Minutes CIRC Meeting

725543

8 May 1972

Present: J.S. Robertson, S.H. Cohn, H.R. Connell, R.A. Love, G.A. Price, N.P. Rathvon, Jr.

The meeting was held in the Small Conference Room of the Medical Research Center and opened by Dr. Robertson at 1400.

The minutes of the previous meeting were accepted as distributed.

The Chairman distributed some copies of "The Institutional Guide to DHEW Policy on Protection of Human Subjects". More copies of the publication have been ordered so that every Committee Member can have a copy.

Dr. Robertson reported on the status of CIRC projects that are on the active list but are overdue for re-review. Of the nine projects in this category, seven will be reclassified as inactive; requests from Dr. Atkins for review of the remaining two are expected. The memorandum to Dr. Cronkite from Dr. Robertson listing the CIRC proposals involved is attached.

The Committee received a communication from Dr. Cotzias requesting that CIRC #58 be made inactive.

The following CIRC proposals were reviewed:

1. CIRC #32, revised. This proposal, "The Study of Polycythemia Vera", was approved as submitted.

2. Annual recertification of CIRC #48 was approved. It was noted that the original form for Initiation or Review of Clinical Investigative Programs was unsigned. The form should be signed by Dr. Shreeve.

3. Annual recertification of CIRC # 63 was approved with the condition that the word radioactive be included on the Consent Form, that is, paragraph 1 on the Consent Form should read: Thyroid uptake with radioactive iodine-123.....

4. CIRC # 82, revised. The proposal was approved subject to clarification on the Consent Form of whether 50 calendar days or 50 samplings is intended. It is suggested the wording on the Consent Form be: "..... be obtained 3 mornings a week and for a total period of 50 days".

The Committee then entered into a discussion of the procedure for recording patient's x-rays and whether the x-rays should be included in the patient's radiation record. No action was taken in this matter.

The meeting was adjourned at 1615.

Respectfully submitted,

Helen R. Connell

Helen R. Connell

Enc.

Memorandum to Dr. E.P. Cronkite
from Dr. J.S. Robertson

1179829

Brookhaven National Laboratory
The Medical Research Center
Upton, L. I., New York
REPOSITORY Claudio Holding Area Bldg 494
COLLECTION Committee - Clinical Investigations and Use of Radioisotopes
BOX No. 4
FOLDER CIRC #18

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 17 April 1972

TO: E. P. Cronkite

FROM: J. S. Robertson

SUBJECT: C I R C

Reference: CIRC minutes for meeting of 3 April 1972.

As indicated in the referenced minutes, the CIRC is concerned about the continued appearance of certain projects on the active list but which are over two years out of date and for which requests for review have not been received. It is proposed that these now be reclassified as inactive. They can, of course, subsequently be restored to the active list through the usual procedure.

Specifically, it is proposed that the following projects be relegated to the inactive list:

CIRC NO.	Date Orig.	Principal Investigator	Description
2	6/30/64	Dr. Cronkite	H-3 Cell Kinetics
2A	2/28/67	Dr. Cronkite	C14 Labelled Pyrimidine
15	6/30/64	Dr. Atkins	TC-99M Scanning TC04
15A	2/5/65	Dr. Atkins	TC-99M Scanning TC-S
18	6/30/64	Dr. Cronkite	CO-60 ECIB
18A	12/15/64	Dr. Cronkite	CO-60 ECIB leukemia
18B	2/25/65	Dr. Cronkite	CO-60 ECIB pre kidney transplant
18C	7/12/65	Dr. Schiffer	CO-60 ECIB amphotericin B
18D	1/27/69	Dr. Rai	ECIB CLL

JSR:mas

1179830

The Committee on Clinical Investigations and Uses of Radioisotopes hereby approves the program with the following title:

EXTRACORPOREAL IRRADIATION OF THE BLOOD.

CIRC # 18 has been assigned to this program.

Walton W. Shreeve, M.D., Ph.D., Chairman

Eugene P. Cronkite, M.D.

Eckart Schackow, M.D.

Melvin H. Van Woert, M.D.

James S. Robertson, M.D., Ph.D. (ex officio)

Date April 30, 1964

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179831

C/6.18

V.P. Bond

FORM FOR INITIATION OR REVIEW OF CLINICAL

INVESTIGATIVE PROGRAMS

(Submit original only to Department Chairman)

A. Title of the proposal: Extracorporeal Irradiation of the Blood.

B. Sponsoring physician(s): E.P. Cronkite, L. Schiffer

C. Responsible investigator(s): Drs. Cronkite, Schiffer, Chanana, Stryckmans

D. Brief description of the study, including its general goals and purpose, and pertinent information on past studies: (Attach additional sheets if necessary.)

Techniques for irradiation of the blood have been established in cows and shown to be relatively innocuous and quite satisfactory as a means of producing lymphocyte depletion of the body for prolonged periods. There are theoretical reasons to believe that lymphocyte depletion would be beneficial in the so-called autoimmune diseases. (L.E.D., collagen diseases etc.) and of course in lymphomatous disorders.

The following specific initial study is proposed in severe lupus erythematosis and in patients with lymphoma and leukemia except granulocytic that have not responded satisfactorily to established therapy.

At a later stage in development of the procedure, if results warrant it, patients may be used in earlier phases of their disease states.

First, semipermanent artery to vein Teflon-Silastic bypasses will be established as for renal hemodialysis. Second, extracorporeal irradiation of the blood will be undertaken for increasing periods of time utilizing the maximum flow rate attainable and a transit dose in the irradiation field which is to be determined by further study. (See later) The patients will receive heparin infusion into the blood flowing out of the body and protamine to neutralize the heparin in the inflow blood. (conti. separate sheet)

E. Reasons why the investigation(s) are to be performed on human subjects.

Application of therapy in human disease.

F. Type of patient in which the study is to be done (including approximate number of subjects, if known; special restrictions or requirements; method of obtaining consent; etc.):

The initial patient in each disease state will be evaluated before the second patient is studied. If results are encouraging, a sufficient number will be evaluated to see if this mode of therapy should commence earlier than presently established therapy. The situation will be explained to patients and relatives by Dr. Cronkite and/or Dr. Schiffer and only those patients will be studied who agree to the procedure.

1179832

G. 1. Are drugs not in the U. S. Pharmacopoeia (USP) or the NNR being used or contemplated for use? Yes____ No X

2. Is an unusual use of a drug(s) accepted by the USP or NNR contemplated? (An example would be the use of an accepted drug in dosages far exceeding the recommended limits or for purposes distinctly different from the usual indications cited.) Yes X No____

3. Are any biological products to be administered that do not bear on their containers or labels notation of approval by the Biological Control Division of the National Institutes of Health? Yes____ No X

4. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered? Yes X No____

5. Are any (other) unusual procedures being performed or proposed which in your judgment may entail a special hazard - particularly a hazard above and beyond any imposed by accepted diagnostic and therapeutic measures for that patient? Yes X No____

6. Are any radioisotopes to be administered to human beings? Yes X No____

a. If yes, are the radioisotopes to be used solely within the limits of procedures, specifically described in the USP? Yes X No____

Describe the radioisotopic preparation(s):

b. Or are the radioisotopes to be used only in accordance with a project previously approved by the former Radioisotope Committee of this Department? Yes X No____

Note the project number: - 0 -

IF ANY OF QUESTIONS 1 THROUGH 5 ARE ANSWERED AFFIRMATIVELY, a detailed analysis of the potential hazards must be appended, including pertinent bibliographic citations and other relevant information.

IF QUESTION 6 IS ANSWERED AFFIRMATIVELY, a completed supplementary form for Radioisotope Administration to Human Beings must be appended. However, this form need not be filed provided that question 6a or 6b is also answered affirmatively. A separate form must be submitted for each radioisotopic species to be administered.

Eugene P. Cronkite

Sponsoring Physician
Eugene P. Cronkite, M. D.

Committee on Clinical Investigations and Uses of Radioisotopes

L.M. Schiffer, M.D.

Approval recommended ✓ Date 4/20/64

Disapproval_____ Date_____

V. P. Bond JUN 29 1964

V. P. Bond, M. D.
Chairman, Medical Department

1179833

6/25/63
mlk

D. Brief description of study continued:

The amounts of heparin and protamine will exceed the amounts ordinarily used for anticoagulation but will be similar to that used in established renal hemodialysis.

Hemorrhage should be minimized since protamine will be metered in to neutralize the effects of heparin within the body.

The hazard (and obviously there is some) can not be quantitated. However, the establishment of an A-V shunt in older individuals with impaired myocardium or in L.E. myocarditis might precipitate congestive heart failure. These are hazards that are present and must be accepted if one is to pursue the possible effectiveness of the procedure in the selected human diseases noted.

Lajtha (*) has performed extracorporeal irradiation of the blood on two leukemic patients without reported harmful effects.

In cows after a mean red cell dose of greater than 200,000 rads hemolysis commences when the transit dose is 450-900 rads. Accordingly, the transit dose will be kept as low as possible in the first runs, and blood and urine will be continuously monitored for hemoglobinemia, and hemoglobinuria.

Further Patient Safeguards:

1. Adequate supplies of fresh blood will be made available through previously contacted donors.
2. Multichannel monitoring of vital signs, electrocardiogram, temperature, blood plasma etc., will be maintained.
3. Cardiac Pacemaker and defibrillator will continuously be available.
4. The operative procedure will be performed in the operating room and the patient will be transferred to one of the isolation rooms on Pavillion III. The Co^{60} irradiator will be installed, for the time of the procedure, in the central room of the isolation quarters.
5. Multiple blood volumes will be performed using Volemetron techniques to monitor the procedure.
6. Blood chemistries, especially K^+, BUN, Na^+, and uric acid and blood pH, will be done frequently.
7. Evaluation of the effectiveness of the procedure will be performed by the investigators and an impartial clinical investigator. Organ size, node size, white blood cell count, clinical symptoms, bone marrow, and weight will be evaluated.

Reprints attached.

Extracorporeal Irradiation I, II, III.
Extracorporeal Irradiation of Blood: Calculations of the Radiation Dose.
Lymphocyte Production Measured by Extracorporeal Irradiation, Cannulation and Labeling Techniques.
The Combined Application of Lymph Duct Drainage and Extracorporeal Irradiation of the Blood in the Study of Lymphopoiesis.
* Extracorporeal Irradiation of the Blood. A Possible Therapeutic Measure.

1179834

SUPPLEMENTARY FORM FOR RADIOISOTOPE
ADMINISTRATION TO HUMAN BEINGS

A. Radioisotope

1. Species: (Radioisotope or labeled compound, eg. $Na^{24}Cl$ or 1-C^{14}- glucose) Only those studied

2. Physical characteristics: (Physical half-life; decay scheme (or type, energy and relative frequency of major emissions)

3. Source: (BNL reactor, cyclotron, hot lab.), commercial supplier, etc.)

4. Preparation: (Target material, quantity, special problems)

5. Specific activity and isotopic purity of administered material:

6. Radioassay and calibration procedures: (Include validation to be performed at BNL prior to use)

7. Vehicle and route of administration:

8. Procedures for control of sterility and pyrogenicity: (Or note that commercially supplied isotopes are certified as ready for administration to human beings.) All equipment will be sterile and pyrogen free (30% H_2O_2) washed with sterile, pyrogen free water, dried and finally sterilized with ethylene dioxide. All drugs are USP.

9. Extraneous effects, if pertinent: (Such as pharmacological or toxic actions of the parent compound or vehicle, etc.) None

B. Radiation Dosage

1. Biological half-life or half-lives, including slow components:

   None

2. Organ, cellular, or subcellular localization: (Should account for the effects of special drugs or agents on altering the natural distribution of the radioisotope)

   a. Critical or "target" organ(s): } NA
   b. Gonadal exposure: }

1179835

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 3/3/72

TO: Dr Cronkite

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 18

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 18 is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 10/28 19 64. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval?_____

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed _____

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179836

The Committee on Clinical Investigations and Uses of Radioisotopes hereby approves the program with the following title:

Addendum to Extracorporeal Irradiation of Blood.

CIRC # 18 has been assigned to this program.

Walton W. Shreeve

Walton W. Shreeve, M.D., Ph.D., Chairman

Eugene P. Cronkite

Eugene P. Cronkite, M.D.

Lewis M. Schiffer

~~XXXXXXXXXXXXXXXXXXXX~~ Lewis M. Schiffer, M.D.

Melvin H. Van Woert

Melvin H. Van Woert, M.D.

J. S. Robertson

James S. Robertson, M.D., Ph.D. (ex officio)

Date October 28, 1964

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179837

Addendum to Clinical Investigative Program for Extracorporeal Irradiation of Blood.
(CIRC #18)

1. In view of the lack of adequate therapeutic measures now available for these disease states, and because ECI potentially is useful in their treatment, It is proposed that patients with subacute and acute granulocytic leukemia and monocytic leukemia be admitted to the initial study group. The initial study group of patients includes those with chronic lymphocytic leukemia and acute lymphoblastic leukemia.

Lewis H. Schiffer

1179838

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 3/3/72

TO: Dr Conte

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 18A

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 18A is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 12/15 19 64. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval?_____

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed _____

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179839

18a

December 15, 1964

Dr. W. Shreeve

Ann Kirkpatrick

CIRC Proposals

Dr. Bond has today approved the Addendum and Revision to CIRC #18, Extracorporeal Irradiation of the Blood. A copy has been forwarded to the sponsoring physician, Dr. E. P. Cronkite.

ajk

1179840

Rec'd

The Committee on Clinical Investigations and Uses of Radioisotopes hereby approves the program with the following title:

Extracorporeal Irradiation of the Blood, Addendum and Revision to

CIRC # 18a has been assigned to this program.

Walton W. Shreeve

Walton W. Shreeve, M.D., Ph.D., Chairman

Eugene P. Cronkite

Eugene P. Cronkite, M.D.

Lewis Schiffer

~~Edward Schaffer~~, M.D.
Lewis Schiffer,

Melvin H. Van Woert

Melvin H. Van Woert, M.D.

J. S. Robertson

James S. Robertson, M.D., Ph.D. (ex officio)

Date December 1, 1964

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179841

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 30 November 1964

TO: V. P. Bond, via Chairman of Committee on Clinical Invest. & Isotopes

FROM: E. P. Cronkite

SUBJECT: Addendum and Revision to Clinical Res.

Program Entitled: Extracorporeal Irradiation of the Blood (E.C.I.)

1. In the approved project we are authorized to treat patients with leukemia who have not responded to established therapy.

2. In this addendum and revision we are requesting that we be authorized to treat by E.C.I. untreated acute and chronic lymphocytic leukemia of the adult that has reached the stage that necessitates treatment. Rationale follows:

a. Acute lymphocytic leukemia of the adult responds poorly and for short periods of time to chemotherapy. Chemotherapy frequently eradicates normal hemopoiesis and the patient dies from the sequelae of marrow aplasia. E.C.I. of the blood has been done on one patient with acute lymphocytic leukemia by Thomas. A short remission was obtained. We have placed A-V shunts in three patients now. There have been no side effects and E.C.I. has been carried out for over two weeks in two patients with acute myelocytic leukemia. There has been minor favorable effect on the course of the disease (blast count lower, neutrophils up somewhat). No undesirable effects of the shunt or E.C.I. have been observed. It is believed that we will learn a substantial amount from the study of untreated acute lymphocytic leukemia of the adult. E.C.I. may have some therapeutic value. If, over a 2-4 week period there is no benefit, shunts will be removed and orthodox therapy instituted.

b. Chronic lymphocytic leukemia appears to be a disease in which a slowly enlarging mass of longer-lived lymphocytes encroaches upon the marrow and the lymphoreticular system. For years no therapy is needed. The indications for therapy are combinations of anemia, thrombopenia, granulopenia and organomegaly. Accepted therapy today is a combination of local and generalized therapy with radiation or alkylating agents, blood transfusions prn and corticosteroids at various stages, e.g. hemolytic phase. Striking benefits accrue to the patient for various periods. However, all patients, if they live long enough, suffer irreversible suppression of normal hemopoiesis and frequently die from sequelae of marrow aplasia. The disease in which E.C.I. may be of most benefit is chronic lymphocytic leukemia that is in need of therapy. If the leukemic cells are long-lived, as our thymidine and cytidine studies indicate, it should be possible to deplete the body of the parasitic lymphocytes by killing them with repetitive sessions of E.C.I. for days or weeks. If such happens and the growth pattern of the leukemic lymphocytes is not accelerated, a remission should be induced until the mass of leukemic cells is repleted. Upon depletion

1179842

V. P. Bond, M. D. 30 November 1964

of leukemic cells (subsidence of splenomegaly, adenopathy, lymphocytosis, etc.), anemia, thrombopenia and well-being should improve. The AV shunt would be removed and the patient observed. Experience with renal hemodialysis has shown that AV shunts can be replaced many times; thus E.C.I. can be repeated often, hopefully staving off the institution of generalized chemotherapy or radiotherapy with its deleterious effects. We are confident that there is little hazard to E.C.I. with the exception of that associated with any minor surgical operation in potentially thrombopenic individuals. If a trial period of E.C.I. of 2-4 weeks does not induce clearcut favorable signs, it will be terminated and orthodox therapy started.

3. In view of the preceding rationale, it is specifically requested that we be authorized to commence study and therapy by E.C.I. of adult patients with acute lymphocytic leukemia and chronic lymphocytic elukemia that may need therapy.

Committee on Clinical Investigations and
Uses of Radioisotopes

Approval recommended ✓ Date 12/1/64

Disapproval — Date —

V P Bond DEC 15 1964

V. P. Bond, M.D.
Chairman, Medical Department

1179843

The Committee on Clinical Investigations and Uses of Radioisotopes hereby approves the program with the following title:

Extracorporeal Irradiation of the Blood, Addendum and Revision to

CIRC # 18a has been assigned to this program.

Walton W. Shreeve, M.D., Ph.D., Chairman

Eugene P. Cronkite, M.D.

Lewis Schiffer, M.D.

Melvin H. Van Woert, M.D.

James S. Robertson, M.D., Ph.D. (ex officio)

Date December 1, 1964

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179844

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 30 November 1964

TO: V. P. Bond, via Chairman of Committee on Clinical Invest. & Isotopes

FROM: E. P. Cronkite

SUBJECT: Addendum and Revision to Clinical Res. Program Entitled: Extracorporeal Irradiation of the Blood (E.C.I.)

1. In the approved project we are authorized to treat patients with leukemia who have not responded to established therapy.

2. In this addendum and revision we are requesting that we be authorized to treat by E.C.I. untreated acute and chronic lymphocytic leukemia of the adult that has reached the stage that necessitates treatment. Rationale follows:

a. Acute lymphocytic leukemia of the adult responds poorly and for short periods of time to chemotherapy. Chemotherapy frequently eradicates normal hemopoiesis and the patient dies from the sequelae of marrow aplasia. E.C.I. of the blood has been done on one patient with acute lymphocytic leukemia by Thomas. A short remission was obtained. We have placed A-V shunts in three patients now. There have been no side effects and E.C.I. has been carried out for over two weeks in two patients with acute myelocytic leukemia. There has been minor favorable effect on the course of the disease (blast count lower, neutrophils up somewhat). No undesirable effects of the shunt or E.C.I. have been observed. It is believed that we will learn a substantial amount from the study of untreated acute lymphocytic leukemia of the adult. E.C.I. may have some therapeutic value. If, over a 2-4 week period there is no benefit, shunts will be removed and orthodox therapy instituted.

b. Chronic lymphocytic leukemia appears to be a disease in which a slowly enlarging mass of longer-lived lymphocytes encroaches upon the marrow and the lymphoreticular system. For years no therapy is needed. The indications for therapy are combinations of anemia, thrombopenia, granulopenia and organomegaly. Accepted therapy today is a combination of local and generalized therapy with radiation or alkylating agents, blood transfusions prn and corticosteroids at various stages, e.g. hemolytic phase. Striking benefits accrue to the patient for various periods. However, all patients, if they live long enough, suffer irreversible suppression of normal hemopoiesis and frequently die from sequelae of marrow aplasia. The disease in which E.C.I. may be of most benefit is chronic lymphocytic leukemia that is in need of therapy. If the leukemic cells are long-lived, as our thymidine and cytidine studies indicate, it should be possible to deplete the body of the parasitic lymphocytes by killing them with repetitive sessions of E.C.I. for days or weeks. If such happens and the growth pattern of the leukemic lymphocytes is not accelerated, a remission should be induced until the mass of leukemic cells is repleted. Upon depletion

1179845

V. P. Bond, M. D. 30 November 1964

of leukemic cells (subsidence of splenomegaly, adenopathy, lymphocytosis, etc.), anemia, thrombopenia and well-being should improve. The AV shunt would be removed and the patient observed. Experience with renal hemodialysis has shown that AV shunts can be replaced many times; thus E.C.I. can be repeated often, hopefully staving off the institution of generalized chemotherapy or radiotherapy with its deleterious effects. We are confident that there is little hazard to E.C.I. with the exception of that associated with any minor surgical operation in potentially thrombopenic individuals. If a trial period of E.C.I. of 2-4 weeks does not induce clearcut favorable signs, it will be terminated and orthodox therapy started.

3. In view of the preceding rationale, it is specifically requested that we be authorized to commence study and therapy by E.C.I. of adult patients with acute lymphocytic leukemia and chronic lymphocytic elukemia that may need therapy.

Committee on Clinical Investigations and
Uses of Radioisotopes

Approval recommended ✓ Date 12/1/64

Disapproval — Date —

V P Bond 1964

V. P. Bond, M.D.
Chairman, Medical Department

1179846

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 3/3/72

TO: Dr Cronkite

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 186

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 186 is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 2/25 19 65. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval?_____

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed _____

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179847

The Committee on Clinical Investigations and Uses of Radioisotopes hereby approves the program with the following title:

Addendum II to Clinical Investigation Program for Extra-corporeal Irradiation of Blood.

CIRC # 18(b) has been assigned to this program.

Walton W. Shreeve

Walton W. Shreeve, M.D., Ph.D., Chairman

E. P. Cronkite

Eugene P. Cronkite, M.D.

Lewis M. Schiffer M.D.

~~Eckart Schackow, M.D.~~ Lewis M. Schiffer, M.D.

Melvin H. Van Woert

Melvin H. Van Woert, M.D.

J. S. Robertson

James S. Robertson, M.D., Ph.D. (ex officio)

Date February 25, 1965

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179848

Rec'd 2/11 Initial Approval: VB

V.P. Bond, M.D., Chairman
Clinical Investigation Committee #18(b)

Addendum II to Clinical Investigation Program for Extracorporeal Irradiation of Blood.

Animal studies by Dr. Cronkite and his group indicate that skin homograft rejection is delayed by extracorporeal irradiation of blood. We intend to take advantage of this delay in rejection by "conditioning" patients with ECI prior to kidney homotransplantation. Kidney homotransplantation will not be performed in this institution. Dr. John Merrill of Peter Bent Brigham Hospital, Boston, Massachusetts has agreed to send us patients, with A-V shunts already in place, on whom we will do the ECI. They will return to Boston, receive their transplant, and perhaps return at intervals for further ECI. These patients will have no renal function and extrarenal dialysis will be necessary to support life before transplantation. The dialysis will be performed in Boston. In addition to the information obtained from the homotransplantation experiments, valuable hematologic data on the effects of ECI in non-leukemic individuals will be obtained.

Lewis M. Schiffer

Lewis M. Schiffer, M. D.

Committee on Clinical Investigations and Uses of Radioisotopes
Approval recommended XX Date 2/25/65
Disapproval - Date -

V.P. Bond

V. P. Bond, M.D. Chairman, Medical Dept.

aw 2/1/65

1179849

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 3/2/72

TO: Dr Lorfuto

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 18C

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 18C is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 7/29 19 65. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval?_____

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed _____

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179850

The Committee on Clinical Investigations and Use of Radioisotopes hereby approves the program with the following title:

ADDENDUM III to EXTRACORPOREAL IRRADIATION OF THE BLOOD

CIRC # 18(c) has been assigned to this program.

George C. Cotzias, M.D., Chairman

Lewis M. Schiffer, M.D.

Knud N. Knudsen, M.D.

Walton W. Shreeve (Acting Chairman)
Walton W. Shreeve, M.D., Ph.D. (ex officio)

Date: JUL 29 1965

Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179851

12 July 1965
Dr. L. M. Schiffer
Received 7/14/65 Initial Approval:
CIRC 18(c)

V.P. Bond, M.D.,
Chairman

III Addendum to Extracorporeal Irradiation of the Blood (Protocol CIRC #18.)

Two drugs are to be used in conjunction with these studies that have not yet been officially approved by the FDA. Both drugs have extensive backgrounds in animal and human use and their dosage, therapeutic index and side effects are known. The appropriate FDA forms for investigation of new drugs have been filed.

Amphotericin B (Fungizone, E. R. Squibb) supplied as a troche in 10 mgm tablets is to be used as an antimycotic agent. Better results have been obtained with this drug than with Nystatin (Mycostatin, E. R. Squibb). Side effects are negligible, the drug being non-absorbable. Dosage is 3 to 4 troches daily.

Approval recommended ✓ Date 8/5/65

Disapproval_____ Date_____

V. P. Bond

V. P. Bond, M.D., Chairman, Medical Department

1179852

12 July 1965
Dr. L. M. Schiffer

Azathioprine (Imuran, Burroughs Wellcome and Company) is a thiopurine analogue designed to be an immunosuppressive and antineoplastic agent. It is also known as B.W. 57-322 and 6-(1-methyl -4 nitro -5 imidozolyl) thiopurine. For leukemic patients the effectiveness of Imuran is similar to that of 6-mercaptopurine to which it partially degrades. For suppression of the immune response it has a higher therapeutic index than 6-MP. It is planned to use this drug in accordance with the protocol involving the renal homotransplant patients. The same dosage schedule that is instituted by Dr. Merrill in Boston will be followed at Brookhaven. This amounts to 1-4 mgm/kg body weight, orally daily. Hematologic, hepatic and renal function will be followed closely.

1179853

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 3/3/72

TO: Dr Cronkite

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 18D

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 18D is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 1/23 19 69. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

Approximately how many patients have been submitted to the experimental regime since the last approval?_____

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER _____ IS: Continuing ☐

Inactive ☐

Signed _____

Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179854

The Committee on Clinical Investigations and Use of Radioisotopes hereby approves the program with the following title:

EXTRACORPOREAL IRRADIATION OF THE BLOOD (ECIB)

CIRC # 18 d has been assigned to this program.

George C. Cotzias.

George C. Cotzias, M.D. Chairman

Harold L. Atkins

Harold Atkins, M.D.

Donald C Borg

Donald C. Borg, M.D.

Horton A. Johnson

Horton A. Johnson, M.D.

Date: January 23, 1969

Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Committee on Clinical Investigations and Uses of Radiosotopes

Approval Recommended ✓ Date 1/23/69

Disapproval _____ Date _____

E.P. Cronkite

E.P. Cronkite, M.D.
Chairman, Medical Department

Jan 27, 1969

Date

1179855

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: January 23, 1969

TO: Dr. Eugene P. Cronkite

FROM: Clinical Investigation Committee
G. C. Cotzias, Chairman

SUBJECT: Addendum and revision to CIRC #18 - ECIB

g.cc.

The Committee on Clinical Investigations and Isotopes unanimously approves this modification of proposal CIRC #18. Questions pertaining to technical problems have been satisfactorily answered by Drs. Chanana and Rai. There is sufficient evidence in humans and animals to indicate that the proposal is safe. We are unanimously agreed on the high scientific and clinical merits of this revision.

cc: Dr. A. Chanana
Dr. K. Rai
Dr. H. L. Atkins
Dr. D. C. Borg
Dr. H. A. Johnson

117985b

CIRC # 18(d)
1-10-69

E.P. Cronkite, M.D.
Chairman

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 8 January 1969

TO: Dr. E.P. Cronkite, through the Committee on Clinical Investigations and Isotopes

FROM: Dr. K.R. Rai, Dr. A.D. Chanana

SUBJECT: ADDENDUM AND REVISION TO CIRC #18 - ECIB

PROGRAM ENTITLED: Extracorporeal irradiation of the blood (ECIB).

In this addendum and revision we request authorization to treat patients with chronic lymphocytic leukemia (CLL) in the early stage of the disease by:

A. ECIB

B. Extracorporeal irradiation of lymph (ECIL) and thoracic duct drainage of lymphocytes.

SPONSORING PHYSICIANS: Dr. K.R. Rai, Dr. A.D. Chanana

RESPONSIBLE INVESTIGATORS: Dr. K.R. Rai, Dr. A.D. Chanana, Dr. G.P. Tauro, Dr. E.P. Cronkite

REVIEW OF STATUS OF CIRC #18 AND ADDENDA:

CIRC #18, as approved originally in April 1964 (with Dr. E.P. Cronkite and Dr. L.M. Schiffer as sponsoring physicians), authorized the application of ECIB in the treatment of autoimmune diseases, lymphoma and leukemia (except granulocytic) that did not respond satisfactorily to the established therapy. It was stipulated in the protocol that if the results warranted, at a later stage in the development of the procedures, patients may be treated in the earlier phases of their disease states.

In October 1964 an addendum was approved (sponsored by Dr. Schiffer) to permit treatment of sub-acute and acute granulocytic leukemia and monocytic leukemia by ECIB.

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In December 1964 an addendum and revision (18a) (sponsored by Dr. Cronkite) was approved to authorize treatment of untreated acute and chronic lymphocytic leukemia in adults who had reached the stage that necessitates treatment.

Addenda 18(b) and (c) concern ECIB in kidney transplantation and in conjunction with drugs (Amphotericin B and Imuran) which, at that time, were not approved by U.S.F.D.A. , and these addenda are not relevant to our present proposal.

RATIONALE FOR THE PROPOSED ADDENDUM AND REVISION:

In the intervening period since approval of CIRC #18, extensive experience has been gained with regard to the use of ECIB in the therapy of CLL at a stage in the disease when treatment was warranted. The results of this trial of therapy have been encouraging, and have been submitted for publication by Schiffer et al.[1] (preprint attached). A reprint of our recently published report on the experience with arteriovenous shunts in leukemic patients is also attached.[2]

Keeping in mind the nature of the disease (CLL), as outlined in CIRC #18a (Dr. Cronkite's memo of 30 November 1964, paragraph 2b), it would now seem appropriate to investigate the treatment of CLL by depletion of body of the leukemic lymphocytes at an early stage of the disease. The aim would be to reduce the mass of the leukemic cells in order to delay the onset of symptoms.

The lymphocytes in the peripheral blood originate in the lymph nodes, bone marrow, spleen and probably in the thymus, and it has been shown that there is a recirculating population of lymphocytes moving from the peripheral blood to the lymph nodes,[3] re-entry to the peripheral blood being via the thoracic duct lymph. This recirculation has been shown to occur in hematologically normal man,[4] and in the presence of CLL.[5]

Lymphocytopenia has been produced in CLL by ECIB by our group[1] and by others.[6,7] As the blood lymphocyte count falls during ECIB, there is usually an accompanying reduction in the size of the enlarged lymph nodes and spleen, as evidenced by a node biopsy or lymphangiogram and in vivo scans of spleen.

Our group has also gained much experience in the technique and maintenance of thoracic duct cannulation in cattle since the original report.[8] Subsequently, detailed techniques of such cannulations in human beings have also been reported by several workers.[9,10] A profound fall in the output of lymphocytes in the thoracic duct lymph and in the blood lymphocyte count is achieved by extracorporeal irradiation of lymph (ECIL) as reported by us[11-13] and by continuous drainage of thoracic duct lymph.[14-17]

It is therefore proposed to couple thoracic duct cannulation with ECIB in order to deplete the body, as far as possible, of the pool of mobilizable lymphocytes. The procedures proposed to be employed would be: (1) Extracorporeal irradiation of the lymph, or (2) continuous centrifugation of the thoracic duct lymph. In either case, the lymph would be returned to the patient. The technique which would be used for the thoracic duct cannulation would be identical with that proposed in CIRC #2(b) (copy attached).

The method of irradiating the thoracic duct lymph would be identical to that used for ECIB, with the exception that the period for irradiation would not be limited by harmful effects to the red cells and could be extended up to 24 hours per day, and that a completely closed system will be employed. Continuous centrifugation of lymph is now being successfully carried out in animals by our group, and it is proposed to use this technique to deplete the lymph of lymphocytes in human CLL. This method is preferred because cell-free lymph is returned to the patient, thereby preventing any disturbance in the physiology of fluid, electrolytes and proteins, etc.

Associated with the above study, it is proposed to gain information regarding the cell pool size, proliferation rate and mobilization, using techniques of cell labeling, as detailed in CIRC #2 (copy attached).

In view of the preceding rationale, it is requested that we be authorized to commence study and therapy of patients with early CLL, using a combination of ECIB and thoracic duct lymph irradiation or centrifugation.

PATIENT CONSENT:

All procedures to be carried out, plus all foreseeable complications and dangers, will be explained to the patient on at least two separate occasions by one of the responsible investigators. The next of kin will also have the procedures explained. Having been given an adequate opportunity to question the investigators, if the patient and concerned next of kin are agreeable for the procedures to be carried out, a permission form will be given to the patient for his study and signature.

At no time will any pressure be put on the patient, and no guarantees will be given to the patient. Circumstances arising during the course of investigation may cause alteration of the proposed study if deemed necessary in the interest of the patient.

The individual patient's own welfare will be of paramount consideration at all times.

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REFERENCES

1. Schiffer, L.M., Atkins, H.L., Chanana, A.D., Cronkite, E.P., Greenberg, M.L., Okuyama, S., Rai, K.R., Stryckmans, P.A., Vincent, P.C., Extracorporeal irradiation of blood in man. IV: Treatment of chronic lymphocytic leukemia. Submitted Ann. Int. Med. (copy of preprint attached).

2. Chanana, A.D., Cronkite, E.P., Greenberg, M.L., Rai, K.R., Schiffer, L.M., Stryckmans, P.A., Vincent, P.C., Experience with arteriovenous shunts in leukemic patients. Arch. Surg. 97, 154-160, 1968 (reprint attached).

3. Gowans, G.L., Knight, E.J., The route of recirculation of lymphocytes in the rat, Proc. Roy. Soc. B 159, 257, 1964.

4. Perry, S., Irvin, G.L. III, Whang, J., Studies of lymphocyte kinetics in man, Blood 29, 22-28, 1967.

5. Binet, J.L., Villeneuve, B., Becart Renee, Logeais, Y., Laudat, P. et Mathey, J., Temps de passage dans le canal thoracique des lymphocytes du sang de la leucemie lymphoid chronique, Nouv. Rev. Fr. d'Hematologie 7, 621-624, 1967.

6. Thomas, E.D., Epstein, R.B., Eschbach, Jr., J.W., Prager, D., Buckner, C.D., Marsaglia, G., Treatment of leukemia by extracorporeal irradiation. New Engl. J. Med. 273, 6-11, 1965.

7. Storb, R., Epstein, R.B., Buckner, C.D., Thomas, E.D., Treatment of chronic lymphocytic leukemia by extracorporeal irradiation. Blood 31, 490-502, 1968.

8. Chanana, A.D., Cronkite, E.P., Semipermanent extracorporeal arteriovenous and thoracic duct-venous shunts in cattle. Am. J. Vet. Res. 27, 683-688, 1966.

9. Artz, C.P., Hargest, T.S., Sarles, H.E., Technique for cannulation of thoracic duct. Surg., Gyn., Obst. 124, 1085-1087, 1967.

10. Tilney, N.L., Murray, J.E., Chronic thoracic duct fistula. Operative technic and physiologic effects in man. Ann. Surg. 167, 1-8, 1968.

11. Joel, D.D., Chanana, A.D., Cronkite, E.P., Schiffer, L.M., Modification of skin allograft immunity by extracorporeal irradiation of lymph. Transplantation 5, 1192-1197, 1967.

12. Cronkite, E.P., Extracorporeal irradiation of blood and lymph. Experimental studies on homotransplantation and human leukemia. BNL #10403.

13. Cronkite, E.P., Chanana, A.D., Schnappauf, Hp., Extracorporeal irradiation of blood and lymph in animals. Its effect on homografts and on lymphoma. New Engl. J. Med. 272, 456-461, 1965.

14. Tunner, W.S., Carbone, P.P., Blaylock, K., Irvin, G.L., Effect of thoracic duct drainage on the immune response in man. Surg., Gyn., Obst. 121, 334-338, 1965.

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15. Tilney, N.L., Murray, J.E., The thoracic duct fistula as an adjunct in immunosuppression in human transplantation. Transplantation 5, 1204, 1967.

16. Sarles, H.E., Remmers, A.R., Conales, C.O., Fish, J.C., McKay, G., Hawthorne, S., Ritzman, S.E., Suppression of cellular immunity by lymph duct drainage in man (abstract). Clinical Res. 16, 83, 1968.

17. Cronkite, E.P., Jansen, C.R., Rai, K.R., Cottier, H., Fliedner, T.M., The combined application of lymph duct drainage and extracorporeal irradiation of the blood in the study of lymphopoiesis. In the Guiness Symposium on Cell Proliferation, Trinity College, Dublin. Blackwell Publishers, England, page 125, 1963.

1179862

Declared inactive since nothing has been done on study in a long time

by Mr Finn

1179863

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: June 10, '71

TO: Dr. A. D. Chanana

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 18E

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 18E is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on APRIL 20, 19 70. Do you wish to make any substantive changes in your proposal? NO

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office? _____. Please include the nature and frequency of such effects.

The program has not been initiated so far. There have been some delays in getting the renal transplant program off the ground at the Meadowbrook Hospital

Approximately how many patients have been submitted to the experimental regime since the last approval? NONE

The Sponsoring Physician on this proposal is Chanana & Cronkite. Has there been a change of Sponsoring Physician or Responsible Investigators? NO

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER 18E IS: Continuing ☑

Inactive ☐

Signed Arjun Dev Chanana June 11, 1971
Date

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179864

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 31 March 1971

TO: Chairman, Clinical Investigation & Uses of Radioisotopes Committee

FROM: A. D. Chanana, M.D.

SUBJECT: CIRC # 18E ANNUAL REVIEW

At this time I have no change to report with regard to the proposal as originally submitted, and accepted as CIRC # 18E.

ADC:mas

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The Committee on Clinical Investigations and Use of Radioisotopes hereby approves the program with the following title:

Pre & Post Transplant ECIB on patients from the Meadowbrook Hospital

CIRC # 18 (e) has been assigned to this program.

Harold L. Atkins

Harold Atkins, M.D., Chairman

D. C. Borg

Donald C. Borg, M.D.

S. H. Cohn

Stanton Cohn, Ph.D.

Horton A. Johnson

Horton A. Johnson, M.D.

Kanti R. Rai

Kanti Rai, M.D.

Date: 4/20/70

Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Committee on Clinical Investigations and Uses of Radioisotopes

Approval Recommended X Date 4/20/70

Disapproval _____ Date _____

E. P. Cronkite

E.P. Cronkite, M.D.
Chairman, Medical Department

4/23/70

Date

1179866

Committee on Clinical Investigations and Use of Radioisotopes
Meeting of April 20, 1970

Present: Drs. Cohn, Borg, Rai, Johnson and Atkins

The following proposals were acted upon:

a) CIRC 18(e) - Pre & Post Transplant ECIB on patients from Meadowbrook Hospital. There is no change in the proposal as originally stated and the purpose of submission was to bring the committee records up-to-date with information obtained to date. There was unanimous approval.

b) CIRC 53 - Studies of fat Cellularity and Lean Body Mass in Grossly Obese Children. This was approved with minimal discussion. No irradiation or administration of drugs is contemplated.

c) CIRC 54 - In vivo activation analysis of patient with severe Cushing's Disease. This proposal is for one patient only, a 15 year old boy. The proposal was approved with the proviso that the form be amended to state, in effect, that radiation exposure from the activation will be minor compared to other irradiation the patient will receive during his workup for his disease. Periodic examinations of the lens of the eye was recommended.

Respectfully submitted,

Harold L. Atkins

Harold L. Atkins, M. D.

/bn

cc: Committee Members

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CIRC #18 (e)
4-13-70

E. P. Cronkite, M.D.
Chairman

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 8 April 1970

TO: Dr. E. P. Cronkite, via Chairman of Committee on Clinical Investigation and Isotopes.

FROM: Dr. A. D. Chanana - Dr. E. P. Cronkite

SUBJECT: ADDENDUM & REVISION TO CIRC # 18

Program Entitled: Extracorporeal Irradiation of the Blood.

CIRC # 18b, authorized us to utilize extracorporeal irradiation of blood for "conditioning" the kidney allograft recipients. This approval of the CIRC was obtained on February 25, 1965. As a result of this authorization, 4 patients with renal transplants were treated with ECIB in collaboration with Dr. J. Merrill of Peter Bent Brigham Hospital, Boston. Two of these patients showed a definite response to ECIB, during rejection episodes. This collaborative study has been inactive for some years and is not expected to be revived.

A similar study, in collaboration with the Meadowbrook Hospital, Renal Diseases Department, is under consideration and the first patient for ECIB treatment is expected to be available in the next month or two. The protocols are essentially similar to those authorized in CIRC # 18b, but in view of some further progress in the use of ECIB in Clinical and Experimental renal transplantation, uptodate information is provided for the perusal of the Committee in the following appendices.

Appendix # 1. Extracorporeal Irradiation of the Blood (ECIB) in Renal Transplantation.

Appendix # 2. Methodology, Extracorporeal Irradiation of Blood (ECIB). Includes the proposed protocols for ECIB of pre- and post transplant ECIB of patients from the Meadowbrook Hospital.

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All of the surgical transplantation work will be carried out at the Meadowbrook Hospital. Patients requiring ECIB will be transferred to the Medical Department, Brookhaven National Laboratory

In view of these considerations, it is requested that we be authorized to carry out pre- and post transplant ECIB on patients from the Meadowbrook Hospital.

ADC:mas

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Extracorporeal Irradiation of Blood (ECIB) in Renal Transplantation

The influence of radiation upon immunity was discovered by Benjamin and Sluka[1] in 1908, when they observed the suppression of antibody production in antigen stimulated animals. In 1950, Dempster et al[2], observed survival twice as long in irradiated as in non-irradiated rabbits. The lymphocyte family of cells is very sensitive to radiation[3]. The basic reason to apply radiation in the management of allotransplants is to kill the lymphocytes that are present and to suppress new production.

Although irradiation to the whole body is very efficient in suppressing immunity, this procedure is complicated by the production of serious injury in particular to the hemopoietic tissues and the intestinal epithelium, which is dose dependent. One must give a dose of suprelethal radiation in animals for the maximum suppression of immunity and prolongation of allograft survival. This must be followed by bone marrow transplantation to prevent the effects of irreversible bone marrow depression. Unfortunately the bone marrow transplantation also restores the immunological capability of the host. In such a situation, survival benefit to the transplanted organ will result only if the donors of the bone marrow and the transplanted organ were to be

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identical. Such a combination is certainly not practical for routine human transplantation. Moreover, secondary disease (graft versus host disease), produced by the reaction of the grafted immunologically competent cells in the bone marrow against the host tissues is a serious, disabling, and frequently fatal disease.

In view of these difficulties with whole body radiation, the idea of peripheral destruction of blood lymphocytes by ECIB as an aid in the management of organ transplantation is rather attractive. Our group at the Brookhaven National Laboratory pioneered the application of extracorporeal irradiation of blood and lymph for the studies of (i) lymphopoiesis[4] (ii) transplantation immunity[5] and (iii) leukemic cell proliferation[6]. These techniques have now spread to other centers in this country and abroad. ECIB not only induces severe and sustained blood lymphocytopenia[4] but also produces depletion of lymphocytes from the lymphoid organs such as lymph nodes, the thymus, and the spleen[7]. This tissue depletion is due to the fact that lymphocytes are constantly recirculating from blood to the lymphoid organs. ECIB has no deleterious effect on the body at large. One is concerned about the effects of ECIB on the following constituents of the blood: (1) Proteins (2) Granulocytes (3) Erythrocytes (4) Platelets and (5) Lymphocytes. Within the range of radiation employed for ECIB, it is very unlikely that one can produce deleterious effects on plasma proteins. Rosenau and Moon[8] have shown that whereas the immune competent cells can be inactivated by relatively low doses of irradiation, considerably higher doses are required to interfere with the function of antibodies (proteins) in the plasma. Moreover the blood half time of some of the

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plasma proteins is so short that intermittent repetitive ECIB would hardly interfere with the normal turnover rates of these proteins. Blood granulocytes have a blood half life time of approximately 7 hours. Here again the effects of intermittent, repetitive ECIB can be ignored for all practical purposes due to a very high turnover rate of these cells in the blood. In addition to these theoretical considerations, we have not observed any deleterious effects of ECIB on plasma proteins and blood granulocytes, both in animal and human studies during the past years.

Erythrocytes[9,10] and platelets[11] can suffer damage as a result of radiation. Fortunately, the lymphocytes are far more radiosensitive than erythrocytes and platelets. This marked difference in radiosensitivity has enabled us to carry out ECIB in human patients (leukemia,[12-15] renal transplantation[16]) without producing undue damage to blood erythrocytes and platelets. It has been possible to keep the total dose of ECIB below the threshold required for damage to erythrocytes. This dose monitoring to erythrocytes involves detailed, time consuming mathematical calculations[17]. In order to unable us to keep daily charts of radiation dose to erythrocytes during sessions of ECIB, appropriate computor programs have been utilized. Since the computor facilities are located at the Brookhaven National Laboratory, we have had no difficulty in tailoring ECIB schedules for individual patients.

Our group at the Medical Department Brookhaven National Laboratory started to investigate the role of ECIB in allograft

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rejection in 1963. The results of these investigations in brief are:

1. Intermittent, repetitive ECIB prolonged the skin allograft survival time of calves to 2 to 3 times the survival time in control calves.[5,18]

2. Combination of Imuran and ECIB was slightly more effective in prolonging the calf skin allograft survival time than ECIB alone. Imuran alone in the doses employed in these studies had no beneficial effect.[19] Combination of thymectomy and ECIB has also been studied[20].

3. Techniques employing regional extracorporeal irradiation have demonstrated the anatomical pathways involved in skin allograft rejection and have also shown the ability of extracorporeal irradiation to interfere with the function of immunologically activated lymphocytes. Utilizing regional extracorporeal irradiation, we were able to prolong the skin allograft survival in calves, for the duration of the treatment (up to 68 days)[21,22]

4. We have been investigating the role of ECIB in renal transplantation in goats for about one year, and the results so far are as follows:

a. Survival time of bilaterally nephrectomized goats has ranged from 8-10 days.

b. Survival time of bilaterally nephrectomized goats with renal allotransplants has ranged from 15-18 days.

c. Survival time of bilaterally nephrectomized goats with renal transplants, receiving ECIB to approximately 5 blood volumes a day for 10-20 days has ranged 14-24 days

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d. Survival time of 3 bilaterally nephrectomized goats with renal transplants receiving ECIB to 20-30 blood volumes a day for 5-7 days has been 25, 28 and 85 days. Further studies with different schedules of ECIB are currently under progress.

Since 1965, experience with ECIB in human renal transplantation has been accumulating at various centers as summarized below:

1. In 1965 we treated 4 patients at the Medical Department, Brookhaven National Laboratory with post transplant ECIB. These studies were carried out in collaboration with Dr. J. P. Merrill of the Peter Bent Brigham Hospital, Boston, Massachusetts. In two of these patients, it was possible to reduce the dose of immunosuppressive drugs due to improvement in transplant function following ECIB[10].

2. Maginn et al[23] (Cambridge, England) were able to reverse an acute early rejection episode in one patient following ECIB. There was, however, no response to ECIB in another patient suffering from a late rejection episode.

3. Persson et al[24] (Gotberg, Sweden) have employed ECIB in human renal transplantation since 1965. As of early 1969, they had treated 18 patients with ECIB and standard immunosuppression, and 60 patients with standard immunosuppression alone. Their conclusions of this experience are as follows:

a. In patients receiving ECIB, there were significantly smaller numbers of early rejection episodes.

b. In patients receiving ECIB, there was a significantly higher number of functioning transplants.

4. In 1967, Winkelstein et al[25] (UCLA, California) reported the

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use of ECIB in 3 patients with renal transplants. They reported good function in two of these patients. The third patient had received only 4 hours of ECIB.

5. Wolfe et al[26] (Medical College of Virginia) have reported success with ECIB in controlling early acute rejection episodes, when there has been no response to standard immunosuppressive regimen.

6. Weeke et al[27] (University of Copenhagen, Denmark) have recently reported their results in all patients receiving ECIB. They reported only two minor episodes of rejection in this group. Drs. Weeke and Anderson[28] inform us that there are two groups in Denmark engaged in renal transplantation. The protocols of these two groups are essentially similar except for the use of ECIB by Weeke et al. From the preliminary analysis of the data, it appears as if the results of the unit employing ECIB as an adjunct are better than the other unit. There is a very significant reduction in the early acute rejection episodes in the ECIB group.

In all the clinical studies carried out so far, ECIB has been utilized as an adjunct to the standard immunosuppressive therapy. Such studies can only show certain trends with or without ECIB. In order to more precisely define the role of ECIB in renal allotransplantation, further animal studies are desirable. We intend to continue our studies of ECIB in goat renal transplants with and without the addition of other immunosuppressive regimens, in order to define the best possible schedule of ECIB.

Despite the need for additional animal studies, we feel that there is enough data available from animal and human studies to justify the use of ECIB as an adjunct for the management of renal transplant patients at the Meadowbrook Hospital, and at the Hospital of Medical Research Center, Brookhaven National Laboratory.

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References

1. Benjamin, E., and Sluka, E.: Antikorperbildung nach experimentaller Schadigung des hamatopoetischen Systems durch Rontgenstrahlen. Wien Klin, Wschr. 21, 311, 1908.

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27. Personal Communication.

28. Personal Communication.

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METHODOLOGY

Extracorporeal Irradiation of Blood (ECIB)

A. TECHNIQUE

The potential recipients of renal transplants have either a arteriovenous shunt or a arterio-venous fistula for hemodialysis.

For ECIB, the arterial and venous ends of the fistula are connected to the two free ends of the silastic tube coil (medical grade silicone) that is wound around the source of radiation (gamma or beta source). The blood flows from the arterial end to the venous end via the irradiator. Pumping of blood is not required. The length of the silastic tube coil varies from 8 to 12 feet and of the part of the coil exposed to the source of radiation varies from 6 inches to 18 inches. The blood is irradiated while in transit thru that part of the coil which is exposed to the radiation source. The radiation dose received by the blood (transit dose) during one passage thru the coil exposed to the radiation is dependent upon the flow rate of the blood, the volume of the coil and the dose rate of the source which is fixed by the radioactive decay.

The blood volume of the patient is determined by ^{51}Cr label, radio-iodine label or from body weight data. From the flow rate of the blood thru the coil (flow rate is determined by injecting a 0.5ml bubble of air on the arterial side and timing its arrival on the venous side), the time required for irradiation of one blood volume is determined. From these data the following can be determined.

1. Time required for a specified number of blood volumes to be irradiated/session.
2. Number of transits of blood thru the irradiator.

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3. The transit dose received by the blood. The transit dose can be varied either by changing the length of the coil exposed to the source or by changing the position of the source inside the coil.

For calculation of the cumulative dose to erythrocytes during each session and over a protracted cource of ECIB, the data obtained daily is fed to the computor. The information received from the computor enables us to safely plan the ECIB schedules.

At the end of each ECIB session, the blood in the silastic coil is returned to the patient and shunt short-circuited. The extra-corporeal shunt volume during ECIB is so small (10-30 ml) that priming with normal saline is quite adequate. There is no loss of blood in the extracorporeal coils.

In some patients, due to a tendency for the blood to clot in the extracorporeal coils, heparinization is required during ECIB.

ECIB can be carried out simultaneously with hemodialysis. The blood can be shunted thru the irradiator either before its arrival at the dialysis machine or after its departure from the dialysis machine.

B. EQUIPMENT AND SPACE

Currently, the Hospital of the Medical Research Center, Brookhaven National Laboratory, is equipped with a two bed unit containing a gamma source of radiation (^{60}Co, 3,000 curies). Two patients can receive ECIB simultaneously. Dependent upon the time required for each session of ECIB for individual patients, 2 to 6 patients can receive ECIB/day. One ECIB nurse can carry out the procedure on two patients at a time.

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The unit is not used for any other purpose. During ECIB, patients stay in the bed. The unit is equipped with a television set for the benefit of the patients.

Entry to this unit is strictly restricted to authorized personnel. Use of cap, mask, gown and shoe covers is essential prior to the entry to this room.

Since the radioactive source is not portable, the patients have to be brought to the source rather than the other way around. Fortunately the ECIB unit is adjacent to the pavilion (one bed/room, 11 rooms) where the potential transplant recipients will enter. Facilities for strict isolation of patients, if required, are available.

For a source to be portable, it will have to be a beta source, as gamma sources require too heavy a lead shielding. So far there were no satisfactory beta ray sources available. Currently we are in the process of investigating a promising commercially available beta source. If the animal trials turn out to be satisfactory, then it would be advisable to procure this source, particularly for post transplant ECIB, where it is not feasible to move the patient from his own room. Moreover treatment of some of the post transplant rejection episodes could also be carried out at the Meadowbrook Hospital.

C. PERSONNEL:

1. ECIB Nurse As described under "technique", the ECIB procedure at the Hospital of the Medical Research Center, Brookhaven National Laboratory is carried out by nurses who have been trained for this procedure.

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For Hematological investigations:

a. Daily complete blood counts, before and at the end of each ECIB session.

b. Blood volume measurements

c. Technical help in research studies associated with hemopoiesis during ECIB.

3. Supervision

Dr. E. P. Cronkite, Medical Department, Brookhaven National Laboratory

Dr. A. D. Chanana, Medical Department, Brookhaven National Laboratory

4. Resident Staff

It will be mandatory to have one resident available for the day to day management of potential recipients during their stay at the Hospital of the Medical Research Center, Brookhaven National Laboratory.

D. MISC. MATERIALS

Silastic medical grade tubing is the only substantive material required for ECIB. Individual coils are prepared for patients and at the end of each session of ECIB, the coils are thoroughly cleaned with detergents and deionized water prior to autoclaving. The coils are changed when the accumulative dose of radiation received by the Silastic approaches 5 mega rads.

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E. PROPOSED ECIB SCHEDULE

I. PRETRANSPLANT ECIB

Potential recipients will be admitted to the Hospital of the Medical Research Center, Brookhaven National Laboratory, a few days prior to transplantation.

Daily repetitive. ECIB will be carried out in order to bring blood lymphocyte count down to approximately 10-20% of the pre-treatment level. The total number of blood volumes irradiated will range from 50-200, depending upon the transit dose employed. The patients will return to the Meadowbrook Hospital for transplantation.

II. POST TRANSPLANT ECIB

(INITIALLY FOR EARLY REJECTION EPISODES AND LATER FOR ROUTINE IMMUNE SUPPRESSION).

Until suitable beta sources become available, the post transplant ECIB will be carried out at the Hospital of the Medical Research Center, Brookhaven National Laboratory. Depending upon the transit dose employed, about 5 to 20 blood volumes will be irradiated daily for up to 7 days or so.

These schedules of ECIB will be kept under constant review, in order to incorporate the information that becomes available from the current animal studies.

F. ROUTINE INVESTIGATIONS DURING ECIB

Daily complete blood counts at the beginning and end of each ECIB session.

a. Total or Differential W.B.C.

b. Hgb

c. Hct

d. Platelet Count

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e. Reticulocyte Count

f. M.C.V.

CIRC #18 (a)
4-13-70

E. P. Cronkite, M.D.
Chairman

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 8 April 1970

TO: Dr. E. P. Cronkite, via Chairman of Committee on Clinical Investigation and Isotopes.

FROM: Dr. A. D. Chanda - Dr. E. P. Cronkite

SUBJECT: ADDENDUM & REVISION TO CIRC # 18

Program Entitled: Extracorporeal Irradiation of the Blood.

CIRC # 18b, authorized us to utilize extracorporeal irradiation of blood for "conditioning" the kidney allograft recipients. This approval of the CIRC was obtained on February 25, 1965. As a result of this authorization, 4 patients with renal transplants were treated with ECIB in collaboration with Dr. J. Merrill of Peter Bent Brigham Hospital, Boston. Two of these patients showed a definite response to ECIB, during rejection episodes. This collaborative study has been inactive for some years and is not expected to be revived.

A similar study, in collaboration with the Meadowbrook Hospital, Renal Diseases Department, is under consideration and the first patient for ECIB treatment is expected to be available in the next month or two. The protocols are essentially similar to those authorized in CIRC # 18b, but in view of some further progress in the use of ECIB in Clinical and Experimental renal transplantation, uptodate information is provided for the perusal of the Committee in the following appendices.

Appendix # 1. Extracorporeal Irradiation of the Blood (ECIB) in Renal Transplantation.

Appendix # 2. Methodology, Extracorporeal Irradiation of Blood (ECIB). Includes the proposed protocols for ECIB of pre- and post transplant ECIB of patients from the Meadowbrook Hospital.

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All of the surgical transplantation work will be carried out at the Meadowbrook Hospital. Patients requiring ECIB will be transferred to the Medical Department, Brookhaven National Laboratory

In view of these considerations, it is requested that we be authorized to carry out pre- and post transplant ECIB on patients from the Meadowbrook Hospital.

ADC:mas

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Minutes CIRC Meeting

8 May 1972

Present: J.S. Robertson, S.H. Cohn, H.R. Connell, R.A. Love, G.A. Price, N.P. Rathvon, Jr.

The meeting was held in the Small Conference Room of the Medical Research Center and opened by Dr. Robertson at 1400.

The minutes of the previous meeting were accepted as distributed.

The Chairman distributed some copies of "The Institutional Guide to DHEW Policy on Protection of Human Subjects". More copies of the publication have been ordered so that every Committee Member can have a copy.

Dr. Robertson reported on the status of CIRC projects that are on the active list but are overdue for re-review. Of the nine projects in this category, seven will be reclassified as inactive; requests from Dr. Atkins for review of the remaining two are expected. The memorandum to Dr. Cronkite from Dr. Robertson listing the CIRC proposals involved is attached.

The Committee received a communication from Dr. Cotzias requesting that CIRC #58 be made inactive.

The following CIRC proposals were reviewed:

1. CIRC #32, revised. This proposal, "The Study of Polycythemia Vera", was approved as submitted.

2. Annual recertification of CIRC #48 was approved. It was noted that the original form for Initiation or Review of Clinical Investigative Programs was unsigned. The form should be signed by Dr. Shreeve.

3. Annual recertification of CIRC # 63 was approved with the condition that the word radioactive be included on the Consent Form, that is, paragraph 1 on the Consent Form should read: Thyroid uptake with radioactive iodine-123.....

4. CIRC # 82, revised. The proposal was approved subject to clarification on the Consent Form of whether 50 calendar days or 50 samplings is intended. It is suggested the wording on the Consent Form be: "..... be obtained 3 mornings a week and for a total period of 50 days"

The Committee then entered into a discussion of the procedure for recording patient's x-rays and whether the x-rays should be included in the patient's radiation record. No action was taken in this matter.

The meeting was adjourned at 1615.

Respectfully submitted,

Helen R. Connell

Helen R. Connell

Enc.

Memorandum to Dr. E.P. Cronkite
from Dr. J.S. Robertson

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