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Revised

12/15/71

The Medical Research Center

Brookhaven National Laboratory

Upton, L. I., New York

REPOSITORY Records Holding Area Bldg. 494

COLLECTION Committees - Clinical Investigations and use of Radioisotopes

BOX No. 4

FOLDER 28A

1180185

Minutes CIRC Meeting

13 December 1971

Present: G.C. Cotzias, G. Chikkappa, H.R. Connell, R.A. Love

Absent: G.A. Price, N.P. Rathvon, Jr.

The meeting was held in the Small Conference Room of the Medical Research Center.

Dr. Cotzias opened the meeting at 1500.

CIRC #28 was approved but with the qualification that the need to bring patients from Montreal and the status of these patients while they are at Brookhaven be clarified.

Informed Consent Forms #14 (48) and #46 (49) were approved with the modification that the comparison between a regional radiation dose from a diagnostic x-ray procedure and a total body irradiation be eliminated. The following wording is suggested:

"The maximum whole body radiation dose received....."

"This radiation dose is modest and of the same magnitude as that received by tissues in the average standard diagnostic x-ray procedure".

The CIRC number's to which this approval will apply will be numbers:

36	54
36A	61
36C	67
36D	72
51	

Consent forms 14+46 revised 12/15/71

CIRC #36A was approved with the qualification that the revised statements in Informed Consent Forms #46 (49) and #14 (48) be used.

The exception to CIRC #72 to include a patient less than 18 years of age was deemed unwarranted and therefore not approved.

The meeting was adjourned at 1630.

Respectfully submitted,

Helen Connell

Helen Connell

cc: CIRC Committee
Mr. Finn
Dr. Aronson
File

118018b

HOSPITAL OF [illegible] MEDICAL RESEARCH CENTER,
BROOKHA[illegible] NATIONAL LABORATORY
Upton, New York 11973

CLINICAL INVESTIGATION AUTHORIZATION FORM

Purpose of Review: Initial ☐ Revision ☐ Continuing ☒ Addendum ☐

Title: Cerebral Blood Flow (Reactivation)

CIRC# 28

Assigned on (date) 7/14/66

To Chairman, CIRC,

The proposal for clinical investigation identified by the above CIRC number and title is forwarded herewith for review and recommendation.

R B Aronson, / Dec 10, 197[illegible]
~~E.P. Cronkite, M.D., President of Staff~~ Acting Chairman — Date

To President of Staff,

The Clinical Investigation and Uses of Radiosotopes Committee reviewed the above identified proposal on Dec 1971 and recommends approval with the following modifications:

The status of the patients from Montreal while here must be thoroughly specified. The Committee wonders why all patients must come from abroad

J.S. Robertson, Chairman	George C. Cotzias G.C. Cotzias, Alt. Chairman	Helen R. Connell H.R. Connell
S.H. Cohn	E.A. Popenoe, Alternate	R.A. Love
G. Price	G. Chikkappa	N.P. Rathvon, Jr.
S.E. Duby, Alternate	A.P. Wolf, Alternate	

To Dr Robertson,

The above titled and numbered proposal is approved subject to the following:

Investigational Consent No 50 has been established for this CIRC.

E. P. Cronkite 15 Dec '71
E.P. Cronkite, M.D., President of Staff — Date

1180187

CIRC form #1 5/12/71

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE:

TO:

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

SUBJECT: CIRC Proposal 28

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 28 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 7/14/66 19 66. 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? NO. Please include the nature and frequency of such effects.

NONE

Approximately how many patients have been submitted to the experimental regime since the last approval? 0

The Sponsoring Physician on this proposal is J. S. ROBERTSON. 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 28 IS: Continuing [X]

Inactive [ ]

Signed J. S. Robertson 10 Dec 1971
Date

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

1180188

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 10 December 1971

TO: CIRC

FROM: Dr. James S. Robertson JSR

SUBJECT: CIRC - 28

1. CIRC 28 was originally approved 7/14/66. However, no clinical studies were ever actually done under this authorization because further instrument development work was desired. This has now been achieved, as has associated changes in the computer program used in the analysis of the data.

2. Renewal of the authorization is requested.

3. Animal studies involving four dogs have been conducted during the past year. These have served to confirm the feasibility and utility of the method. No untoward effects were observed in these studies.

4. The proposed future studies are the same as stated in the original proposal with the following changes:

   a. Instead of patients from Dr. Bateman's service being used, patients will be brought from Montreal by Dr. Yamamoto. These will be male or female adults in general good health, although some may have clinical suspicions of brain tumors.

   b. Pregnant females will be excluded.

   c. Up to ten subjects will be studied.

JSR:mas

1180189

-50-

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

NAME

UNIT NO.

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Cerebral Blood Flow

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

In high concentrations Krypton gas has a narcotic effect. However, in these studies only tracer concentrations will be used, for which there are no known effects. The radiation dose to the lungs will be less than 0.1 rad and for the rest of the body it will be much less. Although any radiation is considered potentially harmful, there are no known effects at the dose levels to be used.

The study requires the use of a face mask for controlling the gases being breathed and this involves minor physical discomfort.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

Form 1913 1180190

BROOKHAVEN NATIONAL LABORATORY

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.

Principal Investigator	CIRC #
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

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

1180191

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)
Kr^{79} gas

2. Physical characteristics: (Physical half-life; decay scheme (or type, energy and relative frequency of major emissions)
34 hours; β^+ 5%; EC 95%. β^+ .598 MeV, X-ray spectrum

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

4. Preparation: (Target material, quantity, special problems)
20% enriched Kr^{78} for 3 days at 10^{13} n/cm^2 sec

5. Specific activity and isotopic purity of administered material:
Per cc: Kr^{79} 1.3 mCi; Kr^{85m} (4.4 h) 0.002 mCi; others negligible

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

7. Vehicle and route of administration:
Inhalation

8. Procedures for control of sterility and pyrogenicity: (Or note that commercially supplied isotopes are certified as ready for administration to human beings.) Not applicable

9. Extraneous effects, if pertinent: (Such as pharmacological or toxic actions of the parent compound or vehicle, etc.)
Not narcotic at levels to be used

B. Radiation Dosage

1. Biological half-life or half-lives, including slow components:
95% a few minutes, rest (fatty tissues) about 4 hours

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): Lung; whole body

b. Gonadal exposure: Less than 0.1 rad (lungs get maximum of 0.1 rad)

1180192

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.

Assuming total absorption in the lung tissue (1000 grams) 1 mc of the β^+ gives:

$(.0355)\ (0.598)\ (\frac{1000}{1000})\ (.05) = .0011$ rad/min

The EC conversion X-rays could give a maximum of:

$(.0355)\ (1.614)\ (1)\ (.95) = 0.053$ rad/min assuming 100% absorption in the lungs. Thus 5 mc would give a maximum dose of 0.132 rad if retained for 30 seconds. This overestimates the dose, and the literature puts the figure below 0.1 rad for 5 mc.

Permission is asked for the use of 20 mc in divided doses of 5 mc each.

C. Radiological Health Aspects

1. Hazards to other patients and to personnel from external or internal radiation: May be up to 5 mr/hr during procedure; negligible after a few minutes.

2. Monitoring procedures, if necessary:
Survey meters

3. Special procedures for handling waste products, excreta, biological samples, etc., where indicated:
Discharge to atmosphere

4. Plan for isotope accountability, if required:
Not applicable

ak

June 25, 1963

1180193

however, this system has never been applied to the study of cerebral blood flow before. One of the advantages of the positron detecting system is that equal efficiency can be obtained within the field sensed by positron coincidence detecting system. Recently, Dr. Robertson made remarkable advancement of this positron detecting system to obtain a three dimensional distribution of positron emitting tracer in the cross-section of brain by multipole positron detecting system with use of the I.B.M. 7094 computer.

Since this multipole positron detecting system provides an equal response of count-rate in every portion of the cross-section of the human head and dividing the cross-section of the human head into the 384 units of known volume, the problem faced by the gamma-detecting method for study of regional cerebral blood flow would therefore be solved with this positron detecting system.

Krypton-79 is a positron emitting inert gas with short physical half-life of 34 hours. This radioisotope has been used as a high-energy gamma-emitting tracer for total cerebral blood flow study by Lewis group. This radioisotope can be easily produced in cyclotron by deutron bombardment of potassium bromide.

An atraumatic method of inhalation can be used for administering this Kr-79 for our study because the multipole positron detecting system can differentiate easily extracerebral blood flow from cerebral blood flow. Also the radiobiological effect to the whole body and critical organ with this method is neg-

1180194

ligible since most of the Krypton-79 will be removed from the lung after the first circulation. According to the previous study after inhalation with non-rebreathing system of 5 mc. of Krypton-79 in man will give only less than 0.1 rad to the lungs which is the highest radiation dose in the body.

This method can therefore provide information of quantitative assessment of microregional cerebral blood flow on the cross-section of the head with atraumatic procedure and negligible radiation to the body. Furthermore, this method is not only useful for clinical investigation of alterations of regional cerebral blood flow in diseases, but also has great potentials for investigating alterations of microregional cerebral blood flow under physiological and pathological conditions in man.

1180195

PROCEDURE.

1. Properties and production of Krypton-79:

   The physical half-life of Krypton-79 is 34 hours and its decay scheme includes K-capture positron emission, and at least 15 transitions ranging in energy from 44.5 to 833.4 Kev. (1)

   It can be produced by deutron bombardment of potassium bromide in a cyclotron, or neutron bombardment of enriched Krypton-78.

2. Administration of Kr-79:

   The Kr-79 is administered to the subject in the inspired air which is prepared by flushing the contents of the tonometer into a spirometer and diluting with room air to a final concentration of 100 uc per litre.

   Administration is through a non-rebreathing system with collection of the expired air in a Douglas bag.

3. Radiobiological effects:

   Under the conditions of these experiments, the highest radiation dosage is in the lungs and has been calculated to be less than 0.1 rad. (2)

4. Subjects:

   a) Physiological study.

      10 to 20 healthy individuals completely free of neurological as well as cardiovascular diseases of the

1180196

following age groups will be subjected to this study to obtain normal value of microregional cerebral blood flow on the cross-section of the human brain.

1) Age factors:
   a) 20 to 40 year group.
   b) 40 to 50 year group.
   c) 50 to 60 year group.
   d) Over 60 years.
2) Positioning factors:
   a) Sitting position.
   b) Lying position.
   c) After excess exercise.
3) During sleep.
4) Alteration of regional cerebral blood flow after physiological stimulation, such as photo-stimulation.
5) Under various levels of pCO_2 and pO_2 of blood condition.

b) Pathological state:
1) Alteration of regional cerebral blood flow in the hypertensive cases.
2) Alteration of regional cerebral blood flow in Parkinson's disease.
3) Alteration of regional cerebral blood flow in the occlusive cerebrovascular disease with correlation to the neurological deficit and cerebral angiographic findings.

1180197

4) Alteration of regional cerebral blood flow in brain tumor cases.

5) Effects of change of regional cerebral blood flow under certain medications.

1180198

REFERENCES.

1. THULIN, S.: Studies in nuclear spectroscopy with electromagnetically separated gaseous isotopes.
Ark. Fysik., 9, 137, 1955.

2. WECHSLER, R. L.: Effect of acceleration upon cerebral metabolism and cerebral blood flow.
U.S. Naval Air Development Center, Aviation Medical Acceleration Laboratory, Johnsville, Pa., Aug. 1952, Report No. NADC-NA-5202.

1180199

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28, 28A, 31A, 31B, 36, 36C, 36D, 36F, 42, 52, 53, 54

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

PURPOSE OF REVIEW:

- [ ] INITIAL
- [ ] ADDENDUM
- [ ] REVISION
- [x] RECERTIFICATION
- [ ] REACTIVATION

TO CHAIRMAN, CIRC:
THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HEREWITH FOR REVIEW AND RECOMMENDATION.

Change of Sponsoring Physician on the above CIRC's

E.P. Cronkite 15 Oct '73
E.P. CRONKITE, M.D., Chairman, Medical Deparment — Date

TO CHAIRMAN, MEDICAL DEPARTMENT:
THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON Nov. 19, 1973 AND RECOMMENDS Approval
WITH THE FOLLOWING MODIFICATIONS:

Edwin A. Popenoe		Helen A. Connell
E.A. POPENOE, Chairman	N.P. RATHVON, Jr., Alt. Chairman	H.R. CONNELL
L.D. HAMILTON	P.S. Papavasiliou	R.A. Love
	P.S. PAPAVASILIOU	R.A. LOVE
Glenn A. Price		U. Reinke
G.A. PRICE	S.H. COHN, Alternate	U. REINKE
D.N. SLATKIN, Alternate	A.P. WOLF, Alternate	

TO Drs. Robertson & Atkins,

THE ABOVE TITLED AND NUMBERED PROPOSAL IS Approved SUBJECT TO THE FOLLOWING:

E.P. Cronkite 21 Nov '73
E.P. CRONKITE, M.D., Chairman, Medical Deportment — Date

1180200

CIRC Form 1 10/4/73
Form 1936B

MAYO CLINIC
ROCHESTER, MINNESOTA
55901

TELEPHONE 282-2511
AREA CODE 507

October 9, 1973

Dr. Harold Atkins
Medical Department
Brookhaven National Laboratory
Upton, L.I., New York 11973

Dear Hal:

Doctor Aronson called me regarding a problem that will come up soon regarding my being the sponsoring physician for a number of CIRC projects. Until the afternoon of my departure, I had thought that you would be acting head of Medical Physics and that this area of responsibility would automatically be assumed, but the way things are, a more formal agreement seems to be required. I am named on the following CIRC's: 28, 28A, 31A, 31D, 36, 36C, 36D, 36F, 42, 52, 53, and 54. Doctor Aronson can give you the titles of these or you perhaps have them on your copy of the CIRC list. Some, such as 31A and D, are yours anyhow. The question is whether you are agreeable to taking over this aspect of the others. Some will be up for review soon, so Doctor Aronson would like to have an agreement established.

SHOULD BE 31B HA 10/17

We do not seem to be out of the woods on ^{123}I yet, the ^{123}I uptakes being somewhat higher than the ^{131}I uptakes, though not as bad as the graph I sent you. We would be interested in hearing how yours are running. Thanks for the "spectrum". However, this is really an analysis of the spectrum by a computer. I would like to see the input data. One final thought, if the uptakes are exactly equal, the cross talk correction should have no effect.

Sincerely yours,

J. S. Robertson

James S. Robertson, M.D., Ph.D.

JSR:mjk

cc: Dr. R. B. Aronson

I accept the above noted responsibility. Harold L. Atkins 10/15/73

Noted. SH. Cohen 10-15-73

1180201

Minutes CIRC Meeting

29 October 1973

Present: E.A. Popenoe, H.R. Connell, R.A. Love, P.S. Papavasiliou, G.A. Price
U. Reincke

Absent: N.P. Rathvon, Jr.

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

The minutes of the previous meeting, 24 September 1973 were accepted as distributed.

Communications received:

Copy of the letter to Dr. Atkins from Dr. Robertson dated 9 October 1973 requesting Dr. Atkins assume responsibility of Sponsoring Physician for CIRC's 28,28A,31A,31B,36,36C,36D,36F,42,52,53, and 54.

Memorandum to CIRC from Dr. Zanzi dated 18 October 1973, concerning the modification to CIRC's #103 and 86.

Memorandum to CIRC from Dr. Atkins of 24 October 1973 amending CIRC 15F-Revised 10/2/73.

CIRC#103 was reviewed first and approved with the following qualifications:

1) It be specified that no pregnant women will be involved.
2) Consent form #3 for ^{18}F bone scan should include the extent of the radiation involved.
3) The total radiation dose from all procedures involved in this study should be stated-per quarter.
4) It is noted that the letter to Dr. Roginsky from Dr. Crampton 27 September 1973 is unsigned.
5) It is understood that Consent Form #60 will be modified to include ^{125}I.

CIRC #92 Addendum for FD1571 (Supplements#3 & 4) and CIRC #36H Addendum were approved without modification, Dr. Papavasiliou abstaining.

CIRC #15F Revised 10/2/73 was reviewed for revision and reactivation. Dr. Atkins was asked into the meeting to answer questions about the dose of DTPA to be used and to clarify some of the answers given in the Authorization form.

Dr. Atkins informed the Committee there is a consent form for this procedure even though it was not included in the material distributed to the Committee.

CIRC 15F Revised 10/2/73 was approved with the following modifications in

CIRC form 2-1:

1) Paragraph A should read: "and 2-3 mCi of ^{99m}Tc-DTPA"
2) Paragraph F, question 1 is answered "Yes".

Approved for recertification were:

CIRC#15 Rev. 9/7/72
CIRC#56

The Committee then discussed CIRC # 64 Rev. 10/17/73 which had been approved for reactivation on an emergency basis 18 October 1973.

The meeting was adjourned at 1510.

Respectfully submitted,

Helen R. Connell

Helen R. Connell

1180203

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28, 28A, 31A, 31B, 36, 36C, 36D, 36F, 42, 52, 53, 54

CLINICAL INVESTIGATION AUTHORIZATION FORM

PURPOSE OF REVIEW:

☐ INITIAL ☐ ADDENDUM

☐ REVISION ☐ RECERTIFICATION

☐ REACTIVATION

TITLE:

TO CHAIRMAN, CIRC:

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HEREWITH FOR REVIEW AND RECOMMENDATION.

Change of Sponsoring Physician on the above CIRC's

E.P. Cronkite 15 Oct '73

E.P. CRONKITE, M.D., Chairman, Medical Deparment — Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON Nov. 19, 1973 AND RECOMMENDS Approval

WITH THE FOLLOWING MODIFICATIONS:

Edwin A. Popenoe — E.A. POPENOE, Chairman

N.P. RATHVON, Jr., Alt. Chairman

Helen A. Connell — H.R. CONNELL

L.D. HAMILTON

P.S. Papavasiliou — P.S. PAPAVASILIOU

R.A. LOVE

Glenn A. Price — G.A. PRICE

S.H. COHN, Alternate

U. Reinke — U. REINKE

D.N. SLATKIN, Alternate

A.P. WOLF, Alternate

TO Drs. Robertson & Atkins,

THE ABOVE TITLED AND NUMBERED PROPOSAL IS Approved SUBJECT TO THE FOLLOWING:

E.P. Cronkite 21 Nov 73

E.P. CRONKITE, M.D., Chairman, Medical Department — Date

1180204

CIRC Form 1 10/4/73 11/27 copy to Robertson, Atkins, Clemes, Dall, [illegible], Harrison

Minutes CIRC Meeting

24 September 1973

Present: E.A. Popenoe, H.R. Connell, R.A. Love, P.S. Papavasiliou, G.A. Price, N.P. Rathvon, Jr.

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

The minutes of the previous meeting, 30 July 1973 were accepted as distributed.

Communications received: Dr. Popenoe's letter to Dr. E.L. Saenger of 31 July 1973 and Dr. Saenger's reply to Dr. Popenoe of 8 August 1973.

The first proposal considered was CIRC 28A-Addendum. It was noted that the Sponsoring Physician, Dr. J.S. Robertson will be on a leave of absence from BNL for one year. Also discussed was the radiation dose calculation for ^{123}Xe. The Committee approved 28A subject to the condition that another physician be appointed Sponsoring Physician during Dr. Robertson's absence.

CIRC 93A-Addendum was discussed next. The proposal was approved. However, one member took issue with the "yes" answer given to question 6a, section F of the Clinical Investigation Proposal.

CIRC 99 Rev.-Revision was reviewed next. Dr. Atkins was invited into the meeting to answer questions of the Committee concerning this proposal and also CIRC 101.

CIRC 99 REV was approved with the following changes agreed to by Dr. Atkins:

1) In the Clinical Investigation Proposal: Section F, question 3 be answered "yes", question 4d be answered "not applicable" and question 6a answered "no".

2) On the Consent Form the words " 1/100 of that incurred from the usually used iodine-131 and" be omitted.

CIRC 100 was approved without qualification.

CIRC 101 was approved with the following changes:

1) In the Clinical Investigation Proposal: Section F, question 3 be answered "yes", question 4d be answered "not applicable", and question 6a be answered "no".

CIRC 102 was approved with the qualification that the Consent Form indicate that some radiation is involved in the procedure. In addition the Committee recommends that in section C of the Clinical Investigation Proposal the word "only" be omitted, i.e. "Will do as requested or clinical indications present".

CIRC 36G was discussed next. It was noted that Dr. Saenger's remarks to the Committee concerning this procedure indicate that the radiation hazard due to the neutron dose did not worry him.

After deliberation CIRC 36G was approved.

1180205

At the end of the meeting a general discussion of the participation of some patients in more than one investigative procedure took place. In particular, the concern of the Committee is the patient admitted to the Hospital under one program and then asked to be a subject in another program.

The meeting was adjourned at 1550.

Respectfully submitted,

Helen R. Connell

Helen R. Connell

1180206

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

103

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

NAME

UNIT NO.

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Cerebral blood flow studies with ^{123}Xe

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

A short lived radioactive gas, Xe-123, will be inhaled. The radiation dose in the lung is comparable to that received in a year from naturally present radiation. The dose for the rest of the body is much less, about like a chest x ray.

There will be some temporary discomfort from the use of a mask during the inhalation of the gas.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

1180207

Form 1913 103

WILLIAM FEINDEL
Director
Chairman of Neurology & Neurosurgery
William Cone Professor of Neurosurgery

FRANCIS MCNAUGHTON
Professor of Neurology
Senior Consultant

PRESTON ROBB
Professor of Neurology and Neurologist-in-Chief

GILLES BERTRAND
Professor of Neurosurgery and Neurosurgeon-in-Chief

R. G. B. GILBERT
Professor, Anaesthesia

MONTREAL NEUROLOGICAL INSTITUTE
Department of Neurology and Neurosurgery
McGill University
and
MONTREAL NEUROLOGICAL HOSPITAL
3801 University Street - Montreal 112, Canada

WILDER PENFIELD *Honorary Consultant*
K. A. C. ELLIOTT *Honorary Consultant in Neurochemistry*
HERBERT JASPER *Consultant in Neurophysiology*
THEODORE RASMUSSEN *Consultant in Neurosurgery*

CHRISTIAN PRIMAVESI
Administrator

PIERRE GLOOR
Professor, Electroencephalography & Clinical Neurophysiology

LEONHARD WOLFE
Professor, Neurochemistry, Donner Research Laboratory

GORDON MATHIESON
Neuropathology

BRENDA MILNER
Professor, Psychology

ROMEO ETHIER
Neuro-Radiology

July 12, 1973

Dr. J. S. Robertson
Head, Medical Physics Division
Medical Research Center
Brookhaven National Laboratory
Upton, L.I. New York, 11973

Dear Dr. Robertson:

As I mentioned in our recent telephone conversation, I am planning to be in the Brookhaven National Laboratory from August 13 to 17 to make further progress with our project.

I am writing a letter to Dr. Iwai to request a couple of his patients for our study. I am planning to use Krypton-79 for these patients. However, as I discussed with you, if Mr. Powell Richards will provide us with Xenon-123, I would like to use it also for a comparative study. As you know, this Xenon-123 has a 2.1 hour of physical half-life and emits positron and E.C. It is also a side-product of iodine-123 which will be produced by 62-65 Mev bombardment of the potassium iodide-127. The Xenon is also more soluble to the blood than Krypton, therefore, this will give more count rate in our study. I understand the production of Xenon-123 is relatively easy and I hope Powell will let us know whether or not we can have the Xenon-123 during the week of August 13th by the beginning of August.

I would be much obliged if you would get a permit from the Isotope Committee for the use of Xenon-123 in patients. (I realize that this is very short notice). I would also appreciate it if you could make arrangements to obtain 4 or 5 vials of Krypton-79 from Rita.

I am planning to bring my family with me but have made arrangements to stay with friends in Bellport. I am looking forward to seeing you again.

Yours sincerely,

Lucas

Lucas Yamamoto, M.D.

LY:cd

1180208

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28A

CLINICAL INVESTIGATION PROPOSAL

Title:
Cerebral blood flow studies with ^{123}Xe

Sponsoring Physician J. S. Robertson Principal Investigator Y. L. Yamamoto

Other Investigators:

A. **Brief Description of Proposed Study.** Include general goals and purpose, methods to be used. Mention any radiopharmaceuticals and unofficial drugs to be used, abnormal diets or deprivations (See E).

Tracer doses of Radioactive Xenon-123 will be administered by inhalation to selected patients and normal subjects for studies of brain circulation. The principles involved are similar to those for Krypton-79, as described in CIRC 28. (See next page.)

B. **Pertinent Information on Related Prior Clinical, Animal and Laboratory Studies.** Include quantitative toxicity data for drugs. Cite literature by author, title and publication.

Xenon is an inert gas which has narcotic properties in high (50%) concentrations. No pharmacological or toxic effects are known for the low concentrations (2%) to be used. (See next page.)

C. **Reasons for Performing the Studies on Human Beings and Approximate Number to be Studied.**

The physiology of the human brain is the area of interest. Extrapolation from animal data is unreliable.
Up to 20 subjects or patients will be studied.

D. **Type of Patient to be Studied.** Include age range, sex, disease, stage of treatment, inclusion or exclusion of pregnant or potentially pregnant females.
Patients involved in this study are referrals from or also studied at the following institution(s)

Attach statement from institution(s) indicating the review committee approval is current.
Adults of either sex with or without brain disease are to be studied. (See next pg.)

E. **Dose Schedule for Drugs or Radiopharmaceuticals to be Used.**
The gas will be administered by inhalation. Up to 20 cc of the radioactive gas, depending on the activity attainable, will be mixed with 1 liter of air and inhaled from a rebreathing system. After one minute of rebreathing, the system will be switched to ordinary air, with the exhaled air being collected in a Douglas bag. This washes the Xenon out of the lungs in a few minutes.

Supplement to questions A. B. and D of Page 1 of Clinical Investigation Proposal:

A. Tracer doses of Xe-123 will be introduced by inhalation and its appearance and distribution in the brain will be determined by multiple positron detector system and computer analysis. Since Xenon gas is more soluble to the blood than Krypton-79 gas is, and the abundance of positron emission in Xe-123 is much greater (ten times) than in the Krypton-79, we wish to make comparative studies between these two positron emitting inert gases.

B. The radioactive Xenon gas (mainly gamma-emitting Xenon-133) has been extensively used in humans for pulmonary perfusion as well as cerebral blood flow studies for the last 10 years without any toxic effects.

1. B. L. Mallett and N. Veall
The measurement of regional cerebral clearance rates in man using Xenon-133 inhalation and external recording.
Clinical Science 29: 179-191, 1965.

2. N. Veall and B. L. Mallett
Regional cerebral blood flow determinations by ^{133}Xe inhalation and external recording.
Clinical Science 30: 353-369, 1966.

3. K. B. Jensen, et al.
Cerebral blood flow evaluated by inhalation of ^{133}Xe and external recording.
Clinical Science 30: 485-494, 1966.

D. Pregnant females will be excluded. Patients from Drs. Cotzias' and Iwai's service will be subjected to physiological and pathological studies. Non-patient volunteers will also be utilized. An informed written consent will be obtained from individuals to carry out this test.

1180210

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28A

CLINICAL INVESTIGATION PROPOSAL (Cont'd.)

F. Details of Special Materials or Procedures.	*YES	NO
1. Is any drug that falls into one or more of the following categories to be used? (If yes, indicate which)	X	
a) unofficial drug or biological product (drug not listed in the USP or NNR)	X	
b) official drug but for purposes other than those listed?		X
c) official drug in doses exceeding or means of administration different from those listed?		X
(An answer "no" to 1. indicates that either no drugs, or only official drugs for the listed purposes and in the listed doses is/are to be used.)		
2. Are any unlicensed biological products to be administered?		X
3. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered?	X	
**4. Is a radionuclide to be administered? (If no, skip to question 5)	X	
a) Specify nuclide and chemical form Xenon-123 gas		
b) Is the radionuclide one not listed in the USP?	X	
c) Is the purpose for its use one not listed in the USP?		
d) Does the dose exceed that listed in the USP?		
5. Are any other procedures to be used that exceed the ordinary diagnostic and therapeutic measures for the patient concerned and that may entail a hazard, discomfort or embarassment to the patient?		X
***6. a. Is a direct benefit to the patient to be expected?		X
b. Will the study contribute to the diagnosis, treatment or knowledge of the patient's disease?	X	

G. I am familiar with the AEC requirement to abide by (a) the HEW's policies on institutional review of experiments involving human subjects and (b) FDA policies on investigational drugs and activities. This clinical investigation will be carried out in conformance with these policies. In particular, informed consent statements will be obtained.

James S. Robertson 30 July 73 — Sponsoring Physician — Date

L. Kaufman 17 Aug. 73 — Principal Investigator — Date

*If any question 1 through 5 is answered yes, append a discussion of the potential hazards including pertinent literature citations or indicate where discussed in accompanying IND request. (Note that an answer NO to 4b, c, and d is sufficient for question 4.)
**If answer to 4 is yes, and the answer to 4b is yes, append a completed CIRC form 2-3 and 2-4 (Supplementary Information on Radionuclide Administration).
***If answer to both 6a and 6b are no, append explanation.

SUPPLEMENTARY INFORMATION ON RADIONUCLIDE ADMINISTRATION

A. Radionuclide

1. **Species:** (Radionuclide or labeled compound, eg. ^{24}NaCl or 1-^{14}C-glucose)

   Xenon-123 as elemental gas

2. **Physical Characteristics:** (Physical half-life; decay scheme, or type, energy, and relative frequency of major emissions; average β energy if known)

   Physical Half-life 2.1 hours. Decays to I-123 (13.3 hours)
   Decay by β^+ or Electron Capture and X rays
   Energies β^+ 1.5 MeV max., 8 X rays 0.090 MeV - 1.10 MeV.

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

   Hot Lab, BNL

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

   Production is by ^{127}I (p,5n) ^{123}Xe reaction

5. **Specific Activity and Isotopic Purity of Administered Material:**

   1 to 2 mCi ^{133}Xe/ml, other activities negligible.

6. **Radioassay and Calibration Procedures:** (Include validation to be performed at BNL prior to use)

   Gamma ray spectroscopy.

7. **Vehicle and Route of Administration:**

   Inhalation of gas mixed with air.

8. **Procedures for Control of Sterility and Pyrogenicity:** (Or note that commercially supplied isotopes are certified as ready for administration to human beings)

   Not required.

9. **Side Effects, If Pertinent:** (Such as pharmacological or toxic actions of the parent compound or vehicle, etc.)

   None known at levels to be used.

B. Radiological Health Aspects

1. **Hazards to Other Patients and to Personnel From External or Internal Radiation** (e.g. mr/hr. at 1 meter)

   During the procedure the radiation level near the patient may be up to 5 mr/hr. After a few minutes it becomes negligible.

2. **Monitoring Procedures, If Necessary:**

   Survey meters.

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

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CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

NAME

UNIT NO.

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Cerebral blood flow studies with ^{123}Xe

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

A short lived radioactive gas, Xe-123, will be inhaled. The radiation dose in the lung is comparable to that received in a year from naturally present radiation. The dose for the rest of the body is much less, about like a chest x ray.

There will be some temporary discomfort from the use of a mask during the inhalation of the gas.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

1180213

Form 1913 108

BROOKHAVEN NATIONAL LABORATORY

11/10 19

Memo to Mr. Finn Dept.

Mr. Yamamoto would like copy of CIRC # 28 to send to the Can. AEC, Ottawa as proof that there is Kr-79 at BNL.
He wants to use Kr-79 in Canada.
Mr. Yamamoto will be here 11/11.
O.K.?

from Dept. (over)

FORM NO. 112-A
UPTON, N. Y. 2-57-180M

BROOKHAVEN NATIONAL LABORATORY

19

Memo to Dept.

Official Med. Report.
File copy -
Do not remove from folder.

from Dept.

FORM NO. 112-A
UPTON, N. Y. 2-57-180M

1180214

WILLIAM FEINDEL
Director
Chairman of Neurology & Neurosurgery
William Cone Professor of Neurosurgery

FRANCIS MCNAUGHTON
Professor of Neurology
Senior Consultant

PRESTON ROBB
Professor of Neurology and Neurologist-in-Chief

GILLES BERTRAND
Professor of Neurosurgery and Neurosurgeon-in-Chief

R. G. B. GILBERT
Professor, Anaesthesia

MONTREAL NEUROLOGICAL INSTITUTE
Department of Neurology and Neurosurgery
McGill University
and
MONTREAL NEUROLOGICAL HOSPITAL
3801 University Street - Montreal 112, Canada

WILDER PENFIELD *Honorary Consultant*
K. A. C. ELLIOTT *Honorary Consultant in Neurochemistry*
HERBERT JASPER *Consultant in Neurophysiology*
THEODORE RASMUSSEN *Consultant in Neurosurgery*

CHRISTIAN PRIMAVESI
Administrator

PIERRE GLOOR
Professor, Electroencephalography & Clinical Neurophysiology

LEONHARD WOLFE
Professor, Neurochemistry, Donner Research Laboratory

GORDON MATHIESON
Neuropathology

BRENDA MILNER
Professor, Psychology

ROMEO ETHIER
Neuro-Radiology

July 26, 1973

Dr. J. S. Robertson
Head, Medical Physics Division
Medical Research Center
Brookhaven National Laboratory
Upton, L.I. New York, 11973

Dear Dr. Robertson:

Enclosed please find the proposal for our Xenon-123 study. I would appreciate it if you would check it before submitting it to the Isotope Committee.

Thanking you,

Yours sincerely,

Lucas

Lucas Yamamoto, M.D.

LY:cd
Enclosure

1180215

Supplement to Page 4, Clinical Investigation Proposal:

Using MIRD methods: replace

A. Lung: target organ

Assuming total absorption in the lung tissue (1000 grams)

1 mCi of the β^+ gives:

$$\frac{2.13}{60} \times (0.49) \times \frac{1000}{1000} \times 0.8 = 0.0128$$

EC gives:

$$(0.0355) \times (0.148) \times \frac{1000}{1000} \times 0.2 = 0.001$$

Therefore a total of 0.0138 rads/mCi/min

Thus 20 mCi would give a maximum dose of <u>0.138</u> rads if retained for 30 seconds.

As was pointed out in Krypton-79 permit, this is an overestimate (100% absorption of the EC X-ray is assumed).

B. Total Body

If 10% of the total dose is uniformly distributed throughout the body, the positron and EC dose would be 0.138 x 0.14 x 0.1 = <u>0.002 rads</u> for 20 mCi of Xenon-123 for 30 seconds.

Therefore, 20 mCi of Xenon-123 gives one-third of radioactive dose to the lungs and whole body as compared to 15 mCi of Krypton-79 which was previously reported.

118021b

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28

PURPOSE OF REVIEW:

☐ INITIAL ☐ ADDENDUM

☐ REVISION ☒ RECERTIFICATION

☐ REACTIVATION

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

CEREBRAL BLOOD FLOW

TO CHAIRMAN, CIRC:

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HEREWITH FOR REVIEW AND RECOMMENDATION.

x E.P. Cronkite 20 Feb 73

E.P. CRONKITE, M.D., Chairman, Medical Deparment — Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON March 12 73 AND RECOMMENDS Approval

WITH THE FOLLOWING MODIFICATIONS:

J.S. ROBERTSON, Chairman	George C. Cotzias G.C. COTZIAS, Alternate Chairman	H.R. CONNELL
S.H. COHN	Edwin A. Popenoe E.A. POPENOE, Alternate	R.A. LOVE
Glen A. Price G. PRICE	G. CHIKKAPPA	N.P. Rathvon N.P. RATHVON, JR.
D.N. SLATKIN, Alternate	A.P. WOLF, Alternate	

TO Dr's Robertson and Yamamoto

THE ABOVE TITLED AND NUMBERED PROPOSAL IS approved SUBJECT TO THE FOLLOWING:

Consent form #85 to be used

E.P. Cronkite 26 Mar 73

E.P. CRONKITE, M.D., Chairman, Medical Department — Date

1180217

CIRC Form 1 9/1/72

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28, 28A, 31A, 31B, 36, 36C, 36D, 36F, 42, 52, 53, 54

CLINICAL INVESTIGATION AUTHORIZATION FORM

PURPOSE OF REVIEW:

TITLE:

☐ INITIAL ☐ ADDENDUM

☐ REVISION ☐ RECERTIFICATION

☐ REACTIVATION

TO CHAIRMAN, CIRC:

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HEREWITH FOR REVIEW AND RECOMMENDATION.

Change of Sponsoring Physician on the above CIRC's

E.P. Cronkite 15 Oct '73
E.P. CRONKITE, M.D., Chairman, Medical Deparment — Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON Nov. 19, 1973 AND RECOMMENDS Approval

WITH THE FOLLOWING MODIFICATIONS:

Edwin A. Popenoe — E.A. POPENOE, Chairman

N.P. RATHVON, Jr., Alt. Chairman

Helen A. Connell — H.R. CONNELL

L.D. HAMILTON

P.S. Papavasiliou — P.S. PAPAVASILIOU

R.A. Love — R.A. LOVE

Glenn A. Price — G.A. PRICE

S.H. COHN, Alternate

U. Reinke — U. REINKE

D.N. SLATKIN, Alternate

A.P. WOLF, Alternate

TO Drs. Robertson & Atkins,

THE ABOVE TITLED AND NUMBERED PROPOSAL IS Approved SUBJECT TO THE FOLLOWING:

1180218

E.P. Cronkite 21 Nov '73
E.P. CRONKITE, M.D., Chairman, Medical Department — Date

CIRC Form 1 10/4/73 11/27 copy to Robertson, Atkins, Clemes, Dall, Chairman, Harrison

Form 1936B

L. Harrison

From

ECT
-D Pt Consent # 50

DATE 4/2/73

MESSAGE

Please discontinue the use of Pt Consent # 50. This has been replaced by # 85.

SIGNED Carole

REPLY

—FOLD

DATE

SIGNED

SENDER—RETAIN YELLOW COPY - SEND WHITE AND PINK COPIES WITH CARBON INTACT

1180219

Minutes CIRC Meeting

12 March 1973

Present: G. C. Cotzias, R. A. Love, E. A. Popenoe, G. A. Price, N. P. Rathvon, Jr.

Absent: G. Chikkappa, H. R. Connell

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

An addendum to CIRC 96A, entitled "Long-Term Treatment of Osteoporosis," was considered. The addendum would authorize the inclusion of a specific patient who was not in the post-menopausal range. After consideration, the addendum to CIRC 96A was approved.

CIRC 28, "Cerebral Blood Flow," was considered and approved for recertification.

CIRC 15B, "Comparison of Tc^{99m} and Ferrous citrate-iron-52 as a Scanning Agent," was considered. It was noted that the form of consent made no reference to the radioactivity of the technetium, and it was recommended that the consent form be brought up-to-date by including the language customarily used in procedures involving radionuclides. Subject to this condition, CIRC 15B was approved for recertification.

An addendum to CIRC 91, "Measurement of Calcium Absorption Using Dual Tracer Technique (^{87m}Sr and ^{47}Ca)," was considered. The addendum adds Dr. Roginsky and Dr. Zanzi as investigators. Dr. Love made available to the Committee copies of a letter to FDA notifying FDA of the intention of using more than 10 patients. After consideration, the addendum was approved.

It was urged that every effort be made to hold meetings when our usual and prettier secretary can be present.

The meeting was adjourned at 1430.

Respectfully submitted,

NPR Jr.

N. Peter Rathvon, Jr.

1180220

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

CIRC No. 28

CIRC STATUS MEMO

To: Dr Robertson Date: 1/19/73

Please indicate below whether this proposal is continuing or inactive. If continuing, complete the entire form, and 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), since the last CIRC approval date. Also please add any additional information which may be of use to the Committee in its deliberations. If inactive, merely sign and return this form.

If this form is not returned by 1/31/73, approval of the proposal will automatically be discontinued.

1/30/73 Requested extension - awaiting Dr Yamamoto's signature

R.B. Aronson 19 Jan '73
R.B. Aronson, Ph.D., Associate Chairman Date

To R.B. Aronson,

CIRC PROPOSAL NUMBER 28 IS: Continuing ☒ Inactive ☐

Proposed substantive changes are attached (see memo)

Adverse effects that have not already been reported to the Department Chairman include:

none

Since the last approval 1 patients have been submitted to the experimental regime.

The Sponsoring Physician as of this date is J. S. Robertson

The following changes in Investigators should be noted: none

The following IND #'s have been obtained for specific compounds used in this proposal:

Compound _____ IND # _____ Compound _____ IND # _____

none

The investigational consent form(s) used in this project are numbered (old 50 - revised) (will be renumbered when approved.) and copies are attached.

Signed L. Yamamoto 2/12/73 J S Robertson 2/6/73
Principal Investigator Date Sponsoring Physician Date

Y. L. YAMAMOTO
(Montreal)

1180221

Form 1970

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: February 6, 1973

TO: C I R C

FROM: J. S. Robertson

SUBJECT: CIRC-28 UPDATE

1. Approval for continuation of the project "Cerebral Blood Flow" is requested.

2. This project was approved in 1966 and was reapproved on 15 December 1971.

3. Although it had been thought that clinical studies could begin a year ago, it was found desirable to do further instrumentation development work, computer programming, and animal studies, and only one human subject has actually been studied.

4. A newer decay scheme (copy attached) than the one previously used assigns 9% of the decays to β^+ emission and 91% to electron capture (vs 5% and 95%). Also it is to be noted that in the previous calculation the maximum β^+ energy (0.598 MeV) rather than the average (0.2 MeV) was used. Thus a revised dose calculation for 1 mCi in the lung is:

$$\beta+ \quad \left(\frac{2.13}{60}\right) \quad (0.2) \quad \left(\frac{1000}{1000}\right) \quad (0.09) = .000639$$

$$\left(\frac{(\text{g-rad}) \ / \ (\mu\text{Ci-hr}) \ (\text{Mev/dis})}{\text{min/hr}}\right) \quad (\text{MeV}) \quad \left(\frac{\mu\text{Ci}}{\text{gm}}\right) \quad \left(\frac{\beta^+}{\text{dis}}\right) \qquad \text{rads/(mCi-min)}$$

EC

EC (.0355) (1.62) (1) (0.91) = 0.0523

Total 0.0529 rads/(mCi-min)

(The dose from β^+ annihilation γ's is negligibly small for the lung.) Because of the preponderance of the EC dose, this is substantially the same result as before, with 5 x 0.5 x 0.0529 = 0.132 rads for 5 mCi in the lungs or 0.396 rads for 15 mCi in the lungs for 30 seconds. As was pointed out before, this is an overestimate, (100% absorption of the EC X-Rays is assumed) and the doses used in the literature are lower.

1180222

If all the activity were uniformly distributed throughout the body, the β^+ and EC dose would be lower by the ratio $\frac{1000 \text{ grams}}{70000 \text{ grams}}$, or $\frac{.396}{70}$ = 0.0056 rads. Here, however, the annihilation γ's become more important, and contribute (0.0355) (1.02) (1000/70000) (0.09) (0.47) = 0.00002 rads/(mCi-min) or 0.00015 rads for 15 mCi for 30 seconds. The total whole body dose is thus about 0.006 rads for 15 mCi ^{79}Kr for 30 seconds.

5. The limited experience mentioned above indicates that the originally proposed dose of 5 mCi at one time may be too low to give statistically reliable data. Therefore authorization is requested to increase the dose to the 10 to 15 mCi range. As per the above calculations, the highest radiation dose is received by the lungs. For 15 mCi the dose to the lungs is less than 0.4 rad and the dose to the total body is less than 0.01 rad. (The circulating concentration of Krypton is much less than the concentration in the lungs.) The rapidity of the dynamics makes more precise calculations of the dose impossible without more detailed data which are currently not available.

The original proposal was for a total of 20 mCi in divided doses of 5 mCi each. It is now proposed to limit the study to two exposures of 10 to 15 mCi each, so the accumulated dose is about the same as originally proposed for four exposures.

6. Female patients in the reproductive age span will be excluded from the study unless there is positive information that precludes the possibility of their being or becoming pregnant.

7. As per the previous plan, some of the patients would be ones with suspected brain tumors, brought from Montreal. However, if suitable patients can be made available from one of the BNL services, these will be used. The criteria for suitability include that they have not been subjects for other studies involving irradiation.

8. It is further requested that some of the subjects to be studied may be normal volunteers, preferably male laboratory employees with non-radiation exposure jobs. The nature of the studies makes it important to have normal controls for comparison with suspected pathological findings.

9. A total of up to ten subjects will be studied.

Reference (for radiation dose constants)

MIRD pamphlets 1-3, J. Nuclear Medicine, February 1968.

1180223

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
Upton, New York 11973

-85-

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

NAME

UNIT NO.

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Cerebral Blood Flow

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

In high concentrations Krypton gas has a narcotic effect. However, in these studies only tracer concentrations will be used, for which there are no known effects. For the maximum dose of 15 mCi the radiation dose to the lungs will be less than 0.4 rad and for the rest of the body it will be less than 0.01 rad. (Natural background gives a dose of about 0.120 rad/year.) Although any radiation is considered potentially harmful, there are no know effects at the dose levels to be used.

The study requires the use of a face mask for controlling the gases being breathed and this involves minor physical discomfort.

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

1180224

Form 1913 RL

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
50 Upton, New York 11973

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

NAME

UNIT NO.

PAVILION OP

I understand that the physicians at the Hospital of the Medical Research Center, Brookhaven National Laboratory are engaged in research and study of the nature of diseases and of new methods of diagnosis and treatment. I have been informed of the anticipated duration of hospitalization and the nature of the procedure, study, or drug under clinical investigation known as:

Cerebral Blood Flow

I understand that the nature of this procedure, study, or drug is experimental, and that at the present time no assurance can be given that my participation will be directly beneficial to me. I have been informed that the timing and sequence of these studies may not be revealed to me. I understand that in the opinion of the investigators responsible for this project and of the Review Board (Clinical Investigations Committee), I should be informed of the following possible hazards and inconveniences before agreeing to this clinical investigation:

or the maximum dose of 15 mCi

In high concentrations Krypton gas has a narcotic effect. However, in these studies only tracer concentrations will be used, for which there are no known effects. The radiation dose to the lungs will be less than 0.1 rad and for the rest of the body it will be less. Although any radiation is considered potentially harmful, there are no known effects at the dose levels to be used.

0.4

The study requires the use of a face mask for controlling the gases being breathed and this involves minor physical discomfort.

than 0.01 rad. (Natural background gives a dose of about 0.120 rad/year.)

I have been informed of the above. I have also been informed of the customary procedures. These may or may not be used. I have been offered the opportunity for further discussion of this procedure, study, or drug with the attending physician.

I voluntarily consent to participate in the above studies with an understanding of the known possible effects or hazards that might occur in the course thereof, and with the further understanding that not all effects of such procedure, study, or drug are known.

PATIENT'S NAME _____

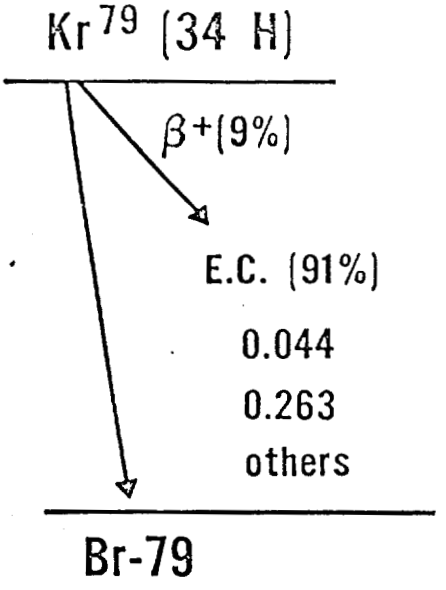
SIGNED BY: _____
(Patient or Legal Guardian)

WITNESS: _____

I, the undersigned, herewith affirm that I have explained the above to Mr. (Mrs.) (Miss) _____ and I am willing to answer further inquiries.

_____ M.D. DATE _____

1180225 Consent #50 – See revised Consent – New number will be issued.



1) $_{35}Br^{79} + _{1}H^{2} \longrightarrow _{36}Kr^{79} + 2n$

2) $_{36}Kr^{78} + _{0}n^{1} \longrightarrow _{36}Kr^{79} + r$

Montreal 70-0930

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