Radionuclide Committee will also pass on each of the carbon-11 labeled agents. Following approval by these two committees an IND application will be made to the FDA before clinical investigation is commenced.

V. Responsibility of Principal Investigator:

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

Starting Date: Committee will be required to act on applications for each individual carbon-11 labeled agent as they become available.

Signatures:

<u><i>C. Lowell Edwards</i></u>	Principal Investigator
<u><i>R. L. Hayes</i></u>	Co-Investigator
<u><i>Lee C. Washburn</i></u>	Co-Investigator
<u><i>Bruce W. Wieland</i></u>	Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature	<u><i>Donald Anderson</i></u>
Title	<u>Chairman, Medical Division</u>
Institution	<u>Medical Division, ORAU</u>
Date	<u>February 28, 1974</u>

1030607

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities

Date: February 28, 1974

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

Co-Investigators: R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CARBON-11 LABELED COMPOUNDS FOR ORGAN AND TUMOR
LOCALIZATION.

I. Objectives of Experiment:

The major goal of this proposed research is to investigate the value of certain organic compounds labeled with carbon-11 ($T_{1/2} = 20$ min) in the detection of malignant neoplasms, with the ultimate objective the development of radiopharmaceutical agents and methods for the early diagnosis of cancer in man. Another objective is to develop new and better agents for visualizing and assessing the structure of specific organs, such as the pancreas.

This general proposal for the use of carbon-11 labeled compounds is generated by the need for review certification to satisfy the funding requirements of the National Cancer Institute (NCI) for grants involving research in human subjects. The grant entitled "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine" (RO1 CA14669-01) is presently in funding review by NCI. According to NCI regulations, certification must be within the twelve-month period prior to the beginning date of the grant. Note that each labeled compound will be submitted individually for review by the Committee on Human Studies following necessary synthetic and pre-clinical work.

II. Methods of Procedure:

In general the carbon-11 labeled compounds (examples listed in III-1) will be synthesized at the 86" cyclotron at the ORNL Y-12 Plant. After preliminary separation and purification, the labeled material will be transferred to the Medical Division where the final purification and sterilization will be made in the new clean room facility (laminar flow hoods). The exact methods used will depend on the individual compound involved. Following administration to patients multiple rectilinear and positron camera images will be obtained during a period of approximately

1030608

1-1/2 hours. Appropriate samples of blood and urine will be obtained for assay. Occasionally linear scans will be obtained. Patients will be adults with known cancer.

III. Possible Hazards and Their Evaluation:

1. Chemical:

The carbon-11 labeled compounds will be either carrier-free or in a state of very high specific activity. Consequently toxicity considerations will be minimal. Nevertheless each compound will be evaluated on its own for possible toxic effects following the adoption of a final synthetic scheme and testing in animals. As previously stated this information will be relayed to the Committee for their evaluation. Carbon-11 labeled compounds now under consideration are the following:

- a. 1-aminocyclopentanecarboxylic acid.
- b. tryptophan
- c. estradiol
- d. thymidine
- e. hyaluronidase
- f. ethidium bromide

These compounds have been established (from literature citations or ^{14}C tracer work at the Medical Division) as having potential as rapid organ and tumor localizing agents. There will be a continuing search in the course of this project for other agents as candidates for carbon-11 labeling.

2. Radiation Dose:

Carbon-11 has a 20.3 min half life decaying by positron emission (99+%). Because of its short half life the radiation dose to patients will be minimal. Each labeled compound will necessarily have to be evaluated on its own following distribution studies in animals at the specific activity levels planned for human administration. However, 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.

IV. Radionuclides and New Drugs:

Carbon-11 will be present in each of the agents to be tested clinically. The radiation dose from carbon-11 is discussed in III-2 above. The initial drugs to be tested are listed in III-1. As previously stated, each drug will receive thorough preclinical testing in animals and each will then be referred individually to the Committee for their evaluation. The ORAU

Medical Radionuclide Committee will also pass on each of the carbon-11 labeled agents. Following approval by these two committees an IND application will be made to the FDA before clinical investigation is commenced.

V. Responsibility of Principal Investigator:

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

Starting Date: Committee will be required to act on applications for each individual carbon-11 labeled agent as they become available.

Signatures: C. Lowell Edwards Principal Investigator
R. L. Hayes Co-Investigator
Lee C. Washburn Co-Investigator
Washburn Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Donald Andrews
 Title Chairman, Medical Division
 Institution Medical Division, ORAU
 Date February 28, 1974

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator R. L. Hayes Ident. No. 37

Project Title Carbon-11 Labeled Compounds for Organ and Tumor Localization

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

No human experimentation proposed at this time. (Form filled out to fulfill NIH requirements.)

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:

No risks; no experiments.

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

See above

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

Proposal for human studies to be submitted at a later time.

5. Other committee comments:

Approve _____

Disapprove _____

Donald G. Andrews M.D.
Chairman of Committee

11 December 1973

Date _____

25 Jan 1975 - Superseded by no. 38 & 39

1030611

MEMORANDUM

Dr. Gould Andrews

DATE April 10, 1974

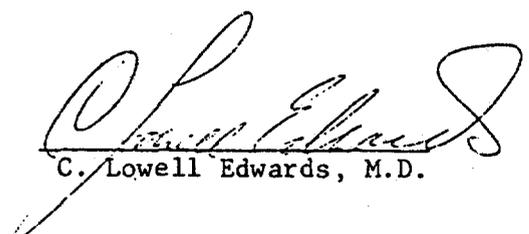
SUBJECT Two New Proposals to ORAU-ORNL Committee on Human Studies

COPIES TO

During the week of March 4-8 I contacted each of the six other members of the ORAU-ORNL Committee on Human Studies regarding two proposals circulated to them by mail on February 18, 1974. These proposals were (1) Esterase Activity and Mammalian Reproduction with Dr. R. L. Tyndall as principal investigator and (2) the one to cover animal studies designed to lead up to subsequent proposals for human use of carbon 11 with Dr. R. L. Hayes as principal investigator. *No 37*

In my phone and personal contact with the members of the committee none raised any objection, and it was agreed to approve these proposals without a meeting.

I suggest that these proposals be entered in our book and circulated for signatures as necessary.



C. Lowell Edwards, M.D.

gd

cc: Committee on Human Studies:

A. B. Brill
 M. E. Koons
 R. D. Lange
 T. A. Lincoln
 B. M. Nelson
 J. B. Storer

Dr. R. L. Hayes
 Dr. R. L. Tyndall

1030612

MEMORANDUM

TO Dr. EdwardsDATE 8 March 1974SUBJECT "Carbon-11 Labeled Compounds for Organ and Tumor Localizations" *No. 37*COPIES TO File

Mel Koons sent the following comment concerning your proposal:

"The project entitled "Carbon-11 Labeled Compounds for Organ and Tumor Localizations" meets with my approval, subject to the conditions stated in Dr. Edwards' letter to the Committee dated February 28." MEK

Gould A. Andrews

pe

1030613

OAK RIDGE ASSOCIATED UNIVERSITIES
INCORPORATED
P. O. BOX 117
OAK RIDGE, TENNESSEE 37830

Es 3. 1. 1974
F. ...
Date ... 11/74

AREA CODE 615
TELEPHONE 483-8411

February 28, 1974

TO: Committee on Human Studies

- Gould Andrews
- A. B. Brill
- M. E. Koons
- R. D. Lange
- T. A. Lincoln
- B. M. Nelson
- J. B. Storer

*... erod for file & for RH -
CLE -*

37
#38

We regret to have to bother you with this application at this time. However, as stated in the application, Dr. Hayes' grant for developing carbon-11 radiopharmaceuticals for human use is in funding review. He has been informed that he must have your committee's approval for this research which ultimately will lead to human experimentation.

We, Dr. Hayes and I, view this application as being merely extended to meet these requirements of NCI which we neither understand nor wish to challenge. I believe the wording in the application is such that it is clear we are not asking approval to use any isotope or drug in any patients. When this investigation has advanced to the point of human trials, the testing of each carbon-11 labeled drug will be regarded as a separate experiment and approval for its testing will be obtained from your committee before any is given to humans.

I plan to contact each of you by telephone Wednesday or Thursday, March 6-7 regarding Dr. Tyndall's proposal and would like to receive your comments about this one also.

1030614

March 74 Qualified Approval - B. J. P.

I have read the attached application (Ident No 35)

C. Lowell Edwards
C. Lowell Edwards, M.D.

dated 28 Feb 1974 and agree that approval for use of each agent to be administered to humans must be deferred pending presentation of data including studies in animals. However, I see no reason for delaying in vitro and animal studies in use of the agents listed

OAK RIDGE ASSOCIATED UNIVERSITIES

INCORPORATED

P. O. BOX 117

OAK RIDGE, TENNESSEE 37830

AREA CODE 615
TELEPHONE 483-8411

February 28, 1974

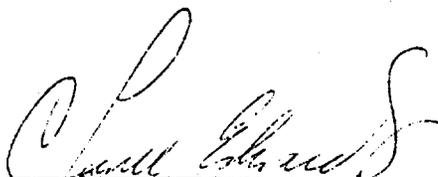
TO: Committee on Human Studies

- Gould Andrews
- A. B. Brill
- M. E. Koons
- R. D. Lange
- T. A. Lincoln
- B. M. Nelson
- J. B. Storer

We regret to have to bother you with this application at this time. However, as stated in the application, Dr. Hayes' grant for developing carbon-11 radiopharmaceuticals for human use is in funding review. He has been informed that he must have your committee's approval for this research which ultimately will lead to human experimentation.

We, Dr. Hayes and I, view this application as being merely extended to meet these requirements of NCI which we neither understand nor wish to challenge. I believe the wording in the application is such that it is clear we are not asking approval to use any isotope or drug in any patients. When this investigation has advanced to the point of human trials, the testing of each carbon-11 labeled drug will be regarded as a separate experiment and approval for its testing will be obtained from your committee before any is given to humans.

I plan to contact each of you by telephone Wednesday or Thursday, March 6-7 regarding Dr. Tyndall's proposal and would like to receive your comments about this one also.



C. Lowell Edwards, M.D.

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 12, 1975

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

Co-Investigators: G. A. Andrews, M.D.
R. L. Hayes, Ph.D.
L. C. Washburn, Ph.D.
B. W. Wieland, Ph.D.

Title of Project: CLINICAL USE OF CARBOXYL-LABELED ^{11}C -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 carboxyl-labeled ^{11}C -1-aminocyclopentane-carboxylic acid (ACPC) as a potential tumor-imaging agent. This work is being supported by NIH Grant 1 R01 CA 14669-01. This application is a re-submission of Ident. No. 38 (January 25, 1975) which the committee had given provisional approval.

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.

1030616

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.

Starting Date: October 1975

Signatures: Karl F. Hulme Principal Investigator
Gould Andrews 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 Acting Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date September 12, 1975

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 carboxyl-labeled ^{11}C -1-aminocyclopentanecarboxylic acid for tumor detection.

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: Carboxyl-labeled ^{11}C -1-aminocyclopentanecarboxylic 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 approximately 0.25 rad to the whole body.
4. Blood samples (2 ml) will be drawn at intervals during a period 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 _____

1030618

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

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

Project Title Clinical Use of Carboxyl-labeled ¹¹C-1-Aminocyclopentane-
Carboxylic Acid for Tumor Detection

1. In the opinion of this committee ~~the risks~~ ^{that} to the rights and welfare of the subjects in this project or activity are ~~are~~ *will be protected.*

The committee states that adequate safeguards against ~~these risks~~ *any untoward effects* 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 informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no psychological or sociological risks will exist for the subjects involved in this project.

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

5. Other committee comments:

Approve _____

Chairman of Committee _____

Disapprove _____

Date _____

1030619

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-3-¹¹C]
(¹¹C-DL-Tryptophan) for Pancreas Imaging

Proposal No.: 39a Date Approved: 2/21/80

3/2/81

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

Since April 1980 we have studied 9 patients under our amended IND. The results indicate that DL-tryptophan is rapidly taken up by cerebral structures in the brain, and in a few patients human/normal brain ~~to~~ concentration ratios are close to 1:1.

The last progress report to FDA was sent on Oct 20, 1980. Initial results have been presented at several national and international meetings. A paper is in preparation.

2. Report any complications.

None of the patients had any side effects or toxic manifestations from the ¹¹C-DL-tryptophan.

1030620

3. Are there any planned changes?

No changes are anticipated.

4. Do you wish the project to be continued?

Yes.

5. Comments.

None

1030621

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

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

1030622

MEMORANDUM

Dr. K. F. Hübner FROM ¹⁹⁸² 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

1030623

To Karl F. Hübner, M.D. From Dianne Gresham
Dr. Lange
Date June 22, 1983 Copies to 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

1030624



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

1030625

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.

1030626

MEDICAL AND HEALTH SCIENCES DIVISION
OAK RIDGE ASSOCIATED UNIVERSITIES, OAK RIDGE, TN

AMENDMENT TO IND 12,967

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

In the original IND 12,967 we have proposed to evaluate ^{11}C -DL-tryptophan 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-tryptophan to include patients with brain tumors. This study will consist of observations of the metabolism of ^{11}C -DL-tryptophan as evidenced by the localizing properties of the radiopharmaceutical in brain tumors (gliomas and meningiomas) and the relative specificity of tryptophan in certain brain tumor cell types. This hypothesis is supported by recent data from Robertson (in press, Journal of Neurosurgery).

Patients (approximately 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-tryptophan or detrimental radiation effects from the ^{11}C present. We will start our studies with full diagnostic doses (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-tryptophan?
2. Will the uptake of ^{11}C -DL-tryptophan in human brain tumors be sufficient to permit brain tumor imaging?
3. What is the optimum dose and scanning time for brain tumor visualization?

1030627

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.

1030628

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-1-¹¹C
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-1-¹¹C.
2. The drug contains the radioactive isotope ¹¹C 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

1030629

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-tryptophan-¹¹C 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-tryptophan-¹¹C.
2. The drug contains the radioactive isotope ¹¹C 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

1030630

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner Ident. No. 39a

Project Title USE OF ¹¹C-DL-TRYPTOPHAN 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 (by mail vote 11/79)

1030631

Disapprove

Robert W. Targy
Chairman of Committee

2/21/80

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

(April 26, 1985)

39a Use of 11C-DL-Tryptophan 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.

1030632



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 *Lynn Reeves*
 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 ¹¹C-DL-Tryptophan for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 39a Date Approved: 1980
Dr. Crook 4/19/85
 Signature of Principal Investigator Date Signed

1. Report progress made in past year:
 No clinical studies performed.

2. Report any complications:
 None

1030633

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1030634

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 ¹¹C-DL-Tryptophan for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 39a

Date Approved: 2/21/80

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 6 months.

2. Report any complications.

N.A.

1030635

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.

1030636

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-Tryptophan for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 39a Date Approved: 2/21/80

Karl F. Hübner

4/6/83

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

Two brain scans were done

^{11}C -DL-tryptophan may be more useful for amino acid studies of the brain than ^{11}C -DL-valine.

2. Report any complications.

No complications.

1030637

3. Are there any planned changes?

No changes planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

No comments

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: Use of ¹¹C-DL-Tryptophan for Localization of Brain Tumors by Positron Emission Computed Tomography

Proposal No.: 39a Date Approved: 2/21/80

Signature of Principal Investigator

Date Signed

1. Report progress made in past year. *Reporting period 3/1/81 - 3/31/82*
No studies were done; no progress.

2. Report any complications. *N.A.*

1030639

3. Are there any planned changes? No.

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

5. Comments. ^{The main} Reason for the apparent slow progress is long down time of the Cyclotron (June 1, 1981 - Jan 7, 1982) -



Oak Ridge
 Associated Post Office Box 117
 Universities 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 *Lynn Reeves*
 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~~ *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-Tryptophan [Side Chain-3-¹¹C]
 (¹¹C-DL-Tryptophan)

Proposal No. 39 Date 1976

JRC *5/14/86*
 Signature of Principal Investigator Date Signed

1. Report progress made in the past year.

No pt. studied

2. Report any complications. *None*

1030641

3. Are there any planned changes? *NO*

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

5. Comments. *✓*

1030642



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

ORAU/ORNL
Committee on Human Studies

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

Proposal No. 39

Date Approved: 1976

[Signature]
Signature of Principal Investigator

5/14/87
Date Signed

1. Report progress made in the past year. —

2. Report any complications.

NA1030643

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes.

5. Comments.

1030644

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 11 February 1974

Principal Investigator: Fred L. Snyder

Co-Investigators: _____

Title of Project: LIPID MARKERS IN HUMAN LEUKEMIC CELLS

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

I. Objectives of Experiment

In the proposed investigation we plan to assay O-alkyl and O-alk-1-enyl synthesizing enzymes in whole blood and in purified cells from normal individuals and patients afflicted with chronic and acute forms of leukemia. In connection with these enzyme assays, we also plan to carry out a detailed analysis of the lipid classes and their fatty acid composition to see if any distinguishing characteristics can be detected at various stages of development in different types of leukemia.

II. Methods of Procedure

Only blood samples will be analyzed. Typical volumes will range from 5 to 50 ml depending on the type of analysis to be carried out. The total number of samples will depend on the number of patients available.

III. Possible Hazards and their Evaluation

No hazards will be involved, since the analyses will require blood sampling procedures that are identical to those used for other clinical chemistry assays.

IV. Radioisotopes and New Drugs

None.

1030646

For D. A. Human Studies
Committee

Title of Project: LIPID MARKERS IN HUMAN LEUKEMIC CELLS

Ident. No. 40

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date 1 July 1974

Signatures: *Paul Snyder* Principal Investigator

_____ Co-Investigator

_____ "

_____ "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature *Gould Andrews*

Title Chairman, Medical Division

Institution Oak Ridge Associated Universities

Date February 11, 1974

1030647

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Fred Snyder Ident. No. 40

Project Title Lipid Markers in Human Leukemic Cells

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:

Although this proposal would undoubtedly be approved, since it was not formally presented to the Committee we cannot consider that it has been approved. Consideration of it could be reopened at a later date.

* Approve _____

Disapprove _____

Gould Cutners
Chairman of Committee

Feb. 11, 1974

Date

1030648

* Hold in abeyance

MEMORANDUM

TO Dr. G. A. Andrews FROM Fred Snyder 
DATE 6 September 1977 COPIES TO Files
SUBJECT PROPOSAL BEFORE COMMITTEE ON HUMAN STUDIES NO. 40.

Please remove the proposed grant (your No. 40) from your active files.

This proposal entitled "Lipid markers in human leukemic cells" was funded for one year by the Leukemia Research Foundation July 1, 1974 through June 30, 1975. A request for renewal was not submitted.

1030649

SEP 06 1977

February 11, 1974

Leukemia Research Foundation, Inc.
Chicago, Illinois

As chairman of our committee on Human Studies I am able to state that this committee will approve of Dr. Snyder's application. Since it involves only studies on blood samples of modest size, it is not necessary for the committee to meet in advance of sending the application. However, we will meet and approve the work before the work actually starts.

Gould A. Andrews, M.D.
Gould A. Andrews, M.D.

1030650

MEMORANDUM

TO Dr. SnyderDATE 3 February 75SUBJECT Proposed study: Lipid Markers in Human Leukemic CellsCOPIES TO File

As you know, on the basis of conversations held recently by telephone, we did not find it feasible to present the proposal, "Lipid Markers in Human Leukemic Cells," to our committee on human research. If you intend to go forward with work on this project, I believe we could probably get approval by mail, and I would be glad to work with you on adding a few points to your application which need to be included.

Gould A. Andrews, M.D.

pe

1030651

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: 5 March 1975

Principal Investigator: G. A. Andrews

Co-Investigators: W. Gibbs

C. Borkowski

K. Hubner

J. Harter

Title of Project: Clinical Testing of a Line Scanning Proportional
Counter Camera

I. Objectives of Experiment:

A special camera has been developed by C. J. Borkowski, M. K. Kopp, and J. A. Harter of Oak Ridge National Laboratory. This instrument gives promise of producing images of better resolution than can be obtained with existing nuclear medical equipment, although in its present version it will be largely limited to nuclides of relatively low energies — i. e., perhaps below 100 Kev. We propose to test the device on patients given diagnostic doses of ¹²⁵I as sodium iodide and ^{99m}Tc as pertechnetate to determine the quality of the images obtained. Where possible the two nuclides will be compared and, possibly opportunity will arise to compare the images with surgical specimens or with scans made on more conventional instruments.

II. Methods of Procedure:

Patients will be selected who are clinically believed to be in need of a thyroid scan because of nodules, enlargement, or asymmetry, or because of disturbances in thyroidal function. (This procedure will not per se provide quantitative data on thyroid function but such data will be obtained, where indicated, by chemical tests). We will attempt to obtain scans on at least ten patients, with the ^{125}I , of which about half will also have the pertech-netate scan done separately. Should preliminary results prove interesting, and clinically useful, the study might be extended to two or three times this number of patients. Doses will be $100\mu\text{c}$ of ^{125}I and 1 to 5 mc. of $^{99\text{m}}\text{Tc}$.

III. Possible Hazards and their Evaluation:

The diagnostic dose of ^{125}I appears the only possible hazard. The PDR (Physicians' Desk Reference for Radiology and Nuclear Medicine) on page 77 gives the following data:

<u>Thyroid Scan</u>	<u>Usual Dose</u>	<u>Radiation Dose in Rads to Thyroid</u>
^{131}I	0.05 Mc	65 - 90
^{125}I	0.05-1.0	45 - 90
$^{99\text{m}}\text{Tc}$	1	0 - 2

The added dose from pertechnetate is very slight and is believed justified. The possibilities that some portion of the detector might fall on the patient, or that the increased pressure within the detecting instrument could cause an explosion have been considered and we believed so remote as to be inconsequential.

IV. Radioisotopes and New Drugs

Both of these nuclide preparations are already in clinical use and available from standard sources.

The reason for submitting this proposal to the Committee is that it falls within the definition of a research project, particularly because a new instrument is being used.

- V. The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date _____

Signatures: Principal Investigator: _____

Co-Investigators: _____

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature _____

Title _____

Institution _____

Date _____

1030654

ORAU Consent for an Experimental Test

We solicit your assistance in our effort to carry out our mission — that of developing new techniques for using radioactive isotopes in medicine.

A new detector and scanning system has been developed at the Oak Ridge National Laboratory by Dr. Borkowski and his staff. It has been thoroughly tested in the laboratory and found to be safe, and is now ready to be tried on patient volunteers. When used with radionuclides of low energy radiation, it promises to produce better quality scans than present clinical scanning equipment.

We are seeking your cooperation in allowing us to make scans of your thyroid gland using this instrument. The experimental procedure involves no risk to you. Unless otherwise indicated, you will receive no additional radiation from this study. Only isotopes and dosages already established as safe and acceptable for thyroid scan studies will be used in the study.

The scans made with the new instrument will be compared to those made with standard scanners and the results may be used in scientific publications in which the tests are reported.

Since the instrument has not been tested in human patients we cannot promise any special benefit to you from your participation.

M.D.

Signature

I have read the above and found it to faithfully represent the description and conditions of the experimental test as described to me by Dr. _____ and that I willingly authorize the staff at ORAU to carry out the above described experimental test on me and to use the data and scans in their scientific publications.

Signature

Date _____

1030655

COMMENTS ON TRIALS WITH THE ORNL LINE SCANNING
PROPORTIONAL COUNTER (LSPC)

In the early experiments with this instrument there were distortions of the images. In some cases the thyroid gland appeared to be made up of broad transverse bars (with rounded ends) of activity. In other early scans the results came out as a group of very coarse rounded dots; these, too, were believed not to represent the true anatomical situation (although they might have been accepted as such if we were scanning a very thin slice of thyroid tissue). Another problem of the early images was that they did not indicate the size of the thyroid. All of these defects were eliminated, and the instrument was compared with the Picker scanner or the Ohio Nuclear scanner which yielded life size film images, and in some instances, colored scans on paper.

Each patient was given 0.1 mCi of ^{125}I orally and scanned usually at 24 hours (occasionally also at 48 hours) on both the LSPC and one of the standard scanners.

The results were as follows:

1. There was generally good correlation with the two types of images.
2. The LSPC as used sometimes showed evidences of activity beyond the limits of the image made with the standard scanner; thus a hypo-functioning nodule at the edge of the gland was sometimes better seen.
3. On the other hand, functioning nodules (not suppressing thyroid stimulating hormone) seemed delineated at least as well in the standard scan, but we need more cases to be sure of this.
4. There is some definite advantage in having more than one image to look at; we see this even when two serial images were made

1030656

with the standard scanner and without changing the instrument settings.

5. The use of a smaller number of counts with some LSPC images was sometimes helpful in that it emphasized the really high activity areas. The same thing would probably have been achieved with the Picker scanner by changing settings to make the recording with less sensitivity.
6. Our series of cases unfortunately included very few with thyroid nodules. For this reason we are not yet able to say which instrument was most sensitive in showing differences of count rate within the thyroid.
7. With whatever type of instrument that is used, it would be advantageous to store the data in a computer so that different levels of count rate could be used in print-outs; for example, when looking for slight activity at the edge of the thyroid or in looking for mildly hyperfunctioning nodules (not suppressing uptake in normal areas) within the thickest and most active part of the gland. Incidentally, the color scan recordings on paper were only slightly helpful in the latter situation, because of the arbitrary counting levels needed to change the color and because we were not always sure that this part of the scanning device was promptly and uniformly responsive to changing counting rates.

COMMENTS ON TRIALS WITH THE ORNL LINE SCANNING
PROPORTIONAL COUNTER (LSPC)

In the early experiments with this instrument there were distortions of the images. In some cases the thyroid gland appeared to be made up of broad transverse bars (with rounded ends) of activity. In other early scans the results came out as a group of very coarse rounded dots; these, too, were believed not to represent the true anatomical situation (although they might have been accepted as such if we were scanning a very thin slice of thyroid tissue). Another problem of the early images was that they did not indicate the size of the thyroid. All of these defects were eliminated, and the instrument was compared with the Picker scanner or the Ohio Nuclear scanner which yielded life size film images, and in some instances, colored scans on paper.

Each patient was given 0.1 mCi of ^{125}I orally and scanned usually at 24 hours (occasionally also at 48 hours) on both the LSPC and one of the standard scanners.

The results were as follows:

1. There was generally good correlation with the two types of images.
2. The LSPC as used sometimes showed evidences of activity beyond the limits of the image made with the standard scanner; thus a hypo-functioning nodule at the edge of the gland was sometimes better seen.
3. On the other hand, functioning nodules (not suppressing thyroid stimulating hormone) seemed delineated at least as well in the standard scan, but we need more cases to be sure of this.
4. There is some definite advantage in having more than one image to look at; we see this even when two serial images were made

1030658

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator G. A. Andrews Ident. No. 41

Project Title Clinical Testing of a Line Scanning Proportional Counter Camera

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

The radiation dose to the thyroid, while within accepted limits, is higher than the minimal that could be used for the clinical information.

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:

We have hopes of getting greater detailed information on thyroid nodules.

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

The procedure is explained to the patient and written consent is obtained.

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

Relative value of the results as compared with conventional scanning.

5. Other committee comments:

Approve X

Disapprove _____

Robert W. Savage
Chairman of Committee

27 August 1975
Date

1030659

MEMORANDUM

TO Committee on Human Studies FILE DATE 18 March 1975
SUBJECT Proposal No. 41 - Clinical Testing of a Line Scanning Proportional Counter
COPIES TO: File

I have had a verbal communication from Mel Koons, Robert Lange, John Storer, Lowell Edwards, Thomas Lincoln on this proposal and all have agreed on it. As a suggestion of Mr. Koon's, one additional word was inserted in the patient permission form. Dr. Brill has not been heard from because he is in South America. However, it is our belief that we are justified in proceeding with this study as we have the unanimous agreement of the other members of the committee.

Donald Andrews
Gould Andrews, M.D.

GAA:kn

1030660

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

11 March 1975

Memo to: Committee on Human Studies

Brill, A. B.
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lange, Robt D.
Storer, John B.

Subject: CLINICAL TESTING OF A LINE SCANNING PROPORTIONAL COUNTER CAMERA (Identification 41)

I am sending out a proposal that has little that is new in it mainly testing of an improved detection instrument developed by Cas Borkowski's group. We will probably reach you by telephone for your reaction, since we would like to get this work started quite promptly.



G. A. Andrews, Secretary

17 March 1975

This is a correction to the memo of 11 March 1975, i.e. Page 2, the sentence beginning "Doses..." should read 125I instead of 131I.

1030661

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

11 March 1975

Memo to: Committee on Human Studies

Brill, A. B.
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lange, Robt D.
Storer, John B.

Subject: CLINICAL TESTING OF A LINE SCANNING PROPORTIONAL COUNTER CAMERA (Identification 41)

I am sending out a proposal that has little that is new in it mainly testing of an improved detection instrument developed by Cas Borkowski's group. We will probably reach you by telephone for your reaction, since we would like to get this work started quite promptly.

G. A. Andrews, Secretary

1030662

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: April 15, 1975

Principal Investigator: Richard L. Tyndall, Ph.D.

Co-Investigator: Robert Lange, M.D.

Title of Project: PLASMA ESTERASE ANALYSIS IN CYCLIC NEUTROPENIC HUMANS

I. Objectives of Experiment:

Our studies in cyclic neutropenic dogs indicate serum esterase alteration correlates with marrow function. It is important to determine if plasma esterases in humans are physiologic indicators of marrow function which could be used clinically to predict impending blast cell crisis or to assess therapy in human leukemias.

II. Methods of Procedure:

Blood was drawn via finger prick three times a week for eight weeks from J. L. Law, Sophia Law, Pat Law, Susan Law, Janice Law, Brian Law, Jimmy Law, and C. G. Law.

III. Possible Hazards and their Evaluation: None.

IV. Radioisotopes and New Drugs: None.

V. Responsibility of Principal Investigator:

Before blood samples were obtained the procedures for obtaining the samples and the reason for obtaining them were discussed orally with each individual concerned. Likewise individual consent forms were prepared for and signed by the donors prior to collecting the samples. These signed consent forms are in the possession of Dr. Robert Lange.

Starting Date: July 1, 1974.

Signatures: *Richard Z. Lippold* Principal Investigator

Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature *Donald A. Anderson MD*

Title *Director of Clinical Applications*

Institution *ONAV*

Date *25 April '75*

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to:

Committee on Human Studies

Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
→ Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould A. Andrews

Gould A. Andrews

Enclosure

APPROVED: John B. Storer Date 5/1/75

1030665

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to: Committee on Human Studies

Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
→ Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould A. Andrews

Gould A. Andrews

Enclosure

APPROVED: _____

A. Lincoln

Date

4-31-75



1030666

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to: Committee on Human Studies

Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould A. Andrews
Gould A. Andrews

Must excuse myself from this
one since blood was drawn
under my direction RPL

Enclosure

APPROVED: _____ Date _____

1030667

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to:

Committee on Human Studies

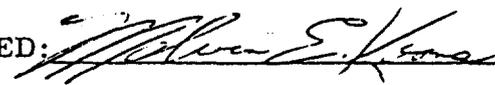
Andrews, G. A.
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Edwards, C. Lowell (ex officio)
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I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)


Gould A. Andrews

Enclosure

APPROVED:

 Date May 2, 1975

1030668

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to: Committee on Human Studies

→ Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould A. Andrews

Enclosure

APPROVED: *Gould A. Andrews*

Date 12 May 75

1030669

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to: Committee on Human Studies

Andrews, G. A.
→ Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould Andrews

Gould A. Andrews

Enclosure

APPROVED: i. B. Brill Date June 24, 1975

1030670

Oak Ridge Associated University

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

PL1

Telephone 615 483

28 April 1975

To:

Memo to:

Committee on Human Studies

Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robt D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

Princi

Co-Inv

Title

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

I. C

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Gould A. Andrews

Enclosure

II. M

J. L.
and C.

APPROVED: _____ Date _____

III. F

IV. F

1030671

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

28 April 1975

Memo to:

Committee on Human Studies

Andrews, G. A.
Brill, A. Bertrand
Edwards, C. Lowell (ex officio)
Koons, Melvin E.
Lange, Robert D.
Lincoln, Thomas A.
Lushbaugh, C. C. (ex officio)
Storer, John B.

I am sending you a format for a very simple experiment. If you will approve this, please sign and return. (Ident. No. 42: Plasma Esterase Analysis in Cyclic Neutropenic Humans, Richard L. Tyndall and Robert Lange.)

Gould A. Andrews

Gould A. Andrews

Enclosure

APPROVED: _____ Date _____

1030672

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 6-5-75Principal Investigator: D. C. Swartzendruber, Ph.D.Co-Investigators: C. C. Lushbaugh, M.D.Bill Nelson, M.D.

Title of Project: Morphogenesis of Colon Cancer: Electron
Microscopic Study of Human Adenocarcinomas

I. Objectives of Experiment:

Our objectives are to compare and correlate our findings in experimentally induced colon cancers in rodents and spontaneously occurring colonic cancers in marmosets with those in human colorectal adenocarcinomas. We intend to submit a grant request to NIH to support this work and prior approval for the use of human tissues is required by NIH.

II. Methods of Procedure:

Only tissue samples obtained from surgical resection and fixed by Dr. Bill Nelson, pathologist at East Tennessee Baptist Hospital or obtained by arrangements through other pathologists in the area will be used in our human studies. Our concentration is on tumors of the GI tract, mainly colorectal, but occasionally other tumors, e.g., ovarian, might be examined also for comparative purposes. We will use only material that has been deemed by the participating medical team, physicians, surgeon, and pathologist, necessary to remove at surgery. No requests will be made to obtain healthy tissues other than those removed by the decisions of the medical team during surgery.

III. Possible Hazards and their Evaluation:

None to the patients resulting from our handling of the surgically removed tissues.

IV. Radioisotopes and New Drugs

Not applicable.

1030673

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 6-5-75Principal Investigator: D. C. Swartzendruber, Ph.D.Co-Investigators: C. C. Lushbaugh, M.D.Bill Nelson, M.D.

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III. Possible Hazards and their Evaluation:

None to the patients resulting from our handling of the surgically removed tissues.

IV. Radioisotopes and New Drugs

Not applicable.

1030675

Title of Project: Morphogenesis of Colon Cancer

Ident. No. 43

V. Responsibility of Principal Investigator:

We will obtain materials only from the attending pathologist with the cooperation of the surgical team that has already received the patient's permission to undergo the necessary surgery. This statement will also include permission to publish or disseminate the information gained from our study and that the patient's rights to confidentiality will be upheld.

Starting Date July 1, 1975

Signatures: *J.C. Swartz* Principal Investigator
W. H. ... Co-Investigator
Bill Nelson "
_____" "
_____" "
_____" "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing on the institution:

Signature *[Signature]*

Title Acting Chairman,

Institution Medical and Health Sciences
Division

Date June 20, 1975

Lush -

I got a note from Lange pointing out that he had not received an answer on your proposal on human color as with Szentgyorgyi + Nelson -

I react in an "approval" response.

The purple flowers are globe amaranth (goussierina) - Yeah, I found it in my ^{garden} book. It's a kind of straw-flower or "everlasting".

What does Lange think about "procedural matters" are? I need to learn your ideas of the "power flow" on this committee

For instance, I don't believe that Robert Lange and you can make the decision to wait until January to comply with NIG requirements and those ^{of} the by-laws of this ⁿⁱ Committee as approved by ERDA. What do you think?

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator D. C. Swartzendruber Ident. No. 43

Project Title Morphogenesis of Colon Cancer: Electron Microscopic Study of Human Adenocarcinomas

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

None as long as confidentiality is maintained.

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:

Any increased understanding of the nature of colon cancer might lead to better management.

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

Surgical team will cooperate in obtaining permission to use tissue and publish results while maintaining confidentiality.

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

Results of EM studies as correlated with histologic type and clinical course.

5. Other committee comments:

Approve _____

Disapprove _____

Robert D. Lantz
Chairman of Committee

27 August 1975
Date

1030679

ORAU-ORNL HUMAN STUDIES COMMITTEE

Project Title: Morphogenesis of Colon Cancer: Electron Microscopic
Study of Human Adenocarcinomas (#43)

Investigators: Don Swartzendruber, Ph.D.

This project was placed on concluded or inactive status on
4/1/81. The documentation will be kept
(date)

on file in the Committee's records for at least three years.

If you should wish to reactivate the project, the Committee's approval must be obtained; but if still appropriate, the original written proposal may suffice.

Please return the following form to the secretary of the Committee.

I am aware that the project Morphogenesis of Colon Cancer: Electron
Microscopic Study of Human Adenocarcinomas

is no longer on the approved list of the ORAU-ORNL Human Studies Committee, and I have informed all coinvestigators (if any were originally listed) of this fact.



Senior Investigator

1030680

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. D. C. Swartzendruber
 FROM: Dianne Gresham, Secretary - Committee on Human Studies
 RE: Progress Reports
 DATE: February 27, 1981

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 17, 1981. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Morphogenesis of Colon Cancer: Electron Microscopic Study of Human Adenocarcinomas

Proposal No.: #43 Date Approved: 8/27/75

Donald Swartzendruber 3.2-81
 Signature of Principal Investigator Date Signed

1. Report progress made in past year. *No work on the case done during past year. Not required to continue the project as will terminate from ORAU in June,*

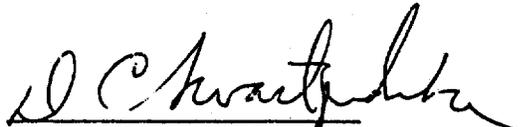
2. Report any complications.

1030681

MEMORANDUM

Dr. Gould A. Andrews FROM Dr. D. C. Swartzendruber
DATE September 26, 1977 COPIES TO File
SUBJECT STATUS OF PROJECT

In reference to your memo concerning the status of our project, "Morphogenesis of Colonic Cancer", we still receive surgical specimens from Dr. Bill Nelson as outlined in our previous proposal. We are interested in continuing this project on a modest (- 6 specimens/year) scale.


D. C. Swartzendruber

DCS:kn

1030682

SEP 26 1977



1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920

OFFICE OF THE DIRECTOR
(615) 971-3166

THE UNIVERSITY OF TENNESSEE
MEMORIAL RESEARCH CENTER

August 8, 1975

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

Dear Lush:

Have received approvals from 4 members of the committee on the proposal entitled Morphogenesis of Colon Cancer: Electron Microscopic Study of Human Adenocarcinomas. Perhaps Andy and Mel Koons are on vacation because I have not received a reply from them.

Andy, you, and I think we should have a meeting to settle procedural matters. Randy Brill would rather do it by mail. Do you think we can wait until January? For the next two months I will be away more than I am here.

Sincerely,

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

RDL:mse

cc: Dr. Andrews 8/13

1030683

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

June 30, 1975

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

- G. A. Andrews
- A. B. Brill
- M. E. Koons
- R. D. Lange
- C. C. Lushbaugh
- T. A. Lincoln
- J. B. Storer

disqualified as co-invest.

Subject: Morphogenesis of Colon Cancer: Electron Microscopic Study of Human Adenocarcinomas

This proposal has been submitted by Drs. D. C. Swartzendruber, C. C. Lushbaugh, and Bill Nelson, and I would like to have your opinion of it.

Approve _____

Disapprove _____

Believe meeting is necessary for consideration _____

Comment _____

Andrews
G. A. Andrews, M.D.
Secretary

→ P. S. Please send your reply directly to Dr. Lange

Ident. No. 44

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: Richard L. Tyndall

Co-Investigators: J. C. Daniel, Jr.

Title of Project: Amoeboid Cells in Human Placenta

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

1030685

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

I. Objective of Experiment

To determine if antisera prepared against a recently discovered [new] species of acanthamoeba isolated from cultured human chorio-carcinoma cells reacts with selected cells of human placenta.

II. Methods of Procedure

Placentas will be obtained at random from the Obstetrics Department of the Oak Ridge Hospital. No drugs, no screening or patient identification will be needed. Duration of the experiment will be from 6-12 months.

III. Possible Hazards and Their Evaluation

None

IV. Radioisotopes and New Drugs

None

1030686

Title of Project: Amoeboid cells in Human Placenta

Ident. No. _____

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date Feb 1976

Signatures: [Signature] Principal Investigator

[Signature] Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature [Signature]

Title Chairman, Medical and Health Sciences Div.

Institution Oak Ridge Associated Universities

Date 2-23-76

1030687

DRAFT
GAA:cw
12/4/75

OAK RIDGE NATIONAL LABORATORY
CONSENT FOR EXPERIMENTAL STUDIES ON PLACENTAL TISSUE

I, _____, of my own free will do consent to the
(Name)

donation for basic scientific study of a portion of placental tissue from my
expected delivery. I understand that this study will not alter in any way the
conduct of the delivery, and therefore, involves no risk to me or my baby.

I also understand and agree to the following:

- 1) I will derive no medical benefit from this study, but will
be making a contribution to scientific research.
- 2) The results of this study may be published in the scientific
literature, but will not indicate me by name as a donor of tissue.
- 3) Nothing in this study will interfere with the examination of the
placenta in the standard way as arranged by my personal physician.

DATE

SIGNED

WITNESS _____

1030688

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Richard L. Tyndall Ident. No. 44

Project Title Amoeboid Cells in Human Placenta

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 (by mail)

1030689

Robert W. Lang, MD
Chairman of Committee

Disapprove

June 25 1976

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

February 20, 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
T. A. Lincoln
J. B. Storer
J. B. Woods
C. C. Lushbaugh, ex officio

SUBJECT: Amoeboid Cells in Human Placenta

This proposal has been submitted by Drs. Richard L. Tyndall and J. C. Daniel, Jr., and I would like to have your opinion of it.

Approve _____

Disapprove _____

Believe meeting is necessary for consideration _____

Comment _____

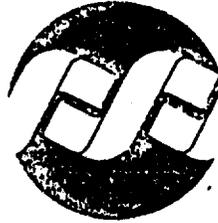


G. A. Andrews, M.D.
Secretary

GAA:dgb

P.S. Please send your reply directly to Dr. Lange.

1030690



1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37820
OFFICE OF THE DIRECTOR
(615) 871-3165

THE UNIVERSITY OF TENNESSEE
MEMORIAL RESEARCH CENTER

April 12, 1976

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

Dear Lush:

Some time ago I started receiving replies concerning the proposal submitted by Dr. R. Tyndall and J. C. Daniel. Two members of the committee have not responded. Among the remaining members, the project was approved by five, and one member thought a meeting was necessary.

Sincerely yours,

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

RDL/mse

Andy - Can you find out who needed the meeting and what his problem was? Then, if his problem still exists could you then put it on the agenda for the May 11 meeting?

1030691

*Dint
4/15/75*

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 - Oak Ridge, Tennessee 37830

Telephone 615 483-8411

April 15, 1976

*Human Use Committee file
for May 11th*

Dr. Richard L. Tyndall
Building 9207, Y-12 Plant
Oak Ridge, Tennessee 37830

Dear Dick:

The proposal submitted by you and Dr. Daniel entitled "Amoeboid Cells in Human Placenta" has been approved by most of the members of the Committee on Human Studies. One member raised a series of questions, and unfortunately, this member will not be present at our next meeting which is scheduled for May 11.

Therefore, it seems to me that it would be desirable to solve the problem by correspondence, if possible. The questions raised are as follows:

1. What are you going to tell the patient about the results of the test?
2. If only a few patients react, does this have any significance to either the mother or the baby?
3. Does this mean either existing or past infection with acanthamoeba?
4. If so, what does that mean to the patient?
5. Do the investigators have any obligation for later follow-up or notification if this finding is ever thought to have any clinical significance?

If you could send me a note with answers or comments on these questions, I would be glad to make it available to members of the Committee.

Sincerely,

Andy

Gould A. Andrews, M.D.

GAA:dgb

1030692

cc: ✓ Dr. C. C. Lushbaugh

Oak Ridge Associated Universities

Incorporated

P.O. Box 117 · Oak Ridge, Tennessee 37830

Telephone 615 483-8411

April 15, 1976

Dr. Richard L. Tyndall
Building 9207, Y-12 Plant
Oak Ridge, Tennessee 37830

Dear Dick:

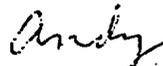
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3. Does this mean either existing or past infection with acanthamoeba?
4. If so, what does that mean to the patient?
5. Do the investigators have any obligation for later follow-up or notification if this finding is ever thought to have any clinical significance?

If you could send me a note with answers or comments on these questions, I would be glad to make it available to members of the Committee.

Sincerely,



Gould A. Andrews, M.D.

GAA:dgb 1030693

cc: Dr. C. C. Lushbaugh

OAK RIDGE NATIONAL LABORATORY

OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION



POST OFFICE BOX Y
OAK RIDGE, TENNESSEE 37830

May 4, 1976

Dr. Gould A. Andrews, M.D.
Medical Division
ORAU
P.O. Box 117
Oak Ridge, Tennessee 37830

Dear Andy:

Realative to the questions raised by one of the members of the Committee on Human Studies (see enclosed copy of your letter), I would answer as:

1. We will tell the patient nothing about the results because:
2. The results would have no known significance to mother or baby.
3. Finding of amoeboid cells in the placenta does not imply infection with Acanthamoeba and so:
4. It would mean nothing to the patient.
5. We are attempting to isolate amoeboid cells normally present in human placenta and if successful will determine if such cells share any antigens in common with species of pathogenic Acanthamoeba. No infection is implied and no obvious obligation is evident.

If further questions arise please don't hesitate to ask for classification.

Best regards,

A handwritten signature in dark ink, appearing to read "Tyndall", written over a horizontal line.

Richard B. Tyndall

RRT/jj

enclosure

1030694

MEMORANDUM

TO Dr. T. A. Lincoln

DATE June 21, 1976

SUBJECT Attached material

COPIES TO File

The other members of the Committee on Human Studies have approved Dr. Tyndall's proposal. I wonder if you feel your questions have been satisfactorily answered by this letter from him?

Andy

Gould A. Andrews, M.D.

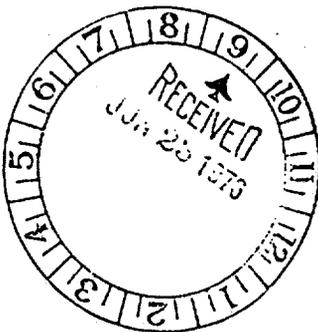
GAA:dgb

Enclosures

Gould:

I approve Dr. Tyndall's proposal as submitted.

Tom
T. A. Lincoln, M.D.



1030695

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

September 27, 1977

To: Dr. Gould Andrews

From: R. L. Tyndall

The two projects involving human use, i.e. esterase analysis of uterine materials and amoeboid cells in placental tissue, have been cancelled and no longer involve the human use committee. Individuals involved in these projects are aware of their inactive status.

If and when these projects are reactivated it would be under the jurisdiction of the University of Tennessee human use committee. Thanks for your past involvement in this matter.

RLT:cr

1030696

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

May 5, 1976

Principal Investigator: Karl F. Hübner, M.D. (ORAU) (9/29/77 MINUTES)
~~G. A. Andrews, M.D. (ORAU)~~

Co-Investigators: ~~K. F. Hübner, M.D. (ORAU)~~
F. V. Comas, M.D. (UTMRCH)
A. W. Nies, M.D. (Vanderbilt University)
R. L. Hayes, Ph.D. (ORAU)
L. C. Washburn, Ph.D. (ORAU)

Title of Project: PHASE I STUDIES OF THE RADIOPROTECTIVE AGENT
S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC
ACID (WR-2721)

I. Objectives of Experiment:

The long range objective of this study is the use of WR-2721, a radio-protective drug, to enhance the effectiveness of external radiation therapy of malignant disease. Two related aspects of clinical benefit can be postulated:

1. Using standard radiation doses, the drug could reduce undesirable side effects resulting from radiation injury of normal tissues without diminishing its effectiveness on a malignancy.
2. This drug might allow the administration of higher doses of radiation with greater anti-tumor effect without increasing the injury to normal tissues.

Both of the above postulates assume that the protection afforded by the drug is much greater for normal tissues than for tumors and that the radio-sensitivity of tumors remains essentially unchanged by the drug. This has been well documented in numerous animal studies (for details see IND to be submitted to FDA).

The short term objectives of this study are:

1. To test the safety of the drug administered intravenously in radio-protective doses in man.
2. To study the pharmacokinetics of the drug using a ³⁵S-labeled preparation.

1030697

II. Methods of Procedure:

The WR-2721 to be used will be supplied through the office of Dr. M. H. Heiffer, Chairman, Department of Pharmacology, Walter Reed Army Institute of Research, Washington, D.C. Sulfur-35 labeled WR-2721 will be synthesized by L. C. Washburn. (Details of the synthesis, purification, storage and quality controls to be exercised on both unlabeled and ³⁵S-labeled WR-2721 are detailed in the IND to be sent to FDA.)

Subjects will be between ages 21 and 75 with advanced malignancies. They will be ambulatory. These patients will not be receiving radiation on the day WR-2721 is administered. They will not be receiving cancer chemotherapy but may receive medication for relief of specific symptoms. Blood urea nitrogen should be less than 30 mg% and creatinine clearance greater than 50 ml/min. Serum bilirubin, lactic dehydrogenase (LDH) and glutamic oxalic transaminase (SGOT) will be within normal limits. Serum calcium and phosphorus will be normal. The arterial pressure must be greater than 100 mm Hg with an orthostatic drop of less than 20 mm Hg. The studies will be conducted under continuous observation by physician-investigators.

Patient-volunteers will be admitted to the University of Tennessee Memorial Research Hospital, Knoxville, Tennessee. Required laboratory values will be obtained prior to accepting the volunteer into the study.

During the dose-ranging study there will be at least one day between doses. In the first patient, the initial dose will be 0.2 mg/kg given intravenously by infusion pump over 10 minutes. Dose ranging will result in dose increases as follows: at doses of less than 2 mg/kg each subsequent dose will be 3 times the previous non-toxic dose. Between 2 and 10 mg/kg the increments will be double the preceding dose and at doses over 10 mg/kg the increments will be 130% of the previous dose. If no effect is seen in any one patient after a total of 4 doses, no further drug will be given to that patient.

The next patient will be begun at an initial dose that is 30 to 40% the maximal dose given to the preceding patient without significant toxicity. There will be a similar incremental sequence until 20 mg/kg has been given. If at any point during an infusion the suggestion of an unwanted effect is observed, the infusion rate will be attenuated or stopped. Also the development of any evidence of toxicity will be taken as an indication for considering decreasing the increment in the next dose to an amount less than that planned when no effect is seen.

Once 20 mg/kg is reached, subsequent patients will be initiated with a dose no greater than 8 mg/kg and the dose increments will be from 1.5 to 2.0 times the previous dose, based on the experience gained. At least 5 patients will be evaluated with the 20 mg/kg infusion.

The blood pressure will be measured in the supine and standing positions four times daily. On the day of drug administration, the blood pressure and pulse (supine) will be measured 5 minutes after starting the infusion, at its completion, then each 15 minutes for 1 hour, and for each hour for 4

1030698

hours. An electrocardiogram displayed on a monitor will be continuously monitored during the drug infusion and for the following hour.

Prior to drug administration the following laboratory studies will be done in addition to a physical examination: (1) 12 lead electrocardiogram; (2) liver function studies: SGOT, LDH, alkaline phosphatase, total serum proteins, serum albumin, prothrombin time, and bilirubin; (3) formed elements of the blood will be examined including packed cell volume, reticulocyte count, platelet count, white blood cell count and differential; (4) renal function evaluation including urinalysis, serum creatinine, blood urea nitrogen and creatinine clearance; (5) fasting blood sugar, electrolytes; and (6) calcium, inorganic phosphorus. Items 2 through 6 will be repeated 3 times weekly while the patient is receiving the drug. Item 6 will be repeated one hour following drug administration.

Dosage Schedule

<u>Day</u>	<u>Patient 1</u>	<u>Patient 2</u>	<u>Patient 3</u>	<u>Patient 4</u>	<u>Patient 5-8</u>
1	0.2 mg/kg	1.5 mg/kg	4.0 mg/kg	8 mg/kg	8 mg/kg
2					
3	0.6 mg/kg	3.0 mg/kg	8.0 mg/kg	12 mg/kg	12 mg/kg
4					
5	1.8 mg/kg	6.0 mg/kg	12.0 mg/kg	16 mg/kg	16 mg/kg
6					
7	3.6 mg/kg	10.0 mg/kg	16.0 mg/kg	20 mg/kg	20 mg/kg

If there are no toxic effects at any doses, patients 5-8 could receive only 3 doses: 8 mg/kg, 14 mg/kg, 20 mg/kg.

The ultimate use of WR-2721 will require multiple doses given daily or every other day 30 minutes prior to the tumor irradiation. To be certain that cumulative drug effects do not occur, pharmacokinetic studies at the probably effective dose will be necessary. Parameters measured will include: (1) elimination half-life; (2) apparent volume of distribution; and (3) plasma clearance, renal clearance. The same or similar subjects as in the phase I tolerance protocol will be used. At least four patients will be investigated.

The ³⁵S-labeled WR-2721 will be given at a level of 3.5 μ Ci/kg in a 20 mg/kg total dose, prepared aseptically from sterile powder and water. Venous blood will be drawn and serum frozen. Initially samples will be taken at 0, 2, 5, 10, 15, 30, 45, 60, 90 min. and 2, 4, 8, 12, and 24 hours after beginning the drug infusion. (In subsequent studies, sample times may vary to optimize the pharmacokinetic information depending on the initial results.) Urine will be collected 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours.

III. Hazards and Their Evaluation:

The toxicity of WR-2721 has been studied extensively in a number of different animals and the maximum dosage of WR-2721 (20 mg/kg) to be tested in this study does not appear to pose any great hazard to man. (Details of the results of animal studies are given in the IND.)

1030699

The intravenous dose which might afford radioprotection for normal tissues in man is estimated from experimental data to be 20 to 40 mg/kg. WR-2721 has previously been administered to 36 healthy volunteers in single oral doses up to 1500 mg. Toxicity included nausea and vomiting and diarrhea at the high doses. Chemical tests showed a transient small fall in serum calcium, rise in serum phosphorus and rise in serum creatinine. No other abnormal findings were noted.

Studies with ³⁵S-labeled WR-2721 in experimental animals have indicated an oral absorption in rodents of at least 30-40%. The drug is rapidly metabolized after intravenous administration and most of the drug is excreted by 48 hours after dosing. Cardiovascular effects of WR-2721 are not prominent. Intravenous boluses of 100 mg/kg in dogs and cats produced some pharmacologic evidence of ganglionic blockade but minimal drop in arterial pressure and no cardiac arrhythmias.

IV. Radioisotopes:

Sulfur-35 is a pure beta emitter (0.17 Mev) with a half-life of 87 days. The ³⁵S-labeled WR-2721 will be administered at a level of 3.5 µCi/kg (~250 µCi/70 kg). ORAU Internal Dosimetry Center has estimated that the whole body radiation dose (assuming uniform distribution and no excretion) will be 4.5 rads/mci (~1.1 rads/250 µCi). The dose should actually be a great deal less because of rapid excretion, i.e., approximately one-tenth.

V. Responsibility of Principal Investigator:

Patient volunteers will be recruited from patients in UTMCH and surrounding hospitals. An informed consent will be obtained from each patient (those 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 tolerance test with no promise of medical care beyond the period of this specific test.

Starting Date: August 1976.

Signatures: _____ Principal Investigator
 _____ Co-Investigator
 _____ Co-Investigator
 _____ Co-Investigator
 _____ Co-Investigator
 _____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the Institution:

Signature _____

Title Chairman, Medical and Health Sciences Division

Institution Oak Ridge Associated Universities

Date _____

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)

Tolerance test of S-2-(3-Aminopropylamino)ethylphosphorothioic Acid (WR-2721).

I have been fully informed of the possible discomforts and risks involved in testing this drug and realize that the procedure will not be of benefit to me but that it possibly will be to others. 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.

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 _____

1030702

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. (9/29/77 Minutes)
~~C. A. Andrews, M.D.~~ Ident. No. 46

Project Title Phase I Studies of the Radioprotective Agent S-2-(3-Aminopropylamino)
Ethylphosphorothioic Acid (WR-2721)

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.

Special care must be taken to avoid coercion of patients.

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

The consent form must include a listing of possible hazards. It will be necessary to get the approval of the UTRCH Committee on Human Experimentation.

4. Other committee comments:

Approve x

1030703

Robert D. Lange M.D.
Chairman of Committee

Disapprove

ORAU-ORNL HUMAN STUDIES COMMITTEE

Project Title: PHASE I STUDIES OF THE RADIOPROTECTIVE AGENT S-2-
(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID (WR-2721) (#46)

Investigators: Karl F. Hübner, M.D.

This project was placed on concluded or inactive status on
4/1/81. The documentation will be kept
(date)
on file in the Committee's records for at least three years.

If you should wish to reactivate the project, the Committee's approval must be obtained; but if still appropriate, the original written proposal may suffice.

Please return the following form to the secretary of the Committee.

I am aware that the project Phase I Studies of the Radioprotective
Agent S-2-(3-Aminopropylamino)ethylphosphorothioic Acid (WR-2721)

is no longer on the approved list of the ORAU-ORNL Human Studies Committee, and I have informed all coinvestigators (if any were originally listed) of this fact.

Karl F. Hübner
Senior Investigator

1030704

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: Phase I Studies of the Radioprotective Agent S-2-(3-Aminopropylamino) Ethylphosphorothioic Acid (WR-2721)

Proposal No.: 46 Date Approved: 5/11/76

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

Our entire supply of WR-2721 has been given to Dr. J. Yulish who has nearly finished Phase I studies at the University of New Mexico under their § 501 IND.

2. Report any complications.

~~As~~ As far as we know, no complications have occurred.

1030705

3. Are there any planned changes?

It appears that the Mid HSE is not going to work any longer with WR-272, neither independently or in collaboration with other institutions.

4. Do you wish the project to be continued?

I wish to discontinue the project.
A termination report will be prepared for F&A.

5. Comments. None

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

January 10, 1977

Dr. William J. Gyarfas, Director
Division of Oncology and Radiopharmaceutical
Drug Products
Bureau of Drugs
Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

IND

Dear Dr. Gyarfas:

This is in reference to our Notice of Claimed Investigational Exemption for a New Drug (IND) for S-2-(3-Aminopropylamino)-ethylphosphorothioic Acid (WR-2721), IND number 12,782, which was submitted on September 3, 1976.

It was stated in the IND that the WR-2721 to be used in the study was to be supplied through the office of Dr. Melvin H. Heiffer, Chairman, Department of Pharmacology, Walter Reed Army Institute of Research, Washington, D.C., and that over 500 grams of highly pure drug (lot AN) was being reserved for the proposed studies. However, analytical testing of the purity of lot AN prior to its administration to patients revealed the presence of unexpected impurities. We have available approximately 300 grams of WR-2721 (lot AH, which also came originally from Dr. Heiffer's laboratory, and was recrystallized three times at ORAU), and which, unlike lot AN, has an acceptable level of purity. This quantity is more than adequate for the proposed studies.

We propose then to change the drug lot used in the clinical studies as described above and for the reasons outlined above.

We are assuming that this letter will serve as a revision of the IND, and we will not start the study during the next 30 days. If you wish further information, it can be supplied by Dr. Lee Washburn of Oak Ridge Associated Universities.

Sincerely,

Gould A. Andrews

Gould A. Andrews, M.D.

GAA:dgb

cc: Dr. Al Biggs
Dr. Frank Comas
Dr. Anthony Girardi
Dr. Ray Hayes
Dr. Melvin Heiffer

Dr. C. C. Lushbaugh
Dr. Alan Nies
Dr. William Ulrich
Dr. Lee Washburn
Dr. John Yuhas

1030707

749 12, 772

Oak Ridge
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Post Office Box 117
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Medical and
Health Sciences
Division

August 17, 1977

IND 12,782

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

Dear Mr. Podliska:

This is a follow up on our telephone conversation and a yearly report on our study of the radiation protective agent WR-2721.

We are reporting that no clinical trials have been started as yet but that most of the year has been required for preparation and testing of the drug. Purified material from Lot AH has been formulated by Ben Venue Laboratories of Bedford, Ohio. Samples have been sent to Dr. Peter Lim of Stanford Research Institute and to Dr. Lee Washburn of Oak Ridge Associated Universities for testing.

By this autumn preparations are expected to be complete for initial clinical testing.

Sincerely,

Gould Andrews

Gould A. Andrews, M.D.
Principal Investigator

AVG
10/24

Anthony J. Girardi, Ph.D.
Director, East Tennessee Cancer
Research Center

GAA/sw

cc: Frank Comas
Karl Hübner
C. C. Lushbaugh

1030708

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

M E M O R A N D U M

TO: ORAU/ORNL Committee on Human Studies
FROM: Karl F. Hübner, M.D. *KFH*
RE: WR-2721 PROPOSAL
DATE: February 14, 1978

We would like to modify the pre-test laboratory criteria for patient selection for WR-2721 Phase I studies. We want to make this change because we found that the few patients that would have been eligible could not be taken into the study because of laboratory abnormalities especially elevated LDH values.

We would like to drop the requirement that the LDH should be normal before giving WR-2721. We would still have an appropriate evaluation of the liver function by determining serum bilirubin and SGOT levels. Please indicate on the attached card your approval or disapproval of this change and return it as soon as possible in the enclosed self-addressed, stamped envelope.

We will make the request for obtaining permission for this change from FDA after receiving your response to the change.

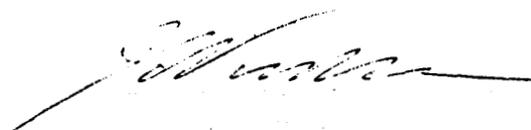
KFH:dg

1030709

CHANGE IN PROTOCOL OF WR-2721 - Identification No. 46 - IND No. 12,782

I approve of the change requested in the protocol for WR-2721 Phase I studies as explained to me by Dr. Karl F. Hübner in his memo of 2/14/78.

I disapprove of the change requested in the protocol for WR-2721 Phase I studies as explained to me by Dr. Karl F. Hübner in his memo of 2/14/78.



CHANGE IN PROTOCOL OF WR-2721 - Identification No. 46 - IND No. 12,782

I approve of the change requested in the protocol for WR-2721 Phase I studies as explained to me by Dr. Karl F. Hübner in his memo of 2/14/78.

I disapprove of the change requested in the protocol for WR-2721 Phase I studies as explained to me by Dr. Karl F. Hübner in his memo of 2/14/78.

Oak Ridge
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Universities

Post Office Box
Oak Ridge, Tennessee 37830
Telephone (615) 487-8111

Medical and
Health Sciences
Division

M E M O R A N D U M

TO: ORAU/ORNL Committee on Human Studies
FROM: Karl F. Hübner, M.D. *KFH*
RE: WR-2721 PROPOSAL
DATE: February 14, 1978

We would like to modify the pre-test laboratory criteria for patient selection for WR-2721 Phase I studies. We want to make this change because we found that the few patients that would have been eligible could not be taken into the study because of laboratory abnormalities especially elevated LDH values.

We would like to drop the requirement that the LDH should be normal before giving WR-2721. We would still have an appropriate evaluation of the liver function by determining serum bilirubin and SGOT levels. Please indicate on the attached card your approval or disapproval of this change and return it as soon as possible in the enclosed self-addressed, stamped envelope.

We will make the request for obtaining permission for this change from FDA after receiving your response to the change.

KFH:dg

1030711

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

March 9, 1979

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

Dear Mr. Podliska:

IND 12,782 - Progress Report

In our previous report we indicated that the clinical part of the WR-2721 project never got initiated at the University of Tennessee Hospital and Memorial Research Center in Knoxville. This was because of a lack of suitable patients. This situation has not changed. However, in the meantime, Dr. M. M. Kligerman, Director of the Cancer Research and Treatment Center at the University of New Mexico, has filed an IND on the same compound based on our IND and the WR-2721 drug as formulated by the Medical and Health Sciences Division of ORAU.

ORAU staff will collaborate with the University of New Mexico group in Phases I and II of the study as well as in the biodistribution and kinetic studies with ³⁵S-labeled WR-2721 (the latter will be prepared by the ORAU Radiopharmaceutical Development Group).

I shall keep you informed on our continued involvement in this project.

Sincerely,

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

KFH:dg

1030712

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 _____.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Phase I Studies of the Radioprotective Agent S-2-(3-Aminopropylamino)ethylphosphorothioic Acid (WR-2721)

Proposal No.: 46 Date Approved: 1976

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

No patients have received WR-2721 under the ORAU IND ^{at the Med School of NM.} 17 patients have been given ~~WR-2721~~ WR-2721 formulated at ORAU. At dose levels of 10 mg/kg (half of the final dose that we have proposed) only minimal signs of toxicity (nausea) have been observed. The study continues here.

2. Report any complications. none

3. Are there any planned changes?

We are negotiating a collaborative project with Dr. Stroup ~~at the~~ ^{of} Dept. of Radiation Biology at Vanderbilt University.

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

5. Comments. *None*

MEDICAL AND HEALTH SCIENCES DIVISION (MHS-D)
OAK RIDGE ASSOCIATED UNIVERSITIES (ORAU), OAK RIDGE, TENNESSEE 37830

AMENDMENT TO IND 13,383

Use of ^{68}Ga -EDTA Aerosol for Quantitative Ventilation Studies by Positron
Emission Computed Tomography (ECT)

We propose to test the use of ^{68}Ga -EDTA for diagnostic evaluation of lung air spaces by positron emission computed tomography (ECT). One distinct advantage of any ^{68}Ga labeled radiopharmaceutical, if proven useful, is that ^{68}Ga (T-1/2 68 min), unlike ^{13}N and ^{11}C agents, is readily available from a ^{68}Ge -generator with a 287 day half life. Clinical diagnostic applications of ^{68}Ga -EDTA aerosol ECT would complement perfusion studies with ^{68}Ga -labeled microspheres (3M) as described in our IND 16,363.

Preparation and Administration of ^{68}Ga -EDTA Aerosol

Gallium will be prepared by the procedure described in IND #13,383.

Aerosol production and inhalation will be done according to the method of Taplan and Chopra (1, 2). A copy of the most recent version of Dr. G. Taplan's procedure is attached to this amendment.

The ^{68}Ga -EDTA will be of high specific activity (0.5 to 1 mCi/ml) so that small volumes may be nebulized in a relatively short time for fairly rapid administration of the dose. The dose of ^{68}Ga -EDTA aerosol proposed in this study is not to exceed an activity of 1.5 mCi of ^{68}Ga per study. The chemical quantity of Na_2EDTA will not exceed 3 mg.

Patient Population of the Study

Patients to be included in this study are patients with one of three pulmonary disease states:

- (a) Sarcoidosis
- (b) Radiation fibrosis or pneumonitis
- (c) Chronic obstructive pulmonary disease (COPD)

The patients are going to be studied on an outpatient basis referred by the UT-Memorial Hospital Radiology Department, Radiation Oncology Department, and the Knoxville Pulmonary Group.

Control subjects are not included. Test results will be compared to diagnostic findings and values obtained with conventional diagnostic modalities. In addition, patients who are scheduled to receive radiation therapy to the chest (patients with mammary carcinoma, and patients with Hodgkin's Disease) offer the opportunity to compare "normal" test results collected before the start of treatment or from areas of the lung not directly affected by the treatment with results obtained with ^{68}Ga -EDTA aerosol.

1030715

A sample of the "Informed Consent Form" for this study is attached to this amendment.

Summary of Research Protocol

Ten to 20 patients are scheduled for each disease category.

(a) Sarcoidosis patients are scheduled to have physiologic pulmonary function studies and a chest radiogram and tomographic ECT scans with ^{68}Ga -EDTA aerosol and ^{68}Ga -microspheres at the time of diagnosis and at 3 months intervals as the course of the disease may indicate.

(b) Patient selected for radiation therapy (to the axillae, the cervical and mediastinal regions) will have the same studies as indicated for patients under (a) above on the following schedule: before beginning radiation therapy, at 4 weeks or 2/3 of the way through the treatment period, at the end of therapy, and at monthly intervals for a period of 9 months following completion of radiotherapy.

(c) Patients with COPD will only have one set of studies, since changes of pulmonary function are likely to occur only slowly in this type of disease. However, changed pulmonary function due to COPD could provide a good test for the sensitivity and specificity offered by the different diagnostic methods to be compared in this study.

It is anticipated that the study will be completed within two years after approval of this amendment to IND #13,383.

Risks from ^{68}Ga -EDTA Aerosol Lung Studies

No chemical or pharmaceutical risks can be foreseen with the chemical amounts of ^{67}Ga and EDTA as proposed for this clinical investigation. The risk from the radiation associated with the use of ^{68}Ga -EDTA by inhalation is exceedingly small. The ORAU Internal Dose Information Center estimates the radiation dose from ^{68}Ga -EDTA aerosol to be 2.8 rad/mCi, assuming complete deposition in the lungs with no loss from that organ during decay.

References

Taplin, George V., and Chopra, Sawtantra K. Inhalation lung imaging with radioactive aerosols and gases. Prog. Nucl. Med., 5, 119-143, 1978.

Taplin, George V., and Chopra, Sawtantra K. Lung perfusion-inhalation scintigraphy in obstructive airway disease and pulmonary embolism. Rad. Clin. of N. Amer., 16, 491-513, 1978.

Internal Approval of this Amendment Was Obtained

Internal approval of this amendment was obtained by the ORAU Medical Isotopes Committee on May 21, 1979 and by the ORAU/ORNL Committee on Human Studies on July 2, 1979.

Starting Date: August 15, 1979

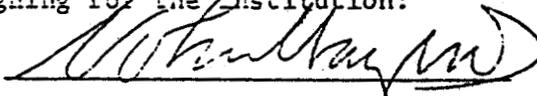
Signatures: Karl F. Holmes Principal Investigator
Raymond L. Hayes Co-Investigator

Division Review:

The application described above has been reviewed and approved.

Official signing for the Institution:

Signature:



Title: Chairman, Medical & Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: 7/9/79

1030717

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 (circle):

- (a) Pulmonary perfusion study with ^{99m}Tc -microspheres.
- (b) Pulmonary ventilation study with ^{133}Xe nenon.
- (c) Pulmonary perfusion study with ^{68}Ga -microspheres.
- (d) Pulmonary ventilation study with Gallium-68 ethylenediamine-NNN'N'-tetraacetic acid (^{68}Ga -EDTA) aerosol.

I understand that procedures (a) and (b) are routine diagnostic tests and the perfusion study with ^{68}Ga -microspheres and the ventilation study with ^{68}Ga -EDTA aerosol are experimental in nature, but only to the extent that the radioactive label of the microspheres is a different one and that EDTA is being used instead of diethylenetriaminepentaacetic acid (DTPA). This new label (^{68}Ga Gallium) permits the use of a special scanner (ECAT) for detailed 3-dimensional pictures of the lung. The amount of EDTA present in the aerosol is only a very small fraction of the amounts used in medical practice for treatment purposes. I have been assured that the same pharmaceutical and radiological precautions are being exercised with the experimental procedures as with procedures (a) and (b). The risk of these is small with regard to radiation dose which is about two times as high in procedures (c) and (d) as for procedures (a) and (b) combined.

There should not be any pharmacological effect, and the number and size of microspheres injected is so small that no problems are anticipated.

I have been fully informed of the possible risks and understand that the results of this diagnostic procedure may not necessarily be of benefit to me. I understand that these tests are part of a research program and do not object if any information relating to my case is published in professional journals or medical books, or used for other purposes which my physician deems 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 am not to be identified by name.

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: _____

1030718

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 diagnostic procedure:
(myself)

- (a) Pulmonary ventilation study with ^{133}Xe Xenon.
- (b) Pulmonary perfusion study with $^{99\text{m}}\text{Tc}$ -microspheres.
- (c) Pulmonary perfusion study with ^{68}Ga -microspheres.
- (d) Pulmonary ventilation study with Gallium-68 ethylenediamine-NNN'N'-tetraacetic acid (^{68}Ga -EDTA) aerosol.

I have been informed that procedures (a) and (c) are routine diagnostic procedures for the detection of lung disease. The perfusion study with ^{68}Ga -microspheres is experimental in that the radioactive label is only new and different from $^{99\text{m}}\text{Tc}$ (technetium). The microspheres are the same for procedures (b) and (c).

The study with ^{68}Ga -EDTA aerosol is similar to routine aerosol studies with $^{99\text{m}}\text{Tc}$ -DTPA studies. The ^{68}Ga -label permits the use of a special scanner (ECAT) for detailed 3-dimensional pictures of the lung.

I understand that the microspheres are microscopically small particles that will lodge in a small number of capillaries in my lung and that the staff of ORAU makes every effort to control and check the number and the size of these particles so that the risk of blocking a larger than intended number of lung capillaries will be exceedingly small. The risks involved in these procedures are very minimal. Risks from the ^{68}Ga -EDTA aerosol are not known; however, the amount of EDTA is only a small fraction of what is being used in medical practice for treatment purposes.

I understand that procedures (c) and (d) are experimental. The experimental nature is explained by the difference of the type of radioactive label and use of a different detector or scanner than in procedure (a) and (b). The scanner to be used is an ECAT scanner.

The radiation dose from the radioactive portion of these scanning agents to the lungs and/or whole body is exceedingly small (less than 3 rad) when compared to the doses of radiation that I will receive in the course of my radiation therapy (several 1000 rads).

(Radiation Pneumonitis)

1030719

The information gained from these studies may be helpful in recognizing early radiation pneumonitis which might develop as a complication of my radiation therapy. However, there is no assurance that this will be the case or that it will be of help to the radiotherapist in the management of my treatment.

I understand that these tests are part of a research program and do not object if any information relating to my case is published in professional journals or medical books, or used for any other purpose which my physician deems proper in the interest of medical education, knowledge, or research; provided, however, it is specifically understood that in such publication or use I am not to be identified by name.

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: _____

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615-433-5411 576-3098

Medical and
Health Sciences
Division

M E M O R A N D U M

TO: ORAU/ORNL Committee on Human Studies
FROM: Dianne Gresham *dg*
DATE: June 6, 1979
RE: Amendment #48a

An amendment for proposal #48 (IND 13,383) is enclosed for your review. The original proposal was submitted to the Committee and approved on April 27, 1977. However, the FDA now requires all amendments to be reviewed and approved by the Committee before FDA will consider it. A voting form is attached to Amendment 48a; please study the amendment carefully and return the voting form to me at your earliest convenience in the enclosed self-addressed envelope.

Your cooperation in expediting your response to the amendment will be greatly appreciated.

dg

Attachments

MEDICAL AND HEALTH SCIENCES DIVISION (MHSD)
OAK RIDGE ASSOCIATED UNIVERSITIES (ORAU), OAK RIDGE, TENNESSEE 37830

AMENDMENT TO IND 13,383

Use of ^{68}Ga -EDTA Aerosol for Quantitative Ventilation Studies by Positron
Emission Computed Tomography (ECT)

We propose to test the use of ^{68}Ga -EDTA for diagnostic evaluation of lung air spaces by positron emission computed tomography (ECT). One distinct advantage of any ^{68}Ga labeled radiopharmaceutical, if proven useful, is that ^{68}Ga (T-1/2 68 min), unlike ^{13}N and ^{11}C agents, is readily available from a ^{68}Ge -generator with a 287 day half life. Clinical diagnostic applications of ^{68}Ga -EDTA aerosol ECT would complement perfusion studies with ^{68}Ga -labeled microspheres (3M) as described in our IND 16,363.

Preparation and Administration of ^{68}Ga -EDTA Aerosol

Gallium will be prepared by the procedure described in IND #13,383.

Aerosol production and inhalation will be done according to the method of Taplan and Chopra (1, 2). A copy of the most recent version of Dr. G. Taplan's procedure is attached to this amendment.

The ^{68}Ga -EDTA will be of high specific activity (0.5 to 1 mCi/ml) so that small volumes may be nebulized in a relatively short time for fairly rapid administration of the dose. The dose of ^{68}Ga -EDTA aerosol proposed in this study is not to exceed an activity of 1.5 mCi of ^{68}Ga per study. The chemical quantity of Na_2EDTA will not exceed 3 mg.

Patient Population of the Study

Patients to be included in this study are patients with one of three pulmonary disease states:

- (a) Sarcoidosis
- (b) Radiation fibrosis or pneumonitis
- (c) Chronic obstructive pulmonary disease (COPD)

The patients are going to be studied on an outpatient basis referred by the UT-Memorial Hospital Radiology Department, Radiation Oncology Department, and the Knoxville Pulmonary Group.

Control subjects are not included. Test results will be compared to diagnostic findings and values obtained with conventional diagnostic modalities. In addition, patients who are scheduled to receive radiation therapy to the chest (patients with mammary carcinoma, and patients with Hodgkin's Disease) offer the opportunity to compare "normal" test results collected before the start of treatment or from areas of the lung not directly affected by the treatment with results obtained with ^{68}Ga -EDTA aerosol.

1030722

A sample of the "Informed Consent Form" for this study is attached to this amendment.

Summary of Research Protocol

Ten to 20 patients are scheduled for each disease category.

(a) Sarcoidosis patients are scheduled to have physiologic pulmonary function studies and a chest radiogram and tomographic ECT scans with ^{68}Ga -EDTA aerosol and ^{68}Ga -microspheres at the time of diagnosis and at 3 months intervals as the course of the disease may indicate.

(b) Patient selected for radiation therapy (to the axillae, the cervical and mediastinal regions) will have the same studies as indicated for patients under (a) above on the following schedule: before beginning radiation therapy, at 4 weeks or 2/3 of the way through the treatment period, at the end of therapy, and at monthly intervals for a period of 9 months following completion of radiotherapy.

(c) Patients with COPD will only have one set of studies, since changes of pulmonary function are likely to occur only slowly in this type of disease. However, changed pulmonary function due to COPD could provide a good test for the sensitivity and specificity offered by the different diagnostic methods to be compared in this study.

It is anticipated that the study will be completed within two years after approval of this amendment to IND #13,383.

Risks from ^{68}Ga -EDTA Aerosol Lung Studies

No chemical or pharmaceutical risks can be foreseen with the chemical amounts of ^{67}Ga and EDTA as proposed for this clinical investigation. The risk from the radiation associated with the use of ^{68}Ga -EDTA by inhalation is exceedingly small. The ORAU Internal Dose Information Center estimates the radiation dose from ^{68}Ga -EDTA aerosol to be 2.8 rad/mCi, assuming complete deposition in the lungs with no loss from that organ during decay.

References

Taplin, George V., and Chopra, Sawtantra K. Inhalation lung imaging with radioactive aerosols and gases. Prog. Nucl. Med., 5, 119-143, 1978.

Taplin, George V., and Chopra, Sawtantra K. Lung perfusion-inhalation scintigraphy in obstructive airway disease and pulmonary embolism. Rad. Clin. of N. Amer., 16, 491-513, 1978.

Internal Approval of this Amendment Was Obtained

Internal approval of this amendment was obtained by the ORAU Medical Isotopes Committee on May 21, 1979 and by the ORAU/ORNL Committee on Human Studies on

1030724

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 diagnostic procedure (circle):
(myself)

- (a) Pulmonary perfusion study with ^{99m}Tc -microspheres.
- (b) Pulmonary ventilation study with $^{133}\text{Xenon}$.
- (c) Pulmonary perfusion study with ^{68}Ga -microspheres
- (d) Pulmonary ventilation study with ^{68}Ga -EDTA aerosol

I understand that procedures (a) and (b) are routine diagnostic tests and the perfusion study with ^{68}Ga -microspheres and the ventilation study with ^{68}Ga -EDTA aerosol are experimental in nature, but only to the extent that the radioactive label of the microspheres is a different one and that EDTA is being used instead of DTPA. This new label ($^{68}\text{Gallium}$) permits the use of a special scanner (ECAT) for detailed 3-dimensional pictures of the lung. The amount of EDTA present in the aerosol is only a very small fraction of the amounts used in medical practice for treatment purposes. I have been assured that the same pharmaceutical and radiological precautions are being exercised with the experimental procedures as with procedures (a) and (b). The risk of these is small with regard to radiation dose which is about two times as high in procedures (c) and (d) as for procedures (a) and (b) combined.

There should not be any pharmacological effect and the number and size of microspheres injected is so small that no problems are to be anticipated.

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 do not object if any information relating to my case may be published in professional journals or medical books, or used for any other purpose which my physician may deem proper in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified by name.

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: 1030725 Witness: _____

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 diagnostic
(myself)
procedure:

- (a) Pulmonary ventilation study with $^{133}\text{Xenon}$
- (b) Pulmonary perfusion study with $^{99\text{m}}\text{Tc}$ -microspheres
- (c) Pulmonary perfusion study with ^{68}Ga -microspheres
- (d) Pulmonary ventilation study with ^{68}Ga -EDTA aerosol

I have been informed that procedures (a) and (c) are routine diagnostic procedures for the detection of lung disease. The perfusion study with ^{68}Ga -microspheres is experimental in that the radioactive label is only new and different from $^{99\text{m}}\text{Tc}$ (technetium). The microspheres are the same for procedures (b) and (c).

The study with ^{68}Ga -EDTA aerosol is similar to routine aerosol studies with $^{99\text{m}}\text{Tc}$ -DTPA studies. The ^{68}Ga -label permits the use of a special scanner (ECAT) for detailed 3-dimensional pictures of the lung.

The risks involved in these procedures are very minimal, but I understand that the microspheres are microscopically small particles that will lodge in a small number of capillaries in my lung and that the staff of ORAU makes every effort to control and check the number and the size of these particles so that the risk of blocking a larger than intended number of lung capillaries will be exceedingly small. Risks from the ^{68}Ga -EDTA aerosol are not known. The amount of EDTA is only a small fraction of the amounts that are being used in medical practice for treatment purposes.

I understand that procedures (c) and (d) are experimental. The experimental nature is explained by the difference of the type of radioactive label and also by using a different detector or scanner than in procedure (a) and (b). The scanner to be used is an ECAT scanner.

The radiation dose from the radioactive portion of these scanning agents to the lungs and/or whole body is exceedingly small (less than 3 rad) when compared to the doses of radiation that I will receive in the course of my radiation therapy (several 1000 rads).

(Radiation Pneumonitis)

1030726

The information gained from these studies may be helpful in recognizing early radiation pneumonitis which might develop as a complication of my radiation therapy. However, there is no assurance that this will be the case or may be of help to the radiotherapist in the management of my treatment.

I understand that these tests are part of a research program and do not object if any information relating to my case may be published in professional journals or medical books, or used for any other purpose which my physician may deem proper in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified by name.

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: _____

(Radiation Pneumonitis)

1030727

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831
Telephone ~~615-472-8444~~ 576-3098

Medical and
Health Sciences
Division

July 9, 1979

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:

Amendment to IND 13,383

The clinical investigations with ⁶⁸Ga-EDTA under IND 13,383 as originally approved by FDA in April, 1977, were to include diagnostic studies and imaging of kidneys and bladder, the brain, and soft tissue tumors. A progress report for this project was sent to you on August 7, 1978.

We would like to expand the diagnostic use of ⁶⁸Ga-EDTA for certain lung diseases and request your permission to submit an amendment to the IND #13,383. The amendment and the study protocol are attached on a separate sheet for your consideration.

Sincerely,

Karl F. Hübner
Karl F. Hübner, M.D.

KFH:dg

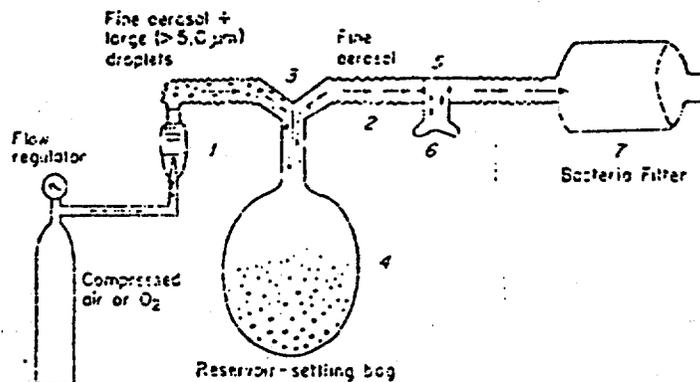
Enclosure

1030728

UCLA AEROSOL INHALATION APPARATUS AND PROCEDURE

(G.V. Taplin, M.D. and Dennis Elam, M.S.)

DIAGRAM-ADMINISTRATION SYSTEM



LIST OF COMPONENTS

- 1) Positive Pressure Nebulizer (driven by compressed air or oxygen at a flow rate of 10 liters/minute).
- 2) Disposable tubing
- 3) "Y" Connector
- 4) Reservoir-Settling bag (removes aerosol droplets $>2.0 \mu\text{m}$ by sedimentation, impaction and turbulence).
- 5) Two-way breathing valve
- 6) Mouthpiece
- 7) Bacteria Filter (traps any aerosol leaving the system from patient's exhaled air)

ADMINISTRATION PROCEDURE

- 1) Assemble system as shown in diagram and shield behind 1/8 inch lead. Rinse the reservoir-settling bag (4) with saline and attach to the "Y" connector (3) with a large rubber band. (This wetting of the bag decreases the amount of aerosol that will stick to it).
- 2) Explain the procedure to the patient.
- 3) Fill the Nebulizer with high specific activity $^{99\text{m}}\text{Tc-DTPA}$ (15-20 $\mu\text{Ci/ml}$, 3-4 ml total).
- 4) Clamp the tubing between the bag and the two-way breathing valve with a hemostat. (See (2) in diagram).
- 5) Turn the O_2 on to a flow rate of 10 liters/minute and fill the bag with aerosol
- 6) When the bag is full, turn the O_2 off.
- 7) Attach nose clip to patient. (Be certain that no air can pass in or out of his nose).

1030729

- 8) Simultaneously, place the mouthpiece between the patient's lips and teeth and unclamp the hemostat.
- 9) Instruct the patient to relax and to breathe as normally as possible.
- 10) Inhale the patient until the count rate over the posterior chest indicates $\sim 2-3$ mCi retained (~ 150 K counts/min/mCi with our camera). This usually takes 2-3 minutes.
- 11) Turn O_2 back on anytime the bag appears about $\frac{1}{2}$ full. This will usually be necessary several times during the inhalation procedure, depending upon the patient's tidal volume. (Occasionally, the O_2 is left on throughout the inhalation procedure).

If after explaining the procedure (step 2) to the patient, he still seems apprehensive, run through the entire procedure using saline in the nebulizer instead of Tc-DTPA.

The extremely ill patient may need frequent interruptions during the inhalation procedure. Interruptions after every 30 seconds of inhalation are quite possible without jeopardizing the quality of the examination. (Be sure to turn O_2 off and clamp tubing with hemostat to prevent radioactive contamination).

1030730

Oak Ridge
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Telephone 615-483-8411
(615) 576-3098

Medical and
Health Sciences
Division

September 5, 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, MD 20857

Dear Dr. Gyarfas:

IND 13,383

This is the second progress report on clinical diagnostic applications with gallium-68-EDTA (IND 13,383). Only three additional patients have been studied with this radiopharmaceutical since August of 1978. These patients belonged in the category of "renal disease" and "detection of obscure soft tissue tumors." The imaging was done with the EG&G-ORTEC ECAT scanner. So far, the results have not been very encouraging despite the advantage of the three-dimensional display capability of the ECAT scanner.

We would like to try this radiopharmaceutical in a few patients with brain tumors which could be easily studied on an outpatient basis. Previously, we have reported good results with ^{68}Ga -EDTA in patients with strokes. It was hoped to try ^{68}Ga -EDTA in patients early after a CVA (within 24 hours) in order to determine whether ^{68}Ga -EDTA when used with positron emission computerized tomography might not be superior to other diagnostic or imaging procedures. Unfortunately, these patients are usually too ill to justify their transportation to the Medical and Health Sciences Division for an investigative procedure. With brain tumor patients, especially early in the course of their disease, outpatient studies should be feasible.

The ORAU-ORNL Committee on Human Studies granted continuation of this project when it was discussed with the Committee on March 20, 1979.

Sincerely,



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

1030731

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 488-6777 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

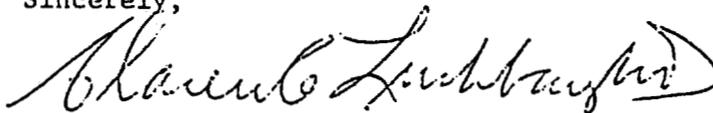
IND 13,383

Dr. Robert Kessler has sent to us Form 1573 with the request to become a co-investigator under our ^{68}Ga -EDTA IND (IND 13,383). I am sending the original and a copy of the completed Form 1573 to you.

Enclosed are also the 0-2 MeV energy spectrum of the ^{68}Ge - ^{68}Ga eluate, a description of the method, some data on ^{68}Ge breakthrough, a drawing of the modified NEN gallium-68 germanium-68 generator, and the CV's of the NIH investigators.

I am submitting this information and material to you for your consideration and approval.

Sincerely,



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

CCL:dg

Enclosure

1030732

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: ⁶⁸Ga-EDTA for Studies of Brain Lesions, Soft Tissue
~~Malignancies, and Kidneys~~

Proposal No.: 48 and 48a Date Approved: 1977 and 1979

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

Only one additional study with ⁶⁸Ga-EDTA was done since the last report.

2. Report any complications. None

1030733

3. Are there any planned changes? None

4. Do you wish the project to be continued?

Yes; we anticipate to use ^{68}Ga -EDTA more often in the future, especially in view of a new collaborative project with Vanderbilt University and UT-Medical Center at Memphis. This project includes the use of ^{14}C -DL-tryptophan and ^{14}C -DL-valine in the differential diagnosis of gliomas and meningiomas.

5. Comments. None

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

(615) 576-3098

August 13, 1980

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

Dear Dr. Gyarfas:

IND 13,383

This is the third progress report on clinical diagnostic applications with Gallium-68-EDTA which was originally approved in 1977 for patients with renal disease, brain lesions, and soft tissue tumors. An amendment for using ^{68}Ga -EDTA as an aerosol to study lung diseases was submitted on July 9, 1979.

Only one additional brain scan was done with ^{68}Ga -EDTA (no side effects) since the last report. We anticipate using ^{68}Ga -EDTA more often in the future, especially if a new collaborative project with Vanderbilt University, the University of North Carolina, and The University of Tennessee Center for the Health Sciences at Memphis is funded. This project is concerned with the differential diagnosis of gliomas and meningiomas.

Application of ^{68}Ga -EDTA for lung studies has been postponed since reliable quantitative positron emission tomographic studies have not been possible with the existing software and hardware. The principal investigator has reported to the ORAU/ORNL Committee on Human Studies the status of this IND and was given permission to continue this project on March 25, 1980.

1030735

Dr. Gyarfas

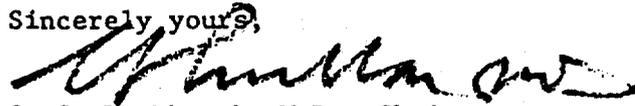
-2-

August 13, 1980

I should mention that Dr. Robert Kessler at NIH has submitted Form 1573 to FDA on October 24, 1979, when he requested becoming a co-investigator under this IND. To my knowledge no patient studies with ^{68}Ga -EDTA have been done at NIH as yet.

I hope that this information is sufficient for your records.

Sincerely yours,



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

CCL:dg

1030736

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.)

AMENDMENT TO IND 13,383 (IDENT. #48) USE OF ⁶⁸GA-EDTA
Title of Project: AEROSOL FOR QUANTITATIVE VENTILATION STUDIES BY POSITRON
EMISSION COMPUTED TOMOGRAPHY (ECT)
Proposal No.: 48a Date Approved: 7/27/79

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

No ⁶⁸ga. 2352 microsphere studies were done since April 1980

2. Report any complications. N.A.

1030737

3. Are there any planned changes? No .

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

5. Comments. See project 54 .

1030738

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Karl F. 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 IND 13,383 (Ident. #48) Use of ⁶⁸Ga-EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)
Proposal No.: 48a Date Approved: July 27, 1979

Signature of Principal Investigator

Date Signed

1. Report progress made in past year.

Two patients with sarcoidosis were examined with this technique.

Progress has been made in software development for quantitative data analysis only very recently.

2. Report any complications. None

1030739.

3. Are there any planned changes? *None*

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

5. Comments. *It is anticipated that more patients will be studied, now that we have improved the quantitation of method for tomographic lung studies.*

MEMORANDUM

Dr. K. F. Hübner FROM Dianne Gresham^{10/2}
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.)

Amendment to IND 13,383 (Ident. #48) Use of ^{68}Ga -EDTA
Title of Project: Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)
Proposal No.: 48a Date Approved: 7/27/79

Karl F. Hübner 4/6/83
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.

1030742

3. Are there any planned changes?

No changes planned.

4. Do you wish the project to be continued?

Yes

5. Comments.

If quantitative analysis of P.E.T. data in the thorax can be improved we hope to be able to enter more patients into this project.

1030743



To Karl F. Hübner, M.D. From Dianne Gresham
Dr. Lange
Date June 22, 1983 Copies to 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

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 IND 13,383 (Ident. \$48) Use of ⁶⁸Ga-EDTA
Aerosol for Quantitative Ventilation Studies by Positron Emission
Computed Tomography (ECT).

Proposal No.: 48a Date Approved: 7/27/79

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.

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. Comments.

None.



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

1030747



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 *Lynn Reeves*
 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 13,383 Use of ⁶⁸Ga-EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)

Proposal No.: 48a Date Approved: 1979

[Signature] 4/19/85
 Signature of Principal Investigator Date Signed

1. Report progress made in past year:

No clinical studies performed.

2. Report any complications:

None

1030748

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

1030749

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

(April 26, 1985)

48a Amendment to IND 13,383 Use of ⁶⁸Ga-EDTA Aerosol for Quantitative
Ventilation Studies by Positron Emission Computed Tomography (ECT)
(Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1030750

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 48a

Project Title AMENDMENT to IND 13,383 (Ident. #48) USE OF 68GA-EDTA AEROSOL
FOR QUANTITATIVE VENTILATION STUDIES BY POSITRON EMISSION COMPUTED TOMOGRAPHY (ECT)

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

1030751

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

7/27/79



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 *Lynn Reeves*
ORAU/ORNL Committee on Human Studies
SUBJECT: PROGRESS REPORTS

4/28
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 Use of ⁶⁸Ga-EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)

Proposal No. 48a Date 1979
[Signature] *3/14/79*
Signature of Principal Investigator Date Signed

1. Report progress made in the past year.

No pts studied

2. Report any complications.

None

1030752

3. Are there any planned changes?

no

4. Do you wish the project to be continued?

yes

5. Comments.

✓



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

Memorandum
 Date: _____
 To: _____
 From: _____

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: 48a Amendment to IND 13,383 Use of ⁶⁸Ga-EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)

Proposal No. 48a

Date Approved: 1979

J. Crook

 Signature of Principal Investigator

5/14/87

 Date Signed

1. Report progress made in the past year. _____

2. Report any complications. *NA*

1030754

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes.

5. Comments.

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. James Crook

Title of Project: 48a Amendment to IND 13,383 Use of ^{68}Ga -EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)

Date Approved: 1979

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

7. Continue

1030756

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

April 6, 1983

TO: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities (ORAU)
Oak Ridge National Laboratory (ORNL)

FROM: Karl F. Hubner, M.D., ORAU

SUBJECT: AMENDMENT TO IND 13,383 FOR CLINICAL USE OF ^{68}Ga -EDTA
(COMMITTEE IDENT. NO. 48).

In the original Ident. No. 48 proposal to the Committee and the subsequent IND 13,383 that was approved by the Food and Drug Administration, it was stipulated that an alumina- ^{68}Ge generator system, obtained from New England Nuclear (NEN), would be used as the source of the ^{68}Ga for the proposed ^{68}Ga -EDTA studies. This generator system yields the desired ^{68}Ga -EDTA directly, since ^{68}Ga is eluted with a 0.005 M solution of EDTA. The ^{68}Ga -EDTA preparation obtained is contaminated with a small but acceptable amount of ^{68}Ge (see Committee Ident. No. 48). A recently developed 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., $\sim 2 \times 10^{-4}\%$ of the ^{68}Ga present. 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. For these reasons it is felt that it would now be advisable to use this new generator system as the source for the ^{68}Ga used in the studies involved in Ident. No. 48. [Furthermore, since the ^{68}Ga is obtained directly in the chloride form with the new SnO_2 - ^{68}Ge generator system, it would not be necessary to make conversions of ^{68}Ga -EDTA to ^{68}Ga chloride (required for preparations of ^{68}Ga -labeled microspheres, Ident. No. 54, and ^{68}Ga -labeled hydrous ferric oxide colloid, Ident. No. 68), if this new generator system were adopted as the source of ^{68}Ga for all of our ^{68}Ga preparations.] Approval is therefore requested for use of the NEN SnO_2 - ^{68}Ge generator system as the source of ^{68}Ga for the preparation of ^{68}Ga -EDTA (Ident. No. 48, IND 13,383). Similar requests are being made for Ident. No. 54 (IND 16,363) and Ident. No. 68 (IND 20,003).

The 1 N HCl solution of ^{68}Ga obtained from the SnO_2 - ^{68}Ge generator system will be evaporated to dryness. After the residual $^{68}\text{GaCl}_3$ 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.

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

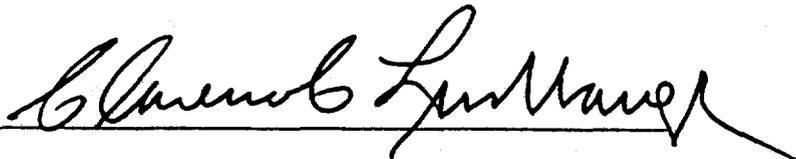
1030757

DIVISION REVIEW:

The above application has been reviewed and approved.

Official signing for the institution:

Signature: _____



Title: Chairman, Medical and Health Sciences Division

Institution: Oak Ridge Associated Universities

Date: April 6, 1983



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

1030759

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Karl F. Hübner, M.D. Ident. No. 48b

Project Title Amendment to IND 13,383 for Clinical Use of ⁶⁸Ga-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:

1030760

Approve x (4/12/83)

Robert H. Toney, M.D.

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.)

Amendment to IND 13,383 for Clinical Use of ⁶⁸Ga-EDTA

Title of Project: _____

Proposal No.: 48b Date Approved: 4/12/83

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.

1030761

3. Are there any planned changes?

No changes.

4. Do you wish the project to be continued?

Keep active.

5. 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 *Lynn Reeves*
 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 13,383 for Clinical Use of ⁶⁸Ga-EDTA

Proposal No.: 48b Date Approved: 1983
[Signature] 4/19/85
 Signature of Principal Investigator Date Signed

1. Report progress made in past year:
 No clinical studies performed.

2. Report any complications:
 None

1030763

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments:

None

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

(April 26, 1985)

48b Amendment to IND 13,383 for Clinical Use of ^{68}Ga -EDTA (Crook)

Progress

No clinical studies performed.

Complications

None.

Changes

No changes.

Continuation

Keep active.

Comments

None.

*inactivated by
Committee 5/6/85*

1030765

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

February 24, 1977

Co-principal Investigators: Gary de Mik
Head R & D
Manpower Development Division
Oak Ridge Associated Universities

Michael E. Gordon
Associate Professor
College of Business Administration
University of Tennessee

Title of Project: Development and Psychometric Testing of
Organizational Communication Measuring
Instruments.

Note: The proposal is currently being considered
for funding by the National Science Founda-
tion (NSF #77-07079). ORAU will be the
grantee institution.

I. Objectives of Experiments:

The major goal of this research is to advance the state-of-the-art of measuring communication behavior in organizational settings. An overriding concern will be the development and psychometric testing of communication measures that can practically and economically be applied in ongoing organizations.

II. Methods of Procedure:

Instrument development and psychometric testing will be accomplished in a series of studies extending over a 24 month period. Questionnaires will be administered to organizational members assessing the structure of communication networks, the effectiveness of communication practices, and satisfaction with organizational communication.

To enhance the generalizability of the results, communication data will be collected from several organizations. In most cases employees will fill out the questionnaires during working hours. Securing the participation of organizations will be facilitated by the concern managers have for the quality of communication within their organization and the belief that poor

1030766

communications are the root cause of many organizational problems. Initial contact has been made with two Federal agencies (Department of Agriculture and the Internal Revenue Service) who have expressed an interest in participating in certain phases of the research.

Since the purpose of the research is to develop reliable and valid communication measures, a specific description of the measures cannot be given at this time. However, the generic nature of the information to be collected can be described. Subjects will be asked to provide data regarding the frequency and direction of communication activities related to task, social, and innovative content areas; and perceived effectiveness and satisfaction of communication within their organization.

A sociometric questionnaire will be used to assess structural characteristics of communication networks. Previous researchers¹ have developed instruments on which respondents indicate the frequency (using a five-point scale) of communication with every other member in the network.

A check-list questionnaire will be developed to assess the effectiveness of communication within the organizations studied. Respondents will indicate whether certain critical communication incidents² have occurred in their organizations during some specified period of time. Adequate measures of the quality of organizational communication have not been previously developed, but a start in that direction has recently been made by Roberts and O'Reilly.³ On their instrument subjects use a seven-point scale to respond to various questions such as "How accurate is the communication you receive?" and "Do you ever feel that you receive more information than you can efficiently use?"

Test-retest procedures will be used to determine the stability of communication characteristics over time and the reliability of the instruments. Some subjects will receive two administrations of the same instrument separated by an interval of four months. It is anticipated that approximately one hour of each subject's time will be required.

III. Possible Hazards and their Evaluation:

Subjects participating in this research are judged to be not "at risk." The procedures are non-reactive and rather benign. Sensitive or highly personal information will not be collected.

Nonetheless, proper precautions will be taken to safeguard the confidentiality of an individual's questionnaire responses. In particular, only summary data for all subjects will be made available to the employing organization. Also, members of an organization may decline to participate without penalty.

There are two features of the proposed research that further reduce the possible risk to subjects. First, no manipulation of either organizational or individual variables will be accomplished. The researchers will measure naturally occurring events rather than measuring the effects of some intervention. Second, unlike much of psychological research this research is non-deceptive. The nature and purpose of the project can be fully explained to subjects before they agree to participate.

IV. Radioisotopes and New Drugs:

None.

V. Responsibility of Principal Investigators:

Communication data will be collected from several organizations. The proprietary nature of organizational information will be carefully protected. Identifiers will be maintained only for purposes of follow-up procedures in reliability assessment and will be destroyed when follow-up has been accomplished. Subjects will be informed that their responses will be used for research purposes only and will be treated as being strictly confidential.

Proposed Starting Date: May 1977

Footnotes

¹Monge, P. R. & Lindsey, G. N. The study of communication networks and communication structure in large organizations. Paper presented to the International Communication Association, New Orleans, Louisiana, April, 1974.

Rogers, E. M. & Agarwala-Rogers, R. *Communication in Organizations*. New York: The Free Press, 1976.

²Flanagan, J. C. The critical incident technique. *Psychological Bulletin*, 1954, 51, 327-358.

³Roberts, K. H. & O'Reilly, C. A. III Measuring organizational communication. *Journal of Applied Psychology*, 1974, 59, 321-326.

Signatures of Co-Principal Investigators:

Gary de Mik
Gary de Mik

Michael E. Gordon
Michael E. Gordon

DIVISION REVIEW:

The application described above has been reviewed and approved:

Official signing for the institution:

Signature

[Handwritten Signature]

Title

Chairman, Medical and Health Sciences Division

Institution

Oak Ridge Associated Universities

Date

3/14/77

RHG:dsw

1030769

REVIEW AND ACTION

ORAU/ORHL Committee on Human Studies

Principal Investigator Gary de Mik and Michael E. Gordon Ident. No. 49

Project Title DEVELOPMENT AND PSYCHOMETRIC TESTING OF ORGANIZATIONAL
COMMUNICATION MEASURING INSTRUMENTS

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.

It is particularly important that confidentiality of individual questionnaires be maintained.

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.

An introductory statement requested by the Committee, as has been added to the proposal, is to be used on every questionnaire.

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

Routine follow-up.

4. Other committee comments:

Approve

1030770
X

Signature:

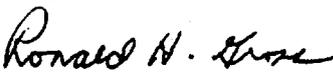
Robert Lange (Robert Lange, M.D)

MEMORANDUM

TO Dr. Clarence C. Lushbaugh FROM Ron Gross - MDD
DATE February 8, 1977 COPIES TO File
SUBJECT PROPOSAL FOR USE OF HUMAN SUBJECTS

Enclosed are nine copies of our proposal for use of human subjects for the NSF project, "Development and Psychometric Testing of Organizational Communication Measures." We would appreciate it if the Committee on Human Studies could review the proposal as soon as possible.

Scott Lawyer has gone over the proposal and had no changes to suggest.



Ron H. Gross

RHG:dsw
enclosures

MEMORANDUM

Gary de Mik and Michael E. Gordon FROM Medical and Health Sciences Division
DATE 2/18/77 COPIES TO File
SUBJECT EVALUATION BY COMMITTEE ON HUMAN STUDIES FOR PROPOSAL ENTITLED DEVELOPMENT
AND PSYCHOMETRIC TESTING OF ORGANIZATIONAL COMMUNICATION MEASURING INSTRUMENTS

As secretary of the Committee on Human Studies, I would like to suggest some possible additions to your proposal which might facilitate its evaluation by the members. The proposal seems to lack specificity, and the reader does not get a very clear idea of what you intend to do. It is not evident whether you are developing and evaluating methods of communication or are developing and measuring "instruments" (?questionnaires) for testing methods of communication.

It seems to me that the psychological stress that might be generated would relate to job security and relationships with supervisors. Employees who are asked to fill out a questionnaire at work may not be easily convinced that their answers will be truly confidential.

Some specific questions that occur to me are as follows:

1. Are workers to fill out the questionnaires during working hours?
2. What are the "follow-up procedures in reliability assessment," and do these involve further questioning of the same worker?
3. What companies or organizations are involved, and what is the attitude of management toward the study?
4. Can an employee decline to participate without penalty?
5. Could you give an example of the type of questionnaire to be used and a reference to some similar previous study.
6. What would be the end point of the study, when questionnaires would be destroyed?

Since our next committee meeting is on March 3, it will be necessary to have a rather hasty response if we are to get the proposal out for evaluation.



Gould A. Andrews, M.D.

1030772

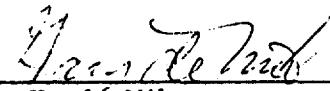
MEMORANDUM

TO Gould A. Andrews FROM MDD
DATE February 24, 1977 COPIES TO File
SUBJECT PROPOSAL FOR USE OF HUMAN SUBJECTS FOR RESEARCH PROJECT ENTITLED
"DEVELOPMENT AND PSYCHOMETRIC TESTING OF ORGANIZATIONAL MEASURING
INSTRUMENTS."

Thank you for your comments regarding the subject proposal. We have reviewed the proposal to increase its specificity and have addressed the several points you mentioned in your memo.

Please let me know if you or other members of the Committee have further questions. If it would expedite the process I would be willing to appear before the committee on March 3rd and answer specific questions at that time.

We are interested in getting the human subjects approval to NSF as soon as possible as it is the only piece lacking for their review of our proposed research.



Gary H. de Mik

GDM:dsw
Incl: 8 copies of Proposal

STATEMENT TO APPEAR ON COMMUNICATION QUESTIONNAIRE AS PART OF INSTRUCTIONS

This questionnaire is designed to measure certain characteristics of communication within your work group. Your participation in this research is voluntary. We would appreciate your cooperation in completing this form, but you may at any time decide not to participate further. The information you provide will be used for research purposes only and only summary statistics will be reported. Your responses are confidential and will not be released.

(In most cases individuals will be asked not to sign their names or otherwise identify themselves.)

1030774

MEMORANDUM

1 ✓ Dr. G. Andrews FROM Manpower Research Programs
DATE September 27, 1977 COPIES TO file
SUBJECT STATUS OF PROJECT: DEVELOPMENT AND PSYCHOMETRIC TESTING OF ORGANIZATIONAL
COMMUNICATION MEASURING INSTRUMENTS.

The above named project, previously approved by the Committee on Human Studies, was not funded by N.S.F. At present we have no plan to seek funding for the study elsewhere.

We appreciate the helpfulness of the Committee.



Gary H. de Mik
Director

GHdM:dh

1030775

SEP 27 1977