

RECAP SHEET

The Medical Research Center

Brookhaven National Laboratory

Upton, L. I., New York

R

Title: Studies of Calcium Kinetics in Man

Spon. Phys: A. Vaswani Prin. Invest: S.H. Cohn

Investigational Consent 414

IND#4390-Calcium 47-Annual Rept. due 3/83

Pregnant females excluded
pts. are over 21 years of age

Pts. (no limit on # of pts.)

1969-1971-20 pts.	4/76-4/77 - 0 pts.
1971-1972-30 pts.	4/77-4/78 - 0 pts.
1972-1973-36 pts.	4/78-5/79 - 0 pts.
12/73-10/75-31 pts.	5/79-2/80 - 0 pts.
	2/80-1/81 - 0 pts.

PURPOSE: To elucidate some of the processes in growth and remodeling of the skelton, particularly in cases of distrubed skeletal metabolism. The comparative kinetics of Ca are characterized in terms of accretion, exchange and biological turnover.

<u>APPROVALS</u>	
<u>HSRC</u>	<u>DEPT.</u>
<u>Initial</u>	
2/28/67	3/9/69
<u>Continuing</u>	
10/4/71	10/12/71
<u>Recertification</u>	
11/10/72	12/19/72
<u>Recertification</u>	
1/14/74	1/16/74
<u>Modification</u>	
(Change in investigat.	
9/15/75	9/16/75
<u>Revision & Recert</u>	
4/13/76	4/16/76
<u>Recertification</u>	
5/11/77	5/17/77
<u>Recertification</u>	
4/17/78	5/19/78
<u>Recertification</u>	
5/9/79	7/26/79
<u>Modification & Re</u>	
(Change in dose cal-	
culations	
2/13/80	3/6/80
<u>Recertification</u>	
2/11/81	3/4/81
<u>Recertification</u>	

REPOSITORY Records Holding Area, Bldg. 494

COLLECTION Committee-Clinical Investigations and Uses

BOX No. 4 of Radioisotopes

FOLDER CIRC #10A

BROOKHAVEN NATIONAL LABORATORY
MEMORANDUM

DATE: March 23, 1982
TO: HSRC, Dr. Chanana
A. Harrison, J. Matkovich
FROM: D.C. Borg *DCB*
SUBJECT: Inactive CIRC

On March 21, 1982, CIRC 10A entitled "Studies of Calcium Kinetics in Man" and consent 414 were declared inactive.

DCB/ck

1179568

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

PAV. _____

O.P. _____

I.M. _____

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

-414-

I understand that research patients of the Hospital of the Medical Research Center, Brookhaven National Laboratory, are asked to participate in procedures and studies not established as current medical practice but which are undertaken to discover and evaluate new methods of diagnosis and treatment of certain diseases and to study the nature of a disease, or the effectiveness of current methods of treatment, in the hope that a better understanding will lead to more effective control and even its eradication.

I understand that the procedure explained below 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 the study may not be revealed to me.

The following has been stated to me by Dr. _____:

The procedure to be performed "Study of Calcium Kinetics (^{47}Ca)" involves the intravenous injection of a small dose of radioactive calcium (^{47}Ca). The small dose of radio-calcium (about 20 micro curies) and the short radiological half-life of this radioisotope (109 hours) give a radiation exposure to the individual (0.07 rads to the whole body; 0.37 rads to the bone marrow) which is comparable to many standard diagnostic radiographic procedures. This last radiation exposure is 2 to 3 times the normal background radiation received by an individual in one year.

This procedure is experimental in the sense that it is not utilized in routine studies of disorders of calcium metabolism. However, it gives unique information about the turnover of the calcium of the human organism. The procedure has been applied for several years to a better understanding of several metabolic bone diseases or clinical conditions.

The attendant discomforts and risks derived from the vein puncture necessary for the injection ^{47}Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures.

In addition, you will be requested to keep a constant diet for 2 days, to collect 24-hr urine samples and to receive a small dose of calcium supplement by mouth during approximately 8-10 days. No direct benefit should be expected with this test. There is no appropriate alternative procedure.

I have been advised that if I wish a more detailed explanation of any of these matters it will be given. (If additional information is given, a summary should be attached.) I understand that in the event of physical injury resulting from the research procedures medical treatment will be provided free of charge; however monetary compensation is not available.

I understand I am free to withdraw my consent and discontinue participation in this activity at any time, without prejudice to me.

I have read the foregoing and hereby consent to participate in this procedure.

PATIENT'S NAME _____

SIGNED BY: _____

(Patient and, when necessary, Legal Guardian)

(Date)

WITNESS: _____

(Date)

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 _____

CIRC No.

10A

CLINICAL INVESTIGATION AUTHORIZATION FORM

PURPOSE OF REVIEW:

TITLE:

Studies of Calcium Kinetics in Man

- INITIAL
- ADDENDUM
- REVISION
- RECERTIFICATION
- REACTIVATION

TO CHAIRMAN, HSRC.

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

Annual Recertification

R B Aronson 1/16/81
Acting Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE HSRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON 2/11/81 AND RECOMMENDS Approval
WITH THE FOLLOWING MODIFICATIONS:

Rewrite sentence starting with "In addition" along the lines of sentence in consent 377

2/17/81
copy to
Dr. Vaswani
2/21/81
second

Michael Gold
M. GOLDMAN, Chairman

N.P. Rathvon, Jr.
N.P. RATHVON, JR., (Alternate Chairman)

H.R. Connell
H.R. CONNELL

M. Miller
M. MILLER

L. SBARRA

A.B. Brini
A. ZANZI

D.R. Christman
D.R. CHRISTMAN

C.B. MEINHOLD

E.P. CRONKITE

D.D. JOEL, Alternate

J. BATEMAN, Alternate

C.W. FLOOD, Alternate

K. Batchelor
J.P. STONE, Alternate
K. BATCHELOR, Alternate

L. OWEN, Alternate

W. SHREEVE, Alternate

P. CHANDRA, Alternate

TO Drs. Vaswani & Cohn,

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

1179570

Consent 414 will be used on this CIRC (replaces consent 359 that is now inactive)

D. Borg 3/4/81
D.C. BORG, M.D., Chairman, Medical Department Date

cc: Dr. Chanana, A. Harrison, J. Matkovich

CIRCULAR

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

Studies of Calcium Kinetics in Man

INITIAL

REVIEW

REAFFIRM

11A

TYPE OF REVIEW:

ADDENDUM

RECERTIFICATION

Modification

TO CHAIRMAN, HSRC.

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HERewith FOR

Change in dose calculations

D. Boig
D.C. Boig, M.D., Chairman, Medical Dept.

AND RECOMMENDATION.

1/17/80
Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE HSRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON 2/13/80 AND RECOMMENDS WITH THE FOLLOWING MODIFICATIONS:

Approved

M. Goldman, Chairman

N.P. Rathvon, (Alternate Chairman)

Robert R. Dorems

R. DOREMS

D.R. Christman

D.R. CHRISTMAN

K. Batchler

Alternate

Alternate

H.R. CONNER

Marilyn E. Miller

M. MILLER

C.B. MEINHOLD

E.P. CRONKITE

L. Sbarra

D.D. JOEL, Alternate

TO Drs. Zanzi and Cohn

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

Approved for annual recertification and modification

Consent 359 to be used on this CIRC (replaces 341)

D. Boig
D.C. Boig, M.D., Chairman, Medical Dept.

3/6/80
Date

cc: Above investigators, Dr. Chanana, A. Harrison, J. Matkovich

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

PAV. _____

O.P. _____

I.M. _____

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

-341-

I understand that research patients of the Hospital of the Medical Research Center, Brookhaven National Laboratory, are asked to participate in procedures and studies not established as current medical practice but which are undertaken to discover and evaluate new methods of diagnosis and treatment of certain diseases and to study the nature of a disease, or the effectiveness of current methods of treatment, in the hope that a better understanding will lead to more effective control and even its eradication.

I understand that the procedure explained below 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 the study may not be revealed to me.

The following has been stated to me by Dr. _____:

The procedure to be performed "Study of Calcium Kinetics (^{47}Ca)" involves the intravenous injection of a small dose of radioactive calcium (^{47}Ca). The small dose of radio-calcium (about 20 micro curies) and the short radiological half-life of this radioisotope (109 hours) give a radiation exposure to the individual (0.07 rads to the whole body; 0.37 rads to the bone marrow) which is comparable to many standard diagnostic radiographic procedures. This last radiation exposure is 2 to 3 times the normal background radiation received by an individual in one year.

This procedure is experimental in the sense that it is not utilized in routine studies of disorders of calcium metabolism. However, it gives unique information about the turnover of the calcium of the human organism. The procedure has been applied for several years to a better understanding of several metabolic bone diseases or clinical conditions.

The attendant discomforts and risks derived from the vein puncture necessary for the injection ^{47}Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures.

In addition, serial samples of urine and feces, necessitating a constant diet will be obtained.

There is no comparable alternative procedure to obtain this information.

I have been advised that if I wish a more detailed explanation of any of these matters it will be given. (If additional information is given, a summary should be attached.) I understand that in the event of physical injury resulting from the research procedures medical treatment will be provided free of charge; however monetary compensation is not available.

I understand I am free to withdraw my consent and discontinue participation in this activity at any time, without prejudice to me.

I have read the foregoing and hereby consent to participate in this procedure.

PATIENT'S NAME _____

SIGNED BY: _____

(Patient and, when necessary, Legal Guardian)

(Date)

WITNESS: _____

(Date)

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 _____

Minutes of the
BNL Human Studies Review Committee

February 13, 1980

Present: D. Christman, R. Doremus, M. Miller
Also present: Alternate Chairman - N.P. Rathvon
Alternates - K. Batchelor, P. Chandra, C. Flood
Secretary - C. Kerr
Excused: H. Connell, E. Cronkite, M. Goldman, L. Sbarra, I. Zanzi

The meeting, held in the large Conference Room in the Medical Department of the Medical Research Center, was called to order by the Alternate Chairman, N.P. Rathvon at 1400.

The minutes of the previous meeting, December 12, 1979, were accepted as distributed.

Committee approval was given for the following:

1. Dr. Wolf's request that CIRC 144 be rescheduled to appear on the April agenda
2. New Sponsoring Physicians on the following CIRC's:
 - CIRC 45R - Dr. Brill
 - 56 - Dr. Brill
 - 70 - Dr. Brill
 - 145 - Dr. Brill
 - 146 - Dr. Chandra
 - 166 - Dr. Chanana
3. Dr. Rampal be added as an investigator to CIRC 144.

CIRC 74 - "Neutrophilic Granulocytopoiesis in Normal Man and Leukemias" - Annual recertification approved.

CIRC 108 - "Glucagon in the Treatment of Paget's Disease of Bone" - Annual recertification was approved providing the following changes are made:

1. Insert the word "annual" before "maximum permissible dose" in the footnote of consent form #355 - "Radiation Dose Summary"
2. Include in the protocol that the patient will be encouraged to void his or her bladder at the proper time.

CIRC 56 - "Blood Pool and Spleen Scanning with ^{99m}Tc-Labeled Red Cells" - Addendum. Dr. Atkins' request to do an evaluation of spleen uptake of heat damaged Tc-RBC in normal individuals was approved. HSRC's only recommendation is that in "D. Type of Patient to be Studied" the word "potentially" be changed to "possibly".

CIRC 10A - "Studies of Calcium Kinetics in Man" - Annual recertification and modification. HSRC approved this CIRC for annual recertification as well as for the change in dose calculations. Mr. Rathvon will answer Dr. Borg's memo of 1/17/80 asking if HSRC is satisfied with the standard operating practices regarding the checking of dose calculations. The Committee stated that they were satisfied that all the new calculations are correct and that they will request recalculations of dose rates submitted prior to 1977.

1179573

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: Feb. 27, 1980

TO: D. C. Borg
FROM: N. P. ^{MB}Rathvon, Jr.
SUBJECT: CIRC 10-A

In forwarding CIRC 10-A to HSRC for recertification, you noted the recalculation of dosages involved and invited our attention to the implication of such recalculations.

The Committee is satisfied that the new calculations are proper and are based on more up-to-date methods of calculation.

To ensure that all human subjects being exposed to radiation in the course of research are given accurate information, the Committee requests that recalculation of dose rates be done similarly for each procedure involving rates based on calculations made prior to 1977.

cr

Carole,

Please keep a copy of this memo in your book or folder and at the time the CIRC Status Memo is sent out to the PI send along a notice of HSRC's request when appropriate (i.e. when dose calculations are older than 1977).

DeB 2/28/80

1179574

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

CIRC No. 10A

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE: Studies of Calcium Kinetics in Man

PURPOSE OF REVIEW:

- INITIAL
- ADDENDUM
- REVISION
- RECERTIFICATION
- REACTIVATION

TO CHAIRMAN, HSRC.

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

Annual recertification

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

Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE HSRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON May 9, 1979 AND RECOMMENDS Approval

WITH THE FOLLOWING MODIFICATIONS:

Consent 234 should set forth what the radioactive ~~exposure~~ dose is & what this amounts to in terms of normal background or permissible exposure to a radiation worker.

3/14/79 Copy to Dr. Cohn

N. Peter Rathon
N.P. RATHON, Jr., Chairman

Michael Gold
M. GOLDMAN (Alternate Chairman)

Helen B. Connell
H.R. CONNELL

Marilyn E. Miller
M. MILLER

K. KNUDSEN

I. ZANZI

R. DOREMUS

D.R. CHRISTMAN

C.B. MEINHOLD

D.C. BORG

D.D. JOEL, Alternate

Charles W. Flood
J. BAZMAN, Alternate
C.W. FLOOD, Alternate

J.P. Stone
J.P. STONE, Alternate

Glen Price
G.A. PRICE, Alternate

L. OWEN, Alternate

P. Chandra
W. SHREEVE, Alternate
P. CHANDRA, Alternate

TO Dr. Zanzi, Cohn, and Babu,

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

Consent 341 will be used on this CIRC. Consent 234 is now inactive.

1179575

D.C. Borg, M.D., Chairman, Medical Department

7/26/79
Date

cc: Dr. Chanana, A. Harrison, J. Matkovich

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

PAV. _____

O.P. _____

I.M. _____

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

-341-

I understand that research patients of the Hospital of the Medical Research Center, Brookhaven National Laboratory, are asked to participate in procedures and studies not established as current medical practice but which are undertaken to discover and evaluate new methods of diagnosis and treatment of certain diseases and to study the nature of a disease, or the effectiveness of current methods of treatment, in the hope that a better understanding will lead to more effective control and even its eradication.

I understand that the procedure explained below 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 the study may not be revealed to me. The following has been stated to me by Dr. _____:

The procedure to be performed "Study of Calcium Kinetics (^{47}Ca)" involves the intravenous injection of a small dose of radioactive calcium (^{47}Ca). The small dose of radio-calcium (about 20 micro curies) and the short radiological half-life of this radioisotope (109 hours) give a radiation exposure to the individual (0.03 rads to the whole body; 0.03 rads to the bone marrow) which is comparable to many standard diagnostic radiographic procedures. This last radiation exposure is 2 to 3 times the normal background radiation received by an individual in one year.

This procedure is experimental in the sense that it is not utilized in routine studies of disorders of calcium metabolism. However, it gives unique information about the turnover of the calcium of the human organism. The procedure has been applied for several years to a better understanding of several metabolic bone diseases or clinical conditions.

The attendant discomforts and risks derived from the vein puncture necessary for the injection ^{47}Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures.

In addition, serial samples of urine and feces, necessitating a constant diet will be obtained.

There is no comparable alternative procedure to obtain this information.

I have been advised that if I wish a more detailed explanation of any of these matters it will be given. (If additional information is given, a summary should be attached.) I understand that in the event of physical injury resulting from the research procedures medical treatment will be provided free of charge; however monetary compensation is not available.

I understand I am free to withdraw my consent and discontinue participation in this activity at any time, without prejudice to me.

I have read the foregoing and hereby consent to participate in this procedure.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient and, when necessary, Legal Guardian) (Date)

WITNESS: _____
(Date)

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 _____

Minutes of the
BNL Human Studies Review Committee
May 9, 1979

Present: D. Borg, H. Connell, M. Miller, N. Rathvon
Also present: Alternates - P. Chandra, C. Flood, M. Goldman, G. Price, J. Stone
Secretary - C. Kerr
Excused: D. Christman, R. Doremus, K. Knudsen, I. Zanzi
Absent: L. Owen

The meeting, held in the large Conference Room in the Medical Department of the Medical Research Center, was called to order by Mr. Rathvon at 1400.

The minutes of the previous meeting 11 April 1979, were accepted as distributed.

All of the following CIRC's were approved for annual recertification:

- CIRC 36G - "Epidemiology of Post-Menopausal Osteoporosis - Prevention with Estrogens"
- CIRC 70 - "Detection of Impaired Pulmonary Function with Mass-Spectrographic Tracer Technique"
- CIRC 96 Rev.2 - "Long Term Study of Osteoporosis and Imperfecta Tarda (OIT) in Adults"
- CIRC 113 - "Labeling of Blood Elements with Radioactive Nuclides"
- CIRC 146 - "DNA Repair - Human and E coli Photo Reactivating Enzymes"
- CIRC 152 - "Photoreactivation in Human Skin"
- CIRC 153 - "Epidemiology of Magnetic Effects on Humans"

CIRC 165 - A new proposal entitled "Diurnal Variations in Erythropoietin Levels and the Effect of Exercise on Erythropoietin Levels" was approved.

CIRC 154 - "The Efficacy of Biofeedback for the Treatment of Essential Hypertension" - Annual recertification approved. HSRC suggests that the SUNY Consent be changed to: Benefits expected: "possible" instead of "significant"; a sentence be added relating to the treatment and compensation to be provided if physical injury occurs.

CIRC 15 Rev. - "Clinical Use of ^{99m}Tc Sulfur Colloid" - Annual recertification. Approved providing Consent 275 includes the actual dosage and amount of activity given.

It was the consensus of the Committee that clinical procedures not involved in research need not be reviewed. The Chairman promised to review this matter.

CIRC 63 Rev. - "Evaluation of Iodine-123 as Sodium Iodide" - Annual recertification. Approved with the following modification: Consent 236 state the radiation dose and amount of activity given. The Committee also questioned whether this material is carrier free.

CIRC 10A - "Studies of Calcium Kinetics in Man" - Annual recertification. The Committee suggests that Consent 234 state what the radioactive dose is and what this amounts to in terms of normal background or permissible exposure to a radiation worker. Pending these changes the CIRC was approved.

1179577

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

CIRC No. 10A

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

Studies of Calcium Kinetics in Man

PURPOSE OF REVIEW:

- INITIAL
- ADDENDUM
- REVISION
- RECERTIFICATION
- REACTIVATION

TO CHAIRMAN, HSRC.

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

Annual Recertification

E.P. Cronkite 17 April 78
E.P. CRONKITE, M.D., Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE HSRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON 5/17/78 AND RECOMMENDS approval WITH THE FOLLOWING MODIFICATIONS:

		U. REINCKE, Alternate
N.P. RATHVON, Jr., Chairman	<u>Rudolf R. Dromas</u> I. ZANZI	C.W. FLOOD, Alternate
L.D. HAMILTON (Alternate Chairman)	<u>F.R. Christman</u> R. DOREMUS	J.P. STONE, Alternate
<u>Helen Connell</u> H.R. CONNELL	D.R. CHRISTMAN	<u>Glenn A. Price, acting ch</u> G.A. PRICE, Alternate
<u>Marilyn Miller</u>	C.B. MEINHOLD	L. OWEN, Alternate
<u>M. Miller</u> M. MILLER	D.C. BORG	W. SHREEVE, Alternate
<u>R.A. Love</u> R.A. LOVE	D.D. JOEL, Alternate	<u>P. Chandra</u> P. CHANDRA, Alternate

TO Drs. Zanzi, Cohn, Kapoor and Babu,

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

Consent # 234 to be used on this CIRC.

1179578

E.P. Cronkite 5/19/78
E.P. CRONKITE, M.D., Chairman, Medical Department Date

cc: Dr. Chanana, J. Matkovich, A. Harrison

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

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

P.A.V. _____

O.P. _____

I.M. _____

-234-

I understand that research patients of the Hospital of the Medical Research Center, Brookhaven National Laboratory, are asked to participate in procedures and studies not established as current medical practice but which are undertaken to discover and evaluate new methods of diagnosis and treatment of certain diseases and to study the nature of a disease, or the effectiveness of current methods of treatment, in the hope that a better understanding will lead to more effective control and even its eradication.

I understand that the procedure explained below 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 the study may not be revealed to me.

The following has been stated to me by Dr. _____:

The procedure to be performed "Study of Calcium Kinetics (^{47}Ca)" involves the intravenous injection of a small dose of radioactive calcium (^{47}Ca). The small dose of radiocalcium (about 20 micro curies) and the short radiological half-life of this radioisotope (109 hours) give a radiation exposure to the individual which is comparable to a standard diagnostic radiographic procedure.

This procedure is experimental in the sense that it is not utilized in routine studies of disorders of calcium metabolism. However, it gives unique information about the turnover of the calcium of the human organism and may guide my physician in prescribing treatment for me. The procedure has been applied for several years to a better understanding of several metabolic bone diseases or clinical conditions.

The attendant discomforts and risks derived from the vein puncture necessary for the injection ^{47}Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures.

In addition, serial samples of urine and feces, necessitating a constant diet.

There is no comparable alternative procedure to obtain this information.

I have been advised that if I wish a more detailed explanation of any of these matters it will be given. (If additional information is given, a summary should be attached.)

I understand I am free to withdraw my consent and discontinue participation in this activity at any time, without prejudice to me.

I have read the foregoing and hereby consent to participate in this procedure.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient and, when necessary, Legal Guardian) (Date)

WITNESS: _____
(Date)

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 _____

Minutes of the

BNL Human Studies Review Committee

11 May 1977

Present: A. Ansari, D. Christman, H. Connell, R. Doremus, R. Love, N.P. Rathvon,
I. Zanzi
Also present: Alternate - L. Owen
Secretary - C. Kerr
Absent: D.C. Borg
Excused: C. Meinhold

The meeting was held in the Large Conference Room of the Medical Research Center and called to order by Mr. Rathvon at 1405.

The minutes of the previous meeting held on 9 March 1977 were accepted as distributed.

All of the following CIRC's were approved for annual recertification:

<u>CIRC#</u>	<u>Title</u>
15 Rev.	Clinical Use of ⁹⁹ Tc Sulfur Colloid
26 Rev.	Technetium-99m Labeled Human Serum Albumin (produced by the stannous ion method): ^{99m} Tc-SHA(Sn)
42	¹⁸ F Bone Scanning
62	Medical Studies of Marshallese People Accidentally Exposed to Radioactive Fallout in 1954
63 Rev.	Evaluation of Iodine-123 as Sodium Iodide
70	Detection of Impaired Pulmonary Function with Mass-Spectrographic Tracer Technique
113	Labeling of Blood Elements with Radioactive Nuclides
123	Clinical and Metabolic Evaluation of the Response of Renal Osteodystrophy to the Treatment of Diet; 25 Hydroxycholecalciferol; 1-alpha Hydroxycalciferol and 1,25 Dihydroxycholecalciferol
136	Evaluation Human Calcitonin BA 47175 Treatment of Paget's Disease of Bone

CIRC 10A Rev. "Studies of Calcium Kinetics in Man" and CIRC 108 "Glucagon in the Treatment of Paget's Disease of Bone" were approved for annual recertification providing that the third paragraph on consent form 175 be changed to read:

"The attendant discomforts and risks derived from the vein puncture necessary for the injection of ⁴⁷Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures."

1179580

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

CIRC No. 10 A. Rev.

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE: Studies of Calcium Kinetics in Man

- PURPOSE OF REVIEW:
- INITIAL
 - ADDENDUM
 - REVISION
 - RECERTIFICATION
 - REACTIVATION

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

Annual Recertification

E.P. Cronkite 18 April 77
E.P. CRONKITE, M.D., Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:
THE HSRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON May 11, 1977 AND RECOMMENDS Approved
WITH THE FOLLOWING MODIFICATIONS:

Investigational Consent #175 should be revised to read:

3rd paragraph The attendant discomforts and risks derived from the vein puncture necessary for the injection ⁴⁷Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days) are the remote possibility of pain, bleeding or infection at the site of the vein punctures.

N.P. Rathvon, Jr.
N.P. RATHVON, JR., Chairman

L.D. HAMILTON (Alternate Chairman)

H.R. CONNELL

R.A. Love
R.A. LOVE

D.D. JOEL, Alternate

R. Doremus
D.R. CHRISTMAN

C.B. MEINHOLD

D.C. BORG

A. UPTON, Alternate

U. REINCKE, Alternate

C.W. FLOOD, Alternate

J.P. STONE, Alternate

G.A. PRICE, Alternate

L. OWEN, Alternate

W. SHREEVE, Alternate

I. ZANZI

TO Drs. Zanzi, Cohn, Babu, Kalici, Brennan,

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

Investigational consent #234 to be used on this CIRC (replaces #175).

1179581

E.P. Cronkite 17 May 77
E.P. CRONKITE, M.D., Chairman, Medical Department Date

cc: Dr. Chanana, A. Harrison, J. Matkovich

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

P.A.V. _____

O.P. _____

I.M. _____

CONSENT FOR PROCEDURE, STUDY, OR
DRUG UNDER CLINICAL INVESTIGATION

-175-

I understand that research patients of the Hospital of the Medical Research Center, Brookhaven National Laboratory, are asked to participate in procedures and studies not established as current medical practice but which are undertaken to discover and evaluate new methods of diagnosis and treatment of certain diseases and to study the nature of a disease, or the effectiveness of current methods of treatment, in the hope that a better understanding will lead to more effective control and even its eradication.

I understand that the procedure explained below 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 the study may not be revealed to me. The following has been stated to me by Dr. _____:

The procedure to be performed "Study of Calcium Kinetics (^{47}Ca)" involves the intravenous injection of a small dose of radioactive calcium (^{47}Ca). The small dose of radiocalcium (about 20 micro curies) and the short radiological half-life of this radioisotope (109 hours) give a radiation exposure to the individual which is comparable to a standard diagnostic radiographic procedure.

This procedure is experimental in the sense that it is not utilized in routine studies of disorders of calcium metabolism. However, it gives unique information about the turn-over of the calcium of the human organism and may guide my physician in prescribing treatment for me. The procedure has been applied for several years to a better understanding to several metabolic bone diseases or clinical conditions.

The attendant discomforts and risks, apart from the theoretical risk associated with any amount of radiation, derive from the vein puncture necessary for the injection ^{47}Ca and for several blood samples (approximately 2 ml (cc) of plasma per day up to ten days). There is the remote possibility of pain, bleeding or infection at the site of the vein punctures.

In addition, serial samples of urine and feces, necessitating a constant diet.

There is no comparable alternative procedure to obtain this information.

I have been advised that if I wish a more detailed explanation of any of these matters it will be given. (If additional information is given, a summary should be attached.)

I understand I am free to withdraw my consent and discontinue participation in this activity at any time, without prejudice to me.

I have read the foregoing and hereby consent to participate in this procedure.

PATIENT'S NAME _____

SIGNED BY: _____
(Patient and, when necessary, Legal Guardian) (Date)

WITNESS: _____
(Date)

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 _____

Minutes
of the
BNL Human Studies Review Committee

10 February 1976

Present: N.P. Rathvon, Jr., A.N. Ansari, D.C. Borg, D.R. Christman, H.R. Connell,
R. Doremus, I. Zanzi

Also present: Alternates - C.W. Flood, L.D. Hamilton
Others - C. Kerr

The meeting was held in the Hospital Conference Room of the Medical Research Center and called to order by Mr. Rathvon at 1400 hrs.

The minutes of the previous meeting, 20 January 1976 were accepted as distributed.

CIRC 999 - It is noted for the record that a special request to do a clinical study on a 13 year old child with a question of Meckel's diverticulum was approved on January 28, 1976.

Mr. Rathvon informed the Committee that occasionally a patient is admitted to BNL on an established CIRC while a research patient elsewhere with investigative drugs approved at the other institution for administration during his stay at BNL. He in his capacity as BNL Council had advised Dr. Cronkite that it was not necessary for the research program of the institution to be submitted to the BNL-HSRC for approval. He asked if any HSRC member disagreed with this opinion. His view was supported by the other members.

CIRC 10A, "Studies of Calcium Kinetics in Man", was submitted for revision and annual recertification. After a lengthy discussion the Committee decided to defer action until the next meeting. Mr. Rathvon will speak to Dr. Atkins, the Sponsoring Physician in reference to the following: 1) a revised consent, 2) clarification of dose calculation, 3) type of patient to be selected, and 4) number of doses given per patient.

The Committee agreed with Dr. Borg's suggestion that it review guidelines with regard to radiation dose in diagnostic, therapeutic and research studies.

CIRC 105, "Study of the Effects of Thiazide on Essential Hypertension", presented for annual recertification was approved subject to preparation of a revised consent on the new form with terminology more understandable to the layman.

Mr. Rathvon asked Dr. Hamilton to chair the next portion of the meeting concerning CIRC's 96R and 36G which had been first reviewed on 1/20/76 when Dr. Hamilton had served as Chairman.

CIRC 96 Rev., "Long-term Treatment of Osteoporosis" had been approved on 1/20/76 for the portion concerning estrogens, subject to submission of a new consent form. The revised consent was approved by the Committee and will be numbered 170.

1179584

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: February 27, 1976

TO: CIRC

FROM: S. H. Cohn *SHC*

SUBJECT: Review of CIRC 10A

In response to your request of 2-10-76, we are submitting the following information.

- 1) a revised patient consent
- 2) clarification of dose calculation according to the new MIRD procedure
- 3) Ca-47 is administered twice to each patient spaced 1 to 6 months apart
- 4) The type of patient to be selected for this procedure remains the same as described in Section D in our Clinical Investigation Proposal.

These patients will be largely uremic patients with osteo-dystrophy receiving various forms of therapy. However any patient with a disorder of calcium metabolism may be a subject for this procedure. Patients are referred from or also studied at NCMC.

- 5) It is expected that the kinetic information derived from this procedure will assist the physician in directing the individual patient's therapeutic program and therefore be of direct benefit to the patient.

1179585

Title: Studies of Calcium Kinetics

Sponsoring Physician ..Harold L. Atkins..... Principal InvestigatorStanton H. Cohn.....

Other Investigators: Dr. Zanzi

Dr. Abesamis-Research Collaborator-Nassau County Medical Center

- 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).

The purpose of this study is to elucidate some of the processes in growth and remodeling of the skeleton, particularly in cases of disturbed skeletal metabolism. The comparative kinetics of Ca are characterized in terms of accretion, exchange and biological turnover.

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

A previous study of six patients is reported in "Comparative Kinetics of Ca⁴⁷ and Sr⁸⁵ in Man, "Radiation Res. 19: 104, 1963. S.H. Cohn, S.W. Lippincott, E.A. Gusmano and J.S. Robertson.

Effect of High Calcium diet on parameters of Calcium metabolism in osteoporosis, S.H. Cohn, C. Dombrowski, W. Hauser, H.L. Atkins, J. Clin. Nutri. 21, 1246, 1968.

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

It is desired to study the above parameters in human beings as information on their skeletal metabolism will hopefully be of indirect benefit to the individual pts.

These studies have been conducted on lower animals, and their skeletal metabolism has been found to differ significantly. Number of patients to be studied open.

- D. **Type of Patient to be Studied.** Include age range, sex, disease, stage of treatment; inclusion or exclusion of pregnant or potentially pregnant females, legally incompetent persons.

No specific limitations on categories of patients are made but most will be pts. with various disorders of calcium metabolism. Patients will be inpatients generally, although there may be pts. from other hospitals in conjunction with collaborative research projects. Pts. are over 21 years, but pregnant females are excluded.

Patients involved in this study are referrals from or also studied at Nassau County Medical Center

Attach statement from the institution(s) indicating their review committee approval is current.

Indicate other investigative programs patients in this study may also participate in. CIRC 36A, 96R.

E. Dose Schedule for Drugs or Radiopharmaceuticals to be Used.

F. Details of Special Materials or Procedures.

1. Is any drug that falls into one or more of the following categories to be used? (If yes, indicate which)
 - a) unofficial drug or biological product (drug not listed in the USP or NNR).....
 - b) official drug but for purposes other than those listed?
 - c) official drug in doses exceeding or means of administration different from those listed?.....

(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?
3. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered?
- **4. Is a radionuclide to be administered?
- (If no, skip to question 5)
 - a) Specify nuclide and chemical form $^{47}\text{Ca Cl}_2$
 - b) Is the radionuclide one not listed in the USP?
 - 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 embarrassment to the patient?
- ***6. a. Is a direct benefit to the patient to be expected?
- b. Will the study contribute to the diagnosis, treatment or knowledge of the patient's disease?

	*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).....		
b) official drug but for purposes other than those listed?		
c) official drug in doses exceeding or means of administration different from those listed?.....		
(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?	X	
(If no, skip to question 5)		
a) Specify nuclide and chemical form <u>$^{47}\text{Ca Cl}_2$</u>		
b) Is the radionuclide one not listed in the USP?		X
c) Is the purpose for its use one not listed in the USP?		X
d) Does the dose exceed that listed in the USP?		X
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 embarrassment 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.

Harold L. [Signature] 10/7/75 Stanley H. [Signature] 10/7/75
 Sponsoring Physician Date 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.

B. Radiological Health Aspects

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

None

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

No special procedure required.

3. **Special Procedures for Handling Waste Products, Excreta, Biological Samples, etc., Where Indicated:**

None

4. **Plan for Isotope Accountability, If Required:**

Half-life 4.9 days precludes any residual activity.

C. Radiation Dosage

1. **Biological Half-Life or Half Lives:** (including slow components and fraction involved)

Physical $t_{1/2}$ in 4.9 days and is therefore limiting.

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):** BONE

b. **Gonadal Exposure:** Only gonadal exposure is from γ of bone deposited Ca^{47} . Gamma dose taken to be the same as dose to central axis of body as determined in attached calculation. The dose is well below the MPD for gamma radiation.

3. **Sample Calculations:** Dosage should be calculated for the whole body and for "target" or other separate organs, where indicated. Prototype equations are desired; not extensive calculations. Where applicable, the Medical Internal Radiation Dose (MIRD) Committee's recommended methods (J. Nuclear Medicine Supplements) should be used. Otherwise, standard dosage equations from references such as Hine and Brownell's *Radiation Dosimetry*, and the *National Bureau of Standards Handbook 69*, should be used where possible and the reference cited. The relationship to the administered dose should be made clear.

Total (β, γ) dose = 344 mr (calculations are attached).

The dose from Ca^{45} contaminant is included in the above figure and the calculation is presented. Since Ca^{47} , Sc^{47} , Ti^{47} , the dose from Sc^{47} was also calculated and found to be insignificant. This calculation is also attached.

On the basis of the radiation dose calculated, $60\mu\text{c}$ of Ca^{47} would be a safe dose, i.e., it would not exceed 0.3 rad/wk averaged over 13 weeks (ICRP).
Ref: Hine and Brownell.

1179588

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
- 74 - 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:

Study of Calcium Kinetics (^{47}Ca)

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:

The radiation exposure to the individual is very small. There may be a minor discomfort associated with the taking of blood samples.

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 _____

1179589

Pertinent information:

Following I.V. injection in man, the initial fall in plasma Ca^{47} is primarily due to the equilibration of Ca^{47} within the exchangeable Ca space. Equilibration is reached in 1-2 days in man, and the subsequent fall in plasma Ca^{47} is due to the excretion and accretion by the skeleton. As the whole-body retention of Ca^{47} may be measured with the whole-body counter, the rate of accretion and the size of the exchangeable calcium space can be calculated.

Fifty-eight per cent of I.V.-injected Ca goes to the skeleton. Ninety-nine per cent of the Ca in the total body is in the critical organ, the skeleton. The biological half-life of Ca is a complicated function of which the longest component is several years at least (not known).

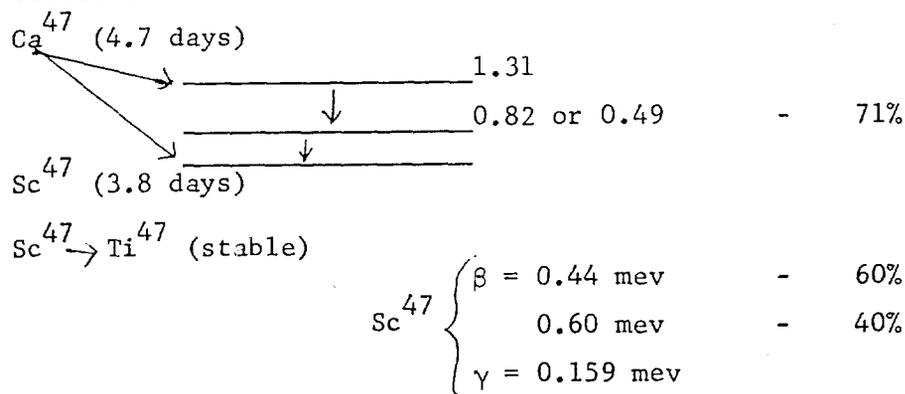
Ca^{47} , as a new tracer, has had only limited application for clinical study. The references listed cover some of the reported clinical experiences with the isotope.

Course of study:

Patients are to be followed for 10 days after I.V. injection of $\text{Ca}^{47}\text{Cl}_2$. Six blood samples are to be taken at daily intervals and three whole-body counts at 1, 5 and 10 days after Ca^{47} administration.

Isotope:

$\text{Ca}^{47}\text{Cl}_2$ in isotonic sterile solution, pH=5.

Decay Schedule

Source: Abbott, Oak Ridge, List # 7781

Preparation: Ca^{46} (n, γ) Ca^{47} requires enriched Ca^{46} (.0032% mass abundance).

Isotopic purity: Ca^{46} enrichment accompanied by enrichment of Ca^{44} , Ca^{44} (n, γ) Ca^{45} .

Ca^{45} is therefore a by-product that can be reduced by appropriate means. The product as sold does have 5% or greater Ca^{45} present. No other gamma-emitting contaminants are present, as verified by gamma-ray spectroscopic analysis prior to use.

Specific activity: 5mc/mg

Assay and calibration: Will use Oak Ridge calibration and check at BNL as much as possible.

Chemical form: CaCl_2 in saline, sterile.

Route of administration: I.V.

Extraneous effects anticipated: None

Sterility and pyrogenicity: Solution will be sterile. Pyrogenicity will be checked by injection into rabbit.

It is felt that on the basis of the radiation dose calculated, it would be safe to administer a total of 60 μc of Ca^{47} . This dose would not exceed the weekly exposure 0.3 rad/wk averaged over 13 consecutive weeks, as stated by the International Commission on Radiological Protection. In practice the 0.3 rad dose may be exceeded if the subject is not consistently exposed or if the dose is of diagnostic or therapeutic value.

Health Physics Aspects:

No hazard to other patients.

No special procedures required for handling waste products other than those required for handling I^{131} uptake patients, for example.

No special monitoring techniques.

No accountability required because of the short half-life of the isotope.

STATE UNIVERSITY
OF NEW YORK
DOWNSTATE MEDICAL CENTER

• DEPARTMENT OF MEDICINE

July 10, 1974

Dr. E.P. Cronkite
Brookhaven National Laboratory
Upton, Long Island 11973

RE: CIRC #112

Dear Dr. Cronkite:

Your memorandum of June 26, 1974 was just received because it was originally addressed to Stony Brook instead of the Downstate Medical Center in Brooklyn. I am hastening to clarify any discrepancy:

#1 The decision as to whether or not a female patient is pregnant prior to total body neutron activation analysis, will be determined at the Downstate Medical Center based upon history, physical examination and pregnancy tests, if indicated.

#2 Regarding CIRC 10 A: The Ca-47 radioisotope turnover studies will be performed at the Clinical Research Center of Downstate Medical Center. This has been approved by the Health Sciences Review Committee on Investigations Involving Human Subjects at this institution. It is my understanding that a copy of this approval has been forwarded to you. If additional information regarding the Ca-47 studies is required please contact me.

I hope that the above explanations will clarify any misunderstandings.

Very truly yours,

Florence Shai MD
Florence Shai, M.D.

FS:rw

7/13/74 Copy sent to Dr Chanana for info.
ck

1179592

Original in CIRC 112 file

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

CIRC No. 10A

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

Studies of Calcium Kinetics in Man

- PURPOSE OF REVIEW:
- 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.

E.P. Cronkite 9 Jan '74
 E.P. CRONKITE, M.D., Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON Jan. 14, 1974 AND RECOMMENDS recertification
 WITH THE FOLLOWING MODIFICATIONS:

- None -

Edwin A. Popenoe
 E.A. POPENOE, Chairman

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

Helen E. Connell
 H.R. CONNELL

G.A. Price
 G.A. PRICE

P.S. PAVASILIOU

R.A. Love
 R.A. LOVE

D.N. SLATKIN, Alternate

S.H. COHN, Alternate

U. Reincke
 U. REINCKE

A.P. WOLF, Alternate

TO Drs. Atkins, Cohn and Zanzi,

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

Investigational Consent # 74 to be used on this CIRC.

For the record-IND 4390 Annual Report to FDA submitted April 12, 1973.

E.P. Cronkite 16 Jan '74
 E.P. CRONKITE, M.D., Chairman, Medical Department

1179593

CIRC No. 10A

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

Studies of Calcium Kinetics in Man

PURPOSE OF REVIEW:

- 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.

E.P. Cronkite 24 Oct 72
E.P. CRONKITE, M.D., Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON Nov 10 72 AND RECOMMENDS Approval
WITH THE FOLLOWING MODIFICATIONS:

1) That "no hazards" be removed from the informed consent form
 2) That a statement be added to the informed consent form explaining the administration of a radioactive isotope

<u>J.S. ROBERTSON, Chairman</u>	<u>George C. Cotzias</u> G.C. COTZIAS, Alternate Chairman	<u>Helen B. Connell</u> H.B. CONNELL
<u>S.H. COHN</u>	<u>E.A. POPENOE, Alternate</u>	<u>R.A. LOVE</u>
<u>G. PRICE</u> <u>Daniel N. Slatkin</u> D.N. SLATKIN, Alternate	<u>G. CHIKKAPPA</u>	<u>N.P. RATHVON, JR.</u>
	<u>A.P. WOLF, Alternate</u>	

TO S.H. Cohn and H.C. A. Usain

THE ABOVE TITLED AND NUMBERED PROPOSAL IS approved SUBJECT TO THE FOLLOWING:
New consent form # 74 complies with committee report and to be used with CIRC

E.P. Cronkite 19 Dec 72
E.P. CRONKITE, M.D., Chairman, Medical Department Date

1179594

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY

- 74- 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:

Study of Calcium Kinetics (^{47}Ca)

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:

The radiation exposure to the individual is very small. There may be a minor discomfort associated with the taking of blood samples.

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 _____

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

CLINICAL INVESTIGATION AUTHORIZATION FORM

Purpose of Review: Initial Revision Continuing Addendum

Title: STUDIES OF CALCIUM KINETICS IN MAN

CIRC#	<u>10A</u>
Assigned on (date)	<u>17 Feb 1967</u>

To Chairman, CIRC,

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

REQUEST RECERTIFICATION BY PROPERLY CONSTITUTED "COTZIAS COMMITTEE"; NOTE SUGGESTIONS OF 7 JULY 1971 AND CONSENT FORM (#-10-) ARE INCORPORATED IN RECORD.

E. P. Cronkite 29 Sept '71
 E. P. Cronkite, M.D., President of Staff Date

To President of Staff,

The Clinical Investigation and Uses of Radiosotopes Committee reviewed the above identified proposal on Oct 4 '71 and recommends approval with the following modifications:

<u>J. S. Robertson</u> J. S. Robertson, Chairman	<u>G. C. Cotzias</u> G. C. Cotzias, Alt. Chairman	<u>H. R. Connell</u> H. R. Connell
<u>S. H. Cohn</u> <u>G. Price</u> G. Price	<u>E. A. Popence</u> E. A. Popence, Alternate	<u>R. A. Love</u> R. A. Love
<u>S. E. Duby</u> , Alternate	<u>A. P. Wolf</u> , Alternate	<u>N. P. Rathvon, Jr.</u>

To Dr Cohn and Atkins,

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

Investigational Consent No. 10 established for CIRC 10A

E. P. Cronkite 12 Oct '71
 E. P. Cronkite, M.D., President of Staff Date

CLINICAL INVESTIGATION PROPOSAL

TITLE: STUDIES OF Calcium Kinetics
in MAN

CIRC # 10 A

Assigned

on (date)

2-28-67

June 10, '71

Sponsoring
Physician Dr. H. L. Atkins

Principal
Investigator Dr. S. H. Cohn

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).

The purpose of this study is to elucidate some of the processes in growth and remodeling of the skeleton, particularly in cases of disturbed skeletal metabolism. The comparative kinetics of Ca are characterized in terms of accretion, exchange and biological turnover.

- B. Pertinent information on related prior clinical and laboratory studies. Include quantitative toxicity data for drugs. Cite literature by author, title and publication.

A previous study of six patients is reported in "Comparative Kinetics of Ca⁴⁷ and Sr⁸⁵ in Man, "Radiation Res. 19: 104, 1963. S.H. Cohn, S.W. Lippincott, E.A. Gusmano and J.S. Robertson.

- C. Reasons for performing the studies on human beings and approximate number to be studied.

Effect of High Calcium diet on parameters of Calcium metabolism in osteoporosis, S.H. Cohn, C. Dombrowski, W. Hauser, H.L. Atkins, J. Clin. Nutri. 21, 1246, 1968.

It is desired to study the above parameters in human beings as information on their skeletal metabolism will hopefully be of indirect benefit to the individual patients.

- D. Type of patient to be studied. Include age range, sex, disease, stage of treatment, inclusion or exclusion of pregnant females.

These studies have been conducted on lower animals, and their skeletal metabolism has been found to differ significantly. Number of patients to be studied open.

No specific limitations on categories of patients are made but most will be patient with various disorders of calcium metabolism. Patients will be inpatients generally, although there may be patients from other hospitals in conjunction with collaborative research projects. Patients are over 21 years, but pregnant females are excluded.

Written informed consent is obtained for each patient.

- E. Dose schedule for drugs or radiopharmaceuticals to be used.

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CLINICAL INVESTIGATION PROPOSAL (continued)

CIRC#	10 A
Assigned on (date)	2-28-67
	June 10, '71

F. Details of special materials or procedures.

	YES *	NO
1. Are any investigational drugs to be used (ones not in the USP or NNR)?		✓
2. Is a drug listed in the USP or NNR to be used		
a. in doses exceeding those listed?		✓
b. for purposes other than those listed?		✓
3. Are any biological products to be administered that do <u>NOT</u> bear on their containers or labels notations of approval by the Biological Control Division of the National Institutes of Health?		✓
4. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered?	✓	
** 5. Are any radionuclides to be administered?	✓	
If yes, a. is the radionuclide form one listed in the USP?		✓
If yes, give nuclide and chemical form <u>47Ca Cl₂</u>		
b. is the radionuclide to be used within the doses and for the purpose approved in the USP.		✓
6. Are any other procedures to be used which exceed the ordinary diagnostic and therapeutic measures for the patient concerned and which may entail a hazard, discomfort or embarrassment to the patient?		✓
*** 7. a. Is a direct benefit to the patient to be expected?	✓	
b. Will the study contribute to the diagnosis or treatment of the patient's own disease?	✓	
8. 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?		

Harold L. Atkins
 Sponsoring Physician

S. H. Cohn
 Principal Investigator

* If any question 1 through 6 is answered yes, append a discussion of the potential hazards including pertinent literature citations (note that a yes answer to 5a & 5b is sufficient for question 5) or indicate where discussed in accompanying IND request.

** If answer to 5a or 5b is no, append a completed Supplementary Form on Radionuclide Administration (CIRC form 3-1 & 3-2, 4/15/71).

*** If answer to 7a or 7b is no, append explanation.

CLINICAL INVESTIGATION PROPOSAL

SUPPLEMENTARY FORM ON RADIONUCLIDE ADMINISTRATION

CIRC# 10 A

Assigned
on (date) 2-28-67

June 10, '71

A. Radionuclide

- Species: (Radionuclide or labeled compound, eg. $^{24}\text{Na Cl}$ or $1\text{-}^{14}\text{C-glucose}$)
 $\text{Ca}^{47}\text{Cl}_2$
- Physical characteristics: (Physical half-life; decay scheme or type, energy and relative frequency of major emissions, energies)
 $t_{1/2} = 4.9 \text{ d}$ $\text{Ca}^{47} \rightarrow \text{Sc}^{47} \rightarrow \text{Ti}^{47}$ (see attached sheet)
- Source: (BNL reactor, cyclotron, hot lab., commercial supplier, etc.)
 Ca^{47} - Abbott, Oak Ridge - List No. 7781
- Preparation: (Target material, quantity, special problems)
 Ca^{46} (n, γ) Ca^{47} from enriched Ca^{46}
- Specific activity and isotopic purity of administered material:
S.A. = 5 mc/mg. The product as sold does have about 5% Ca^{45} contamination.
- Radioassay and calibration procedures: (Include validation to be performed at BNL prior to use)
 - Gamma ray spectroscopic analysis.
 - Assay of Ca^{47} and Ca^{45} , using previous calibration standards.
- Vehicle and route of administration:
20 μc CaCl_2 in sterile saline - I.V.
- Procedures for control of sterility and pyrogenicity: (Or note that commercially supplied isotopes are certified as ready for administration to human beings.) Injection solution sterilized and tested for pyrogenicity by rabbit injection.
- Side effects, if pertinent: (such as pharmacological or toxic actions of the parent compound or vehicle, etc.)
None

B. Radiological Health Aspects:

- Hazards to other patients and to personnel from external or internal radiation (e.g. 1 mR at 1 meter):
No
- Monitoring procedures, if necessary:
No special procedure required.
- Special procedures for handling waste products, excreta, biological samples, etc., where indicated:
None
- Plan for isotope accountability, if required:

Half-life 4.9 days precludes any residual activity

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CLINICAL INVESTIGATION PROPOSAL

SUPPLEMENTARY FORM ON RADIONUCLIDE ADMINISTRATION
(Continued)

CIRC#	10 A
Assigned on (date)	2-28-67 June 10, 71

C. Radiation Dosage

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

Physical $t_{1/2}$ in 4.9 days and is therefore limiting.

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): BONE

b. Gonadal exposure: Only gonadal exposure is from γ of bone deposited Ca^{47} . Gamma dose taken to be the same as dose to central axis of body as determined in attached calculation. The dose is well

3. Sample calculations: (Dosage should be calculated for the whole body and for "target" or other separate organs, where indicated.) Prototype equations are desired; not extensive calculations. Where applicable, the Medical Internal Radiation Dose (MIRD) Committee's recommended methods (J. Nuclear Medicine Supplements) should be used. Otherwise, standard dosage equations from references such as Hine and Brownell's Radiation Dosimetry, and the National Bureau of Standards Handbook 69, should be used where possible and the reference cited.

Total (β, γ) dose = 344 mr (calculations are attached).

The dose from Ca^{45} contaminant is included in the above figure and the calculation is presented. Since $\text{Ca}^{47} \rightarrow \text{Sc}^{47} \rightarrow \text{Ti}^{47}$, the dose from Sc^{47} was also calculated and found to be insignificant. This calculation is also attached.

On the basis of the radiation dose calculated, 60 μc of Ca^{47} would be a safe dose, i.e., it would not exceed 0.3 rad/wk averaged over 13 weeks (ICRP). Ref: Hine and Brownell.

HOSPITAL OF THE MEDICAL RESEARCH CENTER,
BROOKHAVEN NATIONAL LABORATORY
-10- 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:

Calcium balance study.
With calcium-47 ($^{47}\text{Ca Cl}_2$)

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:

There are no hazards.

The inconvenience will be the taking of several blood samples and the collection of urine and stool specimens,

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 _____

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Rev. 1-5-50
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The Committee on Clinical Investigations and Use of Radioisotopes
hereby approves the program with the following title:

CIRC # 10a has been assigned to this program.

George C. Cotzias.
George C. Cotzias, M.D., Chairman

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

Herbert Savel
Herbert Savel, M.D.

Knud Knudsen
Knud Knudsen, M.D.

Date: February 28, 1967
Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Approval recommended Date 3/9/67
Disapproval Date _____

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

1179602

2/21/67 approved

V. P. Bond, M.D.

CIRC - 10a
(H-64)

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: February 3, 1967

TO: Clinical Isotope Committee
FROM: Dr. S. H. Cohn
SUBJECT: Approval for clinical tracer study

We would like to perform further clinical studies as described in clinical isotope request H-64 which permits the use of ^{47}Ca in tracer amounts. Since there have been several modifications in the original protocol, we would appreciate your review.

The other investigators involved in the present study include Dr. H. L. Atkins and Dr. J. S. Robertson.

The general protocol is the same except that two tracer doses of ^{47}Ca (20 μc) will be administered to each patient one month apart, and each patient will receive supplemented diets of Ca gluconate (2.5 g/d) during this interval. A compartmental analysis involving the use of the computer is used for the determination of the various parameters of skeletal metabolism, as described in Cohn, S. H. *et al.*, "Formulation and testing of a compartmental model for Ca metabolism in man," Radiation Res. 26: 319, 1965.

In the specific study planned, the therapeutic effects of a high Ca diet on patients with senile osteoporosis will be evaluated clinically, radiographically, by bone density measurements, hydroxyproline excretion, whole-body counting measurements, and by the use of the ^{47}Ca kinetic study described.

Our hypothesis states that the basic defect in senile osteoporosis, i.e., loss of bone mass, results from an increased bone resorption rate with the accretion rate into bone remaining normal. The high Ca diet, therefore, should act to diminish the bone resorption rate without affecting the accretion rate leading to an increased bone mass or density and a diminution of the osteoporosis.

To accomplish these objectives, 8 patients, 60-70 years old, with advanced senile osteoporosis will be selected from the Suffolk Infirmary (under the same arrangement set up by Dr. Jesseph three years ago). After the patient undergoes a period of equilibration on the standard BNL diet (0.8 g/day) of Ca, 20 μc of ^{47}Ca will be administered and the above kinetic study will be carried out over a 10-day period.

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Once the base line for the various parameters of Ca metabolism is established for each patient, they will be placed on a Ca gluconate supplemented diet (2.5 g/day) for 20 days. At the end of this time the patients will receive a second tracer injection of ^{47}Ca (20 μc) and the kinetic study will be repeated for a 10-day period.

The alteration in the values of the parameters of skeletal metabolism, compartment sizes and intercompartmental fluxes resulting from the high Ca diet should test the above hypothesis. Following the high Ca diet the balance between bone resorption and accretion should be shifted to one more closely resembling non-osteoporotic patients of the same age. Presumably this study would provide a more sensitive test of the value of a high Ca diet in the treatment of osteoporosis than can be obtained by balance studies or radiography alone.

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