

BROOKHAVEN NATIONAL LABORATORY

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MEMORANDUM

DATE: 24 March 1971

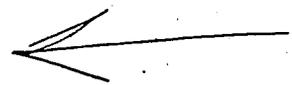
TO: A. Harrison

FROM: E. P. Cronkite, M.D. *E. P. Cronkite*

SUBJECT: CIRC Numbers

The following CIRC #s are inactive. Except for completing old records, they should not be used for identifying patient activity until reactivation is formally approved.

<u>Principal Investigator</u>	<u>CIRC #</u>
Dr. Cronkite	3 4 20 23 35 35A
Dr. Dahl	5 6 14 25
Dr. Jesseph	1
Dr. Robertson	9 10 16 28
Dr. Schiffer	22



The Medical Research Center
Brookhaven National Laboratory
Upton, L. I., New York

EPC/ck
cc: CIRC Committee
Mr. Finn
Dr. Dahl

REPOSITORY Records Holding Area Bldg. 494
COLLECTION Committee - Clinical Investigations and uses of Radioisotopes
BOX No. 4
FOLDER CIRC # 22

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

STUDY OF DISTRIBUTION AND MOVEMENT OF LEUKOCYTES THROUGH
AND FROM THE PERIPHERAL BLOOD

CIRC # 22 has been assigned to this program.

George C. Cotzias, M.D., Chairman

Lewis M. Schiffer
Lewis M. Schiffer, M.D.

Knud N. Knudsen
Knud N. Knudsen, M.D.

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

Date: JUL 29 1965

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

1179969

FORM FOR INITIATION OR REVIEW OF CLINICAL
INVESTIGATIVE PROGRAMS

Initial approved
Bond
V. P. 03 and 4. 4.
Chairman

(Submit original only to Department Chairman)

- A. Title of the proposal: Study of distribution and movement of leukocytes through and from the peripheral blood.
- B. Sponsoring physician(s): E.P. Cronkite, L. M. Schiffer
- C. Responsible investigator(s): L. M. Schiffer, M. L. Greenberg, P. A. Stryckmans, A. D. Chanana and E. P. Cronkite
- D. Brief description of the study, including its general goals and purpose, and pertinent information on past studies: (Attach additional sheets if necessary.)

Please see attached sheets.

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

Please see attached sheets.

- 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.): Patients with leukemia who have been accepted for extracorporeal irradiation of the blood, an approved project (CIRC-18), will be studied. Later if information becomes available to show that the dose is substantially lower than calculated then the procedure will be used in renal transplant patients and patients with autoimmune disease of various organs.

1179970

SUPPLEMENTARY FORM FOR RADIOISOTOPE
ADMINISTRATION TO HUMAN BEINGS

A. Radioisotope

1. Species: (Radioisotope or labeled compound, eg. Na ²⁴Cl or l-C¹⁴ - glucose)
Selenomethionine - Se⁷⁵
2. Physical characteristics: (Physical half-life; decay scheme (or type, energy and relative frequency of major emissions) Se⁷⁵ has T 1/2 of 127 days. It has a complex gamma spectrum with 0.27 Mev (71%), 0.14 Mev (24%), 0.08 Mev (14%) and 0.41 Mev (14%) photons. There are x-rays emitted during electron capture. There is no beta emission.)
3. Source: (BNL reactor, cyclotron, hot lab.), commercial supplier, etc.)
Commercial supplier.
4. Preparation: (Target material, quantity, special problems)
It is produced by biosynthesis in yeast grown on a low sulfur medium containing Selenium⁷⁵.
5. Specific activity and isotopic purity of administered material:
1.9-10 mc/mg., 20-200 µc/ml.
6. Radioassay and calibration procedures: (Include validation to be performed at BNL prior to use)
Radioassay and calibration are done by the commercial supplier.
7. Vehicle and route of administration:
Tagged leukocytes will be given intravenously.
8. Procedures for control of sterility and pyrogenicity: (Or note that commercially supplied isotopes are certified as ready for administration to human beings.) It is provided by the supplier in a sterile, pyrogen free solution. Each cc. contains not more than 10 mg. 2-aminoethanethiol as an antioxidant, sodium chloride for isotonicity, and 0.9% benzylalcohol as a preservative. Sodium hydroxide may be present to adjust the pH to 3.5 to 7.0.
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:
It is 23 days when injected intravenously in solution. It is unknown when injected in cells since the answer depends upon the information we are seeking.
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): Probably reticuloendothelial system and/or blood.
 - b. Gonadal exposure: Approximately the same as whole body. Urinary excretion is not expected to be rapid enough to make the bladder a strong gamma source to the gonads.

1179973

3. Sample calculations: (Dosage should be calculated for the whole body and for "target" or other separate organs, where indicated)
Summary equations are desired; not extensive calculations. Standard dosage equations from references such as Hine and Brownell's Radiation Dosimetry, National Bureau of Standards Handbook 69, and BNL Hospital Form 1167-A should be used where possible and the reference cited.

See attached sheets.

C. Radiological Health Aspects

1. Hazards to other patients and to personnel from external or internal radiation: If all of the injected dose remained in the patient without any excretion another person who was 100 cm. from the patient would receive $\frac{N\Gamma}{d^2}$ rads per hour = $\frac{(0.2)(1.84)}{100^2} = 3.68 \times 10^{-5}$. This is not felt to be a hazard.
2. Monitoring procedures, if necessary: Not required.
3. Special procedures for handling waste products, excreta, biological samples, etc., where indicated: Urine and stools will be saved and aliquots tested for radioactivity. This is being done as part of the study and collections will continue as long as any significant radioactivity is found.
4. Plan for isotope accountability, if required: Not required.

The maximum permissible burden of Se^{75} for occupation exposure is 90 μc for kidney, 100 μc for liver, 200 μc for spleen and 100 μc for total body. (NCRP Handbook 69). No standard has been established for Selenomethionine- Se^{75} .

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TITLE: Study of distribution and movement of leukocytes through and from the peripheral blood.

Items - B-3, D, and E.

As part of the evaluation of normal distribution, movement, and life span of peripheral blood leukocytes and the influence of extracorporeal irradiation of the blood, an approved project (CIRC-18), it is desirable to label these cells with something which is easily measured and does not interfere with their normal functions. A search for such a material suggested Selenomethionine- Se^{75} , an analog of the natural amino acid which would be incorporated into the protein of a metabolizing cell. Se^{75} is easily counted in a gamma scintillation counter. Though there would be some turnover of the Selenomethionine in the cell, this should not be a problem for interpretation of the data from relatively short-lived cells.

Selenomethionine- Se^{75} has not yet been accepted for USP, NF, or NNR, but it has been used in man extensively for pancreatic^{1,2} and, less extensively, for parathyroid,³ prostate,⁴ and parotid⁴ scanning in doses of about 3 μ c/kg. For scanning, it is injected intravenously in solution rather than primarily bound in leukocytes as we propose. When injected in solution, however, the total human body dose is estimated at about 600 m rads delivered over several months as deduced from data from rats;¹ this data indicated a biologic half life of 15-20 days.¹ Furthermore, 4% appeared in erythrocytes⁷ and 25% was incorporated in plasma proteins.

The whole body dose assuming no loss of 200 μ c of injected selenomethionine- Se^{75} in a 70 Kg. man 180 cm tall can be calculated with the following formula.⁵

$$D_{\beta+\gamma} = CT (73.8 \bar{E}_{\beta} + 0.0346 \bar{E}_{\gamma}) = 3.18 \text{ rads}$$

Using the same assumptions, if the blood (5000 gm) is the critical organ and all radiation were absorbed there, dose = 36.5.

Similarly, if a 1700 gm liver and 300 gm spleen were the critical organs, dose = 67 rads to the liver and 42.5 rads to the spleen.

These dosage calculations represent maxima, of course, because they assume that physical T 1/2 = biologic T 1/2 = effective T 1/2. A somewhat comparable situation for comparison purposes, however, exists with the use

1179976

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of diisopropylfluorophosphate - P^{32} for studying granulocytes. In this case 40% of the administered radioactivity was found in the urine within the first eight hours after infusion and thereafter the biologic half-life was approximately six days and effective half-life 4.4 days.⁶ A similar biologic half life for our study would reduce the dose 20- fold.

We have done some preliminary studies with selenomethionine- Se^{75} . 80-100 μc were used to label one liter of thoracic duct lymph (lymphocytes) from a cow, then injected intravenously. 20-30 minutes later there was no radioactivity measurable in the blood. Radioactivity appeared in thoracic duct lymphocytes after 1-2 hours and reached a maximum at 10 hours. At 20 hours 10% of the injected radioactivity had come out of the thoracic duct. These observations indicate that the injected cells were viable and that the label was usable for at least this length of time. In another study human cells had 2-15% uptake after a one hour in vitro incubation.

We propose the following protocol for this study:

1. Determine the percent uptake of selenomethionine- Se^{75} into the patient's leukocytes in vitro during a one hour incubation.
2. Phlebotomize the patient of 500 ml blood (red cells will be reinfused so that there will be no net loss of these cells.).
3. Using the information obtained in step 1, incubate with an amount of Selenomethionine- Se^{75} such that the leukocytes to be reinjected will contain no more than 200 μc .
4. Centrifuge at 1000 rpm for 20-30 minutes and remove the plasma (containing the unbound excess of Selenomethionine- Se^{75}).
5. Reinfuse the labeled cells into the patient.
6. Take serial blood specimens for scintillation counting.
7. Do serial whole body and external liver and spleen probe counting.
8. Collect urine and feces for determination of radioactivity.
9. Uptake of the compound into individual cell types in a given patient will be estimated by radioautographs of the same blood incubated in vitro with tritiated methionine.

Permission is requested to inject up to 200 μc selenomethionine - Se^{75} in the above manner with each study, 1-3 studies being done in each patient.

1179977

1. Blau, M., Nanske, R. F., Bender, M. A., J. Nucl. Med. 3:202, 1962.
2. Haynie, T. P., Svoboda, A. C. Zuidema, G. D., J. Nucl. Med. 5:90, 1964.
3. Beirerwaltes, W. H., Di Giulio, W., Sisson, J. C., Scintillation Scanning in Clinical Medicine, J.L. Quinn, III ed., pp58-68, W. B. Sanders Co., Philadelphia and London, 1964.
4. Bender, M. A. and Blau, M., p.88, in Scintillation Scanning in Clinical Medicine, J.L. Quinn, III ed. W. B. Sanders Co., Philadelphia and London, 1964.
5. Quimby, E. H. and Feitelberg, S., in Radioactive Isotopes in Medicine and Biology - Basic Physics and Instrumentation. 2nd ed. p. 120, Lea and Eebiger, 1963.
6. Mauer, A. M., Athens, J. W., Ashenbrucker, H., Cartwright, G. E., Wintrobe, M. M., J. Clin. Inv., 39:1481-1486, 1960.
7. Penner, J. A., Clin. Res. 17:228, 1964.
8. Penner, J. A., Clin Res. 17:277, 1964.