

ORAU/ORNL COMMITTEE ON HUMAN STUDIES
ORAU PROTOCOLS AND RELATED DOCUMENTS
INACTIVE PROPOSALS (FILE 1)

ORAU/ORNL COMMITTEE ON HUMAN STUDIES
REPOSITORY + EDUCATION, MEDICAL SCIENCES DIR.
ORAU/ORNL ASSOC. UNIVERSITIES/ORNL
COLLECTION RIDGE NAT'L LAB (ORAU/ORNL)
BOX NO VANCE ROAD FACILITY, Nm. 202A
FOLDER ORAU-30016 - FILE 1

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Dr. R. L. Hayes Identifying No. /

Project Title: "Clinical Trial of ¹¹³In^m as a Kidney and Bone Scanning Agent"

Comments:

After discussion, the proposal was approved after appropriate clearances have been made.

NOT RECOMMENDED

Approved: 9/15/67 (date)

Disapproved: (date)

(in charge was Sec)
Secretary, Committee on Human Studies

Adopted 4-67

1030205

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Dr. R. L. Hayes Identifying No. 2

Project Title: "Clinical Trial of ⁶⁸Ga-Labeled Hydrous Ferric Oxide Colloid
for Bone Marrow Scanning"

Comments:

After discussion, the proposal was approved after appropriate clearances have been made.

Approved: 9/15/67 (date)

Disapproved: _____ (date)

Secretary, Committee on Human Studies

13 Aug 71 Minutes: cancelled

Adopted 4-67

1030206 .

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Dr Helen Wilson Identifying No. 3

Project Title: "Immunotherapy of Acute Leukemia"

Comments:

This project invoked a great deal of discussion about possible risks to the recipient of irradiated malignant cells. The members of the committee approved the plans for at least a few more studies since the risks are most certainly minimal, but recommended that possible other methods for obtaining specifically sensitized malignant cells be explored.

Approved: 9/15/67 (date)

Disapproved: _____ (date)

Secretary, Committee on Human Studies

13 Aug 71 7:10 AM

Adopted 4-67

1030207

September 8, 1967

Robert D. Lange, M. D.
Assistant Director
U. T. Memorial Research Center
1924 Alcoa Highway
Knoxville, Tennessee 37920

Dear Bob:

This paper explains what we have been trying to do in clinical immunotherapy, and I believe includes a fairly adequate discussion of the possible hazards involved. Appended to the paper is a memo from Dr. Helen Vodopick suggesting changes in the protocol.

I wonder if this information will be adequate as a basis for discussion at our meeting on September 15.

Sincerely,

Gould A. Andrews, M. D.

GAA/pe

Enclosures

*same letter, same date, (same enclosures)
To Dr. Robert Keyes - Vanderbilt.*

1030208

MEMORANDUM

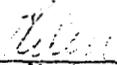
TO Those Listed Below DATE July 11, 1967
SUBJECT PROTOCOL FOR THE IMMUNOTHERAPY OF ACUTE LEUKEMIA
COPIES TO File

After our discussion with Dr. Peter Alexander, it was felt that our protocol for the immunotherapy of acute leukemia should be amended. Enclosed is a revision of the protocol which incorporates some of these changes that were proposed.

Please feel free to make any further amendments. If there is any omissions which should be included, please note this also.

We would hope to have a "working" protocol ready in expectation for our next suitable patient. I would appreciate it if you would forward your comments to me so that a written final plan can be drawn up.

Thank you for your help.



Helen A. Vodopick, M.D.

/1

Copies To: ✓ Dr. Andrews
Dr. Congdon
Dr. Edwards
Dr. Gengozian

1030209

Andrew

AMENDED PROTOCOL FOR THORACIC DUCT CANNULATION - LYMPHOCYTE INFUSION

1. Disease -

leukemia untreated - probably child,

or solid tumor, incurable but to apparent limited extent.

ABO compatible normal person to receive killed malignant cells and to donate "sensitized thoracic duct lymphocytes.

2. Collection of malignant cells - either leukemic cells obtained by bone marrow aspiration (anticoagulant 4% K₂ EDTA) or piece of solid tumor minced and washed with Tc 199. For preservation: autologous serum 50% + 20% DMSO in Tc 199; ratio 1:1 with cell suspension.

a) Freeze by means of slow freeze liquid nitrogen (1°C/min) to preserve these cells for future use;

b) Remove DMSO before irradiation and wash with Hank's buffered salt solution;

c) Irradiate with 10,000 R or more just before giving.

3. Route of sensitizing dose - intralymphatic into normal recipient.

Use Sweeney adaptor to remove large particles.

4. Thoracic duct cannulation of "sensitized" recipient -

Time of cannulation: Day 4-7. Check for pyroninophilic cells in thoracic duct lymph and in blood smears (possibly use this to determine when cannulation should be done).

5. Before infusion of lymphocytes into recipient -

a) leukemic - patient should be in full remission. No steroids are given during administration. Stop antileukemic drugs just before commencing lymph infusion.

After infusions - ? continue antileukemic drugs.

b) solid tumor - ? immunosuppressive agent to patient before sensitized lymphocytes are given.

1030210

6. Lymph collections -
 - a) room temperature
 - b) anticoagulant heparin, ~100 u, in 25 ml 5% dextrose/water
 - c) spin blood bottles, 200 x g
 - d) do not wash cells (keep lymph to minimum)
 - e) Collections every 3 hrs - check sizing (pick up larger pyroninophilic cells later this way)
 - f) Keep sufficient number of cells for
 - 1) cell count
 - 2) smears - Wright's and methyl green - pyronine Y stains
 - g) Infuse into patient as soon as processed.
7. Rx for reaction - to control possible graft versus host reaction.
 - a) steroids
 - b) Imuran - when temperature rises, diarrhea, skin rash, not attributable to anything else occurs.
8. Evaluation of effect -
 - a) Clinical remission or regression of tumor
 - b) In vitro testing.

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Gangjian Identifying No. 4
Project Title: "Marrow Grafting Following Total-Body Irradiation"

Comments:

An on-going study, presented and discussed, 9/15/67

Reapproved by 707/13 (19 Dec '72)

Approved: _____ (date) ^{Continuation approved} 9/15/67

Disapproved: _____ (date)

Secretary, Committee on Human Studies

Adopted 4-67

1030212

PROGRESS REPORT
HUMAN BONE MARROW TRANSPLANTATION

OF

ORAU MEDICAL DIVISION

19 Dec 72

Using the procedures outlined in the protocol for therapeutic allogenic transplantation of human bone marrow as approved by this committee, we have performed three bone marrow transplants up to this date. The patients receiving this kind of treatment were two males, 51 years and 41 years old, and one woman, 53 years of age. All of these patients had acute granulocytic leukemia. In two of these patients we found a histocompatible donor according to the HL-A typing and the results of the mixed lymphocyte cultures. In the 41 year old man we did not find an identical donor and the HL-A typing indicated a D match, which means a difference of at least 3 antigens. In this third case there was also a slight reactivity in mixed lymphocyte cultures.

All of these patients received anti-human thymocyte globulin and total body irradiation with 500 R as pre-grafting immunosuppression. The anti-human thymocyte globulin was generally tolerated well, except for the last patient, who reacted with severe fever spikes following most of the daily injections of the horse globulin. Each of the patients tolerated the radiation very well. Except for slight nausea following the total body irradiation (only the second patient vomited) the only symptom experienced by the patients was drowsiness which was in part due to the phenothiazide medication used to suppress nausea and vomiting. We do not believe the immunosuppression shortened the life of any of these patients.

1030213

The transfusion of the bone marrow cells went without any complications, especially there were no indications of embolism. The total number of bone marrow cells infused into these three patients ranged between 15×10^9 to 18×10^9 cells. All of these patients received post-transplant immunosuppression with intermittent doses of methotrexate as outlined in the protocol. The dose of the methotrexate was varied according to the clinical course of the patients. Our first patient received a total of 440 mg of methotrexate up to the 117th day post-transplant. The second patient received a total dose of 140 mg the last which was given on day 21. No further methotrexate was considered for the second patient because of abnormal liver function studies. The total dose of methotrexate given to the third patient was 195 mg.

The two patients who received HL-A identical bone marrow grafts showed well-documented evidence for a successful take of the bone marrow graft. This evidence was derived from red cell markers and white cell markers. In the third patient we had no evidence for a successful graft, and had to conclude that the bone marrow graft was not accepted. In none of the patients did we see any signs or laboratory evidence for graft-versus-host disease. With regard to the third patient, this would also indicate that we did not obtain a successful graft. The survival time of these patients was 122 days respectively, 92 days for the patients with the HL-A identical graft. The patient with the mismatched bone marrow lived for 60 days following the transplant. All three of the patients died with pneumonia or septicemia, although the first patient's death was more likely the result of pulmonary embolism and renal failure and the last 2 patients died with their leukemia in relapse.

1030214

With regard to the stage of leukemia we observed that in the first patient there was no recurrence of leukemia. He died from causes unrelated to his leukemia, and on autopsy there was no evidence of leukemia. The second patient (female) showed initial absence of leukemia cells from the blood or bone marrow. However, approximately 10 1/2 weeks after the transplant she developed a sudden blast cell crisis, subsequently to which she died from septicemia. In the third patient we never saw evidence for a successful take of the graft and we never observed a complete disappearance of leukemic cells from the peripheral blood and/or bone marrow.

1030215.

No. 5 Use of Radioiodine in Surgical Removal of Ca of Thyroid

Between 1950 and 1974, 150 patients with cancer of the thyroid were admitted to the ORINS/ORAU Medical Division. Of these 117 received at least one dose of therapeutic iodine-131 as part of their therapy in addition to surgery. As of our last information 87 of the patients are still living. As of October 1974 this investigation has been terminated and we are now in the process of compiling the data and evaluating the clinical course of these patients.

1030216 .

Memorandum

Dec. 11, 1973

Re: Proposal No. 5 (Old, 1967, or preceding...)

Title: Use of Radioactive Iodine in Surgical Removal of
Thyroid Cancer

This project was started before the formation of the Committee on Human Studies. No formal project proposal is in the Committee files. At the December 1973 meeting Dr. Edwards reported that work is continuing.

Polly Edwards

Note from Dr. Andrews:

"We are to talk about this project in about six months." (2 May 1974)

1030217

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: _____ Identifying No. 5

Project Title: "Use of Radioiodine in Surgical Removal of Thyroid Cancers"

Comments:

An ongoing study, presented and discussed.

continuing, (11 Dec 73)

Continuation approved 9/15/67

Approved: _____ (date)

Disapproved: _____ (date)

Secretary, Committee on Human Studies

Adopted 4-67

1030218

To: Committee on Human Studies
 Oak Ridge Associated Universities
 Medical Division

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

(Three copies required. Use reverse side of these forms if additional space is needed.)

Date June 10, 1969

I. Senior Investigator: Edward Balish, Ph.D.
 Co-Investigators: C. Lowell Edwards, M.D.

 Title of Project: A Study of Infections in Cancer Patients.

II. Objectives of Experiment: (Use additional blank pages if needed.)

The study will be directed toward the infections that complicate, and often prematurely terminate, intensive chemotherapy and radiotherapy of cancer. The objectives will be to determine the causes of these infections and better ways of preventing them with the following specific aims:

- (1) To develop procedures for the care and management of these patients during therapy in a sterile (ultraclean) environment using a new laminar-air-flow clean-room facility, and to test the facility for its use in reducing the incidence of infection during this vulnerable period.
- (2) To test regimens for bowel sterilization with antibiotics and reducing flora of skin and mucous membranes. Further, to assess the value of these procedures in the ultraclean facility.
- (3) To identify, in these patients, the microorganisms involved in infections, their portal of entry and response to therapy.

Adopted 4-67

1030220

Page 1A - Objectives of Experiment:

(4) To characterize the microflora (mouth, nasopharynx, gastrointestinal tract, respiratory tract) of cancer patients in order to determine whether or not shifts in the microflora occur coincident with therapy and whether or not such shifts in the microflora are related to infectious complications. Thus the relative roles played by microorganisms from the endogenous flora and those microorganisms not considered as part of the normal flora can be more critically evaluated.

(5) To determine whether cancer therapy is responsible for the development of a more antibiotic-resistant bacterial flora.

(6) To detect alterations in host defense mechanisms that may be induced by immunosuppressive cancer therapy.

III. 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. (Use additional blank pages if needed.)

(1) Patients in ORAU hospital with malignant disorders of the hemopoietic system receiving intensive chemotherapy or radiotherapy.

a. Randomization of patients after criteria have been met of:

(1) Type of disease - acute leukemia; chronic leukemias; stage III and IV lymphoma and Hodgkin's disease; other disseminated malignant neoplasms.

(2) Mode of therapy - radiation or suppressive chemotherapy that can be expected to cause granulopenia below $1,000/\text{mm}^3$.

(3) Informed consent - patients judged psychologically able to tolerate this closed environment for extended periods for a minimum of two weeks; possibly up to 6 months in certain patients, and willing to accept randomization and the prescribed antibiotic regimen.

Continued on Page 2A

IV. Possible hazards and their evaluation:

We anticipate no unusual hazards to be associated with operation of the laminar-flow patient facilities. The use of oxygen tents will not be feasible, and patients requiring oxygen will be administered oxygen through a nasal mask. The use of oxygen at 5 liters per hour (0.15 cubic feet per hour) is well below the fresh air intake of 200-300 cubic feet per minute and will prevent any hazardous concentration of oxygen in the room. A through-the-wall oxygen system is available to preclude the use of oxygen tanks in the patient room.

III. Methods of Procedure (Continued):

b. The patient will be placed in the unit for 2 to 3 days, or where possible longer, before beginning therapy to obtain baseline flora.

c. Antibiotic regimen:

(1) Gut - after giving patient an enema and cathartics: a regimen such as nystatin, 1,000,000 or more units q 4-6 h; gentamicin, 200 mg q 4 h; oxacillin, 0.5 g q 4-6 h on a continuous basis.

(2) Skin and mucosal surfaces - shampoo and bathe daily with pHisoHex or Betadine. Daily Betadine douche and vaginal nystatin suppositories for females. Sprays of neomycin, bacitracin, and oxacillin into nose and mouth, q.i.d.

(3) If *Pseudomonas* is cultured, polymyxin B will be added by appropriate routes.

(4) With persistence of resistant organisms, other appropriate antibiotics will be given on the basis of in vitro sensitivity studies.

(5) Clinical infections will be treated with specific agents.

(6) Newer, more effective agents or regimens will be adopted as they become available.

(7) "Controls" will be housed identically in the "clean" rooms and will receive the same isolation procedures.

Infections will be treated with specific agents.

(2) To compare the relative importance of endogenous and exogenous microorganisms in infections of immunologically repressed patients, we will study patients receiving similar therapy in standard hospital rooms and also in Ultraclean Laminar Flow rooms using sterile techniques to prevent contact contamination of patients. The air in the laminar-flow facilities will be essentially free of microorganisms. The air, randomly selected sections of the walls and floors, and the fixtures will be monitored routinely for organisms. We will also monitor the microflora of personnel who have access to the rooms. The patient will be given a sterile diet and drinking water.

(3) Operating protocol for Ultraclean Laminar-Air-Flow rooms: Routine entry from the preparation room to the clean patient rooms will be limited to authorized, trained personnel. Gas or steam sterilization procedures will be used on all linens, utensils, or any other items introduced into the room. Until our microbiological sampling indicates otherwise, all personnel will be required to wear sterile gloves, hair covers, masks, gowns, and shoe covers. However, it may be possible later to eliminate some of the sterile clothing, since industrial laminar-flow facilities have been operating with simpler protective coverings and have no increased contamination problems. Experience and the training of all personnel to avoid contact contamination may justify similar moves on our part. The use of the room's toilet facilities is still controversial at this time. Our accumulated experience will also determine whether it will be necessary to resort to portable toilets and bathing facilities. However, the patient will be the only one using the

III. Methods of Procedure (Continued):

facilities in his room, which will be disinfected routinely. The presence of toilet facilities may, in fact, prove superior to having nurses wash and minister to the patient where there is a higher chance of nosocomial infections. The problem of certain patient diagnostic procedures, such as X rays or isotope scanning, which usually require transporting the patient, is anticipated and specialized techniques (portable laminar flow stretchers) may have to be devised. It is anticipated that such procedures will generally be carried out before immunological suppression and will be kept to a necessary minimum during the period of confinement.

(4) Survey of Microflora in Patients:

a. We will characterize the microbial flora present on the skin, in the mouth, nasopharynx, gastrointestinal tract, and respiratory tract, before, during, and for several weeks after therapy. Blood and urine samples will also be cultured periodically. The microbiological survey will be carried out 2 to 3 times a week and will include enumerations of the total aerobic and anaerobic flora: coliforms; *Lactobacilli*; enterococci; *Clostridia*; *Bacteroides*; aerobic and anaerobic spores; *Proteus* sp.; *Pseudomonas* sp.; Diphtheroids; *Staphylococci*; *Streptococci*; Pneumococci; *Neisseria* sp.; Fungi; and Mycoplasma. Protocol for bacteriology on patients housed in laminar-flow rooms is as follows:
Microbiology on Patients: The following assays will be carried out 2 to 3 times per week in patients who can tolerate the necessary intubation.

<u>Specimen</u>	<u>Media to be used with each specimen</u>
Nasal swab	Eosin Methylene Blue Agar
Throat swab	MacConkey Agar
Sputum	<i>Salmonella-Shigella</i> Agar
Gastric washing	Blood Agar (aerobic, anaerobic, and CO ₂)
Small intestine (duodenum, jejunum, ileum)	Mannitol Salts Agar
Rectum and anus	Phenyethyl Alcohol Agar (aerobic and anaerobic)
Skin	<i>Lactobacillus</i> Agar (aerobic and anaerobic)
Urine	<i>Mitis-Salivarius</i> Agar
Blood (1 specimen/wk unless otherwise indicated)	<i>Streptococcus faecalis</i> Agar
	PPLO Agar and PPLO Broth (aerobic and anaerobic)
	Sabouraud Dextrose Agar
	Mycosel Agar

A total of 10-12 specimens will be collected from the patient twice each week. About 10-13 different kinds of selective media will be employed with each specimen. Plating these specimens in 2-3 dilutions for quantitative as well as qualitative enumeration of bacteria, yeasts, and fungi would entail about 1000 culture plates/patient/week. An additional 500 plates per week could be anticipated from the monitoring of the laminar-flow rooms and personnel. We expect that, with experience, the microbiological assay of rooms, personnel, and patients will be reduced.

b. Antibiotic Sensitivity: Antibiotic sensitivities of predominant microorganisms in the flora will be assayed before, during, and

III. Methods of Procedure:

after various therapeutic procedures, since immunosuppressive therapy may be responsible for mutations in the microbial components of the flora; such mutants may be more antibiotic-resistant and possibly more virulent.

c. To obtain a more specific identification of predominant bacterial species, and to detect any increase in their virulence, serotyping, and/or phage typing of the predominant microorganisms in the flora will be carried out. The latter two techniques will be performed routinely on the major components of the microflora; especially when a component of the flora is associated with infection. Serotyping and phage typing will allow us to detect more subtle alterations in the flora than could be observed by routine plating on selective media. Data on specific serotypes and phage types from the alimentary tract, respiratory tract, etc., will aid in locating portals of entry and may allow us to determine that entry by some portals is facilitated during various forms of immunosuppressive therapy.

(6) Characterizations of Degree of Immunosuppression:

- a. Complete blood counts and bone-marrow studies.
- b. Serum complement levels.
- c. Serum gamma globulins; 7S, 19S fractions.
- d. Bactericidal tests with serum. Both gram-positive and gram-negative bacteria and *Candida albicans* isolated from patients will be used to determine the influence of immunosuppressive therapy on the bactericidal potential of serum and on phagocytic function. Bactericidal effects of serum will be measured by doing viable plate counts, at intervals up to 24 hr after selected microorganisms are placed in contact with the patient's serum. The capacity of phagocytes to engulf bacteria will be measured by centrifuging a quantitated suspension of leukocytes and bacteria after various periods of incubation at 37°C. Viable plate counts on the supernatant and on the pelleted leukocytes which have engulfed test microorganisms will allow us to estimate the capacity of phagocytes to engulf and kill bacteria.

V. Radioisotopes and New Drugs:

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

Not applicable

VI. Responsibility of Senior Investigator:

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

Starting Date 1 January 1970

Signatures:

Edward Balish
Investigator

Joseph Edward Stone
Investigator

Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

Ray M. Quinlan MD
Chairman

June 13, 1969
Date

REVIEW AND ACTION
Committee on Human Studies
Oak Ridge Associated Universities
Medical Division

Principal Investigator: Edward Balish, M.D. Identifying No. 7

Project Title: "A Study of Infections in Cancer Patients"

Comments:

It is noted that not all patients would have small intestinal specimens obtained three times weekly and that only adults would have bowel sterilization procedures. The committee expressed concern that all patients should be informed that it was possible for them to withdraw without prejudice. A new consent form is to be prepared. The committee urged that the senior investigators keep a continued surveillance for possible drug reactions and emergence of any drug resistant organisms. It was also emphasized that the committee be informed at each meeting about the results of this project

Approved: July 10, 1969 (date)

Disapproved: _____ (date)

Secretary, Committee on Human Studies

not authorized.

Adopted 4-67

1030227

To: Committee on Human Studies
Oak Ridge Associated Universities
Medical Division

ORAU-8

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

(Three copies required. Use reverse side of these forms if additional space is needed.)

Date July 10, 1969

I. Senior Investigator: Helen Vodopick, M.D.
Co-Investigators: Francis Goswitz, M.D.
C. Lowell Edwards, M.D.
Frank Comas, M.D.
Title of Project: Study of Granulocyte Kinetics in
Myeloproliferative Diseases

II. Objectives of Experiment: (Use additional blank pages if needed.)
Purpose:

Characteristic patterns of white blood cell destruction and re-generation have been found after total-body irradiation and in some instances after local irradiation in humans. Local irradiation to the spleen in chronic myelogenous leukemia can produce a remission akin to that seen after total-body irradiation. Mechanisms by which these changes occur are unknown.

Altered production by measuring the granulocyte turnover time, change in the half-disappearance time of white blood cells and shifts in circulating versus marginated WBC pools will be measured before and after either splenic or total-body irradiation used as treatment for patients with myeloproliferative disorders.

Adopted 4-67

(continued)

1030228

II. Objectives of Experiment (continued):

Application of this information for treatment of hematopoietic disorders with irradiation would be the ultimate aim. In addition, mechanism of WBC injury by irradiation may be better defined.

III. 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. (Use additional blank pages if needed.)

Radioisotope:

^{32}P -DFP (diisopropyl fluorophosphate) will be used to label the granulocytes according to the procedure described by Athens and co-workers (Blood 14:303, 1959). Both in vitro and in vivo labeling of granulocytes will be performed. With the in vitro method, 30-40 microcuries of ^{32}P and 120-150 micrograms of DFP are added to a transfusion pack containing 300-400 ml of blood which is then given intravenously to the patient. In vivo labeling of granulocytes is accomplished by the intravenous injection of 400 microcuries of ^{32}P and 2 mg of DFP. Both of these methods have been used extensively and reported in the literature.

(continued)

IV. Possible hazards and their evaluation:

Radiation Dose:

Radiation dosage after the in vitro type of study in normal subjects has been reported by Mauer and co-workers (J. Cl. Invest. 39:1481, 1960). It was found that the ^{32}P -DFP was bound firmly to erythrocytes, leukocytes, platelets and plasma proteins, and therefore 30 microcuries of isotope were distributed predominantly in the blood estimated to be 5 kg with little radioactivity reaching the bone marrow or other tissue. In three subjects, urinary excretion of radioactivity was studied and 40% of the administered dose appeared in the urine within the first 3 hours after infusion of the labeled blood. They stated that the biologic half-life of ^{32}P was approximately 6 days and effective half-life was 4.4 days. The infinite dose of radioactivity administered to blood was calculated to be about 560 millirads. This dose did not take into consideration the excretion of ^{32}P -DFP by routes other than the kidneys.

Athens and co-workers (Blood 14:303, 1959) calculated radiation dose after in vivo administration of a maximum of 400 microcuries of ^{32}P -DFP and reported that "a 70 kg man would receive 0.24 equivalent roentgens on the first day and 9.04 equivalent roentgens total dose."

III. Methods of Procedure (continued):

Subject:

Patients with myeloproliferative disorders, such as chronic myelogenous leukemia, polycythemia rubra vera, and myelofibrosis will be studied before and after either local (splenic) irradiation or total-body irradiation (LETBI or METBI).

Procedure:

In vitro labeling studies will require 3-4 days. Blood samples will be drawn at frequent intervals on the first day of the study and then daily for 3-4 days (T_0 , 1, 3, 6, 9, 12, 20, 36, 48, 72, 96 hrs). In vivo studies will require an extended period of study with four samples of blood drawn on the day of initiation of study and then one sample of blood drawn each day for the next 20 days. Granulocyte separation will be necessary on all these samples. Disposal of the washes and waste will be performed under the direction of the radiation safety office.

IV. Possible Hazards and their Evaluation (continued):

Drug Toxicity:

DFP toxicity: In the studies performed by Dr. Athens (ref. above) no serious reactions had occurred in any of the 120 human subjects that had received parenteral doses. After intramuscular administration of 2 mg DFP, moderate to severe pain at the site of injection lasted as long as 30 minutes. A total dose of 4 mg given I.V. to each of four subjects produced in three of them anorexia, nausea and cramps which lasted as long as 24 hours. When the dose of DFP was 3 mg or less, no symptoms were encountered.

This compound is commercially available in sealed ampules or multidose vials. The compound is dissolved in propylene glycol, which is sterilized by gamma radiation (2.5 Megarads). No pyrogenic reactions to these compounds have been reported.

The ^{32}P -DFP is also assayed by us for DFP content, radioactivity and radiopurity. The methods used are those published by Athens and co-workers (Blood 14:303, 1959).

V. Radioisotopes and New Drugs:

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

Approved 22 February 1968

VI. Responsibility of Senior Investigator:

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

Starting Date May, 1968

Signatures: Allen Jodowski, M.D.
Investigator

Investigator

Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

Gerald Andrews
Chairman

May 1968
Date

REFERENCES

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 - (2) Cohen, J. A. and Warringa, M. G. P. J. The fate of P^{32} labeled diisopropylfluorophosphate in the human body and its use as a labelling agent in the study of the turnover of blood plasma and red cells. *J. Clin. Invest.*, **33**, 459 (1954).
 - (3) Leeksa, C. H. W. and Cohen, J. A. Determination of the life span of human blood platelets using labeled diisopropylfluorophosphate. *J. Clin. Invest.*, **35**, 964 (1956).
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 - (5) Mauer, A. M., Athens, J. W., Ashenbrucker, H., Cartwright, G. E. and Wintrobe, M. M. Leukokinetic Studies II. A method for labeling granulocytes *in vitro* with radioactive diisopropylfluorophosphate (DFI 32). *J. Clin. Invest.*, **39**, 1481 (1960).
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REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Dr. Helen Vodopick Identifying No. 8

Project Title: Study of Granulocyte Kinetics in Myeloproliferative Diseases

Comments:

Dr. Vodopick was present for this discussion. The project was approved. The only question was in regard to which "consent form" would be used.

Approved: July 10, 1969(date)

Disapproved: _____(date)

Secretary, Committee on Human Studies

Still considered active; no new development (11 Dec 73)

*Cancelled
21 Jan 1975*

Adopted 4-67

1030234

To: Committee on Human Studies
Oak Ridge Associated Universities
Medical Division

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

(Three copies required. Use reverse side of these forms if additional space is needed.)

Date July 10, 1969

I. Senior Investigator: C. L. Edwards, M.D.
Co-Investigators: R. L. Hayes, Ph.D., N. Tehranian, M.D.
R. Kniseley, M.D., F. Goswitz, M.D.
R. Tanida, M.D., and H. Vodopick, M.D.
Title of Project: Tumor Scanning with Gallium-67

II. Objectives of Experiment: (Use additional blank pages if needed.)
The overall objective of this study is to evaluate gallium-67 citrate as a radiopharmaceutical for scanning tumors of the bone and soft tissues.

Phase I of the study will involve obtaining data on safety and radiation dosimetry. Phase II will be a test of efficacy in which we hope to learn what types of tumors can be detected through their ability to concentrate gallium-67. Phase III will be to determine reliability in distinguishing benign from malignant lesions.

Adopted 4-67

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II. Objectives of Experiment (continued)

Through each of the specific phases, it is our aim to evaluate various scanning techniques, scanning times, doses, and equipment for optimum information. It is also our objective to learn what we can regarding the mechanism of gallium-67 tumor localization.

III. 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. (Use additional blank pages if needed.)

Phase I includes giving up to 5 mCi/70 kg body weight of carrier-free gallium-67 citrate to approximately 50 patients with known malignant neoplasms. Blood clearance, whole-body retention, urine and fecal excretion data will be compiled where possible from which internal radiation doses will be calculated. Terminal patients will be included in the study and data obtained from external counting will be supplemented with assay of tissue obtained at autopsy.

Phase II will be limited to patients with known malignant neoplasms that can be presumed to be life-shortening, i.e., excluding curable skin cancers, etc. A large number of patients (more than 100) will be needed to meet the objectives of Phase II. (continued)

IV. Possible hazards and their evaluation:

Phase I studies are designed specifically to assess the radiation hazard from the preparation. Each batch will be pyrogen tested and terminally sterilized, thereby reducing the hazard of untoward pyrogenic reaction to a minimum.

Patients with severe bowel disorders could experience difficulty with the laxatives. Laxatives will be omitted where such a hazard is recognized clinically.

III. Methods of Procedure (continued):

Each patient selected for Phases I and II studies will be given an intravenous infusion of carrier-free gallium-67 as citrate. Blood samples of 3 ml will be obtained at 5, 15, 30, and 60 minutes (or other similar but more appropriate times) to determine blood clearance. Whole body counts and whole body scans will be made daily for at least 3 days and appropriate area scans will be made at 24 hours or later according to the individual case. The patient will be given a laxative (usually 30 ml of milk of magnesia and 15 ml of cascara sagrada) hs daily X 3 and an enema just prior to the whole body or abdominal scans.

Occasionally a patient fulfilling the above criteria will be given a dose for the explicit purpose of obtaining assays from tissues at autopsy, if the patient is suspected to be terminal or for assay of a surgical specimen if he is to undergo any exceptional surgery.

V. Radioisotopes and New Drugs:

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

The use of this preparation in this study has been approved by the Isotope Committee of the ORAU Medical Division, and an application for exemption (IND 5489) has been filed with the FDA.

VI. Responsibility of Senior Investigator:

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

Starting Date July 1969

Signatures: *[Signature]*
Investigator

Investigator

Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

Zorob Andrews
Chairman

July 69
Date

TUMOR SCANNING WITH GALLIUM-67

C. L. Edwards, M.D., and R. L. Hayes, Ph.D.

Since the beginning, clinical scintiscanning has been concerned largely with locating tumors. By far the greatest success has been achieved with organ specific scanning agents such as Tc-99m pertechnetate for the brain, ^{131}I for the thyroid, colloidal ^{198}Au for the liver, and ^{85}Sr for the bones. The early success in developing specific organ scanning techniques and the obvious need for a more general method of locating tumors has nurtured the hope, as yet vain, that a particular radiopharmaceutical could be found that would concentrate in any or all tumors irrespective of type or location. A number of agents have been subjected to limited clinical investigation. These include iodide, iodinated albumin, iodinated fibrinogen, ionized mercury as well as labeled chlormerodrin, and selenium as selenite, selenate and selenomethionine. More complex chemicals, such as the porphyrins have also been studied. Each has had only limited success and none has achieved wide clinical application. We now know that carrier-free gallium when injected intravenously as citrate is also concentrated in some human neoplasms. The mechanism of the localization is obscure but apparently not specific for any one histological type.

Approximately one year ago, while evaluating gallium as a bone scanning agent, we observed concentrations of radioactive gallium in the non-osseous tumor of a patient with Hodgkin's disease. This has led to a study of gallium-67 as a broad spectrum scanning agent for osseous or non-osseous tumors. Hayes

1030240

and associates have found excellent intracellular localization of gallium in a transplantable malignant, poorly differentiated neoplasm that grows in Fischer-344 inbred rats (Fig. 1). The scan shows the radioactivity in the tumor of the rat's thigh with lesser concentrations of the gallium in the liver and skeleton. This tumor comprised approximately 1% of the rat's body weight, but retained approximately 30% of the injected radioactivity. This animal tumor appears to be a suitable model for further experiments.

Gallium-67 is accelerator produced and has been made available to us by the Isotope Development Center of the Oak Ridge National Laboratory. It has many radiation characteristics of an ideal scanning agent. Table 1 lists some of the physical characteristics of gallium-67. Its 78-hour half-life is convenient. It decays by electron capture, giving off four main gamma rays. The moderate energies of the 184 and 296 Kev gammas are suitable for use with commercially available scanners and scintillation cameras.

For this study, scans were made using a spectrometer window setting of 160 to 320 Kev. After sterilization and pyrogen testing, the carrier-free gallium-67 citrate (7 mg sodium citrate per kg) is administered intravenously in doses of 70 microcuries per kilogram. Approximately 10-15% of the dose is excreted in the feces and 20-30% is excreted in the urine. To rid the bowel of radioactivity, we give the patient a daily laxative and administer enemas just prior to scanning. Scans can be made at 24 hours but better contrast is obtained at 48 hours. The internally absorbed radiation dose is estimated to be 0.3 rads per millicurie to the whole body assuming no excretion and uniform distribution.

The dose to the bone is estimated to be 2.0 rads per millicurie assuming 100% deposition in the bone.

We have now studied 41 patients with a variety of incurable tumors using carrier-free gallium-67 citrate. In 23 patients the scans have demonstrated tumor sites well enough to be judged as clinically useful. Table 2 lists the types of patients included in this study and a classification as to whether the scans were positive or negative from the standpoint of their being judged as clinically useful in locating tumors.

LYMPHOMAS

Of the 41 patients studied, 23 have been patients with some form of malignant lymphoma. This reflects the patient population peculiar to our hospital rather than any presumption of efficacy, although from the beginning it was hoped that the procedure would assist the staging of Hodgkin's disease and other lymphomas. Six patients with reticulum cell sarcoma were scanned and all six showed significant localization in the tumor.

Case 1 (Fig. 2). This 6-year-old boy had a rapidly enlarging tumor of the left axilla extending into the left side of his neck with considerable tenderness and edema. Histologically it proved to be a reticulum cell sarcoma. The whole body scan made at 24 hours after the dose of gallium shows most of the radioactivity to be in the tumor.

Case 2 (Fig. 3). This patient is a 73-year-old man with an obvious tumor of the neck which was neither tender or edematous. Histologically the tumor was shown to be a reticulum cell sarcoma. The scan of the head and torso shows nearly all the retained radio-

activity to be present in the tumor. Notice particularly the activity in the liver compared to the tumor. The anterior scan of the neck shows the tumor to consist of a number of masses.

Case 3 (Fig. 4). This patient is a 45-year-old lady with a rapidly enlarging abdominal mass. The mass was biopsied at laparotomy and was shown to be a reticulum cell sarcoma. The scans show this mass to be comprised of several tumors. This is particularly apparent on the lateral scan. The lesion in the neck, located under the insertion of the sternocleidomastoid and clavicle was asymptomatic and had eluded the attention of the patient as well as a number of examiners.

Case 4 (Fig. 5). This patient is a 73-year-old female with Hodgkin's disease involving the lymph nodes of the neck. Histologically this was described as a Hodgkin's granuloma. The nodes were tender to touch and can be clearly seen on the neck scan made three days after the injection of the isotope. Unlike the nodes in Case 2, these are not huge. The whole-body scan made six days after the dose shows the radioactivity still in the cervical nodes. In contrast to the previous cases with very large tumors, only a small fraction of the retained radioactivity appears in the tumor. Most of the activity is distributed in the liver, spleen, and the central skeleton. The picture is reminiscent of a scan with a radioactive colloid. We now recognize this as the normal distribution in patients without tumor or at least without tumor localization.

Case 5 (Fig. 6). This 54-year-old man with Hodgkin's disease involving principally the lymph nodes in the right lung had been

subjected to a thoracotomy in an effort to establish the diagnosis. These enlarged nodes can be clearly seen on the X ray and on the scan. The scan also shows activity along the trachea presumably in the paratracheal lymph nodes and in the opposite lung.

One of the more obvious possible clinical applications of tumor scanning would be in the staging of Hodgkin's disease. To be of help it must be capable of detecting tumors not otherwise easily demonstrated, especially small tumors deep in the abdomen. In 5 of the 11 patients with Hodgkin's, we were unable to detect tumors on the scans. In each the disease involved small periaortic lymph nodes demonstrated by lymphangiography.

On the other hand, the upper abdomen is an area that is particularly difficult to evaluate in patients with lymphoma and to a certain extent other tumors. Large tumors can exist there while producing very few symptoms and only subtle changes on X rays. It is difficult and hazardous to fill these nodes for lymphangiography.

Case 6 (Fig. 7). This patient is a 28-year-old female with Hodgkin's disease of approximately six years duration. During the course of her illness, she has had repeated episodes of local tumor treated with teletherapy. The small scan at the lower left shows gallium concentrated in inguinal and iliac lymph nodes that were palpably enlarged. The rectangle indicates the limits of the field of irradiation given as treatment shortly after the scan.

The larger scan at the right, made 7 months later, is actually a composite of anterior scans of the chest and abdomen joined together. The patient had returned with fever, anorexia, and

weight loss. Enlarged nodes were found in the left inguinal area but seemed hardly enough disease to account for her symptoms. Lymphangiography showed some involvement in the left iliac nodes and extensive collateral circulation in the pelvis. Nodes higher up could not be seen. The scan shows radioactivity corresponding to these enlarged iliac lymph nodes, but in addition, activity in left axillary nodes, mediastinal tumor, a larger collection of tumor in the upper abdomen just below the diaphragm. This is precisely in the area that is so difficult to evaluate. The epigastric tumor was not palpable but did produce anterior displacement of the stomach when examined with a barium meal.

Four patients with lymphocytic lymphosarcoma were studied and none showed tumor localization, while both patients with the lymphoblastic form of the disease showed good tumor localization.

Case 7 (Fig. 8). This 83-year-old male with lymphoblastic lymphosarcoma was complaining of enlarging lymph nodes in the neck, axillae, and groin. He unfortunately responded poorly to treatment and died two weeks after the scan was made. Permission for an autopsy could not be obtained, but we did get consent to biopsy organs with a needle. Using a large bore biopsy needle, tissue was obtained for histologic examination and radioassay. The concentration of gallium-67 in the tumor was found to be 5-10 times that in the liver, 10-20 times that in the spleen, and 50 to over 100 times that in the blood and muscle. The concentration of the radioactivity in the different nodes corresponded to the viability of the tumor and varied inversely with the amount of fibrosis and necrosis.

OTHER TUMORS

Of the patients with nonlymphomatous tumors, we found good localization in 3 of 4 patients with bronchogenic carcinoma, but none in 3 patients with multiple myeloma and 2 patients with medullary carcinoma of the thyroid. Three patients with metastatic adenocarcinoma, one of which had a poorly differentiated thyroid carcinoma, showed good tumor localization.

Case 8 (Fig. 9). This patient is a 52-year-old man with bronchogenic carcinoma. On chest X ray he had extensive involvement of the right lower lobe. The scan shows radioactivity corresponding to the lesion plus activity localized in the right upper quadrant. This activity was interpreted as in the liver but since we see so little in the other normal sites, namely, the spleen and central skeleton, it may indicate extensive hepatic metastases. Unfortunately, the patient died elsewhere without the benefit of an autopsy

Case 9 (Fig. 10). This patient is a 73-year-old man with a rapidly enlarging goiter and pulmonary metastases visible on X ray. A total thyroidectomy was done and the lesion was shown to be a poorly differentiated thyroid carcinoma. The pulmonary metastases failed to concentrate any iodine and almost no selenomethionine or indium. The scan made with gallium shows most of the radioactivity to be in the pulmonary metastases.

In considering the possible mechanisms for gallium tumor localization, it was thought that this most likely was related somehow to the protein-binding properties of gallium. It is known that minute quantities of gallium injected intravenously are

quickly bound to plasma protein. Since it was also known that indium behaves similarly when injected intravenously in a carrier-free state, the previous patient (Case 9) was given an intravenous injection of indium-113m citrate, but the scan showed no tumor localization.

TUMORS OF THE BONE

For years it has been known that soluble gallium injected intravenously will be concentrated in bones. Gallium-68 given with stable carrier gallium has been used as a bone scanning agent, although the necessity of giving carrier obviates wide clinical application as yet. As carrier-free ⁶⁷Ga will also localize in skeletal tumors, it can be used to detect osseous and non-osseous tumors.

Case 10 (Fig. 11). This 17-year-old girl has widely disseminated Ewing's sarcoma. The scan shows numerous osseous metastases, her skull, humerus, ribs, spine, and pelvis.

Case 11 (Fig. 12). This patient is a 62-year-old man with disseminated poorly differentiated adenocarcinoma. The diagnosis was made after he had become paraplegic due to tumor involving the vertebrae. After a laminectomy he was irradiated with relief of his paraplegia only to develop pain in his pelvis and shoulders. The scans show extensive tumor localization. The tumors were not palpable but have produced minimal changes on the X ray indicative of osseous involvement.

Case 12 (Fig. 13). This 30-year-old man with stage IV B Hodgkin's disease has osseous and non-osseous tumors shown on the scan. The scan of the shoulder shows activity in the left humerus and axillary node. The scan of the pelvis shows activity in iliac nodes and the ilium.

DISCUSSION

Based on our observations in patients and animals to date, we believe that the gallium is localized intracellularly in some but not all viable malignant neoplasms. Once the gallium is in the tumor it stays for days. The gallium concentration in the tumor at the expense of the hepatic, splenic, and skeletal localizations suggesting some competitive relationship. The mechanism is unknown nor is it known whether there is more than one mechanism for the localization in osseous lesions. The concentration in the tumor is not affected by the amount of citrate given while adding carrier gallium reduces the tumor to bone ratio even with very low levels of carrier.

What is the significance of these findings? First, there is the possible, but as yet unproven, clinical usefulness of gallium-67 as a broad spectrum tumor scanning agent. Whether it becomes useful clinically will depend upon how reliably it will show small lesions deep in the body. So far it has not done particularly well in this regard. Perhaps a better understanding of the mechanism of the localization will lead to methods of enhancing the tumor concentration or at least augment the contrast between tumor and nontumor tissue. It is conceivable that with better scanning skill or equipment we could have detected tumor in more of the small abdominal nodes in the patients with Hodgkin's disease.

Because of mutual interest in this area, we provided Winchell and _____ of the Donner Laboratory some of the gallium-67 preparation. They gave some to several patients who were then

studied with the tomographic scanner designed by Anger. With their instrument they were able to detect a small epigastric Hodgkin's tumor that was later confirmed at laparotomy. The tumor had not been seen with lymphangiography. This or other instrumentation innovations may make the small internal lesions more readily detectable.

The second point of significance is that here is a previously unknown relationship between a simple metal and certain malignant tumors. A better understanding of this relationship may shed further light on the metabolism of tumors. Obviously further experiments with animal and human neoplasms must be carried out.

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Dr. C. Lowell Edwards Identifying No. 9

Project Title: "Tumor Scanning with Gallium-67"

Comments:

The committee noted with favor that cooperative studies were being carried out with established investigators. It was noted that ORAU was legally responsible for material sent out for human use.

Jan. 75 (See attached report)

act...

Approved: July 10, 1969 (date)

Disapproved: _____ (date)

Gould Andrews
Secretary, Committee on Human Studies

Adopted 4-67

1030250.

No. 9 Tumor Scanning with ^{67}Ga

This project is being continued to collect more data especially on patients previously studied. To date 357 patients have been scanned with ^{67}Ga at ORAU. Some of these have been studied as part of other specific investigations such as scandium-augmented ^{67}Ga study and the comparison of ^{111}In with ^{67}Ga .

The Cooperative Group study is completed except for compiling the rest of the data, evaluating and reporting the results. No untoward reactions have been reported from the Cooperative Group and none were seen in our 357 patients.

1030251

MEMORANDUM

TO Dr. Andrews DATE 20 June 1969

SUBJECT TUMOR LOCALIZATION OF GALLIUM-67 IN EXPERIMENTAL ANIMALS

COPIES TO Dr. Kniseley, Files

Normal-Animal Tissue-Distribution

Administration of carrier-free gallium-67 to animals results in localization of the radionuclide primarily in the bone, liver, spleen, bone marrow, and kidney. The relative localization in various tissues is affected both by age of the animal and the strain. Some recent evidence indicates that sex may also be a factor.

Animal Tumors Studied

A number of rat and mouse tumors both transplanted and spontaneous have been investigated. All have shown localization of gallium-67 in the tumor tissue but the relative concentration compared to other tissues was often rather poor. Best results so far have been obtained with the Comas "RFT" tumor, the AKR mouse spontaneous thymoma, the R-3259 transplanted rat hepatoma, the ESR-586 transplanted mouse preputial gland tumor, and the Walker-256 transplanted rat tumor, approximately in that order of degree of localization. The RFT tumor is a transplanted tumor developed by Dr. Comas from a spontaneous tumor arising in an irradiated Fischer-344 rat. Attached is a gallium-67 scan of an animal bearing this particular tumor. The tumor mass constituted about 1% of the body weight and contained about 20-30% of the administered dose. The tumor is very slow-growing, poorly differentiated, but is as yet of unidentified origin although Dr. Nelson feels that it is possibly from epithelial tissue. The transplant has been found to metastasize after a period of 4 months. In our studies we have normally used the tumor after an implant period of 5 to 6 weeks at which time the tumor weighs 2 to 3 g. Because of the high localization of gallium-67 in the RFT tumor, we have used it as a model tumor in most of our studies.

Localization Studies

Light microscopic and electron microscopic autoradiographic studies show that the localization in the RFT tumor is associated with viable tumor cells and much less with areas of necrosis. A print of a 14-power microscopic autoradiogram is attached. Tissue assay of RFT tumors and Walker-256 tumors also indicate that the gallium-67 is associated to a much greater extent with viable than with necrotic tumor tissue. Some subcellular fractionation studies of the RFT tumor have been made. We are still in the process of developing more precise separation techniques; however, results so far indicate that the gallium-67 is associated mainly with the mitochondrial and microsomal fractions. Only approximately 10% of the tumor-tissue activity is found in the final supernatant after ultracentrifugation and only approximately 20% (2% of tissue activity) is dialyzable. Studies with the AKR mouse

1030252

spontaneous thymoma indicate that the degree of gallium-67 concentration in the thymus increases with the degree of involvement with lymphoma (microscopic examination by Dr. Nelson). I should add further that the autoradiographic studies indicate that there is concentration of grains over the individual tumor cells. In the RFT tumor it seems fairly clear that the concentration of gallium-67 is intracellular.

Localization with Time

The concentration of gallium-67 in the RFT tumor at 4 hours is approximately 50% of maximum concentration; however, other tissues are quite high at this time. Distribution appears to be complete by 24 hours and does not change essentially except for a lowering of the blood through a period of 5 days.

Effect of Citrate Dose

Citrate is used simply as a solubilizing agent and in the original human studies an arbitrary level of 7 mg citrate/kg body weight was used. Subsequent studies have indicated that there is no significant change in tissue distribution in the RFT tumor rat down to a level of 0.07 mg citrate/kg body weight.

Effect of Size (Age) of Transplant

A distinct increase in RFT tumor concentration of gallium-67 was observed in 3-week transplants when compared to 5-week transplants. The tumor concentration did not appear to decrease at a later time (10 weeks) but this possibly was caused by the effect of age on the host. Another experiment will have to be run in which the age of the animals is kept constant and the tumor transplant age varied.

Effect of Stable Gallium

Administration of stable gallium along with gallium-67 lowers, as one would predict from previous studies, the deposition in soft tissues and increases that in the bone and the kidney. The tumor tissue concentration also decreases with the result that the relative concentration in the tumor remains about the same although the absolute amount is considerably reduced. This would indicate that the gallium "binding sites" in the RFT tumor are saturable.

Comparison of Gallium-67 with other Tumor Scanning Agents

As a test of the uniqueness of gallium-67 localization in the RFT rat tumor, studies have been carried out with iodinated albumin, ⁷⁵Se selenomethionine, and ²⁰³Hg chlormerodrin. The iodinated albumin was studied at 1 day and 5 days after administration; the other two were studied at 1 day. In all three cases there was very poor relative concentration of the agents in the tumor tissue (1/10 or less that of gallium-67). Indium-114m has also been studied at 1 day and 5

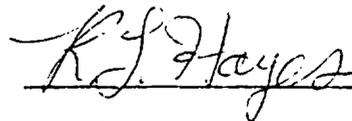
days after administration with similar poor results. The indium and selenium-methionine results are consistent with results in humans in the clinical program.

Attempts to Enhance Relative Gallium-67 Tumor Localization

As pointed out above, stable gallium is not effective as enhancing agent since it apparently saturates tumor binding sites as well as those in soft tissues. Various chelating agents (stronger than citrate) have been used in an attempt to decrease the concentration in bone as well as that in soft tissues but with no positive results. Interestingly enough it has been found that scandium administered either before or with gallium-67 causes (as would be predicted from previous studies) rapid clearance of gallium-67 from soft tissues in the RFT tumor rat but does not decrease the concentration in the tumor tissue itself. Evidence so far with the RFT tumor indicates that better relative tumor localization of gallium-67 (or gallium-68) might be achieved with scandium in as little time as 2 to 4 hours after administration as compared with those obtained at 24 hours with gallium-67 alone.

Summary

Gallium-67 tumor localization appears to be associated with viable tumor tissue. The localization is probably intracellular. Time and citrate dose do not affect the tumor localization. There appears to be some size (age) effect. Stable gallium saturates tumor "binding sites." A number of other tumor agents compare poorly with gallium-67. There is a possibility of enhancing the relative localization of gallium-67 at early time periods.



R. L. Hayes

RLH/v

Attachments

1030254



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

IND 5489

APR 27 1976

Gould A. Andrews, M.D.
Oak Ridge Associated University, Inc.
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 Gallium-67 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 October 10, 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.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

APR 30 1976

1030255

Oak Ridge Associated Universities

Incorporated

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

Telephone 615 483-8411

*Re: Gallium-67 studies
Jan. 25, 1974*

*Copy of book
is in Edinburgh
and Helsinki*

April 30, 1976

William J. Gyarfas, M.D.
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

Dear Dr. Gyarfas:

Since the first of October, 1974, we have given 98 intravenous doses of Gallium-67 here at the Medical and Health Sciences Division of Oak Ridge Associated Universities. There has been no untoward reaction to any of these injections.

The material was obtained from New England Nuclear Company, and in some instances reporting was requested by the company and presumably has been forwarded to you. The dose that we have used has been 70 microcuries per kg with a maximum of 6 millicuries.

We hope that this information will fulfill your needs, and we will be glad to answer any further questions you may have.

Sincerely,

Gould A. Andrews

Gould A. Andrews, M.D.

GAA:dgb

1030256



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

IND 5489

AUG 21 1977

Gould A. Andrews, M.D.
Oak Ridge Associated University, Inc.
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug for Gallium-67 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 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

1030257

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

September 19, 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:

This is in response to your recent letter concerning our IND on Gallium-67 Citrate. In view of the fact that this agent was approved by FDA in May, 1976 for general diagnostic use, we believe that our IND should be discontinued since our current applications fall within this use.

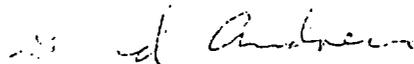
We are continuing to use it as a cancer localizer. Most of the patients we are now studying have cancer of the lung, but a few other types of malignancies are included. Further investigations are likely to be refinements of procedures already published or comparisons with other diagnostic radionuclide preparations.

As a result of the introduction of Gallium-67 by ORAU, a cooperative group of investigators at many institutions carried out an extensive study. Several publications have been made or are in preparation. We are sending you three copies of a recent report on Hodgkin's disease that is representative of this output. The agent is now widely used in many countries.

The requirements in the last paragraph of your letter appear to be satisfied. Some of the investigators have left our staff; those remaining are aware that ^{67}Ga is now a standard radiopharmaceutical. We purchase the product as it is needed and thus do not have any residual supplies to dispose of.

Please let us know if further information is needed.

Sincerely,



Gould A. Andrews, M.D.

GAA:dgb

1030258



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

DEC 15 1977

IND 5489

Gould A. Andrews, M.D.
Oak Ridge Associated University, Inc.
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Andrews:

We acknowledge receipt of your September 19, 1977 communication regarding your discontinued Notice of Claimed investigational Exemption for Gallium-67 Citrate.

The submission notifies us that clinical investigation has been discontinued.

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

The discontinuance procedure is now considered complete. 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. Gyrfas

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

1030259

To: Committee on Human Studies Page 1
Oak Ridge Associated Universities
Medical Division

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

(Three copies required. Use reverse side of these forms if additional space is needed.)

Date 9-18-69

I. Senior Investigator: C. L. Edwards
Co-Investigators: C. C. Lushbaugh, Helen Vedovich, Francis A. Gaswitz, Bill Nelson, R. M. Katseler, and G. A. Andrews
Title of Project: "Studies of Total-Body Irradiation in Patients with Hematologic Disorders"

II. Objectives of Experiment: (Use additional blank pages if needed.)
The objectives are (1) to develop better irradiation methods for therapy; (2) to improve methods for assessing and treating accidental gamma and neutron radiation injury; (3) coincidentally to collect and evaluate critically information potentially useful to NASA in dealing with high levels of occupational radiation exposures in space exploration; and (4) to devise new and more precise end-points that define the radiation dose response in man.

Certain selected chronic malignant diseases, particularly chronic leukemias and lymphoma, can be controlled effectively by total-body irradiation. More information is needed on how this treatment can best be applied. Also there is an urgent need to understand the clinical physiologic events that occur after total-body irradiation so that accidental and military exposures (or exposures in space exploration) can be most intelligently treated. Laboratory and clinical observations are made on patients irradiated for malignant disease, at the

Adopted 4-67

II. Objectives of Experiment:

Page 2

medium-exposure-rate total-body facility (METBI) comprised of eight 500-curie ^{137}Cs sources providing a homogeneous irradiation field with a dose rate between 1 and 4 R/min. The low-exposure total-body irradiator (LETBI) is also in operation and at present provides exposures of 1 to 5 R/hr in a homogeneous field of gamma radiation provided by 10 cobalt-60 sources.

The experimental high-dose-rate unit at UT-AEC provides 50-75 R/min exposures from ^{60}Co sources.

The study will emphasize:

1. Precise measurements of irradiation dose and dose rate.
2. Frequent blood counts and bone-marrow examinations at specified days to permit comparison between patients and groups of patients.
3. Careful monitoring of symptoms and biochemical changes which may indicate physiologic effects of irradiation.
4. A comparison of different doses, dose rates, and protracted versus fractionated doses as to therapeutic effect, symptoms produced, hematologic and biochemical responses.

III. 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. (Use additional blank pages if needed.)

A. Selection of Patients.

Patients will be selected from among the patient population as referred to the Medical Division. The selection will not be randomized but only patients meeting the following criteria as to diagnosis and manifestations of their disease will be selected.

Diagnoses:

1. Polycythemia vera
2. Chronic granulocytic leukemia
3. Chronic lymphocytic leukemia
4. Lymphosarcoma

Manifestations:

1. Thrombocytosis
2. Leukocytosis
3. Symptomatic lymphadenopathy, non-hemolytic anemia without thrombocytopenia
4. Bone-marrow invasion plus those in #3 above.

1030261

Some of these patients will be exposed to 100-250 R total-body irradiation in the LETBI (1.5 R/hr) facility or by fractionated daily doses of 30 R/day in the METBI (1.5 R/min) facility. Others will be treated with 50-100 R exposure in the METBI facility.

Each patient will be followed with frequent blood counts, cultures, and chemistry determinations prior to, during, and for a period of at least 6 weeks after exposure (sample protocol for METBI, 100 R; LETBI, 250 R; METBI, 150 R fractionated, enclosed). During this time he will receive no other specific therapy unless, (1) he was being maintained on some chemotherapy prior to and during the pretreatment period, e.g. prednisone; (2) his condition is judged to be deteriorating after treatment without hope of response to the irradiation and it is the consensus of the clinical staff that some other form of treatment is indicated.

Therapeutic benefit will be assessed on the basis of:

Diagnosis:

1. Polycythemia
2. Chronic granulocytic leukemia
3. Chronic lymphocytic leukemia
4. Lymphosarcoma

Criteria:

1. Return of the platelet count to normal
2. Relief of symptoms, such as pruritis
1. Return of RBC to normal
2. Reduced cellularity of bone marrow to normal
3. Reduction in splenomegaly
4. Relief of symptoms, general malaise, etc.
1. Reduction in size of lymph nodes
2. Improved RBC values
3. Reduction in splenomegaly
4. Improved symptoms, e.g. reduction in discomfort, improved sense of well being
1. Reduction in tumor and organomegaly
2. Reduced bone marrow tumor
3. Improved RBC values
4. Improved symptoms

The therapeutic response to various radiation regimens will be compared with each other and with other methods of treatment.

B. Radiation Protocols.

1. Single dose

- a. METBI - 50 R, 100 R at 1.5 R/min. Approximately 90 treatments have been given to about 75 patients. Only a few additional patients are planned for this series.
- b. LETBI - 50 - 250 R at 1.5 R/hr (up to about 9 days in the unit). Twenty patients treated. We hope to add about one patient a month for the next 3 years.
- c. UT-AEC High-Rate Irradiator - 50 - 100 R at 50 R/min. None treated till now. Objective: to determine dose-rate effect on the degree of response (compared to group A,B) in 3 cases of chronic granulocytic leukemia. Similar comparison may be possible in the other disease categories (5-10 patients/disease).

2. Fractionated Doses.

- a. METBI up to 250 R at 1.5 R/min with daily doses of approximately 30 R. Five patients treated. Objective: to add enough patients to make a valid comparison with the same total dose in LETBI protracted to the same time span.
- b. Repeated low-dose maintenance exposures in METBI or LETBI (weekly or monthly doses in the 10 - 30 R range). None treated. Numbers to be included in the series depends on availability of patients and results of early studies. Five to ten patients in each disease category would be desirable.

III.

C. Laboratory Studies (see copy attached protocol).

1030263

We have considered the following possible hazards:

1. Overdose of radiation due to technical failure. Both the LETBI and METBI facilities are especially designed to eliminate any possible defect in position of sources that might alter the dose. Extensive dosimetry is done with each exposure in both facilities. Before the high-dose-rate exposure field at UT-AEC is used we will plan carefully, with our radiation safety staff, methods of eliminating any possibility of accidental overexposure there.
2. Electrical shock during exposure. Because of the physiologic monitoring during the prolonged LETBI exposure we have considered the possibility of electrical shock to the patient. The monitoring device includes an electrode to the patient's chest that is grounded. If a short should occur in any improperly grounded electrical device operated by the patient, a fatal shock could occur. To protect against this, isolation transformers have been put in for the two lamps and television set operated by the patient. A further study is being undertaken to check on the grounding of the light fixtures in the room, and particularly of a dimming device for overhead lights which the patient sometimes operates.
3. Excessive depression of normal marrow elements after irradiation. Careful assessment of the patients' hematologic status is made before treatment is given. Patient selection and choice of radiation dose are carefully planned to reduce this hazard. A number of patients with diseases falling in the appropriate categories are eliminated because of low platelet counts or other evidences of inadequate marrow reserve. If patients do develop severe marrow depression we are prepared to give a protected environment and supportive therapy, including platelet transfusions and antibiotics based upon extensive bacteriologic studies directed by Dr. Balish.
4. Less than optimal long-term results. We are aware, we believe, of the various controversies over the treatment of these diseases and we try to select patients in line with our best judgement so as not to deprive them of benefits at least equal to "standard" therapy.

In polycythemia vera, the evidence of Modan that ^{32}P causes an increased incidence of acute leukemia has not been entirely accepted. We are cognizant of the deliberations of the polycythemia study group under Dr. Louis Wasserman and are prepared to modify our plan, or eliminate this group of patients if this appears indicated.

In chronic granulocytic leukemia the report of D.A.G. Galton, et al, indicates that patients given splenic irradiation and a variety of other types of external radiation develop earlier blast cell transformations than patients treated with busulfan. E. E. Osgood, on the basis of a very careful long-term study, finds that carefully titrated doses of ^{32}P give results better than any other form of reported treatment. Our past use of total-body irradiation may not be as good since it is not as well titrated as Osgood's ^{32}P . We are conscious also of the problems of busulfan including a significant incidence of early over-treatment and certain peculiar late metabolic complications.

In chronic lymphocytic leukemia there is a good deal of difference of opinion about the value of suppressive therapy, with many hematologists tending to believe that in patients who are tolerating the disease well, the less therapy the better. We recognize the possible validity of this viewpoint and adopt it with some patients, excluding them from the total-body radiation ~~series.~~ ~~series.~~

V. Radioisotopes and New Drugs:

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

VI. Responsibilities of Senior Investigators:

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

Starting Date	<u>Continuing</u>	Signatures:	_____
			Investigator

			Investigator

			Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

Chairman

Date

IV. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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:

Ongoing

Signatures:

C. Lowell Edwards, M.D. Investigator

W. W. Bushbarr Investigator

Helena Podopieck, M.D. Investigator

Francis A. Goswitz Investigator

Bill M. Nelson

Robt. W. Kennedy

Donald Andrews

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Donald Andrews Chairman

Date: 18 Sept 69

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: C. Lowell Edwards Identifying No. 10

Project Title: Studies of Total-Body Irradiation in Patients with Hematologic Disorders

Comments:

The committee approved this project but recommended the purchase of new dosimetry equipment for the METBI facility to allow continuous monitoring.

Approved: Sept 18, 69 (date)

Disapproved: _____ (date)

Robert W. Lanza M.D.
Secretary, Committee on Human Studies

Still active (11 Dec. 73)

Cancelled Jan 25, 1975 (See attached report)

Adopted 4-67

1030269 .

No. 10 Studies of TBI in Patients with Hematologic Disorders

With the closing of the clinical facility, the therapeutic total-body irradiation project was discontinued after a total of 194 patients received exposures of 50 R to 250 R in METBI or LETBI. See 1973 Research Report ORAU-123, page 5, and an updated Table 1. These patients are no longer being followed at ORAU. The data are being compiled for publication.

1030270

To: Committee On Human Studies
Oak Ridge Associated Universities
Medical Division

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

Date: 9 September 1969

I. Senior Investigator: Francis A. Goswitz, M.D.
Co-Investigators: Helen Vodopick, M.D.
C.C. Lushbaugh, M.D., Ph.D.
C.L. Edwards, M.D., Clinical Staff
Title of Project: Blood Lymphocyte Survival and
Distribution in Patients with
Lymphoproliferative Disorders

II. Objectives of Experiment:

The primary objective of this experiment is to determine the survival and distribution of the blood lymphocyte in patients with various lymphoproliferative disorders. Untreated patients will be compared with those taking medication (antilymphocyte chemotherapy) or those having completed a course of total-body irradiation.

To obtain data about lymphocyte mass, blood volume measurements are indicated. Human radioiodinated serum albumin ($R^{125}ISA$) will enable us to quantitate the plasma volume. When chromium-51 is the radioisotope used to label lymphocytes, red cell mass can also be determined since the chromate ion will attach to erythrocyte membranes. Proportion of erythrocytes labeled depends upon the number of these cells present in the ^{51}Cr -labeled lymphocyte preparation.

Distribution of the blood lymphocyte is followed by repeated linear (profile) scans and by external counting at the body surface over liver, heart, spleen, sacrum, and a peripheral lymph-node site. Whole-body retention of the radioisotope injected will be evaluated by periodic total-body counts. Radioassay of blood, plasma, and urine samples (first 10 days of study) provides additional information about the retention as well as excretion of chromium-51.

III. Methods of Procedure:

At least five untreated patients in each disease category should be studied. These diseases are acute lymphocytic leukemia, chronic lymphocytic leukemia, and certain malignant lymphomas with an absolute blood lymphocytosis. Labeling cells at the time of an indicated blood transfusion in some patients will permit a comparison with normal lymphocytes. At present, I don't believe AEC approves administration of radioisotopes to healthy volunteers which would permit collection of data regarding normal blood lymphocyte kinetics.

Five or more patients who just completed a course of total-body irradiation (250 R or less) will be studied to note the effects of this treatment on the leukemic lymphocyte's survival. Similarly, the same number of patients being treated with prednisone or chlorambucil will require study to determine the effects of these drugs on the blood lymphocyte.

Either one of two radioisotopes will be used to label the blood lymphocytes. Chromium-51 as sodium chromate, approximately 250 microcuries, is the maximum amount of radioactivity that can be counted in a patient in the low-level whole-body counter. In the patients studied to date, we find that the trivalent chromium-51 attached to plasma proteins is excreted into the urine. By day 10, only about 10% of the radioisotope may be retained within the patient. Such a decrease in radioactivity demands now the withdrawal of 50 ml of whole blood in order that sufficient lymphocytes can be separated to obtain reliable radioassay data. Although these blood samples after day 10 are collected once weekly or biweekly, the question arises whether or not more radioisotope should be injected initially. A dose of 2 millicuries of chromium-51 is presently under consideration. If this dose is injected, and assuming that 10% of chromium-51 will be retained on day 10, then the whole-body counting could not begin until this date.

The other radioisotope to be used later after the chromium-51 data has been completed, is selenium-75 methionine. Only a dose between 25-30 microcuries of the ⁷⁵Se will be injected intravenously into these patients. In contrast to chromium-51, the selenium-75 attached to plasma proteins is not excreted into the urine. The patient may retain about 60% of this dose on day 160. The reason for repeating the lymphocyte survival distribution and retention study with ⁷⁵Se methionine is to compare these results with the ⁵¹Cr data.

In the study of these patients we try to choose a time period when the lymphocyte mass remains constant as determined by the absolute blood lymphocyte count.

IV. Possible Hazards and Their Evaluation:

In a memorandum sent to me last September 16, 1968, Mr. Cloutier mentioned that the whole-body radiation dose to a patient from ⁵¹Cr-tagged lymphocytes would be 0.42 millirad per microcurie administered, if the isotope is uniformly distributed in the body. In a second memorandum of February 14, 1969 (copy also enclosed) Mr. Cloutier estimated the following radiation dose from ⁵¹Cr-labeled lymphocytes injected intravenously on the basis of preliminary biologic data that we provided for him:

27 millirads/microcurie if 40% of the administered dose is uniformly distributed in the spleen.

2.2 millirads/ microcurie if 30% of the administered dose is uniformly distributed in the liver

1.5 millirads/microcurie if 20% of the administered dose is uniformly distributed in the bone marrow.

Thus, 3 millicuries of ⁵¹Cr-labeled lymphocytes would provide a maximum radiation exposed dose to the spleen of 81 rads. Since excretion of the radionuclide definitely occurs, this amount of injected radioactivity provides no hazard for the patient with chronic lymphocytic leukemia. Wagner estimated 0.3 microcuries of ⁵¹Cr-labeled red cells would expose the spleen to 6 rads, whole-body to 70 millirads.

At a later date, lymphocyte survival would be restudied by labeling lymphocytes with L-selenomethionine-⁷⁵Se. Approximately 25 microcuries of selenium-75 with the following specifications should be used: specific activity 1-6 microcurie/mg

selenomethionine; concentration 0.25 microcurie/ml; radio-chemical purity greater than 95%. Lymphocytes incorporate small amounts of ⁷⁵Se-selenomethionine into globulin protein even in unstimulated tissue cultures (Chenget al, J. Nuc. Med. 10:63, 1969).

Sodee (Nucleonics 23, 7, 78-81, 1965) calculated a whole-body radiation dose in man of 2.5 rads for a standard diagnostic dose of 250-300 microcuries given intravenously to scan the pancreas. On this basis, 25 microcuries would provide a whole-body radiation dose of only 0.25 rads. The gonads would receive a marginally greater dose, but the kidneys a much higher dose of 1.4 rads.

Selenium-75 has a moderately long physical half-life of 120 days. Its principal gamma energies are at 0.269 Mev. (71%) and 0.138 Mev. (24%). Values for E_β, the average beta energy, actually represents low-energy x-ray emission associated with the electron capture process. Selenomethionine like methionine, has a biologic half-life of 100 to 144 days. When 210 microcuries of ⁷⁵Se selenomethionine is injected intravenously, Numerof (Recent Advances in Nuclear Medicine, Appleton-Century-Crofts, p. 83, 1966) states 10% of the administered dose goes to the liver and 7% to the pancreas. Total radiation dose estimated to the whole body is 1.5 R, to the liver 0.06 R, and to the pancreas 0.06 R.

V. Radioisotopes and New Drugs:

This study does not involve the use of any new radioisotopes or drugs.

VI. Responsibility of Senior Investigator:

It is understood that the principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject under study.

Signatures: Francis A. Gravitz
Investigator

Investigator

Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

Chairman

Date

1030275.

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Goswitz Ident. No. 11

Project Title Blood Lymphocyte Survival and Distribution in Patients
with Lymphoproliferative Disorders

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

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

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

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

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

5. Other committee comments:

Approve _____

Chairman of Committee

Disapprove _____

Date

Cancelled (25 Jan. 75) - Never activated

1030276

PROGRESS REPORT
HUMAN BONE MARROW TRANSPLANTATION

OF

ORAU MEDICAL DIVISION

19 Dec 72

Using the procedures outlined in the protocol for therapeutic allogenic transplantation of human bone marrow as approved by this committee, we have performed three bone marrow transplants up to this date. The patients receiving this kind of treatment were two males, 51 years and 41 years old, and one woman, 53 years of age. All of these patients had acute granulocytic leukemia. In two of these patients we found a histocompatible donor according to the HL-A typing and the results of the mixed lymphocyte cultures. In the 41 year old man we did not find an identical donor and the HL-A typing indicated a D match, which means a difference of at least 3 antigens. In this third case there was also a slight reactivity in mixed lymphocyte cultures.

All of these patients received anti-human thymocyte globulin and total body irradiation with 500 R as pre-grafting immunosuppression. The anti-human thymocyte globulin was generally tolerated well, except for the last patient, who reacted with severe fever spikes following most of the daily injections of the horse globulin. Each of the patients tolerated the radiation very well. Except for slight nausea following the total body irradiation (only the second patient vomited) the only symptom experienced by the patients was drowsiness which was in part due to the phenothiazide medication used to suppress nausea and vomiting. We do not believe the immunosuppression shortened the life of any of these patients.

1030277

The transfusion of the bone marrow cells went without any complications, especially there were no indications of embolism. The total number of bone marrow cells infused into these three patients ranged between 15×10^9 to 18×10^9 cells. All of these patients received post-transplant immunosuppression with intermittent doses of methotrexate as outlined in the protocol. The dose of the methotrexate was varied according to the clinical course of the patients. Our first patient received a total of 440 mg of methotrexate up to the 117th day post-transplant. The second patient received a total dose of 140 mg the last which was given on day 21. No further methotrexate was considered for the second patient because of abnormal liver function studies. The total dose of methotrexate given to the third patient was 195 mg.

The two patients who received HL-A identical bone marrow grafts showed well-documented evidence for a successful take of the bone marrow graft. This evidence was derived from red cell markers and white cell markers. In the third patient we had no evidence for a successful graft, and had to conclude that the bone marrow graft was not accepted. In none of the patients did we see any signs or laboratory evidence for graft-versus-host disease. With regard to the third patient, this would also indicate that we did not obtain a successful graft. The survival time of these patients was 122 days respectively, 92 days for the patients with the HL-A identical graft. The patient with the mismatched bone marrow lived for 60 days following the transplant. All three of the patients died with pneumonia or septicemia, although the first patient's death was more likely the result of pulmonary embolism and renal failure and the last 2 patients died with their leukemia in relapse.

1030278

With regard to the stage of leukemia we observed that in the first patient there was no recurrence of leukemia. He died from causes unrelated to his leukemia, and on autopsy there was no evidence of leukemia. The second patient (female) showed initial absence of leukemia cells from the blood or bone marrow. However, approximately 10 1/2 weeks after the transplant she developed a sudden blast cell crisis, subsequently to which she died from septicemia. In the third patient we never saw evidence for a successful take of the graft and we never observed a complete disappearance of leukemic cells from the peripheral blood and/or bone marrow.

MEMORANDUM

TO: Dr. F. G. ...

DATE February 14, 1968

SUBJECT: RADIATION DOSE TO ADMINISTERED ^{51}Cr -LABELED LYMPHOCYTES

COPIES TO: File

As you requested, we have calculated the radiation dose from ^{51}Cr -labeled lymphocytes to the spleen, liver, and bone marrow. These calculations are only as valid as the assumptions made on the biological parameters; i.e., concentration in the organ and half time of the material in the organ. The following table lists the results.

<u>Reference Organ</u>	<u>Assumptions</u>	<u>Radiation Dose from ^{51}Cr Administered I.V. on Labeled Lymphocytes (millirads per microcurie)</u>
Spleen	40% of administered dose uniformly distributed in spleen 56-day biological half time	27
Liver	30% of administered dose uniformly distributed in liver 80-day biological half time	2.2
Bone Marrow	20% of administered dose uniformly distributed in marrow 50-day biological half time	1.5*

*The estimation of 12.7 millirads per microcurie of administered ^{51}Cr -labeled cells listed in our memo of 9-16-68 was based on 100% of the material uniformly distributed in the blood and remaining there until complete physical decay.

These estimates should be revised as new biological information becomes available and before these numbers are published in any official publication.

Robert J. Cloutier

1030280

MEMORANDUM

TO: Dr. F. Coswicz

DATE September 16, 1968

SUBJECT: RADIATION DOSE FROM ADMINISTERED ^{51}Cr COPIES TO: File

The whole-body radiation dose to a patient from administered ^{51}Cr -tagged lymphocytes would be 0.42 millirad per microcurie administered, if the isotope is considered uniformly distributed in the body.

The dose to the blood would be 12.7 millirads per microcurie of administered ^{51}Cr if the isotope is uniformly distributed in the blood and no excretion occurs.

The doses calculated are quite dependent on isotope distribution and retention. Different assumptions for either parameter would alter the reported doses.

Roger J. Cloutier
Roger J. Cloutier

w

1030281-01
1030281-02
1030281-03
1030281-04
1030281-05
1030281-06

APPLICATION FOR USE OF HUMANS AS EXPERIMENTAL SUBJECTS

- I. Senior Investigator: C. L. Edwards
Co-Investigators: R. L. Hayes
N. Tehranian

TITLE: Scanning tumors of the retroperitoneal lymph nodes after intralymphatic injection of radioactive gallium.

II. Objectives of Experiment:

The principle objective is to test the hypothesis that tracer amounts of gallium citrate will concentrate in tumors involving the lymph nodes but not in the normal lymph nodes when the nuclide is injected into the afferent lymphatics.

Assuming the hypothesis is correct, we will then evaluate the procedure as a method of demonstrating involvement of the retroperitoneal lymph nodes by Hodgkin's disease or other lymphomas in comparison with lymphangiography using a radioopaque oil (Ethiodal).

III. Methods

At least 12 patients with known disseminated malignant lymphoma will be tested. Of these at least 6 will be patients with peripheral lymph node tumors which are known to concentrate gallium. Each patient must have a clinical indication for lymphangiography, e.g., 1) initial staging of the disease; 2) search for occult lesions accounting for symptoms. Each patient will be studied with an intravenous gallium study before or after the intralymphatic study.

Each patient is prepared as for an ordinary lymphangiogram. The feet are scrubbed with Betadine solution, rinsed with 70% alcohol and dried. In a surgically clean field approximately 0.5-1.0 ml of alphazurine or other suitable dye is injected subcutaneously into the four interdigital spaces of each foot. When the small subcutaneous lymphatics on the dorsum of the foot are visualized, under local anesthesia, a small transverse incision 1/2 to 1 inch in length is made over a superficial lymphatic vessel picked for prominence and accessibility. An intralymphatic cannula is inserted into the opened lymphatic and anchored in place with a fine suture.

The tubing connected to the lymphatic cannulae is filled with saline prior to insertion in the vessel. The other end of the tubing is connected to a syringe containing 10 ml of an isotonic saline solution containing up to 1 mCi of carrier-free gallium-67 or up to 5 mCi of gallium-68. The gallium solution is injected slowly, manually or with a pump, into the lymphatic vessels. This is then followed by 10 ml of normal saline and up to 10 ml of Ethiodal. Total injection time is approximately one hour for the radioactive gallium, one hour for the saline, and two hours for the Ethiodal. The patient will be positioned on the radiolucent stretcher and the progress of the radioactive infusion will be monitored using the Anger camera. Upon completion of the radioactive infusion, the patient will be moved on the stretcher into position over the X-ray table where the Ethiodal infusion can be monitored with X rays.

IV. Possible Hazards

The hazards of lymphangiography are well established and documented in the open literature. The chief hazard is that of lipid emboli to lung or in the presence of a right to left vascular shunt the emboli may find their way to the brain. The recommended precautions of limiting the volume of the Ethiodal to no more than 20 ml and taking at least one hour for injection. During the infusion the progress of the lipid will be followed and the injection discontinued when it reaches the midabdominal nodes or sooner if there are excessive anastomoses.

The infusion of isotonic solutions into the lymphatics is believed as innocuous a procedure as a comparable intravenous infusion, although the rate of infusion will by necessity be slower. Intralymphatic injections of radioactive colloids have been used as therapy of malignant lymphomas and have proved to be effective and safe. In the case of radioactive colloids the normal lymph nodes receive the highest concentration of radioactivity; tumor bearing nodes the least. Studies in normal animals (4 dogs) at this facility indicate that the distribution of tracer amounts of gallium citrate injected intralymphatically resemble that injected intravenously. The exception is first in lymph nodes along the lymphatic vessel retains 10-15 times that in the opposite extremity (0.005-0.010% of dose/gm) which is similar for I.V. doses.

The whole body exposure to gallium-67 and gallium-68 assuming uniform distribution is 0.3 Rads/mCi and 0.3 Rads/5 mCi respectively.

1030284

V. Radioisotopes and New Drugs

The radioisotopes used in this study will be approved by the isotope committee of ORAU Medical Division and an application for exemption will be submitted to the F.D.A. as an amendment to IND-5489.

VI. Responsibility of Senior Investigator:

It is understood that the principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject under study.

Signatures:

Investigator

Investigator

Investigator

V. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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: December '69

Signatures: C. James Edwards, Jr. Investigator
R. L. Hayes Investigator

Investigator

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Donald Andrews Chairman

Date: Sept 16, 69

Revised October 1969

103028b

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: C. Lowell Edwards Identifying No. 13

Project Title: Scanning Tumors of Retroperitoneal Lymph Nodes After
Injection of Radioactive Gallium

Comments:

The committee approved this project, but it was pointed out that the greatest danger may reside in the lymphangiogram procedure. The danger of performing the procedure in patients with pulmonary disease was noted.

Approved: Sept 18, 69 (date)

Disapproved: _____ (date)

Robert W. Lang, M.D.
Secretary, Committee on Human Studies

March 27, 72 "in a bag"

Not recommended Dec. 73

25 Jan 1975 [unclear]

Adopted 4-67

1030287

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 19 Dec. 72

Principal Investigator: N. Gengozian

Co-Investigators: C. Lowell Edwards

Helen Vodopick

Karl Hubner

Title of Project: Therapeutic Allogeneic Transplantation of Human Bone Marrow: (1) Request to increase radiation dose (2) Request to include patients with aplastic anemia.

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.

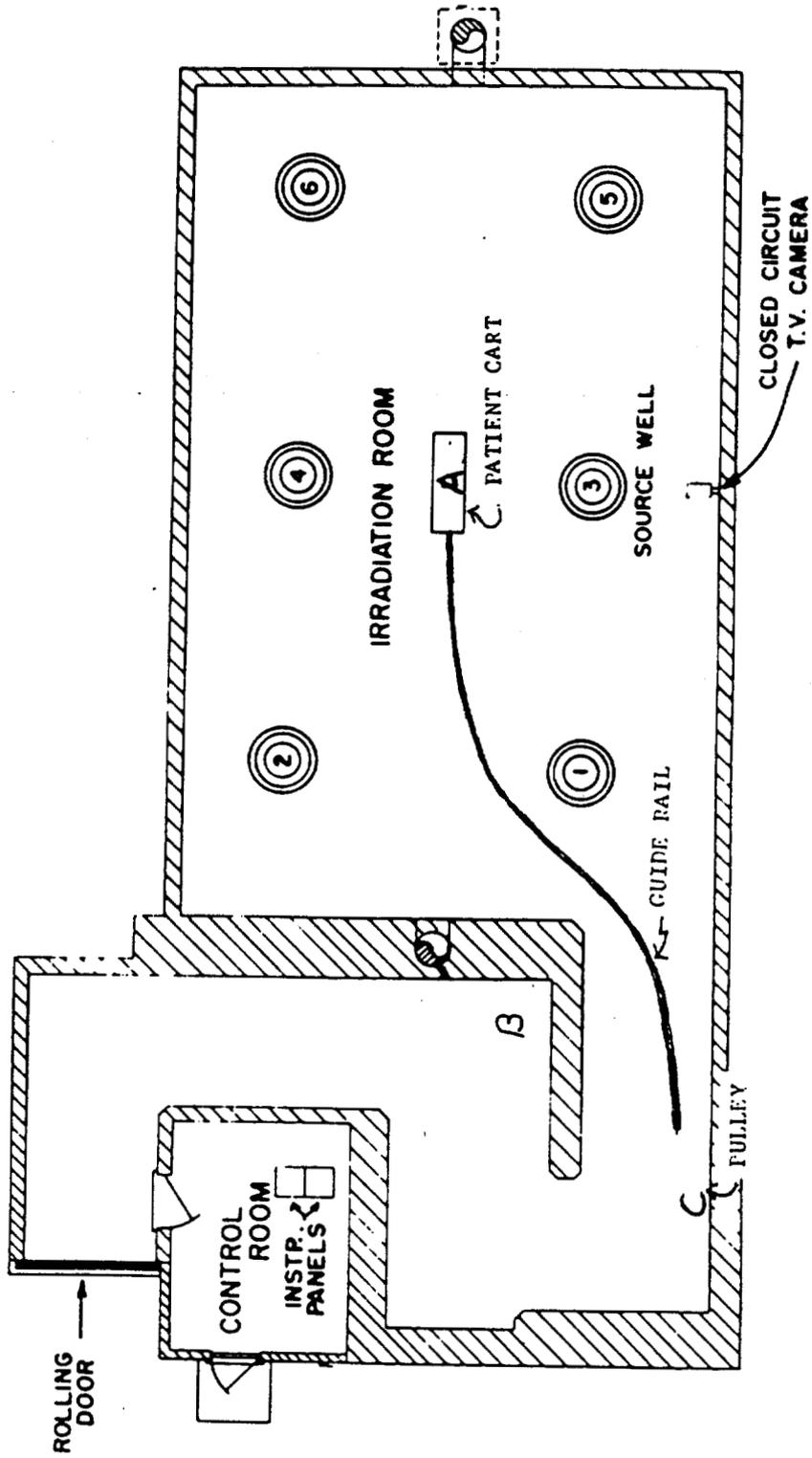
III. Possible Hazards and their Evaluation:

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

1030288



VARIABLE DOSE RATE FACILITY — FLOOR PLAN

FIGURE 1

1030290

AMENDMENT #1 TO THE PROTOCOL ON
THERAPEUTIC TRANSPLANTATION OF HUMAN BONE MARROW

We have now the experience of three bone marrow transplants and feel that the procedure outlined in the protocol is safe and allows us to graft bone marrow successfully if host and recipient are HL-A and MLC identical. We also feel that the immunosuppressive procedure with anti-lymphocyte globulin and total-body irradiation does not seem to shorten the patient's survival, even in the event of a non-acceptance of the graft as we have seen in the third of our transplant patients.

The first change of the protocol which we should like to make concerns the irradiation dose. Under the current protocol the patients are being exposed to 500 R (in air, midline dose). This dose corresponds to approximately 370 rads as the average absorbed dose by the total body. With this irradiation dose in conjunction with the pre-treatment with horse and anti-human thymocyte globulin, we have been able to achieve a bone marrow graft in the first two patients without difficulty. Apparently the resulting immunosuppression was sufficient to allow acceptance of the allogenic HL-A and MLC identical graft and to prevent graft-versus-host disease.

In the third case where the same amount of irradiation and the same treatment with anti-thymocyte globulin was used we had no evidence for an acceptance of the graft, which was not identical with regard to the HL-A antigens and according to the results of mixed lymphocyte cultures. We saw no signs of a graft-versus-host disease, and the patient survived way past the period at which one would expect a fatal graft-versus-host disease. We conclude that the immunosuppression given failed to suppress the host sufficiently

to accept an allogenic bone marrow graft with the antigenic differences in the HL-A system. In retrospect it may have been wise to have used a higher radiation dose before the transplant.

With these observations in mind, we should like to increase the radiation dose, especially in cases where more immunosuppression seems to be indicated. Of course, an alternative would be to increase the dosage of anti-thymocyte globulin and extend the immunosuppressive therapy before the transplant and into the immediate post transplant period. This, however, would not be desirable, since the biological activity of anti-thymocyte globulin might interfere with the successful engraftment of the bone marrow transplant. We therefore would prefer to increase the irradiation dose, since the immunosuppressive and tissue toxic effects of the irradiation are limited in time and should not interfere with the graft. Investigators in other centers report the use of up to 1,000 rads in preparation of patients for bone marrow grafting. In these centers the dose rates at which these irradiations are performed are much lower than the dose rate we use. Comparing dose rates, our dose would have to be raised to approximately 800 rads at 40 R per minute to be comparable to 1,000 rads at 5R per minute. We would like to increase our irradiation dose up to a level of 800 rads. The advantage of using a higher irradiation dose would be greater immunosuppression which appears to be needed for patients who have a donor who is less than HL-A identical (B, C or possible D matches). But even for leukemic patients with an HL-A identical donor greater immunosuppression would be desirable since HL-A typing and MLC does not seem to detect all histocompatibility differences. Since the

1030292.

prognosis for the leukemic patients selected for bone marrow grafting is so poor, we feel that a good immunosuppression should be attempted with a higher irradiation dose. Furthermore, a greater radiation effect on the leukemic process is desirable.

The intensive supportive care including housing of the patient in the laminar flow unit and continuous bacteriological surveillance will be the same as for the patients previously treated.

With the first three transplant patients we have demonstrated that we are able to carry these patients safely through the post-irradiation period following an exposure to 500 R.

AMENDMENT #2 TO THE PROTOCOL ON
THERAPEUTIC TRANSPLANTATION OF HUMAN BONE MARROW

The indication for bone marrow transplantation shall be extended for patients with aplastic anemia (idiopathic and secondary). For those patients whose prognosis is potentially better than that of patients with acute leukemia we would use the previously approved radiation dose of 500 R (370 rads). But we would like to have the option to use a higher dose, since principally the same arguments with regard to HL-A and MLC matching apply to these patients. However, with approval we would like to gradually increase the radiation dose for these patients and evaluate the feasibility of higher radiation doses (up to 800 rads) for these patients with regard to tolerance and side effects as we go along.

A patient with aplastic anemia is considered to be a candidate for a marrow graft only if;

- A. He has at least one living, healthy sibling, or parent, who could be a donor.
- B. The patient, parent, or other involved family members agree in principle and are willing to participate in the effort after a thorough explanation of the procedure.

The pre-selection laboratory studies shall be the same as indicated on page 2 and 3 of the original proposal for bone marrow grafting in man.

Conditions to be met in patients with aplastic anemia and potential recipients of allogenic bone marrow grafts:

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- A. The donor must be old enough and large enough to assure a sufficient amount of bone marrow for the transplant.
- B. Each patient should have a satisfactory trial with combined corticosteroid-androgen therapy with no evidence of spontaneous recovery before a bone marrow graft is attempted.

1030295

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator N. Gengozian Ident. No. 13 (Amend. to)

Project Title Therapeutic allogeneic transplantation of human bone marrow

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

These are discussed in the minutes of the meeting and in the proposal.

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:

The possible therapeutic value of marrow transplantation justifies the risks.

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

The previously approved consent forms will be satisfactory.

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

Should poor results be obtained in aplastic anemia, the committee recommends a different form of immunosuppression be considered and the committee consulted after not more than 6 patients.

5. Other committee comments.

Approve x

Disapprove _____

Gould Andrews
Chairman of Committee

19 December 72
Date

Active 11 Dec 73

25 Jan 1975 Cancelled see minutes

APPLICATION FOR USE OF HUMANS AS EXPERIMENTAL SUBJECTS

- I. Senior Investigator: Nazareth Gengozian, Ph. D.
- Co-Investigators: C. L. Edwards, M. D.
- H. A. Vodopick, M. D.
- Karl Hübner, M. D.

TITLE: Therapeutic allogeneic transplantation of human bone marrow.

II. Objectives of Experiment:

- A. Therapeutic: Develop techniques for achieving allogeneic bone marrow grafts in humans as treatment of:
 - 1) patients with incurable hematological disorders and immunological deficiency diseases, and
 - 2) persons accidentally exposed to total-body irradiation potentially lethal due to hematologic depression.
- B. Scientific: Demonstration that total body irradiation at a high dose rate in combination with anti-lymphocyte-globulin (ALG) is useful immunosuppressive regimen to induce tolerance to a foreign bone marrow graft in man.

The therapeutic goals are replacement of an abnormal or damaged hematopoietic systems with normal bone marrow or the transplantation of a functioning immune-system.

As an adjunct to chemotherapy of leukemia, the transfer of lymphoid cells with the bone marrow might interfere with the growth of any malignant cells that had not been eliminated by the preceding chemotherapy or total-body irradiation.

Radiation accident victims might not require additional immunosuppression, depending on the time elapsed between the accidental irradiation and the planning of a bone marrow transplant for such a patient.

III. Methods of Procedure:

A. All patients included in this proposed study shall be subjected to a series of supportive laboratory observations and clinical investigations of scientific interest:

1. HEMATOLOGY: Frequent (at least twice a week) complete blood counts will be made on the patient throughout the period of hospitalization. Fresh whole blood and blood components are available through the Knoxville Blood Bank. Occasionally patients with chronic granulocytic leukemia or thrombocytosis, primary or due to polycythemia, will be used as donors of leukocytes or platelets, in which case the plasmaphoresis will be done here using the Fenwal double bag technique, and all blood irradiated with 1500 R to prevent engraftment from the transfused cells.
2. BACTERIOLOGIC: Bacteriologic survey of the patient will be taken at regular intervals throughout the period of study to monitor the changes in the bacterial flora coincident with the various treatments. The emergence of pathogenic strains will be readily detected and treated with appropriate antibiotics without reliance on the patients' developing clinically detectable infectious complications.
3. CLINICAL CHEMISTRY: In addition to the necessary clinical electrolyte chemistry, enzymes (LDG, SGOT, SGPT) will be followed to determine evidence of hepatic injury, and the BUN will be followed for evidence of renal impairment either from the ALG, radiation, or the antibiotics.
4. CLINICAL PHYSIOLOGY: Before, during, and periodically after the irradiation the patient will be monitored on the physiologic monitor with continuous EKG, pulse, respiration, and temperature.

5. CLINICAL IMMUNOLOGY: The patient will be carefully watched for reactions to ALG and for signs and symptoms of a GTH reaction. Before immunosuppression and after we will determine immunoglobulins and determine the degree of immunosuppression by skin tests.
6. SCIENTIFIC OBSERVATIONS: The success of the graft will be measured by the following observations in addition to the clinical observations of the patient:
 - 1) Hematology - CBC and platelets, reticulocyte counts, differential counts on the circulating leukocytes and bone marrow aspirate.
 - 2) Cytogenetic - Karyotypes of the patients' circulating lymphocytes and bone marrow cells will be compared with donor cells.
 - 3) Immunologic - HLA profile of leukocytes, RBC subgroups, and genetic variants of immunoglobulins will be determined for comparison with donor and recipient.

B. Patient Selection: Patients with acute leukemia (children and adults) and patients with chronic granulocytic leukemia in blast cell crisis are prospective candidates for bone marrow transplants. Later in the program, which is tentatively planned for at least three years, we might include patients with aplastic anemias, hemoglobinopathies and immune deficiency diseases. Approximately 3 to 5 bone marrow transplants per year are planned at this time, although it is difficult to anticipate how many patients will eventually be treated this way.

A patient with leukemia is considered a candidate for a marrow graft attempt only if:

- a) he has at least one living healthy sibling who could be a donor.
- b) patient, parent, or other involved family members agree in principle and are willing to participate in the effort after a thorough explanation.

Each patient selected for possible bone marrow transplantation shall have:

- 1) RBC typing prior to any transfusion of whole blood or separated blood constituents (but previous blood transfusions should not exclude the patient eo ipso).
- 2) typing for leukocyte antigens (HL-A) of patient and all possible donors.
- 3) the histocompatibility test as provided by the mixed lymphocyte culture (MLC), which should be performed bidirectionally between him and all possible donors.
- 4) the best available chemotherapy.

Bone marrow transplantation will be performed only if histocompatibility tests, MLC, and HL-A typing indicate a match.

Conditions to be met in children with acute leukemia:

- a) The donor must be old and large enough (approximately 10 to 12 years old or 70 to 90 pounds) so an adequate number of marrow cells can be obtained for transplantation.
- b) The recipient should be at the end of the second remission of his disease before transplant will be attempted. Transplant is also considered if two drugs or drug combinations failed to produce an initial remission.

It is difficult to define "end of the second remission" clinically, but the following guidelines shall be used:

A relapse is strongly suspected when:

the physical examination shows a re-occurrence of splenomegaly and palpable enlargement of the lymph nodes.

the patient has symptoms severe enough to reduce the physical activity.

the hemogram shows < 9.0 g% Hgb, < 1000 neutrophils/mm³, $> 5\%$ blast cells and $< 75,000$ thrombocytes.

1030300

the bone marrow examination (evaluation of at least 400 nucleated cells) reveals more than 10-25% blasts or more than 40-70% lymphocytes plus blast-like cells.

Conditions to be met in adults with acute leukemia:

In adults, transplants will be attempted during the first remission as soon as more than 25% of the bone marrow cells are identified as leukemic and immature. Adolescents will be treated as adults unless they clearly have a lymphocytic leukemia or an unusually good (long) first remission.

Conditions to be met in patients with chronic granulocytic leukemia:

A transplant will be performed in those patients as soon as practical after the blast cell crisis has been diagnosed.

Conditions to be met in patients with chronic lymphocytic leukemia:

Transplants will be attempted in patients with progressive anemia and/or thrombocytopenia due to marrow involvement after the disease is shown to be resistant to corticosteroids and chemotherapy.

Preparations for bone marrow transplant:

If all previous conditions and criteria are met and the decision to go ahead with the transplantation, the patient will be transferred to the Laminar Flow Unit (LFU). All patients in the LFU will receive controlled diets, germicidal baths, and mucous membrane gavage. Prophylactic antibiotics may be used in selected patients according to another protocol and will be maintained as long as the patient is in the LFU. On the day the patient is brought into the sterile environment, immunosuppressive treatment with antilymphocyte globulin (ALG) is started. The patient will receive one daily dose of 10 mg/kg (or constant daily dose of 500 mg) intravenously from day-8 to day-1.

During the one week course of immunosuppression with ALG, the patient may receive some antileukemia therapy, but no corticosteroids.

On day 0 the patient will be irradiated with 500 R to his whole body at a rate of 40 R/min. The total body irradiation will be given at the UT AEC farm High Dose Rate ⁶⁰Co Irradiator. The patient will be kept under sedation during the day of irradiation.

Special precautions will be taken to avoid microbiobial contamination of the patient during the transport to and from the irradiation facility as well as during the irradiation. The patient will be covered with sterile sheets and wear a surgical face mask at all times that he is outside the Laminar Flow Unit. Immediately after return to the Laminar Flow Unit, specimens for bacterial cultures will be taken from the patient's face (skin), and nares, /throat.

Bone marrow transplant.

Donor: The marrow aspiration will be done under general anesthesia (or spinal anesthesia if general anesthesia is contraindicated). Volumes of 2-3 ml each will be taken from multiple (30-40) sites from his pelvic bones and collected in TC-199 culture medium containing phenol-free heparin (5000 units per 200 ml TC-199) as anticoagulant. The final cell suspension will be passed through a 200 μ mesh stainless steel or nylon filter before transfusion.

Recipient: Twenty-four hours after total-body irradiation and forty-eight hours after the last ALG injection, the patient will receive the transplant, approximately 20×10^9 nucleated bone marrow cells, corrected for contamination with peripheral blood nucleated cells. The infusion will be given intravenously during a period of 30 to 45 minutes.

1030302

IV. Possible hazards and their evaluation.

The hazards to the patient from this protocol are of several kinds:

purely technical and accidental, or as direct or indirect effect of the treatment.

- a) Mismatching of tissue types could result in an immediate rejection of the graft leaving an immunosuppressed patient to face the potentially fatal consequences of 500 R total-body irradiation. Or a less extremely mismatched transplant could result in a severe and fatal graft vs host (GvH) reaction.

We are confident that we are able to avoid a major mismatch by doing two histocompatibility tests between donor and recipient, the HL-A matching, and the mixed lymphocyte culture, both of which will be done twice.

- b) Bacterial contamination is a serious hazard for an immunosuppressed patient. Close bacteriological surveillance, antimicrobial prophylaxis and nearly sterile environmental conditions before and after irradiation of the patient should reduce this hazard. The irradiation is going to be given in a facility where large farm animals are irradiated. We are aware of possible contamination of a patient in such a facility. A fastidious clean-up of the area with antiseptic solution will be carried out. The patients will be protected during the irradiation as well as in transit by wearing sterile gowns and masks.

- c) Radiation accident: We might be confronted with the situation where the irradiation sources cannot be turned off (removed) after completion of the 500 R dose to the patient. Precautions are being taken for this unlikely event. A plan for removing the patient, stretcher and all from the radiation area within 10-15 seconds after discovery of the accident has been developed.*

*See attachments. (To follow under separate cover)

This additional irradiation would result in no more than 10 additional R of total-body irradiation, exceeding the intended dose by only 2%.

- d) Unavailability or loss of bone marrow cells. The unavailability of bone marrow cells from a recipient after the patient has received 500 R total-body irradiation is a hazard with significant risk. There is the obvious but remote possibility that the donor may have an accident or illness on the day of the scheduled transplant or that a severe complication from general anesthesia might interfere with the donation of bone marrow cells.

We feel this is a very slight risk we have to take. The donor will be admitted to our hospital on the day the recipient receives total-body irradiation. The donor will get a thorough physical examination as required for general anesthesia, prior to the irradiation of the patient. Furthermore, extreme caution will be executed in the handling of the bone marrow specimen so that it will not be accidentally lost. It should be emphasized that with this dose, spontaneous recovery under intensive supportive care is possible, perhaps even with a radiation-induced temporary remission of the primary disease.

- e) Pulmonary embolism. This complication is possible when such a large number of cells (20×10^9) are being transfused intravenously within a relatively short time. Careful filtration of the bone marrow cell suspension should eliminate this risk.
- f) Total-body irradiation. A total-body irradiation dose of 500 R could be fatal even in a normal person but spontaneous recovery of the bone marrow has occurred after exposure to 300-350 R. This recovery begins at around 30 days after exposure of normal persons. In children with

acute leukemia, recovery starts about 30 days after total-body irradiation. With 500 R, severe hematologic suppression will occur, but recovery is possible with intensive supportive care, thrombocyte and leukocyte transfusions, and antimicrobial therapy.

- g) Immunosuppression with ALG. Treatment with antilymphocyte serum or with anti-lymphocyte globulin is not without hazards or risks. (See attachment "RISKS, SIDE EFFECTS, AND DISADVANTAGES OF THE USE OF ANTILYMPHOCYTE SERUM (ALS) OR ANTILYMPHOCYTE GLOBULIN (ALG) IN MAN")

Before ALG treatment is started, the patient shall have a skin test with normal or ALG horse serum. If there is no indication of a hypersensitivity state according to an intracutaneous test within 20 min, the ALG will be given with an infusion of 500 ml physiological saline intravenously over a period of two hours. During ALG treatment, blood counts will be done daily.

- h) Graft vs. host (GVH) reaction. With the advent of tissue typing, donor recipient matching can be achieved even in allogenic situations. The possibility of finding a matched pair is enhanced by studying genetically related subjects, especially siblings, rather than those who are unrelated.

The present criteria of matching requires identification of presently known human leukocyte antigens (H-LA) and testing for histocompatibility by the mixed leukocyte culture test (MLC). If these two tests suggest a "match" between donor and recipient, the chances of getting a graft to take in an immunosuppressed recipient are almost 100%. A correlation between the success of the graft and the occurrence of the GVH reaction has been shown. The GVH reaction is a problem whenever a successful allogenic bone marrow graft is achieved. The severity of the GVH

reaction appears to be related to several factors.

- i) How well the donor and recipient match. Bone marrow transplantation between identical twins has been performed regularly with no GVH. In these cases, the tissues naturally match perfectly. Tissue typing and the MLC do allow some judgment regarding the antigenetic similarity or dissimilarity of non-identical-twin siblings.
- ii) Strength of dissimilar antigens. The tests for tissue typing detect only the presently known leukocyte antigens. It is recognized that there are other leukocyte antigens still to be discovered. The relative importance of both the known and unknown leukocyte antigens in relation to the graft vs. host reaction is not established but the MLC test gives some indication of the patient's reactivity to the donor's antigen and vice versa.
- iii) Number of bone marrow cells transfused. With an increase in number of bone marrow cells transfused, an increased number of immunologically competent cells are also given. The numerical ratio between the hematopoietic cells and immunologically competent cells is unknown. The GVH is caused by the latter cells reacting against the host tissue and therefore a larger number of immunologically competent cells (transplanted) results in a more severe GVH.
- iv) Third party GVH. One additional risk of GVH results from the possibility of a graft resulting from any transfused whole blood, granulocytes, or platelets given as supportive care after the bone marrow engraftment. All such transfusions will be exposed to 1500 R bag dose in order to avoid a "take" of third party lymphocytes.

Although careful selection of donor eliminating any major mismatch either by HL-A typing or MLC appears to decrease the chances of a severe reaction, some GvH reaction is still a real and almost certain complication and each successful allogenic bone marrow graft. Moreover, it can often be controlled by programmed administration of certain cytotoxic drugs; e.g., cyclophosphamide and Methotrexate. The beneficial effect has been observed only when the drug treatment has been started within 4 days after the transplant. In addition to careful selection of the donor, we will treat the patient with Methotrexate 0.5 mg/kg (or 10 mg/sq meter) on days 1, 3, 6, and 11 after the transplant followed by smaller doses at weekly intervals.

- v. Host vs Graft (HvG) reaction. Previous studies on marrow transplantation in mice that had received sub- or midlethal doses of radiation have shown that this procedure may be more deleterious than radiation treatment only. Thus, depending upon the donor-host genetic relationship, the amount of radiation administered and the amount of marrow injected, an increased mortality greater than with radiation alone may occur (Gengozian, N. and Makinodan, T.: J. Immunol. 77:430, 1956; Gengozian, N. and Makinodan, T. Cancer Research 17:970, 1957). This phenomenon, referred to as the "MLD killing effect," has been attributed to an acute reaction of the host's immune system to the foreign marrow with incomplete elimination of the marrow graft along with failure of the host's hemopoietic system to recover adequately from aplasia induced by the radiation.

Such an effect has not yet been reported in humans even in those situations where the radiation dose was apparently insufficient to permit marrow grafting; i.e. chronic graft rejections in man have been reported but a syndrome similar to the MLD effect in animals has not been observed. In our proposed protocol, prior treatment of the patient with ALG, should, in combination with the 500 R irradiation completely suppress the host's immune system, preventing any early and rapid rejection of the foreign graft. However, it is recognized that our proposed regimen is of an experimental nature and chronic rejection of the graft may occur. If hematologic and other clinical signs indicate an ongoing rejection process, the patient will be placed under intensive supportive care, receiving thrombocyte and whole blood transfusions along with antimicrobial therapy.

1030308

RISKS, SIDE EFFECTS, AND DISADVANTAGES OF THE USE OF ANTILYMPHOCYTE SERUM
(ALS) OR ANTILYMPHOCYTE GLOBULIN (ALG) IN MAN

1. RISKS

a. Immunological

Acute Systemic Anaphylaxis: This complication of ALS treatment may be expected and is, according to the literature, observed in 15% to 20% of patients treated with antilymphocytic antibody.

Apparently this complication occurs particularly in patients which had previous experience with antibodies raised in the species of serum donors which have also produced the ALS. It also appears that this violent and life-threatening reaction occurs more likely in patients treated with rather small doses of ALS over a longer period of time. Therefore the risk of inducing such a reaction should be greatly reduced by giving large, possibly tolerogenic, doses of ALS during a short period. Of course the tolerogenic dose for man is not known, but it certainly lies above 4 mg of ALG per kg/day as used currently. With 500 mg of ALG per day as Dr. Gengozian proposed we might be close to a tolerogenic dose. Dr. Gengozian's immunosuppressive regime calls for a short treatment period of one week only, avoiding the risk presented by long antiserum treatment.

Some workers recommend to induce tolerance with nonspecific serum proteins of the species donating the ALS before giving the specific antiserum. It is certainly recommended to test each

patient (skin test) before treatment with ALG for his reactivity against the antiserum of the species in question in order to avoid any immediate acute anaphylactoid reactions.

It may be of comfort to know that according to the literature none of the anaphylactic reactions observed by investigators who used ALG or ALS in man was unmanageable. In the event of acute systemic anaphylaxis, the treatment with ALG should be stopped at once, the patient treated conventionally, and immunosuppressive therapy could be continued with ALG of another species if available.

Serum Sickness: Urticaria, oedema, arthralgia, and nephropathy have been seen in patients treated with ALS or ALG. Clinically however the problem is less problematic than an acute anaphylactic reaction. With regard to the risk of serum sickness treatment with ALS or ALG can hardly be regarded as experimental. Serum sickness is an accepted risk of serum therapy of different clinical indications.

Serum Nephritis: Serum nephritis may be a serious problem in patients treated with ALS developing an irreversible chronic glomerulonephritis. I have not seen any reports with regard to this risk, but it is conceivable that an immunosuppressive anti-serum (ALS) prevents the production of antibodies required to convert the antigen into an excretable immune-precipitate. It is known from animal experiments that renal symptoms disappear in experimental serum nephritis as soon as the animals produce a sufficient amount of antibody against the responsible antigen. With regard to

leukemia patients receiving immunosuppression with ALG the expected benefit of a successful marrow graft should outweigh the risk of a chronic serum nephritis.

Masugi Nephritis: Again no references are found in the literature reporting this type of nephritis. In the case of the Masugi nephritis specific antibody is responsible for the nephrotoxic glomerulonephritis. A crude ALS may well contain antibodies specifically directed against renal tissue and cause this type of nephritis. This possibility must be considered since tissue antigens may not be confined to the cells of a well-defined organ only, but rather may be universal although with variable antigenic strength. Renal antigen and other tissue antigens may be present on the lymphoid cells used in the production of an ALS. Highly purified anti-lymphocyte antisera may eliminate this remote risk.

Infections: ALS induces a lymphopenia with varying degree, not necessarily related to its potency to prolong graft survival. Such a lymphopenia will reduce the patient's resistance to infections. In addition ALS, especially in a crude form may contain specific antibodies against immunoglobulins.

The lymphopenia and possibly reduced immune globulin levels result in an insufficient defense mechanism of a patient treated with ALS. A controlled "bacteriological" environment (laminar flow unit) and continuous bacteriological surveillance of such a patient are absolutely indicated.

ALS is not the only immunosuppressant bringing the risk of infections to the patients; so do all other effective "immunosuppressive" agents almost or already accepted as "conventional" therapy. Highly purified ALG should not have any anti-globulin activity on existing, preformed antibodies.

2. Hematological

Crudely obtained ALS may contain antibodies against bone marrow cells, specific anti-red cell, anti-granulocyte, and anti-platelet antibodies. Any of these effects is of course undesirable because of the obvious clinical consequences. Purification of ALS to ALG and proper absorptions according to corresponding test results will eliminate such undesirable effects. It is known that the anti-RBC activity in ALS is almost exclusively present in the 19s fraction of the antiserum and the antilymphocyte antibody is 7s immunoglobulin. Antigranulocyte antibody, which would interfere with phagocytosis and the bactericidal elimination of microorganisms, may be greatly reduced by immunizing ALS producers with highly purified lymphoid cells. It almost appears that the purification of the antigen (lymphocytes) is by far more important than the purification of the antiserum. Absorption is usually cumbersome and invariably results in a partial loss of specific antibody activity.

3. Oncological

Immunosuppressive therapy: Given not only for transplantation purposes, increases the risk of tumors in patients. Immunosuppression may suppress an immunosurveillance system which is responsible for the elimination of mutant cells. Different kinds of malignant neoplasias have been observed in patients treated with ALS, especially lymphoreticular malignancies, renal tumors, and one ovarian carcinoma. This risk is going to increase with better and better immunosuppressive therapy. I don't think anyone knows how to eliminate this danger of ALS treatment. The decision to use or not to use ALS in a patient who has already a highly malignant disease can only depend on the professional recognition of the greater evil.

B. SIDE EFFECTS

Pain, swelling, and inflammation at the injection site of ALS are frequently observed with varying degrees of severity. The symptoms appear to be less severe if a highly pure ALG is used or if the injection is given i.v. Most patients develop fever after the injection. Urticaria, pruritus, a skin rash and periorbital oedema are not infrequent allergic side effects following an injection of ALS.

C. DISADVANTAGES OF ALS WITH REGARD TO OUR THERAPEUTIC OBJECTIVE

Interference with adoptive transfer: An expected immunotherapeutic effect of immunocytes transferred with a bone marrow transplant may be hindered by the presence of high levels of ALS in the recipient.

Interference with "take" of bone marrow graft: An extremely crude ALS with anti-bone marrow activity may attack the transplanted marrow, even when ALS treatment is stopped 48 hrs before grafting. Horse serum proteins have been found in patients 27 to 175 days after the last injection of ALS. This however is nonspecific protein most likely and probably not specific ALS. An interference with the graft seems to be unlikely, if the ALS is purified and only given before grafting.

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January 2, 1970

PATIENT TREATMENTS AT THE VARIABLE DOSE RATE IRRADIATION FACILITY

Safety

The ORAU Medical Division anticipates conducting total-body irradiation of patients in the UT-AEC Agricultural Research Laboratory's Variable Dose Rate Facility (VDRIF). This report will serve as a guide for the safe performance of that operation.

1. Approval

A. ORAU

The protocol for patient irradiation must have the approval of the ORAU Medical Division's Human Use Committee and the Medical Division Chairman. Each patient must also sign the release form required for all nonroutine medical procedures.

B. UT

Each use of the VDRIF by ORAU must be approved by the Director of the UT Agricultural Research Laboratory or his alternate.

2. Responsibility

A. ORAU

(1) Safety

The ORAU Medical Division will be responsible for the safety of the patient and ORAU personnel during use of the VDRIF. The Radiation and Chemical Safety Office will have personnel present during each patient irradiation to ensure the safety of ORAU employees and to assist in any radiation emergency situations.

1030318

(2) Dosimetry

Radiation dosimetry will be performed by the ORAU Radiation Dosimetry section and the ORAU Radiation and Chemical Safety Office.

B. UT

Operation of the Variable Dose Rate Irradiation Facility will be performed by the regular UT-AEC staff. Safety of UT personnel will be the responsibility of the UT operator.

3. Safety Procedures

A. General

While working in the irradiation facility, all ORAU personnel will abide by the requirements of the UT Safety Manual for the VDRIF and by the instructions of the facility operator. ORAU personnel must also abide by the requirements of the ORAU Radiation Safety Policies and Procedures Manual.

B. Normal Irradiation Procedure

The patient will be secured on the stretcher cart and positioned at location A (Fig. 1) in the VDRIF. Two ORAU employees, one from the Radiation and Chemical Safety Office, will remain within the exclusion area at position B during the irradiation to assist in emergency removal of the patient. Since the radiation level at this point is about 20 mR/hr, the exposure these persons will receive during patient treatment will be less than 5 mR. All other personnel will remain in the control room. The interlocked control-room door must remain open during patient irradiation to allow communication between the control room and the two persons who have remained within the facility entranceway.

Five of the six sources will be used for irradiation. Source No. 1 will remain off. During irradiation a back-up timer will be operated in the control room to verify the correct operation of the control console timer. The patient will be irradiated at an exposure rate of 40 R/min for periods ranging from 1.4 to 15 minutes. The alarm which normally sounds before the start of an irradiation will be disconnected during patient treatments for the psychological well-being of the patient. After the treatment the patient will be removed from the facility and returned to the ORAU Medical Division.

C. Emergency Removal of Patients from the Irradiator

Although it is highly unlikely that the sources will fail to shut off at the end of the treatment, provisions have been made for emergency action in case of such a failure. A safety analysis of the VDRIF indicates that two malfunctions of the unit could result in the failure of one or more of the sources to shut off at the end of the prescribed treatment time. One of the malfunctions would be a power failure during irradiation. If this occurred, all sources would remain in the ON position. The second possible malfunction would be mechanical binding of the source-drive system. This could result in one or more of the sources remaining exposed.

If sources fail to shut off at the end of the prescribed treatment period or if power is lost at any time during the irradiation, the patient must be removed from the high radiation field as quickly as possible. In the process of "rescuing" the patient, radiation exposures of others must be kept as low as possible. To make removal quicker and easier, a guide rail will be temporarily attached to the floor

of the irradiation facility (Fig. 1). The patient cart has been equipped with rollers that ride on the guide rail and control the direction of travel of the cart. A rope attached to the cart will pass through a pulley at position C to the location of the "rescuers." As shut-off time nears, someone at the control panel will initiate a countdown. If the unit operates properly, the sources should return to their shield within about 4 seconds after the desired exposure time elapses. If for any reason the sources do not shut off within 10 seconds, the stretcher will be pulled from the irradiation position and into the entranceway. Rescuers will remain behind the wall while pulling the stretcher from the area. When the stretcher reaches the end of the guide rail, the rescuers will quickly enter the entranceway and pull the stretcher around the corner.

An estimate of the radiation exposures received by the patient and the rescuers during the emergency removal of the patient has been calculated.

Patient:

Exposure during removal	~ 10 R
Prescribed treatment	50 to 600 R

Each Rescuer:

Exposure during rescue	~100 mR
Permissible quarterly exposure	3000 mR

The exposures during the emergency removal will be low compared to the treatment exposure and the permissible exposure limits. The dosimeters worn by the patient and the rescuers will be checked to determine the accumulated exposure.

1030321

If, for some reason, the stretcher and patient can not be removed by the above procedure, the pneumatic clutch which permits bypassing the source-drive motor will be opened in an attempt to return the sources to the OFF position. The final alternative will be to enter the irradiation facility and manually remove the patient.

After the removal of the patient, return of the sources to the OFF position shall be the responsibility of the UT-AEC staff.



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



Roger J. Cloutier
Radiation and Chemical Safety Officer

No patient should be admitted for possible bone marrow graft unless the following conditions are met:

- 1) The prospective recipient ^{has} at least one sibling in reasonably good health who could serve as a donor.
- 2) The patient, parent, or other involved family members agree in principle and are willing to participate in the effort after a thorough explanation.

ACUTE LEUKEMIA

Each patient is to be regarded as a potential candidate for bone marrow grafting, and as such should have -

- 1) RBC typing prior to any transfusion *[if possible but should not exclude on this basis]*
- 2) WBC antigens (HCA) identified *for patient & donors*
- 3) Treated with the best available drug or drug combinations as soon as feasible after the diagnosis is made.

*CC check
all patient
transmission*

CHILDREN

- 1) Sibling donor must be old enough and large enough *(10-12)* to get an adequate number of cells for transplanting. *(60 #)*
- 2) Transplant will be attempted *at the end of the* ~~only after relapse~~ ~~from~~ second remission or after the failure of two drugs or drug combinations to produce a good remission.

ADULT

- 1) Transplant will be attempted ~~after a relapse~~ from the first remission or after two drugs or drug combinations fail to produce a remission.
- 2) Adolescents will generally be treated as adults unless the leukemia is clearly lymphocytic or if the first remission is

CHRONIC GRANULOCYTTIC LEUKEMIA

- 1) Patients with CGL, if they meet the general requirements, should have RBC typing and leukocyte antigen typing done prior to their developing the blast cell crisis.
- 2) A transplant will be attempted in those patients with suitable donors and otherwise qualify as soon as practical after the blast cell crisis has been diagnosed.
- 3) The transplant attempt may be preceded by some antileukemic drug to reduce the population of leukemia cells.
- 4) Patients with a great deal of myelofibrosis should probably be excluded.

CHRONIC LYMPHOCYTTIC LEUKEMIA

Transplants will be attempted in patients with progressive anemia and/or thrombocytopenia due to marrow involvement after the disease is shown to be resistant to corticosteroids and chemotherapeutic agents.

V. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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. 1970

Signatures: *[Signature]* Investigator
[Signature] Investigator
[Signature] Investigator
Karl F. Hubert Investigator

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

[Signature] Chairman

Date: Jan 19, 1970

OAK RIDGE ASSOCIATED UNIVERSITIES

INCORPORATED

P. O. BOX 117

OAK RIDGE, TENNESSEE 37830

August 1, 1972

AREA CODE 615
TELEPHONE 483-8411

To: Committee on Human Studies

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

The Medical Division has been carrying out a research project entitled "Therapeutic Allogeneic Transplantation of Human Bone Marrow." This is based on a very extensive write-up that was presented to the Committee in December 1969 and approved in January 1970. The purpose of the present communication is to call your attention to our desire to extend this kind of treatment to patients with aplastic anemia and to provide an opportunity for comments from the Committee.

You will recall that the protocol involves one week of treatment with antilymphocyte globulin, then total-body irradiation to an air dose of 500 R and the infusion of bone marrow from a selected sibling.

So far this has been undertaken in three patients, all adults with acute leukemia. The first man had a distinct graft and remission but died about four months later of complications of cardiac and pulmonary disease without clearly demonstrable graft-vs-host reaction, and with no evidence of persistent leukemia detectable at autopsy. The second patient also had a clear-cut graft and a brief clinical remission, but within a few weeks after the treatment she developed a recurrence of her leukemia which proved fatal. The third patient is only two weeks from the time of marrow infusion. He is doing reasonably well. His bone marrow shows erythroid regeneration but the blood values do not yet demonstrate evidence of graft.

Dr. Edwards, Dr. Gengozian, and our clinical staff wish to undertake this same treatment in a patient with aplastic anemia who is seriously ill and who has been deemed by his physicians as unresponsive to therapy. His outlook at present is considered extremely poor. It is proposed to use exactly the same protocol including total-body irradiation. The reasons for this are that the protocol has proved effective in achieving a graft in the first two patients, and it appears that this program of treatment would allow a reasonable chance for maintaining the patient through the postirradiation period, even if no graft were achieved.

The original proposal stated that the patients initially selected would have acute leukemia and later the program might be extended to include patients with aplastic anemia, hemoglobinopathies, and immune deficiency diseases.

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1030326

The earlier reservation about aplastic anemias was that this disease has some possibility of spontaneous recovery and therefore the potentially hazardous and untried protocol might not be justified. In view of the experience so far it is the impression of our clinical staff that this no longer holds true, and that for a patient with aplastic anemia who has a poor prognosis and has not responded to treatment, this protocol would be a desirable one. The clinical staff has considered the possibility of undertaking a modified procedure without the irradiation; they feel, however, that this might deprive the patient of an opportunity to have a successful graft.

Since the patient who is being considered for this treatment is in a precarious situation, there may be need to proceed promptly, if the program is approved. Therefore, we plan to check with the members of the Committee by telephone.

Gould A. Andrews
Chairman of Committee

pe

1030327

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

August 8, 1972

AREA CODE 615
TELEPHONE 483-8411

To: Committee on Human Studies

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

Re: "Therapeutic Allogeneic Transplantation of Human Bone Marrow"
— in patients with aplastic anemia — (See memo Aug. 1)

I called the members of the committee who were available, with the following results:

Dr. Lincoln was strongly in favor.

Mr. Koons said he assumed that there were no legal problems. He assumed that we would have the same forms and protective mechanisms as used for the other patients. He, of course, did not have any opinion on the medical merits.

Dr. Brill said that he felt that he would like to leave his approval depending on that of Dr. Lange. He felt that Lange had more experience with this kind of disease. If Lange says yes, Brill will go along gladly. He has no inclination to veto the project but simply wants to wait for Lange's opinion.

Dr. Storer is out of town and is expected back in a day or two.

Dr. Lange said that he was hesitant to approve the complete study with the radiation therapy for two or three reasons: He felt that the trial of oxymetholone had not been more than a minimal one and he wondered if it shouldn't be tried for a few weeks longer. He also thought that since there were two good potential donors, one might try first to give the graft with only the antilymphocyte globulin, omitting the hazardous total-body irradiation with the thought that if this fails, later on one could use the total-body irradiation in a second trial with the other donor. The third point was that Dr. Lange felt that he was not sufficiently familiar with the literature on this topic and would like to learn a little more about it.

Original Signed By
GOULD A. ANDREWS

Gould A. Andrews

cc: Drs. Edwards, Hahn, M. J. ...

1030328

MEMORANDUM

G. A. Andrews

14

TO Committee on Human Studies, Medical Division, ORAUDATE June 2, 1970SUBJECT Tracer Study with ⁶⁷GaCOPIES TO File

This confirms the phone discussions about a tracer study in two human volunteers to determine the rate of removal of a gallium-67 citrate - labeled autologous plasma when injected subcutaneously between the toes.

Reason for Study: This is a pilot study simply for radiation dose calculations. A protocol is in preparation proposing to visualize lymph node drainage after scanning doses of gallium-67 citrate have been injected subcutaneously (the dose in that proposal would be of the order of 2 millicuries total dose given in 0.5 millicurie injections to four sites between the toes).

Dose: In the tracer study 5 microcuries would be given to one site on each foot between the toes. This dose has been approved by the Committee on Human Use of Radioisotopes of the Medical Division (25 May 1970).

Consent: Established procedures for informed consent will be followed.

Approval: Members of the committee without dissenting vote concur in this tracer study.

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

To:
C. L. Edwards
John Storer
Mel Koons
B. Nelson
Tom Lincoln
A. B. Brill
Robert Lange

old - two formal proposals

1030329

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
 Medical Division
 Oak Ridge Associated Universities

Date: 11 November 1970

Senior Investigator: Bill Nelson, M. D.

Co-Investigators: Lowell Edwards and Clinical Staff

Title of Project: Histologic changes in the skin related to the
graft-versus-host (GVH) reaction after marrow
transplantation.

Use Following Format (Original and one copy):

I. Objectives of Experiment:

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 ORAU Medical Division Isotope Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

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I. Objectives of Experiment:

The expectation of successful human marrow transplantation is accompanied by the prospects of diagnosis and management of the GVH reaction. Clinical experience is already adequate to indicate a clinical syndrome of diarrhea, skin rash, and weight loss but objective signs are needed to distinguish early GVH from drug reactions, infections, and other complications related or incidental to the experimental procedure. Histologic changes are characteristic in experimental animals and in the few human autopsies. The present study is designed to refine the criteria for recognition of GVH reactions in skin biopsies. Essential to this purpose is a thorough grasp of the histologic changes to be anticipated after treatments used for transplantation, especially total-body irradiation, chemotherapy, corticosteroids, and antilymphocyte globulin.

II. Methods of Procedure:

We will biopsy the skin at the times scheduled for sampling marrow with various irradiation procedures, including the marrow transplantation project. Our routine already calls for stabbing the skin with a scalpel before using the marrow needle. This reduces the possibility of introducing bacteria into the bone, and keeps skin fragments from occluding the needle or confusing the interpretation of the marrow smears. The proposed modification is to perforate the skin with a biopsy punch rather than a scalpel. Because the early GVH changes are subtle, techniques for cleansing the skin and local anesthesia require consideration to avoid artifact. Punches 2 to 5 mm in diameter are specially designed to attach to an electric drill for skin biopsies. The rotating punch is rapidly passed through the dermis and withdrawn. The subcutaneous fat is transected and the specimen placed in cold buffered gluteraldehyde. Shortly thereafter the specimen is bisected, one portion embedded in paraffin, and the other half processed for electron microscopy.

In addition to the skin biopsies taken with diagnostic marrow aspirations, similar biopsies will be taken from ten healthy volunteers. Some of these may be employees and others donors for marrow transplantation who will have been given a general anesthetic, providing a control for possible artifacts caused by local anesthesia.

Histologic evaluation will include a prompt pathology report after each biopsy, with extra sets of slides prepared for special stains and for an objective evaluation by one or more pathologists after adequate collection of samples. (We do about 200 marrow aspirates annually and should be able to collect enough suitable controls in two years; the collection of GVH biopsies will depend on the number and success of marrow transplantations.)

III. Possible Hazards and Their Evaluation:

Our major concern is with the possibility of bleeding or infection of the biopsy wound. The usual aseptic technique will be used and extra care is indicated in patients with severe thrombocytopenia or skin infections. The wound will be only slightly larger than that routinely made for marrow aspirates; the edges will be brought together and covered by a sterile adhesive bandage. Healing should be complete in two weeks and no significant morbidity is anticipated.

1030331

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: TEST OF EXERCISE TOLERANCE WHILE RIDING THE ERGOMETER
("STATIONARY BICYCLE") WITH BLOOD TESTS, CONTINUOUS EKG AND OTHER PHYSIOLOGIC MONITORING
(State nature of test)

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
Name

the proposed test to be given _____
Name

including the following: FREQUENCY OF BLOOD TEST, AMOUNT OF EXERCISE, THE RISK OF
OVER EXERCISING AND ASSURANCE THAT HE MAY STOP AT ANY POINT HE WISHES DURING
THE EXERCISE.
SHE

Investigator Date

Proposal No. 16 (Lushbaugh, et al.)

CONSENT FOR EXPERIMENTAL TEST

1030332 .

REVIEW AND ACTION
Committee on Human Studies -
Oak Ridge Associated Universities
Medical Division

Principal Investigator: Bill Nelson, M.D. Identifying No. 15

Project Title: "Histologic Changes in the Skin Related to the Graft-
versus-Host (GVH) Reaction After Marrow Transplant-
ation"

Comments:

Application was approved with the recommendation that Dr. Nelson, Edwards, or other physicians, will tell the patient that the skin biopsy is a special experimental procedure, but of little hazard, and will obtain written consent on an appropriate form.

Approved: Aug 13, 1971 (date)

Disapproved: _____ (date)

R. Kinch

Secretary, Committee on Human Studies

pe

25 January 1975 Cancelled

Adopted 4-67

1030333

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: June 1, 1971

Senior Investigator: C. C. Lushbaugh

Co-Investigators: R. C. Ricks

Allen Webb

Title of Project: Changes in blood enzyme levels following
exercise and/or total-body irradiation
in man.

Use Following Format (Original and one copy):

I. Objectives of Experiment:

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 ORAU Medical Division Isotope Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

more-

1. Objectives of Experiment:

The objective is to determine changes in blood enzyme levels (e.g. lactic acid dehydrogenase, creatine phosphokinase, SGOT, SGPT, aldolase, HBOH, and maleic dehydrogenase) in selected patients undergoing total-body radiation therapy and volunteers who are involved in periodic controlled exercising testing (bicycle ergometry).

II. Methods of Procedure:

Blood samples (10 ML) will be drawn by qualified clinical laboratory personnel employed by ORAU. Patients and unirradiated volunteers will be selected on the basis of their willingness and ability to exercise. No patient will be included in the project without prior permission of their attending physician. Volunteers must be in average or better physical condition. Before entering the program all test individuals will be subjected to moderate exercise levels to determine any lack of exercise ability. No severe exercise will be employed at any time. Heart rate, EKG, and respiratory wave form will be monitored before, during, and after exercise.

Exercise test sessions will last for ~ 1 hour, the majority of the time being spent in post exercise physiologic monitoring. Sessions may be repeated on a daily basis (5/week or 3/week, etc.) and last for periods up to one month. Blood will be drawn in relation to each exercise test session or at least 3 times per week. The study will be an ongoing project.

III. Possible hazards and their evaluation:

Care will be taken to insure that all blood samples are obtained under aseptic conditions and that no excessively high exercise workloads are employed throughout the study.

IV. Radioisotopes and new drugs:

No isotopes or drugs will be administered in relation to this program.

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: C. C. Lushbaugh, M.D. Identifying No. 16

Project Title: "Changes in Blood Enzyme Levels Following Exercise
and/or Total-Body Irradiation in Man"

Comments:

The committee approved this proposal with the following recommendations:

- a. An informed consent should be recorded in the hospital notes of patients, and a written consent should be obtained from normal volunteers who serve as controls.
- b. Appropriate resuscitation equipment should be present in the exercise area, including a defibrillator. Personnel trained to operate the defibrillator should be on hand, and an alarm system to call a closely available physician should be operative.

Approved: Aug. 13, 1971 (date)

Disapproved: _____ (date)

R. K. Kusy
for Secretary, Committee on Human Studies

Dec '73: Active; all radiation patients being studied.

Jan '75: Cancel; no program since 1972.

pe

Adopted 4-67

1030338 .

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: TEST OF EXERCISE TOLERANCE WHILE R DING THE ERGOMETER
("STATIONARY BICYCLE") WITH BLOOD TESTS, CONTINUOUS EKG AND OTHER PHYSIOLOGIC MONITORING
(State nature of test)

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
Name

the proposed test to be given _____
Name

including the following: FREQUENCY OF BLOOD TEST, AMOUNT OF EXERCISE, THE RISK OF
OVER EXERCISING AND ASSURANCE THAT HE MAY STOP AT ANY POINT ^{SHE} HE WISHES DURING
THE EXERCISE.

Investigator Date

Proposal No. 16 (Lushbaugh, et al.)

CONSENT FOR EXPERIMENTAL TEST

1030339

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: 8 July 1971

Senior Investigator: L. Gavle Littlefield

Co-Investigators:

Title of Project: Chromosomal breakages in fibroblasts from
women taking oral contraceptives

Use Following Format (Original and one copy):

I. Objectives of Experiment:

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 ORAU Medical Division Isotope Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

more-

- I. Objectives of Experiment: To determine whether there are increased chromosomal breakages in skin fibroblasts from women who are taking oral contraceptives compared to normal who are not taking hormone medications.
- II. We will obtain skin biopsies (approximately 1 mm³) from 5 women who are taking oral contraceptives and from 5 control women, on 4 occasions during the course of 1 year. The time required for obtaining each biopsy should be no longer than 10-15 minutes. We plan to take biopsies from the forearm of each subject after anesthetizing a small area of skin by an intradermal injection of 0.1 to 0.2 cc 1% Xylocaine.
- III. We do not anticipate that this procedure will present any major hazards. We will use sterile disposable needles and syringes for administration of the anesthetic, and sterile skin punch blades for excising the small piece of skin. All participants will be questioned about possible allergies to Xylocaine before beginning the project. As with any small cut or scratch the possibility of a local infection cannot be ruled out; however, care will be taken to cleanse the area of the arm before the biopsy procedure, and to cover the lesion immediately after the skin has been removed.
- IV. This study will not involve any new drugs or isotopes.

1030341.

OAK RIDGE ASSOCIATED UNIVERSITIES

WHOLE BLOOD AND/OR SKIN BIOPSY 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, and/or _____ mm² of my own skin, by direct skin biopsy.

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 skin 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 skin or the use thereof.

_____ 0 - 100 cc	\$ 5.00}	
_____ 101 - 200 cc	10.00}	
_____ 201 - 300 cc	15.00}	BLOOD
_____ 301 - 400 cc	20.00}	
_____ 401 - 500 cc	25.00}	
_____ 1 - 2 mm ²	10.00}	SKIN

This _____ day of _____, 19__.

Name of Donor (Please print)

Signature of Donor

Mail check to

City State Zip

Witnesses:

Account to Charge: _____

Blood received by

Division approval

1030343.

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Gayle Littlefield, Ph.D. Identifying No. 17

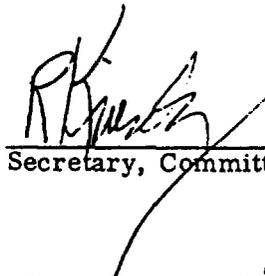
Project Title: "Chromosomal Breakages in Fibroblasts from Women
Taking Oral Contraceptives"

Comments:

The group moved approval on Dr. Littlefield's proposal on the assumption that a physician would administer the anesthetic and take the biopsy. It was recommended that the consent forms should be revised so that skin biopsy is specified. The question was raised concerning the experimental design. Would the injected Xylocaine anesthetic affect chromosome breakages? Dr. Nelson noted that a small area anesthetic block surrounding the biopsy site would eliminate this possible distortion. Approval was modified to permit the biopsy site to be optional, not limited to the forearms. It was also modified to permit 2 mm. in diameter samples.

Approved: Aug. 13, 1971(date)

Disapproved: _____(date)


for Secretary, Committee on Human Studies

1973: from C.L. Edwards - "concluded"

pe

Adopted 4-67

1030344 .

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: December 20, 1971

Senior Investigators: Raymond L. Hayes

Co-Investigators: C. Lowell Edwards

Bill M. Nelson

Title of Project: SCANDIUM-AUGMENTED GALLIUM LOCALIZATION
IN TUMORS - PHASE I AND PHASE II STUDIES

PHASE I

I. Objectives of Experiment

- a) To determine whether giving scandium along with radioactive gallium increases the relative concentration of the gallium in tumors by accelerating clearance from normal tissues (except bone and kidney) but not tumors, as has been shown in experimental animals.
- b) To determine whether or not scandium can be safely used in this way.
- c) To determine whether this agent is clinically useful in augmenting the diagnostic value of radiogallium.

II. Methods of Procedure

a) Material

Scandium citrate (1.5 molar ratio of Sc to citrate) will be prepared and stored in vials. The methods of insuring sterility and freedom from impurities and pyrogens will be as listed in the IND for the Food and Drug Administration.

b) Dosage

The following sequence of intravenous doses is proposed, with the understanding that it will be stopped at any point at which toxicity arises or at which suitable or optimal results appear to have been obtained:

Doses

0.005	mg	Sc/Kg	(as citrate)	- 3 patients
0.05	"	"	"	"
0.1	"	"	"	"
0.25	"	"	"	"
0.5	"	"	"	"
0.75	"	"	"	"
1.0	"	"	"	"

These patients would all receive small doses (less than 100 μ c) of ^{67}Ga within an hour after the scandium. The minimal effective dose in the rat appears to be 0.5 mg Sc/Kg.

c) Data to be collected

Complete blood counts will be done before and at 1 and 2 weeks after each injection to look for evidence of hematologic activity.

Fibrinogen, partial thromboplastin, prothrombin time, and bleeding and clotting times, will be obtained before injection and at 1 and 2 weeks after injection.

Blood, urine, and stool excretion levels, as well as whole-body counts, for the radiogallium for several days after injection will be measured to determine whether the scandium changes distribution and excretion. Urine will be assayed for stable scandium.

d) Selection of patients

These will be patients deemed suitable for gallium scans for diagnosis of tumors. The patients will already have known malignant tumors. The special scandium study will be done usually one week before a standard radiogallium diagnostic study which will serve as a control for the study of scandium plus gallium.

PHASE II

1. Assuming zero or minimal toxic symptoms in the Phase I study, and evidence of an effect on radiogallium behavior, a suitable dose of scandium will be given with doses of gallium large enough for scanning. We will determine how soon after a dose a suitable scan can be obtained to demonstrate tumors. We will also determine if scandium affects the amount of gallium in the bowel.
2. We will collect whole-body retention data on 20 patients for radiation dosimetry.
3. We will include patients who are going into surgery or might die in the near future; this is for the purpose of studying tissue distribution of gallium and scandium.

III. Possible Hazards and their Evaluation

1. Acute chemical toxicity of scandium. On the basis of animal studies there appears to be no significant hazard in the doses proposed. (See IND).
2. Chronic chemical toxicity of scandium. Multiple or high-dose toxicity has been followed for three years in rabbits and 90 days in dogs. On the basis of these studies there is some evidence of decreased red cell production at very high doses. We deem no serious hazard at the doses proposed.
3. When scandium and other trivalent metals are given along with adrenaline to animals, a bleeding disorder associated with intravascular clotting has been observed. (Ref. Selye, H., Tuchweber, B., and Rchan, P.: Metal-Induced Sensitization for the Production of Different Types of Tissue Reactions by Adrenaline, Brit. J. Exp. Path. Vol. 47, No. 3, June 1966, pp. 281-285.) This study was made with large doses of scandium (40 - 80 mg/kg) and is not believed a serious hazard in the proposed studies, which do not include administering adrenaline (see IND).
4. An antithromboplastic effect of scandium has been reported (Ref. Chargaff, E., and Green, C. J., Biol. Chem., 173, 663, 1948). We found little or no effect in rabbits at doses 10 times those proposed.

IV. Radioisotopes and New Drugs

The radiogallium will be used in ways already established. The scandium is a new drug. Scandium oxide will be purchased from:

Alfa Inorganics, Inc. (99.9% pure)
Congress Street (99.99% pure)
Beverly, Massachusetts 01915

or

Electronic Space Products, Inc.,
854 S. Robinson
Los Angeles, California 90026

It will be converted to citrate and administered in sterile pyrogen-free isotonic solution. The molar ratio of citrate to scandium will be 1.5 to 1.

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: A test of the safety of injected scandium citrate
and its effect upon the distribution and excretion of gallium-67.
(State nature of test)

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
Name

the proposed test to be given _____
Name

including the following: Frequent blood samples, urine and stool
collections, whole body counts, and the fact that it has not been previously
tested in humans.

Investigator

Date

CONSENT FOR EXPERIMENTAL TEST

1030348

SCANDIUM STUDY:

Patient was informed that:

- 1) He may have his gallium-67 scan whether or not he agrees to participate in the scandium study.
- 2) No toxic effects are known or expected at the proposed doses.
- 3) In much higher doses (more than 10X maximum proposed dose) in animals, it has produced a mild reversible anemia thought to be due to interference with the utilization of iron.
- 4) In animals, much of the scandium is sequestered in macrophages of the liver, spleen, and bone marrow where it apparently remains for long periods of time.

Date

Physician's Signature

Patient's Name

Number

1030349 .

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

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

(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

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

WITNESS: _____

I have talked with _____ about
the proposed course of treatment to be given _____
including the following: * _____
Name Name

Physician Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

REVIEW AND ACTION

ORAU Medical Division - Committee on Human Studies

Principal Investigator: Raymond L. Hayes Ident. No. 18

Project Title: Scandium-Augmented Gallium Localization in Tumors - Phase I and Phase II Studies

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

The potential risks are that a remote possibility of an unusual human sensitivity would lead to some totally unexpected toxic response to the scandium. If so, this would have to represent a sensitivity many-fold that of the various species of animals so far studied.

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:

Although the possible benefits for scanning procedures in the individual patients first given scandium are not likely to be very great, it is possible that a more adequate tumor-localizing scan will be obtained. In view of the very small risks, this seems a justifiable procedure.

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

The informed consent procedures, plus an additional statement for the record indicating specific topics that will have been discussed with the patient, are approved as revised.

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

The committee asks the investigators to report at least once per year to the committee. Reports should be made at shorter intervals if untoward toxicity arises, unless the experiment is therefore immediately discontinued.

- (5) Other committee comments:

None

Approved: 1/31/72

Disapproved: _____ (date)

Donald A. Andrews
Chairman

In agreement Dec 73

Revised August 1971

1030351

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

AREA CODE 615
TELEPHONE 483-8411

January 31, 1972

Dr. Raymond L. Hayes
Medical Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830

Dear Doctor Hayes:

The Committee on Human Studies approved the proposal of Hayes, Edwards, and Nelson entitled: "Scandium-Augmented Gallium Localization in Tumors - Phase I and Phase II Studies." They asked that in addition to the form to be signed by the patient consenting to the study, there be a record placed on the chart, as developed by Dr. Edwards during the meeting, indicating the nature of the information conveyed to the patient by the person who discussed the research with him. Otherwise the proposal was approved as stated. The investigators are obligated to communicate with the committee at least yearly on the status of the research, and if any untoward reactions occur, are obligated to either discontinue the research or communicate with the committee for further guidance.

Sincerely,

Gould A. Andrews, M.D.
Chairman,
Committee on Human Studies

GAA/pe

cc: Dr. Edwards
Dr. Nelson

1030352.

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

AREA CODE 615
TELEPHONE 483-8411

February 2, 1972

Department of Health, Education, and Welfare
Food and Drug Administration
Division of Oncology and Radiopharmaceuticals
Room 11-B 21
5600 Fisher's Lane
Rockville, Maryland 20852

Gentlemen:

On 31 January 1972, we sent your office an Investigational New Drug Application for the use of Scandium Citrate. We have since noted two typographical errors in the material submitted.

Please correct line 6, paragraph 2, page 2 to read "grade sodium hydroxide..." Also the first word of sentence 4 in paragraph 4 on page 3 should be "Tumor."

Thank you for your help in making these corrections.

Sincerely yours,

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

GAA:bbc

1030353



Copy to ... 2/6/72

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

IND 8598

March 1, 1972

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

Dear Dr. Andrews:

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

Sponsor: Gould A. Andrews, M.D.

Name of Drug: Scandium Citrate

Date of Notice: January 31, 1972

Date of Receipt: February 2, 1972

IND Number Assigned: 8598

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 at your earliest convenience:

1. The histopathology results of the intravenous acute toxicity study and the intravenous repeated dose toxicity study in rabbits should be submitted in detail.

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

1030354

3/3/72

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

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

1030355

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

AREA CODE 615
TELEPHONE 483-4411

June 21, 1972

IND 8598

Earl L. Meyers, Ph.D., Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Dear Doctor Meyers:

We are writing to report that we have had an apparent reaction to scandium citrate. This occurred in the first patient to receive the dose of 0.125 mg/ kilo. It was characterized by brisk intravascular hemolysis occurring four to six hours after the injection. There was associated hemoglobinuria. The patient made a satisfactory recovery.

Until we can clarify the situation, we have suspended all human injections of scandium. We are investigating the situation further, and will file an amendment with a more complete report.

Sincerely,

Gould A. Andrews, M.D.
Chairman,
The Medical Division

GAA/pe

Date 6-21-72
Copies to R. Hayes
EL Edwards

1030356

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: 28 January 1972

Senior Investigator: Helen Vodopick, Goswitz, M.D.

Co-Investigators: Ten-ching L. Lee, Ph.D.

Title of Project: Regulation of Granulopoiesis

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 ORAU Medical Division Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

V. Responsibility of Senior 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 ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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: Pending approval

Signatures: Allen Tadopick Poswitz, MD Investigator

"
"
"

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Gerald Andrews
Chairman

Date: 7 Feb 72

I. Objectives of Experiment:

To determine the relationship of granulocyte chalone and serum antichalone to the alterations in leukocyte production seen in myeloproliferative disorders. The ultimate goal is to determine whether abnormalities of production or breakdown of these substances are part of the etiology of leukemia. Identification and characterization of chalone and antichalone will be pursued. The application of such information to the therapy of these disease states in man can be appreciated.

II. Methods of Procedure:

During a period of three years we will obtain blood samples anticoagulated with heparin from normal volunteers and patients with chronic granulocytic leukemia and other myeloproliferative disorders. Signed consent from both volunteers and patients will be obtained after explaining the purpose of the procedure.

Proper cleansing of the site with 70% alcohol will immediately precede the venipuncture. Sterile disposable needles will be used. The volume of blood needed will depend on the patient's white blood cell count; the amount obtained from normals will be 50-100 ml and from leukemic and other patients with myeloproliferative diseases will be half this amount.

The control group will consist of 10 normal volunteers. A total of three to four blood samples from each donor will be obtained at equally spaced intervals during the first year. During the second year of study, one or two samples of the same volume will be needed from this group.

After we have been able to establish the reproducibility of our in vitro bioassay system, we will obtain blood samples from patients with myeloproliferative disorders. We hope to study ten patients with chronic granulocytic leukemia and four patients with polycythemia rubra vera.

Patients with these disorders, receiving therapeutic irradiation, either total body or splenic, will have samples drawn before, during, and after treatment. Thus each of the 14 patients will have 3 samples assayed. These samples will be timed to correspond with changes in the white blood cell count.

During the third year of study, we anticipate that larger samples of plasma (~200 ml) obtained by means of plasmaphoresis will be needed to isolate and hopefully purify chalone and antichalone. No patient with a hematocrit of less than 30% will be used. The procedure will be supervised by a physician. The interval between such plasmaphoresis will be at least three months.

1030359

Sterile bags commercially available for this purpose will be used. The separation of the plasma from the cellular elements will be done in a closed system technic (double bag collection unit with connecting tubing) so that the cellular elements which will be returned to the donor will not be exposed to any possible contamination. The estimated time from removal to reinfusion of red blood cells will be less than one hour.

III. Possible Hazards and Their Evaluation:

The possible complications of venipuncture are hematoma and infection. Hematoma can best be prevented by adequate pressure to the site of venipuncture. If a hematoma does occur, absorption of it can be facilitated by application of warm compresses. Infection can be avoided by cleansing of the venipuncture site thoroughly with 70% alcohol and by using sterile disposable needles. The volume of blood removed should cause no compromise of the circulatory system. Blood counts on all normal donors and patients are obtained at the time of each blood sample.

When phlebotomies are performed, the procedure will be under the direct supervision of a physician. If any signs or symptoms of circulatory compromise are observed, (increase in pulse rate to over 100/min, nausea, vomiting, drop in blood pressure) the phlebotomy will be stopped immediately. The patient will be placed in a Trendelenburg position. Usually these symptoms are transient and respond to conservative management.

IV. Radioisotopes and New Drugs:

The volunteers and patients will receive no radioisotopes or new drugs.

REVIEW AND ACTION

ORAU Medical Division - Committee on Human Studies

Principal Investigator: Helen Vodopick, M.D. Ident. No. 19

Project Title: Regulation of Granulopoiesis

- (1) In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are:
At this time the committee approves only the portion of the work in normal subjects. It is believed that the risks of drawing blood samples are extremely small. Written, signed permission will be obtained from the normal subjects who provide blood.

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:

There is not expected to be any benefit for the donors or any direct benefit likely for the patient donors. Eventually the study might result in a better understanding and treatment of leukemia.

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

The standard consent procedure signed by the patients and normal donors will be adequate.

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

The committee recommends that Dr. Vodopick inform the committee as soon as she is ready to start on the part of the study involving patients. This will assume that some progress has been made on the assay procedure.

- (5) Other committee comments:

None

Approved: 1/31/72

Disapproved: _____(date)

Donald A. Andrews

Chairman

1030361

MEMORANDUM

o Vodopick (Grant) FileDATE Feb. 21, 1972

SUBJECT _____

COPIES TO _____

With reference to Dr. Chalkley's letter to Dr. Andrews, of February 3, 1972, Dr. Andrews said that Dr. Vodopick has submitted what was required..... I presume this included form NIH 1611. (From GAA's office we are to submit the "compliance" form, and revised PHS assurance.)

Polly

1030362

Regulation of Granulopoiesis - Vodopick

ATTACHMENT B

This institution will provide whatever professional attention or facilities are required to safeguard the rights and welfare of human subjects.

- (5) The signatures, names, and occupations or titles of the members of the committee are listed below.

Thomas A. Lincoln, MD
 Signature Name Occupation or Title

Bill M. Nelson, MD
 Signature Name Occupation or Title

A. B. Bice, M.D.
 Signature Name Occupation or Title

W. E. Koenig
 Signature Name Occupation or Title

Robert D. Lang, MD
 Signature Name Occupation or Title

John B. Stone
 Signature Name Occupation or Title

Donald A. Andrews
 Signature Name Occupation or Title

Signature Name Occupation or Title

Signature Name Occupation or Title

Date of Committee Approval Jan. 31, 1972



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

December 30, 1971

1716

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

Dear Dr. Andrews:

The critical line in our July 8, 1971, letter was the last: "If you wish consideration for a "general" assurance please respond with a listing of all projects involving human subjects, whether supported by DHEW or by other sources, that are under active review by your institutional committee."

Attached is a listing of all DHEW programs currently requiring review of projects involving human subjects. The Department has finally required use of this procedure by its grantees and contractors, the Department of Defense and the AEC are using it in special cases on an informal basis. The Food and Drug Administration requires use of the procedure for all investigational new drug studies carried out under exemptions from the labelling provisions of the Food, Drug, and Cosmetic Act.

If you are-or should be- reviewing a significant number of concurrent projects, we will be glad to renegotiate your assurance. The list first, please, and Happy New Year.

Sincerely yours,

D. T. Chalkley, Ph.D.
Special Assistant to the Director
Division of Research Grants

Enclosure

1030364

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PROGRAMS REQUIRING INSTITUTIONAL REVIEW OF GRANT AND CONTRACT
APPLICATIONS AND ACTIVITIES
FOR COMPLIANCE WITH
DHEW POLICY
PROTECTION OF HUMAN SUBJECTS

I. Office of Education

Bureau of Education for the Handicapped-all grants and contracts
National Center for Educational Research-all grants and contracts

II.. Public Health Service (includes Food and Drug Administration, Health Services
and Mental Health Administration, and National Institutes of Health)

Research Project Grants (except R09, R13 programs)
Program Projects and Center Grants (except P06, P07, P09 programs)
General Support (Research Related)
 General Research Support
 Health Sciences Advancement Awards
 Biomedical Sciences Support Grants
Fellowships (except F05, F15)
Research Career Awards
Research Training (except T07, T09, T13, T14, T15)
Research Contracts

III. Social and Rehabilitation Services

Aging Research and Development Grants (OAA Title IV)
Child Welfare Demonstration Grants (SSA Title IV)
Hospital Improvement Grants (HIP)
Hospital Staffing Grants (HIST)
Public Assistance Demonstration Grants (SSA Title XI, Section 1115)
Rehabilitation Research and Development Grants (VRA Title IV)
Rehabilitation Research and Training Grants (VRA Title IV) except as
specifically exempted by Regional Mental Retardation Consultant
Rehabilitation Service Grants (VRA Title IV)
Rehabilitation SWEAT Grants (VRA Title IV)
Social Welfare Cooperative Research and Development Grants (SSA Title XI
Sec 1110)

1030365



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

January 17, 1972

1716

Mr. William G. Pollard
Executive Director
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830

Dear Mr. Pollard:

One of the awarding units of the Department of Health, Education, and Welfare has recently called our attention to the fact that it is reviewing a proposal from your institution which involves the use of human subjects, 1 R01 CA 13042-01, "Regulation of Granulopoiesis," Dr. Helen V. Goswitz.

Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the Department of Health, Education, and Welfare is the responsibility of the institution which receives or is accountable to the DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of the Department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an appropriate institutional committee as well as by an appropriate professional committee within the responsible component of the Department.

The institution must submit to the Department of Health, Education, and Welfare, for its review, approval, and official acceptance, an assurance of its compliance with this policy.

In our letter of December 16, 1971, Dr. Gould A. Andrews, Chairman, was notified that your "general" assurance was being inactivated as far as new and competing renewal grants are concerned and that such grants would now be subject to the "special" assurance mechanism. The enclosed example should be completed, typed on your letterhead, and forwarded to this office.

A prompt and complete reply may avoid interruption in the processing of an application, or if it is already approved, a delay in the award of funds.

Sincerely yours

Mark H. Conner, Ph.D.
Institutional Relations Section
Division of Research Grants

Enclosure

1030366

EXAMPLE OF A STATEMENT OF COMPLIANCE

SPECIAL INSTITUTIONAL ASSURANCE IN CONNECTION WITH
SINGLE PROJECTS INVOLVING HUMAN SUBJECTS

(0) The (name of institution) will comply with the policy for the protection of human subjects participating in projects or activities supported by grants and contracts made by the Department of Health, Education, and Welfare. This policy requires a review independent of the investigator or director to safeguard the rights and welfare of those subjects. An initial review of the application for a grant or contract identified as _____ submitted by this institution on behalf of _____ indicates that:

(1) In the opinion of this committee the risks to the rights and welfare of the subject 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. Documentation is attached.

(4) The committee agrees to arrange for a continuing exchange of information and advice between itself and the investigator or director, particularly to deal with proposed changes in project or activity design, or with emergent problems which may alter the investigational situation with regard to the criteria cited above. This exchange will be implemented through:

1030367

This institution will provide whatever professional attention or facilities are required to safeguard the rights and welfare of human subjects.

- (5) The signatures, names, and occupations or titles of the members of the committee are listed below.

Signature	Name	Occupation or Title

Date of Committee Approval _____

- (6) Official signing for Institution

Signature _____

Name _____

Title _____

Institution _____

Address _____

Telephone Number _____

Date _____

INSTRUCTIONS

An acceptable special institutional assurance consists of a properly completed formal statement of compliance with Department of Health, Education, and Welfare policy (see Attachment B), signed by a committee of not less than three members and by an official authorized to sign for the institution. The explanatory paragraphs which follow refer to the corresponding section of the attachment.

- (0) This should identify the application for a grant, contract, or award by its identifying number, where known, or by its full title. The name should be that of the investigator, program director, fellow, or other individual immediately responsible for the conduct of the work.
- (1) The committee should identify in general terms those risks that it recognizes as probable occurrences; i.e., "Aggravation of anxiety status through contact with interviewers," "Preservation of confidentiality of data," "Renal injury subsequent to multiple biopsy," "Possibility of side reactions to drugs," "Possible local hematosis and nerve injury associated with venipuncture."
- (2) The committee should identify the benefits to the subject or to mankind in general that will accrue through the subject's participation in the project. This should be followed by a brief discussion, weighing the risks against the benefits.
- (3) Consent procedures should be described and the minimum statement to be used should be attached. "Students responding to the attached advertisement will be interviewed." "The project outline will be submitted to the executive council of the P-TA." "Individual teachers will be asked to allow an observer in the rooms chosen." "Superintendents of several state mental hospitals will be approached. The attached statement to the next of kin

1030369

or guardian will be signed by the principal investigator and the superintendent."

"The following special consent form will be signed by each subject and his or her spouse or next of kin before acceptance of the subject." "No prior consent will be sought. The following debriefing schedule will be followed within 30 minutes after completion of the test."

- (4) This should indicate whether the investigator or director will be required to submit written reports, or to appear for interviews, or will be visited by the committee or committee representatives, and at approximately what intervals these steps will be carried out.
- (5) No further explanation is necessary.

(The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of the project. The committee may be an existing one, or one especially appointed for the purpose. The institution may utilize staff, consultants, or both. The membership should possess not only broad competence to comprehend the nature of the project, but also other competencies necessary in the judgments as to acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. The committee's maturity and experience should be such as to justify respect for its advice and counsel.)

(No individual involved in the conduct of the project shall participate in its review, except to provide information to the committee.)

1030370

(Committee members should be identified in the assurance by name, positions, earned degrees, board certifications, licensures, memberships, and other indications of experience, competence, and interest.)

The completed assurance should be attached to the application, or returned directly to the office requesting its submission.

1030371

Information for attachment B for Dr. Vodopick's grant. (I'm not sure this should be labeled as attachment B...but it fulfills the questions there.)

Item 0

Has to do with the identification of the grant, etc.....type as it appears

Item 1.

The committee recognizes the risks involved with drawing moderate samples of blood, somewhat larger than are usually obtained for chemical determinations but much smaller than are usually obtained for transfusion purposes. This might involve the possibility of hemorrhage at the site of venipuncture, the possibility of infection, or the possibility of cardiovascular disturbance. These risks are considered to be very slight.

Item 2.

The possible benefit of these studies would be a better understanding of the nature of leukemia, and conceivably an improvement in the treatment of this disease. It is not highly likely that the initial patients studied would benefit from this directly, but they would have an opportunity to contribute indirectly to other patients. Similarly, the normal donors would not be expected to benefit directly. In a procedure involving so little risk as giving blood samples, it is not deemed necessary to show direct benefit to the subjects.

Item 3

Adequate consent procedures will be used; an example of the form is enclosed. The normal donors and the patients will both know the purpose for which the blood is being drawn and will be true volunteers. No special benefits will be offered to the patients in return for volunteering and they will be given the same general treatment as those

1030372

62

who do not volunteer. A small financial remuneration will be given to the normal volunteer who donate blood.

Item 4

The investigator will be ^{asked} ~~required~~ to report at least yearly to the committee and to be available for interviews if necessary. The investigator is asked to determine whether or not the assay procedures are successful, using only blood from normal volunteers. Once the procedures are worked out, the committee will be glad to consider the extension of the proposal involving blood from patients ^{with} ~~from~~ leukemia.

Item 5

The committee unanimously approves the initial phase of the project. The investigator appeared before the committee and provided information but did not participate in the decision. The committee represents diverse skills, educational backgrounds, and points of view, including several who are ^{not} affiliated with Oak Ridge Associated Universities. (Attach, I guess, some brief information about the committee members and then complete that list of names with titles, etc., and GAA to sign as institutional representative. Get from Dr. Vodopick copies of whatever forms she is going to use to have the donors, both normal and patients, sign at the time they give the blood samples.)

(c.v.)
Enc



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

February 3, 1972

1716

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

Dear Dr. Andrews:

The list of projects under review by your committee, furnished with your letter of January 28, 1972, is quite impressive. We will reactivate your former Public Health Service assurance pending receipt of an assurance of compliance with the present DHEW policy.

Our request of January 17, 1972, to Mr. William G. Pollard, Executive Director, for a special assurance in connection with your pending proposal, 1 R01 CA 13042-01, "Regulation of Granuopoiesis," Dr. Helen V. Goswitz, may be disregarded. This proposal should be reviewed by your committee in accordance with the terms of your PHS assurance and certification of that review should be forwarded to the National Cancer Institute. You may use the enclosed form NIH 1611 for this purpose.

The requirements for compliance with Department of Health, Education, and Welfare policy are set forth in the enclosed letter. The revision of your PHS assurance should be submitted as soon as possible so that review may be completed prior to the July 1, 1972, deadline.

Sincerely yours,

D. T. Chalkley, Ph.D.
Special Assistant to the Director
Division of Research Grants

Enclosure

1030374

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

AREA CODE 615
TELEPHONE 483-8411

January 31, 1972

Dr. Helen Vodopick
Medical Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830

Dear Doctor Vodopick:

The Committee on Human Studies approved the first stage of your proposed study on "Regulation of Granulopoiesis." They requested that you not undertake studies on abnormal bloods from leukemic patients until the initial assay procedure has been worked out and until you communicate with the committee informing it of your desire to proceed with the abnormal bloods. The committee asks that you get a written form from each donor of blood, whether patient or normal volunteer, indicating his understanding of the use of the blood, and his voluntary participation in the research project. They also ask that you report back to the committee on a yearly basis about the status of the project.

Some members of the committee pointed out that it would be very important that none of the ORAU employes feel coerced or obligated, in connection with their jobs, to participate in the donation of blood.

Sincerely,

Gould A. Andrews, M.D.
Chairman,
Committee on Human Studies

GAA/pe

1030375

Human Use Committee

19 December 1972

Regulation of Granulopoiesis

Progress Report:

In our original proposal on a study of chalone and antichalone, we had projected a three year study. During this time we had hoped to obtain blood from normal volunteers and patients with chronic granulocytic leukemia and with other myeloproliferative disorders for analysis. Signed consent from all donors would be obtained after explaining the purpose of the procedure. Appended is the consent form used.

In the first year of study we had anticipated that we would have completed studies on a control group of 10 normal volunteers. A total of three or four blood samples would be drawn at equally spaced intervals from each donor during the year. (This portion of our study had been approved by the Human Use Committee in January 1972)

However in setting up the experimental procedures we used rat granulocytes and serum to evaluate technical variabilities. We are now ready to commence our studies on normal volunteers as initially proposed.

After finishing our studies on the normal volunteers, we would hope to commence at the end of the next year our studies on patients with myeloproliferative disorders. Initially we would need single 50 ml or less samples of whole blood; the amount needed will vary according to the individual's blood count.

Prior approval from the Human Use Committee will be sought before we proceed to other experiments in which larger volumes of blood or plasma might be needed.

H. Vogelstein, M.D.

W;rr

1030376

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: December 11, 1973

Senior Investigator: Helen Vodopick Goswitz, M.D.

Co-Investigator: Ten-ching Lee, Ph. D.

Title of Project: Regulation of Granulopoiesis

I. Objectives of Experiment:

We wish to continue our search for granulocytic chalone, an inhibitor of granulocytic production.

Identification and characterization of this chalone will be pursued.

II. Methods of Procedure:

Since chalone is found in the tissue which production it regulates, we attempted to recover sufficient number of granulocytes for our assay procedure.

During the first year of our study we were able to harvest a large number of granulocytes from rat peritoneal exudate. Aqueous extract of these granulocytes was fractionated by gel filtration. The ability of these fractions to inhibit the incorporation of tritiated thymidine into rat marrow suspension was used to measure the presence of chalone. Specific fractions appeared to have such inhibitory capacity.

Extending these studies to human granulocytes we were able to find a substance extracted from sonicated human granulocytes which had similar inhibitory properties against rat marrow suspension.

During the next year of study, we wish to repeat some of our experiments with normal human granulocytes and to begin studies on granulocytes obtained from patients with myeloproliferative disorders, especially chronic granulocytic leukemia.

Blood will be obtained by venipuncture after proper cleansing of the site with 70% alcohol. Because of the relatively small number of granulocytes in the whole blood of normal volunteers, we have had to collect a unit of blood (~ 500 ml) from these people in order to harvest enough granulocytes to carry out our studies. We will need less blood from patients with chronic granulocytic leukemia who have an elevated granulocyte count. Approximately 50-100 ml of blood will be drawn. If more than this amount is drawn, we will return the red

1030377

blood cells under aseptic conditions to the donor. Sterile bags commercially available for this purpose will be used. The separation of granulocytes from red cells will be carried out in a closed system (primary bag and satellite bag connected by tubing). Thus the possibility of contamination in the separation process will be nil. We hope to study the granulocytes obtained from ten patients.

Patients with myeloproliferative disorders who receive therapeutic irradiation, either total body or splenic, will have samples drawn before, during, and after such treatment.

After the procedure is explained, appropriate consent forms are signed by the donor.

III. Possible Hazards and Their Evaluation:

The possibility of hematoma or infection at the venipuncture site may occur.

Infection can be avoided with thorough cleansing of the venipuncture site. Pressure at the site of venipuncture will prevent the occurrence of hematoma.

Blood counts are performed on all blood donors and patients at the time of each blood donation.

When phlebotomies are performed, any sign of circulation compromise will dictate the procedure be stopped immediately. Symptomatic treatment, cold compress and Trendelenburg position will be used. These symptoms are transient and respond to conservative management.

IV. Radioisotopes and New Drugs:

No volunteers or patient will receive radiosotope or new drugs.

Starting Date: Part of study in progress - reviewed 19 December 1972, approved 31 January 1972. Patient studies to begin pending approval.

Signature: *William Bedapick Rosvick, MD* Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Signature *James G. Andrews*

Title *Chairman*

Institution *FRAX Medical Division*

Date *11 Dec 73*

1030378

To Committee
25 Jan 75

No. 19

Goswitz
5 R01 CA 13042-03

-3-

Summary:

Over the past several years evidence has accumulated that humoral regulators of the hematopoietic system exist. Those substances thought to inhibit mitosis are called chalone and those which stimulate cell production antichalone. To be classified as a chalone, several criteria must be fulfilled: (1) a mitotic inhibitor; (2) noncytotoxic; (3) reversible action; (4) tissue specific; (5) species nonspecific. Chalone is supposedly produced by the tissue whose proliferation it controls. Antichalone found in serum negates the action of chalone.

In our assay system for chalone, rat marrow suspension was used as target cells. The incorporation of tritiated thymidine into cells synthesizing DNA in short term culture was measured by liquid scintillation counting and autoradiography. Quantitative cell count of the marrow suspension pre- and post-incubation was performed to show that cytotoxicity was absent. Biological substances to be tested for inhibitory properties were fractionated by gel filtration into their components according to molecular weight.

During the past three years we have tried to find granulocytic chalone in rat peritoneal exudate, serum of gray collie dogs, and human granulocytes. Our initial isolation of inhibitory factor from "conditioned media" of rat granulocytes appeared to be successful; however, later experiments showed the reduced incorporation of tritiated thymidine in rat marrow suspension was caused by a hypermolar solution of sodium chloride and magnesium chloride which had been eluted from a Sephadex G-25 column and concentrated by lyophilization.

1030379

To obtain better separation of the salt fraction from the inhibitory fraction in which we were interested, we changed our gel filtration system to Sephadex G-50 superfine. Using this latter column we have found three separate fractions obtained from extract of disrupted human granulocytes which reduced the incorporation of tritiated thymidine into rat marrow suspensions. These three inhibitory fractions were recovered: (1) one immediately after the void volume was eluted; (2) the second was recovered in the V_e/V_o range at which a molecular weight of 1400 would be eluted; and (3) the third was found after the entire bed volume had been collected.

We subsequently found that the fraction presumably containing macromolecules (the fraction collected immediately after the void volume was eluted) did not consistently cause reduced incorporation of tritiated thymidine by rat marrow cells. Therefore, we concentrated our attention on the two other inhibitory fractions. These two fractions, one with a V_e/V_o range of 2.3 - 2.7 and the other with a V_e/V_o range of 2.7 - 3.0, caused 35 and 90% reduced uptake of tritiated thymidine, respectively.

We then took rat marrow suspension which was incubated with the fractions previously shown to have inhibitory properties. After five hours of incubation, these cells were washed free of inhibitory substance. Controls without inhibitory material were treated in a similar fashion. When these cells were tested for their ability to incorporate tritiated thymidine, the cells inhibited with fraction, V_e/V_o 2.3 - 2.7, recovered completely and the cells inhibited with fraction V_e/V_o 2.7 - 3.0 recovered only partially. Quantitative chamber counts of the cell suspensions remained unchanged. No demonstrable damage had occurred during the washing process.

1030380

Although granulocytic chalone presumably stops granulocytic precursors at the G-1 phase of the cell cycle, the synthesis of RNA and the metabolism of amino acids by these same cells should not be impaired. We used tritiated uridine to measure RNA synthesis and tritiated leucine to measure amino acid metabolism. The same inhibitory fractions which caused reduced tritiated thymidine incorporation were added to replicate rat marrow suspensions to which either labeled uridine or leucine was added.

No incorporation of tritiated uridine by the rat marrow cells occurred when either of these two fractions were present in the suspending medium. After additional sets of marrow cells were incubated separately with the inhibitory fractions for five hours, the cells washed and retested for uridine utilization had only partially recovered.

Similar tests with tritiated leucine also showed that marrow cells were inhibited from utilizing this amino acid in the presence of the inhibitory fractions and did partially recover after its removal. These findings would suggest that marrow precursor cells had been put into a metabolic limbo during which more than one cellular function had been halted at least temporarily.

We were able to narrow the range at which the two inhibitory fractions were eluted. One had a V_e/V_o of 2.18 - 2.24 and the other at a V_e/V_o of 2.46 - 2.52. Other conditions such as temperature and eluent play a role in the elution pattern of compounds from a Sephadex column and suspending medium and amount of fetal calf serum influence marrow survival. Therefore, these factors should be kept in mind when comparing results from other laboratories.

1030381

Characterization and identification of these inhibitory substances
remain to be done.

1030382

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: _____

(State nature of test)

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
Name

the proposed test to be given _____
Name

including the following: _____

Investigator Date

1030384

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Helen Vodopick Ident. No. 19 - Extension

Project Title Regulation of Granulopoiesis

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

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: Worth while research.

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

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

5. Other committee comments: None.

1030385

Approve X

Bened Andrews
Chairman of Committee

Disapprove _____

11 December 73
Date

25 Jan 75 Cancelled. See minutes. (Report attached)

No. 19. Regulation of Granulopoiesis

This project is being terminated with Dr. Vodopick's resignation from ORAU. Progress toward the goals of the project will be summarized in her report to NIH which will be added to these notes when completed. Blood from approximately 50 normal (nonpatient) human volunteers were studied. Volunteers were all compensated according to ORAU policy and fee schedule.

1030386

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 19, 1972

Investigators: C. Lowell Edwards, M.D. (ORAU)
J. M. Yuhas, PhD (ORNL)
R. L. Hayes, PhD (ORAU)
G. A. Andrews, M.D. (ORAU)
L. C. Washburn, PhD (ORAU)
Frank Comas, M.D. (UTMRC)

Title of Project: USE OF RADIOPROTECTIVE DRUGS IN RADIATION THERAPY:
Phase I Studies - The metabolism of ³⁵S Labeled
S-2-(3-aminopropylamino)ethyl phosphorothioic acid
in humans.

I. Objectives of Experiment:

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

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

Obviously both of the postulates above assume that the protection afforded by the drug is much greater for normal tissues than tumor and that the radio-sensitivity of the tumor remains essentially unchanged by the drug. Working with the proposed radioprotective drug S-2-(3-aminopropylamino)ethyl phosphorothioic acid hydrate (WR-2721) Yuhas and Storer have shown this radioprotective drug protects the normal tissues leaving the tumor tissue unprotected in animals having a transplantable mammary tumor (J. Nat. C. Inst. 42: 331, 1969) and a urethane-induced lung tumor (unpublished results).

The short term objectives of this study are:

PHASE I: Test the safety of the drug administered intravenously in radio-protective doses in man.

Study the metabolism and tissue distribution of the drug using a ³⁵S labeled preparation.

1030387

PHASE II: Application to be submitted later.

Determine the dose necessary to produce optimum radiation protection.

PHASE III: (Application to be submitted pending completion of Phase I & II)

Determine the therapeutic efficacy for clinical radiotherapy of a variety of tumors.

II. Methods of Procedure:

The preparation and testing of the drugs as discussed below in IV.

Phase I studies will be carried out according to the following outline:

1A. Selected patients with malignant tumors will be informed of the proposal and allowed to volunteer as participants (See paragraph V).

Three volunteer patients will receive an intravenous infusion of 1 mg/kg WR2721 labeled with S-35 (0.25 mCi/70kg). Blood samples will be drawn from the opposite arm at 10, 30 and 60 minutes and at 2 hours. All urine will be collected at 1 and 2 hours and then at 24 hours. Prior to and for one hour after the infusion the following measurement will be recorded:

1. Blood pressure (3 times or until stable) prior to the injection every 5 minutes for 30 minutes after the injection, then every 15 minutes until 2 hours or until stable).
2. Pulse
3. Pulmonary rate
4. EKG
5. Skin temperature
6. Rectal temperature
7. Skin moisture

1B. After completion of 1A and barring any untoward reaction, the same tests will be repeated on 3 volunteer patients receiving 3 mg/kg WR-2721 labeled with S-35 (0.25 mCi/70kg).

1C. After completion of 1B the same tests will be repeated successively with increasing doses of WR-2721 at increments of 6 mg/kg, 12 mg/kg, 24 mg/kg, and 50 mg/kg. Three patient volunteers will be tested at each dose of WR-2721 and each dose will be labeled with S-35 (0.25 mCi/70 kg). These doses will be administered to patients receiving radiation therapy.

1D. After the completion of 1B and barring any untoward effects, approximately 6 patients undergoing surgery either for excision or biopsy of a tumor will be given WR-2721, 1 mg/kg with S-35 (0.25 mg/kg) 1/2 hour before anticipated removal of the tissue. The tissue will then be assayed for ³⁵S comparing the concentration of the isotopically labeled drug in the tumor, normal tissue and blood.

1030388

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 20

Project Title Use of Radioprotective Drugs in Radiation Therapy: Phase I Studies
-- The Metabolism of ³⁵S Labeled S-2- (3-aminopropylamino) Ethyl
Phosphorothioic Acid in Humans.

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:

not activated
HOLD UP.

25 Jan 1975
no progress; no human
proposal submitted.

Approve _____

Donald Andrews
Chairman of Committee

Disapprove _____

19 December 1973

Date

1030389

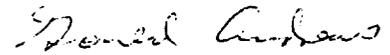
See GAA Memo: Draft proposal only; more animal work needed; will be presented (for human studies) at a later date. Draft of preliminary proposal in file.

Subject: Proposal No. 20 - "Use of Radioprotective Drugs in Radiation
Therapy: Phase I Studies -- The Metabolism of ³⁵S Labeled
S-2-(3-aminopropylamino) Ethyl Phosphorothioic Acid in Humans

From: G. A. Andrews

Date: 2 May 74

This proposal was discussed at the meeting of the Committee on Human Studies on 19 December 1972 and a draft was made available; however, it was decided that the proposal would not be presented because certain basic animal work was still needed before human trials could be undertaken. A copy of the preliminary draft is in the file.


G. A. Andrews

pe

1030390

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 19 Dec. 72

Principal Investigator: M. G. Hanna, Jr.

Co-Investigators: K. Hubner

N. Gengozian

A. Solomon

S. Krauss

Title of Project: Mechanism of Immunotherapy of Human and Animal
Cancers by Intralesional Injection of Mycobacterium Bovis (BCG)

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

1030391

Title of Project: Mechanism of immunotherapy of human and animal cancers
by intralesional injection of Mycobacterium Bovis (BCG)
Ident. No. 21 _____

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 19 Dec 72

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

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Gonell Andrews
Title Chairman
Institution ORAU Medical Division
Date 19 Dec 72

1030392

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator M. G. Hanna, Jr. Ident. No. 21

Project Title Mechanism of Immunotherapy of Human and Animal Cancers
by Intralesional Injection of Mycobacterium Bovis (BCG)

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

Covered adequately in the write-up of the proposal and the minutes of the discussion of the committee.

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:

This is a possible treatment for patients with inoperable carcinoma.

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

The consent forms presented with the proposal are adequate.

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

Routine follow-up of the research results.

5. Other committee comments:

See comment on minutes concerning possible occurrence of clinical infection with BCG.

1030393

Approve X

Gerald Andrews
Chairman of Committee

Disapprove _____

19 Dec. 72
Date

not active but holding pending Dr. Hanna's return 11 Dec 73
25 Jan 75 - cancel - no activity since last meeting (11 Dec 73)

Minutes of the Meeting of the CRC Joint Committee for
Human Participation in Experimental Procedures

September 25, 1972

The meeting convened at 4:00 p.m. and adjourned at 5:25 p.m. Those present were:

Co-chairmen

Dr. John Storer
Dr. Robert Lange

Committee

Mr. Melvin Koons
Dr. Gould Andrews ✓
Dr. Tom Lincoln
Dr. Alfred Beasley
Dr. Don Miller
Dr. Mary Rose Gram

Ex-officio

Dr. Charles Congdon
Dr. Frank Kenney

Item. Committee discussed at length the proposal entitled: Mechanism of Immunotherapy of Human and Animal Cancers by Intralesional Injection of Mycobacterium Bovis (BCG). The committee had the benefit of having the investigators present so that any questions regarding the program could be answered.

The committee approved this project if the protocol would be rewritten to include the following points:

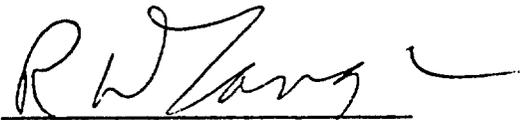
1. No patient should be entered in the study in lieu of urgent, palliative "conventional" therapy. The initial patients should be those deemed to have incurable neoplasms. After the safety of the procedure has been demonstrated, the committee will consider relaxing this requirement.
2. The type of informed consent in use at ORAU should be adapted for this study. A draft of same, drawn specifically for this proposal will be prepared.
3. In a discussion of possible hazards, further explanation of the possibility of dissemination of tumor by needle trauma should be mentioned along with an amplified discussion of the possibility of untoward allergic reactions. In the latter regard mention should be made as to who will perform the injections and that the necessary anti-allergic therapeutic agents and equipment will be kept available.

1030394

4. Page 7 of the proposal where the use of non-viable cell preparations is discussed the committee feels that some appropriate references documenting that 5000 R x-ray is a tumor-cell-lethal dose should be cited. Also in the next sentence, that only irradiated tumor cells will be used.
5. Although obvious, the committee felt that the investigators should be cautioned that the committee must approve, before there is any change in the method of enrolling patients in the study.

Meeting adjourned at 5:25 p.m.

Submitted:



Robert D. Lange, M.D.
Co-chairman

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MECHANISM OF IMMUNOTHERAPY OF HUMAN AND ANIMAL CANCERS
BY INTRALESIONAL INJECTION OF MYCOBACTERIUM BOVIS (BCG)

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I. Identification of Project:

Principal

Investigators: M. G. Hanna, Jr., Ph.D. (ORNL), K. Hubner, M.D. (ORAU),
N. Gengozian, Ph.D. (ORAU), A. Solomon, M.D. (UTMRC),
and S. Krauss, M.D. (UTMRC)

Title of Project: Mechanism of Immunotherapy of Human and Animal Cancers
by Intralesional Injection of Mycobacterium bovis (BCG)

Institutions: Oak Ridge National Laboratory
Oak Ridge Associated Universities
University of Tennessee Memorial Research Center and Hospital

II. Scope and Objectives of Experiment:

Human tumors appear to bear antigens analogous to the so-called tissue specific transplantation antigens (TSTA) of animal tumors. Evidence from clinical and laboratory observations indicate that immunological mechanisms may be capable of suppressing the growth of such tumors. The immune response responsible for this action is of the delayed hypersensitivity type (i.e., cell-mediated immunity).

During the last few years the most promising results from immunotherapeutic treatment of human cancer have been obtained by nonspecific stimulation of various components of the immune system with sensitizing agents ranging from organic molecules such as dinitrochlorobenzene (DNCB) to complex antigenic systems such as Mycobacterium bovis (BCG). To date, some degree of therapeutic success has been achieved by intralesional BCG treatment of malignant melanomas, as demonstrated by Dr. Donald Morton at UCLA, as well as a variety of epidermoid tumors and metastatic tumors associated with carcinoma of the breast, as shown by Dr. Edmund Klein at Roswell Park, Buffalo, New York. Also, Dr. George Mathé, France, has found that systemic administration of BCG by application at the extremities (cutaneous scarification) has produced beneficial immunotherapeutic results for acute lymphocytic leukemias in man.

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Concurrent with these clinical approaches, a major experimental effort has been devoted toward elucidating the mechanism of BCG-mediated tumor regression in animal systems. As a result of this effort, a relevant experimental model for immunotherapy has been developed with inbred strain-2 guinea pigs, utilizing a transplantable syngeneic hepatocarcinoma. Histopathological and functional immunologic data gained from this experimental model indicate that the mechanism of tumor regression and elimination of regional lymph node metastases, as elicited by BCG, is a nonspecific stimulation of the reticuloendothelial system. It appears that the granulomatous reaction developed after BCG stimulation at the tumor site and in the draining lymph node, creates a physiologically altered and possibly detrimental environment for tumor growth. The major killer cells in this system are cells of the macrophage-histiocyte series. There is presently little or no evidence to support the view that an immunologically specific histiocyte hypersensitivity to the tumor is developed.

Under normal conditions, tumor growth may precede the development of specific cell-mediated immunity to a degree which constantly provides a favorable advantage to the tumor system. The development of a granulomatous reaction at the tumor site and in the regional lymph nodes during the early stages of metastasis focuses the macrophage-histiocyte component of the immune response on these regions and confines and destroys the major mass of tumor, while probably releasing processed tumor antigen. This release initiates the development of systemic cell-mediated immunity capable of seeking and eliminating the small percentage of tumor cells which have bypassed or escaped from the granulomatous reaction. The major difference between therapy by tumor excision or by induction of a granulomatous reaction is a quantitative difference in systemic release of processed tumor antigen, which accounts for the difference in degree of specific cell-mediated immunity.

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In this experimental guinea pig model, the BCG anti-tumor reaction has been described as a two-phase response, first involving an initial specific immune reactivity to the BCG organism and, second, a nonspecific reactivity which produces the effective anti-tumor response. The first phase thus requires immunologic competence. This is supported by the fact that antilymphocyte therapy, while not altering tumor growth during the initial treatment period, is capable of completely eliminating the intralesional BCG anti-tumor effect. This fact is consistent with clinical studies in which the best immunotherapeutic results with BCG have been achieved in patients demonstrating skin test reactivity to DNCB, a classic sensitizing agent.

We now find ourselves at a point in cancer research where, for a promising new mode of treatment, we have a relevant experimental model from which to gain insight into potential mechanisms of tumor therapy and to apply this information towards the effective treatment of human neoplasia. Although we have some correlated clinical and experimental data on the function of immunologic competence during the first stage of the BCG-mediated reaction, there is little or no data in man on the second nonspecific granulomatous phase. A major question that must be answered is whether the dramatic and apparently essential histopathological reaction which develops in the tumor and regional lymph nodes of BCG-treated guinea pigs also occurs in humans. This information is critical, since in the guinea pig model this phase appears to be required for the tumor-killing effect. If in man, as in the experimental model, the role of the granulomatous response and the involvement of the macrophage-histiocyte component are directly correlated, we are in a position to explore and elucidate the mechanism in the animal model and at the same time develop alternatives for therapy in man. In this way the mechanisms by which BCG leads to regression of established tumors and elimination of regional and disseminated

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metastases can be defined, as well as the condition or requirements for this treatment as applied to human tumors.

The following studies aim at elucidating the events of BCG-induced tumor regression and elimination of metastases in humans and experimental animals, and are proposed with the objective of providing a solid experimental basis for immunotherapeutic measures in man.

III. Procedures:

A. Patient Selection

Patients with the following neoplasms are potential candidates for this immunotherapy program: basal cell carcinoma of the skin; multiple malignant melanomas of the skin; carcinomas which have metastasized to the skin such as carcinoma of the kidney, carcinoma of the breast, etc.; head and neck cancers such as carcinoma of the parotid gland, etc. The superficial location of these tumors makes them particularly suitable for the procedure, which involves intralesional injection of BCG, followed by excision of the tumor and, when feasible, the draining lymph nodes.

No patient will be entered in this study in lieu of definitive conventional therapy, i.e., surgery, radiotherapy, or chemotherapy.

Ideally, to be selected for the study, a patient should not have received any prior treatment for his tumor, or any treatment that might be considered immunosuppressive. However, this condition may not be absolutely met, and suitability of each patient for the study will be evaluated on the basis of his past treatment and response, clinical status, and prognosis. The selection of patients will be decided by the principal investigators in conjunction with the patient's physician. A basis of the patient's selection will be that the delay

of treatment for the purpose of these experiments will not be detrimental to the patient's prognosis after conventional therapy. Criteria for patient selection will be that the experimental procedure will not jeopardize or postpone any curative therapy of the lesion, i.e., surgery, radiotherapy, or chemotherapy.

Additional approval of the Institutional Human Use Committees will be obtained before changing the method or criteria of enrolling patients in the study.

Informed consent will be obtained from all patients selected for this study. The methods by which "informed consent" will be obtained are indicated on page 2 of the University of Tennessee's application for Review of Research Involving Human Subjects, Form B, July 12, 1972 (Addendum No. 1). The Consent Form, the Summary of Explanation to Patient for Obtaining Informed Consent and Narrative Summary of Explanation and Approval (Addendum No. 2, No. 3, and No. 4).

B. Patient Preparation

Patients will be hospitalized throughout the course of the study at either the Oak Ridge Associated Universities Medical Division or the Clinical Cancer Unit, University Hospital, Knoxville. Prior to immunologic testing the patients will have a complete medical evaluation with particular emphasis to the status of the cancer.

1. The testing of the patient with a battery of common test antigens will be performed in order to assess cutaneous cell-mediated immune responsiveness. These tests will be designed to determine the immunologic competence (cell-mediated immune capacity) of the patients prior to treatment. Also, the capability of sensitization to DNCB and development of delayed-type hypersensitivity to DNCB will be evaluated in these patients. Patients should be negative for PPD skin tests at the highest concentration, for example, second strength testing (0.005 mg of PPD).

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While there is no clinical evidence at the present time that BCG treatment of tumors of PPD-positive patients is hazardous, we will still exert caution on this point. A determination of whether this is a critical consideration will be made in preliminary studies with marmosets, both immunized and nonimmunized against human BCG vaccine preparations, and injected intravenously with BCG.

2. PHA response of peripheral blood lymphocytes will be tested in vitro in order to test immunologic competence, as measured by blastogenesis.

C. Experimental Procedure

1. Surgical biopsies will be performed for diagnostic purposes, as well as tissue culture* and frozen storage of the tumor. Following this, intralesional injection of BCG will be performed. The BCG will be obtained from both the University of Illinois and the University of Toronto. Both sources have been approved by the FDA for human use and will be obtained by use of the approved Investigative New Drug (IND) application numbers obtained by UTMRC and ORAU. The Bureau of Biologics, FDA, has assigned to us for this study on September 27, 1972, the code number BB-IND639. The vaccines will be freeze-dried preparations, to be resuspended in saline prior to use. The vaccines will be assayed for the number of viable organisms. The dose of viable organisms will initially be 24×10^6 viable BCG per 1-centimeter-diameter tumor. Modification of viable BCG dose will be predicted on results. The limitation on the size of tumor injected will be determined by feasibility of surgical excisional biopsy. Utilizing aseptic techniques, the organisms will be injected around and into the tumor in such a way as to penetrate the tumor site and drain by the afferent lymphatics into the regional nodes. This procedure has been shown in guinea pigs and in superficial tumors of man to be the best method for developing a granulomatous reaction.

*A human tumor tissue culture facility has been established in the laboratory of Dr. Carman Lozzio (UTMRC), as a cooperative effort among UTMRC, ORNL, and UTK.

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2. Fourteen to 21 days after injection of BCG, the tumor will be removed surgically. The draining lymph nodes will also be excised, if feasible.

3. Conventional management of the patient will then be carried out.

4. Acquisition of data:

(a) Standard histology will be performed in conjunction with and using the specification of the Pathology department of the respective institution. Tissue will be prepared for acid-fast, reticular, hematoxylin and eosin, and amyloid stains.

(b) Electron microscopic evaluation of tissues and lymph nodes.

(c) Periodic blood samples will be taken. Peripheral blood lymphocytes will be isolated and tested in in vitro cytotoxicity tests against tumor, if frozen or tissue culture tumor cells are available. These tests will be done in collaboration with Dr. Joseph Coggin of the UT Microbiology Department. Blood lymphocytes will also be used in migration-inhibition studies using guinea pig macrophages as indicator cells to test for induced sensitivity toward tumor antigens. Serum will be stored in a central facility and will be tested for complement-dependent antibody cytotoxicity reactions and other appropriate tests.

(d) If frozen or cultured tumor samples are available, patients will be tested for delayed-type hypersensitivity reactions using nonviable autologous tumor cells injected intradermally. The cells will be rendered nonviable by irradiation (10,000 R). Also, frozen irradiated (10,000 R) tumor cells will be spread on coverslips and the coverslips applied to scarified areas of the skin for assay of cell-mediated immunity as measured by the skin window technique.

(e) Follow-up on patient's immune status using DNCB and PPD skin sensitivity reaction.

(f) Continued evaluation of tumor growth and clinical status of patient.

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IV. Possible Hazards:

A. A Delay of Conventional Therapy

One basis of patient selection was that the delay of treatment for the purpose of these procedures was not deemed detrimental to the patient's prognosis after conventional therapy. Also, any emergency situation which arises has priority and will be performed in deference to the experimental procedure. In selected patients with multiple or recurrent tumor nodules, after intralesional sensitization with BCG, and where conventional therapy is not applicable, intralesional injection of PPD will be performed.

B. Local Reactions at the Site of BCG Inoculations

These might include infection of the site of experimental treatment by microorganisms other than tubercle bacilli, and sensitivity to other products in growth culture. Also there may be an inflammatory granulomatosis at the site of tumor injection with tumor necrosis which may delay healing. These complications have not occurred in the experimental model or in the previously referred clinical therapeutic trials in man.

C. Systemic Anaphylactic Reaction Based Upon Previous Sensitization

The possibility of an anaphylactic reaction to the BCG injection has been considered. Some patients have a flu-like syndrome after intradermal inoculation of BCG. This is of transient occurrence and is treated symptomatically. The possibility of a delayed type hypersensitivity reaction to BCG is remote in that only PPD-negative patients will be selected. Initially, we plan to have patients hospitalized throughout the entire course of study and subject to close observation. The necessary anti-allergic therapeutic agents and equipment will be kept readily available. Also, experimental studies in a laboratory primate are in progress to evaluate the effects of BCG injection into a sensitized animal.

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D. Infection Due to Impaired Immunologic Competence

In patients with impaired immunologic competence, a possibility of prolonged fevers, hepatosplenomegaly, or abnormalities in liver function tests, as well as systemic infections, might occur. This particular hazard will be minimized if patient selection is made with careful attention to adequate immunologic competence of the patient.

E. Dissemination or Enhancement of Tumor Growth

Although there is a possibility that tumor cells may be disseminated by trauma of intralesional injection, this hazard is deemed no greater than that arising from conventional needle aspiration or biopsy of a tumor. Further, the patients selected for this study will have had dissemination (metastasis) of tumor. We cannot conclude the possibility of enhanced tumor growth after intralesional injection of BCG; however, no positive data for tumor enhancement have been obtained in experimental systems using viable BCG.

V. Potential Benefits:

The patient is not simply being used in a data acquisition manner, since every indication from both the existing clinical and experimental data is that one benefit derived by the patient in which this immunotherapeutic step has been inserted between diagnosis and conventional therapy, will be that the patient will have a higher level of tumor specific cell-mediated immunity than he would have had if the BCG intralesional injection had not occurred, and if conventional therapy alone had been performed. This benefit will be obvious, since this level of systemic cell-mediated immunity will be the most critical aspect of his prognosis; that is, this level of specific cell-mediated immunity will be effective in combating distant metastases not affected by conventional therapy, or even by the locally induced granulomatous response.

VI. Additional Animal Studies (Guinea Pig and Marmosets):

The following studies have been or will be performed prior to the therapeutic studies in man:

A. Histopathology

Histopathology of intradermal tumors and draining lymph nodes after initial tumor burden of 10^6 cells and intralesional injection of BCG. In this study we will use one of the BCG sources used for the human patients; that is, a source cleared for human use, and compare the response to that obtained with BCG from the Trudeau source, which has been generally used in this experimental model.

B. Studies of Tumor-Specific Immunity

Transfer of immune lymphocytes from guinea pigs with systemic immunity to test for passive immunization in normal animals in order to determine degree of systemic cell-mediated immunity. In guinea pigs in which tumor has regressed as a result of this treatment, second set rejections will be attempted by reimplantation of tumor. Studies in our laboratory indicate that the animal is indeed immunized and has a strong systemic cell-mediated immune response which causes the tumor to be rejected as the second-set reaction.

C. Consequences of Systemic BCG Administration

Injection of BCG in the thyroid gland and/or intravenously in BCG-vaccinated and PPD-negative guinea pigs and marmosets. This attempt will be used to define the risk of tuberculin shock in patients that are PPD positive.

VII. Perspective:

This protocol is designed to provide evidence in man regarding an immunotherapeutic mechanism characterized in animal systems, and suspected to exist in man, which causes tumor regression and elimination of regional metastases. The proposed studies are particularly relevant to a report dated August 7, 1972,

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which was submitted to Dr. Frank Rauscher, Director of the National Cancer Institute, from Dr. William Terry, Chief, Immunology Branch, Division of Cancer Biology and Diagnosis, NCI. This report was a consensus developed by a committee of prominent tumor immunologists concerning the challenges presented by Dr. Rauscher to the Conference on Immunology of Carcinogenesis,* regarding the role of immunology in the current national cancer program. The report consists of discussion and recommendations. Regarding the question, "Against what types of tumors and under what conditions can immunotherapy be directly applied with demonstrable beneficial effects?" the following recommendation was made: "do appropriate human and animal studies to define the mechanisms whereby presently used immunotherapy causes death of tumor cells, in order that better immunotherapy can be devised." This protocol attempts to fulfill the above recommendation.

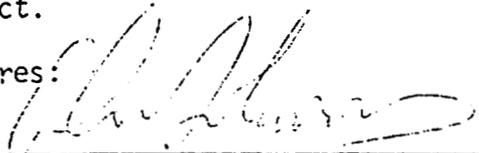
*Conference held May, 1972, in Gatlinburg, Tennessee, sponsored by the National Cancer Institute, organized by the Biology Division, ORNL.

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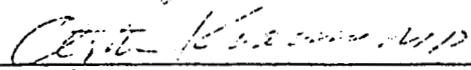
VIII. Responsibility of Principal Investigators:

The principal investigators are aware of the objectives and methods of the Department of Health, Education, and Welfare procedures concerning research involving human subjects as stated in the Grants Administration Manual, Chapters 1-40, "Protection of Human Subjects" dated April 1, 1971 and will abide by them. In addition, the following responsibilities will be accepted:

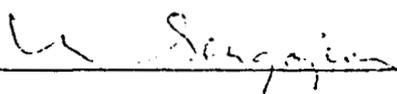
1. Approval will be obtained from the Human Use Committee prior to instituting any major change in project protocol.
2. Development of any unexpected risks will be brought to the attention of the Committee.
3. Signed consent statements will be kept from each experimental subject for the duration of the project and for at least three years thereafter.
4. A status report will be submitted at 12-month intervals or as indicated attesting to the current status of the project.

Signatures: 

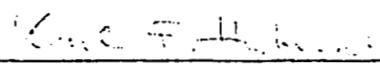
Date: Aug 6, 1972



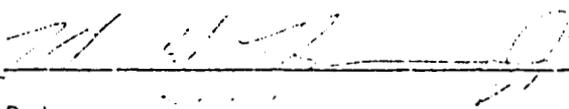
Date: Sept 6, 1972



Date: 9-6-72



Date: Sept 6 1972



Date:

IX. Departmental Review:

The application described above has been subjected to departmental review and has been approved.

Signatures:

Department Head:

Howard F. Allen

Date:

9/7/72

Department Head:

Donald L. ...

Date:

7 Sept 72

Department Head:

Amy ...

Date:

9/12/72

ADDENDUM 1Methods of Obtaining "Informed Consent" from Subjects:

Informed consent must be documented; a copy of the consent form used MUST be included with Form B for committee review.

The definition of informed consent is as follows:

"Informed consent is the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity.

The basic elements of informed consent are as follows:

1. A fair explanation of the procedures to be followed, including an identification of those which are experimental.
2. A description of the attendant discomforts and risks;
3. A description of the benefits to be expected;
4. A disclosure of appropriate alternative procedures that would be advantageous for the subject;
5. An offer to answer any inquiries concerning the procedures;
6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.

In addition, the agreement, written or oral, entered into by the subject, should include no exculpatory language through which the subject is made to waive, or appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.

The actual procedure in obtaining informed consent and the basis for committee determinations that the procedures are adequate and appropriate are to be fully documented. The documentation will follow one of the following three forms:

1. Provision of a written consent document embodying all of the basic elements of informed consent. This form is to be signed by the subject.
2. Provision of a "short" form written consent document indicating that the basic elements of informed consent have been presented orally to the subject. Written summaries of what is to be said to the patient are to be approved by the committee. The "short" form is to be signed by the subject and an auditor-witness to the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons obtaining the consent on behalf of the institution and by the committee, and is to be retained in its records.
3. Modification of either of the above two primary procedures. All such modifications must be approved by the committee in the minutes signed by the committee chairman.

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ADDENDUM 2

CONSENT FOR EXPERIMENTAL PROCEDURE

I authorize the performance upon _____ of the
 (Myself or name of patient)
 following experimental procedure: tests of circulating and cell-mediated immunity,
 intralesional injection of BCG organisms; biopsies of lesions.

The nature and purpose of the experimental procedure, the risks involved,
 possible side effects, and the possibilities of complications have been explained
 to me. I understand that the procedure is part of a research project; that it may
 not result in a treatment for my disorder nor directly benefit me; that the specific
 procedures to be performed on me are primarily for gathering information related to
 my disease and treatment thereof.

Further, I consent to the publication of any information learned from this
) experimental procedure.

I have been informed that I may, at any time, withdraw from continued partici-
 pation if I so desire.

Date: _____

Signature: _____
 (Patient, Parent, or Guardian)

Date: _____

Witness: _____

I have talked with _____ about the proposed procedure to
 (Name)
 be performed on _____ in the presence of the witness
 signing this consent form. I explained fully the procedure in accordance with the
 attached "Summary of Explanation to Patient for Obtaining Informed Consent for
 Experimental Procedure," dated _____, and initialed by me.

Date: _____

Investigator: _____

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ADDENDUM 3SUMMARY OF EXPLANATION TO PATIENT FOR OBTAINING
INFORMED CONSENT FOR EXPERIMENTAL PROCEDURE

In the presence of _____ the patient was informed of
(Witness)
the following:

A. Background

- The purposes of the experimental project and the objectives sought.
- The participating organizations (NCI, UTMRC, etc.).
- How and why the patient was selected.

B. Patient Preparation

- A general description of the medical evaluation procedures, including the common test antigens to be used, number of times blood will be withdrawn, side effects, etc.
- Where and for how long the patient will be hospitalized; the duration and frequency of follow-up visits required, including what will be done to him at such visits.

C. Experimental Procedure

- A detailed description of the experiment, including numbers and types of surgical procedures (and the physical discomforts associated with them), how the BCG will be injected, when the tumor and lymph nodes (if applicable) will be removed, and what blood samples will be taken.

D. Possible Hazards

- Should an emergency situation arise because of the delay of conventional treatment, the emergency will have priority.
- Possible local reactions at site of BCG inoculations were described.

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- Possible systemic anaphylactic reaction was mentioned. Explained that such a possibility was remote since patient is PPD-negative.
- The possibility of a transient flu-like syndrome or a local or systemic infection was discussed.

E. Potential Benefits

- Higher level of tumor specific cell-mediated immunity may result from BCG injection. Long-range benefits of this possible immunity were explained.

F. Other

- Explained that he could withdraw at any time from the experiment merely by making his decision known to me or his personal physician.
- Explained that this experiment may not "cure" his cancer but that the lessons learned will contribute to the advancement of cancer research.
- Patient agreed to allow his test results to be included in publications of experiment results generally.
- Other matters included in the briefing are listed: (If none, so state.)

The patient was offered throughout the explanation session the opportunity to ask questions.

Date: _____

Investigator: _____

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ADDENDUM 4

NARRATIVE SUMMARY OF EXPLANATION TO THE PATIENT FOR INFORMED CONSENT

You are being asked to participate in an experimental project which has as its ultimate aim the application of immunologic methods to the treatment of cancer, that is the use of the body's own defenses in the elimination of cancer cells. To this end we are proposing to inject a readily excessible tumor, usually on the skin, with a measured amount of BCG organisms. This is a modified strain of tubercle bacillus which has been used for many years in order to enhance immunity to tuberculosis and in that context has proven safe and efficacious. The present use of BCG, however, must be considered experimental and is designed only to contribute knowledge towards the treatment of cancer.

We plan to inject a measured number of living organisms into the skin tumor. Prior to this, a small portion of the tumor, or an adjacent tumor, will be biopsied in order to make sure we are dealing with a metastatic lesion of cancer. Fourteen to twenty-one days after injection of the organism, the surgeon will remove the small skin tumor and lymph nodes which drain this area if such a lymph node biopsy is feasible. Following this biopsy, your physician will plan further treatment if required. You have been skin tested for the presence of allergy to the products of the tubercle bacillus, and, if a positive skin test is obtained indicating prior exposure to tuberculosis at some time, then the injection of BCG will not be given, in order to minimize any risks which may arise from hypersensitization. You may expect to find some localized redness, swelling, itching, and possibly drainage from the injection site for a period of several weeks afterwards, but this may be expected to heal over possibly leaving an area of scarring. You have symptoms of "flu" for several days after the injection of BCG.

While the prime purpose of this experiment is to determine if the reaction at the site of the tumor to this injection is similar to that observed in the experimental animal (in which the animal tumor is eventually destroyed by the body's own inflammatory cells), it is possible that no benefit may ensue from this injection. If that is the case, then the physician will still have learned something about the limitations of this method of immunotherapy in the treatment of human cancer. If the reaction to the injection in the tumor is similar to that in the experimental animal, then this opens up possibilities for further treatment of yourself or other patients by this method and may actually compliment other more conventional therapy.

If you have any inquiries concerning the procedures involved, please do not hesitate to ask now or at any subsequent time. You, of course, are free to withdraw your consent to this procedure at any time, either before or sometime during the experimental period. You will be asked to sign permission (consent form) for this study, and a witness who will be present when the procedure is explained to you will also be asked to sign the "Summary of Explanation to Patient" form.

D R A F T

CONSENT FOR EXPERIMENTAL PROCEDURE

I authorize the performance upon _____ of the
(Myself or name of patient)
following experimental procedure: _____

(State briefly the nature of procedure)

The nature and purpose of the experimental procedure, the risks involved, possible side effects, and the possibilities of complications have been explained to me. I understand that the procedure is part of a research project; that it may not result in a treatment for my disorder nor directly benefit me; that the specific procedures to be performed on me are primarily for gathering information related to my disease and treatment thereof.

Further, I consent to the publication of any information learned from this experimental procedure.

I have been informed that I may, at any time, withdraw from continued participation if I so desire.

Date: _____

Signature: _____
(Patient, Parent, or Guardian)

Date: _____

Witness: _____

I have talked with _____ about the proposed procedure
(Name)
to be performed on _____ in the presence of the witness signing this consent form. I explained fully the procedure in accordance with the attached "Summary of Explanation to Patient for Obtaining Informed Consent for Experimental Procedure," dated _____, and initialed by me.

Date: _____

Investigator: _____

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SUMMARY OF EXPLANATION TO PATIENT FOR OBTAINING
INFORMED CONSENT FOR EXPERIMENTAL PROCEDURE

In the presence of _____ the patient was informed of
(Witness)
the following:

A. Background

- The purposes of the experimental project and the objectives sought.
- The participating organizations (NCI, UTMRC, etc.).
- How and why the patient was selected.

B. Patient Preparation

- A general description of the medical evaluation procedures, including the common test antigens to be used, number of times blood will be withdrawn, side effects, etc.
- Where and for how long the patient will be hospitalized; the duration and frequency of follow-up visits required, including what will be done to him at such visits.

C. Experimental Procedure

- A detailed description of the experiment, including numbers and types of surgical procedures (and the physical discomforts associated with them), how the BCG will be injected, when the tumor will be removed, and other invasions of the body (e.g., lymph node removal, blood samples).

D. Possible Hazards

- Should an emergency situation arise because of the delay of conventional treatment, the emergency will have priority.
- Possible local reactions at site of BCG inoculations were described.
- Possible systemic anaphylactic reaction was mentioned. Explained that such a possibility was remote since patient is PPD-negative.
- The possibility of infection was discussed (e.g., prolonged fevers, systemic infections, etc.).

E. Potential Benefits

- Higher level of tumor specific cell-mediated immunity may result from BCG injection. Long-range benefits of this possible immunity were explained.

F. Other

- Explained that he could withdraw at any time from the experiment merely by making his decision known to me or his personal physician.
- Explained that this experiment may not "cure" his cancer but that the lessons learned will contribute to the advancement of cancer research.

F. Other - cont'd

- Patient agreed to allow his test results to be included in publications of experiment results generally.
- Other matters included in the briefing are listed: (If none, so state.)

The patient was offered throughout the explanation session the opportunity to ask questions.

Date: _____

Investigator: _____

10/3/72

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MEMORANDUM

TO Dr. Andrews DATE April 4, 1973

SUBJECT Consultation with Dr. Mavligit regarding the use of BCG at MD Anderson

COPIES TO Dr. Edwards

First I would like to mention a few things about the BCG Program at the Department of Developmental Therapeutics at the MD Anderson Hospital.

The group of Dr. Hersh is using BCG in patients with malignant melanoma and the group of Dr. Freireich apparently is using BCG in some of their patients with acute leukemia. The basis for the use of BCG in these diseases is the idea to enhance an existing immune capacity or to reconstitute cellular immune capacity in tumor patients. All of the patients included in these programs are first evaluated with regard to their immune capacity. Actually I believe that they test all of their tumor patients. The antigens used for immunological evaluations are Dermatophytin O, Dermatophytin, Varidase, mumps, Candida, and key hole limpet hemocyanin (KLH). The first five antigens are used in order to check existing delayed type hypersensitivity and KLH is injected in order to test the capacity of the patients regarding the humoral antibody response. In addition each patient is tested or sensitized against Di-chloro-nitro benzene (DNCB) testing the capacity for cellular hypersensitivity.

Dr. Hersh and his group have observed a decline of immunocompetence with increasing cycles of chemotherapy in leukemia. The in vitro PHA response also declines with chemotherapy about 5 days following a chemotherapy cycle. Subsequently the PHA response rebounds and even over-shoots. They do delayed type hypersensitivity skin tests (DHS) for each course of chemotherapy and they found that with progression of the disease a regression of the DHS was a common observation. In general they first observed an initial improvement of the DHS after beginning therapy of leukemias but then the DHS activity declines.

Dr. Mavligit has looked at the blastogenic response of tumor patients against their own (autochthonous) tumor cells. This test was done like a mixed lymphocyte culture except that the patient's lymphocytes are incubated with their own tumor cells (taken from the first original biopsy) and the blastogenic response is measured by the uptake of 3-H thymidine. For instance in 10 patients with localized tumor the average counts per minute were 4,300; in 13 patients with wide spread tumor only 1,900 CPM were seen. On the other hand the PHA response in the same patients showed little difference. Dr. Mavligit has also used solubilized tumor antigen and lymphocytes and found that 10 out of 24 patients responded well to their own solubilized tumor antigens. The question is however whether they are indeed looking at tumor specific antigen only. This is likely since they have not seen any response whatsoever by using normal control lymphocytes and allogeneic tumor cells.

They have also started to use solubilized (3M KCL extract) tumor antigen for skin testing of cancer patients. This however seems only to work if the patients are not anergic. If one correlates the blastogenic stimulation index and the 12 months survival of melanoma patients one sees that approximately 80% of patients having an index greater than 10 are still alive.

1030419

after 12 months, less than 40% if the index is between 3 and 10 and about 20% only if the stimulation index is smaller than 3. They have obtained similar results in patients with acute leukemia. Nonspecific immunotherapy (BCG) is recommended for advanced or minimal disease.

The BCG treatment (scarification) is mostly used in patients with malignant melanoma, stage III, if all the disease tissue is removed as much as possible. This program has been activated now at the MD Anderson Hospital for the past 18 months. The median survival time of the Stage III melanoma without BCG treatment is 13 months. With BCG treatment is also 13 months. However, only 1 patient has died in the BCG program since (5 months) so that definite prolongation of the mean survival time is to be expected in the patients receiving the BCG treatment.

In addition to the program which utilizes BCG only they have a program which employs chemotherapy, that is Imidazole Carboxamide (DIC) plus BCG. They have 96 patients now in this series. These patients get DIC 250 mg per mm² q.d. times 5. This is repeated every 21 days. BCG is given on day 7, day 12, day 17 and then weekly. These studies are still in progress but from the data that I have seen it appears that DIC plus BCG is definitely better than DIC plus Procarbazine which is another alternative on their protocol. The 350 day survival time with BCG plus DIC is between 50 and 60% whereas the 250 day survival time for patients treated with DIC plus Procarbazine is less than 25%.

I have seen several patients with melanoma and with acute leukemia who came to the BCG lab at the MD Anderson Hospital for treatments. I have observed 7 or 8 treatments and have been permitted to do two treatments myself.

The procedure of the scarification is simple and can be performed by a nurse. A 5 x 5 cm area over the arm or thigh is scarified in a checker-board fashion with 10 lines across in each direction. Capillary bleeding or oozing is induced and 6×10^7 or 6×10^8 BCG are spread into the bleeding field and dried into a crust. This treatment is given weekly for 13 weeks and then spread out to every 2 weeks for several months and probably past 12 months.

I have seen one patient with melanoma complicated by a pulmonary metastasis who is now free of disease since November 1971 when BCG treatments were started. I have spoken with a patient with acute myelogenous leukemia who is now in his 3rd year of his disease and on BCG treatment for the past 12 months; he is still in complete remission.

The reactions from progressive scarification treatments include local heat ("fever"), fever, systemic flu like symptoms and lymphadenitis. Previous fields of scarification will become reactivated as the immunity of the patient improves.

The BCG scarification treatment has a low morbidity, it could potentially be applied widely and it is cheap.

1030420

The group at MD Anderson Hospital has found that the BCG source Tice from Chicago, Illinois, appears to be more effective in patients with melanoma and the French source of BCG from the Pasteur Institute from Paris appears to be more effective in patients with leukemia. In none of the patients treated with the scarification method has disseminated BCG disease been observed.

It would be no difficult task to adopt such a BCG program for the ORAU Medical Division treating patients with acute leukemia or melenomas. (By the way the people at MD Anderson have also treated a few patients with lymphoma and lymphosarcoma with BCG. But I have not seen any detailed data of the results obtained with these diseases.) The question is whether we should start a BCG program and if so should we take this more nonspecific approach of scarification which apparently enhances cellular immunity in a nonspecific way or should we proceed with the recently proposed protocol by Dr. Mike Hanha who claims that the intralesional injection of BCG increases specific tumor immunity. At the present time I am somewhat reluctant to go ahead with the intralesional injections of BCG since the group at MD Anderson has seen severe systemic febrile reactions in several patients and anaphylactic shock in one patient and disseminated tuberculosis in another after using BCG by intratumor injection. I will contact Dr. Stephen Krauss at the UTMRC and will discuss the possibilities of a cooperative study involving the use of BCG in treatment of leukemia patients and melenoma patients. I don't think that we have enough patients at the ORAU Medical Division ourselves to make it a worthwhile separate new study.

Karl F. Hubner



UNION CARBIDE CORPORATION
 NUCLEAR DIVISION
 P. O. BOX Y, OAK RIDGE, TENNESSEE 37830

OK
 11-3-72
 } Copies to Karl +
 Lowell
 Guss
 Dr. Anderson

October 3, 1972

Dr. Robert P. Lang
 Assistant Director
 University of Tennessee
 Memorial Research Center
 1924 Alcoa Highway
 Knoxville, Tennessee 37920

Dear Bob:

Enclosed are drafts of a "Consent" form and an "Explanation to Patient" form that are suggested for use in the proposed BCG experiment.

I want to emphasize these are only suggested forms, particularly the explanation form. Some of what I said may not make sense because of my unfamiliarity with the medical terms. I think you will see what I am trying to get at, however, so feel free to make changes.

If I can be of any further assistance, please call me at 483-8611, extension 3-5979.

Sincerely,

M. E. Koons

MEK:bsw

Enclosures

1030422

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Principal Investigator: C. L. Edwards *C. L. Edwards* Date 19 Dec. 72

Co-Investigators: R. L. Hayes
Bill Gibbs *William B. Gibbs*
Frank Goswitz *Francis A. Goswitz*

Title of Project: Comparison of Indium-111 and Bismuth-206 with Gallium-67
as Tumor-Scanning Agents

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: Comparison of Indium-111 and Bismuth-206 with Gallium-67
as Tumor-Scanning Agents

Ident. No. 22

V. Responsibility of Principal Investigator:

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

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

Starting Date _____

Signatures:	<u>C. Paul Edwards</u>	Principal Investigator
	<u>R. J. Hayes</u>	Co-Investigator
	<u>Francis A. Serenity</u>	"
	<u>William H. Biffo</u>	"
	_____	"
	_____	"

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Donald Andrews
 Title Chairman
 Institution CRAU Medical Division
 Date 19 Dec 72

1030424

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: Comparison of Indium-111 and Bismuth-206 with
Gallium-67 as tumor-scanning agents.

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: _____

1030425

I have talked with _____ about the nature, purpose and risks of the proposed experimental test on _____ and included in my description the following specific points.

- 1.) No acute or chronic ill effects are expected from the test.
- 2.) _____ mCi of _____
_____ mCi of _____ Will be administered intravenously.
_____ mCi of _____
- 3.) The radiation received from the isotopes will be less than _____ rads to the whole body and well below levels thought to be hazardous to patients with known cancers.
- 4.) No chemical or toxic effects are expected because of the extremely minute (tracer) quantities of each element in the dose.
- 5.) Blood samples for measuring the radioactivity in the blood of approximately 10 ml each will be taken _____ times during the _____ day period after the injection.
- 6.) Scans (pictures) will be made _____ hours after the injection.
- 7.) Tumor tissue removed at surgery will be tested for radioactivity.
- 8.) Other tissues removed as part of the surgical operation (such as lymph nodes, biopsies of the liver, spleen, muscle and skin) will also be tested for radioactivity.

Investigator

Date

1030426

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 22

Project Title Comparison of Indium-111 and Bismuth-206 with Gallium-67
as Tumor-Scanning Agents

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

As described in the proposal

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:

An improved diagnostic agent for cancer would have distinct benefit justifying the slight risk.

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

Approval forms as used with gallium-67 should be appended to the proposal and the minutes of the committee.

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

Standard follow-up as with other research projects.

5. Other committee comments:

Samples of patient consent forms should be sent out to the committee.

Approve X

Disapprove _____

Geneal Andrews
Chairman of Committee

19 Dec. 72

Date

1973: "Moving along using indium and gallium but not bismuth. Hope to do 6 or so studies this year" CLE

103042.1

MEMORANDUM

TO Administrative Memo.DATE December 29, 1971SUBJECT Meeting of December 28 on Radioprotective AgentsCOPIES TO F. Comas, C. L. Edwards, R. L. Hayes, R. M. Kniseley, John Storer, John Yuhas
File

Dr. Storer and Dr. Yuhas talked over the plans for work on radioprotective agents with Kniseley, Edwards, and myself. Hayes was not available. We are planning next week to meet with Dr. George Kallman and expect that he will be able to give us further information of the availability of the material labeled with either sulfur-35 or selenium-75. Yuhas has been in touch with Dr. Rothe and will try to get from him further information about the effectiveness of the selenium compound as a radioprotective agent. Apparently there is not available any very good information indicating whether very small quantities of the chemical would behave in the same way as larger quantities. We are pretty well agreed that we should first give patients very small amounts of the drug W R 2721 labeled with either the sulfur or selenium tags. We might consider using a stable isotopic label to further reduce the possibility of criticism for giving this material to human beings who do not have any opportunity to benefit from it.

We decided that the initial research team probably should include Edwards, Yuhas, Hayes, Kallman, and Comas, assuming that all are willing to participate. Edwards would take the main responsibility for the clinical tests. Yuhas would be a very important member of the team since he knows the most about the subject at hand, but could not take direct responsibility for the clinical procedures. Publications, if and when they develop, would have senior authorships determined on a mutually agreeable basis, perhaps rotating among those members who play the largest part in the work.

Yuhas is collecting information that will be helpful in writing an IND and a proposal for human application.

We also talked about the desirability of having some kind of a working meeting relating to applications of radiosensitizing and radioprotective agents to clinical radiotherapy. A tentative time for this meeting in Oak Ridge would be in the fall of 1972. We know that a somewhat broader meeting on basic radiobiology related to therapy is being planned by Dr. Herman Suit, who has recently moved to Boston from the M.D. Anderson Hospital. There is also presumably some kind of meeting of this sort planned by Dr. William Powers. We do not know exactly what it may consist of. The meeting we have in mind would preferably be for working scientists rather than as a means of communicating to a wider scientific audience in attendance. However, it might be desirable to have the meeting open to all who wish to attend. We think it would be desirable to try to publish the results of the meeting if this could be done in some fairly efficient and inexpensive way. Perhaps papers brought to the meeting could be reproduced in some fashion that would not require retyping or setting up in type. Dr. Storer agreed to call Dr. Goldstein in the Division of Biology and Medicine and see if the AEC could finance such a meeting. If not, we might try to get an application in to NCI by February 1st, although this would be a rather rushed effort.

We also made tentative notes on an application to our human studies committee for this work and the accompanying notes may serve as a starting point for this document.

1030428

G. A. Andrews
Gould A. Andrews

K: C 1-10-7.

INTRA-LABORATORY CORRESPONDENCE
OAK RIDGE NATIONAL LABORATORY

To: G.A. Andrews, C.L. Edwards, R. Kniseley, R. Hayes, F. Comas,
G. Kollman, P. Nettesheim & File

From: J.M. Yuhas

Subject: WR-2721 Studies Relating to Radiotherapy

In order to minimize confusion in my own mind, I have tried to summarize our agreements and plans made during the recent visit of G. Kollman.

P. Nettesheim, G. Kollman, and myself will collaborate on two studies: the distribution and metabolism of 35-S-labelled WR-2721 in mice bearing a transplantable lung squamous cell carcinoma, and the subcellular distribution of 3-H-labelled WR-2721 in a variety of cells as determined by electron microscopic radioautography. The former studies will complement the radiotherapy experiments in this tumor system, and will be performed in Philadelphia on mice supplied by Oak Ridge. The latter studies will be performed locally with isotope supplied in the near future by G. Kollman.

Some corrections should be made regarding the information on the status of WR-2721 studies in humans:

1. WR-2721 has not been given to humans either orally or intravenously,
2. the Army does not plan to give the drug IV, but the PO studies are imminent, as usual,
3. WR-638 ($\text{NH}_2\text{CH}_2\text{CH}_2\text{SPO}_3\text{H}_2$) has been given orally (multiple pills spread over a day) to a highest total daily dose of 5-7 g (100 mg/kg)
4. WR-2823 ($\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{SPO}_3\text{H}_2$) will be tested IV in the near future (this drug has apparent alpha adrenergic blocking activity)

Bill Rothe (Div. Med. Chem., WRAIR) supplied this information, but could not off the top of his head straighten out the question of selenium analogues. A visit to Washington, which I contemplate in the near future, should resolve this.

1030429

The human studies we discussed included those which we have outlined earlier and a study of the ability of human tissues to metabolize WR-2721 in vitro. Since this study can be conducted without isotope, it would appear that this could and should (Kollman) be done in Oak Ridge. No final agreements were made regarding these studies. Two points were raised: the feasibility of doing the experiments and the availability of the isotope. The expertise at ORAU obviously would make the experiments feasible, but the supply of isotope would appear to be a limitation. Kollman agreed to supply limited quantities of the isotope but expressed doubt that he could meet the requirements. If we are to continue serious consideration of these studies, an alternate source of isotope must be considered. Two possibilities appear logical: Oak Ridge itself or the sub-contractor used by the Army. If time were available within the Oak Ridge group, this would be the most convenient and reliable source. Alternatively, Bill Rothe suggested that their contractor could build the isotope, possibly at the expense of the Army, depending on the amount required and the state of their budget.

Lastly, we failed to discuss the possible Oak Ridge meeting on radio-protective and radiosensitizing drugs. I am hurrying to prepare a rough draft of a proposal to the NIH; for submission by February 1. This will be forwarded shortly.

I will travel to Philadelphia in February to discuss further plans with G. Kollman. Perhaps a more final arrangement could be made at that time regarding the source of the isotope for the human studies.

1030430

Excerpted from minutes of the 19 December 72 meeting:

Proposal No. 20 - "Use of Radioprotective Drugs in Radiation Therapy: Phase I Studies -- The metabolism of ^{35}S labeled S-2-(3-aminopropyl-amino) ethyl phosphorothioic acid in humans," - Edwards, Yuhas, Washburn, Comas.

This proposal was discussed especially from the point of view that the initial patients would be volunteers who would have nothing to gain from the procedure and would need to be fully informed of this. It was pointed out that no enzyme measurement or tests of kidney or liver function were planned according to the proposal; Dr. Edwards agreed that the latter, at least, should be included. There was a question about whether a patient might be used more than once, perhaps at different dose levels, and would this be appropriate? Edwards said that because of our small number of available patients, we would like to do this in some cases. The committee's view was that repeated studies in the same patient should not be prohibited, but that due care should be given to the implications of this in each patient, both for the scientific study and for the stress or inconvenience to the patient.

The committee expressed general approval of the project in the proposal but at Dr. Edwards' suggestion, withheld specific approval pending submission by mail of new version of the proposal including the above points and also samples of consent forms and statements of the information to be given to patients, including the specific number of blood samples, etc., required.

Please advise co-investigators.

1030431

STATUS REPORTS

Dec. 11, 1973



PROPOSAL #20

Review of toxicity data revealed ambiguities regarding LD₅₀ in mammals. Before proceeding with the proposal and specifically before submitting application for FDA IND exemption, we have elected to repeat part of the evaluation of the toxicity in two species of animals. New evidence exists to suggest the doses needed for radioprotection and the toxic doses may be significantly lower than previously thought; both may be related to the body surface area rather than body weight. Thus for larger mammals such as man the toxic and therapeutic doses expressed as mg per kg will be different order than that seen in mouse.

Both aspects of this question are being tested..the radioprotective dose in rats or rabbits and the toxic dose in pure bred beagles. Until these data are collected and analyzed we cannot make application to the FDA. An amended proposal will be submitted to this committee at such time as the FDA application is prepared.

In the meantime Dr. Washburn has completed studies on the distribution of ³⁵S-labeled WR-2721 in tumor bearing mice and rats. A manuscript is in preparation shows a lower concentration of the labeled chemical in tumor compared to normal tissues in three of the four models.

PROPOSAL #23

There has been no testing of human subjects under this protocol and we have received no communication from the principal investigator regarding this proposal.

Recommend: This proposal should be inactivated.

PROPOSAL #24

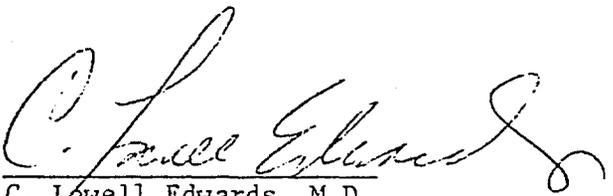
There has been no further correspondence with the student who was acting as liaison between ORAU and the group at Vanderbilt and there is no further interest in this project.

Recommend: The proposed study should be declared inoperative because of lack of activity.

PROPOSAL #25

No patients have been tested with this nuclide and there has been no further contact with Dr. Myers regarding the proposed study.

Recommend: The approval for this study be continued over one more year after which it could be suspended for lack of activity.


C. Lowell Edwards, M.D.



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

IND 13,867

MAR 5 1981

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Rec. 3-16-81

C. C. Lushbaugh, M.D.
Medical and Health Sciences Division
Oak Ridge Associated Universities
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

This is in reply to your letter dated November 5, 1980 in which you informed this office that Medi-Physics, Inc. has modified their Indium In 111 labeling to indicate that the product is no longer being supplied as a radiopharmaceutical but rather as a radiochemical.

This Agency does not consider the Indium 111 as supplied by Medi-Physics, Inc. to be in compliance with applicable federal regulations regarding drugs for use in humans. By informing you of the change in status of this product and in requesting your acknowledgement of this change, Medi-Physics, Inc. is transferring the burden of responsibility for the use of this "radiochemical" in humans from the manufacturer to the user.

In order to continue use of this product in humans, it is required that you submit a commitment to perform adequate quality control tests on the final drug product according to current U.S.P. methodology in order to be in continued compliance with federal regulations.

Should you not agree to supply the commitment, your Notice will be terminated on the basis of 21 CFR 312.1(d)(3) (substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use).

Please respond to this letter within ten working days.

Sincerely yours,

William J. Gyrfas

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

Dr. Nümer

1030433

Oak Ridge
Associated
Universities

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

Medical and
Health Sciences
Division

March 18, 1981

Dr. William J. Gyarfás
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Department of Health, Education, and Welfare
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Gyarfás:

Thank you very much for your recent letter in which you request from our radiopharmaceutical group to make a commitment to perform acceptable quality control tests on Indium-111.

When I first read your letter, I was somewhat puzzled by your reference to my letter (November 5, 1980) in which I informed you about Medi-Physics changing Indium-111 from a radiopharmaceutical to a radiochemical. To my recollection, I have never written the letter you are referring to. I also was puzzled by the IND Number (13,867) on the top of your letter. According to our records IND #13867 has been assigned to ¹¹¹C-labeled aminocyclobutanecarboxylic acid (¹¹¹C-ACBC), and we do not have an IND or an IND number for Indium-111 or radiopharmaceuticals labeled with this radionuclide.

In spite of this slight confusion, I am happy to inform you about ORAU's research activities involving Indium-111. The ORAU/ORNL Committee on Human Studies had approved Indium-111 for a comparative study to evaluate both Indium-111 and Gallium-67 as tumor-scanning agents on December 19, 1972. The studies were done under an IND that had been filed with the FDA by New England Nuclear. The results of the study indicated that Gallium-67 was a better tumor-scanning agent than Indium-111, and no patients have been scanned with Indium-111 in this institute since July 24, 1974. For your information I am enclosing copies of an abstract and a research report on our experience with Indium-111. The project was placed on an "inactive status" on July 10, 1978; and we have no intentions of using Indium-111, either as a tumor-scanning agent or a label for platelets or granulocytes.

Please let me know if I can be of further help to you.

Sincerely,


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

1030434



ORAU-123
Distribution Category UC-48

1973 RESEARCH REPORT

for year ending
December 31, 1973

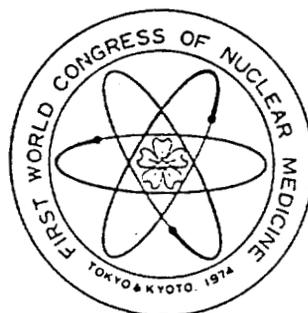


Medical Division
Oak Ridge Associated Universities

1030435

Recent Advances in Nuclear Medicine

Proceedings of
the First World Congress of Nuclear Medicine
Sept. 30–Oct. 5, 1974, Tokyo & Kyoto, Japan



The First World Congress of Nuclear Medicine

1030436

OEAU-ORNL HUMAN STUDIES COMMITTEE

Project Title: Comparison of Indium-111 and Bismuth-206 with Gallium-67
as Tumor-Scanning Agents

Investigators: C. L. Edwards (at another institution)
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 Comparison of Indium-111 and Bismuth-206
with Gallium-67 as Tumor Scanning Agents

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

Karl F. Hübner

Senior Investigator

1030437

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: Committee on Human Studies
Medical Division
Oak Ridge Associated Universities

Date: December 19, 1972

Senior Investigators: Oderr, Charles

Co-Investigators: Morris, A. C.

Edwards, Lowell

Berger, James

Title of Project: Use of External Gadolinium-153 Source for
Timing of Parts of Cardiac Cycle

I. Objectives of Experiment:

To show that ^{153}Gd can be used in a non-invasive technique to record beginning and end of significant parts of the cardiac cycle, notably the left ventricular ejection time (LVET).

We are actually measuring the blockage of gamma rays from the ^{153}Gd by the bolus of blood as it passes through the left ventricle.

Data regarding the usefulness of the LVET is accumulating in the literature, but it will not be a part of our project to study significance, merely to show that the figure can be obtained by a simple non-invasive technique. (Whether LVET is more or less than 0.4 sec seems to be of increasing importance.)

1030438

II. Methods of Procedure:

1. Subjects will lie supine on table or bed while a brief period of heart function, as revealed by densimetry, will be recorded.
2. Normal or near normal subjects from standpoint of heart functions.
3. Only single sessions anticipated for normal subjects; or not more often than three month intervals.
4. Subjects to be selected by Dr. Lowell Edwards.
5. The patient or subject will have a portable chest radiograph in bed (+ 20 MR) from which the correct position for placement of the ^{153}Gd source will be determined.
6. The position of the protected ^{153}Gd is fixed by strong magnets which are attached to it's container.
7. The portal is closed until the actual time for the recording to begin. Remote control for opening and closing of the portal is provided.
8. Studies will be carried out by Dr. Oderr and Mr. Morris.
9. No fluoroscopic studies will be needed.
10. The upper time limit will be signaled by a bell timer.
11. The LVET will be measured by hand from the strip chart record.

III. Possible Hazards and Their Evaluation:

No acute hazards are foreseen. There will be a skin dose to a small area of the back (about one inch diameter) of about 43 mr/min. Most sessions will be limited to about 2-5 minutes. None will exceed five minutes (1/5 roentgen) This will be radiation of \pm 100 KV quality (^{153}Gd with its lower KV components filtered out)

I suggest that he be told that "we have a simple test which we think will be useful in the care of very ill cardiac patients. That the information may help in their recovery from heart attacks."

"There are no more hazards to you that there would be in fluoroscopying your heart. The actual radiation will only be less than half as much."

IV. Radioisotopes and New Drugs:

Not applicable.

1030439

V. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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	_____	Investigator
	_____	Investigator
	_____	Investigator
	_____	Investigator

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

_____ Chairman

Date: _____

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Charles Oderr Ident. No. 23

Project Title Use of External Gadolinium-153 Source for Timing of Parts of
Cardiac Cycle

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

The risks seem almost exclusively limited to the radiation dose from the procedure.

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:

The committee did not go in much depth into any evaluation of the diagnostic information to be obtained from this procedure. The committee is relying on Dr. Edwards to select patients in whom the slight radiation dose will not be too high.

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

A suitable consent form should be appended to the application.

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

Standard follow-up.

5. Other committee comments:

Approve X

Gerald Andrews
Chairman of Committee

Disapprove _____

19 Dec. 72
Date

To inactive file Dec 73

1030441

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 19, 1972

Principal Investigator: Dr. H. Earl Ginn, Chief
Nephrology Division, Vanderbilt University
Dr. Maselyn Freeman
Professor Psychology, Vanderbilt University

Title of Project: Toxic Factors in Uremia: Toward a Rationalized
Design of Dialyzers and Alternate Modes of Therapy

I. Objectives of Experiment:

We request that patients from the Medical Division of Oak Ridge Associated Universities be utilized as an adjunct to the aforementioned project. Such patients would be used as a control group to provide data on other patients with chronic and terminal illnesses.

II. Methods of Procedure:

We propose to test the patients only in the area of Human Performance Analysis. It is hoped that patients chosen will be those with a chronic illness, of a nature that is as serious as chronic nephritis and terminal renal failure so that patients in the experimental protocol and control groups will be closely comparable. The patient will be asked to complete simple learning tasks, simple arithmetic problems, and work motor-skill tasks such as map tracing (connecting dot patterns). The patient is timed during these events so that the investigators can reveal any changes in patterns of achievement in hospitalized patients in the ORAU Medical Division, as contrasted with the patients under the Renal Dialysis Program, and normal individuals.

III. Possible Hazards and their Evaluation:

No hazards.

IV. Radioisotopes and New Drugs:

No radioisotopes or drugs.

V. Responsibility of Senior Investigator:

Patients are requested from the Medical Division under the stipulation that they will be fully informed of the project and their purpose in the program.

1030442

Starting Date:

Signatures

_____ Investigator

_____ Investigator

_____ Investigator

_____ Investigator

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Samuel Andrews Chairman

Date: 19 Dec 72

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator H. Earl Ginn Ident. No. 24

Project Title Toxic Factors in Uremia: Toward a Rationalized Design of
Dialyzers and Alternate Modes of Therapy

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

The only risks would appear to be psychological.

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:

This seems a worth while collaboration with the Vanderbilt research group.

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

No comment was made on consent forms.

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

According to standard procedures.

5. Other committee comments:

Approve X

Genel Andrews
Chairman of Committee

Disapprove _____

19 Dec. 72
Date

1030444

To inactive file - never activated
Dec '73

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date 19 Dec. 72

Principal Investigator: C. L. Edwards

Co-Investigators: W. G. Myers

R. L. Hayes

G. A. Andrews

Title of Project: Clinical Testing of Sr-85m as a Bone Scanning Agent

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.

Title of Project: Clinical Testing of Sr-85m as a Bone Scanning Agent

Ident. No. 25

V. Responsibility of Principal Investigator:

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

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

Starting Date _____

Signatures: [Signature] Principal Investigator

[Signature] Co-Investigator

W.M. L. MURPHY M.D. "

[Signature] "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature [Signature]

Title Chairman

Institution ORAU Medical Division

Date 19 Dec 72

1030446

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

December 19, 1972

Principal Investigator: C. L. Edwards

Co-Investigators: William G. Myers
R. L. Hayes
G. A. Andrews

Title of Project: CLINICAL TESTING OF SR-85m AS A BONE SCANNING AGENT

I. Objectives of Experiment:

The objective of this study is to test Sr-85m as a bone scanning agent in patients with known bone tumors.

II. Methods of Procedure:

Approximately 20 patients with known malignant tumors and known or suspected metastatic disease of the bone will be given up to 30 micro-curies of Sr-85m per kg body weight (~ 2 mCi per patient) by intravenous infusion. Blood samples will be drawn at 10 minutes and at 4 hours to confirm the observation of others regarding the dynamics of intravenously administered isotopes of strontium. Scans will be made on the Anger camera and the whole-body scanner. Where possible these scans will be compared with subsequent scans made with ^{18}F , ^{85}Sr , or Tc-99m polyphosphate.

1030447

III. Possible Hazards and their Evaluation:

The radiation dose resulting from this procedure is quite acceptable:

	ESTIMATED RADIATION EXPOSURE (Rads per mCi of Sr 85m)		
	<u>Sr85M</u>	<u>Sr85</u>	<u>Total</u>
1. Total Body (assuming uniform distribution and no excretion)	0.009	0.046	0.055
2. Total Body (30% uniformly distributed with 12 hr biological half-time, 70% in bone with very long biological half-time)	0.008	0.032	0.040
3. Skeleton (same assumption as (2) above)	0.024	0.10	0.124

Stable strontium (^{84}Sr) will be present in each dose to the extent of 3 μg Sr/kg body weight. The preparation procedures will be tested to assure a product that is sterile and pyrogen free before administering any to humans. Only sterile and pyrogen free reagents will be used. The final product will be filtered through a disposable 0.22 micron Millipore filters into a precapped, sterile vial. Because of the isotopes short half-life it will not be possible to test the final product for sterility and pyrogenicity prior to administration. The ^{84}Sr used to produce the $^{85\text{m}}\text{Sr}$ will be in each case from the same batch of ^{84}Sr (from ORNL) and will have been tested for sterility and nonpyrogenicity in prior dry runs to assure its quality. If the patient develops a febrile or other reaction after a dose, some of the same batch will be tested to determine if the reaction was due to the drug.

IV. Radioisotopes and New Drugs:

This is a new isotope of strontium. An IND exemption (#9020)* has been filed with USFDA since July 1972, and we have received authorization to proceed with the investigation by the Isotope Committee of ORAU.

V. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject 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.

* Appendix A

The subjects will be patients selected on the basis of having a known malignant tumor with a presumption of skeletal metastasis. One senior investigator, a mature scientist with a well-established reputation in Nuclear Medicine, has however indicated a desire to receive a dose.

A thorough explanation of the procedure will be given to each patient before he receives a dose of the isotope. A copy of the consent form is attached as Appendix B.

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Consent for Experimental Test - Bone Scanning with Sr-85m

I have talked with _____ about the proposed test to be given _____. The following points were covered in our discussion and it is my impression that he is informed that:

1. This is an experimental procedure using a new radioactive isotope of Strontium which gives off less radiation but chemically behaves the same as the standard isotope (Sr-85) used for making bone scans.
2. We will be taking blood on at least two occasions and that he will be scanned with our equipment for as much as two hours.
3. We wish to follow this test with a similar test using either Sr-85, F-18, or Tc-99m polyphosphate for comparison.
4. No toxic effects are known or expected at the doses being studied.
5. The test is done for the purpose of developing the test rather than his own immediate benefit, and
6. His refusal will not jeopardize his receiving other benefits from the clinical services of ORAU.

Date

Physician

Patient's Name

Hospital No.

1030450

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: Bone Scan (pictures made with radioactive isotopes)
made with Strontium 85m.

(State nature of test)

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: _____

1030451

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. L. Edwards Ident. No. 25

Project Title Clinical Testing of SR-85m As a Bone Scanning Agent

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

Risks are very small and the benefit of a new diagnostic agent justifies them.

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:

Committee thought the proposal was very well worked out and refers back to it.

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

The consent forms as presented are satisfactory.

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

Standard follow-up.

5. Other committee comments:

1030452

Approve X

Disapprove _____

Donald Andrews
Chairman of Committee

19 Dec 72
Date

Dec 11, 1973: no communication from investigator.

A-

IND 9020

75

INVESTIGATIONAL NEW DRUG APPLICATION

FOR USE OF STRONTIUM-85m

Medical Division, Oak Ridge Associated Universities

Oak Ridge, Tennessee

June 1972

1. NAME OF DRUG: STRONTIUM-85m to be administered by intravenous infusion.

2. COMPONENTS:

- a. Strontium-85m
- b. Sodium chloride
- c. Sodium nitrate
- d. Benzyl alcohol
- e. Water

3. QUANTITATIVE COMPOSITION (per dose):

- a. Strontium-85m: up to 30 μCi $^{85\text{m}}\text{Sr}/\text{kg}$ body weight.
- b. Stable strontium (as chloride/nitrate): up to 3 μg Sr/kg.
- c. Sodium chloride: \sim 30 mg per dose.
- d. Sodium nitrate: up to 4 mg per dose.
- e. Benzyl alcohol: \sim 30 mg per dose.
- f. Water: 2-3 ml per dose.

4. SOURCE OF NEW DRUG SUBSTANCE:

Enriched strontium-84 (supplied by Oak Ridge National Laboratory as nitrate with the following isotopic abundance: ^{84}Sr , 97.63%; ^{86}Sr , 0.53%; ^{87}Sr , 0.22%; and ^{88}Sr , 1.61%) will be activated (^{84}Sr , γ , $^{85\text{m}}\text{Sr}$) in the Oak Ridge Research Reactor for approximately 30 minutes and then prepared for intravenous administration.

5. METHODS, FACILITIES AND CONTROLS:

The activated strontium-84 nitrate (see 4) will be dissolved in normal saline

1030453

containing 0.9% benzyl alcohol (Travenol Laboratories, Inc., Morton Grove, Ill.). After adjustment to physiological pH (with reagent grade sodium hydroxide or hydrochloric acid, if necessary) the solution will then be filtered through a disposable 0.22 micron sterile Millipore filter (Millipore Corp., Bedford, Mass.) into a precapped sterile vial. All glassware used will be presterilized. Each batch of strontium-85m will be given a batch number and all particulars as to its preparation and use will be entered into a master log book. Prior to administration of strontium-85m to humans one or more trial runs will be made to assure that such preparations will meet the United States Pharmacopeia requirements for sterility and nonpyrogenicity. These trials and all subsequent preparations for human use will be made from the same stock of enriched strontium-84 detailed in section 4.

Each batch of strontium-85m will contain minor amounts of 64-day strontium-85 from ^{84}Sr , $n\gamma$, ^{85}mSr , γ , ^{85}Sr interactions. Since the activation time will be short (30 min) and since the half-life of strontium-85m is also short (68 min), the level of strontium-85 contamination will be quite low at the time of administration. At the termination of the reactor activation period each millicurie of strontium-85m will be associated with approximately 0.5 μCi of strontium-85. It is anticipated that the strontium-85m doses will be administered within approximately 2 hours after the withdrawal of the activated strontium-84 from the reactor. This will result in an increase of the strontium-85 contamination level to approximately 2 μCi ^{85}Sr per mCi of ^{85}mSr . We estimate that at this level of contamination for a dose of 30 μCi ^{85}mSr /kg body weight, the strontium-85 contribution to the radiation dose for a patient will be: (1) total body (uniformly distributed, no excretion) 0.046 rads; (2) total body (30% uniformly distributed - 12-hr biological half-time, 70% in bone - very long biological half time) 0.032 rads; (3) skeleton (same assumptions as (2)), 0.10 rads. The radiation dose from strontium-85m itself will be: (1) 0.009 rads, (2) 0.008 rads, and (3) 0.024 rads. The patient radiation dose to be expected from this radiopharmaceutical is thus considered to be well within acceptable levels.

Because the strontium-85m is to be produced by neutron activation of strontium-84 nitrate, a small amount of stable strontium and nitrate ion will necessarily be administered with the preparation. The amounts involved (see section 3) are not considered to constitute any hazard. In the rat the intravenous minimum lethal dose for strontium chloride is reported to be 400 mg/kg and the LD₅₀ for intraperitoneally administered strontium nitrate 540 mg/kg (The Merck Index, 8th edition, 1968).

6. STATEMENT ON INFORMATION AVAILABLE TO SPONSOR:

a. Preclinical Studies.

Strontium-85m has physical properties that make it the ideal gamma-emitting nuclide among the 15 radionuclides of strontium for some in situ and in vivo applications. It decays with 67.7-min half-life to 64.0-day ^{85}Sr in

1030454

-3-

86% of the disintegrations, and by electron capture directly to ^{85}Rb in 14%. The 85% of the 231-keV gamma rays and 14% of 150-keV gamma rays have conversion coefficients that do not exceed a few percent.

Greatly reduced radiation exposures would follow administration of ^{85}mSr instead of ^{85}Sr , or even of 2.81-hr ^{87}mSr , when these gamma-emitting nuclides are used for in situ studies of bone diseases. The 1,360-fold shorter half-life of ^{85}mSr assures that not more than 2 μCi of residual ^{85}Sr remains after administering 1 mCi of ^{85}mSr soon after production (see section 5).

In studies performed by W. G. Myers, University Hospital, Columbus, Ohio (at the Medical Division, Oak Ridge Associated Universities and in cooperation with Oak Ridge National Laboratory) uptake of ^{85}mSr by healing fractures in rat femurs occurred rapidly when studied with a scintillation camera. Since the half-thickness of the gamma rays in lead is less than 1 mm, a 4,000-hole collimator gave excellent resolution. Calculations reveal 58% photopeak efficiency in the 0.5-in.-thick crystal.

b. Previous Marketing.

The radiopharmaceutical has not been marketed nor previously investigated for human use.

c. Drug Combination.

The radiopharmaceutical is not a combination of previously investigated or marketed drugs.

7. LABEL AND INFORMATIONAL MATERIAL:

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

8. SCIENTIFIC TRAINING AND EXPERIENCE OF INVESTIGATORS:

The investigators are well trained, experienced, and familiar with the problems of clinical use of new radionuclides. Their biographies and curriculum vitae are attached.

9. PROGRESS OF THE INVESTIGATION:

The progress of the study will be monitored by the investigators listed. The clinical work will not be started until it has been approved by the Committee on Human Studies of ORAU and ORNL.

1030455

10. CLINICAL STUDIES:

The proposed studies are essentially Phase I and II clinical trials involving fewer than 20 patients with known malignant tumors and known or suspected metastatic disease of the bone. A single exception may be allowed in that one of the senior investigators has expressed a desire to receive a dose of the material; he is a mature scientist near retirement age with extensive experience and a well-established reputation in nuclear medicine.

Because the dynamics of intravenously administered isotopes of strontium given in tracer amounts are well known and adequately publicized, we will do only confirmatory testing of blood disappearance, but no excretion and whole-body retention studies. Instead, data will be collected in the form of photoscans and gamma camera images. Digital data will be recorded and processed by computers to allow quantitative evaluation of the radionuclide concentration in various normal organs and any suspected or known lesions. Where possible, the same patients will be studied later with another skeletal scanning agent such as ^{18}F or ^{85}Sr .

11. The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason for it.
12. The sponsor will notify the investigators if a new drug application is approved.
13. There are no plans for selling this drug; Oak Ridge Associated Universities is a nonprofit corporation, and our interest is only in the basic research phase of this work.
14. We agree to carry out the clinical studies in such a way as to protect the rights and safety of the patients, in conformity with our internal controls and with the policies of HEW, with which we have a "General Assurance" for clinical investigations.

References:

Fleming, W. H., McIlraith, J. D., and King, E. R. Photoscanning of bone lesions utilizing strontium-85, *Radiology* 77: 635 (1961).

Charkes, N. D., and Sklaroff, D. M. Detection of occult metastases to bone by photoscanning with radioisotopes of strontium, p. 235 in *Progress in Clinical Cancer*, I. Ariel (ed.), Grune & Stratton, Inc., New York, 1965.

Myers, W. G. Radiostrontium-85m, *J. Nucl. Med.* 11: 637 (1970) abstr.

1030456

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

AREA CODE 615
TELEPHONE 483-8411

15 January 1973

Dr. William G. Myers
University Hospital
410 West 10th Avenue
Columbus, Ohio 43210

*Dr. W. G. Myers
Some to Bill (73)
to [unclear]
to [unclear]*

Dear Bill:

We recently presented the strontium-85m proposal to Committee on Human Studies and they approved it without any significant questions. We need your signature on the second green sheet to complete the formalities of our records.* Please return the green sheets to us after they are signed. (We listed Lowell Edwards as principal investigator because it is necessary for him to take responsibility for the care of the patients given the new isotope. This does not necessarily mean that he would be senior author on any publication that might arise.)

I don't know just when it will be practical to give some of the ^{Sr}85m to a group of patients. At the moment we are rather pressed with a variety of research activities and paper work involved in trying to keep our funds coming. I do hope that some time within the next few months we can have you visit us and go ahead with the experiments as earlier planned.

We have not heard anything yet about our carbon-11 proposal to NIH, but if it should be funded, we would hope to pick your brains as a consultant on this one also.

I hope all is going well with you. We will look forward to keeping in touch with you.

Sincerely,

Gould A. Andrews, M.D.

GAA/pe

Enclosure

* [unclear]

1030457

MEMORANDUM

TO Committee on Human Studies, Medical Division, ORAUDATE June 2, 1970SUBJECT Tracer Study with ⁶⁷GaCOPIES TO File

This confirms the phone discussions about a tracer study in two human volunteers to determine the rate of removal of a gallium-67 citrate - labeled autologous plasma when injected subcutaneously between the toes.

Reason for Study: This is a pilot study simply for radiation dose calculations. A protocol is in preparation proposing to visualize lymph node drainage after scanning doses of gallium-67 citrate have been injected subcutaneously (the dose in that proposal would be of the order of 2 millicuries total dose given in 0.5 millicurie injections to four sites between the toes).

Dose: In the tracer study 5 microcuries would be given to one site on each foot between the toes. This dose has been approved by the Committee on Human Use of Radioisotopes of the Medical Division (25 May 1970).

Consent: Established procedures for informed consent will be followed.

Approval: Members of the committee without dissenting vote concur in this tracer study.

(Pending Presentation of Proposal)

Gould Andrews

G. A. Andrews, M.D.

To:
C. L. Edwards
John Storer
Mel Koons
B. Nelson
Tom Lincoln
A. B. Brill
Robert Lange

1030458

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator R. L. Hayes (?) Ident. No. 26 ^{ORAU-}

Project Title Tracer Studies on ⁴⁷Sc.

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:

10330459

Approve _____

Chairman of Committee ^{GHA}

Disapprove _____

Date _____

*25 Jan 1975 - withdrawn
never formally presented*

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 Dec 72

Principal Investigator: Dr. K. H. Kim, Physics Dept, N. C. Central Univ.

Co-Investigators: Dr. E. A. Goswitz, Clinical Dept. ORAU

Dr. S. Shafroth, Physics Dept. Univ. North Carolin.

Mr. A. C. Morris, Jr., Instrument Dept. ORAU

Title of Project: "Preclinical Studies of the Application of a
Computer - Interfaced Gamma-Ray Spectrometer
for Dynamic Function Tests."

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

1030460

Title of Project: Preclinical Studies of the Application of a Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests.
 Ident. No. 27

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 Sept '73
 Signatures: K. H. Nelson Principal Investigator
Francis A. Goswitz Co-Investigator
W. Morris "
* Stephen Shyn "
 _____ "
 _____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Donald Andrews

Title Chm.

Institution ORAU Medical Division

Date 19 Dec 72

1030461

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

11 December 1972

Project Title: "Preclinical studies of the application of a computer-interfaced gamma-ray spectrometer for dynamic function tests."

Principal Investigator: Dr. K. H. Kim, Physics Department, North Carolina Central University.

Co-investigators: Dr. F. A. Goswitz, Clinical Department, Oak Ridge Associated Universities; Dr. S. Shafroth, Physics Department, University of North Carolina; and Mr. A. C. Morris, Jr., Instrumentation Department, Oak Ridge Associated Universities.

I. Objectives of Experiment:

This multiprobe counting equipment is being developed for graduate-student training in the Physics Department of North Carolina Central University; Durham, North Carolina. It will serve there to introduce classes to an illustrative kind of medical-nuclear instrumentation, and will provide a means for individual students to conduct thesis experiments. Our plan is to procure and initially test the nuclear-counting and data-processing equipment in one of the physics laboratories at NCCU. When the instrument is operating properly we will conduct experiments using radionuclides in phantoms and small animals. We will also write the programs for controlling our data-reduction processes at that time.

1030462

When the entire system is operating satisfactorily, and at a convenient and appropriate time with the ORAU Medical Division staff, we propose to transport this counting system to Oak Ridge. We would assemble the equipment and operate it in parallel with the routine experiments on the ORAU four-probe counter being conducted by Dr. F. A. Goswitz. If possible, we would use the NCCU equipment alongside the ORAU multiprobe counter for 6 or more studies and make cross-comparisons of the results. After these experiments are completed, the NCCU equipment will be transported back for use in Durham. In this way the clinical utility of this equipment will be verified for its use as a part of the graduate training program at the NCCU Physics Department.

It is our understanding that:

1. The procurement, transport, safe operation, and liability for this special counting equipment is the responsibility of NCCU.
2. All experiments on humans using this equipment will be performed in parallel with the normal four-probe counter experiments done at ORAU, and that no extra doses of radioactive materials will be administered for these special tests.
3. NCCU experiments will not interfere with ORAU's normal, four-probe counting operations.

II. Methods of Procedure:

Procedures used in these studies will be the same as those used in the normal ORAU four-probe counter experiments:

1030463

viz, (1) calibration of counting equipment, (2) positioning of counter probes over organs of interest, (3) injection of a bolus dose of radionuclide, (4) recording of data for approximately 30 min., and (5) termination of study. We would hope to complete 6-12 studies on patients before returning the equipment to North Carolina. This series of studies does not require a particular kind of patient for investigation; the more varied the selection of subjects, however, the better the verification of equipment operation.

III. Possible Hazards and their Evaluation:

We foresee only two remote hazards for this series of tests: (1) electrical shock hazards from the NCCU instrumentation; (2) mechanical injury because of a counting shield falling onto a patient.

Accidents from these hazards will be precluded by:

(a) using 3-wire, grounded power cords on the NCCU equipment, and making ohmmeter checks to insure patency of the ground connection, and (b) performing a careful mechanical check on each detector arm and shield before operation to prevent any malfunction.

IV. Radioisotopes and New Drugs:

Studies using the NCCU equipment will use the same injections of radioactive materials as are used in the current studies with the ORAU four-probe counter. The

1030464

Medical Division most commonly uses ^{198}Au colloid, ^{131}I Rose Bengal, ^{131}I RISA, ^{125}I RISA, $^{99\text{m}}\text{Tc}$, ^{59}Fe , and ^{51}Cr compounds in its four-probe counter Investigations.

V. Responsibility of Principal Investigator:

"Informed Consent" statements are already being obtained from patients being tested with the ORAU four-probe counter. Use of the NCCU equipment is considered to be an extension of these current studies.

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Y. H. Kim Ident. No. 27

Project Title Preclinical Studies of the Application of a Computer -
Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests

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

As stated in the proposal,

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:

The risks are very small and the development of improved medical instrumentation is a justification.

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

Standard Medical Division forms

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

None special.

5. Other committee comments:

None

Approve X

Disapprove _____

Review activated (Jan 75 minutes)
Donald Andrews
Chairman of Committee

19 Dec. 72
Date

1030466

No communication from Investigator. Place in Inactive File
11 Dec 73

CCFY

COPY



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

July 11, 1972

Mr. Walter H. Pattillo, Jr.
Program Director
North Carolina Central University
Durham, North Carolina 27707

Dear Mr. Pattillo:

This is in reply to your letter of June 12, 1972, regarding compliance with Department of Health, Education, and Welfare policy on protection of human subjects.

Responsibility for the protection of human subjects rests with the grantee institution. Therefore, we have no alternative but to ask you to submit a special assurance in connection with Dr. Kim's project, "Pre-Clinical Studies of the Application of a Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests."

Since the testing that will involve human subjects will be performed at the Research Hospital of the Medical Division of the Oak Ridge Associated Universities and that institution holds a general assurance, the requirements for compliance with DHEW policy can be met by submission of an optional special assurance following the format of the enclosed example.

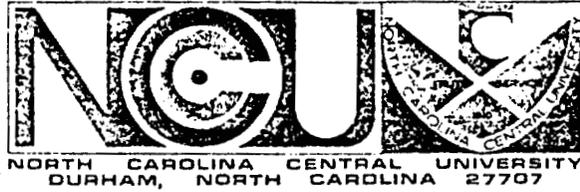
Please let us know if you have any questions. Thank you for your cooperation.

Sincerely yours,

Mark H. Conner, Ph.D.
Institutional Relations Branch
Division of Research Grants

Enclosure

1030467



DEPARTMENT OF BIOLOGY

(Optional special assurance form for a grantee institution carrying out review with the assistance of a committee at an institution with a general assurance).

SPECIAL INSTITUTIONAL ASSURANCE
AND
CERTIFICATION OF REVIEW
OF
SINGLE PROJECT INVOLVING HUMAN SUBJECTS

- (0) The North Carolina Central University will comply with the policy for the protection of human subjects participating in projects or activities supported by grants and contracts made by the Department of Health, Education, and Welfare as described in the Institutional Guide to DHEW Policy on Protection of Human Subjects. This policy requires a group review independent of the investigator or any person having a professional interest in the project in order to safeguard the rights and welfare of those subjects. An initial review of the application for a grant or contract identified as "Pre-Clinical Studies of the Application of a Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests" (Minority Schools Biomedical Support Program, Grant Number 1 SO6 RR 08049-01) submitted by this institution on behalf of Dr. K. H. Kim, Physics Department, was carried out on _____ by the Committee on Human Studies of the Medical Division of the Oak Ridge Associated Universities in accordance with the terms of its assurance to the Department of Health, Education, and Welfare.
- (1) The North Carolina Central University, as the institution to whom the grant or contract is awarded, agrees to take primary responsibility for the protection of human subjects involved in the project or activity regardless of the sites where the work is to be done, and will fully implement the recommendations of the Committee on Human Studies.
- (2) The North Carolina Central University has agreed to continuing review of the project by the Committee on Human Studies of the Medical Division of the Oak Ridge Associated Universities. This review will be implemented in accordance with the terms of the Medical Division of the Oak Ridge Associated Universities' assurance on file with the Department of Health, Education, and Welfare.
- (3) Signature and title of official of grantee institution

Albert N. Whiting
Signature

Chancellor
Title

24 Oct '72
Date

OCT 7 1972

MEMORANDUM

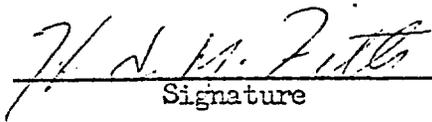
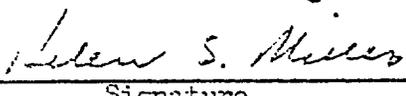
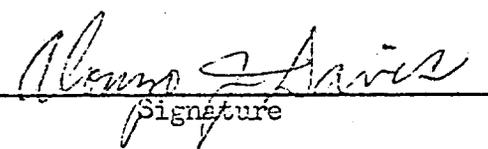
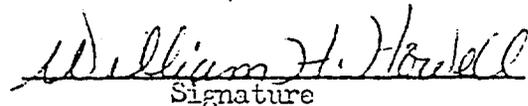
TO: Dr. Leonard Robinson, Vice-Chancellor for Academic Affairs
NORTH CAROLINA CENTRAL UNIVERSITY

FROM: Local Committee on Human Studies, Dr. Howard Fitts - Chairman

RE: Review of Biomedical Project of Dr. K. H. Kim, Physics Department

North Carolina Central University's Local Committee on Human Studies recommends a favorable disposition of the Optional Special Assurance, subject to review by the University's legal counsel, required by the Department of Health, Education and Welfare for Dr. K. H. Kim's Project, "Pre-Clinical Studies of the Application of A Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests" (Minority Schools Biomedical Support Program, Grant # 1 SO6 RR-08049-01).

The signatures, names and titles of the members of the Committee are listed below:

 <hr/> Signature	Professor and Chairman of Health Education Department <hr/> Howard Fitts, Ph.D. - Chairman Name Title
 <hr/> Signature	University Physician <hr/> Robert P. Randolph, M.D. - Name Title
 <hr/> Signature	Nursing Department <hr/> (Mrs.) Helen S. Miller - Chairman, Name Title
 <hr/> Signature	Professor and Chairman Psychology Department <hr/> Alonzo Davis, Ph.D. - Name Title
 <hr/> Signature	Sociology Department <hr/> William H. Howell, Ph.D. - Professor, Name Title

Date of Committee Approval September 29, 1972

1030469

(4) Signature and title of official of assisting institution holding general assurance

Edward C. Anderson 1910
Signature

Chairman National Planning
Title

4 Jan 72
Date

OCT 23 1972

MEMORANDUM

School of Law

October 23, 1972

TO: Dr. Leonard H. Robinson, Vice Chancellor for
Academic Affairs

FROM: Daniel S. Sampson *Daniel S. Sampson/m*

RE: Inquiry Concerning Special Institutional Assurance and
Certification of Review of Single Project Involving
Human Objects

In regard to your inquiry may I state that I have talked with both Dr. Pattillo and Dr. Kim with respect to the purpose, goals operation and limits of this project.

It must be realized that my opinion of the probability of liability on the part of this institution is based on the assumption that the following procedures will be followed:

1. That the Institutional Guide to DHEW policy on the Protection of Human Subjects will be followed.
2. That the rights of patients to confidentiality with regard to the project will be respected.
3. That at no time should the activities of the investigator and his staff cross over the line from technical investigation into the practice of medicine.
4. That the subjects of this investigation (or someone qualified to consent for them) give their consent in writing with full knowledge of the fact that while care will be taken for the protection of human subjects, the project is experimental in nature and there may be residual risks of injury to them beyond the level of accumulated scientific knowledge at this time.
5. That all contact with the patient be external in nature and carried out with the supervision and approval of a licensed physician with expertise in the areas of the investigation.

It is my opinion that if the above guides be followed the risk of liability is minimal.

I understood Dr. Kim to state that the above guides and assumptions will be followed. This opinion is further buttressed by

1030471

Dr. Leonard H. Robinson
Page 2
October 23, 1972

the fact that, I believe, the probability is quite high that a court would conclude that Dr. Kim was an independent contractor or independent operator and not an agent or servant of the school in the sense that the school would be subject to liability for his misfeasances. I cannot be sure that this would always be true, but the probability is that in situations such as this the cases would so hold.

If you should wish to talk to me further about this, I shall be happy to comply.

1030472

C. PROJECT IN THE PHYSICS DEPARTMENT

PRE-CLINICAL STUDIES OF THE APPLICATION OF A COMPUTER-
INTERFACED GAMMA-RAY SPECTROMETER FOR DYNAMIC FUNCTION TESTS

Principal Investigator: K. H. Kim, Associate Professor

DESCRIPTION OF PROJECT

The objectives of this proposal are: two-fold:

- a) To conduct a pre-clinical study of the applications of a computer-interfaced multi-probe gamma-ray spectrometer system for dynamic function tests.
- b) To train science and premedical students and provide them with background and research experiences in the application of nuclear spectrometry to diagnostic medicine.

A method of externally counting the radiation from labeled nuclides within the body is a very useful technique, particularly when dynamic functions of various organs are to be tested. Such a system should however, have the capability of analyzing data while the tests are being performed if it is to have meaningful clinical applications.

A computer interfaced multi-probe gamma-ray spectrometer system will be built. It will be capable of monitoring time-dependent information on the localization and dissipation of labeled radionuclides among the organs in question and of measuring any changes in gamma-ray spectrum due to the scattering of the original photon by hydrogenous matter within the body.

Studies on the various physical parameters affecting changes in the spectrum will be carried out using phantom models and an IBM-360. We will study such physical parameters as the size of the phantom models, the kinds of radionuclide used, the level of the source intensity, combinations of more than one nuclide such as Cr^{51} - Fe^{59} coupling and the focusing depth of the collimator assemblies. Heavy student participation in setting up equipment, instrument testing and computer programing is planned throughout the program.

Summary of the Preliminary Study

During the summer of 1971, a preliminary study was conducted on the clinical application of the computer-interfaced multi-probe gamma-ray counter system with the support of the Medical Division of Oak Ridge Associated Universities, Oak Ridge, Tenn. The system was used primarily to acquire information on the distribution of a labeled compound, Au^{198} in a colloidal form, within the body of patients when it was administered into the vein.

1030473

The radionuclide was intravenously injected into each patient, and the rate of accumulation of the nuclide in various parts of the body was observed. To do this, four detector probes were positioned on the body surface over the liver, spleen, heart and sacrum respectively. The probes detected photons emanating from each of the four areas, and, by adjusting the proper time interval of the readout system, one was able to read the histogram of accumulation of the compound in each organ under study. It was also observed that each probe recorded a quite different pattern depending on the position, as well as on the disease of the patient in question.

A total of 15 clinical tests were performed using A_{u}^{198} and a dose of 0.1 millicurie per sq. meter of body surface area was administered. All patients studied had a malignant hematologic disease. Study on the blood clearance time, uptake ratio of colloids in liver, spleen and in the bone-marrow have been investigated and compared with the whole-body scan. It demonstrated more clearly the dynamic processes occurring in the distribution of the radiocolloid, particularly in reference to clearance from the blood and rate of concentration by the liver, while spleen and marrow concentrated the colloid quickly. One advantage of this method is that it requires far lower doses than conventional techniques, such as rectilinear scanning method.

Although the results of the study are very suggestive, they are only preliminary, and much more work needs to be done before such technique can be applied in clinical situations. An improved detector is needed; one that is more direction sensitive and can detect the effects of the scattering of photons within the body. A new computer program, which can handle various physical parameters, is also needed. Such improvement will be best worked out by conducting research based on the simulated human phantom models of various sizes and using radionuclide of different energy ranges.

A final clinical test will be performed at the research Hospital of the Medical Division at the Oak Ridge Associated Universities in collaboration with the medical staff members.

The following persons have agreed and will serve as consultants in this project:

- a) Mr. Chet Morris, Jr., Senior Scientist, Oak Ridge Associated Universities Medical Division, Oak Ridge, Tenn.
- b) Francis Goswitz, M.D., Senior Clinician, Oak Ridge Associated Universities Medical Division, Oak Ridge, Tenn.
- c) Dr. Steve Shafroth, Professor, Physics Department, University of North Carolina, Chapel Hill, N. C.

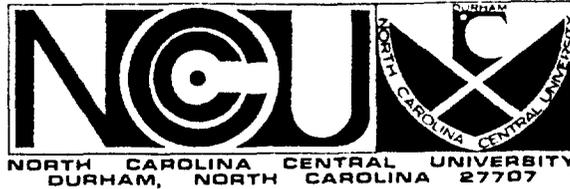
The principal investigator (Dr. Kim) as indicated in the Summary of the Preliminary Study, below, has been developing expertise and procedures primarily through activities at the Medical Division of Oak Ridge Associated Universities, Oak Ridge, Tennessee.

1030474

Continuation Page - 3

The project should be of exceptional value, because of the exposure of participating students to methods of applying modern sophisticated equipment and computers directly to clinical studies. Aspects of this research should provide direct source material for the course in General Physics taught by the investigator to biology and chemistry majors from a biomedical viewpoint.

1030475



November 7, 1972

DEPARTMENT OF BIOLOGY

Dr. Gould Andrews, Chief
The Medical Division,
Oak Ridge Associated Universities
Oak Ridge, Tenn.

Dear Dr. Andrews:

Enclosed are the original and three(3) copies of the Optional Special Assurance required for compliance with DHEW policy in connection with Dr. Kim's project, "Pre-Clinical Studies of the Application of a Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests."

The form has been initiated at North Carolina Central University (NCCU) following a review by NCCU's Local Committee on Human Studies. This form must now be signed by an official of your organization following a review of the project by the Committee on Human Studies.

The completed forms should then be forwarded to Dr. Mark H. Conner (Institutional Relations Branch, Division of Research Grants, DHEW) as indicated on the copy of his enclosed letter(7/11/72). We shall be happy to receive a copy of the enclosed completed form.

If additional information is required by your organization, please do not hesitate to call or write Dr. Kim or me. Thank you for your cooperation in this concern.

Sincerely yours,

W. H. Pattillo, Jr.
Program Director
MSBS(Grant # 1 S06 RR 08049-01)

Tel. 919-682-2171, Ext. 407

Enclosures

1030476



Nov. 27, 1972

(919)682-2171 Ext 451

DEPARTMENT OF PHYSICS

Dr. Gould A. Andrews
Chairman-Committee on Human Studies
Oak Ridge Associated Universities,
Oak Ridge, Tenn. 37830

Dear Dr. Andrews:

This letter, which is long overdue, is to supplement the documents forwarded to you from the Office of the Vice-president for Academic Affairs-Dr. Leonard Robinson-of this University with regards to the Biomedical Support Program supported by the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., under the grant Number 1 SO6 RR-08049-01.

The project under my responsibility within the frame work of the Biomedical Program is to study on the preclinical applications of a computer-interfaced gamma-ray spectrometer for dynamic function studies in Nuclear Medicine.

For dynamic function studies, a set of several scintillations detectors is coupled with minicomputer hardware such as PDP-11/05 through multile mixer input router connected to 1096 ADC. The system will register energy distributions of photons detected over the surface of the patients and the spectrum pattern of any radio-pharmaceuticals will be measured over the energy region of interest. The spectrum pattern should be a very sensitive indicator of how the nuclides are distributed and how much attenuation of photons are involved, particularly when organs under the ribs are to be investigated.

Extensive studies using phantom models will proceed any experimental tests involving human patients or even an animal and I do not foresee the final test before one year from now at the earliest.

However, in order to remove some of the inherent disadvantages associated with the conventional NaI(Tl) scintillation detector system and to achieve a better energy as well spatial resolution in such instrumentations, I believe an entirely different type of detection system should be introduced, particularly for the low energy region. I am very certain a proportional counter of Borkowski type should be seriously considered.

I am planning to include in the project a preliminary study of how actually the proportional counter can be effectively expanded to a larger size in two dimension and how such detector can be applied for practical scanning purposes without a substantial loss in counting efficiency. Mr. Chet Morris has been very kind to arrange all the discussion meeting with Mr. Borkowski's group and I have received a warm encouragement from him and his associate for further support. Again the final test should be performed at the Medical Division of CRAU.

As clearly mentioned in the ruling of the N I H policy, the primary responsibility will be rest on the grantee institution as far as any incident which might arise and

1030477

Copy To Dr. Edwards
11 Dec 72

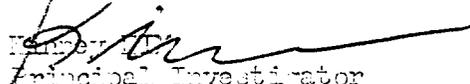
which is directly related with any of the testing of the system involving human studies, however such chance seems to be very remote in view of the fact that such test will be performed and carried out at the Medical Division under the supervision of collaborating physicians. Furthermore any of the test under the project will not require any additional dosage and administration of any untested pharmaceuticals will not be required at all.

The special assurance required by the N I H will certainly be complied with by the grantee institution as outlined in the document. The human studies committee on this campus has already endorsed my project and Dr. Mark W. Conner, Institutional Relations Branch, Division of Research Grant, N I H. should be notified on the outcome upon the endorsement of the assisting institution, the human studies committee of ORAU.

I will surely keep you informed of the progress of the project and I am also seeking the consultations on this project from your staff members, particularly, Dr. Frank Goswitz and Mr. Chet Morris.

My best wishes and the warmest season's greeting to you and all the staff members with whom I have had the pleasure of very valuable working experiences.

Yours very truly


Principal Investigator

RMH/jc

Encl. Summary of project description

Copies to: Dr. Leonard Robinson, Office of the Vice-Chancellor
Dr. Francis Goswitz, Medical Division, ORAU
Mr. Chet Morris, Jr. "

1030478

PRE-CLINICAL STUDIES ON THE APPLICATION OF COMPUTER-INTERFACED GAMMA-RAY
SPECTROMETER FOR DYNAMIC FUNCTION TESTS

Principal Investigator: E. K. HEN, Professor of Physics

DESCRIPTION OF PROJECT

The objectives of this proposal are:

- a) To conduct a preclinical study of the applications of a computer inter-
faced multi-probe gamma-ray spectrometer system for dynamic function tests.
- b) To train science and premedical students and provide them with background
and research experiences in the application of nuclear spectrometry to dia-
gnostic medicine.

A method of externally counting the radiation from labeled nuclides within
the body is a very useful technique, particularly when dynamic functions of
various organs are to be tested. Such a system should however, have the capa-
bility of analyzing data while the tests are being performed if it is to have
meaningful clinical applications.

A computer interfaced multi-probe gamma-ray spectrometer system will be built.
It will be capable of monitoring time-dependent information on the localization
and dissipation of labeled radionuclides among the organs in question and of
measuring any change in gamma-ray spectrum due to the scattering of the original
photon by homogeneous matter within the body.

Studies on the various physical parameters affecting changes in the spectrum
will be carried out using phantom models and an on-line computer such as PDP-
11/05. We will study such physical parameters as the size of the phantom
models, the kind of radionuclide used, the level of the source intensity, comb-
inations of more than one nuclide such as Cr^{51} - Fe^{59} coupling and the focusing
depth of the collimator assemblies. Heavy student participation in setting up
equipment, instrument testing and computer programming is planned throughout
the program.

A final clinical test will be performed at the research Hospital of the Medical
Division at the Oak Ridge Associated Universities in collaboration with the
medical staff members.

MEMORANDUM

TO Dr. G. A. Andrews DATE 5 December 1972

SUBJECT COOPERATION ON DR. KIM'S PROJECT, RECOMMENDATIONS CONCERNING

COPIES TO Dr. Goswitz, Mr. Harmon, file

Dr. Kim and the North Carolina Central University are submitting this grant proposal to DHEW for the design and construction of a multiprobe counting system. If approved, they would eventually use such a system in some of their graduate activities. The development will be completed in Durham, and initial tests will be done there using animal subjects. When these tests are completed, the equipment will be transported here and operated in parallel with some of our four-probe counter studies.

Dr. Kim's request to ORAU is not directed toward doing a large series of studies on some kind of patient abnormality; rather, it is directed toward lending "authenticity" to their project for its acceptance and continued support at NCCU in Durham. After doing some measurements alongside Dr. Goswitz's normal studies here, this equipment, and accumulated data, would be returned to Durham for use in Dr. Kim's department.

I would recommend the following action be taken:

1. This proposal should be brought before the Human Use Committee next week for approval. Afterwards the proposal could be signed by us and forwarded to NCCU.
2. NCCU should agree that their measurements will be performed in parallel with our normal four-probe experiments, and that no extra radioactive doses will be given.
3. NCCU should agree that the transportation, operation, safety, and liability for the special counting equipment is their responsibility.
4. Since this work will require some assistance on our part, NCCU should agree to include cooperating members of our clinical/instrumentation staffs as co-authors on any development paper that might result.

These recommendations should have the concurrence of Dr. Edwards, Dr. Goswitz, and Mr. Harmon.



 A. C. Morris, Jr.

OAK RIDGE ASSOCIATED UNIVERSITIES

INCORPORATED

P. O. BOX 117

OAK RIDGE, TENNESSEE 37830

4 January 1973

AREA CODE 615
TELEPHONE 483-6411

Dr. Mark H. Conner
Institutional Relations Branch
Division of Research Grants
Dept. of Health, Education & Welfare
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Conner:

In compliance with the request by Mr. W. H. Pattillo, Program Director at the North Carolina Central University, I am enclosing the original and three copies of the DHEW Optional Special Assurance required for Dr. K. H. Kim's project entitled "Preclinical Studies of the Application of a Computer-Interfaced Gamma-Ray Spectrometer for Dynamic Function Tests."

The Committee on Human Studies of the Medical Division, Oak Ridge Associated Universities, met on 19 December 1972 and considered Dr. Kim's request. It was approved without modification.

We are looking forward to a collaboration with the NCCU staff on this project.

If there is any further information the ORAU Medical Division can supply, please advise me.

Sincerely yours,


A. C. Morris, Jr.
Senior Scientist

ACM:vrs

cc: Dr. K. H. Kim
Mr. W. H. Patillo, Jr.
~~Dr.~~ G. A. Andrews
Dr. F. A. Goswitz
Mr. J. H. Harmon

Enclosures: DHEW Optional Special Assurance plus 3 copies.

1030481

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: November 28, 1973

Principal Investigator: Francis A. Goswitz, M.D.

Co-Investigators:

Title of Project: Comparison of Indium-111 Chloride and Indium-111 Sulfur Colloid in Evaluation of Bone Marrow Disorders

I. Objectives of Experiment

A. Purpose

The objective is to determine which agent is superior or whether both agents are necessary to evaluate patients with bone marrow disorders or potential marrow abnormalities before and after treatment of their primary disease.

B. Background Information

The marrow can be scanned by labeling the reticulo-endothelial system with radiocolloids (e.g. ^{198}Au) or by labeling the erythron with ^{52}Fe . The ^{198}Au colloid is usually uniform in size but presents a radiation hazard to the liver; $^{99\text{m}}\text{TcS}$ colloid is a larger-size particle and often accumulates in the lung making interpretation between rib and lung uptake difficult. Production problems and a short half-life make ^{52}Fe unavailable for routine use. Iron-59 is unsuitable for conventional imaging. Indium-111, which binds to transferrin, possesses ideal physical and radiobiological characteristics as a tracer. Farrer and associates found selective uptake by bone marrow from ^{111}In -transferrin to be far superior to those of $^{99\text{m}}\text{Tc S}$ colloid in hematologically normal patients (J. Nuc. Med 13: 429, 1972 abstract). Liver and spleen visualized poorly suggesting that ^{111}In was not labeling the reticulo-endothelial system. Non-red marrow of the bones was also poorly visualized. The tracer disappeared from the plasma with a net half-time of about 11 hours, considerably longer than the normal half-disappearance time of 1-2 hours for radioactive iron. There was no incorporation of the tracer into erythrocytes up to 96 hours (certainly some radioiron is utilized normalized by 96 hours), but then it appeared in circulating erythrocytes and leukocytes; white blood cells do not incorporate significant amounts of radioiron (Farrer, American Society of Hematology program, p. 56, abstract 70, 1972).

1030482

Lilien et al (J. Nucl. Med. 14: 184-186, 1973) also felt indium-111 chloride had several properties ideal for marrow imaging and that ionic indium, ^{metabolized} metabolized similarly to iron. When injected intravenously at acid pH, indium binds virtually quantitatively to transferrin and appears to compete with iron for the same binding sites. Reported average plasma half-time disappearance values ranged from 6-10 hours, also longer than radioiron. They suggested that indium is actually incorporated into the metalloporphyrin in the place of iron.

II. Methods of Procedure:

The ¹¹¹In chloride is supplied in dilute hydrochloric acid, approximately 0.03 N HCl from the Oak Ridge National Laboratory or as a radiopharmaceutical from a commercial manufacturer (Medi-Physics, Inc. or New England Nuclear). If the agent is obtained as a radiochemical, the product will be sterilized by autoclaving and Millipore filtration, radioassayed, and then injected intravenously in a dose of 0.5-2 mCi per patient. If it is obtained as a radiopharmaceutical, the compound will be injected as already prepared at its acid pH.

The ¹¹¹In sulfur colloid will be prepared by converting the chloride to the sulfur colloid by the sodium thiosulfate method using the same "Kit" procedure now used in the preparation of ^{99m}Tc sulfur colloid from pertechnetate. If the thiosulfate method fails to provide a satisfactory radiocolloid, we will use the hydrogen sulfide method as developed at Brookhaven National Laboratory (W. Hauser et al: New York State J. Med. 70: 848-854, 1970) or as previously performed by Hayes and his group at the ORAU Medical Division. Pinsky and co-authors (Southern Med. J. Proceedings of Southeastern Soc. N. Med. Meeting November 1-4, 1972) found sulfur colloid prepared by the hydrogen sulfide method to be superior in reticuloendothelial marrow uptake to sulfur colloid prepared by the sodium thiosulfate method.

Total-body rectilinear scans will be performed about 15-60 minutes after injection of the ¹¹¹In chloride. The indium-111 sulfur colloid scan will be done 24 hours after injection of the dose. We anticipate doing 100 scans in patients with a variety of marrow disorders. With our present nuclear medicine staff and their commitments to other studies, the time to accomplish this work would require at least 12 and possibly 18 months.

In 10 patients external organ counting, whole-body retention, and blood samples collected at 1/2, 1, 2, 4, 8, and 24 hours, 5 and 12 days, will be done to compare distribution and disappearance times with the two agents.

III. Possible Hazards and Their Evaluation:

Lilien states that preliminary dosimetry calculations according to Graham indicates a dose of 3.6 rads/mCi to marrow, 4.5 rads/mCi to the liver, and 0.5 rad/mCi to the total body (J. Nuc. Med. 14: 186, 1973). These calculations are based on highly conservative estimates of the biodistribution of indium, studies of which are being undertaken. Indium-111 has a physical half-life of 2.8 days. It decays by electron capture with the emission of two gamma photons, 173 Kev (89% per disintegration) and 247 Kev (94% per disintegration). It is produced by proton bombardment of enriched ¹¹¹Cd at Oak Ridge National Laboratory and supplied to the Medical Division free of cadmium in the carrier-free form.

1030483

The proposed dosage for both indium-111 chloride and sulfur colloid to the patient will be 0.75 mCi/M² body surface area. Both agents will be administered intravenously. Standard man is approximately 1.6 M² so that the total dose injected would be 1.2 millicuries.

No reports can be found in the literature pertaining to the organ distribution of ¹¹¹In sulfur colloid. If it follows the same distribution as ^{113m}In radiocolloid or ^{99m}Tc S colloid, then approximately 80% would distribute to the liver. (Goodwin, Nucleonics, Nov. 1966). He estimates that the radiation dose to the liver is ~0.55 rads/mCi ^{113m}In administered. The biologic half-life is approximately 30 days.

IV. Radioisotopes and New Drugs:

No new radioisotopes or new drugs are requested. No reports regarding the uses of ¹¹¹In sulfur colloid in patients have appeared in the literature to my knowledge, but ^{113m}In colloid has been shown to be an attractive liver and spleen scanning agent. (Goodwin, Stern and Wagner: A new radio-pharmaceutical for liver scanning, Nucleonics, Nov. 1966) (Potchen and Adatepe: Liver and Spleen Scintiscanning with ^{113m}-Indium: A Clinical Pathologic Correlation, Am. J. Roentgenol. 106: 739-744, August 1969).

V. Responsibility of Principal Investigator:

The same ORAU consent form as is required for our other experimental agents will be used in this study to obtain approval from the patient.

Starting Date: January 1, 1974

Signatures: Francis A. Gosserty, M.D. Principal Investigator
_____ Co-Investigator
_____ Co-Investigator
_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Signature _____
Title _____
Institution _____
Date _____

1030484

MEDICAL RADIONUCLIDE COMMITTEE
 Medical Division
 Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Francis A. Goswitz, M.D. PROPOSAL NO. 73-3

DESCRIPTION: Comparison of In-111 chloride and In-111 sulfur colloid in evaluation of bone marrow disorders (Memo of Nov. 28, 1973).

This proposal was considered in two parts. This approval is given for the use of In-111 chloride.

The Committee approves with the following limitations:

Radiopharmaceutical may ~~not~~ be administered to patients under 18 years of age, only if the patient has a malignant hematologic disorder.

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

Other: Radiopharmaceutical may not be used if In-114m is present in an amount that would contribute more than 10% of the In-111 dose.

The Committee disapproves for the following reasons:

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
Berger	<i>[Signature]</i>			12/7/73
Cloutier	<i>[Signature]</i>			12-7-73
Edwards	<i>[Signature]</i>			12-7-73
Harmon			✓	
Hayes	<i>[Signature]</i>			12/7/73
Lushbaugh			✓	

Acknowledgement of Submitter Francis A. Goswitz Date 12/10/73

1030485

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

MEDICAL RADIONUCLIDE COMMITTEE
 Medical Division
 Oak Ridge Associated Universities

PERSON SUBMITTING PROPOSAL Francis A. Goswitz, M.D. PROPOSAL NO. 73-4

DESCRIPTION: Comparison of In-111 chloride and In-111 sulfur colloid in evaluation of bone marrow disorders (Memo of Nov. 28, 1973).

This proposal was considered in two parts. This disapproval is for the the use of In-111 sulfur colloid in humans.

The Committee approves with the following limitations:

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

Radiopharmaceutical may ___ may not ___ be administered to pregnant patients.

Other:

The Committee disapproves for the following reasons:

Additional work needs to be done on the preparation of the sulfur colloid and its distribution and retention in animals.

MEMBER	APPROVAL	DISAPPROVAL	ABSENT	DATE
Berger		<i>[Signature]</i>		12/7/73
Cloutier		<i>[Signature]</i>		12/7/73
Edwards		<i>[Signature]</i>		12/7/73
Harmon			✓	
Hayes		<i>[Signature]</i>		12/7/73
Lushbaugh			✓	

Acknowledgement of Submitter Francis A. Goswitz Date 12/10/73

1030486

Proposal does ___ does not ___ require approval of Committee on Human Studies.

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: November 28, 1973

Principal Investigator: Francis A. Goswitz, M.D.

Co-Investigators:

Title of Project: Comparison of Indium-111 Chloride and Indium-111 Sulfur
Colloid in Evaluation of Bone Marrow Disorders

I. Objectives of Experiment

A. Purpose

The objective is to determine which agent is superior or whether both agents are necessary to evaluate patients with bone marrow disorders -- potential marrow abnormalities before and after treatment of their primary disease.

B. Background Information

The marrow can be scanned by labeling the reticulo-endothelial system with radiocolloids (e.g. ^{198}Au) or by labeling the erythron with ^{52}Fe . The ^{198}Au colloid is usually uniform in size but presents a radiation hazard to the liver; $^{99\text{m}}\text{TcS}$ colloid is a larger-size particle and often accumulates in the lung making interpretation between rib and lung uptake difficult. Production problems and a short half-life make ^{52}Fe unavailable for routine use. Iron-59 is unsuitable for conventional imaging. Indium-111, which binds to transferrin, possesses ideal physical and radiobiological characteristics as a tracer. Farrer and associates found selective uptake by bone marrow from ^{111}In -transferrin to be far superior to those of $^{99\text{m}}\text{Tc S}$ colloid in hematologically normal patients (J. Nuc. Med 13: 429, 1972 abstract). Liver and spleen visualized poorly suggesting that ^{111}In was not labeling the reticulo-endothelial system. Non-red marrow of the bones was also poorly visualized. The tracer disappeared from the plasma with a net half-time of about 11 hours, considerably longer than the normal half-disappearance time of 1-2 hours for radioactive iron. There was no incorporation of the tracer into erythrocytes up to 96 hours (certainly some radioiron is utilized normalized by 96 hours), but then it appeared in circulating erythrocytes and leukocytes; white blood cells do not incorporate significant amounts of radioiron (Farrer, American Society of Hematology program, p. 56, abstract 70, 1972).

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Lilien et al (J. Nucl. Med. 14: 184-186, 1973) also felt indium-111 chloride had several properties ideal for marrow imaging and that ionic indium metabolized similarly to iron. When injected intravenously at acid pH, indium binds virtually quantitatively to transferrin and appears to compete with iron for the same binding sites. Reported average plasma half-time disappearance values ranged from 6-10 hours, also longer than radioiron. They suggested that indium is actually incorporated into the metalloporphyrin in the place of iron.

II. Methods of Procedure:

The ¹¹¹In chloride is supplied in dilute hydrochloric acid, approximately 0.03 N HCl from the Oak Ridge National Laboratory or as a radiopharmaceutical from a commercial manufacturer (Medi-Physics, Inc. or New England Nuclear). If the agent is obtained as a radiochemical, the product will be sterilized by autoclaving and Millipore filtration, radioassayed, and then injected intravenously in a dose of 0.5-2 mCi per patient. If it is obtained as a radiopharmaceutical, the compound will be injected as already prepared at its acid pH.

The ¹¹¹In sulfur colloid will be prepared by converting the chloride to the sulfur colloid by the sodium thiosulfate method using the same "kit" procedure now used in the preparation of ^{99m}Tc sulfur colloid from pertechnetate. If the thiosulfate method fails to provide a satisfactory radiocolloid, we will use the hydrogen sulfide method as developed at Brookhaven National Laboratory (W. Hauser et al: New York State J. Med. 70: 848-854, 1970) or as previously performed by Hayes and his group at the ORAU Medical Division. Pinsky and co-authors (Southern Med. J. Proceedings of Southeastern Soc. N. Med. Meeting November 1-4, 1972) found sulfur colloid prepared by the hydrogen sulfide method to be superior in reticuloendothelial marrow uptake to sulfur colloid prepared by the sodium thiosulfate method.

Total-body rectilinear scans will be performed about 15-60 minutes after injection of the ¹¹¹In chloride. The indium-111 sulfur colloid scan will be done 24 hours after injection of the dose. We anticipate doing 100 scans in patients with a variety of marrow disorders. With our present nuclear medicine staff and their commitments to other studies, the time to accomplish this work would require at least 12 and possibly 18 months.

In 10 patients external organ counting, whole-body retention, and blood samples collected at 1/2, 1, 2, 4, 8, and 24 hours, 5 and 12 days, will be done to compare distribution and disappearance times with the two agents.

III. Possible Hazards and Their Evaluation:

Lilien states that preliminary dosimetry calculations according to Graham indicates a dose of 3.6 rads/mCi to marrow, 4.5 rads/mCi to the liver, and 0.5 rad/mCi to the total body (J. Nuc. Med. 14: 186, 1973). These calculations are based on highly conservative estimates of the biodistribution of indium, studies of which are being undertaken. Indium-111 has a physical half-life of 2.8 days. It decays by electron capture with the emission of two gamma photons, 173 Kev (89% per disintegration) and 247 Kev (94% per disintegration). It is produced by proton bombardment of enriched ¹¹¹Cd at Oak Ridge National Laboratory and supplied to the Medical Division free of cadmium in the carrier-free form.

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The proposed dosage for both indium-111 chloride and sulfur colloid to the patient will be 0.75 mCi/M² body surface area. Both agents will be administered intravenously. Standard man is approximately 1.6 M² so that the total dose injected would be 1.2 millicuries.

No reports can be found in the literature pertaining to the organ distribution of ¹¹¹In sulfur colloid. If it follows the same distribution as ^{113m}In radiocolloid or ^{99m}Tc S colloid, then approximately 80% would distribute to the liver. (Goodwin, Nucleonics, Nov. 1966). He estimates that the radiation dose to the liver is ~0.55 rads/mCi ^{113m}In administered. The biologic half-life is approximately 30 days.

IV. Radioisotopes and New Drugs:

No new radioisotopes or new drugs are requested. No reports regarding the uses of ¹¹¹In sulfur colloid in patients have appeared in the literature to my knowledge, but ^{113m}In colloid has been shown to be an attractive liver and spleen scanning agent. (Goodwin, Stern and Wagner: A new radio-pharmaceutical for liver scanning, Nucleonics, Nov. 1966) (Potchen and Adatepe: Liver and Spleen Scintiscanning with ^{113m}-Indium: A Clinical Pathologic Correlation, Am. J. Roentgenol. 106: 739-744, August 1959).

V. Responsibility of Principal Investigator:

The same ORAU consent form as is required for our other experimental agents will be used in this study to obtain approval from the patient.

Starting Date: January 1, 1974

Signatures: Francis A. Goswitz, MD Principal Investigator
_____ Co-Investigator
_____ Co-Investigator
_____ Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Signature _____
Title _____
Institution _____
Date _____

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Francis A. Goswitz Ident. No. 28

Project Title Comparison of Indium-111 Chloride and Indium-111 Sulfur Colloid
in Evaluation of Bone Marrow Disorders

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:

This proposal was mailed out to the committee prior to the 11 Dec. meeting but the investigator withdrew it from consideration on the day of the meeting since the Medical Radionuclide Committee didn't approve it in its present form.

Approve _____

Disapprove _____

Boyd Andrews
Chairman of Committee

11 Dec. 73
Date

1030490

*No Action
Michelson*

MEMORANDUM

, Isotope Committee

DATE November 28, 1973

SUBJECT COMPARISON OF INDIUM-111 CHLORIDE AND INDIUM-111 SULFUR COLLOID IN EVALUATION OF BONE MARROW DISORDERS (See proposal on this topic submitted to Human Use Committee)

COPIES TO _____

1. Proposal:

Farrer and associates found selective uptake by the bone marrow from ^{111}In - transferrin to be far superior to those of $^{99\text{m}}\text{Tc}$ S colloid in hematologically normal patients (J. Nucl. Med. 13: 429, 1972 (abstract); Blood, December 1972, American Soc. Hematology (abstract). Lilién and co-authors (J. Nucl. Med. 14: 184-186, 1973) confirmed this finding and reported on the value of ^{111}In -chloride as a new agent for bone marrow imaging. Our proposed study is to determine whether ^{111}In -sulfur colloid is superior as a scanning agent or whether both agents are necessary to evaluate patients with bone marrow disorders before and after treatment of their primary disease. ^{111}In -chloride supposedly labels the erythropoietic system of the bone marrow, ^{111}In -sulfur colloid the reticulo-endothelial system.

2. Radioisotope:

Indium-111 has a half-life of 2.8 days. It decays by electron capture with the emission of two gamma photons, 173 Kev (89%/disinteg) and 247 Kev (94%/disinteg.). It may be supplied to the Medical Division free of cadmium in the carrier-free form from the Oak Ridge National Laboratory where it will be produced by proton bombardment of enriched ^{111}Cd . It may also be obtained commercially as radiopharmaceuticals from either Medi-Physics, Inc. or New England Nuclear Company.

3. Chemical Form:

The isotope will be received in the chloride form in dilute HCl. Both Farrer at Montreal and Lilién at UCLA injected ^{111}In -chloride intravenously into humans at an acid pH. We propose to do the same. With the ^{111}In -sulfur colloid we would first try to prepare this agent by the sodium thiosulfate "kit" method as in the case of $^{99\text{m}}\text{Tc}$ S colloid; if this preparation is unsatisfactory, then we will attempt the hydrogen sulfide method of the Brookhaven protocol modified by Hayes and his group.

4. Administration:

Intravenous injection using the same technique as employed now for administration of $^{99\text{m}}\text{Tc}$ S colloid.

5. Dosage:

Farrer used 1-2 mCi of ^{111}In -chloride but Lilién injected 2-5 mCi into each patient. We propose a dose of 0.75 mCi/ M^2 body surface area which means initially a dose range from 0.5-2 mCi per patient. If this dose is too low, then it will be doubled if possible in some patients provided that the patient has a disease which will accept this amount of increased radioactivity.

6. Experimental protocol:

- a. Number and selection of patients: 100 scanning studies, divided between those having positive and negative ^{111}In -chloride and ^{111}In -sulfur colloid scans. Ten patients would be studied with external organ counting (heart, liver, spleen, sacrum), blood sampling at 1, 2, 4, 8, and 24 hours, 5 and 12 days to evaluate plasma disappearance and red-cell utilization, and whole-body counting to determine total-body retention.

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- b. Duration of studies: 12-18 months with our present nuclear medicine staff.
- c. Type and frequency of assay: See 6a above. The urines and stools will not be collected unless we find total-body retention less than 80% by 10 days. Wochner and coworkers in a study for estimation of plasma volume with the use of indium-113m-transferrin found little indium was excreted, 11% in the urine and 4% in the feces. (J. Lab. Clin. Med. 75: 711-720, 1970).
- d. Special procedures: Whole-body scans will be performed in all studies. Liver and spleen scintiphotos with the Anger camera will be requested in all studies since time will not permit always the obtainment of rectilinear scans.

7. Distribution Studies:

Farrer and his associates found that indium-111 chloride disappeared from the plasma with a net half-time of about 11 hours. The plasma disappearance curve had two exponential components, an initial one with a half-time of about 4 hours followed by a slow component with a half-time of about 30 hours. There was no incorporation of the tracer into erythrocytes up to 96 hours. The liver and spleen were poorly visualized according to Farrer, but the liver on the two illustrations in Lilien's article was well-visualized. No information has been reported to my knowledge involving the distribution of indium-111 sulfur colloid in man; we are assuming that its distribution will simulate other radio-colloids.

8. Radiation Dose:

Lilien in his March 1973 article (J. Nucl. Med.) reported that preliminary dosimetry calculations according to Graham would indicate a dose of 3.6 rads/mCi to the marrow, 4.5 rads/mCi to the liver, and 0.5 rad/mCi to the total body. These calculations he stated were based on highly conservative estimates of the biodistribution of indium, studies of which are being undertaken.

9. Related and Pertinent Human Data:

The only total-body scan reports involving the use of indium-111 chloride (transferrin) as a bone-marrow imaging agent are the ones by Farrer and Lilien. Kinetic information on the degree of the agent's utilization in red cells is lacking. Comparison with indium's distribution as a sulfur colloid would help determine the chloride's labeling of non-reticulo-endothelial elements only.

10. Chemical, Radiation and Infectious Hazards:

The ¹¹¹In will be carrier-free since it is produced by proton bombardment; chemical toxicity from indium is therefore not relevant. A microanalytical test for cadmium will be made on each batch of ¹¹¹In on receipt. Spectrometric verification of radionuclide purity of each batch will also be made.

A trace amount of ¹¹⁴In will be present in the preparation due to the presence of small amount of ¹¹⁴Cd in the separated ¹¹¹Cd target material. This is estimated by Oak Ridge National Laboratory to be approximately 0.02% of the ¹¹¹In level (0.2 Ci/mCi ¹¹¹In) at one half-life after termination of the target bombardment. The radiation dose from ¹¹⁴In per Ci is estimated by the Radiation Safety Office to be 0.042 rads to the whole body and 0.41 rad to the bone. Thus, the whole-body dose contribution from the presence of this contaminant will be 0.008, 0.015, and 0.03 rad per mCi of ¹¹¹In.

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one, two and three half-lives after termination of bombardment. The dose to the bone will be 0.082, 0.157, and 0.305 rad/mCi ^{111}In at the same intervals. The total dose due to both ^{111}In and ^{114}In will then be: Bone 2.4, 2.5, and 2.6 rads/mCi ^{111}In , and whole body 0.49, 0.5 and 0.51 rad/mCi ^{111}In at these time intervals.

The ^{111}In solution will be milipore filtered (0.22 micron) into an autoclaved, sealed vial on receipt and tested for pyrogenicity. The preparation of the ^{111}In dose will be carried out in a laminar-flow hood using sterile equipment. Final sterilization will be made through milipore filtration. Ten percent of the preparation will be withheld for testing should the patient show any reaction.

No test for pyrogenicity and no milipore filtration will be performed if the radio-pharmaceutical is obtained from a commercial supplier. Ten percent of the preparation will be withheld for testing, however, should the patient show any reaction.

Same procedure for the ^{111}In sulfur colloid preparation will be performed as is now being done to prepare $^{99\text{m}}\text{Tc}$ sulfur colloid using the sodium thiosulfate procedure.

Starting date: January 1, 1974 pending approval of study by Human Use Committee.

Francis A. Goswitz, M.D.

gd

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MEMORANDUM

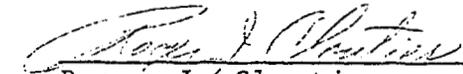
Medical Radionuclide Committee

DATE 3 December 1973

SUBJECT INDIUM-111 CHLORIDE AND INDIUM-111 SULFUR COLLOID

COPIES TO Dr. Andrews, file

Dr. Goswitz has submitted the attached proposal for use of In-111 chloride and In-111 sulfur colloid for our review. He hopes that we will approve the proposal at our 4 December 1973 meeting so that he can submit the proposal to the Committee on Human Studies before their 11 December 1973 meeting. I have also attached Dr. Goswitz's proposal to the Committee on Human Studies.



Roger J. Cloutier

RJC:vrs

Members:

Farger
Cloutier
Edwards
Harmon
Hayes
Lushbaugh

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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 11, 1973

Principal Investigator: Francis A. Goswitz, M.D.

Co-Investigators: C. Lowell Edwards, M.D.
Helen Vodopick, M.D.
Gayle Littlefield, Ph.D.

Title of Project: EFFECT OF SPLENECTOMY AND TOTAL-BODY IRRADIATION ON
ONSET OF BLAST CRISIS AND SURVIVAL IN CHRONIC
GRANULOCYTIC LEUKEMIA

I. Objectives of Experiment:

- A. Background and introduction: Prior studies at NIH and at the Hahnemann Hospital in Philadelphia have revealed that patients who have been splenectomized are easier to manage when the blast crisis ensues than those who are not splenectomized. One explanation for this fact is that the spleen becomes extremely large and often undergoes infarction in the blast crisis. This can cause severe pain and incapacitate the patient. At the same time, the patient's metabolic rate increases, and there is increased weight loss due to the hypermetabolism engendered by this enlarged organ and by its pressure on adjacent gastrointestinal organs. For this reason, some clinicians have considered splenectomy to be in order prior to the onset of the blast crisis merely to make the remaining time for the patient more tolerable and to allow the patient to remain ambulatory for a longer period of time after onset of the blast crisis (Brodski et al, British Journal Haematology, Volume 22:179, 1972). However it has become apparent that with the use of drugs effective in the therapy of acute myelocytic leukemia remissions in the blast crisis can occur. Presently a large scale study is being done in the Eastern Cooperative Oncology Group to determine whether or not splenectomy, with or without intensive combination chemotherapy, utilizing newly acquired drugs might delay the occurrence of the blast crisis and thus prolong the life of the patient.

Recently Bayard Clarkson performed splenectomy in 20 patients with chronic granulocytic leukemia who were in remission and had conversion of the Ph⁺¹ chromosome to Ph⁻¹ in 4 cases. All 4 patients have normal marrows with the longest state of remission being 2 1/2 years (unpublished data).

At the Medical Division of Oak Ridge Associated Universities we have treated patients with chronic granulocytic with total-body irradiation to control their disease. Since the majority of our patients also die from the blast crisis, we would like to determine whether or not splenectomy, with or without total-body irradiation, might also postpone the occurrence of blast crisis.

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B. Purpose of the Study

1. To evaluate the effect of splenectomy made upon the onset of the blast crisis and upon the overall survival of the patient treated with total-body irradiation.
2. To evaluate the effect of total-body irradiation and splenectomy on the Philadelphia chromosome of the patient.

II. Methods of Procedure:

A. Selection of patients

1. Patients with untreated and recently diagnosed chronic granulocytic leukemia who are between 5 and 60 years of age are eligible for the study. Criteria required to make a diagnosis of chronic granulocytic leukemia will include: White count in excess of 20,000, with a slight shift to the left in the neutrophilic series, hypercellular marrow consistent with CML, positive Ph¹ chromosome, a leukocyte alkaline phosphatase score below the lower limits of normal, presence of splenomegaly detected by radiocolloid scan, an elevated serum B-12 and a normal to increased platelet count.
2. The following criteria would make the patient ineligible for study: Patients with previous evidences of polycythemia vera as a primary disease or primary myelofibrosis, or patients who have received prior therapy for induction of a remission. Any patient who has received prior irradiation therapy to the liver or prior chemotherapy will be excluded from this study. Patients entering the study need to be eligible for splenectomy and should not have any major medical contraindications. Patients who do not obtain a complete hematologic remission with the exception of a palpable spleen are ineligible. The spleen should not be palpable more than 10 cm below the costal margin at the time of splenectomy.

B. Mechanics of the study

1. Pretreatment patients will undergo the laboratory studies listed for selection of patients under IIA, 1, and as illustrated on separate protocol sheet.
2. Induction of treatment
 - a. The basic plan of the study is to reduce the blood cell counts to normal or near normal levels with total-body irradiation. In patients with massive spleen this response may be obtained only by treatment with splenic irradiation. Splenectomy should occur only after a complete hematologic remission with the exception of splenomegaly. Patients who did not achieve a complete remission will be ineligible for the remission phase of the study. Complete remission will be defined as: White count between 4,000 and 10,000 per cu mm; absence of a palpable spleen; presence of stable weight; hemoglobin above 12 g %; absence of systemic symptoms such as excessive fatigue, sweating chills, anorexia, or pruritus.

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b. Choice of dose of total-body irradiation to induce a remission:

To induce a remission with total-body irradiation, patients will be given 250 R in the METBI facility at a dose rate of 30 R per day if the white blood cell count is over 300,000 per cu mm, and if the marrow is hypercellular, has granulocytic hyperplasia and plentiful megakaryocytes. Patients may be treated with either 150 R in the METBI facility, or with 250 R in LETBI if the white count is over 150,000 per cu mm, and the platelet count is adequate. Patients may be given 100 R in METBI, or 150 R in the LETBI facility for leukocyte counts over 80,000 per cu mm, and moderate increases in granulocytic and megakaryocytic hyperplasia.

1. If the white count drops to 20,000 per cu mm or less during the treatment, the irradiation is stopped, or withheld until the nadir is reached.
2. If thrombocytopenia occurs with the platelet count less than 100,000 per cu mm, irradiation will also be discontinued until the count rises above 100,000 per cu mm.
3. Possible hazards and their evaluation: Radiation doses will be modified in accordance with toxicity during maintenance or as they present at the time of beginning the next course of radiation treatment.

Hematologic: No total-body irradiation will be given if the platelets fall below 100,000 during maintenance phase or if the white count falls below 3,000.

Associated myelofibrosis: The dose of total-body irradiation will not be changed for the presence of associated myelofibrosis unless these patients have blood counts which prevent treatment.

4. Remission: On achieving remission patients will be separated. Patients with spleens 10 cm or less below the costal margin will undergo splenectomy. Patients with spleens more than 10 cm will be treated first with splenic irradiation. Patients whose spleens do not meet the size requirements for splenectomy after one course of treatment with splenic irradiation will be treated with total-body irradiation alone.

All patients under the age of 60 years who refuse splenectomy and those who are over the age of 60 years will be treated only with total-body irradiation until they enter the blast crisis stage.

- a. If the protocol calls for splenectomy, the operation should be performed relatively soon. Depending upon patient and surgeon availability, this may take one to four weeks. No splenectomy will be performed if the platelet count is over 600,000 per cu mm, or if the white count is over 15,000 per cu mm. It may be necessary to treat some patients with fractionated doses of 30 R or less in our METBI facility in order to achieve these values before doing the splenectomy.

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5. Maintenance: After obtaining a remission, those patients who are splenectomized will not receive additional treatments until the wound is completely healed. Patients will be followed and treated with either fractionated doses of total-body irradiation or protracted doses of total-body irradiation to maintain their remission state. Patients who are treated with 30 R fractionated doses will be easier to follow and maintain their blood cell counts at normal levels. It will be more difficult to maintain in remission patients who are to be treated with protracted doses of total-body irradiation. These patients for the most part would be given 100 or 150 R. This group of patients should not have white counts ever exceeding 50,000 cu/mm or platelet counts exceeding 1,000,000 cu/mm.
6. Splenic infarct: There will be no change in treatment for this condition.
7. Blast crisis: Development of blast crisis will result in discontinuation of total-body irradiation.
8. Measurement of effect, of course, will be determined by whether or not the patients achieve a complete remission, partial remission, or are just improved following treatment.

III. Dose Modification and Toxicity:

Radiation doses will be modified in accordance with toxicity during maintenance or as present at time of beginning the next course of radiation treatment.

- A. Hematologic: No total-body irradiation will be given if the platelets fall below 100,000 during maintenance phase or if the white count falls below 3,000.
- B. Associated myelofibrosis: The dose of total-body irradiation will not be changed for the presence of associated myelofibrosis unless these patients have blood counts which prevent treatment.
- C. Splenic infarct: There will be no change in treatment of this condition.
- D. Blast crisis: The development of blast crisis will result in discontinuation of total-body irradiation.

IV. Measurement of Effect:

- A. Complete remission: Complete remission will be defined as a white count between 4,000 cu/mm and 12,000 cu/mm in the absence of splenomegaly and in the presence of a stable weight. The hemoglobin should be above 12 g % and hematocrit above 36%. Systemic complaints such as excessive fatigue, sweating, fever, night sweats, and anorexia should be absent. If the total-body irradiation therapy would lead to normal platelet count or thrombocytopenia without a change in the white count to 4,000 to 12,000 cu/mm³ or should the patient maintain thrombocytosis ($>450,000/\text{mm}^3$) but change to a normal white blood cell count, then a complete remission will not have occurred. The bone marrow cellularity should return to normal and the GE ratio must not exceed 5:1. Serum vitamin B-12, unsaturated vitamin B-12 binding capacity and leukocyte alkaline phosphatase should be normal. Spleen size should be evaluated by means of the radiocolloid scan.

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- B. Incomplete or partial remission: Partial remission will be defined as the clinical condition whereby the leukocyte count is between 4,000 to 10,000/mm³, the platelet count between 150 to 450,000/mm³, and the hemoglobin above 12 g % and hematocrit above 36% respectively. There should be an absence of myeloblasts and progranulocytes in the blood. Systemic complaints should be absent. The bone marrow should not show greater than moderate hypercellularity. Spleen should not be palpable more than 10 cm below the costal margin. Serum vitamin B-12, unsaturated vitamin B-12 binding capacity and leukocyte alkaline phosphatase should be near-normal levels.
- C. Blastic transformation: The principal features of the blastic transformation include a hypercellular marrow with an increasing percentage of blasts and progranulocytes in the marrow (total greater than 30%), or more than 20% myeloblasts in the circulating blood. In addition, progressive leukocytosis with a decrease in mature granulocytes, decreasing platelet count (below 100,000/mm³), and anemia (Hgb 9 g % or less) unresponsive to treatment. Other evidence would include progressive splenomegaly in patients whose spleen has not been removed, cytogenetic evidence of aneuploidy, extra-medullary tumors, rising leukocyte alkaline phosphatase, bone pain, fever, and chills.

V. Study Parameters:

- A. The same studies presently performed in our total-body irradiation protocol will be continued here.
- B. After splenectomy the same histologic examinations will be done as we do now on the resected spleen as well as cytogenetic analyses.

VI. Termination of Study:

- A. Blast transformation: When this occurs, patients will be withdrawn from the study.
- B. If a life-threatening event should occur to the patient, the patient will be withdrawn from the study.
- C. If the protocol seems contrary to the best interests of the patient, the study may be terminated.
- D. If the patient requests withdrawal, the study will be terminated.

VII. Patient Consent and Role of Surgeons:

- A. ORAU regulations concerning informed consent for this management will be fulfilled. Obviously, patient must approve of the splenectomy and the surgeon must be willing to perform the operation.
- B. Patient has right to choose his own surgeon.
- C. Cost of care: Patient or a third party will pay for the costs of the surgery.

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VIII. Analysis of Results:

- A. The study will focus on:
 - 1. Length of survival.
 - 2. Relative effects on morbidity including duration of time patient is in complete or partial remission.
 - 3. Effect of splenectomy on eradication of the Ph¹ chromosome.
 - 4. Duration of time from onset of disease and from date of splenectomy to onset of the blast crisis.

IX. Consent Forms:

- A. Protocol Laboratory Data Sheet
- B. Consent for Administration of Radioactive Material.
- C. Consent for Operation.
- D. Consent for Experimental Protocol.

X. References:

- A. Williams, W. J. et al, Hematology p. 689, 1972. McGraw-Hill, Inc.
- B. Kahn, S. B. and Brodsky, I.: Therapy of Myeloproliferative Disorders. In Cancer Chemotherapy II. 22nd Hahnemann Symposium. I. Brodsky and S. B. Kahn (Eds.). Grune and Stratton, New York, 1972.
- C. Medical Research Council's Working Party for Therapeutic Trial in Leukemia. Chronic Granulocytic Leukemia; Comparison of Radiotherapy and Busulfan Therapy. Brit. Med. J. 1:201, 1968.
- D. Brodsky, I., Ross, E., Petkov, G., and Kahn, S. B.: Platelet and Fibrinogen Kinetics with (⁷⁵Se) Selenomethionine in Patients with Myeloproliferative Disorders. British J. Haemat. 22: 179, 1972.
- E. Frei, E.: Therapy of Acute Leukemia. In Cancer Chemotherapy II. 22nd Hahnemann Symposium. I. Brodsky and S. B. Kahn (Eds.) Grune and Stratton, New York, 1972.

XI. Isotopes and New Drugs:

No new radioisotopes or new drugs would be involved in this study.

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XII. Responsibility of Principal Investigator:

The necessary requirements will be followed to protect the rights of the patients in gaining informed consent. The surgeon must recognize that the splenectomy is being done as an experimental procedure and that no guarantee regarding the improvement of the chronic granulocytic leukemia will necessarily or always be obtained after this surgery.

Starting Date: January 1, 1974 or earlier if possible.

Signature: Francis A. Gouvytz Principal Investigator
Charles Edwards Co-Investigator
Helene D. Spick Co-Investigator
[Signature] Co-Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Francis A. Gouvytz
Title Chm. The Medical Division
Institution Cornell Ridge Associated Universities
Date 2 May 1974

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Operation

PATIENT _____ AGE _____
DATE _____ TIME _____ A.M. P.M. PLACE _____

1. I hereby authorize the medical staff of the ORAU Medical Division, or such physician as they may designate, to perform upon _____ (state name of patient or myself) the following operation: _____

If in the course of the operation any unforeseen condition arises calling for procedures in addition to or different from those now authorized, I further request and authorize him to do whatever he deems advisable.

2. The nature and purpose of the operation, possible alternative methods of treatment, the risks involved, and the possibility of complications have been fully explained to me, I acknowledge that no guarantee or assurance has been made as to the results that may be obtained.
3. I consent to the administration of anesthesia by or under the direction of a staff member of the ORAU Medical Division or such other qualified person as he may designate. I further consent to the use of such anesthetics as he may deem advisable with the exception of _____ (if none, so state)
4. I consent to the disposal by authorities of the ORAU Medical Division of any tissues or parts which may be removed.
5. I consent to the taking and publication of any photographs in the course of this operation for the purpose of advancing medical education and science.
6. For the purpose of advancing medical education and science, I also consent to the admittance of observers to the operating room.

I CERTIFY THAT I HAVE READ AND FULLY UNDERSTAND THE FOREGOING CONSENT TO OPERATION, THAT THE EXPLANATIONS THEREIN REFERRED TO WERE MADE, AND THAT ALL BLANKS OR STATEMENTS REQUIRING INSERTION OR COMPLETION WERE FILLED IN AND INAPPLICABLE PARAGRAPHS, IF ANY, WERE STRICKEN BEFORE I SIGNED.

Signature of Patient _____

Signature of Patient's Spouse _____

When the patient is a minor or incompetent to give consent:

Signature of person authorized to give consent _____

Relationship to Patient _____

WITNESS: _____

1030503

I have talked with _____
(patient's name or person consenting)
about the contemplated operation and have explained the risk
involved.*

Remarks: _____

Physician

Date

*If sterility, blindness, or loss of hearing is a possibility,
please describe briefly the explanation given to the patient.

1030504

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

CONSENT FOR EXPERIMENTAL STUDY IN CHRONIC GRANULOCYTTIC LEUKEMIA

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

of the following study: Initial treatment with total-body irradiation and if necessary to reduce the size of my spleen, splenic irradiation; splenectomy when my leukemia is satisfactorily controlled.

The nature and purpose of this study, the risks involved, and the possibilities of complications have been explained to me. I understand that this study involves various laboratory tests as listed on the protocol sheet (see attached). I further understand that splenectomy at this stage of chronic granulocytic leukemia is not standard, routine treatment and is accepted as necessary by all physicians. This study is being done to gather information related to my disease and its treatment in possibly obtaining improved health and a longer survival.

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 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: _____

DATE: _____

Investigator

1030505

100K PROTRACTED BY U.S. N/HR. X DURING IRRADIATION
 O AFTER IRRADIATION

L.E.T.B.I.-II

Name SCARBROUGH, ROBERT

number 312662

Day of treatment	Month	Day	Day of week	Notes
F	SEP	5	F	
	SEP	6	M	
	SEP	7	W	
	SEP	8	TH	
	SEP	9	F	
	SEP	10	M	
	SEP	11	TU	
	SEP	12	W	
	SEP	13	TH	
	SEP	14	F	
	SEP	15	M	
	SEP	16	TU	
	SEP	17	W	
	SEP	18	TH	
	SEP	19	F	
	SEP	20	M	
	SEP	21	TU	
	SEP	22	W	
	SEP	23	TH	
	SEP	24	F	
	SEP	25	M	
	SEP	26	TU	
	SEP	27	W	
	SEP	28	TH	
	SEP	29	F	
	SEP	30	M	
	SEP	31	TU	
	OCT	1	W	
	OCT	2	TH	
	OCT	3	F	
	OCT	4	M	
	OCT	5	TU	
	OCT	6	W	
	OCT	7	TH	
	OCT	8	F	
	OCT	9	M	
	OCT	10	TU	
	OCT	11	W	
	OCT	12	TH	
	OCT	13	F	
	OCT	14	M	
	OCT	15	TU	
	OCT	16	W	
	OCT	17	TH	
	OCT	18	F	
	OCT	19	M	
	OCT	20	TU	
	OCT	21	W	
	OCT	22	TH	
	OCT	23	F	
	OCT	24	M	
	OCT	25	TU	
	OCT	26	W	
	OCT	27	TH	
	OCT	28	F	
	OCT	29	M	
	OCT	30	TU	
	OCT	31	W	
	NOV	1	TH	
	NOV	2	F	
	NOV	3	M	
	NOV	4	TU	
	NOV	5	W	
	NOV	6	TH	
	NOV	7	F	
	NOV	8	M	
	NOV	9	TU	
	NOV	10	W	
	NOV	11	TH	
	NOV	12	F	
	NOV	13	M	
	NOV	14	TU	
	NOV	15	W	
	NOV	16	TH	
	NOV	17	F	
	NOV	18	M	
	NOV	19	TU	
	NOV	20	W	
	NOV	21	TH	
	NOV	22	F	
	NOV	23	M	
	NOV	24	TU	
	NOV	25	W	
	NOV	26	TH	
	NOV	27	F	
	NOV	28	M	
	NOV	29	TU	
	NOV	30	W	
	NOV	31	TH	

Hematology
 CBC
 Platelets
 Diff
 Retic
 MARROW (Marrow) (Marrow)
 Serum total bilirubin
 Uric Acid
 LDH
 Serum Brz
 Serum Urost. Br-Bind.
 Serum Urost. Capaith
 Serum Iron
 Serum TIBC
 Leukocyte ALK PO4
 2 tubes heparinized
 blood - Mrs. Colyer
 2cc Serum-RICKS
 12cc EMERY
 Liver, Spleen Scan
 Marrow Scan

Cytogen.
 Luskbaugh, Edwards, Vohovaris, Nemmelton, Chavist, Alizes, D. S. G. G. G. G.

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

CONSENT TO EXPERIMENTAL TREATMENT, TOTAL-BODY IRRADIATION

AND SPLENECTOMY FOR CHRONIC GRANULOCYtic LEUKEMIA

I, _____ do, of my own free will, volunteer and submit to an experimental treatment of my disease, chronic granulocytic leukemia. The nature and purpose of the treatment, possible alternative treatments, the risks involved, and possibilities of complications have been explained to me.

I understand that this treatment is not the usual treatment for my disorder and remains unproven by medical experience so that the consequences may be unpredictable.

Date _____

Patient or person authorized to
consent for patient

WITNESS:

1030507

I have talked with _____ about the
Name
proposed course of treatment to be given _____
Name
including the following:*

1. The planned treatment consists of total-body irradiation and possibly splenic radiation to achieve a remission in the disease; white blood cell count below 15,000/mm³, platelet count below 600,000/mm³, and spleen smaller than 10 cm below rib margin.
2. When the patient is in remission, a splenectomy will be done at the Oak Ridge Hospital of the Methodist Church or another hospital that he (she) selects and by a surgeon of his (her) choice.
3. Throughout the treatment and observation periods, frequent tests and examinations will be done to check on the progress of the disease and its response to therapy. These tests include:
 - A. Blood samples of 5-25 ml up to 3 times a week.
 - B. Bone marrow aspirate or biopsy as required to note the course of the disease.
 - C. Scans of bone marrow, liver and spleen.
4. The risks involved in this treatment plan are A) the early and late risk of irradiation; B) the early and late risks of splenectomy.
 - A. The early risk of TBI is limited to the slight risk of the patient getting a greater exposure than planned, plus the risk that the prescribed dose is too great or that the patient is unusually susceptible to radiation. The degree and duration of the resulting pancytopenia and the risk of infection or bleeding would depend on the magnitude of the over-dosage. We believe that the total risk is minimal because of our built-in controls, our frequent monitoring of the radiation and its effect, and our experience at selecting and predicting the response to single exposures of TBI.

The late risks of TBI include theoretical or possible risk of acceleration of the onset of the blast cell crisis or cataract formation.
 - B. The early risk of splenectomy is that attending any major abdominal surgery with general anesthesia plus the risks of thrombosis or abnormal clotting associated with the post splenectomy thrombocytosis.

The late risks of splenectomy is a possible decreased resistance to infection or other yet unknown or unanticipated risks of splenectomy specifically in this disease.
5. The benefits anticipated from the splenectomy at this stage in CGL include:
 - 1) Elimination of the enlarged spleen which often causes discomfort and other symptoms,
 - 2) Eliminating risks of serious complications, specifically related to the large spleen, viz., splenic infarctions, splenic rupture and hypersplenism,
 - 3) possible subsequent easier management of the CGL and
 - 4) possible longer survival or prolonged remissions.
6. The patient has the right to withdraw at anytime from the study.
7. The patient assumes responsibility to cover the costs of the surgery and hospitalization.

Physician _____

WITNESS _____ (Patient)

Date _____

1030509

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Francis A. Goswitz Ident. No. 29

Project Title Effect of Splenectomy and Total-Body Irradiation on Onset of Blast Crisis and Survival in Chronic Granulocytic Leukemia

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are: The hazard of splenectomy in a patient with a blood disease. Possible unfavorable effect on the course of the disease.

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: Possibility of improved therapy for leukemia.

3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate: An improved consent form was asked for, including indication that alternative forms of treatment are offered here. This has been provided.

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

5. Other committee comments: At the request of the committee no patient under 18 years of age will be included in this study.

Approve

Donald G. Anderson M.D.
Chairman of Committee

Disapprove

11 December 73
Date

1030510

25 Jan 1975 - Cancel; See attached report.

No. 29 Effect of Splenectomy and TBI on Onset of Blast Crisis
and Survival in CGL

Only one patient was treated under this protocol. He experienced no unexpected difficulty or complications, either from the radiation or surgery. He was not maintained in remission after the splenectomy and required subsequent suppressive therapy. He is no longer being followed at ORAU.

1030511

MEMORANDUM

TO Frank GoswitzDATE 8 March 1974SUBJECT Application No. 29 to Human Studies CommitteeCOPIES TO File

I am sending you the following comment from Melvin Koons concerning your application to the Committee on Human Studies. I assume that you will fulfill the suggestion that he has made.

"The consent form for Dr. Goswitz's proposal is satisfactory. However, I feel that the explanation sheet accompanying the consent form could be revised somewhat to give the patient an explanation of the risks involved in more layman's terms. Also, Item No. 7 indicates that the patient assumes the responsibility for the costs of surgery and hospitalization. It appears that this should be given more emphasis and that the patient should specifically indicate his acceptance of that condition, by either signing a statement to that effect or initialing Item No. 7 to indicate that he has definitely agreed to do so."

MEK

Gould A. Andrews

pe

1030512

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

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

Date: 12 September 1973

Principal Investigator: Bill Nelson, M.D.

Co-Investigators: Biophysicist (and Clinician) - to be named

Title of Project: FATE OF LABELED MONONUCLEAR BLOOD CELLS IN TISSUES,
ESPECIALLY IN LYMPH NODES, SPLEEN, AND MARROW.

I. Objectives:

To further characterize those cells separable from blood that can restore hemopoiesis and lymphocytopoiesis after otherwise lethal irradiation. Such cells can be concentrated and stored frozen, and identified by their proliferative potential in vitro and in experimental animals but they are not specifically identified morphologically in man. We intend to obtain data about their fate in human tissues that can be correlated with their physicochemical and immunologic properties. This information will be pertinent to answering questions about the heterogeneity of human blood stem cells, the feasibility of selecting cells with hemopoietic potential or those with immunologic capacity, and ultimately the possibilities of culturing and/or conditioning stem cells for particular transplantation requirements. Experiments in animals give valuable guidelines, but for clinically applicable characterization of mononuclear cell preparations, the distribution studies must also be done in man. (See attached copy of grant proposal. The references to T-cell depletion in blood of Hodgkin's patients are to be noted, in addition to "homing" of B and T cells.)

1030513

II. Methods:

Lymphocytes separated from 500 ml of fresh blood from a patient with proven neoplasm to be subjected to surgical biopsy for diagnostic reasons (e.g., laparotomy for staging of Hodgkin's disease) will be divided into two equal portions and labeled in vitro, one with ^{51}Cr and the other with ^3H -cytidine. A portion of each will be retained for discontinuous density gradient separation (DGS), radioassays (RA), autoradiography (ARG), and other in vitro studies to show the disparities in labeling of the subpopulations of cells called lymphocytes. One selected subpopulation labeled with ^3H -cytidine and another subpopulation labeled with ^{51}Cr will be reinfused intravenously and blood samples taken for DGS, RA, ARG at 7 min, 1 hr, 4 hr, 12 hr, and 24 hr. Scans and external counts of ^{51}Cr will be done at 15 min, 4 hr, and 24 hr. The study is to be initiated 24 hr before the scheduled splenectomy. In association with the customary search for evidence of neoplasm (e.g., with Hodgkin's disease) samples of spleen, liver, lymph nodes, and marrow will be taken for DGS, RA, ARG, and other studies.

We plan to study ten such patients, in each separating and labeling two selected populations of mononuclear blood cells and looking for differences in the rates of disappearance from the blood and in tissue distribution. In some instances, for example, the gamma emitter will be used to label candidates for hemopoietic stem cells, and other cells will have the ^3H label. In other cases we will want to follow B or T cells with scans, while looking in marrow ARG's for localization of hemopoietic stem cells labeled with ^3H .

We will subsequently apply for permission to pursue similar investigations with other radioactive labels, including some presently being developed. If the number of cells obtained from 500 ml of blood is inadequate, we may apply for permission to use leukapheresis or cryopreservation.

1030514

III. Possible Hazards:

Radiation from ^3H has been carefully considered; it requires appropriate radiation safety precautions and monitoring in all phases. The radiation to the patient is far below that producing detectable biologic effects, even if doses up to 2 mCi are used (Bremer, Fliedner, and Schick, 1973, European Journal of Cancer). The cells can be washed, or "cold" cytidine added to minimize ^3H incorporation into nucleic acids in vivo.

The ^{51}Cr dose (0.3 mCi used by Torelli, Vaccari, Curci, and Mauri, 1971, Acta Haemato. 46: 129-135; 1971) (0.5 mCi, Scott et al. 1972 Blood 40: 276-281; 1971) is also acceptable with appropriate precautions. We would select patients who are confident that they will not have more children, although genetic sequelae are remote. Rigorous aseptic technique to avoid bacteriologic contamination is essential. A possible hazard is an adverse psychologic reaction to the procedure, especially the multiple venipunctures and disturbance of rest prior to laparotomy. However, it could be argued that the opportunity to volunteer for such an experiment could also be beneficial psychologically.

The taking of 500 ml of blood could be regarded as a hazard, but any danger would be outweighed by the advantage of having on hand a transfusion unit of fresh autologous red cells. Such a phlebotomy for possible auto-transfusion if needed at surgery has been recommended to avoid the major risks of transfusion: hepatitis and a reaction or sensitization from incompatibility.

IV. Radioisotopes and New Drugs:

^3H cytidine (specific activity about 4.5 Ci/mM, Schwarz BioResearch, Inc., Orangeburg, N. Y.

Cytidine ("cold", 1000-fold concentration of labeled cytidine, or up to 0.0004 mM)

$\text{Na}_2^{51}\text{CrO}_4$ (specific activity about 100-300 mCi/mg)

1030515

V. Responsibility of Principal Investigator:

The principal investigator assumes the responsibility for the selection of patients who will be considered for the study. The study will not be started in any patient if it would interfere significantly with the best possible management of his condition. Should unforeseen events indicate, any studies underway would be interrupted or abandoned, rather than jeopardize the patient's welfare.

Each patient participating would read and have explained to him the attached "Consent for Experimental Test" form, and the physician making this explanation would indorse the attached form headed "A study of the distribution in my body of my white blood cells labeled with radioactive material (chromium-51 and tritiated cytidine)."

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: January 1975 - pending funding of grant.

Signature: Bill M. Nelson Principal Investigator

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature Donald Andrews

Title Chm. Medical Div. ORAU

Institution Oak Ridge Associated Universities

Date 11 Dec. 73

1030516

The study of the destiny in tissues of certain labeled white blood cells.

The patient was informed that:

- 1) The surgical procedure is recommended on the basis of his clinical condition, and does not depend on whether or not he agrees to participate in this study.
- 2) The study requires the removal of 500 ml of the patient's blood ___ hours or ___ days before surgery. Certain white blood cells will be concentrated from this blood, labeled with ^{51}Cr and ^3H , and reinjected into the patient's vein.
- 3) No radiation effect or other injury is expected from the material used, but to avoid any concern over remote genetic consequences, we would do the study only in those patients who did not intend to become parents.
- 4) In addition to the venipunctures required for obtaining the blood and returning the labeled cells, 10-ml venous blood samples would be required thereafter at 7 minutes, 1 hour, 4 hours, 12 hours, and then daily until surgery. Several scans would also be done.
- 5) The tissues taken at surgery would be assayed for the labeled cells without interfering with the diagnostic studies required by the patient's condition.

Date

Physician's signature

Patient's name

Chart No.

1030517

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent for Experimental Test

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

the following: A study of the distribution in my body of my white blood cells labeled with radioactive material (chromium-51 and tritiated cytidine).

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: _____

1030518

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Bill Nelson, M.D. Ident. No. 30

Project Title Fate of Labeled Mononuclear Blood Cells in Tissues, Especially
in Lymph Nodes, Spleen, and Marrow.

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are: Approval not given yet for human work except on blood samples, but expected to be given if animal results justify.

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

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

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

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

5. Other committee comments: See comments in minutes.

Approve Animal studies and work
on human blood samples.
Disapprove _____

Gould Andrews
Chairman of Committee

11 December 73
Date

1030519

25 Jan 75: Cancelled - no progress since last meeting