725520

R

BROOKHAVEN NATIONAL LABORATORY

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

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

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

1179424

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

Studies of Vitamin B_{12} Metabolism in Man

CIRC # 4 has been assigned to this program.

Walton W. Shreeve

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

E. P. Cronkite

Eugene P. Cronkite, M.D.

E. Schackow

Eckart Schackow, M.D.

M. H. Van Woert

Melvin H. Van Woert, M.D.

J. S. Robertson

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

Date November 1, 1963

Place Medical Research Center
Brookhaven National Laboratory
Upton, New York

1179425

FORM FOR INITIATION OR REVIEW OF CLINICAL

INVESTIGATIVE PROGRAMS

(Submit original only to Department Chairman)

A. Title of the proposal: STUDIES OF VITAMIN B_{12} METABOLISM IN MAN.

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

C. Responsible investigator(s): E.P. Cronkite, L. M. Schiffer

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

STUDIES OF VITAMIN B_{12} METABOLISM IN HUMAN BEINGS

Investigators: E. P. Cronkite, L. M. Schiffer, N. Glatstein

Research Collaborator: L. M. Meyer

Experimental Background: The long term distribution and utilization of Vitamin B_{12} in man is not completely understood. Of particular interest to us are the proposed models for B_{12} pools (either single or multiple); the long term retention of cyanocobalamin and its analogues (hydroxocobalamin, Coenzyme B_{12}, Ethylamide, Methylamide, analide and the aquanalide); and relative availability of Vitamin B_{12} in different compartments (anatomical or biochemical) for excretion following large doses of cold B_{12}.

The plasma clearance of Vitamin B_{12} in patients with chronic myelogenous leukemia is prolonged - presumably because of the high binding capacity of their plasma. (See additional sheet)

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

Human subjects are the only creatures who can and do develop spontaneously symptomatic Vitamin B_{12} deficiency states such as megaloblastic anemia and subacute combined degeneration of the spinal cord.

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

1. Patients with Addisonian pernicious anemia or Vitamin B_{12} deficiency anemia from any cause.
2. Patients with chronic myelocytic leukemia.
3. Hematologically normal comparison patients.
4. Patients with Polycythemia Vera.

Oral consent will be obtained by frank discussion with the patients.

1179426

Comparison of these patients with normal controls, utilizing blocking agents of all available B_{12} analogues will also give some insight into problems of pool size and body distribution.

PROPOSED AND CONTINUING CLINICAL RESEARCH PROJECTS CONCERNING VITAMIN B_{12} METABOLISM.

I. Biologicahalf-life of Vitamin B_{12} and analogues.

Objective: The biologicahalf-life of cyanocobalamin is estimated to be between one-half and two-plus years in man. Hydroxocobalamin has been shown to have a similar half-life (Schiffer etaal, unpublished). Our objective in this study is to compare the biologic half-lives of cyanocobalamin and other available analogues (eg. CoE, analide, aquanalide) over a prolonged period of time.

Design: a) Patients will receive, or already have received Co^{60} cyanocobalamin. They will be followed by whole body counting for six months, or more, in order to determine an accurate biologic half-life for cyanocobalamin.

b) They will then receive a labeled Co^{57} or Co^{58}) analogue and will have body counts performed for a similarly prolonged period of time. Rates of isotope disappearance from the body will then be compared.

Patients: Approximately 10-15 patients can be utilized from our list of active patients.

II. Retention of Vitamin B_{12} in patients with pernicious anemia.

Objective: The whole body counter is an ideal tool for measuring body retention of labeled B_{12} in an individual. We have attempted in one patient with pernicious anemia in relapse, to estimate retention of B_{12} by injecting only labeled B_{12} for therapy. Obviously, to prevent exceeding the MPD we have now had to give her cold B_{12}, but we hope to get some idea of her capabilities of retaining injected B_{12} and thus her requirements for maintenance and replacement of body stores. Body counts are correlated with stool and urine excretion whenever possible. Other patients will be utilized in a similar manner when they become available.

1179427

III. B_{12} plasma clearance in patients with chronic myelocytic leukemia and controls.

Objective: To determine the plasma clearance of B_{12} after blocking doses of Vitamin B_{12} and analogues and thus to determine some information regarding the efficiency of blocking agents and plasma pool size and compartments.

Design: Almost 20 patients have been studied to this date. We ordinarily give 1000 μg of B_{12}, or analogue, 24 hours prior to a Co^{57} plasma B_{12} clearance. The plasma retention of labeled B_{12} is measured over a two day period. More recent studies have extended this to ten days. Blocking agents are now being given at shorter intervals than 24 hours eg. 1-6-12-24 hours. Dialysis of the plasma is performed to determine binding ability of the Co^{57} cyanocobalamin.

IV. Plasma Vitamin B_{12} kinetics and chemistry.

Objective: The Vitamin B_{12}'s are converted to hydroxocobalamin and/or coenzyme B_{12} once within the body. The mechanism and kinetics of conversion are unknown as are the pathways of B_{12} once beyond the plasma. Little is known concerning the reentry of B_{12} from storage areas back to plasma and sites of utilization. A pilot study has been performed utilizing the principle of loading with cold B_{12} followed by clearance with Co^{57} B_{12}. This promises to give information regarding "free" and "bound" forms of B_{12}.

Design: Plasma clearances with Co^{57} cyanocobalamin following by 30 minutes and 6 hours an injection of 1000 μg cold B_{12}; straight Co^{57} B_{12} clearances; and clearance following injection of 2 μc Co^{60} cyanocobalamin are planned. Measurements will be made with whole body counting, area counting, plasma and urine counting and chemistry.

Patients: Hematologically normal controls and patients with chronic myelocytic leukemia.

1179428

Details of dose calculation are in H-63 and H-66 and the pertinent references.

Co^{57} B_{12} a) assuming situation 1) 50% in liver 50% total body (most likely clinical situation.

2) 100% total body

3) 100% total liver

b) assuming maximum permissible dose of 20 μc

c) assuming 75 kg man

Situation (2) D = .023 rad - .063 rad total dose

$(\beta + r)$ (a) .1 to .2 milli/day or

.007 - .0014 Rem/week

Maximum permissible

exposure (occupational) → 0.1 Rem weekly

Situation (1) total body $D_{(\beta + r)}$ = .012 - .032 rad

total liver $D_{(\beta + r)}$ = 0.81 - 3.9 rads

Situation (3) total liver dose $D_{(\beta + r)}$ = 1.62 - 7.8 rads

$Co^{60}B_{12}$ a) assuming situation (1) 50% in liver 50% total body

(2) 100% total body

(3) 100% total liver

b) assuming maximum permissible dose of 3 μc

c) assuming 75 Kg man

Situation (2) $D_{(\beta + r)}$ = 1.49 Rad total dose

(a) 3 millirems/day or

.02 Rem/week

Maximum permissible

exposure (occupational) → 0.1 Rem weekly

Situation (1) Total body $D_{(\beta + r)}$ = 0.75 R

Total liver $D_{(\beta + r)}$ = 14.1 R

Situation (3) Total liver dose $D_{(\beta + r)}$ = 28.2 R

1179429

Additional sheet for Item G.

G 1- We have been and plan to continue using several Vitamin B_{12} antagonists or analogues. These compounds have been tested on animal systems and have proven to be as non-toxic and innocuous as the parent compound. (Smith - Vitamin B_{12} antimetabolites - in Vitamin B_{12} and Intrinsic Factor, 2nd European Symposium 1961). Growth inhibition in the chick is reverted by regular Vitamin B_{12}. The analogues we are using as one injection of 1000 μg are:

Coenzyme B_{12}
Methylamide
Ethylamide
Analide
Aquanalide

G 2- We plan to use most of the B_{12} intravenously rather than intramuscularly or orally. There have never been any proven toxic effects from Vitamin B_{12}.

G 4- Normal diagnostic doses of Co^{60} cyanocobalamin are 0.5 μc. We plan to use no more than 3.0 μc $Co^{60}B_{12}$. Normal diagnostic doses of Co^{57} cyanocobalamin are 0.5 μc. We plan to use no more than 20 μc Co^{57} B_{12}.

1179430

Investigator: Reizenstein, P. G.

Title: Extension of permission to use radio-B_{12} (H-63, H-24) to include Co^{57}-B_{12}.

Date: Sept. 28, 1960

Project No.: H-66

Approved:

Committee on Use of Radioactive Isotopes in Patients:

Walton W. Shreeve

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

Victor P. Bond

Victor P. Bond, M.D., Ph.D.

Samuel Fine

Samuel Fine, M.D.

Elmer E. Stickley

Elmer E. Stickley, Ph.D.

J. S. Robertson

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

Lee E. Farr

Lee E. Farr, M.D.
Ex Officio

1179431

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 18 August 1960

TO: Isotope Committee

FROM: P. G. Reizenstein, M. D.

SUBJECT: Extension of permission to use radio-B_{12} (H-63, H-24) to include ^{57}Co-B_{12}.

Since the request with the above numbers was submitted and granted, vitamin B_{12} labeled with ^{57}Co has become commercially available. Since this isotope delivers only 38% of the total cumulative radiation per μc delivered by ^{58}Co, it is requested that B_{12} ^{57}Co may be used in this study instead of ^{58}Co or ^{60}Co-B_{12}.

The source of this isotope, the method of checking specific activities and purities, the patient-material and their care, the purpose of the study and the methods of the study will remain as outlined in request H-63, H-24.

Cobalt-57 decays entirely by electron capture followed by branched gamma ray emission of 0.137 Mev ($\sim$ 7% of disintegration) and by a sequence of 0.123 and 0.014 Mev rays (93%). It has a physical half-life of 270 days.

When calculated according to the formulae described in the original request H-63 and its enclosures, 1μg ^{57}Co-B_{12} retained by the liver delivers a total cumulative dose of 0.1 rad to the target organ (liver) or 38% of that delivered by ^{58}Co-B_{12}.

PGR:aw
cc: Isotope Committee members.

1179432

DECAY SCHEME OF COBALT-57

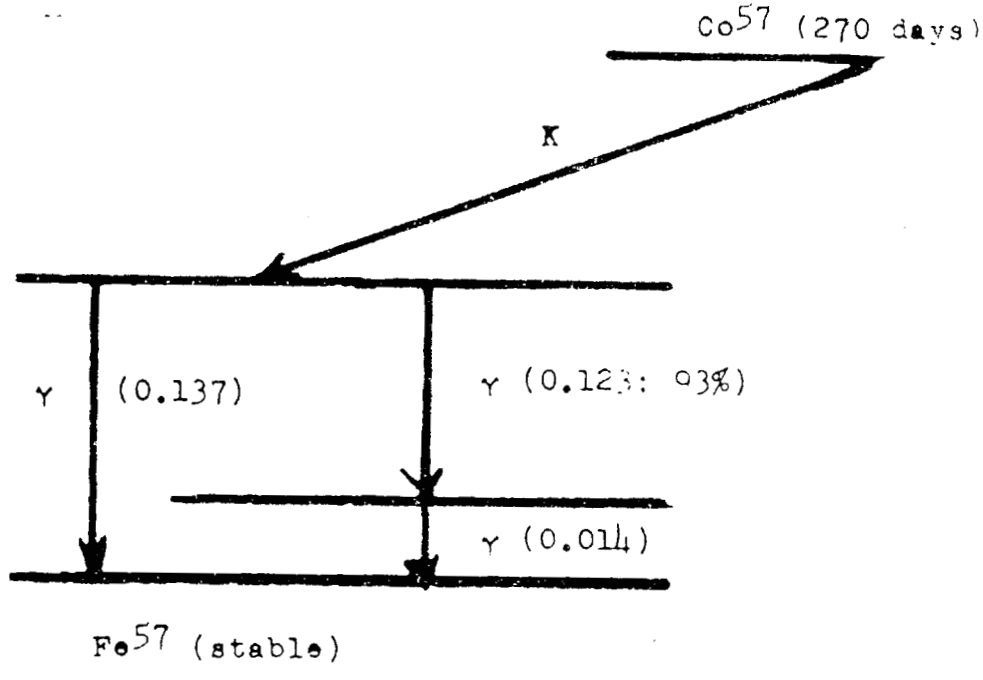


Figure 3

1179433

Investigators: Reizenstein, P. G.

Title: Extension of request H-63 to include 35 μc ^{58}Co instead of 4 μc.

Date: 20 October 1960

Project No.: H-63

is approved with the understanding that the patient described in the request for the use of 35 μc. Co^{58} exemplifies a category of patients for whom older age or limited life expectancy, and/or impaired reproductive capacity, and/or special clinical need is considered to permit the radiation exposure incurred.

Approved:

Committee on Use of Radioactive Isotopes in Patients:

Walton W. Shreeve

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

Victor P. Bond

Victor P. Bond, M.D., Ph.D.

Samuel Fine

Samuel Fine, M.D.

Elmer E. Stickley

Elmer E. Stickley, Ph.D.

J. S. Robertson

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

Lee E. Farr

Lee E. Farr, M.D.
Ex Officio

1179434

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 20 October 1960

TO: Isotope Committee

FROM: P. G. Reizenstein, M. D.

SUBJECT: Extension of request H-63 to include 35μc ^{58}Co instead of 4μc.

Previous studies, described in H-63, indicate a difference in plasma B_{12} clearance between absorbed and injected B_{12}. In the previous studies the amount injected was about 3μc. During the initial period after the injection most of this is rapidly cleared from the plasma and less than 1% remains in the total plasma. For this reason it becomes exceedingly difficult to measure the radio activity in a few milliliters of plasma several weeks after the administration of isotope, even if special gadgets and special shielding and measurement extending over 20 hours are used. This is due in part to the slightly varying background at this laboratory because of argon contamination.

High specific activity B_{12} is now available. Permission is requested for a pilot study in one individual (a woman over 35 years of age who has had a hysterectomy performed) for the oral administration of 20μc ^{58}Co-B_{12} (0.25 μg) on day 1. After following the plasma clearance for 30 days, the same individual will get 15μc (0.25μg) intramuscularly and the plasma clearance will again be followed. The purpose of this study is to compare the clearance of the absorbed with that of the injected B_{12}.

The isotope is obtained from Phillips and Co., Holland, the radiochemical purity is checked by γ-spectroscopy. The chemical purity will not be checked.

The total cumulative radiation dose to the liver from 35μc of ^{58}Co-B_{12} will approximate 9.9 rad (physical half-life 72 days). This is considerably less than the once in a lifetime permissible whole-body dose as given by the NCRP and the ICRP. The amount of radiation to the bone marrow and the methods of calculation and decay scheme are given in H-63.

Dr. Cronkite will be responsible for the patient and I will be in charge of immediate care.

Walton W. Shreeve, M. D.
Elmer E. Stickley
~~Donald O. Borg, M. D.~~
~~John L. Bateman, M. D.~~
James S. Robertson, M. D., Ph. D.
Lee E. Farr, M. D.

PGR:aw

1179435

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 17 June 1960

TO: BNL Committee on Use of Radioactive Isotopes in Human Subjects.

FROM: Peter G. Reizenstein, M. D.
Eugene P. Cronkite, M. D. EPC

SUBJECT: Request for permission to use labeled vitamin B_{12}.

H-63

Project Number: -H-63

Subject Name: Tracer Use of ^{58}Co- and ^{60}Co labeled Vitamin B_{12}.

The following proposal is submitted for the study of the metabolism of labeled vitamin B_{12} in human beings at the Brookhaven National Laboratory Medical Research Center.

The physiological requirements of vitamin B_{12} in human beings is unknown. Likewise the turnover rate of vitamin B_{12} stored in different tissues and administered by different routes is also unknown. The purpose of the present study is to analyze the kinetics of turnover of radio vitamin B_{12} administered by 2 different routes. Three microcuries of cobalt 60 labeled B_{12} are injected intramuscularly and 7 microcuries of 58 cobalt labeled B_{12} are given orally. Previous studies indicate that of the 7 microcuries given orally not more than 4 microcuries will be absorbed and that of the 3 microcuries injected about 2 microcuries will be retained by the body while 1 microcurie will be excreted in the urine during the first 2 days after injection.

The turnover rate of the 2 isotopes will be studied in the whole-body counter. An attempt will be made to study the turnover in single compartments by using surface scanning over the liver and by measuring the serum clearance and serum concentration of the 2 different isotopes with a Penco 100 channel analyzer equipped with a well type scintillation detector.

The patients to be studied will suffer from various diseases, however, no patients with primary disturbance of their B_{12} metabolism will be included. Some probable disease categories in which the patients would fall include psychosomatic disturbances, chronic arthritis, cerebrovascular or cardiac disease, etc. The source of patients is not at the

1179436

present time known. All patients for hematology studies are under the supervision of E. P. Cronkite and the actual day to day care will be by Dr. Reizenstein.

The isotope used in the present study is obtained as a gift from Merck and Company, Rahway, New Jersey. The standard gamma spectrometry of the isotopes employed will reveal the type of isotope used and the dose given. The amounts of labeled vitamin B_{12} given above are intended to be total amounts, no repetition of this dose is planned. The types of energy emissions and half-lifes of the isotopes used are given in the reprint attached to this request. Likewise, the decay schemes of these isotopes are attached in the form of photostats. The specific activity of the B_{12} employed will average 1μc/μg.

The radiation dose delivered to different organs by the radio-vitamin B_{12} retained in the body has been calculated earlier (Reizenstein, P., Acta Medical Scandinavica, Vol. 165, p.467, 1959). Photostat copies of this article, giving detailed calculations, are attached to the present request. "Radioactive Isotopes in Clinical Practice", by E. H. Quimby, S. Feitelberg and S. Silvers (Lea and Febeger, Philadelphia, 1958). The biological half-life employed for the radiation dose calculations is 1 year as estimated on the basis of excretion measurements (Reizenstein, P., Vitamin B_{12}Metabolism, Acta. Medica. Scandinavica, Vol. 165, Suppl. 345, 1959). Additional data collected on earlier patients is included in reprint by Cronkite, et al, Hematologica Latina (attached).

Radiation Dose:

(References: Reizenstein, P., Acta. Medical. Scand. 165, 1, 1959.)

Approximate Cumulative Total Radiation Received by	From 4μc ^{58}Co-B_{12}	From 2μc ^{60}Co-B_{12}	Sum of ^{58}Co and B_{12}
Liver	1.08 rad	5.82 rad	6.9 rad
Ovaries	0.12 rad	0.73 rad	0.85 rad

PGR:aw

1179437

With the understanding that standard gamma spectrometry of Co^{58} and Co^{60} at Brookhaven will include assay *in vitro* of each shipment of the isotopes from Merck and Company before use in patients, the above request (H-63) is hereby approved.

Approved:

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

E. E. Stickley — E. E. Stickley, Ph.D.

D. C. Borg — D. C. Borg, M. D.

John L. Bateman — J. L. Bateman, M. D.

J. S. Robertson — J. S. Robertson, M. D., Ph.D.
Ex-officio

Leo E. Farr — L. E. Farr, M. D.
Ex-officio

1179438

DR. E. FARR

March 7, 1960

BNL Committee on Use of Radioactive Isotopes in Human Subjects.

Peter G. Reizenstein, M. D.

Request for permission to use labeled vitamin B_{12}.

Project Number: H-63

Subject Name: Tracer Use of Labeled Vitamin B_{12}.

The following proposal is submitted for the study of the metabolism of labeled vitamin B_{12} in human beings at the Brookhaven National Laboratory Medical Research Center. Patients with various types of disease will be studied. At the present time it is intended to study between 3 and 6 persons.

The physiological requirements of vitamin B_{12} in human beings is unknown. Likewise the turnover rate of vitamin B_{12} stored in different tissues and administered by different routes is also unknown. The purpose of the present study is to analyze the kinetics of turnover of radio vitamin B_{12} administered by 2 different routes. Three microcuries of cobalt 60 labeled B_{12} are injected intramuscularly and 7 microcuries of 58 cobalt labeled B_{12} are given orally. Previous studies indicate that of the 7 microcuries given orally not more than 4 microcuries will be absorbed and that of the 3 microcuries injected about 2 microcuries will be retained by the body while 1 microcurie will be excreted in the urine during the first 2 days after injection.

The turnover rate of the 2 isotopes will be studied in the whole body counter. An attempt will be made to study the turnover in single compartments by using surface scanning over the liver and by measuring the serum clearance and serum concentration of the 2 different isotopes with a Penco 100 channel analyzer equipped with a well type scintillation detector.

1179439

The patients to be studied will suffer from various diseases, however, no patients with primary disturbance of their B_{12} metabolism will be included. It is intended to choose mainly patients above the child bearing age.

The isotope used in the present study is obtained as a gift to the Laboratory from Merck & Company, Rahway, New Jersey. The standard gamma spectrometry of the isotopes employed will reveal the type of isotope used and the dose given. The amounts of labeled vitamin B_{12} given above are intended to be total amounts, no repetition of this dose is planned.

The radiation dose delivered to different organs by the radio-vitamin B_{12} retained in the body has been calculated earlier (Reizenstein, P., Acta Medical Scandinavica, Vol. 165, p. 467, 1959). Approximately similar types of calculations are contained in the monograph, "Radioactive Isotopes in Clinical Practice," by E. H. Quimby, S. Feitelberg, and S. Silvers, (Lea and Febeger, Philadelphia, 1958). The biological half-life employed for the radiation dose calculations is 1 year as estimated on the basis of excretion measurements (Reizenstein, P., Vitamin B_{12} Metabolism, Acta. Medica, Scandinavica, Vol. 165, Suppl. 345, 1959).

Radiation Dose:

(references: Reizenstein, P., Acta. Medica. Scand. 165, 1, 1959).

Approximate Cumulative total radiation received by	From 4μc ^{58}Co-B_{12}	From 2μc ^{60}Co-B_{12}	Sum of ^{58}Co and ^{60} B_{12}
Liver	1.08 rad	5.82 rad	6.9 rad
Ovaries	0.12 rad	0.73 rad	0.85 rad

Lee E. Farr, M. D., Ex Officio

Walton W. Shreeve, M. D., Chairman

Elmer E. Stickley, Ph.D.

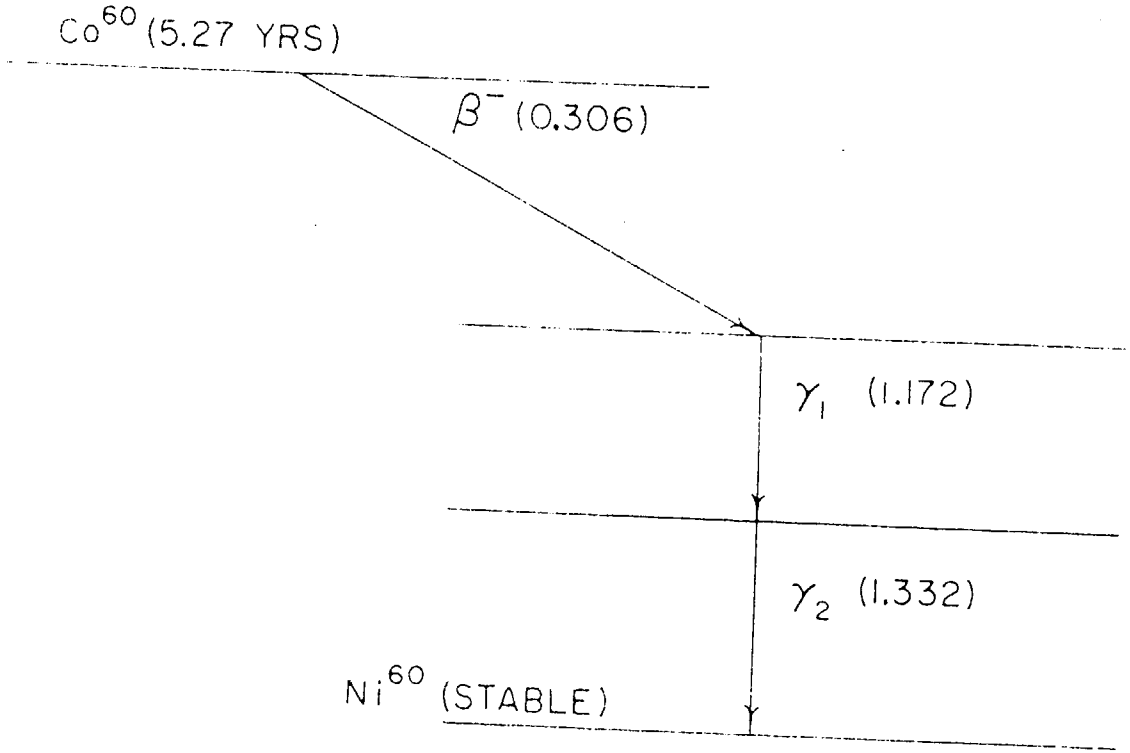
Donald C. Borg, M. D.

John L. Bateman, M. D.

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

1179440

DECAY SCHEME FOR COBALT-'60



1446L11

Dr Frau

12 January 1960

BNL Committee on Use of Radioactive Isotopes in Human Subjects.

Peter G. Reizenstein, M. D.

Request for permission to use labeled vitamin B_{12}.

Project Number:

Subject Name: Tracer Use of Labeled Vitamin B_{12}.

The following proposal is submitted for the study of the metabolism of labeled vitamin B_{12} in human beings at the Brookhaven National Laboratory Medical Research Center. Patients with various types of disease will be studied. At the present time it is intended to study between 3 and 6 persons.

The physiological requirements of vitamin B_{12} in human beings is unknown. Likewise the turnover rate of vitamin B_{12} stored in different tissues and administered by different routes is also unknown. The purpose of the present study is to analyze the kinetics of turnover of radio vitamin B_{12} administered by 2 different routes. Three microcuries of cobalt 60 labeled B_{12} are injected intramuscularly and 7 microcuries of 58 cobalt labeled B_{12} are given orally. Previous studies indicate that of the 7 microcuries given orally not more than 4 microcuries will be absorbed and that of the 3 microcuries injected about 2 microcuries will be retained by the body while 1 microcurie will be excreted in the urine during the first 2 days after injection.

The turnover rate of the 2 isotopes will be studied in the whole body counter. An attempt will be made to study the turnover in single compartments by using surface scanning over the liver and by measuring the serum clearance and serum concentration of the 2 different isotopes with a Penco 100 channel analyzer equipped with a well type scintillation detector.

1179442

The radiation dose delivered to a different organs by the radio-vitamin B_{12} retained in the body has been calculated earlier (Reizenstein, P., Acta. Medica. Scandinavica 167, page 1, 1959).

Radiation Dose:

(references: Reizenstein, P., Acta Med. Scand. 165, 1, 1959).

Approximate Cumulative total radiation received by	From 4μc ^{58}Co-B_{12}	From 2μc ^{60}Co-B_{12}	Sum of ^{58}Co and $^{60}B_{12}$
Liver	1.08 rad	5.82 rad	6.9 rad
Ovaries	0.12 rad	0.73 rad	0.85 rad

Walton W. Shreeve, M. D., Chairman

Elmer E. Stickley, Ph. D.

Donald C. Borg, M. D.

John L. Bateman, M. D.

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

Lee E. Farr, M. D., Ex Officio

PGR:aw

1179443