ORAU-30033

MEDICAL RADIONUCLIDE COMMITTEE MINUTES AND RELATED DOCUMENTS June 29, 1966 - May 25, 1970

ORAU-30033

FORM P-4A

MEMORANDUM

TO Dr. G. A. Andrews DATE June 29, 1966

SUBJECT ADMINISTRATION OF IODINE-131 TO VOLUNTEERS

COPIES TO Dr. Kniseley, Dr. Edwards, Dr. Lushbaugh, Mr. Gibbs, file

Reference material -- regarding possible administration of iodine-131 to volunteers.

Intake (μCi of I-131)	Absorbed Dose to Whole Body After Complete Decay (rads)	Absorbed Dose to Thyroid After Complete Decay (rads)
0.5	1.84×10^{-3}	0.664
1	3.67×10^{-3}	1.33
2	7.34×10^{-3}	2.65
3	11.0×10^{-3}	3.98
4	14.7×10^{-3}	5.31
5	18.4×10^{-3}	6.64
6	22.0×10^{-3}	7.96
7	25.7×10^{-3}	9.29
8	29.4×10^{-3}	10.6
9	33.0×10^{-3}	11.9
10	36.7×10^{-3}	13.3

These dose calculations are based on the standard man who weighs 70 kilograms and who has 20% uptake of iodine-131 by a 20-gram thyroid.

The maximum permissible exposure guides set by the AEC are

3 rem/quarter	5 rem/year	to the whole body
10 rem/quarter	30 rem/year	to the thyroid

Patricia Dalton
Radiation Safety Office

Form P-4

MEMORANDUM

G. A. Andrews DATE July 1, 1966

SUBJECT RESEARCH PROPOSAL FOR USE OF NORMAL HUMAN VOLUNTEERS IN STUDY OF CORRELATION OF WHOLE BODY RETENTION AND THYROID UPTAKE AND LOSS OF IODINE-131.

COPIES TO William Gibbs and file

CORRELATION OF ^{131}I THYROID UPTAKE AND LOSS WITH WHOLE BODY RETENTION

Objectives: To determine -

1. Correlation of percent uptake in thyroid with one and two day whole body retention of ^{131}I;
2. Correlation of percent uptake in thyroid with one and two day urinary excretion of ^{131}I;
3. Correlation of one and two day urinary excretion with whole body retention of ^{131}I;
4. Correlation of chemical PBI with 24 and 48 hour thyroid uptake and whole body retention;
5. Retention half times of unbound (initial urinary excretion) and bound iodine (whole body and thyroid retention);
6. Discrepancy between the thyroid bound iodine regression line and that measured by whole body counting, hoping to measure the rates of utilization of extrathyroidal bound (hormonal) iodine in normal, athyroid, hypo- and hyperthyroid persons.

Research Design: Four groups of 10 persons each will be studied. The groups will consist of normal, thyroidectomized, hypo- and hyperthyroid persons. Each person will receive 6 microcuries of ^{131}I orally. Urinary collection will be made for 24, 48, and 72 hours. Thyroid uptakes will be made by using a 3 x 2 NaI crystal at 6, 24, 48, and 72 hours, and at weekly intervals as long as feasible up to 3 months. Whole body retention measurements will be made at the same intervals. A chemical PBI will be done at time of dosage.

Duration of Study: One year.

C. C. Lushbaugh

bbc

William Gibbs

1079988

FORM P-4A

MEMORANDUM

TO Mr. Roger Cloutier DATE July 5, 1966

SUBJECT USE OF TRACER AMOUNT OF RHENIUM-188 IN VOLUNTEER SUBJECTS

COPIES TO Dr. Andrews, Dr. Knisely, Dr. Edwards, Mr. Rafter, Files

Permission is requested for the use of trace amounts (5 μc) of rhenium-188 in volunteer subjects of the Medical Division staff. This material is carrier-free and obtained from a long-lived parent, tungsten-188 ($t_{1/2}$ = 70 days). Rhenium-188 has a 17 hour half-life and in the perrhenate form has a distribution approximately the same as pertechnetate. The main sites of the concentration are the thyroid and stomach. Miss Dalton has animal data from our work and is presently making dose calculations. The rhenium-188 from the tungsten generator is contaminated with tungsten-188 at a level of 4×10^{-4} %.

ORIGINAL SIGNED BY
R. L. HAYES

R. L. Hayes

:d

FORM P-4A

MEMORANDUM

TO: See Below DATE: July 11, 1966

SUBJECT: Minutes Human Use Committee July 11, 1966
Proposed Tracer Study Using Rhenium-188

COPIES TO: File

Dr. Edwards and Dr. Kaiseley discussed the proposal with Miss Patricia Dalton, acting for the Radiation Safety Office in the absence of Roger Cloutier. Calculations that she had made had been discussed with Mr. Cloutier before his departure, who was of the opinion that this dose would present no objectionable radiation hazard to the volunteer subjects. Approval was granted for the administration of a single oral dose of 5 microcuries of rhenium-188 to the two volunteer subjects.

Original Signed By
Ralph M. Kaiseley, Jr.

R. M. Kaiseley

cc: Dr. Andrews
Dr. Edwards
Mr. Cloutier
Dr. Lushbaugh
Dr. Hayes
Dr. Kaiseley

1079990

FORM P-4

MEMORANDUM

TO ORINS Human Use Committee DATE July 14, 1966

SUBJECT PROPOSED TRACER STUDY OF RHENIUM-188.

COPIES TO Dr. Andrews; Dr. Kniseley; Dr. Edwards; Mr. Cloutier; Dr. Lushbaugh; Mr. Rafter; File

1. Purpose

Rhenium-188 is of interest because of its chemical similarity to technetium. Rhenium-188 has a half-life of 17 hours and can be produced from a tungsten-188 generator. Rhenium is of particular interest because its parent, tungsten-188 has a half-life of approximately 70 days. It is readily produced in a reactor. The long useful life of a rhenium-188 generator makes it superior to a technetium-99m generator from an economic standpoint. The distribution of rhenium-188 in the perrhenate form is similar to that of pertechnetate. It could consequently possibly find use as a thyroid scanning agent. We have been able to produce a sulfur colloid of rhenium-188 and consequently it could also conceivably be used for liver, spleen, and bone marrow scanning. Of particular interest is the fact that there appears to be a difference in the excretory pattern between perrhenate and pertechnetate. In rats, perrhenate is excreted almost exclusively in the urine whereas with pertechnetate the fecal and urinary paths are approximately equal. If the excretory pattern of perrhenate in humans is similar to that of rats, it is conceivable that rhenium-188 could be used as a test for achlorhydria. Normally perrhenate is cycled through the stomach in a manner similar to iodide and pertechnetate. Since there is little fecal holdup of the isotope, achlorhydria might be expected to distinctly increase the rate of perrhenate excretion. Initial studies in humans would be for the purpose of determining the excretory path in humans.

2. Subjects

It is proposed initially to study the retention of rhenium-188 in the pertechnetate form in two volunteer subjects from the Medical Division Staff. The dose administered would be approximately 5 microcuries and the route would be by mouth. The information so obtained could be used to make further dose estimates preliminary to the study of rhenium-188 in patients.

3. Radiation dose

Miss Patricia Dalton of the Radiation Safety Office has supplied the following radiation dose figures for rhenium-188 based on animal data of rhenium-188 administered intravenously in the perrhenate form: whole-body 0.7 rads per millicurie; thyroid 38 rads per millicurie; stomach 32 rads per millicurie. For purposes of comparison iodine-131 would give doses for whole-body, thyroid, and stomach of 3.9, 1400, and 712. It should be pointed out that Miss Dalton's calculations for rhenium-188 involve the assumption of no excretion. Doses for rhenium-188 would be considerably less if excretion were taken into account.

4. Contamination

The rhenium-188 generator consists of tungsten-188 bound to a HZO-1 zirconium oxide support. The rhenium-188 is eluted with a mixture of 95 parts methylethyl ketone, and 5 parts 0.01N hydrochloric acid. Except for initial milkings on the two generators that we have used, the contamination of the eluant with tungsten-188 has been insignificant. At the present time the level is 4×10^{-4}%. This would constitute 4 nanocuries of tungsten-188 per millicurie of rhenium-188, or for the dose planned for the two volunteers, approximately 20 picocuries of tungsten-188. To date approximately 50 milkings have been made without any evidence of increased contamination by the tungsten parent. The contamination level is quite low and it is necessary to wait for practically complete decay of rhenium-188 before a precise contamination value can be arrived at. However, it is possible in the future use of this radioisotope to carry out a preliminary separation test for gross contamination of the eluant with tungsten-188. Since the half-life of rhenium-188 is 17 hours, the milking could be carried out the day before administration so that this test could be made.

5. Toxicity.

No apparent toxic effects have been noticed in rats given I.V. rhenium-188 in a perrhenate form during a period of up to 3 days postadministration. The material has also been tested for pyrogens with a negative result.

As indicated above we presently plan to make a preliminary study in two volunteers to assess the feasibility of further studies in humans. This memorandum constitutes a request for permission to make studies in two volunteers and is also intended as support for future requests should these seem desirable.

R. L. Hayes

/d

FORM P-4

MEMORANDUM

TO Dr. R. M. Kniseley DATE July 12, 1966

SUBJECT ADMINISTRATION OF RHENIUM-188 TO VOLUNTEERS

COPIES TO Dr. Edwards, Dr. Hayes, file

On the basis of animal data supplied by Dr. Hayes, I have estimated the absorbed dose from rhenium-188. These estimates are referred to a 70-kilogram standard man, and it was assumed there was no excretion of the rhenium-188.

Critical Organ	Absorbed Dose per Microcurie Intake (rads/μCi)	Absorbed Dose from 5 Microcuries (rads)
Whole Body	0.000702	0.00351
Thyroid	0.0381	0.191
Stomach	0.0315	0.158

According to Dr. Hayes, the rhenium-188 is contaminated by the parent (tungsten-188, 65-day half-life) at a level of about 0.0005 %.

The following table lists a conservative estimate of the dose from the tungsten contaminant in 5 μCi of rhenium-188. For these estimates it was assumed there was 100 % uptake of tungsten-188 by the critical organ and no excretion.

Critical Organ	Absorbed Dose from ^{188}W Contaminant in 5 μCi ^{188}Re (millirads)
Whole Body	0.0004
Thyroid	0.7
Stomach	0.06
Bone	0.002

For reference, the Radiation Protection Guides established by the AEC recommend the following limits:

Whole body, head and trunk	3 rem/quarter	5 rem/year
Thyroid	10 rem/quarter	30 rem/year

Patricia Dalton

Patricia Dalton
Radiation Safety Office

FORM P-4

MEMORANDUM

TO Human Use Committee DATE September 7, 1967

SUBJECT Clinical Trial of $^{113}In^{m}$ as a Kidney and Bone Scanning Agent

COPIES TO

1. Proposal:

Recent animal studies have indicated that $^{113}In^{m}$ may be of use as both a kidney and bone scanning agent. It is proposed that controlled clinical trials be carried out to determine whether these observations will hold true in man and to what extent this radioisotope may be of use in such scanning procedures.

2. Radioisotope:

Indium-113m has a half life of 1.7 hours. It decays by isomeric transition to stable ^{113}In emitting a 390 kev gamma ray; a 35% conversion occurs. Indium-113m can be obtained carrier free from parent ^{113}Sn ($T_{1/2}$ = 118 days) using a hydrous zirconium oxide generator system. The short half life (low radiation dose) the reasonably low gamma energy (compatible with ^{131}I collimators), and the long half life and modest cost of the parent make $^{113}In^{m}$ an attractive radioisotope from a diagnostic standpoint.

3. Chemical Form:

Indium-113m citrate-saline solution containing stable gallium citrate administered at a level of 0.5mg Ga/Kg of body weight. The molar citrate to gallium ratio will be held at 3:1.

4. Route of Administration:

Intravenous

5. Proposed Dosage:

One to two milicuries for kidney scans; five to ten milicuries for bone scans. See chemical form (3.) for chemical dosage.

6. Experimental Protocol:

a. Number and selection of patients: To be determined by the clinical staff.

b. Duration of studies: Due to the short half life of $^{113}In^{m}$ (1.7 hr.), scanning should be carried out during the same work day and preferably within four hours of administration. The time period for the total investigation will be determined by the clinical staff.

c. Types and frequency of assay: Urine, blood (at half hour intervals during first hour and at one to two hour intervals thereafter through the sixth hour where possible), and other tests deemed desirable by the clinical staff.

7. Animal Studies:

For convenience, high specific activity $^{114}In^{m}$ has been used as a tracer for $^{113}In^{m}$ in most of the animal studies to date. However, $^{114}In^{m}$ and $^{113}In^{m}$ have given comparable results as shown columns 1 and 6 and 4 and 5 of Table 2.

When $^{114}In^{m}$ at a pseudocarrier-free level is administered in the citrate form, the distribution is diffuse as shown by the data in column 1 of Table 1. This type distribution is similar to that obtained with ^{68}Ga and ^{72}Ga. It is apparently due to binding of indium by blood proteins (work by Dr. R. E. Hartman, Summer 1967). Stable gallium appears to compete for these binding sites. The data in Table 1 (columns 1-7) shows that as the amount of stable gallium (citrate form) administered with the $^{114}In^{m}$ was increased, the blood level of $^{114}In^{m}$ rapidly decreased. On the other hand, the concentration of $^{114}In^{m}$ in the kidney and bone increased markedly so that at a level of 5 milligrams gallium per kilogram the ratio of kidney to blood was 40 and that of the femur to blood 14. This distribution pattern persisted through 21 hours (column 8 of Table 1). Figure 1 shows a plot of the three-hour data from Table 1 for the blood, kidney, and average bone. As little as 0.5 milligram gallium per kilogram gives an apparent maximum uptake of $^{114}In^{m}$ in the kidney of the rat.

In columns 1 and 2 of Table 2 are shown the results of a double isotope study using $^{114}In^{m}$ and ^{72}Ga. The results were similar except for the levels in the kidney and blood. Indium-114m appears to deposit in the kidney and remain. Column 3 of Table 2 shows the results of a previous study of ^{68}Ga with the same level of stable gallium. Here again, the amount of the gallium radioisotope present in the kidney at three hours is much less than that for $^{114}In^{m}$. The results in columns 1 and 2 of Table 3 indicate the rapidity with which $^{114}In^{m}$ deposits in the kidney and bone.

Columns 4 and 5 in Table 3 show the results of studies at the 0.5 milligram gallium level when the citrate present was varied. An approximate seven fold increase in the citrate/gallium ratio appears to partially enhance bone deposition, but there is no decrease in blood level. Figure 2 shows a scan and an Anger camera picture of two rabbits given 0.5 milligram gallium per kilogram with $^{113}In^{m}$ (top) and $^{114}In^{m}$ (bottom). The distribution for the $^{113}In^{m}$ rabbit is shown in column 3 of Table 3.

The femur/blood ratio for this animal was 12, decidedly better than that achieved with the rat at the 0.5 milligram gallium level. Should the bone prove to have a promising uptake of $^{113}In^{m}$ in the human, the results in column 6 of Table 3 indicate that possible consideration might be given to solublizing agents other than citrate. The use of nitrilotriacetic acid (NTA) appears to decrease the deposition of $^{114}In^{m}$ in the kidney while increasing that in the bone. The femur/blood ratio is also higher.

8. Radiation Dose:

Based on an extrapolation from rat distribution data, the Radiation Safety Office has calculated that the $^{113}In^{m}$ dose to the human kidney will be 0.31 rads per millicurie administered and that to the bone 0.057 rads per millicurie. Immediate deposition and complete decay in situ was assumed. The whole body dose in the human for $^{113}In^{m}$, assuming uniform distribution and no excretion, is estimated to be 0.022 rads per millicurie administered. A copy of these calculations is available in the Radiation Safety Office.

9. Related and Pertinent Human Data:

Indium-113m has been used for liver, spleen, bone marrow, lung, and brain scanning in humans (Nucleonics, October 1966, November 1966, February 1967; various reports at the June 1967 meeting of Society of Nuclear Medicine, and abstracts in Volume 8, Number 4 of Journal of Nuclear Medicine).

10. Chemical, Radiation, and Infectious Hazards:

Gallium-68 citrate has been under evaluation as a bone scanning agent in the Medical Division's clinical program using levels of stable gallium up to 4 milligrams per kilogram of body weight. The present proposal would involve the use of approximately one-tenth (0.5 milligram per Kg) this amount of gallium.

Associated with the $^{113}In^{m}$ will be a small amount of zirconium (30 micrograms or less). This contaminant is considered to be innocuous by other users of the $^{113}In^{m}$ generator system.

The $^{113}In^{m}$ used, being carrier free, will be present at such a low level on a weight basis (10^{-11} grams per millicurie) as to be completely negligible.

The radiation dose for the levels proposed (see 8 above) is considered to be sufficiently low by present standards. Contamination of $^{113}In^{m}$ with parent ^{113}Sn has repeatedly been found to be less than 0.001% over a period of one year. With this level of contamination, the ^{113}Sn content in the dose per millicurie of $^{113}In^{m}$ administered would be less than 0.02 microcuries (assuming a 1.7 hr. delay after milking). The Handbook 69 permissible body burden for ^{113}Sn is 60 microcuries.

The generator system will be cultured twice weekly to detect the presence of microorganisms. Sterilization will be by micropore filtration (0.22 micron). All the agents used except those obtained from pharmaceutical houses will be checked for pyrogens. Mock dose preparations will be checked at intervals for the presence of pyrogens and a portion of each dose prepared for administration will be held back for testing in the event of reaction.

R. L. Hayes

TABLE 1

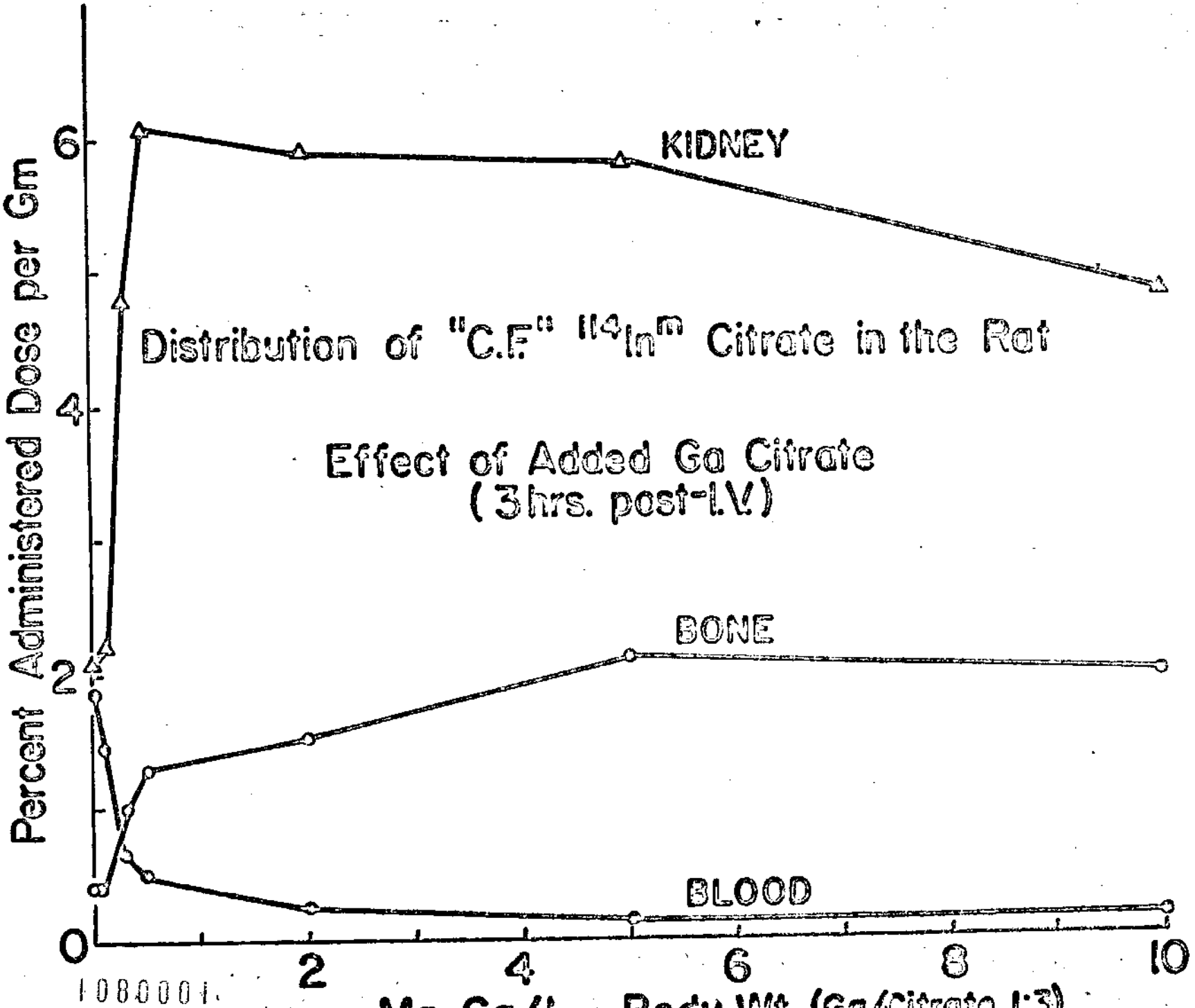
	1	2	3	4	5	6	7	8
	$^{114}In^{m}$ "C.F." 3 hrs 5-25-67	$^{114}In^{m}$ 0.1 mgGa/Kg 3:1 citrate 3 hr 5-23-67	$^{114}In^{m}$ 0.3 mgGa/Kg 3:1 citrate 3 hr 5-24-67	$^{114}In^{m}$ 0.5 mgGa/Kg 3:1 citrate 3 hr 5-22-67 8-22-67	$^{114}In^{m}$ 2.0 mgGa/Kg 3:1 citrate 3 hr 5-17-67	$^{114}In^{m}$ 5.0 mgGa/Kg 3:1 citrate 3 hr 5-10-67	$^{114}In^{m}$ 10.0 mgGa/Kg 3:1 citrate 3 hr 5-11-67 8-24-67	$^{114}In^{m}$ 5 mgGa/Kg 3:1 citrate 21 hr 5-19-67
Liver	0.67	0.53	0.28	0.26	0.25	0.27	0.20	0.37
Spleen	0.58	0.39	0.18	0.15	0.07	0.05	0.06	0.18
Kidney	2.08 (0.10)	2.22 (0.19)	4.79 (0.80)	6.08 (0.76)	5.87 (0.43)	5.78 (0.23)	4.85 (0.46)	5.28 (0.39)
Lung	0.96	0.74	0.44	0.37	0.19	0.16	0.15	0.19
Muscle	0.16	0.18	0.11	0.11	0.04	0.03	0.03	0.03
Rib	0.54 (0.07)	0.50 (0.05)	1.41 (0.26)	1.70 (0.14)	2.18 (0.13)	3.11 (0.20)	2.64 (0.12)	2.30 (0.12)
Femur	0.44 (0.03)	0.44 (0.03)	0.92 (0.11)	1.29 (0.07)	1.44 (0.05)	1.90 (0.12)	1.88 (0.08)	1.51 (0.05)
Calvaria	0.27 (0.01)	0.29 (0.02)	0.65 (0.09)	0.87 (0.04)	0.95 (0.04)	1.31 (0.09)	1.33 (0.07)	1.07 (0.08)
Marrow	1.06	0.58	0.31	0.21	0.15	0.10	0.10	0.23
Blood	1.86 (0.14)	1.46 (0.09)	0.67 (0.10)	0.50 (0.06)	0.26 (0.06)	0.14 (0.02)	0.16 (0.02)	0.13 (0.04)
Total Blood	33	26%	12%	8.8%	4.5%	2.5%	2.8%	2.2
Animals	5	5	5	10	5	5	8	5
K/Bl	1.1	1.5	7.2	12	23	40	30	41
Re/Bl	1.2	0.3	1.4	2.6	5.5	14	12	8.2
Re/M	2.8	2.4	8.4	12	36	63	63	50

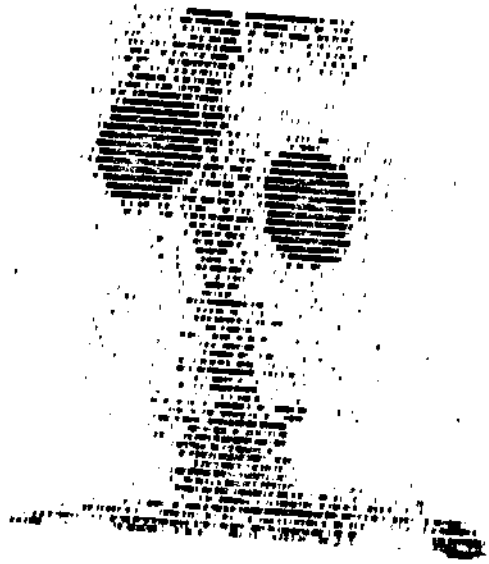
TABLE 2

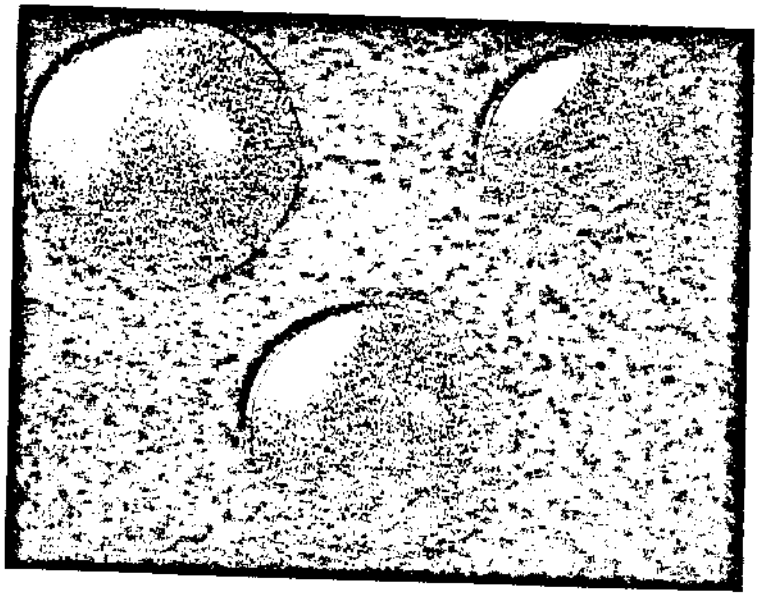
	1	2	3	4	5	6
	$^{114}In^{m}$ 5.0 mgGa/Kg 3:1 citrate 3 hr 5-10-67	^{72}Ga 5.0 mgGa/Kg 3:1 citrate 3 hr 5-10-67	^{68}Ga 5.0 mgGa/Kg 3:1 citrate 3 hr 5-15-67 5-27-67	$^{114}In^{m}$ "C.F." 3 hr 5-25-67	$^{113}In^{m}$ "C.F." 3 hr 5-26-67	$^{113}In^{m}$ 5.0 mgGa/Kg 3:1 citrate 3 hr 6-1-67
Liver	0.27	0.04	0.07	0.67	0.50	0.23
Spleen	0.05	0.02	0.05	0.58	0.45	0.06
Kidney	5.78 (0.23)	0.25 (0.04)	0.29	2.08 (0.10)	2.50 (0.44)	6.43 (0.50)
Lung	0.16	0.04	0.08	0.96	0.67	0.17
Muscle	0.03	0.01	0.02	0.16	0.16	0.03
Rib	3.11 (0.20)	3.12 (0.25)	4.04	0.54 (0.07)	0.59 (0.13)	2.23 (0.21)
Femur	1.90 (0.12)	1.92 (0.14)	2.55	0.44 (0.03)	0.43 (0.07)	1.40 (0.05)
Calvaria	1.31 (0.09)	1.47 (0.13)	1.42	0.27 (0.01)	0.25 (0.03)	1.01 (0.05)
Marrow	0.10	0.06		1.06	0.77	0.10
Blood	0.14 (0.02)	0.05 (0.01)	0.16	1.86 (0.14)	1.41 (0.07)	0.15 (0.06)
Total Blood	2.5	0.9	2.8	33	25	2.6
Animals	5	5	10	5	5	5
K/Bl	40	5	1.8	1.1	1.8	44.0
Fe/Bl	14	38	16	0.2	0.3	9.6
Fe/M	63	190	130	2.8	2.7	47

TABLE 3

	1	2	3	4	5	6
	$^{114}In^{m}$ 5.0 mgGa/Kg 3:1 citrate 3 hr 5-10-67	$^{113}In^{m}$ 5 mgGa/Kg 2:1 citrate 1 hr 10-3-66	$^{113}In^{m}$ 0.5 mgGa/Kg 3:1 citrate 3 hr 6-13-67	$^{114}In^{m}$ 0.5 mgGa/Kg 20:1 citrate 3 hr 5-31-67	$^{114}In^{m}$ 0.5 mgGa/Kg 3:1 citrate 3 hr 5-22-67 8-22-67	$^{114}In^{m}$ 0.5 mgGa/Kg 3:1 NTA 3 hr 6-7-67
Liver	0.27	0.22	0.06	0.29	0.26	0.202
Spleen	0.05	0.09	0.10	0.14	0.15	0.084
Kidney	5.78 (0.23)	4.46	1.84	5.17 (0.73)	6.08 (0.76)	1.971 (0.142)
Lung	0.16	0.25	0.02	0.30	0.37	0.211
Muscle	0.03	0.04	0.003	0.08	0.11	0.074
Rib	3.11 (0.20)		0.24	2.92 (0.37)	1.70 (0.14)	2.899 (0.251)
Femur	1.90 (0.12)	1.14	0.17	1.51 (0.15)	1.29 (0.07)	1.997 (0.176)
Calvaria	1.31 (0.09)		0.21	1.08 (0.10)	0.87 (0.04)	1.351 (0.123)
Marrow	0.10	0.22	0.07	0.22	0.21	0.173
Blood	0.14 (0.02)	0.34	0.01	0.44 (0.09)	0.50 (0.06)	0.334 (0.044)
Total Blood	2.5	5.9	1.5	7.7	8.8	5.85
Animals	5	2	1	5	10	5
K/Blood	40	13	140	12	12	5.9
Femur Blood	14	3.4	12	3.4	2.6	6.0


Distribution of "C.F." $^{114}In^{m}$ Citrate in the Rat
Effect of Added Ga Citrate
(3 hrs. post-I.V.)
Percent Administered Dose per Gm
KIDNEY
BONE
BLOOD
0
2
4
6
8
10
Mg Ga/L... Body Wt. (Ga/Citrate, 1:3)





Minutes

Human Use Committee

September 8, 1967

Present: R. L. Hayes, C. C. Lushbaugh, Roger Cloutier, C. L. Edwards, R. M. Kniseley, and J. H. Harmon

Consideration of Proposal for clinical trial of 113-Indium as a kidney and bone-scanning agent. In consideration of the proposal it was agreed that it would be appropriate to have a clinical trial as proposed, involving 20 to 30 patients with known life-shortening disease, administering a single dose of the agent with gallium carrier at level 0.5 milligrams per kilogram body weight. The procedure would be carried out in situations where it might be of some possible benefit in management of the disorder.

FORM P-4

MEMORANDUM

TO Human Use Committee DATE September 13, 1967

SUBJECT Clinical Trial of ^{68}Ga Labeled Hydrous Ferric Oxide Colloid for Bone Marrow Scanning

COPIES TO

1. Proposal:

To use for bone-marrow scanning in man a special preparation of hydrous ferric oxide colloid labeled with ^{68}Ga. The colloid will have small, relatively uniform particle size which will increase the total uptake of colloid in human bone marrow and decrease variations in deposition caused by alterations in blood flow. The radiation dose to organs other than the bone marrow would be decreased. Animal studies have indicated that this preparation is probably innocuous and safe for human use at the proposed levels.

2. Radioisotope:

Gallium-68 has a half life of 1.1 hours. It decays mainly by positron emission and can be scanned either through positron coincidence techniques or with the Medical Division Whole-Body Scanner using the 0.51 annihilation emission. Purchase of a positron attachment for the Nuclear Chicago Anger Camera has been under consideration. Gallium-68 is available from its long lived parent, ^{68}Ge ($T_{1/2}$ = 280 d), using an aluminum oxide generator system. The short half life of ^{68}Ga plus the possibility of positron coincidence detection makes the isotope attractive as a scanning agent. Although hydrous ferric oxide colloid produced by heat hydrolysis of dilute ferric chloride results in a solution having a low pH, gallium is unique in that it is firmly bound by the colloid under those conditions. Ferric oxide colloid produced by heat hydrolysis yields preparations having a uniform particle size; uniformity of particle size is a highly desirable characteristic in colloid preparations.

3. Chemical Form:

a. Gallium-68 labeled hydrous ferric oxide colloid having a particle diameter of approximately 9 mμ administered at varying levels not to exceed 0.5 mg Fe per kg of body weight. The preparation would also contain, as a stabilizer, either: (1) dextran, clinical grade, non-antigenic, non-pyrogenic, obtained from Pharmachem Corporation, Bethlehem, Pennsylvania or (2) prepared, commercial clinical grade dextran such as Abbott Dextran 6% D5-W. The dose of dextran stabilizer

would not exceed 50 mg/kg body weight (approximately 50 ml 6% clinical dextran for a 70 kg subject). The preparation would be adjusted to pH 6-7 and made isotonic with sodium acetate (0.15 M; approximately 10 mg sodium acetate per kg).

b. Same as (a) except particle size would be 3-4 millimicron in diameter. This particular preparation will not be administered until toxicity studies have been carried out and the committee has reviewed the results.

4. Route of Administration:

Slow intravenous administration. (Volume approximately 60 ml for 70 kg subject.)

5. Proposed Dosage:

Two to four millicuries ^{68}Ga. See (3) for chemical dosage.

6. Experimental Protocol:

a. Number and Selection of Patients:

To be determined by the clinical staff. Should include some subjects suffering from liver disease.

b. Duration of Studies:

The time period for the total investigation will be determined by the clinical staff. Due to the short half life of ^{68}Ga, scanning should be carried out from one to two hours after administration.

c. Types and Frequency of Assay:

Urine during first two hours after administration. Blood at frequent intervals during the first one or two hours after administration, frequency to be determined by level of ferric oxide dose.

d. Special Procedures:

Linear scans to estimate the approximate liver-spleen uptake.

7. Animal Studies:

For convenience, high specific activity ^{72}Ga ($T_{1/2}$ = 14 h) has been used as a tracer for ^{68}Ga. Both ^{72}Ga and ^{68}Ga have given similar distributions under similar conditions.

When dilute ferric chloride solutions are heated to 100°, a colloid of ferric hydroxide is produced by hydrolysis of the salt. The particle size of the colloid formed is rather uniform and may be varied (14 mμ to 2 mμ) by alterations in the heating rate and to a lesser extent by variations in the concentration of ferric chloride. When the colloid is formed in the presence of gallium, the gallium becomes firmly bound to the colloid particles. It remains firmly attached to the colloid in vivo as well. Considerable animal work has been carried out using a gallium labeled colloid preparation having a diameter of approximately 9 mμ. Recently a preparation in the 3-4 mμ range has been under study. Both preparations give good blood disappearance curves as shown in Fig. 1 and Fig. 2. A portion of the data obtained with the 9 mμ preparation is shown in Fig. 3. Four or more animals were used in each study. Except where indicated (4 mg/Fe) sacrifice time was one hour. The total activity in the blood at time of sacrifice was 1% or less in each of the studies. Femoral bone marrow concentrations paralleled the estimated bone marrow content (Fig. 3). These results would appear to indicate that in the rabbit the deposition in the bone marrow may be markedly enhanced by the production of a "blockade". This suggests that the decrease in the blood disappearance rate (Fig. 1) compensates in part for the greater blood flow through the liver-spleen compartment compared to that through the bone marrow compartment. It is anticipated that similar results might be obtained in man, although not necessarily of the same magnitude. A colloid having a smaller particle size than the 9 mμ preparation used in the rabbit study shown in Fig. 3 would be necesary to attain the same number of particles per kilogram of body weight in man. A 3-4 mμ preparation (specified in 3.b.) is now under study.

8. Radiation Dose:

The Radiation Safety Office has estimated that the ^{68}Ga dose to the bone marrow would be 1.0 rads per millicurie assuming a 50% deposition in the bone marrow compartment (normal colloid deposition is of the order of 10% or less). The dose to the liver assuming a normal 90% deposition of the administered dose would be 1.8 rads per millicurie and the whole body dose for uniform distribution 0.067 rads per millicurie.

9. Related and Pertinent Human Data:

Various colloidal iron hydroxide preparations are available for treatment of iron deficiency. Imferon (Lakeside Laboratories) is a colloidal ferric hydroxide-dextran preparation. The proposed preparation (3.A.) should be very similar to Imferon in nature. It will be administered in a much more dilute form (50 milligram per ml for Imferon; 0.5 mg per ml for 3.A). The stabilizer is dextran and the colloid charge is positive as with Imferon. This positive charge plus a close to physiologic pH is reported to enhance the stability of ferric hydroxide colloids in vivo (L. Golberg in Iron in Clinical Medicine, ed. Wallerstein and Mettier, 1958).

10. Chemical, Radiation and Infectious Hazards:

The level of iron proposed (0.5 mg/kg) would not appear to present any hazard. Experiments on rabbits and dogs showed no gross or histologic abnormalities when the ferric oxide preparation (3.A.) was given at a level of up to 10 mg/kg (see Research Report ORAU-101, p. 87). Studies through 35 days in both rabbits and dogs with an ^{59}Fe labeled 3.A. preparation showed that the iron was incorporated into red cells at a rate approaching that of iron-59 ferrous citrate (see Fig. 4).

The sodium acetate employed (10 mg/kg) is of low toxicity. There were no apparent reactions with 3.A. preparations when administered at a level ten times that proposed; also no significant temperature elevation took place. The oral dose for alkaline diuresis is 1.5 grams (5-10 gms. per day).

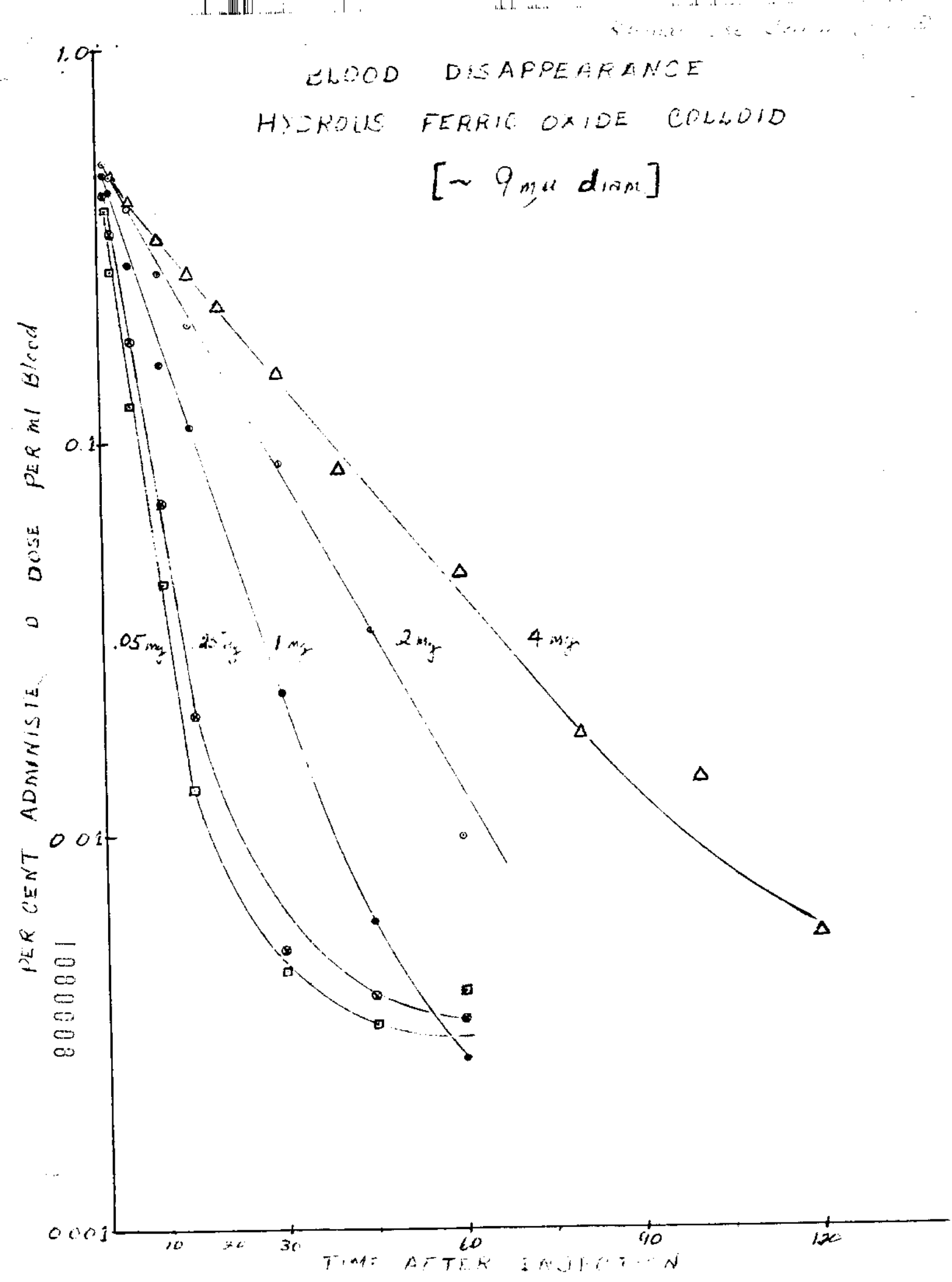
The dextran used as indicated in 3.A. will be of a pharmaceutical grade for intravenous use and at a level well below that normally administered.

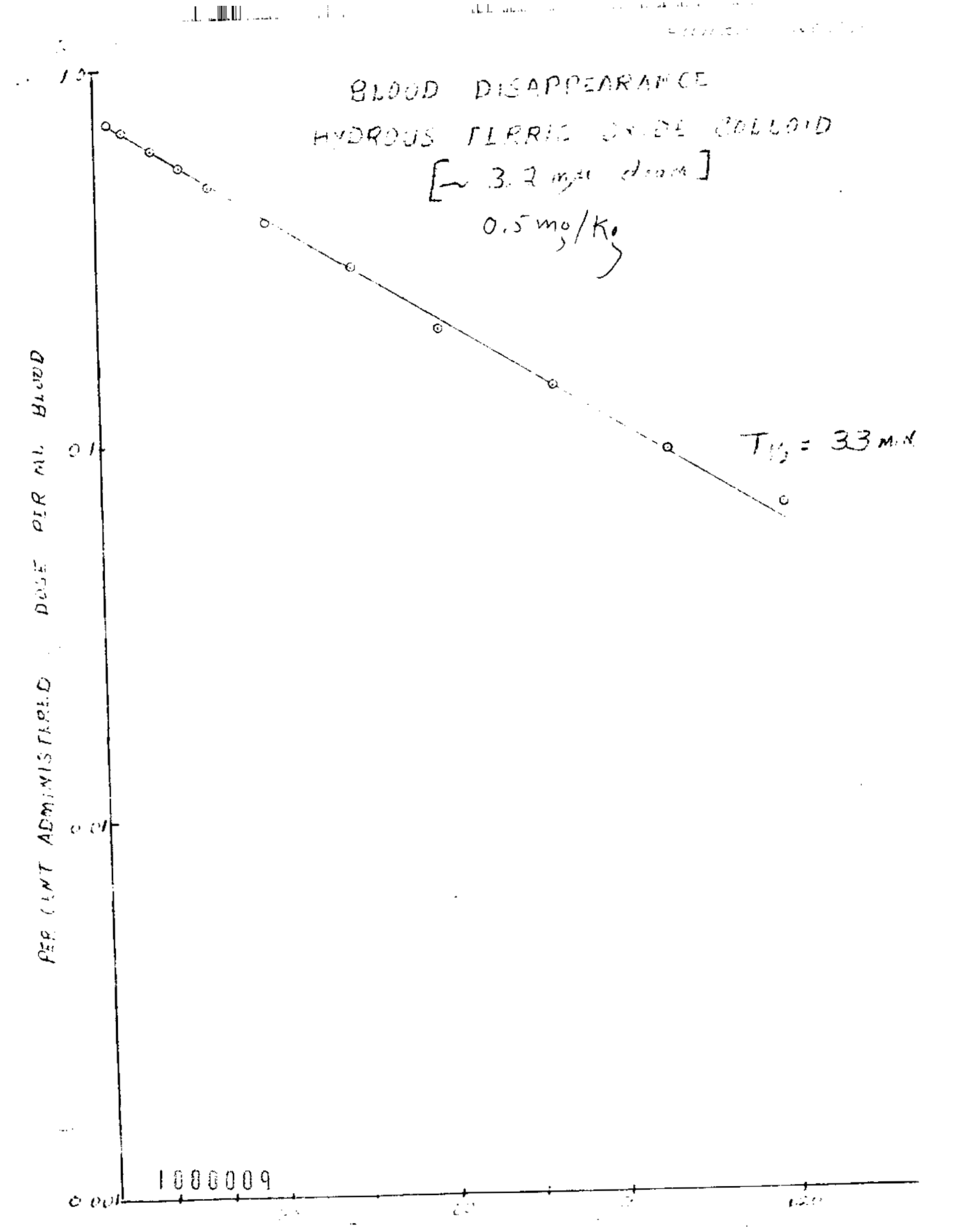
The radiation dose for the levels proposed (see 8 above) is considered to be sufficiently low by present standards. Contamination of ^{68}Ga with parent ^{68}Ge has repeatedly been found to be less than 0.001% over a period of two years. With this level of contamination, the ^{68}Ge content in the dose per millicurie of ^{68}Ga administered would be less than 0.02 microcuries (assuming a 1.1 hr. delay after milking). Germanium is rapidly excreted from the body.

The generator system will be cultured twice weekly to detect the presence of microorganisms. Sterilization will be by micropore filtration (0.22 micron). All the agents used except those obtained from pharmaceutical houses will be checked for pyrogens. Mock dose preparations will be checked at intervals for the presence of pyrogens and a portion of each dose prepared for administration will be held back for testing in the event of reaction.

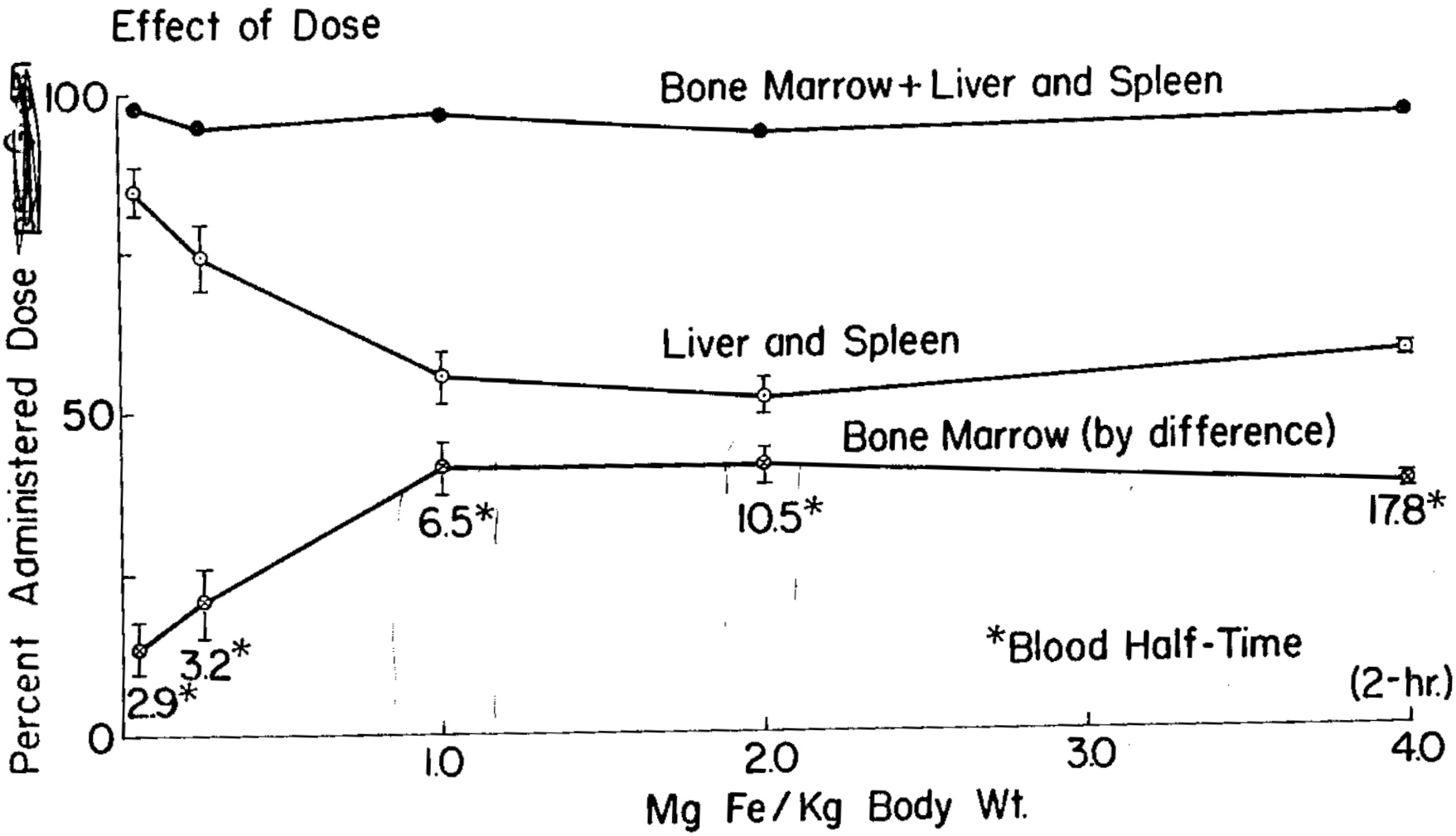
R. L. Hayes

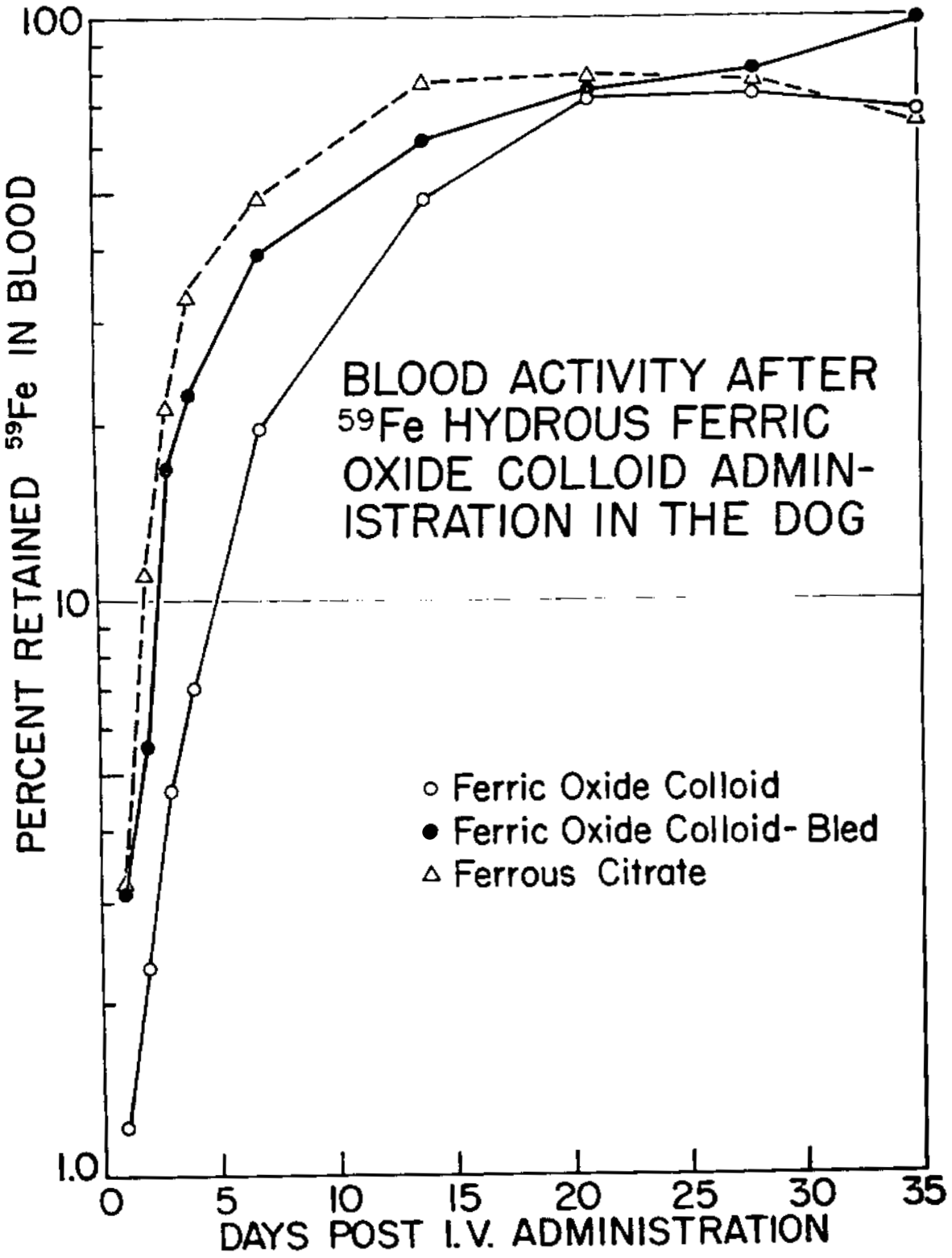
250 mg colloidal Fe + H Dextran given IV clinically


BLOOD DISAPPEARANCE
HYDROUS FERRIC OXIDE COLLOID
[~ 9 mμ diam]
PER CENT ADMINISTERED DOSE PER ml Blood
1.0
0.1
0.01
0.001
.05 mg
.25 mg
1 mg
2 mg
4 mg
10
30
60
90
120
TIME AFTER INJECTION


BLOOD DISAPPEARANCE
HYDROUS FERRIC OXIDE COLLOID
[~ 3.2 mμ diam]
0.5 mg/Kg
$T_{1/2}$ = 33 MIN
PER CENT ADMINISTERED DOSE PER ML BLOOD
1
0.1
0.01
0.001
1000009

Distribution of Ferric Oxide Colloid in the Rabbit




100
10
1.0
PERCENT RETAINED ^{59}Fe IN BLOOD
BLOOD ACTIVITY AFTER ^{59}Fe HYDROUS FERRIC OXIDE COLLOID ADMINISTRATION IN THE DOG
○ Ferric Oxide Colloid
● Ferric Oxide Colloid- Bled
△ Ferrous Citrate
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5
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DAYS POST I.V. ADMINISTRATION

September 13, 1967

Minutes of the Meeting of the Committee on Use of Radioisotopes in Humans

Present: C. L. Edwards, C. C. Lushbaugh, R. M. Kniseley, R. L. Hayes, R. J. Cloutier, and J. H. Harmon

The meeting was held to consider clinical trial of gallium-68 labeled hydrous ferric oxide colloid for bone-marrow scanning.

The concensus of the committee was to approve pilot studies using approximately 30 patients. It is presumed that these will be patients with life-shortening illnesses, with hematologic disorders, such as leukemia, lymphoma, myeloma, myelofibrosis, polycythemia vera, cancers that require radiation or chemotherapy, or other patients over 50, where information concerning the marrow might be useful in the management of the patient's disorder.

Before beginning the study, it is planned to study the FDA regulations on new drugs and to consult with staff members in the Division of Biology and Medicine, Washington, D. C. to resolve the present problem concerning FDA regulation of gallium-68 (since gallium-68 is not under AEC control). In any event we presume that it will be necessary to file an IND for use of the ferric hydroxide colloid.

To the human use committee

Concerning a planned study of sodium-22 retention in normal humans

1. Purpose of experiment.

The development of a new theory (turnover compartmentalization) provides tools for a physically precise and physiologically meaningful analysis of whole-body retention data. The purpose of experiment is to obtain data for a detailed description of sodium metabolism in normal humans, involving both short-term (days after tracer injection) and long-term (weeks or months after tracer injection) kinetics. The result of experiment will be estimates of different exchangeable masses, and their turnovers, into which the total sodium pool may be divided.

2. Experimental procedure.

The experiment starts with intravenous injection of a carefully determined amount of sodium-22 chloride; an alternative, which also has to be tried, is to give this amount by mouth. The retention is then followed by the low-level whole-body counter. During the first weeks measurements will be made daily, but later on less frequently. The total period of observation is planned to exceed 100 days. Simultaneously with these measurements, the specific activity of plasma will be observed. The experiment will hopefully be carried out on four normal humans in as far as known similar physiologic state: in two subjects the tracer is injected intravenously, and the other two receive the tracer by mouth.

3. Estimate of total-body burden.

The physical half-life of ^{22}Na is 950 d, and the biologic half-life 11 d. The experiment seems to require that 10-20 μC_i is given to each participating person. According to calculations made by Miss Pat Dalton, the total body burden would be 0.372 rads if 20 μC_i of tracer is given.

4. Maximum permissible dose recommended.

According to ICRU Committee II (1959) page 41, the maximum persmissible constant total burden for ^{22}Na is 10 μC_i.

5. Test persons.

As the total period of observations is hopefully longer than 100 days, it is almost necessary that the persons participating in the experiment are long-term employees at the Medical Division. It has already been pointed out (Section 2) that the study should be carried out on 4 different persons, of the same sex and pairwise in similar physiologic state (like age and body constitution.)

Per-E. E. Bergner

Per-Erik E. Bergner, M.D.

Members of the Human Use Committee

March 14, 1967

Planned Study of Sodium-22 Retention in Normal Humans

File, Dr. Bergner

There will be a meeting of the Human Use Committee Friday, March 17, at 2:00 p.m. in Dr. Kniseley's office.

Agenda:
Consideration of proposal to use sodium-22 in human volunteers.

Ralph M. Kniseley

to:
Dr. Edwards
Dr. Lushbaugh
Dr. Kniseley
Mr. Cloutier
Dr. Hayes
Mr. Harmon

1080015

Minutes

Human Use Committee

March 17, 1967

Present: C. C. Lushbaugh, R. L. Hayes, C. L. Edwards, R. J. Cloutier, and R. M. Kniseley

Dr. Bergner's proposal of March 14, 1967, was considered. The following consensus was obtained: the experiment as proposed was reasonable, and the committee approved the protocol. The committee assumes that the source of sodium-22, if from a commercial radiopharmaceutical company, would include a warranty as to sterility and pyrogenicity. If not, the Medical Division personnel should carry out sterility and pyrogenicity studies. Secondly, if there was any literature to suggest that sodium retention could materially alter the calculated total-body irradiation exposure to materially increase the exposure, then this should be included in the proposal.

The question of recruitment of volunteer subjects was raised. Roger Cloutier will check with Mel Koons as a first step in establishing a current policy that will not be in conflict with ORO of the AEC, which apparently has some concern about the use of normal volunteer subjects who are contractor employees. It was pointed out by Mr. Cloutier that the AEC already has set some precedents that permit employees to participate in radioisotope studies, (e.g. Idaho Falls study). A policy statement and definition of volunteer subjects and recruitment procedures need to be developed for the Medical Division.

FORM P-8A

MEMORANDUM

TO Dr. Per-Erik E. Bergner and

DATE March 20, 1967

SUBJECT Human Use Committee Meeting, March 17

COPIES TO File

The Human Use Committee met March 17 to consider Dr. Bergner's proposal for use of sodium-22 retention in normal human volunteer subjects. The consensus of the committee is to agree to the planned experiment. As the protocol is established, it should be noted that if the radiopharmaceutical is obtained from a commercial source, some warranty of sterility and pyrogenicity should be obtained. If not, the Medical Division staff should carry out these safety procedures. If there is any literature to suggest that sodium retention could materially alter the body burden from the injected sodium-22, this should be appended to the proposal. The committee is exploring the necessary administrative approvals required to recruit volunteer subjects.

RMX

fb
To:
Dr. Edwards, Dr. Lushbaugh,
Dr. Hayes, Mr. Cloutier, Mr. Harmon
Dr. Kaisaley

1080017

FORM P-

MEMORANDUM

TO ORAU Human Use Committee DATE February 13, 1968

SUBJECT STUDY OF GRANULOCYTE KINETICS IN MYELOPROLIFERATIVE DISEASES

COPIES TO Drs. Andrews, Kniseley, Edwards, Lushbaugh, Hayes; Mr. Cloutier and Mr. Harmon; file.

1. Purpose:

Characteristic patterns of white blood cell destruction and regeneration have been found after total-body irradiation and in some instances after local irradiation in humans. Local irradiation to the spleen in chronic myelogenous leukemia can produce a remission akin to that seen after total-body irradiation. Mechanisms by which these changes occur are unknown.

Altered production by measuring the granulocyte turn-over time, change in the half-disappearance time of white blood cells and shifts in circulating versus marginated WBC pools will be measured before and after either splenic or total-body irradiation used as treatment for patients with myeloproliferative disorders.

Application of this information for treatment of hematopoietic disorders with irradiation would be the ultimate aim. In addition, mechanisms of WBC injury by irradiation may be better defined.

2. Radioisotope:

^{32}P-DFP (diisopropyl fluorophosphate) will be used to label the granulocytes according to the procedure described by Athens and co-workers (Blood 14:303, 1959). Both in vitro and in vivo labeling of granulocytes will be performed. With the in vitro method, 30-40 microcuries of ^{32}P and 120-150 micrograms of DFP are added to a transfusion pack containing 300-400 ml of blood which is then given intravenously to the patient. In vivo labeling of granulocytes is accomplished by the intravenous injection of 400 microcuries of ^{32}P and 2 mg of DFP. Both of these methods have been used extensively and reported in the literature. (See attached reference list.)

3. Subjects:

Patients with myeloproliferative disorders, such as chronic myelogenous leukemia, polycythemia rubra vera, and myelofibrosis will be studied before and after either local (splenic) irradiation or total-body irradiation (LETBI or METBI).

4. Procedure:

In vitro labeling studies will require 3-4 days. Blood samples will be drawn at frequent intervals on the first day of the study and then daily for 3-4 days (T_0, 1, 3, 6, 9, 12, 20, 36, 48, 72, 96 hrs). In vivo studies will require an extended period of study with four samples of blood drawn on the day of initiation of study and then one sample of blood drawn each day for the next 20 days. Granulocyte separation will be necessary on all these samples. Disposal of the washes and waste will be performed under the direction of the radiation safety office.

5. Radiation Dose:

Radiation dosage after the in vitro type of study in normal subjects has been reported by Mauer and co-workers (J. Cl. Invest. 39:1481, 1960). It was found that the ^{32}P-DFP was bound firmly to erythrocytes, leukocytes, platelets and plasma proteins, and therefore 30 microcuries of isotope were distributed predominantly in the blood estimated to be 5 kg with little radioactivity reaching the bone marrow or other tissue. In three subjects, urinary excretion of radioactivity was studied and 40% of the administered dose appeared in the urine within the first 8 hours after infusion of the labeled blood. They stated that the biologic half-life of ^{32}P was approximately 6 days and effective half-life was 4.4 days. The infinite dose of radioactivity administered to blood was calculated to be about 860 millirads. This dose did not take into consideration the excretion of ^{32}P-DFP by routes other than the kidneys.

Athens and co-workers (Blood 14:303, 1959) calculated radiation dose after in vivo administration of a maximum of 400 microcuries of ^{32}P-DFP and reported that "a 70 kg man would receive 0.24 equivalent roentgens on the first day and 5.04 equivalent roentgens total dose."

6. Drug Toxicity:

DFP toxicity: In the studies performed by Dr. Athens (ref. above) no serious reactions had occurred in any of the 120 human subjects that had received parenteral doses. After intramuscular administration of 2 mg DFP, moderate to severe pain at the site of injection lasted as long as 30 minutes. A total dose of 4 mg given i.v. to each of four subjects produced in three of them anorexia, nausea and cramps which lasted as long as 24 hours. When the dose of DFP was 3 mg or less, no symptoms were encountered.

This compound is commercially available in sealed ampules or multidose vials. The compound is dissolved in propylene glycol, which is sterilized by gamma radiation (2.5 Megarads). No pyrogenic reactions to these compounds have been reported.

7. Appended reference list.

Helen Vodopick

Helen Vodopick, M.D.

/weh

In addition to estimating the size of the TBGP and its 2 subcompartments the CGP and MGP, the rate of disappearance of granulocytes from the circulation can be followed. In 45 normal subjects the granulocyte disappearance could be described by a single exponential curve with a half disappearance time (T ½) of 6.6 hours (range 4-9) (Figure 1). The data for granulocyte pool size and disappearance rate are summarized in Table II.

Knowing the total number of granulocytes in the circulation (TBGP) and the rate at which these cells leave the circulation the turnover per day of granulocytes in the blood can be calculated. In a steady state this value represents the number of cells produced and destroyed each day. In 45 normal subjects the mean granulocyte turnover rate (GTR) was 180 x 10^7 cells/kg/day (Table II).

TABLE II

The Total Blood Granulocyte Pool (TBGP), Circulating Granulocyte Pool (CGP), Marginal Granulocyte Pool (MGP), Half-Time Disappearance (T ½) and Granulocyte Turnover Rate (GTR) in Normal Male Subjects (9)

DETERMINATION	MEAN	RANGE
TBGP x 10^7 cells/kg	65	33-117
CGP x 10^7 cells/kg	32	15-54
MGP x 10^7 cells/kg	33	9-79
T ½ (hours)	6.6	4-9
GTR x 10^7 cells/kg/day	180	86-341

The applicability of the technics just described to the study of granulocyte production and destruction in various disease states is apparent. Such studies are under way in this laboratory.

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Editor's Note: Other references which may be of interest to labeled DFP users are:

(10) Oosterbaan, R. A., Jausz, H. S. and Cohen, J. A. The chemical structure of the reactive group of esterases. Biochem. et Biophys. Acta, *20*, 402 (1956).

(11) Schaffer, N. K., Simet, L., Harshman, S., Engle, R. R. and Drisko, R. W. Phosphopeptides from acid-hydrolyzed P^{32}-labeled diisopropylphosphoryl chymotrypsin. J. Biol. Chem., *225*, 197 (1957).

(12) Mazur, A. and Bodansky, O. The mechanism of *in vitro* and *in vivo* inhibition of cholinesterase activity by diisoproplyfluorophosphate. J. Biol. Chem., *163*, 261 (1946).

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(14) Eadie, G. S., Smith, W. W. and Brown, I. W., Jr. The use of DFP^{32} as a red cell tag with and without simultaneous tagging with $Chromium^{51}$ in certain animals in the presence or absence of random destruction. J. Gen. Physiol., *43*, 825 (1960).

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LABELED DFP

Diisopropylfluorophosphate (DFP) is a potent and irreversible inhibitor of cholinesterase, many other esterases and certain proteolytic enzymes possessing esterolytic activity. Labeled DFP is available from NENC labeled with phosphorus-32 or tritium. For autoradiography or studies which must be conducted over fairly long periods of time tritium labeled DFP may be used. Because of the short half life the phosphorus-32 labeled compound is only synthesized every four weeks. In addition NENC has tentative plans to produce diisopropyl-2-C^{14}-fluorophosphate in the spring of 1963. Inquiries are invited.

Price and availability information on the two compounds now available is shown below:

IMPORTANT: New England Nuclear chemicals are sold for investigational use only. Verification of their suitability for use in humans is the sole responsibility of the researcher.

File
6477

Members Human Use Committee February 14, 1968

Meeting of Committee to Discuss "Study of Granulocyte Kinetics in Myeloproliferative Diseases"
File, Dr. Andrews

There will be a meeting of the Human Use Committee in Dr. Kaiseley's office at 4:00 p.m. on Thursday, February 22, to discuss the attached proposal. If there is any conflict in your schedule, please call.

Members:
C. L. Edwards
C. C. Lushbaugh
R. M. Kaiseley
R. L. Hayes
Roger Cloutier
J. H. Harmon

1080022

Minutes

Human Use Committee

February 22, 1968

Subject: Study of Granulocyte Kinetics in Myeloproliferative Diseases, submitted by Dr. Vodopick

Present: R. M. Kniseley, C. L. Edwards, C. C. Lushbaugh, R. L. Hayes, J. H. Harmon, and Helen Vodopick

The committee concurred that the clinical trial as proposed in the February 13 memorandum from Dr. Vodopick would be acceptable and appropriate. In response to queries, the source of the material was to be from Nuclear-Chicago supplied in multidose vials, precautions are adequate to insure bacteriologic safety, and there is no toxicity problem in the propylene glycol. Radiation dose calculations are acceptable in the opinion of Mr. Roger Cloutier, ORAU Radiation Safety Officer.

FORM P-4A

MEMORANDUM

TO ORAU Human Use Committee DATE February 23, 1968

SUBJECT STUDY OF GRANULOCYTE IN MYELOPROLIFERATIVE DISEASES (Feb. 13, 1968)

COPIES TO Dr. Andrews, Dr. Kniseley, Dr. Edwards, Dr. Lushbaugh, Dr. Hayes, Mr. Harmon, File.

The radiation dose due to the in vitro use of $DF^{32}P$ as proposed by Dr. Vodopick will be about as stated in her memo.

The dose from the in vivo study will be somewhat higher. If it is assumed that all the energy is deposited in the blood, the dose for various biological half times will be:

T_{biol}	Total Dose/400 microcuries
∞	60 rads
6 days	18 rads
5 hrs (52%) and 6 days (48%)	9 rads

The model with two biological half times is perhaps the closes to the actual situation. Even in this case, the actual dose will be somewhat lower since some of the betas will penetrate the blood vessel walls and deposit some of their energy outside the blood.

R. J. Cloutier
Radiation Safety Officer

RJC:jb

1080024

FORM P-4

MEMORANDUM

TO Human Use Committee DATE March 13, 1968

SUBJECT Clinical Trial of ^{67}Ga as a Bone Scanning Agent.

COPIES TO Human Use Committee, Dr. Andrews, Mr. Harmon, File

1. Proposal:

Animal studies indicate that ^{67}Ga may have considerable advantage over other radionuclides presently in use for bone scanning in humans. Its half-life (78 hr), and favorable decay characteristics (electron capture, moderate energy gamma rays) should permit camera imaging with millicurie amounts of ^{67}Ga over a period of a week or more without undue radiation dose. This is not possible with radionuclides presently being used for bone scanning (^{47}Ca, ^{85}Sr, ^{87m}Sr, ^{18}F and ^{68}Ga). It is proposed that controlled clinical trials be carried out to determine the usefulness of this radionuclide in bone scanning in man.

2. Radioisotope:

Gallium-67 has a convenient half-life of 78 hr. It can be obtained carrier-free in excellent yield (600 mc/milliampere - hr) by a p,2n reaction on ^{68}Zn (18.6% abundant). Gallium-67 decays by electron capture with the emission of low and moderate energy gamma rays [90(40%), 184(24%), 296(22%), and 388(7%) kev]. There is little internal conversion of these gamma rays.

3. Chemical Form:

Gallium-67 will be administered as the citrate in either a carrier-free form or with added carrier gallium at a level not to exceed that presently being used with ^{68}Ga (4 mg Ga/kg body weight). The molar citrate to gallium ratio will be held between 1.5:1 (higher levels of gallium) and 3:1.

4. Route of Administration:

Intravenous.

5. Proposed dosage:

Two and one half millicures for average adult (70 kg) reduced in proportion for children.

6. Experimental Protocol:

a. Number and Selection of Patients:

Twenty-five patients with known or suspected neoplastic disease of the bone. Several of these patients will be studied at both carrier and carrier-free levels of gallium. In addition, tracer doses will be administered to selected patients undergoing liver biopsy as they become available during the period of study.

b. Duration of Studies:

One year with review of results at that time to determine the desirability of a continuation of the project.

c. Type and Frequency of Assays:

(1) Blood (2 ml) at 0.25, 0.5, 1.0, 2.0, 3.0, and 5.0 hr after administration.

(2) Individual urines through first 24 hr, then daily through 7 days.

(3) All stools through 7 days.

(4) Linear Scans (with integrated whole-body counts) before, 1 hr (without voiding), 4 hr, and then daily through 10 days after administration.

(5) Laxative to be given in evening of the day dose administered.

(6) Whole body scans at 24 and 48 hr after dose.

(7) Camera pictures at intervals as called for by the attending physician.

7. Animal Studies:

Previous studies in the rabbit have indicated that there is early preferential localization of gallium in bone if a sufficient dose of stable gallium (mg/kg level) is administered. At a carrier-free or microgram/kg level the distribution is diffuse. A portion of these results are shown in Figure 1. These studies constitute the preclinical basis for the clinical investigation of ^{68}Ga as a bone scanning agent. Further animal studies have indicated that at 24 hr and after even at carrier-free levels of gallium the deposition of gallium in bone is preferential. At the carrier-free level, however, the ratio of gallium concentration in bone to that in the liver is only 4:1. See Figure 2. When carrier gallium is administered at the modest level of 0.5 to 1.0 mg/kg the bone/liver ratio is considerably improved (10:1). In addition the ratios for other tissues are also improved (bone/blood 50:1, bone/muscle > 100:1). The tissue distribution shown in Fig. 2 persists throughout 3 days. Table 1 shows the gallium distribution with time for a carrier level of 0.5 mg Ga/kg. Thus with a modest amount of stable gallium (0.5 mg) distinctly better preferential bone deposition might be obtained than has been possible at the earlier time period dictated by the half-life of ^{68}Ga where considerably higher levels of stable gallium (2-4 mg/kg) were required.

8. Radiation Dose:

The Radiation Safety Office has calculated that the ^{67}Ga dose to the bone in humans will be 2.08 rads/mc administered. Immediate deposition and complete decay in situ were assumed. The whole-body dose in humans for ^{67}Ga assuming uniform distribution and no excretion is estimated to be 0.336 rads/mc administered. A copy of these calculations is available in the Radiation Safety Office.

9. Related and Pertinent Data:

Gallium-68 has been under clinical investigation at the Medical Division as a bone scanning agent since 1965. One hundred forty-one doses of ^{68}Ga have been administered with levels of stable gallium up to 4 mg/kg. No apparent toxic effects have been noted. Many satisfactory scans have been obtained. The ^{68}Ga deposition (scan) was similar to that of ^{85}Sr.

10. Chemical Radiation and Infectious Hazards:

Gallium-68 citrate has been under evaluation as a bone scanning agent in the Medical Division clinical program using levels of stable gallium up to 4 mg/kg of body weight. The present proposal would involve the use of stable gallium at a level not to exceed that being used with gallium-68. Most doses would be of the order of 1 mg Ga/kg or less, however.

The radiation dose for the levels proposed (see 8 above) is considered to be sufficiently low by present standards. All gallium-67 shipments received will be checked for sterility and pyrogenicity. Sterilization will be by micropore filtration (0.22 microns) or by autoclaving. All agents used except those obtained from pharmaceutical houses will be checked for pyrogens. A portion of each dose prepared for administration will be held back for testing in the event of reaction.

R. L. Hayes

RLH:fed

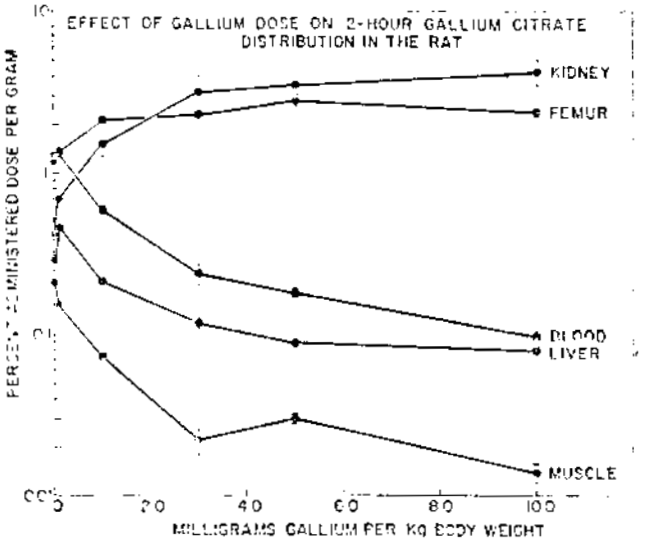

Fig. 1

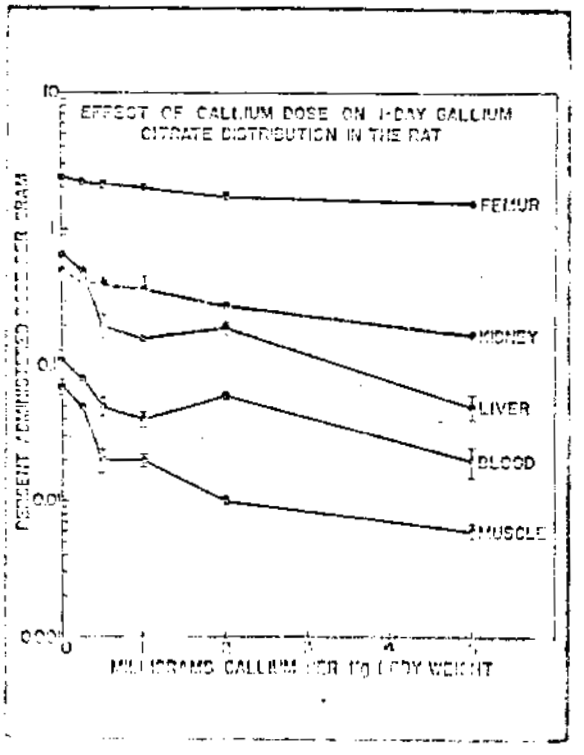

Fig. 2

TABLE 1

DISTRIBUTION OF GALLIUM (0.5 mg Ga/kg) WITH TIME IN THE RAT

Tissue	TIME 2 hr		24 hr		48 hr		72 hr	
Liver	0.16	(0.02)*	0.20	(0.04)	0.23	(0.03)	0.23	(0.04)
Spleen	0.10		0.12		0.19		0.17	
Kidney	0.45	(0.05)	0.40	(0.04)	0.32	(0.02)	0.28	(0.02)
Lung	0.23		0.06		0.06		0.08	
Muscle	0.05		0.03		0.02		0.02	
Rib	2.98	(0.27)	3.13	(0.19)	3.06	(0.25	2.37	(0.21)
Femur	1.82	(0.12)	2.13	(0.14)	1.93	(0.07)	1.95	(0.05)
Calvarium	1.30	(0.11)	1.40	(0.10)	1.25	(0.03)	1.12	(0.07)
Marrow	0.23		0.11		0.18		0.14	
Blood	0.39	(0.09)	0.05	(0.008)	0.02	(0.004)	0.02	(0.009)
Total in Blood	6.74		0.79		0.27		0.30	
Total in GI Tract	NM		2.10		1.63		1.12	
No. of Animals	6		6		6		5	
Average Bone	2.03		2.22		2.08		1.79	
Bone/ Blood	5.3		49		135		105	
Bone / Muscle	38		106		110		112	
Bone/ Liver	12.4		11.2		9.0		7.9	

* Std of the Mean.

Calculated March 13, 1968

COMPARISON OF RADIATION DOSE FROM BONE SCANNING RADIOISOTOPES

	Total Dose per Millicurie Administered in Rads	
Radioisotope	Whole Body*	Bone**
^{68}Ga	0.0528	0.418
^{67}Ga	0.336	2.08
^{85}Sr	13.2	52.7

* Assuming uniform distribution and no excretion

** Assuming 100% uptake and no excretion

Minutes

Human Use Committee

March 15, 1968

Subject: Clinical Trials of ^{67}Ga as a Bone-Scanning Agent

Present: R. L. Hayes, C. L. Edwards, R. J. Cloutier, C. C. Lushbaugh, and R. M. Kniseley

The committee met at 3:00 p.m. to consider the proposal, Clinical Trials of ^{67}Ga as a bone-scanning agent.

The committee concurred that the clinical trial as proposed in the memorandum would be acceptable and appropriate.

FORM F-4

MEMORANDUM

TO Dr. R. I. Hayes DATE January 8, 1970

SUBJECT RADIATION DOSE FROM ^{111}IN AND $^{114}IN^{m}$

COPIES TO File

As you requested, we have calculated the radiation dose to a patient after administration of ^{111}In and the radiation dose from its contaminant, $^{114}In^{m}$. Because of the dfficulty of determining the X rays and Auger electrons emitted in the decay of these two radioisotopes, we have neglected them in the calculations until we can get the computer data from ORNL. When we have additional data, we will recalculate these dose estimates.

	^{111}In (rads/microcurie adm.)	$^{114}In^{m}$ (rads/microcurie adm.)
Whole body - uniform distribution - no excretion	0.00048	0.042
Bone - uniform distribution in bone - no excretion	0.0023	0.41

If you have questions about these estimates, please contact me.

Roger J. Cloutier

w

FORM P-4

MEMORANDUM

TO Isotope Committee DATE January 8, 1970

SUBJECT CLINICAL TRIAL OF ^{111}In AS A TUMOR-SCANNING AGENT

COPIES TO

(1) Proposal:

Hunter and deKock (J Nucl Med 10: 364, 1969) have reported good localization of ^{111}In in animal tumors. To test the significance of their finding it is proposed that a comparison of the distribution of ^{111}In with that of ^{67}Ga be made in patients with diagnosed tumors, i.e., patients be given closely spaced doses of ^{111}In and ^{67}Ga (adjusted to produce similar photon outputs) and scanned under similar conditions. The use of ^{67}Ga in patients has had previous approval.

(2) Radioisotope:

Indium-111 has a half-life of 2.8 days. It decays by electron capture with the emission of two gamma rays, 173 KeV and 247 KeV. It will be produced by proton bombardment of enriched ^{111}Cd at Oak Ridge National Laboratory and supplied to the Medical Division free of cadmium in the carrier-free form.

(3) Chemical Form:

The isotope will be received in the chloride form in dilute HCl. It will be processed and administered as a citrate solution containing a total of 7 mg sodium citrate/kg body weight. The pH will be adjusted to 7.0 ± 0.2.

(4) Administration:

Slow intravenous administration (volume approximately 100 ml).

(5) Proposed dosage:

15 μCi/kg body weight (1 mCi for 70 kg patient).

(6) Experimental Protocol:

(a) Number and selection of patients. 20 patients divided between those having positive and negative ^{67}Ga scans.

(b) Duration of studies. 6 months to one year

(c) Type and frequency of assay. Blood samples at 0.5, 1, 3, 12, 24, 48, and 72 hours. Individual urines during first 24 hours and then at 24-hour intervals thereafter through 7 days. Individual stool specimens through 7 days.

(d) Special procedures. Linear scans, whole-body counts, and whole-body scans using the present ^{67}Ga protocol. Area scans when advisable.

(7) Animal Studies:

Studies in rats have indicated that indium (high specific activity ^{114m}In) has a distribution similar to that of carrier-free ^{67}Ga, but with slower blood clearance and higher liver and spleen deposition. Hunter and deKock have reported localization of ^{111}In in transplanted tumors in rats and in naturally-occurring tumors in dogs (J Nucl Med 10: 344, 1969).

(8) Radiation Dose:

The Radiation Safety Office has estimated that the ^{111}In dose to the whole body, assuming uniform distribution and no excretion, will be 0.48 rads per mCi administered. The dose to the bone, assuming 100% deposition in bone, will be 2.3 rads per mCi administered.

(9) Related and Pertinent Human Data:

This is a new radionuclide and no data on humans is available in the literature. Indium-113m has been used in various pharmaceutical preparations but its half-life is only 1.7 hours and data on it are not relevant to the present proposal.

(10) Chemical, Radiation, and Infectious Hazards:

The ^{111}In will be carrier-free since it is produced by proton bombardment; chemical toxicity from indium is therefore not relevant. A microanalytical test for cadmium will be made on each batch of ^{111}In on receipt. Spectrometric verification of radionuclide purity of each batch will also be made.

A trace amount of 49-day ^{114m}In will be present in the preparation due to the presence of a small amount of ^{114}Cd in the separated ^{111}Cd target material. This is estimated by Oak Ridge National Laboratory to be approximately 0.02% of the ^{111}In level (0.2 μCi/mCi ^{111}In) at one half-life after termination of the target bombardment. The radiation dose from ^{114}In per μCi is estimated by the Radiation Safety Office to be 0.042 rads to the whole body and 0.41 rads to the bone. Thus the whole-body dose contribution from the presence of this contaminant will be 0.008, 0.015, and 0.030 rads per mCi of ^{111}In administered at one, two and three half-lives after termination bombardment. The dose to the bone will be 0.082, 0.157, and 0.305 rads/mCi ^{111}In

at the same intervals. The total dose due to both ^{111}In and ^{114m}In, with the assumptions made in item 8, will then be: bone, 2.4, 2.5, and 2.6 rads/mCi ^{111}In, and whole body, 0.49, 0.50, and 0.51 rads/mCi ^{111}In at these time intervals.

The ^{111}In solution will be Milipore filtered (0.22 micron) into an autoclaved, sealed vial on receipt and tested for pyrogenicity. The preparation of the ^{111}In dose will be carried out in a laminar-flow hood using sterile equipment. Final sterilization will be made through Milipore filtration. Ten percent of the preparation will be held back for testing should the patient show any reaction.

R. L. Hayes

RLH/ns

FORM P-4A

MEMORANDUM

TO Human Use Committee DATE 23 August 1968

SUBJECT CLINICAL TRIAL OF ^{72}GA AS A THERAPEUTIC AGENT IN THE TREATMENT OF SELECTED SOFT-TISSUE NEOPLASMS.

COPIES TO Dr. Andrews, Mr. Harmon, Files

1. Proposal:

Recent trials of ^{67}Ga (Human Use Committee Memorandum dated March 13, 1968) as a clinical scanning agent have shown rapid and very pronounced depositions of this agent in lymphoma, metastatic undifferentiated thyroid carcinoma and bronchogenic carcinoma. In 3 patients the uptake by tumor tissue appeared to be greater than 50% of the dose administered. With patients demonstrating this type of ^{67}Ga tumor localization and with an associated poor response to standard therapy, it is proposed that a course of internal radioisotope therapy with ^{72}Ga be considered.

2. Radioisotope:

Gallium-72 has a half-life of 14.1 hours. It decays by beta emission [Mev β_{max} = 0.66(15%), 0.67(22%), 0.96(30%), 1.49(8%), 1.93(5%), 2.27(4%), 2.54(8%), and 3.18(8%)] with a number of associated high energy gamma rays. The ratio of beta dose to gamma dose in a large tumor mass is estimated to be 1.8. Gallium-72 is pile-produced and can be obtained from Oak Ridge National Laboratory with a specific activity of approximately 40 millicurie/milligram of stable gallium. Activation in the High Intensity Flux Reactor could produce specific activities approximately 10 times greater.

3. Chemical Form:

Gallium-72 citrate-saline solution containing stable gallium at a level no greater than 35 micrograms/kilogram body weight [assuming a 100 millicurie dose (70 kilogram body weight) with a specific activity of 40 millicuries/milligram gallium]. The citrate dose will be held at 7 milligrams/kilogram body weight.

4. Route of Administration:

Intravenous.

5. Proposed Dosage:

The dosage will be determined by the clinical staff for each individual patient through consideration of the ^{67}Ga scan data and in consultation with the radiotherapist. Initially, previous therapy experience with ^{72}Ga (*Radiology 61*, 534, 1953) will be used as a guide.

6. Experimental Protocol:

a. Number and Selection of Patients:

Ten patients will be selected as described in 1. above. After each patient study, a careful assessment of the results will be made to determine whether further trials seem warranted.

b. Duration of Studies:

Radioassays of patients and samples will be carried out through 5 half-lives (72 hours).

c. Type and Frequency of Assay:

(1) Blood (2 ml) at 2, 6, 12, 24, 48, and 72 hours after administration.

(2) Linear scans immediately after, and then at 4, 24, 48, and 72 hours after administration.

(3) Increase fluid intake in all patients during day of dose.

(4) Laxative to be given on the evening of the day the dose is administered and repeated the following evening.

(5) High-level whole-body counts immediately after dose, and then at 24, 48, and 72 hours after administration.

(6) Whole-body scans at 24 and 48 hours after dose.

7. Animal Studies:

Preliminary studies in rats and mice with transplanted tumors indicate a gross alteration in the normal tissue distribution of ^{67}Ga (carrier-free). Most noticeable was the decreased bone deposition. Although deposition in the tumor was considerably greater than in muscle, no tumor deposition in animals (with the exception of two Morris Minimal Deviation Hepatomas) has approached that seen in man. Animal experimentation is continuing. The distribution of carrier-free gallium in normal animals was covered in memorandum dated March 13, 1968, Subject: Clinical Trial of ^{67}Ga as a Bone Scanning Agent.

8. Radiation Dose:

The whole-body radiation dose for ^{72}Ga assuming no excretion and uniform distribution is estimated by the Radiation Safety Office to be 0.82 rads/millicurie. The actual dose to the tumor will be

estimated from previous studies with ^{67}Ga. At the same time a predicted dose to various organs can also be estimated and used as a basis for a decision on the desirability of treatment with ^{72}Ga.

9. Related and Pertinent Data:

The Medical Division has had considerable previous experience with the therapeutic use of ^{72}Ga, (*Radiology 61*, 534, 1953). Although the present proposal deals with a uniquely different therapeutic situation, this previous experience will act initially as a valuable guide.

10. Chemical, Radiation, and Infection Hazards:

Gallium-68 citrate has been under evaluation as a bone-scanning agent in the Medical Division's clinical program using levels of stable gallium up to 4 milligrams/kilogram of body weight. The present proposal would involve the use of stable gallium at a level not to exceed 35 micrograms/kilogram body weight.

The radiation dose levels as previously indicated in Section 8 will be calculated for each individual patient from previous diagnostic results with ^{67}Ga. All ^{72}Ga shipments received will be checked for sterility and pyrogenicity. Sterilization will be by micropore filtration (0.22 microns) or by autoclaving. All agents used except those obtained from pharmaceutical houses will be checked for pyrogens. A portion of each dose prepared for administration will be held back for testing in the event of reaction.

R. L. Hayes

RLH/v

FORM P-4

MEMORANDUM

TO Dr. R. L. Hayes DATE August 23, 1968

SUBJECT RADIATION DOSE FROM ADMINISTERED ^{72}GA

COPIES TO Dr. Edwards, file

The radiation dose a patient might receive from administered ^{72}Ga is given in the following table.

Reference Organ	Assumptions	Radiation Dose (in rads/millicurie administered)
Whole Body	100% uniformly distributed in the body No excretion	0.8
Whole Body	65% of ^{72}Ga in 50% of lungs 35% uniformly distributed in the body No excretion	0.8 *
Lung Tumor	65% of ^{72}Ga in 50% of lungs	44.1

*The absorbed fraction of the gammas emitted by the 65% in the lungs is greater than the absorbed fraction of the gammas emitted by uniformly distributed material; therefore, this radiation dose is applicable only under these specific conditions. This number should not be used in any work for publication until the context has been checked for accuracy. Please note that this number differs from the 1.22 rads/millicurie reported in my memo of August 19 as a result of an overestimation of the beta contribution to the whole body dose in those calculations.

Roger J. Cloutier

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FORM F-4

MEMORANDUM

TO CRAU Human Use Committee DATE March 25, 1968

SUBJECT STUDY OF PLATELET LIFE SPAN IN HUMANS.

COPIES TO Drs. Andrews, Kniseley, Edwards, Lushbaugh, Hayes; Mr. Cloutier and Harmon; file.

1. Purpose:

The life span of platelets in normal persons has been found to be about 10 days. In some patients with low platelet counts, it is impossible to decide whether defective production or increased destruction of platelets is present. To evaluate the platelet kinetics in patients with such disorders is the purpose of this study.

Platelet life span will be measured by following platelets which have been labeled in vitro with a radioisotope. (See procedure below.) Platelet sequestration especially by the spleen will be evaluated by external counting over various organs. Comparative concentration of radioisotope which has localized in these organs over a period of time may provide some pattern to suggest the presence of splenic sequestration. Hopefully these data may be used to decide the need for and to predict the benefits of splenectomy in some cases.

These procedures would be performed before and after such specific therapy, i.e., steroids, splenectomy or other immunosuppressive drugs.

2. Radioisotope:

^{51}Cr-sodium chromate will be used to label platelets according to the method published by Aster and Jandl (J. Clin. Investigation 43:843, 1964). Platelets will be labeled in vitro using 250 microcuries of ^{51}Cr-Na_2CrO_4 to label platelets obtained and separated from a 400-500 ml phlebotomy. (The red blood cells are not labeled in this procedure.) These platelets after a 15 minute incubation period are washed with autologous plasma which is removed before the platelets are transfused into the patient. The platelets are suspended in additional unlabeled autologous plasma. The per cent of ^{51}Cr incorporation of platelets is directly proportional to the platelet concentration. About 8-10% (25 microcuries) of the initial ^{51}Cr sodium chromate used is given to the patient.

3. Subjects:

Initially 4-5 patients without platelet disorder will be studied to assure accurate technic in the performance of this procedure. Then suitable patients with platelet abnormalities will be studied. As stated previously, this procedure would be done before and after therapy that may alter the platelet life span.

4. Procedure:

In vitro labeling studies will require 10 days. One blood sample will be drawn daily. Platelet separation is necessary on all these samples. Disposal of washes and waste will be performed under the direction of the radiation safety office.

5. Radiation dose:

The amount of ^{51}Cr sodium chromate administered to a patient will be approximately 25 microcuries per study. There is no re-utilization of this material by platelets. Urinary excretion is the main route of elimination from the body. Maximal permissible

body burden (continuous dose) is stated to be 800 microcuries - (Report of Committee 2 on Permissible Dose for Internal Radiation (1959) - Health Physics VIII: 44, June, 1960.)

6. Drug Toxicity:

The ^{51}Cr sodium chromate is available commercially. This compound, which has been used for erythrocyte labeling, has also been used for platelet labeling. No known adverse reactions to this amount of this isotope are known.

Vodopick

Helen Vodopick, M.D.

/weh

Minutes

Human Use Committee

August 26, 1968

Subject: Proposal for Clinical Trial of Gallium-72 as a Therapeutic Agent in the Treatment of Selected Soft Tissue Neoplasms (submitted by Dr. Hayes)

Present: R. M. Kniseley, C. L. Edwards, C. C. Lushbaugh, R. L. Hayes, and Roger Cloutier

The committee concurred unanimously that the clinical trial as proposed in the memorandum (23 August) would be acceptable and appropriate and that the risks to the patient appear to be acceptably low. There was general agreement that it would be advisable to reassess the status of the project with the acquisition of data in the early cases to determine whether any adjustment in the approach would be warranted.

FORM P-8

MEMORANDUM

File - Human Use Committee

DATE March 26, 1968

SUBJECT

COPIES TO

A memo from Dr. Vodopick proposes to use chromium-51 for in vitro labeling of platelets for platelet life span studies. The proposal is similar to existing applications of chromium for labeling blood cells, and in the same or lower doses. No review by the Human Use Committee is indicated.

RMK

b

1080043

FORM P-4A

MEMORANDUM

TO Members of the Human Use Committee DATE 3 February 1969

SUBJECT AMMENDMENT TO AUTHORIZATION FOR "CLINICAL TRIALS OF ^{67}GA AS A BONE SCANNING AGENT" (15 MARCH 1968)

COPIES TO Dr. Kniseley, Mr. Cloutier, Dr. Edwards, Dr. Lushbaugh, Mr. Harmon
Dr. Andrews, Files

A meeting of the Human Use Committee is requested for 3:30 p.m. February 4, 1969 for the purpose of considering an ammendment to the memorandum dated March 13, 1968 on the subject "Clinical Trials of ^{67}Ga as a Bone Scanning Agent" which in turn was authorized by the 15 March 1968 Human Use Committee meeting.

It is requested that Section 5 (Proposed Dosage) be ammended to read as follows: "5 millicuries for average adult (70 kg) reduced in proportion for children." This dosage (double that previously authorized) will provide better scanning contrast and extend the period of study.

R. L. Hayes

R. L. Hayes

RLH/v

Attachments (Copies of memoranda dated 13 March and 15 March 1968)

1080044

Minutes

Human Use Committee

February 4, 1969

Subject: Extension Modification of Clinical Trials Using Gallium-67

Present: R. L. Hayes, C. L. Edwards, R. J. Cloutier, C. C. Lushbaugh, and R. M. Kniseley

The committee met at 3:30 p.m. to consider the request for the following modifications:

> Paragraph 6. (1) renewal for an additional year of study; (2) extend the numbers of patients to 100; (3) the patient would have known or suspected neoplastic disease of either bone or soft tissue (favorable localization of carrier-free gallium has been observed both in patients and experimental animals in soft tissue tumors after administration of carrier-free gallium-67); (4) the dose would be increased to 70 microcuries per kilogram. Using the assumptions made in the original proposal, the average dose to bone in humans would be about 10 to 12 rads. This assumes the immediate deposition of the entire amount of administered isotope in the bone and no loss of isotope from the bone. The actual exposure will be considerably lower than this since excretion data show a significant fraction of the administered doses is excreted in the first 24 to 48 hours. For comparison it was pointed out that while the dose from gallium-67 is estimated to be 2.08 rads per millicurie administered, the estimated dose from strontium-85 to bone is 52 rads per millicurie administered.

The committee concurred that the clinical trial as proposed would be acceptable and appropriate.

Minutes

Human Use Committee

January 9, 1970

Subject: Clinical Trial of ^{111}In as a Tumor-Scanning Agent, 1-8-70

Present: R. J. Cloutier, R. L. Hayes, C. L. Edwards, C. C. Lushbaugh, and R. M. Kniseley

Corrections were made in some errors on page 3. Discussion of the chemical toxicity was included. The contaminating cadmium concentrations will be less than 0.03 milligrams per dose to the patient. This represents approximately 1/5000 of a lethal dose for dogs (Specter, Handbook of Toxicology). It is estimated that less than one nanogram of indium as indium-111 will be present. Stable indium has a 2-5 milligram per kilo lethal dose.

The radiation dosimetry calculations are preliminary and are subject to some modification when the computer calculations have been performed. This probably will be less than 20% difference.

The Committee unanimously agreed that the radiation-exposure hazard was quite acceptable, and since the material will be carrier free, no chemical toxic hazard is apparent.

FORM P-4a

MEMORANDUM

TO Dr. Lowell Edwards DATE May 22, 1970

SUBJECT DOSE TO TISSUE FROM GALLIUM-67 INJECTED SUBCUTANEOUSLY

COPIES TO File

.005

As you requested, we have calculated the radiation dose that a patient would receive from the subcutaneous injection of 0.5 millicuries of ^{67}Ga. We have assumed that the ^{67}Ga was initially contained in 1-ml of fluid. Since the volume injected is so small, most of the dose is due to internal conversion electrons, Auger electrons, and X rays. We did not calculate the gamma dose from the injected material or from material at another site since this would contribute less than 5% to the total dose. The doses listed are for subcutaneous tissue in immediate contact with the fluid containing the ^{67}Ga. The dose would decrease rapidly as the distance increased.

	Assumption	Total Dose in Rads per 0.5 mCi Injected
Case 1 - Radioisotope remains at injection site until complete decay	a. isotope remains in 1 milliliter of liquid at injection site	22,000
	b. liquid leaves site of injection and isotope is dispersed in a disc of about 1/2 cm dia.	44,000
Case 2 - Radioisotope rapidly leaves site of injection	a. all activity leaves injection site within 24 hrs (k = 1/24)	2,000
	b. 95% of activity leaves injection site within 24 hrs - 5% remains at injection site until decay	4,000

Roger J. Cloutier

RJC:w

1080047

FORM P-4A

MEMORANDUM

TO Human Use Committee DATE 25 May 1970

SUBJECT Clinical Trial of ^{67}Ga Injected subcutaneously

COPIES TO Dr. Andrews, Mr. Harmon, Files

1. Proposal:

It has been demonstrated (Edwards and Hayes, JAMA May 18, 1970) that ^{67}Ga is selectively deposited in soft tissue tumors. Recent trials with dogs have shown that ^{67}Ga citrate when mixed with autologous plasma and injected subcutaneously will result in visualization of lymph nodes draining the injection site when scanning techniques are used. It is proposed that ^{67}Ga be given subcutaneously to patients with known neoplasms. In this manner increased amounts of ^{67}Ga could be presented to the lymphatic system compared to intravenous injection, increasing the likelihood for tumor visualization in the lymph nodes.

2. Radioisotope:

Gallium-67 has a half-life of 3.3 days. It decays by electron capture emitting gamma rays of 90, 184, and 296 kev. It is produced by proton bombardment of zinc at the Oak Ridge National Laboratory, Oak Ridge, Tennessee, and is supplied to this installation as a dilute (~0.1N) HCl solution of carrier-free ^{67}Ga free of zinc and spectrometrically pure except for small amounts of gallium-66.

3. Chemical Form:

Gallium-67 citrate (citrate 5 milligrams per dose ~~Kilogram Body Weight~~) as used for intravenous scanning will be mixed with autologous serum as a ratio of two parts serum to one part ^{67}Ga citrate. Incubation will be performed for fiteen minutes in a Dubnoff Shaker. Dialysis experiments have shown that ^{67}Ga, after mixing with blood, is bound to the 73,000 moleculer weight β globulin transferrin. The patient's blood will be drawn in a heparinized syringe and centrifuged immediately prior to incubation of the serum and ^{67}Ga citrate.

4. Route of Administration:

The injections will be subcutaneous in the toe webs between the first and second and between the third and fourth toes of each foot, a total of four injections.

5. Proposed Dosage:

2.0 mCi total dose will be given in a volume of 6.0 cc — a dosage of 0.5 mCi in 1.5 cc for each injection site.

6. Experimental Protocol:

a. Number and selection of patients:

TEN ~~The then~~ patients who have documented life threatening neoplasms and who have had previous intravenous ^{67}Ga scans will be selected. After each patient study, a careful assessment of the results will be made to determine whether further trials seem warranted.

1080048

b. Type and Frequency of Assay:

(1) Blood (2 ml) 15, 30, 45, 60 number, 4, 24, 48, and 72 hours after administration.

(2) Linear scans immediately after and then at 4, 24, 48, and 72 hours after administration.

(3) Whole-body scans at 24 and 48 hours after dose and area scans if appropriate.

7. Animal Studies:

Preliminary studies in tumor-free anesthetized dogs indicate rapid uptake of ^{67}Ga citrate and autologous plasma from subcutaneous injection sites in the paws to the regional lymph nodes following passive flexion of the limbs. Scans taken 24 hours after injection show a body distribution similar to what is seen after intravenous ^{67}Ga citrate injection with no discrete node visualization. Linear scan on one dog 70 minutes after injection showed 39.99% of body counts located below the ankles. Another dog at 110 minutes after injection had 3.5% of body counts located below the ankles on the linear scan. Linear scans of three dogs including the two just mentioned showed less than 2.5% of the body counts located below the ankles with linear scanning twenty-four hours after injection.

8. Radiation Dose:

The radiation safety office at ORAU has estimated the radiation dose to the subcutaneous area immediately surrounding the injection site to be 22,000 rads per 0.5 mCi assuming complete decay at the site. Assuming 5% remains at 24 hours and a linear decay, the radiation dose would be 4000 rads per 0.5 mCi injected. From the dog experiments we believe that the majority of isotope leaves the injection site during the first two hours. Hence the radiation dose would be much less than these two estimates listed above.

There is also published date using ^{198}Au colloid injected subcutaneously in the toe webs (Kazem et al, Radiology 90: 905-11, May 1968) using 75-100 mCi of this β emitter per injection site. No local irradiation reactions were reported in 75 patients. In addition, Rösler (Recent Results in Cancer Research, Springer Verlag New York, 1969, p. 252) reports no local acute or late radiation reaction at the site of injection using 0.5 to 1.0 mCi of ^{198}Au colloid.

9. Related and Pertinent Data:

The Medical Division has two years of experience with intravenous ^{67}Ga citrate tumor scanning. In addition, five patients have had ^{67}Ga citrate mixed with autologous plasma and injected directly into the lymphatics by cannulation with follow-up scanning. Although the present proposal deals with a different route of administration, this previous experience will act initially as a valuable guide for interpreting benefits and possible hazards of this procedure.

10. Chemical Radiation and Infection Hazards:

No chemical hazards are anticipated since the preparation is the same as is given intravenously with the exception of the additional autologous plasma and no toxicity has been reported after two years of

intravenous clinical experience. The in-vitro binding of ^{67}Ga to autologous serum proteins is not expected to differ from the in-vivo binding which occurs after intravenous administration of ^{67}Ga citrate.

Sterilization methods will be the same as when used intravenously and the withdrawal of patient blood, centrifugation, and incubation of serum with gallium citrate will be accomplished in disposable sterilized syringe and sterilized 20 cc bottles. A portion of each dose prepared for administration will be held back for testing in the event of reaction.

Patients with clinically evident circulation problems in the extremities will not be included in the experiments to minimize the risk of excess radiation to the feet due to poor uptake. In addition only ambulatory patients will be accepted for the experiments.

Steven H. Ominsky, M.D.

bb

Minutes

Human Use Committee

May 25, 1970

Subject: Clinical Trial of ^{67}Ga Injected Subcutaneously

Present: R. J. Cloutier, C. L. Edwards, R. L. Hayes, R. M. Kniseley, C. C. Lushbaugh, and S. Ominsky

The Isotope Committee met to consider a proposal dated 25 May 1970 for clinical trials of ^{67}Ga injected subcutaneously. It was recommended that two volunteers be given tracer doses (0.005 millicuries to one site on each foot) in order to gain more reliable data on human clearances. We would like to convene then to consider dose calculations that would be based on this new data.

Dr Knisely

FORM P-4

MEMORANDUM

TO Human Use Committee DATE June 4, 1970

SUBJECT CLINICAL TRIAL OF ^{67}Ga INJECTED SUBCUTANEOUSLY

COPIES TO File

I have recalculated the radiation dose that a patient would receive at the injection site from a subcutaneous injection of 0.5 millicurie of ^{67}Ga. I have assumed that the ^{67}Ga was initially contained in 1 ml of fluid. Most of the dose at the injection site is due to internal conversion electrons, Auger electrons, and X rays. Gamma rays would probably contribute less than 5% more to the total dose at the injection site. The doses listed are for subcutaneous tissue in immediate contact with the fluid containing the ^{67}Ga. The dose would decrease rapidly as the distance increases.

The doses given in this memo are considerably lower than those given in my May 22, 1970, report. This is a result of an error I discovered in the original calculations and the fact that I have used real retention data.

Patient 1	% of Activity Remaining	$T_{1/2}$	Dose per 0.5 millicurie Injected
Component 1	62	1.2 hr	41 rads
Component 2	17	5.5 hr	52 rads
Component 3	21	77	903 rads
			Approx. 1000 rads

The total dose Patient No. 1 would have received at the injection site from a 0.5 millicurie injection of ^{67}Ca would have been approximately 1000 rads.

Roger J. Cloutier

RJC:w

1080052

FORM P-4

MEMORANDUM

TO Dr. Steven Orinsky DATE June 8, 1970

SUBJECT DOSE FROM ^{67}Ga INJECTED SUBCUTANEOUSLY

COPIES TO Human Use Committee, file

If you were to inject 0.25 millicuries of ^{67}Ga contained in 2 cc, the maximum dose to the tissue immediately surrounding the injection site would be about 250 rads. The calculations are based on the amount retained and effective half-lives calculated for the patient given a tracer dose injection. Because of diffusion and movement of the isotope at the injection site, the actual dose would probably be no greater than one-half the maximum dose or 125 rads.

Roger J. Cloutier

1080053

TN. Rec'd 5-1-79

DIVISION OF INDUSTRIAL AND RADIOLOGICAL HEALTH

Appendix A

WELL ESTABLISHED MEDICAL USES

ISOTOPE	CHEMICAL FORM	USE
Cesium 137	Encased in Needles and/or Applicator Cells	Interstitial or intracavitary treatment of cancer
Cesium 137	Teletherapy Source	Treatment of cancer
Chromium 51	Chromate	Spleen imaging
Chromium 51	Chromate	Placenta localization [A]
Chromium 51	Chromate	Red blood cell labeling and survival studies
Chromium 51	Labeled Human Serum Albumin	Gastrointestinal protein loss studies
Chromium 51	Labeled Human Serum Albumin	Placenta localization [A]
Chromium 51	Labeled Red Blood Cells	Placenta localization [A]
Cobalt 57, 58 or 60	Labeled Cyanocobalamin	Intestinal absorption studies
Cobalt 60	Teletherapy Source	Treatment of cancer
Cobalt 60	Encased in Needles and/or Applicator Cells	Interstitial or intracavitary treatment of cancer
Gold 198	Colloidal	Liver imaging
Gold 198	Colloidal	Intracavitary treatment of malignant effusions
Gold 198	Colloidal	Interstitial treatment of cancer
Gold 198	Seeds	Interstitial treatment of cancer

ISOTOPE	CHEMICAL FORM	USE
Iodine 131	Iodide	Diagnosis of thyroid function
Iodine 131	Iodide	Thyroid imaging
Iodine 131	Iodide	Treatment of hyperthyroidism and/or cardiac dysfunction
Iodine 131	Iodide	Treatment of thyroid carcinoma
Iodine 131	Iodinated Human Serum Albumin	Blood volume determination
Iodine 131	Iodinated Human Serum Albumin	Brain tumor localization
Iodine 131	Iodinated Human Serum Albumin	Placenta localization [A]
Iodine 131	Iodinated Human Serum Albumin	Cardiac imaging for determination of pericardial effusions
Iodine 131	Iodinated Human Serum Albumin	Cisternography
Iodine 131	Rose Bengal	Liver function studies
Iodine 131	Rose Bengal	Liver imaging
Iodine 131	Iodopyracet, Sodium Iodohippurate Sodium Diatrizoate, Diatrizoate Methyl-glucamine, Sodium Diprotrizoate, Sodium Acetrizoate, or Sodium Iothalamate	Kidney function studies and kidney imaging
Iodine 131	Labeled Fats and/or Fatty Acids	Fat absorption studies
Iodine 131	Chlorografin	Cardiac imaging for determination of pericardial effusions
Iodine 131	Macroaggregated Iodinated Human Serum Albumin	Lung imaging

ISOTOPE	CHEMICAL FORM	USE
Iodine 131	Colloidal Micro-aggregated Human Serum Albumin	Liver imaging
Iodine 125	Iodide	Diagnosis of thyroid function
Iodine 125	Iodinated Human Serum Albumin	Blood volume determination
Iodine 125	Rose Bengal	Liver function studies
Iodine 125	Iodopyracet, Sodium Iodohippurate, Sodium Diatrizoate, Diatrizoate Methyl-glucamine, Sodium Diprotrizoate, Sodium Acetrizoate, or Sodium Iothalamate	Kidney function studies
Iodine 125	Labeled Fats and/or Fatty Acids	Fat absorption studies
Iron 59	Chloride, Citrate and/or Sulfate	Iron turnover studies
Iridium 192	Seeds Encased in Nylon Ribbon	Interstitial treatment of cancer
Krypton 85	Gas	Diagnosis of cardiac abnormalities
Mercury 197	Chlormerodrin	Kidney imaging
Mercury 197	Chlormerodrin	Brain imaging
Mercury 203	Chlormerodrin	Brain imaging
Phosphorus 32	Soluble Phosphate	Treatment of polycythemia vera
Phosphorus 32	Soluble Phosphate	Treatment of leukemia and bone metastasis
Phosphorus 32	Colloidal Chromic Phosphate	Intracavitary treatment of malignant effusions

ISOTOPE	CHEMICAL FORM	USE
Phosphorus 32	Colloidal Chromic Phosphate	Interstitial treatment of cancer
Potassium 42	Chloride	Potassium space studies
Selenium 75	Selenomethionine	Pancreas imaging [B]
Strontium 85	Nitrate or Chloride	Bone imaging on patients with known or suspected cancer
Strontium 90	Medical Applicator	Treatment of superficial eye conditions
Technetium 99m	Pertechnetate	Brain imaging
Technetium 99m	Pertechnetate	Thyroid imaging
Technetium 99m	Pertechnetate	Placenta localization [A]
Technetium 99m	Pertechnetate	Blood pool imaging
Technetium 99m	Pertechnetate	Salivary gland imaging
Technetium 99m	Sulfur Colloid	Liver and Spleen imaging
Technetium 99m	Stannous Polyphosphate	Bone imaging
Technetium 99m	Iron-Ascorbate-Diethylenetriamine Pentaacetic Acid Complex	Kidney imaging
Xenon 133	Free Gas or in solution	Diagnosis of cardiac abnormalities Blood-flow studies Pulmonary function studies
Technetium-99m	DTPA (tin)	Brain imaging Kidney imaging Kidney function studies
Technetium-99m	Human Serum Albumin Microspheres	Lung imaging
Technetium-99m	Aggregated Albumin (Human)	Lung imaging
Technetium 99m	Disodium Etidronate	Bone Imaging
Fluorine 18	Fluoride	Bone Imaging

NOTES

A. Applicant shall confirm that:

1. Test will only be performed in 3rd trimester
2. If the patient is bleeding, and
3. If the obstetrician feels the test is necessary and will be beneficial to the management of the patient.

B. Physician must have been actively engaged in conducting scans for at least six (6) months and have participated in at least three (3) pancreas scans under the supervision of a physician already experienced in this procedure.

ber 20, 1973, make the following changes:

1. In § 101.12, in the group of counties listed in Area I, change "Waulla" to "Wakulla" and add "Escambia".

2. In § 101.13, in the group of counties listed in Area I, add "Stephens" and in the group listed in Area III, add "Glascock".

3. In § 101.25, as follows:

(a) In Area I: change "Montaque" to "Montague", "Beckett" to "Becket" and "Gramby" to "Granby".

(b) In Area II: change "Wichendon" to "Winchendon", "Ashley" to "Ashby", "Harwick" to "Hardwick" and add "Southbridge" and "Warren".

(c) In Area IV: change "Tryngsborough" to "Tyngsborough", "Swamscott" to "Swampscott", "Cohasett" to "Cohassett", "Action" to "Acton" and add "Dracut".

(d) In Area V: change "Abington" to "Abington", "Sudbury" to "Duxbury", "Middleboro" to "Middleborough", "Hardwick" to "Harwich" and add "Norwell" and "Nantuckett".

ATOMIC ENERGY COMMISSION

[10 CFR Part 2]

LICENSING PROCEEDINGS

Proposed Treatment of Proprietary Information; Extension of Time for Comments

On November 15, 1973, the Atomic Energy Commission published in the FEDERAL REGISTER (38 FR 31543) five alternatives it was considering in determining whether further changes should be made in its policy and rules pertaining to disclosure of proprietary information in the area of licensing and regulation. Interested persons were invited to submit comments and suggestions with respect to the five alternatives or other alternatives, together with any other suggestions concerning this matter, by December 31, 1973. In response to a request from Business and Professional People For the Public Interest, the Commission has extended the comment period to February 15, 1974. Copies of comments received may be examined in the Commission's Public Document

and would establish three new groups of medical uses of radioisotopes as follows:

Group III. Use of generators and reagent kits for the preparation and use of radiopharmaceuticals containing byproduct material for certain diagnostic uses.

Group IV. Use of prepared radiopharmaceuticals for certain therapeutic uses, and

Group V. Use of sources and devices containing byproduct material for certain medical uses.

Under this proposed expansion of group licensing, physicians and medical institutions would be licensed to use the byproduct materials for the medical uses designated in one or more of the groups for which the applicant has appropriate facilities, equipment, operating procedures and trained personnel (both physicians and paramedical) to perform the medical procedures and handle the radioisotopes designated in the group or groups.

The groups of licensed uses would be

...ment States. The Chairman of the ...sion, in a letter to the Depart... of Health, Education, and Welfare commenting on their proposal to grant that exemption, expressed the view that eventually an appropriate balance with respect to the regulation of drugs containing byproduct material would involve FDA regulations controlling the pharmaceutical quality of drugs and the safety and efficacy of drugs with respect to the patient, while AEC regulatory controls would govern radiation safety of employees and the public during manufacture and use of the drugs.

The Commission and the FDA are coordinating their respective regulatory programs to provide for a transition from the Commission to the FDA of the regulation of pharmaceutical quality, safety and efficacy of radiopharmaceuticals in such manner as to minimize duplication of regulatory activities, to accomplish the objectives of protecting public health and safety without unduly inhibiting the use of radioactive materials in medicine and to assure no disruption in the supply of these drugs which are of vital importance in many medical applications during the transition period.

On November 3, 1971, the FDA published in the FEDERAL REGISTER (36 FR 21026) a notice of termination, effective December 2, 1971, of the exemption from FDA investigational new drug regulations for AEC and Agreement State regula... radiopharmaceuticals for well e... ed uses and provided for regula... ...y the FDA of such radiopharmaceuticals (21 CFR 130.49—Requirements regarding certain radioactive drugs.) It is expected that the FDA will similarly terminate the exemption for radiopharmaceuticals for investigational uses at an early date.

The groups of uses in § 35.100 would include medical uses of radiopharmaceuticals for which safety and effectiveness have been established and those which are undergoing investigation to establish such safety and effectiveness. For the investigational radiopharmaceuticals and uses included in the licensed groups, a licensee would be required to register with the Commission prior to use of each different type of investigational use to identify the radiopharmaceutical, its intended purpose, and the supplier, and to certify that he would be using the radiopharmaceutical pursuant to a "Notice of Claimed Investigational Exemption for a New Drug" (IND) that has been accepted by the FDA.

The new §§ 32.72 and 32.73 which contain criteria for licensing the distribution of radiopharmaceuticals, and generators and reagent kits for preparation of radiopharmaceuticals, to group-use licensees would require manufacturers to furnish evidence that the radiopharmaceuticals, generators and reagent kits will be manufactured, packaged, and labeled under an effective New Drug Application from FDA, a Biologic Product ... from FDA, or a "Notice of Claimed Investigational Exemption for New Drug" that has been accepted by FDA.

Section 31.11 of 10 CFR Part 31, which provides a general license to physicians, clinical laboratories and hospitals for use of certain radioisotopes for in vitro clinical or laboratory testing, would be amended to add hydrogen 3 (tritium) and iron 59 to the general license. Section 32.71 of 10 CFR Part 32 would be amended to add these isotopes to the provisions for licensing their manufacture and distribution for in vitro use under the general license.

Pursuant to the Atomic Energy Act of 1954, as amended, and section 553 of title 5 of the United States Code, notice is hereby given that adoption of the following amendments to 10 CFR Parts 31, 32, and 35 is contemplated. All interested persons who desire to submit written comments or suggestions for consideration in connection with the proposed amendments should send them to the Secretary of the Commission, U.S. Atomic Energy Commission, Washington, D.C. 20545, Attention: Chief, Public Proceedings Staff, by March 7, 1974. Copies of comments received on the proposed amendments may be examined at the Commission's Public Document room at 1717 H Street NW., Washington, D.C.

1. Section 35.14 of 10 CFR Part 35 is amended to read as follows:

§ 35.14 Specific licenses for certain groups of medical uses of byproduct material.

(a) Subject to the provisions of paragraphs (b), (c), and (d) of this section, an application for a specific license pursuant to § 35.11, § 35.12, or § 35.13 for any medical use or uses of byproduct material specified in one or more of Groups I to V, inclusive, of § 35.100 will be approved for all of the uses within the group or groups which include the use or uses specified in the application if:

(1) The applicant satisfies the requirements of § 35.11, § 35.12, or § 35.13;

(2) The applicant, or the physician designated in the application as the individual user, has adequate clinical experience in the types of uses included in the group or groups;

(3) The applicant or the physicians, technologists, radiological safety personnel and other paramedical personnel who will use the byproduct material have adequate training and experience in the handling of radioactive material appropriate to the uses included in the group or groups;

(4) The applicant's radiation detection and measuring instrumentation is adequate for conducting the procedures involved in the uses included in the group or groups;

(5) The applicant's radiation safety operating procedures are adequate for handling and disposal of the radioactive material involved in the uses included in the group or groups.

(b) Any licensee who is authorized to use byproduct material pursuant to one or more groups in §§ 35.14(a) and 35.100 is subject to the following conditions:

(1) For Groups I, II, and IV, no licensee shall receive, possess, or use byproduct material except as a radiopharmaceutical manufactured in the form to be administered to the patient, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to § 32.72 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State pursuant to equivalent State regulations.

(2) For Group III, no licensee shall receive, possess, or use generators or reagent kits containing byproduct material except generators or reagent kits which are manufactured, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to § 32.73 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State pursuant to equivalent State regulations and no licensee shall use reagent kits which do not contain byproduct material to prepare radiopharmaceuticals containing byproduct material except reagent kits which are approved by the Commission or by an Agreement State for use by persons licensed pursuant to this § 35.14 and Group III of Schedule A, § 35.100, or equivalent Agreement State regulations.

(3) For Group V, no licensee shall receive, possess, or use byproduct material except as contained in a source or device which has been manufactured, labeled, packaged, and distributed in accordance with a specific license issued by the Commission pursuant to § 32.74 of this chapter or in accordance with a specific license issued to the manufacturer by an Agreement State pursuant to equivalent State regulations.

(4) For the investigational uses in §§ 35.100(a) *Group I* (19) (b) *Group II* (25), (c) *Group III* (3), and (d) *Group IV* (9), the licensee shall, prior to the use of each different type of investigational radiopharmaceutical, or generator or reagent kit for the preparation and medical use of investigational radiopharmaceuticals, and prior to use of such investigational ... radiopharmaceutical, generator or reagent kit obtained from each different supplier, file Form AEC-..., "Registration Certificate—Medical Use of Investigational Radiopharmaceutical Under Group License," with the Materials Branch, Directorate of Licensing, U.S. Atomic Energy Commission, Washington, D.C. 20545, and receive from the Commission a validated copy of the Form AEC-... with registration number assigned. The licensee shall furnish on Form AEC-... the following information as may be required by that form:

(i) Name, address and license number of the licensee;

(ii) Name of the radiopharmaceutical, generator, or reagent kit to be used;

(iii) The radionuclide, chemical form, and proposed use of the radiopharmaceutical to be used or prepared and used;

(iv) Name of the manufacturer of the radiopharmaceutical, generator or reagent kit to be used;

(v) Certification that he has in his possession, and will follow, a copy of the plan of investigation outlined in the "No-

tice of Claimed Investigational Exemption for a New Drug" (IND) which has been accepted by the Food and Drug Administration (FDA).

The Commission will not validate a Form AEC-_____ until it has confirmation from FDA that the registrant is an identified investigator in the IND or has otherwise been accepted by FDA as a participant in the investigation.

(5) Any licensee using investigational pharmaceuticals who is required to file Form AEC-_____, "Registration Certificate—Medical Use of Investigational Radiopharmaceutical Under Group License," pursuant to paragraph (b)(4) of this section shall report in duplicate to the Materials Branch any changes in the information furnished by him in the "Registration Certificate—Medical Use of Investigational Radiopharmaceutical Under Group License," Form AEC-_____. The report shall be submitted within 10 days after the effective date of such change.

(6) For Group III, any licensee who uses generators or reagent kits shall follow the instructions for eluting the generator or processing radioactive material with the reagent kit which are approved by the Atomic Energy Commission or an Agreement State and are furnished by the manufacturer on the label attached to or in the leaflet or brochure which accompanies the generator or reagent kit.

(7) For Group IV, any licensee who possesses and uses radiopharmaceuticals for therapy shall assure that patients containing more than 8 millicuries of iodine 131 for the treatment of thyroid carcinoma or patients containing more than 23 millicuries of gold 198 shall be hospitalized.

(8) For Group V, any licensee who possesses and uses sources or devices containing byproduct material shall assure that:

(i) Each source or device containing more than 100 microcuries of byproduct material with a half-life greater than thirty days, except iridium 192 seeds encased in nylon ribbon, shall be tested for contamination and/or leakage at intervals not to exceed six months; and a source or device shall be so tested prior to its first use unless the supplied furnishes a certificate that the source or device has been so tested within six months prior to the transfer;

(ii) The test required by paragraph (b)(8)(i) of this section shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the source or from the surfaces of the device in which the source is permanently or semipermanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Commission;

(iii) If the test required by paragraph (b)(8)(i) of this section reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the source from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the test with the appropriate Atomic Energy Commission Regulatory Operations Regional Office listed in Appendix D of Part 20 of this chapter, describing the equipment involved, the test results, and the corrective action taken;

(iv) The radiation safety and handling instructions approved by the Atomic Energy Commission furnished by the manufacturer on the label attached to the source, device or permanent container thereof, or in the leaflet or brochure which accompanies the source or device, are followed and that such instructions are maintained in a legible and conveniently available form;

(v) A quarterly physical inventory is conducted to account for all sources and devices received and possessed. Records of the inventories shall be maintained for inspection by the Commission and shall include the quantities and kinds of byproduct material, location of sources and devices, and the date of the inventory;

(vi) Needles or standard medical applicator cells containing cobalt 60 as wire shall not be opened by the licensee unless specifically authorized by a condition of a license issued to him by the Atomic Energy Commission;

(vii) Patients containing cobalt 60, cesium 137 and/or iridium 192 implants shall remain hospitalized until the implants are removed.

(c) Any licensee who is licensed pursuant to paragraph (a) of this section for one or more of the medical use groups in § 35.100 also is authorized to use byproduct material under the general license in § 31.11 of this chapter for the specified in vitro uses without filing Form AEC-483 as required by § 31.11(b); *Provided*, That the licensee is subject to the other provisions of § 31.11.

(d) Any licensee who is licensed pursuant to paragraph (a) of this section for one or more of the medical use groups in § 35.100 also is authorized to receive, possess, and use for calibration and reference standards any byproduct material with an atomic number not higher than 83 in amounts not to exceed 15 millicuries total of materials with half lives not longer than seven days and not to exceed 200 microcuries total of materials with half lives longer than seven days.

2. Section 35.100 of 10 CFR Part 35 is amended by changing the title and subtitles, by adding certain new uses to the present paragraphs (a) Group I and (b) Group II, and by adding new paragraphs (c) Group III, (d) Group IV and (e) Group V. The section, as amended, will read as follows:

§ 35.100 Schedule A—Groups of medical uses of byproduct material.

(a) *Group I.* Use of prepared radiopharmaceuticals for certain diagnostic studies involving measurements of uptake, dilution and excretion. This group does not include uses involving imaging and tumor localizations.

(1) Iodine 131 as sodium iodide (NaI^{131}) for measurement of thyroid uptake;

(2) Iodine 125 as sodium iodide (NaI^{125}) for measurement of thyroid uptake;

(3) Iodine 131 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(4) Iodine 125 as iodinated human serum albumin (IHSA) for determinations of blood and blood plasma volume;

(5) Iodine 131 as labeled rose bengal for liver function studies;

(6) Iodine 125 as labeled rose bengal for liver function studies;

(7) Iodine 131 as labeled fats or fatty acids for fat absorption studies;

(8) Iodine 125 as labeled fats or fatty acids for fat absorption studies;

(9) Iodine 131 as labeled iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate for kidney function studies;

(10) Iodine 125 as labeled iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate for kidney function studies;

(11) Cobalt 58 as labeled cyanocobalamin for intestinal absorption studies;

(12) Coblat 60 as labeled cyanocobalamin for intestinal absorption studies;

(13) Chromium 51 as sodium chromate for determinations of red blood cell volume and studies of red blood cell survival time;

(14) Chromium 51 as labeled human serum albumin for gastrointestinal protein loss studies;

(15) Iron 59 as chloride, citrate, or sulfate for iron turnover studies;

(16) Potassium 42 as chloride for potassium space determinations;

(17) Sodium 24 as chloride for sodium space determinations;

(18) Xenon 133 as gas, free or in solution, in prepackaged individual doses only, for blood flow and pulmonary function studies;

(19) Any byproduct material in a radiopharmaceutical and for a diagnostic use involving measurements of uptake, dilution, or excretion for which a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA); *Provided*, That the registration requirements of § 35.14(b)(4) are complied with.

(b) *Group II.* Use of prepared radiopharmaceuticals for diagnostic studies involving imaging and tumor localizations.

(1) Iodine 131 as sodium iodide for thyroid imaging;

(2) Iodine 131 as iodinated human serum albumin (IHSA) for brain tumor localizations and cardiac imaging;

(3) Iodine 131 as iodinated human serum albumin (IHSA) for cisternography;

(4) Iodine 131 as macroaggregated iodinated human serum albumin for lung imaging;

(5) Iodine 131 as colloidal (microaggregated) iodinated human serum albumin for liver imaging;

(6) Iodine 131 as labeled rose bengal for liver imaging;

(7) Iodine 131 as iodopyracet, sodium iodohippurate, sodium diatrizoate, dia- methylglucamine, sodium dipro- or sodium acetrizoate for kidney imaging;

(8) Iodine 131 as sodium iodipamide for cardiac imaging;

(9) Iodine 131 as iodinated human serum albumin (IHSA) for placenta localization;

(10) Chromium 51 as sodium chromate for spleen imaging;

(11) Chromium 51 as labeled human serum albumin for placenta localization;

(12) Gold 198 in colloidal form for liver imaging;

(13) Mercury 197 as labeled chlormerodrin for kidney and brain imaging;

(14) Mercury 203 as labeled chlormerodrin for brain imaging;

(15) Selenium 75 as labeled selenomethionine for pancreas imaging;

(16) Strontium 85 as nitrate or chloride for bone imaging in patients with suspected or diagnosed cancer;

(17) Technetium 99m as pertechnetate for brain imaging;

(18) Technetium 99m as pertechnetate for thyroid imaging;

(19) Technetium 99m as pertechnetate for salivary gland imaging;

(20) Technetium 99m as pertechnetate for blood pool imaging other than placenta localization;

(21) Technetium 99m as pertechnetate for placenta localization;

(22) Technetium 99m as labeled sulfur colloid for liver and spleen imaging;

(echnetium 99m as labeled macba sted human serum albumin for ng imaging;

(24) Xenon 133 as gas, free or in solution, in prepackaged individual doses nly, for heart and lung imaging;

(25) Any byproduct material in a radiopharmaceutical and for a diagnostic se involving imaging for which a "Notice f Claimed Investigational Exemption r a New Drug" (IND) has been acpted by the Food and Drug Administraon (FDA), *Provided*, That the regisation requirements of § 35.14(b)(4) are mplied with.

(c) *Group III.* Use of generators and agent kits for the preparation and use radiopharmaceuticals containing byoduct material for certain diagnostic es.

(1) Molybdenum 99/technetium 99 nerators for the elution of technetium m as pertechnetate for:

(i) Brain imaging;

(ii) Thyroid imaging;

(iii) Salivary gland imaging;

(iv) Blood pool imaging other than cenia localization;

(v) Placenta localization;

(vi) Use with reagent kits for preparan and use of radiopharmaceuticals taining technetium 99m as provide in ragraphs (c)(2) and (2).

2) Reagent kits for preparation of hnetium 99m labeled:

(i) Sulfur colloid for liver and spleen imaging;

(ii) Iron-ascorbate-diethylenetriamine pentaacetic acid complex for kidney imaging;

(iii) Diethylenetriamine pentaacetic acid (Sn) for kidney imaging and kidney function studies;

(iv) Diethylenetriamine pentaacetic acid (Sn) for brain imaging;

(v) Human serum albumin microspheres for lung imaging;

(vi) Polyphosphates for bone imaging;

(vii) Macroaggregated human serum albumin for lung imaging;

(viii) Disodium etidronate for bone imaging.

(3) Any generator or reagent kit for preparation and diagnostic use of radiopharmaceutical containing byproduct material for which generator or reagent kit a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA); *Provided*, That the registration requirements of paragraph 25.14(b)(4) are complied with.

(d) *Group IV.* Use of prepared radiopharmaceuticals for certain therapeutic uses.

(1) Gold 198 as colloid for intracavitary therapy of malignant effusions;

(2) Gold 198 as colloid for interstitial therapy of cancer;

(3) Iodine 131 as iodide for therapy of hyperthyroidism and angina pectoris;

(4) Iodine 131 as iodide for therapy of thyroid carcinoma;

(5) Phosphorus 32 as soluble phosphate for therapy of polycythemia vera;

(6) Phosphorus 32 as soluble phosphate for therapy of leukemia and bone metastases;

(7) Phosphorus 32 as colloidal chromic phosphate for intracavitary therapy of malignant effusions;

(8) Phosphorus 32 as colloidal chromic phosphate for interstitial therapy of cancer;

(9) Any byproduct material in a radiopharmaceutical and for a therapeutic use for which a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been accepted by the Food and Drug Administration (FDA); *Provided*, That the registration requirements of § 35.14(b)(4) are complied with.

(e) *Group V.* Use of sources and devices containing byproduct material for certain medical uses.

(1) Americium 241 as a sealed source in a device for bone mineral analysis;

(2) Cesium 137 encased in needles and applicator cells for topical, interstitial, and intracavitary therapy of cancer;

(3) Cobalt 60 encased in needles and applicator cells for topical, interstitial, and intracavitary therapy of cancer;

(4) Gold 198 as seeds for interstitial therapy of cancer;

(5) Iodine 125 as a sealed source in a device for bone mineral analysis;

(6) Iridium 192 as seeds encased in nylon ribbon for interstitial therapy of cancer;

(7) Strontium 90 sealed in an applicator for therapy of superficial eye conditions.

3. Section 31.11 of 10 CFR Part 31 is amended by adding new paragraphs (a)(4) and (5), by amending the first sentence of paragraph (b), and by amending paragraphs (c)(1) and (d)(1), to read as follows:

§ 31.11 General license for use of byproduct material for certain in vitro clinical or laboratory testing.

(a) A general license is hereby issued to any physician, clinical laboratory or hospital to receive, acquire, possess, transfer, or use, for any of the following stated tests, in accordance with the provisions of paragraphs (b), (c), (d), (e), and (f) of this section, the following byproduct materials in prepackaged units:

* * * * *

(4) Hydrogen 3 (tritium), in units not exceeding 50 microcuries each for use in in vitro clinical or laboratory tests not involving internal or external administration of byproduct material, or the radiation therefrom, to human beings or animals.

(5) Iron 59, in units not exceeding 20 microcuries each for use in in vitro clinical or laboratory tests not involving internal or external administration of byproduct material, or the radiation therefrom, to human beings or animals.

(b) No person shall receive, acquire, possess, use, or transfer byproduct material pursuant to the general license established by paragraph (a) of this section until he has filed Form AEC-483, "Registration Certificate—In Vitro Testing with Byproduct Material Under General License", with the Materials Branch, Directorate of Licensing, U.S. Atomic Energy Commission, Washington, D.C. 20545, and received from the Commission a validated copy of Form AEC-483 with registration number assigned or until he has been authorized pursuant to § 35.14(c) of this chapter to use byproduct material under the general license in this § 31.11. * * *

(c) A person who receives, acquires, possesses, or uses byproduct material pursuant to the general license established by paragraph (a) of this section shall comply with the following: (1) The general licensee shall not possess at any one time, pursuant to the general license in paragraph (a) of this section, at any one location of storage or use a total amount of iodine 125, iodine 131, and/or iron 59 in excess of 200 microcuries.

* * * * *

(d) The general licensee shall not receive, acquire, possess, or use byproduct material pursuant to paragraph (a) of this section:

(1) Except as prepackaged units which are labeled in accordance with the provisions of a specific license issued under the provisions of § 32.71 of this chapter or in accordance with the provisions of a specific license issued by an Agreement State, which authorizes manufacture and distribution of iodine-125, iodine-131, carbon-14,[1] hydrogen-3 (trit-

[1] See Notice of Rule Making, 38 FR 34119, December 11, 1973.

ium), or iron-59 for distribution to persons generally licensed by the Agreement State.

* * * * * *

4. Section 32.71 of 10 CFR Part 32 is amended by adding new paragraphs (b) (4) and (5) and by amending paragraph (c) (1) to read as follows:

§ 32.71 Manufacture and distribution of byproduct materials for certain in vitro clinical or laboratory testing under general license.

An application for a specific license to manufacture or distribute byproduct material for use under the general license of § 31.11 of this chapter will be approved if:

* * * * * *

(b) The byproduct material is to be prepared for distribution in prepackaged units of:

* * * * * *

(4) Hydrogen 3 (tritium) in units not exceeding 50 microcuries each;

(5) Iron 59 in units not exceeding 20 microcuries each.

* * * * * *

(c) Each prepackaged unit bears a durable, clearly visible label:

(1) Identifying the radioactive contents as to chemical form and radionuclide, and indicating that the amount of radioactivity does not exceed 10 microcuries of iodine 131, iodine 125, or carbon 14;[1] 50 microcuries of hydrogen 3 (tritium); or 20 microcuries of iron 59; and

* * * * * *

5. A new § 32.72 is added to 10 CFR Part 32 to read:

§ 32.72 Manufacture and distribution of radiopharmaceuticals containing byproduct material for medical use under group licenses.

An application for a specific license to manufacture and distribute radiopharmaceuticals containing byproduct material for use by persons licensed pursuant to § 35.14 of this chapter for the uses listed in Group I, Group II or Group IV of Schedule A, § 35.100 of this chapter will be approved if:

(a) The applicant satisfies the general requirements specified in § 30.33 of this chapter;

(b) The applicant submits evidence that the radiopharmaceutical containing byproduct material will be manufactured, labeled, and packed in accordance with

(1) An effective new drug application (NDA) or a Biologic Product License from the Food and Drug Administration (FDA); or

(2) A "Notice of Claimed Investigational Exemption for a New Drug (IND) that has been accepted by the FDA;

(c) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byproduct material which is appropriate for safe handling and storage of the radiopharmaceuticals by group licensees; and

(d) (1) The label affixed to each package of the radiopharmaceutical contains information on the radionuclide, quantity, and date of assay and the label affixed to each package, or the leaflet or brochure which accompanies each package, contains a statement that the radiopharmaceutical is licensed by the U.S. Atomic Energy Commission for distribution to persons licensed pursuant to § 35.14 and § 35.100 Group I, Group II, or Group IV of 10 CFR Part 35, as appropriate, or under equivalent licenses of Agreement States;

(2) The labels, leaflets or brochures required by this paragraph are in addition to the labeling required by the Food and Drug Administration (FDA) and they may be separate from or, with the approval of FDA, may be combined with the labeling required by FDA.

6. A new § 32.73 is added to 10 CFR Part 32 to read:

§ 32.73 Manufacture and distribution of generators or reagent kits for preparation of radiopharmaceuticals containing byproduct material.

An application for a specific license to manufacture and distribute generators or reagent kits containing byproduct material for preparation of radiopharmaceuticals by persons licensed pursuant to § 35.14 of this chapter for the uses listed in Group III of Schedule A, § 35.100 of this chapter will be approved if: (See Note 1)

(a) The applicant satisfies the general requirements specified in § 30.33 of this chapter;

(b) The applicant submits evidence that the generator or reagent kit is to be manufactured, labeled and packaged in accordance with

(1) An effective New Drug Application (NDA) or a Biologic Product License from the Food and Drug Administration (FDA), or

(2) A "Notice of Claimed Investigational Exemption for a New Drug (IND)" that has been accepted by the FDA;

(c) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byproduct material contained in the generator or reagent kit;

(d) The label affixed to the generator or reagent kit contains information on the radionuclide, quantity, and date of assay; and

(e) The label affixed to the generator or reagent kit, or the leaflet or brochure which accompanies the generator or reagent kit, contains:

(1) Adequate information, from a radiation safety standpoint, on the procedures to be followed and the equipment and shielding to be used in eluting the generator or processing radioactive material with the reagent kit, and

(2) A statement that this generator or reagent kit (as appropriate) is approved for use by persons licensed by the U.S. Atomic Energy Commission pursuant to §§ 35.14 and 35.100 Group III of 10 CFR Part 35 or under equivalen licenses of Agreement States.

The labels, leaflets or brochures re quired by this paragraph are in addition to the labeling required by FDA and they may be separate from or, with the approval of FDA may be combined with the labeling required by FDA.

Note 1. Although the Commission does no regulate the manufacture and distribution of reagent kits which do not contain byprod uct material it does regulate the use of such reagent kits for the preparation of radio pharmaceuticals containing byproduct mate rial as part of its licensing and regulation of the users of the byproduct material. An manufacturer of reagent kits which do no contain byproduct material who desires t have his reagent kits approved by the Com mission for use by persons licensed pursu ant to § 35.14 and Group III of Schedule A § 35.100 of this chapter may submit the per tinent information specified in this § 32.7

7. A new § 32.74 is added to 10 CF Part 32 to read:

§ 32.74 Manufacture and distribution o sources or devices containing by product material for medical use.

An application for a specific license t manufacture and distribute sources an devices containing byproduct material t persons licensed pursuant to § 35.14 this chapter for the uses listed in Grou V of Schedule A, § 35.100 of this chapt will be approved if:

(a) The applicant satisfies the ger eral requirements in § 30.33 of this cha ter;

(b) The applicant submits sufficie information regarding each type source or device pertinent to an evalu tion of its radiation safety, including:

(1) The byproduct material contained its chemical and physical form, a amount;

(2) Details of design and constructio of the source or device;

(3) Procedures for, and results of, pr totype tests to assure that the source device will maintain its integrity und stresses likely to be encountered in no mal use and accidents;

(4) For devices containing byprodu material, the radiation profile of a pr totype device;

(5) Details of quality control pr cedures to assure that production sourc and devices meet the standards of t design and prototype tests;

(6) Procedures and standards for ca brating sources and devices;

(7) Legend and methods for labeli sources and devices as to their radioa tive content;

(8) Instructions for handling and st ing the source or device from the rad tion safety standpoint; these instructio are to be included on a durable label tached to the source or device or attach to a permanent storage container for t source or device: *Provided*, That instr tions which are too lengthy for such la may be summarized on the label a printed in detail on a brochure wh is referenced on the label;

(c) The label affixed to the source device, or to the permanent storage c tainer for the source or device, conta information on the radionuclide, qu

[1] See Notice of Rule Making, 38 FR 34110, December 11, 1973.

...and date of assay, and a statement ...the (name of source or device) is li-...sed by the U.S. Atomic Energy Com-...ission for distribution to persons li-...ursuant to §§ 35.14 and 35.100 ... of 10 CFR Part 35 or under ...ment licenses of Agreement States; ...rovided, That such labeling for sources ...hich do not require long term storage ...g. gold 198 seeds) may be on a leaflet ... brochure which accompanies the ...ources.

...ec. 81, 161, 182, 183, Pub. L. 83-703, 68 Stat. ...5, 948, 953, 954, as amended (42 U.S.C. 2111, ...2, 2232, 2233))

Dated at Germantown, Md. this 15th ...ay of January 1974.

For the Atomic Energy Commission.

GORDON M. GRANT,
Acting Secretary of the Commission.

[FR Doc.74-1678 Filed 1-18-74;8:45 am]

ENVIRONMENTAL PROTECTION AGENCY

[40 CFR Part 429]

TIMBER PRODUCTS

Proposed Effluent Guidelines and Performance and Pretreatment Standards for New Sources

Correction

In FR Doc. 74-3 appearing at page 938 in the issue of Thursday, January 3, 1974, the material appearing after § 429.-85 and entitled "Criteria for Identification of the Best Practicable Control Technology Currently Available the Best Available Technology Economically Achievable and for New Sources the Best Available Demonstrated Control Technology for Classes and Categories of Point Sources" was inadvertently printed in the FEDERAL REGISTER. It is not a part of the text of the proposed rule and should not be considered as such for purposes of public comment.

Administration, Room 5221, 400 Seventh Street S.W., Washington, DC 20590. It is requested but not required that 10 copies be submitted.

All comments received before the close of business on the comment closing date indicated below will be considered and will be available for examination in the docket at the above address both before and after that closing date. To the extent possible, comments filed after the comment closing date will also be considered by the Administration. However, the rule making action may proceed at any time after that date, and comments received after the closing date and too late for consideration in regard to the action will be treated as suggestions for future rule making. The Administration will consider the relevant material, as it becomes available, in the docket after the closing date, and it is recommended that interested persons continue to examine the docket for new material.

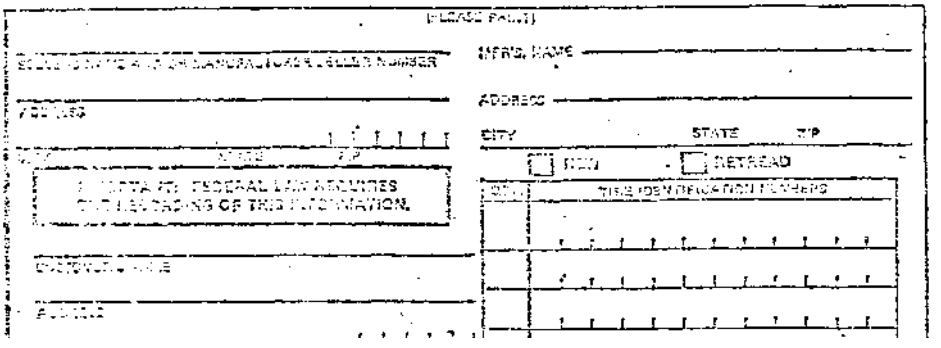
Comment closing date: May 4, 1973.

Proposed effective date: Six months after issuance of the final rule.

This notice of proposed rule making is issued under the authority of sections 103, 112, 113, 119, and 201 of the National Traffic and Motor Vehicle Safety Act, Public Law 89-563, 80 Stat. 718, 15 U.S.C. 1392, 1401, 1402, 1407, and 1421, and the delegations of authority at 49 CFR 1.51 and 49 CFR 501.8.

Issued on March 1, 1973.

ROBERT L. CARTER,
Associate Administrator,
Motor Vehicle Programs.



physician named on the license may obtain basic and clinical radiation safety training and experience to enable them to qualify as authorized users.

3. "A. Byproduct material shall be used by, or under the supervision of, individuals designated by the radiation safety committee.

"B. The use of byproduct material in or on humans shall be by a physician." This condition is used in licenses issued to medical institutions—usually medical schools—whose isotopes committees have set up appropriate administrative procedures, and training and experience criteria, for the committee to approve individual users. This condition also allows other physicians to obtain training and experience under the supervision of a physician designated by the committee as an authorized user.

It is recognized by the Commission that physicians utilize technicians and other paramedical personnel to perform some of the activities and manipulations involved in the medical uses of radioisotopes. In such instances, the physician is still considered to be the user of the radioisotopes. The Commission has developed with the assistance of its Advisory Committee on the Medical Uses of Isotopes a list of responsibilities which shall not be delegated by authorized physician users of radioisotopes—except to other physicians who are under the

intentional medical exposure. Although incidents involving medical exposures have not been required to be reported, 12 instances of misadministrations of radioactive materials involving 20 patients have been brought to the Commission's attention. Since these incidents have generally involved accidental or erroneous exposures of patients to radiation in amounts or forms other than intended, it does not appear appropriate to continue the past practice of not requiring reports of such misadministrations of radioactive materials to medical patients. The proposed new paragraphs (a) and (c) of § 35.33 would require licensees to report misadministrations of radiopharmaceuticals or radiation from byproduct material sources to the Commission. Paragraph (b) of § 35.33 would also require a notification to the patient or to a responsible relative of the patient of a misadministration which would cause a demonstrably adverse effect on the patient unless in the physician's professional judgment such notification would be contrary to the best interests of the patient or a surviving relative of the patient. (In accordance with the Freedom of Information Act and 10 CFR Part 9 of the Commission's rules and regulations, copies of reports filed under these proposed rules, except for any details which would identify the patient, will be available for public inspection.)

Pursuant to the Atomic Energy Act of 1954, as amended, and section 553 of title 5 of the United States Code, notice is hereby given that adoption of the following amendments to 10 CFR Part 35 is contemplated. All interested persons who desire to submit written comments or suggestions for consideration in connection with the proposed amendments should send them to the Secretary of the Commission, U.S. Atomic Energy Commission, Washington, D.C., 20545, Attention: Chief, Public Proceedings Staff by April 23, 1973. Copies of comments on the proposed amendments may be examined at the Commission's Public Document Room at 1717 H Street NW., Washington, DC.

1. The title of 10 CFR Part 35 is amended to read as follows: "Medical uses of radioisotopes (byproduct material)."

2. A new § 35.32 is added to 10 CFR Part 35 to read as follows:

§ 35.32 Conditions of licenses for medical uses of radioisotopes.

(a) The user of radioisotopes in or applied to humans for diagnostic, therapeutic, or investigational purposes shall be a physician authorized by a condition of a general license or a specific license, including a specific license of broad scope, issued by the Commission (authorized physician).

(b) No authorized physician may delegate to persons who are not physicians under the supervision of the authorized physician, the following:

(1) The approval of procedures involving the administration to patients of radiopharmaceuticals or the application to patients of radiation from radioisotope sources,

(2) The prescription of the radiopharmaceutical or source of radiation and the dose or exposure to be administered,

(3) The determination of the route of administration,

(4) The interpretation of the results of diagnostic procedures in which radiopharmaceuticals are administered.

(c) Subject to the provisions of paragraphs (b), (d), (e), (f), and (g) of this section, an authorized physician may permit technicians and other paramedical personnel to perform the following activities:

(1) Preparation and quality control testing of radiopharmaceuticals and sources of radiation,

(2) Measurement of radiopharmaceutical doses prior to administration,

(3) Use of appropriate instrumentation for the collection of data to be used by the physician,

(4) Administration of radiopharmaceuticals and radiation from radioisotope sources to patients, within limits otherwise permitted under applicable Federal, State or local laws.

(d) Authorized physicians who permit activities to be performed by technicians and other paramedical personnel pursuant to paragraph (c) of this section shall:

(1) Prior to such permission, determine that such technicians and other paramedical personnel have been properly trained to perform their duties. This training shall include training in the following subjects, as applicable to the duties assigned:

(i) General characteristics of radiation and radioactive materials.

(ii) Physical, chemical, and pharmaceutical characteristics of each radiopharmaceutical to be used.

(iii) Mathematics and calculations basic to the use and measurement of radioactivity, including units of quantity of radioactivity (curies, millicuries, microcuries) and units of radiation dose and radiation exposure.

(iv) Use of radiation instrumentation for measurements and monitoring including operating procedures, calibration of instruments, and limitations of instruments.

(v) Principles and practices of radiation protection.

(vi) Additional training in the above subjects, as appropriate, when new duties are added.

(2) Assure that such technicians and other paramedical personnel receive appropriate retraining in the subjects listed in paragraph (d)(1) of this section to maintain proficiency and to keep abreast of developments in the field of nuclear medical technology.

(3) Keep records showing the bases for such determinations of proper training, and

(4) Retain responsibility as licensee or authorized user for the satisfactory performance of such activities.

(e) Certification in nuclear medicine technology by the American Registry of Radiologic Technologists or in nuclear medical technology by the Registry of Medical Technologists of the American Society of Clinical Pathologists will be deemed to satisfy the training requirements of paragraph (d) (1) and (2) of this section.

(f) An applicant for a license or for amendment or renewal of a license shall state whether he desires to permit technicians or other paramedical personnel to perform activities pursuant to paragraph (c) of this section and, if so, shall include in his application for license, license amendment, or license renewal a statement of the activities to be performed and a description of an adequate program for training (including retraining as required to keep abreast of developments in technology) such personnel or for otherwise determining that such personnel are properly trained to perform their duties. With respect to licenses in effect on (effective date of rule), a licensee who is permitting or who desires to permit technicians or other paramedical personnel to perform activities pursuant to paragraph (c) of this section shall file the information required by this paragraph with the Director of Licensing, U.S. Atomic Energy Commission, Washington, D.C. 20545, with his next application for amendment or renewal of the license or within 1 year of effective date of rules, whichever occurs first.

(g) Whenever a technician or other paramedical person administers a radiopharmaceutical to a patient by injection, a physician (not necessarily a physician authorized by the Commission to be a user of radioisotopes) shall be immediately accessible.

3. A new § 35.33 is added to 10 CFR Part 35 to read as follows:

§ 35.33 Notifications and reports of misadministrations.

(a) Each licensee shall notify the Director of the appropriate Atomic Energy Commission Regulatory Operations Regional Office listed in Appendix D of 10 CFR Part 20 of the Commission's regulations by telephone and telegraph of any misadministration of radiopharmaceuticals or any misadministration of radiation from teletherapy and brachytherapy sources. This notification shall be made within 24 hours after such misadministration is known. For the purpose of the requirements of this section, misadministration is defined to include the administration of:

(1) A radiopharmaceutical, or radiation from a source other than the one intended,

(2) A radiopharmaceutical or radiation to the wrong patient, or

(3) A dose of a radiopharmaceutical, or [illegible] by the physician or by a route of administration other than that intended by the physician. *

(b) (1) Whenever a misadministration of a radiopharmaceutical or radiation from a teletherapy or brachytherapy

source could cause a demonstrably adverse effect on the patient to whom it was administered, the licensee or the authorized physician shall promptly notify the patient or a responsible relative of the patient of the misadministration unless in the physician's professional judgment such notification would be contrary to the best interests of the patient or a surviving relative of the patient.

(2) If death occurs after a judgment is made by the physician that notification to the patient or a responsible relative of the patient of the misadministration would be contrary to the best interests of the patient and the misadministration may have been a contributory cause of the death, the licensee or the authorized physician shall notify a responsible relative of the patient of the misadministration unless the physician makes an additional determination that such notification would be contrary to the best interests of a surviving relative of the patient.

(c) In addition to the notification required by paragraph (a) of this section, each licensee shall make a report in writing within 10 days to the Director of Regulatory Operations, U.S. Atomic Energy Commission, Washington, D.C. 20545, with a copy to the Director of the appropriate Regulatory Operations Regional Office specified in Appendix D of 10 CFR Part 20, of each misadministration. The report required under this paragraph need not include the name of the patient but shall describe the nature, extent and cause of the misadministration and the corrective steps taken or planned to assure against a recurrence. If the misadministration could cause a demonstrably adverse effect on the patient or if death occurs and the misadministration may have been a contributory cause of the death, the report shall either confirm that the patient or a responsible relative of the patient has been notified of the misadministration as required by paragraph (c) (1) and (2) of this section or shall state that notification was not given because in the physician's judgment such notification would be contrary to the best interests of the patient or a surviving relative of the patient. If the patient or relative is not notified, the physician shall confirm that this decision was reviewed by a local Ethics Committee or an equivalent group of peers and shall state whether or not the committee or group concurred with the decision.

(d) Any notification or report filed with the Commission pursuant to paragraphs (a) and (c) of this section shall be prepared so that any details which would identify the patient will be stated in a separate part of the notification or report.

(Secs. 81, 161, 68 Stat. 935, 948, as amended; 42 U.S.C. 2111, 2201)

Dated at Washington, D.C., this 28th day of February 1973.

For the Atomic Energy Commission.

PAUL C. BENDER,
Secretary of the Commission.

[FR Doc.73-4456 Filed 3-8-73;8:45 am]

FEDERAL POWER COMMISSION

[18 CFR Part 2]

[Docket No. R-478; Order 415-C]

APPLICANTS' ENVIRONMENTAL REPORTS

Proposed Preparation Guidelines

MARCH 2, 1973.

Pursuant to 5 U.S.C. 553, the Commission gives notice it proposes to amend Part 2 of its general rules by adding guidelines for preparation of applicants' environmental reports pursuant to Order No. 415-C. On December 18, 1972, the Commission issued Order No. 415-C (37 FR 28412, Dec. 23, 1972), further prescribing regulations for the implementation of the National Environmental Policy Act of 1969 (83 Stat. 852) (NEPA), and amending §§ 2.80, 2.81 and 2.82 of the general rules (18 CFR 2.80-2.82), § 4.41 of the regulations under the Federal Power Act (18 CFR 4.41), and §§ 157.7 and 157.14(a) of the regulations under the Natural Gas Act (18 CFR 157.7 and 157.14(a)).

The current energy situation has spotlighted the need for speedy and creative solution of environmental problems in the sectors of the energy industry regulated by the Federal Power Commission. The Commission wishes to provide as much guidance as possible to those filing applications under the procedures promulgated in Order No. 415-C. These guidelines are proposed to be added in the form of Appendices to Part 2 of Title 18 CFR to supplement §§ 2.81(a) and 2.82(a). Amendments are also proposed for §§ 2.81(a) and 2.82(a) in order to add the appropriate cross references to the new guidelines.

The guidelines seek to identify information to be supplied by applicants, to provide a basis for the preparation of an environmental report prepared pursuant to §§ 2.81(a) and 2.82(a) of the Commission Regulations, and to provide an insight into the scope of environmental reports required to assure a balanced interdisciplinary analysis of actions significantly affecting the quality of the human environment. The guidelines will also assist the Commission's staff in assessing deficiencies in applicant's environmental reports in cases which involve major Federal actions.

Any interested person may submit to the Federal Power Commission, Washington, D.C. 20426 not later than April 12, 1973, data, views, comments, or suggestions in writing concerning all or part of the amendments proposed herein. Written submittals will be placed in the Commission's public files and will be available for public inspection at the Commission's Office of Public Information, Washington, D.C. 20426, during regular business hours. An original and 14 conformed copies should be filed with the Secretary of the Commission. Submittals to the Commission should indicate the name, title, mailing address, and telephone number of the person to whom communications concerning the proposal should be addressed, and whether the person filing them requests a conference at the Federal Power Commission to discuss the proposed revision. The Commission will consider all such written submittals and responses before issuing an order in this proceeding. The staff, in its discretion, may grant or deny requests for conference.

The proposed amendments to Part 2 of the Commission's general rules would be issued under the authority granted the Federal Power Commission under the Federal Power Act, particularly sections 4, 10, 15, 307, 309, 311, and 312 (41 Stat. 1065, 1066, 1068, 1070; 46 Stat. 798; 49 Stat. 839, 840, 841, 842, 843, 844, 856, 857, 858, 859, 860; 61 Stat. 501; 62 Stat. 614; 16 U.S.C. 797, 803, 808, 825f, 825h, 825j, 825k), and the Natural Gas Act, particularly sections 7 and 16 (52 Stat. 824, 825, 830; 56 Stat. 83, 84; 61 Stat. 459; 15 U.S.C. 717f, 717o), and the National Environmental Policy Act of 1969, Public Law 91-190, approved January 1, 1970, particularly sections 102 and 103 (83 Stat. 853, 854).

Accordingly, it is proposed to amend Part 2, General Policy and Interpretations in Subchapter A—General Rules, Chapter 1, Title 18 of the Code of Federal Regulations as follows:

(1) Amend § 2.81(a) so that it will read:

§ 2.81 Compliance with the National Environmental Policy Act of 1969 under Part I of the Federal Power Act.

(a) All applications for major projects (those in excess of 2,000 horsepower) or for reservoirs only providing regulatory flow to downstream (major) hydroelectric projects under Part I of the Federal Power Act for license or relicense, shall be accompanied by exhibit W, the applicant's detailed report of environmental factors specified in §§ 2.80, 4.41, and Appendix A of Part 2 of this chapter. All applications for surrender or amendment of a license proposing construction, or operating change of a project shall be accompanied by the applicant's detailed report of environmental factors specified in § 2.80 and Appendix A. Notice of all such applications shall continue to be made as prescribed by law.

* * * * *

(2) Amend § 2.82(a) so that it will read:

§ 2.82 Compliance with the National Environmental Policy Act of 1969 under the Natural Gas Act.

(a) All certificate applications filed under section 7(c) of the Natural Gas Act (15 U.S.C. 717f(c)) for construction of pipeline facilities, except abbreviated applications filed pursuant to § 157.7(b), (c), and (d) of this chapter and producer applications for the sale of gas filed pursuant to §§ 157.23-20 of this chapter, shall be accompanied by the applicant's detailed report of the environmental factors specified in § 2.80 and Appendix B. Notice of all such applications shall continue to be made as prescribed by law.

* * * * *

(3) Append to 18 CFR Part 2 Guidelines for Preparation of Environmental Reports as follows:

1080067

PROPOSAL – VOLUNTEERS

MEMO ROUTE SLIP Form AEC-318 (Rev. May 1948) AECM 0240	See me about this. Note and return	For concurrence. For signature.	For action. For your information.
TO (Name and unit) SHOWN LISTED BELOW	INITIALS / DATE	REMARKS Enclosed is a draft copy of a proposed radiation exposure standard covering volunteers for human experimentation. This document was prepared by the Health Protection Branch, ORO. Your comments on the text, concept, feasibility, etc., of the proposed standard will be appreciated. Comments can be directed to either Richard Smith or Robert Poe, extension 3-4113, by August 24, 1973.	
TO (Name and unit)	INITIALS / DATE	REMARKS	
TO (Name and unit) ORIGINAL SIGNED BY WILEY A. JOHNSON	INITIALS / DATE	REMARKS	
FROM (Name and unit) Wiley A. Johnson, Chief Health Protection Branch Safety & Environmental Control Division OSH:RWP		REMARKS	
PHONE NO. 3-4113	DATE 8-20-73		

USE OTHER SIDE FOR ADDITIONAL REMARKS

ADDRESSEES:
G. A. Andrews, ORAU
Roger Cloutier, ORAU
K. D. McCasland, OCC
W. D. Clary, OCC
R. E. Benson, R&TS

1080068

Recommended Radiation Exposure Standard for Human Volunteers

The health protection programs developed by the AEC have not taken into account activities of groups or institutions engaged in human experimentation and the radiation exposures received by individuals participating in these experiments. Radiation standard setting bodies (ICRP, NCRP, EPA) have not established any standards that would regulate medical exposures and likewise have established no standards to regulate exposures received during the development of medical procedures when the exposure is of no medical benefit to the individual. Individuals who participate in these experiments are considered to be "patients" and their radiation exposure information has been treated as medical data and thus considered proprietary information which complicates its review, assessment, and integration into an individual's occupational exposure history.

The Department of Health Education and Welfare has established guidelines to be followed by institutions or individuals receiving HEW support for human experimentation. These guidelines are set forth in The Institutional Guide to DHEW Policy on Protection of Human Subjects. Recently, the AEC adopted this guide as a Commission policy. This guide identified several potential problem areas to be considered when conducting human experimentation, radiation included, but no specific guidance is given for solving any of the identified problems. The AEC requires each contractor, performing human experimentation, to establish a human-use committee of individuals not associated with the experimentation in accordance with the DHEW guidelines. These committees have the authority to approve or disapprove an experiment after considering the moral, ethical, scientific, procedural, and safety implications of the project. The AEC reviews the projects programmatically to determine its acceptance for continued support.

Individuals who participate in human experimentation can be divided into two groups (1) individuals who will receive medical benefit (patients) from their participation in the experiment, and (2) individuals (volunteer human subjects) who will receive no medical benefit but receive some monetary gratuity. It is the latter group which is of concern here. There is, of course, overlap between these two groups. For example, patients undergoing experimental treatment may also act as a volunteer human subject in another experiment and may receive the medical treatment free for their participation.

A literature search for the year 1972 and first quarter 1973 revealed several, not necessarily all, published reports on experiments involving volunteer human subjects which were supported totally or in part by the AEC. These experiments involved, generally, metabolic studies, fetal uptake studies, and organ irradiations. The radiation doses received by the volunteer human subjects range from a few millirem in the metabolic studies up to 600 R in the studies involving the organ irradiation.

A total of 355 volunteer human subjects were identified in five of the eight experiments listed in Table 1. Organ irradiation of prisoners' gonads accounted for 283 volunteers over a nine-year period, and the other 72 participated in the metabolic and fetal uptake studies. These experiments were found to involve all age groups from the unborn child to the 80-year-old adult. In addition to the radiation exposure, it is important to point out that the prisoners volunteering for the gonadal experiments were required to agree beforehand to a vasectomy upon completion of their participation. This brief summary and a realization of the associated legal, moral, ethical, and possible public opinion problems show a definite need for more control in the area of human experimentation.

As the AEC has been actively involved in human experimentation and will probably continue to be, the following recommendations and enclosed draft standard are offered as a starting point on which to build a health protection program for volunteer human subjects, and establish a Commission policy for allowable radiation exposure limits. First, the occupational exposure limit as the maximum allowable exposure should be adopted unless justification is given and concurred in by the enforcing agency for exceeding these limits. The basic justification for adoption of occupational limits is the same as that used to justify the limits themselves. The damage risk at this level of exposure is acceptable. Additionally, the contractor should supply the same radiation exposure information for volunteer human subjects as is supplied for employees and be subject to the accident reporting requirements.

Secondly, the standard health and safety clause should be inserted in all contracts with the AEC which involve human experimentation. Much of the human experimentation being done is carried out under AEC contracts with no health and safety clause. The inclusion of a health and safety clause in these contracts along with the establishment of exposure standards would allow AEC more control than it now has over the safety of volunteer human subjects.

Thirdly, all contractors to the AEC involved in human experimentation should receive a periodic health protection review. This review would have the effect of enforcing the health and safety clause of the contract in that records and other matters related to health protection would be appraised. Recommendations for the improvement of safety programs would be made and enforced. These reviews would be the subject of a report to the contract administrator.

These recommendations are practicable. They would bring uniformity of allowable exposure risk and provide guidance to the committees of the various institutions as to what the AEC feels is an acceptable risk. In addition, the Commission would be better able to carry out its safety responsibilities and help maintain exposures at a low level. In addition, reports of misadministrations and unexpected exposure problems would be of benefit to both the AEC and other investigators involved in human experimentation.

The concept of exposure standards for volunteer human subjects is not new. In 1966 two papers were given on the subject at different professional meetings.[1,2] One paper suggested that volunteer human subjects be exposed to no more radiation than allowed the general population. The other paper described a standard in effect at Idaho which utilizes, with one exception, occupational exposure limits. This exception reduces the allowable exposure to body organs, with the exception of the thyroid, to the levels allowed for the whole body.

The problems associated with human experimentation are many. This report has not attempted to address problems dealing with informed consent, or any of the many legal problems. This report has attempted to show the need for a Commission policy for human experimentation, and has offered a position for consideration.

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1 LeRoy, G. V. "Guidelines for Safe Use of Radiopharmaceuticals" AEC Symposium Series 6, Radioactive Pharmaceuticals, April 1966, pp 669-677.

2 Sill, C. W. "Some Guidelines for Studies Involving Internal Administration of Radioactive Materials to Human Volunteers" Proceedings of 12th Annual Bioassay and Analytical Chemistry Meeting, October 1966, Conf. 661018 Biology and Medicine (TID-4500).

TABLE I

AEC SUPPORTED HUMAN RESEARCH FOUND IN CURSORY LITERATURE SEARCH AND ORO ADMINISTERED CONTRACTS

Lathrop, Katherine A. "Radiation Dose to Humans from ^{75}Se-L-Selfe-Nomethianine," J. Nuel. Med. Suppl. 13, No. 6, April 1972.

Heller, Carl G. "Effects of Ionizing Radiation on the Testicular Function of Man," Report AT-(45-1)-1780, May 1972. 5 patients

Thorslund, T. W. "Effects of X-Ray Irradiation on Human Spermatogenesis" Report (NASA-TM-X-2440), January 1972.

Spencer, H., Hardy, E., et al "Strontium-90 Calcium Interrelationships in Man," Health Physics, Vol. 24, pp 525-533, May 1973.

Cohn, S. H., et al, "Absolute Measurement of Whole Body Potassium by Gamma-Ray Spectrometry" Journal of Nuclear Medicine, Volume 11, No. 6, pp 239-246, 1970.

Lloyd, R. D., et al "^{83}Rb and ^{137}Cs, Metabolism in Persons Effected by Muscle Disease," Report 12381 (CON-119-247), October 1972.

Dyer, N. C. "Human Fetal Radiation Dose from ^{59}Fe Administered to the Mother during Pregnancy" Dissertation Vanderbilt University, May 1972, prepared under Contract AT-(40-1)-2401.

Artey, S. R., et al "Radiation Dose to Infants from ^{75}Se-l-Selenomethionine" Annual Report on the Contract AT-(40-1)-3734, October 5, 1972.

PROPOSED STANDARD

Policy

Radiation protection standards applicable to AEC and AEC contractor operations shall be established to protect volunteer human subjects participating in studies involving the administration of external radiation or internally deposited radionuclides.

AEC and AEC contractor operations shall be conducted in such a manner as to assure that radiation exposure to the volunteer human subjects are limited to the lowest levels practical for meaningful experimental results.

Objectives

To establish radiation protection standards for AEC and AEC contractor operations involving studies of the administration of radiation or radioisotopes to volunteer human subjects.

Definitions

a. Volunteer Human Subject: An individual who gives his informed consent freely to participate in a study which contributes no direct medical benefit to that individual.

b. Patient: An individual who agrees to participate in a study designed to diagnose or treat an illness or disorder with which the individual is or believed to be afflicted.

c. Critical Organ: The body organ which receives the most damage from internally deposited radionuclides.

d. Dose Commitment: The lifetime dose which an organ is committed to by the presence of a radionuclide in that organ.

Applicability

The Standard set forth in this chapter applies to and shall be followed by Headquarters Divisions and Offices, Field Offices, and AEC contractors.

Coverage

a. This Standard shall govern ionizing radiation exposure to volunteer human subjects.

b. This Standard does not apply to ~~patients undergoing~~ treatment or diagnosis by a physician for a known or suspected illness or disorder using experimental or developmental techniques.

Experimental Protocol

All studies and recruitment practices involving volunteer human subjects shall be in strict accordance with The Institutional Guide to DHEW Policy on Protection of Human Subjects. Where discrepancies between the DHEW policy and this Standard exist, this Standard shall apply.

Selection of Volunteer Human Subjects

The following guidelines shall be used when selecting volunteer human subjects:

1. individuals must have reached their 18th birthday,

2. the following groups of individuals are listed in the order of preference:

    a. for medical studies, subject should be patients for whom some medical benefit can be derived. It should be pointed out that physician-patient relationships are not subject to this chapter.

    b. volunteers should come from the general population,

    c. only as a last resort should occupational workers be allowed to volunteer.

3. for exposure control purposes, the occupational worker must come from the agency or contractor performing the study,

4. the informed consent of all subjects must be in accordance with the DHEW guide, and

5. a competent medical judgment made prior to experimentation must result in the determination that participation in a study should not produce adverse effects upon his physical well being.

Standard for External and Internal Exposure

For the purposes of the study, a volunteer human subject shall be considered to be an occupational worker and subject to all radiation monitoring, exposure recording, and reporting requirements set forth in AEC Manual Chapters 0502, 0524, 0525. A volunteer human subject shall not be exposed to amounts of both external and internal radiation which would deliver a combined dose in one quarter or one year in excess of the amount allowed for

an occupational worker. If the critical organ can be defined, the dose commitment for that organ will not be exceeded. In the case of women of reproductive age, the dose and/or dose commitment shall be controlled so as to assure the dose to the fetus during the entire gestation period does not exceed 0.5 Rem. In the case of occupational workers participating in a study, their total dose from both their work and the study shall be added and shall not exceed the allowable dose for an occupational worker.

Records

Records shall be maintained in accordance with applicable AEC Manual Chapters.

Reports

1. Annual

   Annual radiation exposure reports submitted in accordance with AEC Manual Chapters 0502 and 0525 for volunteer human subjects shall be separate from those submitted for employees.

2. Termination

   Upon the termination of the study or the termination of the individual participating in the study, and in the case of occupational worker termination of employment, a termination report will be filed in accordance with AECM-0525.

Misadministration

In the event a volunteer human subject receives an amount of radiation or radioisotope other than the planned amount or in excess of the exposure limits, the AEC and the individual involved shall be so notified as soon as after discovery as possible but not to exceed 24 hours. Reports of misadministrations are subject to investigation under AECM-0502.

Deviations

Any deviation from this Standard shall require prior approval of the Atomic Energy Commission.

Policy of Medical Division, Oak Ridge Associated Universities, Concerning Recruitment of Human Volunteers

March 23, 1967

I. Definition of Normal Human Subject Volunteer -

A person in apparent sound physical and mental health, 21 years of age or older, participating without coercion as a subject in a medical research project. This category is to be distinguished from a "patient volunteer" who registers in the Medical Division as a patient for the investigation and possible treatment of a medical disorder.

II. Recruitment -

1. Methods should be discreet and in the bounds of propriety. Solicitation in public communications media can be made only through the Human Use Committee (procedure attached).
2. Conscious efforts will be made with ORAU employees to have recruitment free of any suggestion of coercion or implication that participation is expected. For example, announcements that ask for volunteers will be used rather than personal solicitation. Participation or non-participation shall have no bearing on merit evaluations, status, or promotion in ORAU. An ORAU employee should have concurrence of his supervisor so that regular work assignments are not handicapped.
3. A reimbursement may be offered to the volunteer.

III. Release Form - An agreement signed and witnessed that:

1. Participation is of the person's own volition,
2. Subject understands that this experience is for experimental purposes, not for diagnosis or treatment.
3. Subject understands the nature, procedures, and probable effects, if any, of the experiment. (These features should be listed or described briefly in the agreement.)
4. The volunteer, whether or not he is an employee of ORAU, is not considered an employee insofar as the experiment is concerned.

Gerald A. Andrews M.D.

Chairman, Medical Division

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to administer to _____ the following radioactive substance _____ Nuclide _____ Chemical

_____ Dose _____ Route of administration

The purpose of this procedure has been explained to me as being:

_____

_____

_____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

_____ Name of patient

_____ Date

1080078

AUTHORIZATION FOR THE ADMINISTRATION OF RADIOACTIVE SUBSTANCE MED-148(2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon _____
(myself or name of patient)
of the following treatment: _____

_____

_____

_____
(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: _____ _____
(Patient or person authorized to consent for patient)

WITNESS: _____

_____

I have talked with _____ about
Name
the proposed course of treatment to be given _____
Name
including the following:* _____

_____

_____ _____
Physician Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

1080079

CONSENT TO EXPERIMENTAL TREATMENT

MED-146 (2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES

WHOLE BLOOD AND/OR SKIN BIOPSY PROCUREMENT, RELEASE AND PAYMENT AUTHORIZATION

I, the undersigned, do hereby acknowledge that I have on this day, of my own free will and accord, delivered and sold to the Oak Ridge Associated Universities (hereinafter referred to as "Association") _____ cc's of my own blood, by direct vein aspiration, and/or _____ mm^2 of my own skin, by direct skin biopsy.

It is understood that I am to be paid the specified sum by the Association in consideration of which I do hereby release and discharge the Association, its successors and assigns, from all claims, actions and causes of action, at law or in equity, which I do now or may hereafter have against the Association, resulting from or growing out of the sale of said blood and/or skin and its removal from my body. It is further understood and agreed that I am to retain no control whatsoever over the said blood and/or skin or the use thereof.

_____	0 - 100 cc	$ 5.00}	
_____	101 - 200 cc	10.00}	
_____	201 - 300 cc	15.00}	BLOOD
_____	301 - 400 cc	20.00}	
_____	401 - 500 cc	25.00}	
_____	1 - 2 mm^2	10.00}	SKIN

This _____ day of _____, 19__.

_____ _____

Name of Donor (Please print) Signature of Donor

_____

Mail check to

_____

City State Zip

Witnesses:

_____

_____

Account to Charge: _____

_____

Blood received by

_____

Division approval

1080080

OAK RIDGE ASSOCIATED UNIVERSITIES

WHOLE BLOOD PROCUREMENT, RELEASE, & PAYMENT AUTHORIZATION

I, the undersigned, do hereby acknowledge that I have on this day, of my own free will and accord, delivered and sold to the Oak Ridge Associated Universities (hereinafter referred to as ("Association") _____cc's of my own blood, by direct vein aspiration.

It is understood that I am to be paid the below specified sum by the Association in consideration of which I do hereby release and discharge the Association, its successors and assigns, from all claims, actions and causes of action, at law or in equity, which I do now or may hereafter have against the Association, resulting from or growing out of the sale of said blood or its removal from my body. It is further understood and agreed that I am to retain no control whatsoever over the said blood or the use thereof.

____	0 - 100 cc	$5.00
____	101 - 200 cc	10.00
____	201 - 300 cc	15.00
____	301 - 400 cc	20.00
____	401 - above	25.00

This _____ day of _____, 1970.

_____ _____

Name (Please Print) Signature of Donor

_____

Mail Check To

_____

City State Zip

Witnesses:

_____

_____

Account to Charge: _____

_____

BLOOD RECEIVED BY

_____

DIVISION APPROVAL

_____

1086081

P-67 (7-50)
Oak Ridge Institute of Nuclear Studies
Medical Division

RADIOISOTOPE TREATMENT

Patient's Name_____ No._____
Date_____
Time_____

Isotope_____ Dose_____
Source _____
Shipment No. _____
Dose Measured by_____
Method_____
Dose Approved by_____
Route of Administration_____
Administered by_____
Wt. Carrier Added_____
Wt. Inactive Isotope_____
Remarks_____

_____

Isotope _____Dose_____ Date_____
Time_____
Source _____
Shipment No. _____
Dose Measured by_____
Method _____
Dose Approved by_____
Route of Administration_____
Administered by_____
Wt. Carrier Added _____
Wt. Inactive Isotope_____
Remarks _____

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Isotope_____ Dose_____ Date_____
Time_____
Source _____
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Dose Measured by_____
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Dose Approved by_____
Route of Administration_____
Administered by_____
Wt. Carrier Added _____
Wt. Inactive Isotope_____
Remarks _____

_____

RADIOISOTOPE TREATMENT

1080082

AEC, Oak Ridge, Tenn. 8-15-50-1000-A7736

For our file
cc to Edwards
Lustbader
Kniebes
Hayes
Abrutzer
Harmon
5/16/67

JOURNAL OF NUCLEAR MEDICINE 8:70-73, 1967

Guidelines and Criteria for a Committee Authorizing the Use of Radioactive Isotopes in Humans[1]

Joseph P. Kriss, Raymond Barrall, Robert Greenberg, Gerald Hanks, Charles E. McLennan and Edward Siegel

Palo Alto, California

INTRODUCTION

The increased use of radioactive nuclides in the diagnosis and treatment of human medical ills and in the investigation of the nature of pathophysiologic states in humans carries with it the obligation to provide adequate safeguards to the recipients of such nuclides while at the same time not hampering or restricting unreasonably the activities of qualified clinicians and investigators. Such obligations are undertaken at the local level by institutional isotope committees and, increasingly, by state governments entering into agreement with the Atomic Energy Commission. However, the guidelines which govern the decisions of such authorizing bodies are not readily available and may in some instances be unspecified or be understood, rather than transcribed. In connection with the application by Stanford University to the State of California for broad licensure for the use of radioactive substances and radiation-producing machinery, the isotope committee for human use, with the approval of the State Bureau of Radiologic Health, has formulated the following set of guidelines and criteria to be used in reviewing submitted protocols within its jurisdiction. While some of the items may be especially applicable to our own institution, we believe that the document as a whole has wide applicability and may be useful to those in other institutions who bear a responsibility similar to that of our committee.

GUIDELINES AND CRITERIA FOR FUNCTIONING OF ISOTOPE COMMITTEE FOR HUMAN USE, STANFORD UNIVERSITY SCHOOL OF MEDICINE

1. *Applications*

a. Applications will be accepted only from full-time or voluntary members of the faculty of the School of Medicine, but not from medical students, interns,

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[1]Departments of Medicine, Radiology, Pediatrics and Gynecology and Obstetrics, and the Health Physics Office, Stanford University, Palo Alto, California.

residents, technicians, fellows, or research assistants. The latter may participate in a study under the preceptorship of a faculty member. In general, applications will come from members of clinical departments who are licensed clinicians. In the unusual circumstance where the principal investigator is not a physician, collaboration and appropriate assistance by a physician colleague is mandatory.

b. The application must be reviewed and approved by the Health Physics office before being considered by the committee.

c. The application must include a protocol of the proposed plan of study which includes the following items:

1. Title of the study.
2. Brief statement of proposed plan.
3. Rationale and justification for the study, including information available from other laboratories and/or in lower animals or *in vitro* systems.
4. Number and type of subjects to be studied.
5. Dose, route and rate of administration, specific activity and chemical form of radionuclide.
6. Calculations of expected radiation dose to critical organs or parts of organs and the whole body.
7. Method of handling any special problems such as disposal of excreta, hospitalization, radionuclidic contamination, spillage, monitoring, etc.
8. Instrumentation available for making measurements.
9. List of personnel (with titles) assisting the investigator.
10. Complete record of that training and experience of the investigator and assisting personnel which pertains to the use of radioactive materials. Specify that training which was (1) basic (or pre-clinical) training in the facts of radioactivity and the techniques of using radioactive isotopes and (2) general clinical training in uses the same as, or closely related to, the uses proposed by the applicant. In listing experience with this or equivalent radioisotope applications, indicate the numbers of such procedures performed and the numbers of patients studied or treated. Dates, institutions, and preceptors should be given, where appropriate. If these data are more conveniently supplied by preceptoral statements or certificates, copies may be attached. Include, also, any current or previous radioisotope licenses or authorizations. This information need be filed only once and will be consulted by the Committee in evaluating subsequent applications.
11. A statement indicating that the subjects or responsible relatives will be well-informed of the nature and purpose of the study.

2. *The applicant*

The full-time faculty in the clinical departments are composed of individuals with a combined research, and patient care orientation and almost all have had previous experience in research, in many cases extensive experience. The committee, therefore, has reason to expect considerable sophistication with respect to

general research methodology proposed in submitted protocols. The investigator's experience with radioisotopes and tracer methodology may be considerably more limited. This experience will be reviewed by the committee in the context of the proposed protocol. For example, a proposed experiment involving a new therapeutic radioisotopic procedure would require as a minimum previous specialized training in nuclear medicine or radiotherapy or both, while a metabolic study involving the sampling of blood after intravenous administration of H^3 or C^{14}-labeled amino acid or glucose would require knowledge of the nature of these soft β emitters, proper method of handling, knowledge of the means of their detection and measurement, and an understanding of the dosimetric considerations involved in their use *in vivo*. A statement by the investigator outlining his previous experience with isotopes and isotopic methodology will be accepted as fact without further certification. Uncertainties concerning an individual's qualifications may be resolved by the chairman's requesting clarifying discussions between the applicant and one or more members of the committee, or by issuing an invitation to the applicant to appear before the committee upon the request of any committee member.

An applicant who has had a protocol previously approved by the Human Use Committee need not re-submit his experience record with each new application; a reference to the earlier protocol will suffice.

3. *The Protocol*

Comment on General Principles of Ethics Governing Human Experimentation:

The committee approves the Code of Ethics of the World Medical Association which was approved in June 1964 and is known as the Declaration of Helsinki. (1). However, it is not the proper function of the Isotope Committee to police or enforce the provisions of this document, but rather to evaluate those special aspects of a proposed investigation which involve questions of radiation exposure to patients and personnel.

In recommending approval of an application, the committee will be guided mainly by gaining positive assertions to the following questions:

1. Is it probable that the proposed study will yield the specific data the investigator wishes to obtain?
2. Is the proposed dose neither unduly high nor unduly low to obtain this information?
3. Is it probable that the target organ(s) is correct as stated in the protocol?
4. Are the dosimetric calculations correct or is there adequate literature documentation of expected radiation dosages?
5. Is it unlikely that the information desired cannot be as accurately, easily, quickly or safely obtained by other methods? or in other species?
6. Is the risk to healthy subjects (if any) negligible?
7. Is the radiation risk to ill subjects small or negligible in comparison to the risk of the disease itself?

It is expected that the following additional items will be considered by the

individual clinical investigator before undertaking his research. The committee at its discretion may seek clarification on any of the points.

1. The potential value of the information presumably to be gained, either to the patient or to society as a whole.
2. The physical (non-radiation) or psychic trauma of the procedure.
3. The relevance of the measured parameter to a given disease state.
4. The relationship between the investigator and the patient's responsible physician.
5. Approval by the Food and Drug Administration to use the proposed material.

4. *Follow-up Review*

The committee may request a summary report from the investigator (a) at the end of the proposed study, (b) at the end of a calendar year of operation, or (c) at any time if requested by the Health Physics office for due cause.

Stanford University Isotope Committee for Human Use.
Joseph P. Kriss, M.D., Chairman
Mr. Raymond Barrall
Robert Greenberg, M.D.
Gerald Hanks, M.D.
Charles E. McLennan, M.D.
Edward Siegel, Ph. D.

REFERENCE

1. *Brit. Med. J.* 2, No. 5402, 177, 1964 (July 18).

5. P. Pychlau and E. Bunde, *Br. J. Radiol.* 38, 875 (1965).
6. B. M. Wheatley and J. Geilinger, The Methods Used to Estimate the Whole Body Integral Dose of Radiation, Appendix C, 113–123, of MRC Special Report Series No 295, "*Leukaemia and Aplastic Anaemia in Patients Irradiated for ankylosing spondylitis*", HMSO, London (1957).
7. T. E. Burlin, Private Communication to BCRU (1968).
8. *ICRP Publication* 15, Protection Against Ionizing Radiation from External Sources, A Report of Committee 3 of the International Commission on Radiological Protection, p. 20, para 178, Pergamon Press, Oxford (1971).
9. G. M. Ardran, J. Hamil, E. Emrys-Roberts and R. Oliver, *Br. J. Radiol.* 63, 391 (1970).
10. *Le Système International d'Unités*, OFFILIB, 48 rue Gay-Lussac, F 75 Paris 5. Also published independently in the English language by the National Bureau of Standards, U.S.A., and by Her Majesty's Stationery Office, U.K., under the title "*The International System of Units*" (1970).

Health Physics Pergamon Press 1973. Vol. 24 (April), pp. 446–448. Printed in Northern Ireland

Radiation Experimentation on Children

(*Received* 29 *September* 1972)

Any Radiation Safety Officer whose bailiwick includes a hospital or medical school is likely, from time to time, to be faced with the problem of investigators wishing to use radiation experimentally on humans. When such a proposal involves minor children, particular moral and legal dilemmas arise.

The moral issue is necessarily part of the legal issue. Radiation Safety Committee members, prior to considering a decision in such a matter, will find it prudent to seek legal counsel. Individual committee members may have strong moral convictions. However, interjecting such opinions into the discussion may amount to a subjective judgment of another's moral philosophy and can lead to fruitless argumentation.

The RSO is often the only non-physician on the committee and must be prepared to assert himself. Litigation problems and malpractice suits are potentially serious and can involve not only investigators, but committee members, various "John Does" and the RSO himself.

The Problem of "Informed Consent"

In response to a recent request for an opinion, I received a letter from one of the assistant counsels in the legal department of the University. The following quotes are from this letter. "At present a parent or legal guardian may not legally grant such consent." (Children are not the legal property of parents.) "However, the law does not state that experiments on minors may not be legally conducted. Therefore the law is unsettled in this area. In this regard, use of such word (consent) cannot be taken to imply that such "consent" is legally sanctioned. I have suggested to other campuses that the word "permission" be substituted in order that there is no misunderstanding."

This distinction between the words "consent" and "permission" is hairline at the best, and puzzling at the worst. How can the word "consent" be legally proscribed and the word "permission" be legally acceptable (depending on which is used), when both apply to the same situation, i.e. unowned property—and when the end result is the same, whichever word is used?

Regardless of the distinction between the words "consent" and "permission", I think the word "informed" is the one which is going to hit the RSO in the eye. With so much still unknown about both latent and genetic effects of radiation, is informed consent (or permission) possible? It is probable in many, if not most cases, that the physician attempting to impart this type of information to a parent, is himself incompletely or incorrectly informed. On the other hand, should the physician have the best information available, is the parent capable of assimilating it with real understanding?

Legal Problems

A later paragraph of this letter indicates another legally undefined area in regard to genetic damage.

"During our discussion you raised the question whether University policy would include the offspring of individuals who participated in an experiment who receive injuries (genetic imbalance). I indicated to you that the question has never been raised previously and thus University policy does not address itself to this issue. In my opinion, the Office of the President would look favorably upon a modification to University policy to include offspring. I am therefore bringing this matter to the attention of Special Assistant _____ for resolution."

Insurance Coverage

The last paragraph offers some assurance of insurance coverage for members of the review committee, including the RSO.

"If a minor, although not injured, sought general damages from the University or his parents, or both, for requiring him to participate as a medical research subject, the individual committee members would be covered by the University's insurance policy. In this regard, please refer to the memorandum from Dr._____ to all Chancellors, dated_____. This memorandum included copies of pertinent correspondence, and thus I will only quote from the covering statement of Dr._____ .

"It has come to our attention that there is some concern on the campuses over the possible liability of a member of a campus review committee that may incur as a result of approving certain research projects involving human subjects. We have received several assurances in this regard from the office of the General Counsel advising us that the Regents would not only assume the defense of a member of a human ects review committee, but would satisfy any gment entered against him except in cases of actual fraud, corruption or actual malice."

I use the words "some assurance" because of the words "although not injured". Nothing is said here in reference to an *injured* minor. However, the paragraph attributed to Dr._____ appears to indicate coverage would be complete. I asked the assistant counsel, in the case litigation arose after a committee member or an investigator had left University employment, whether he would still be covered and was assured he would be.

Troublesome Questions

(1) In several proposals I have reviewed, the investigator has stated that experimentation on children will be limited to children with terminal disease or limited life expectancy. This is the type of moral question alluded to earlier. Certainly a sick child would have less toleration for the radiation nsult than a well child. I think such a statement mplies the investigator's belief that a terminal child s of less value to society and that therefore such xperimentation is more acceptable to society. his may be correct, but is the frame of reference rrect? Should not the value the sick child places his own life be uppermost, and of no less concern an that of a well child?

(2) In decisions involving medical experimenta- n o minors (or adults, for that matter) two and irreconcilable viewpoints become .... Whether one viewpoint is more legitimate the other appears to be more a problem for a philosopher than for an expert on radiation effects. (It is worth considering whether the review committee should include a faculty member of the Philosophy Department, who is unacquainted with radiation.)

(a) Because of the investigator's orientation, he will be inclined to the view that likely damage to the experimental subject is poorly documented and in a statistical sense, trivial—that possible damage to the subject (should the experiment prove successful) would be offset by improved diagnosis and treatment for a multitude of patients in the future.

(b) On the other hand, the Radiation Safety Officer, because of his background and training (where every exposure in excess of occupationally exposed limits is a serious event) will tend to feel experimental dosages, especially when far exceeding occupational limits, are not justifiable. He will tend to feel that welfare of the individual (and the individual's offspring) is paramount and offsets results, which, because of the very nature of experimentation, have doubtful and uncertain benefit to future patients. For an objective appraisal of some of the above questions, see Stanbury's paper "On the Use of Radioisotopes in Human Experimentation".[1] This paper contains an extensive bibliography (55 references) on the subject. Unfortunately, none of them present the legal viewpoint.

(3) Consider a hypothetical case where a minor, experimentally exposed to radiation, develops leukemia—regardless of the cause—10 yr after the experiment. Consider further that as a result, he sues the University for a million dollars. It would seem that only the amount of the settlement would be in doubt.

Reducing Exposures

(a) Occupational over-exposures to radiation are usually accidental. Since fundamental radiobiological processes (formation of ion pairs and free radicals) at the cell level are on the time scale of 10^{-7}–10^{-16} sec,[2] administration of chemical ion and free radical scavengers after exposure is not practical. However, in a planned experimental exposure, this procedure would be possible. Compounds such as cysteine, cysteamine and AET have been shown to be effective scavengers in animal work.[3] These agents are toxic in themselves, however, and must be administered in precise amounts throughout the period of exposure as they degrade and are excreted rapidly. Administration of such agents would seriously complicate an experimental procedure, and it would not be surprising if

the physician failed to give serious consideration to their suggested use.

(b) Prior to an experimental exposure, the possibility should be investigated of blocking organs which are not of interest in the study.

Dosage Calculations

Our hospital review committee has adopted the policy that, in any non-routine administration of radioisotopes to humans, the physician in charge must demonstrate capability of performing the absorbed dose calculations by actually doing them. It then becomes the task of the Radiation Safety Officer to review the calculations. Having done this for a period of years, I have been left with the impression that the medical school curriculum might well include additional courses in mathematics. Positive and negative powers tend to get confused, and decimal points move hither and thither like drops of mercury. I have found errors as large as 6 orders of magnitude on occasion.

Unless the physician has a preferred reference source, I refer him to the 3rd edition of JOHNS[4] for simplified but accurate computational methods. It is important to note that in the 2nd edition of Johns, dosages were based on essentially complete absorption of gamma radiation. Consequently, total dose figures (depending on the radionuclide) based on 2nd edition methods tended to be as much as 3–5 times greater than if calculated by the more accurate and refined method of the 3rd edition.

Conclusion

The Radiation Safety Officer, presumably, is the Review Committee's expert on biological effects of radiation. As such, it is his responsibility to assert himself in the area of his expertise. Such a stand can be difficult in a committee, which, with the exception of himself, is composed of physicians who are passing on a (possibly over-enthusiastic) fellow physician's proposal.

Understandably, the physician regards himself as the final arbiter in the matter of his patient's diagnosis, prescriptions and health. It is reasonable to assume this attitude would carry over to an experimental subject in his care. I mention this, as outside interference with the physician's prescription of radiation, whether diagnostic or experimental, can be touchy, indeed. Before advising the physician his calculations are in error, it is well to double-check, or if in doubt, to have another physicist check. Also, bringing the error to the physician's attention requires some diplomacy, if good working relations are to be maintained. Either confronting him with the error at a committee meeting, or advising him of it in a typed memo is almost certain to arouse his embarrassment and resentment. The typed memo is an especially poor device, as it not only becomes a record, but may be available to other eyes.

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The University Radiation Safety Officer as a Teacher

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AT the last meeting of the Campus Radiation Safety Officers we gave a presentation discussing the Radiation Safety Officer (RSO) as a teacher. The following material is submitted for the information of others who may have an interest in this topic.

This discussion will consider the involvement in teaching of not only the RSO but also the Radiation Safety Office and the University Radiation Safety Committee. The first question that arises is, "Should the RSO be involved in teaching?" Our answer to this is Yes, any radiation protection professional and his staff are involved in teaching in some form. Good radiation safety depends upon educating the radiation users to good health physics practice. In addition, on the University campus a number of the members of the Radiation Safety Committee are teachers and they are obliged to carry radiation safety back to the classroom and lab. Therefore, the question is not IF but HOW the RSO should be involved in teaching.

Having declared the appropriateness of teaching, attention can then be directed to the manner of involvement; this involvement might be the responsibility for one or more of the following:

ON THE USE OF RADIOISOTOPES IN HUMAN EXPERIMENTATION

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Henri Becquerel first recognized that there are risks involved in exposure to radioactive isotopes in 1901, 5 years after he had discovered radioactivity. A short time after he had carried a sample of uranium in his pocket, he observed that the skin near his pocket developed first erythema and then tissue necrosis which he attributed to the radioactive properties of the specimen (*1*). The earliest experiments on man using a radioactive tracer were those of Blumgart and his associates when they used radium for measuring the rate of blood flow (*2*). Formal experimentation in man with artificial radioisotopes began in 1939 with studies of the fate of radiosodium, radioiodine and other radioactive substances (*3*). Since 1945 labeled compounds have become widely used and have become indispensable tools in clinical investigation.

In pursuing their research on human subjects, investigators have inevitably been confronted by the necessity of selecting a dose of a size that would permit answers to their inquiries without endangering the patient or his progeny, and they have found that the required information is often unavailable. This essay is an attempt to formulate a set of guidelines for the selection of a dose limit for radioactive isotopes in the course of human experimentation.

Discussions of radiation dose effects in man generally begin with the premise that most radiation-induced mutations are harmful. This is based on extensive experience in the radiation genetics of model systems such as bacteria, the fruit fly and the mouse, and there is little reason to doubt that the principles gleaned from these studies apply to man as well. There is no *a priori* reason for suspecting that mutations induced by man-made radiation are different in character from those arising in the course of natural radiation: presumably an increase within broad limits in the rate of these mutations in man would not change the course of evolutionary history; rather, it would only accelerate it.

Be this as it may, and accepting the fact that all radiation above the natural background is undesirable, there are certain rules governing the human use of radioisotopes which can be accepted without argument. One of these is that the radiation dose should be no more than the minimum required for the task at hand. Also, within the framework of available knowledge, the value of the findings must outweigh the risk to the subject. This judgment must be intuitive, because just as it is difficult to evaluate the risks of a small dose of a radioisotope, it is almost as impossible to prejudge the value of new information. Another rule is that in all respects, the proposed experiment must conform to the ethical standards which have been established by the scientific community. Still another principle, which has often been incorporated into standards for human experimentation such as in the Declaration of Helsinki, requires that informed consent be obtained. This is particularly difficult when radioactive isotopes are involved because of the uncertainty of the term "informed." Consent, yes; this is legalism. But how are we to inform a subject of the risks involved in administering a radioactive isotope at specified dose?

RADIOBIOLOGICAL CONSIDERATIONS

In order to approach the problem it is necessary to take a brief excursion into radiobiology. When penetrating radiation passes through the cell, some of it may be absorbed and give up its energy, producing ion pairs and highly reactive free radicals. These may damage critical structures within the cell, and especially DNA, the genetic arbiter. Bases may be chemically changed or DNA strands broken.

A striking feature of the radiation effect is that much of it can be repaired (*4–6*). Not only are there means for scavenging free radicals before they cause damage, but also much of the change in the DNA strand may be repaired through remarkably efficient enzyme activity. If unrepaired, damage is often lethal

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at the time of subsequent attempts at cell division, and that cell is eliminated. The intensity of the radiation injury to tissues is governed by the dose, the type of radiation, the specific cell type, the rate at which the cell is dividing and the stage in the division process at the time of radiation. Radiation may be several-fold more damaging if it is delivered as a single high intensity event than if the same total dose is extended over a longer time span (*7,8*).

Radiation may have both somatic and genetic effects. We are concerned here with the possibility that small doses may cause accelerated aging, neoplasia or genetic change. Life shortening in experimental animals appears to be an acceleration of all those phenomena which result in the death of the animal. There appears to be about a 1–5% life-shortening effect per 100 rads (*9*). Upton *et al* (*10*) found a linear effect on the life span of mice extending down to 10 rads. Preliminary analysis of the life experience of the survivors of the Hiroshima and Nagasaki incidents has suggested a slightly reduced life expectancy among those who received more than 100 rads (*11*). Examination of life tables of American radiologists who died between 1935 and 1944 disclosed a tendency toward life shortening when compared to life expectancy among other physicians (*12*). During that period protection procedures were not as rigorous as they are now, and many radiologists may have accumulated more than 2000 rads. Radiologists exposed more recently appear to have the same life expectancy as other physicians (*13*). While on present evidence it cannot be denied that radiation may shorten the life expectancy of exposed persons, there is good reason to believe that if there is an effect it is small in magnitude and would approach the vanishing point in experimentation involving any reasonable dose of radioisotopes.

Radiation is particularly damaging when delivered to the fetus, or to the ovary or testis before conception (*14–18*). An increase in spontaneous abortion and miscarriage and of childhood leukemia and tumors occurred after the Hiroshima and Nagasaki incidents (*19,20*). There was an increase in fetal wastage for several years after the heavy exposure on Rongelap which occurred following one of the Pacific bomb tests (*21*). It has been said that malignant neoplasms and leukemia are more common in children of mothers who had received radiation for diagnostic purposes during pregnancy (*22*), but this cannot be viewed as an established fact since statistical difficulties have plagued the relevant studies, particularly the choice of control groups. Claims have recently been made in the popular press of greatly reduced fertility and heightened infant mortality and childhood leukemia in areas lying in the fallout path after some of the atomic bomb tests in this country (*23,24*). Fortunately these claims have now received the kind of rigorous independent evaluation which they deserve and they appear to be highly dubious (*25,26*).

LEUKEMOGENESIS

Leukemia is a real problem after radiation. Current estimates based on the assumption of a linear dose-effect relationship are that one new case of leukemia is caused by each rad of bone marrow radiation per million subjects per year during an average 20-year period (*27*). In other words, there is one chance in 50,000 of inducing leukemia in a patient who receives 1 rad of bone marrow radiation. These figures are developed primarily from high levels of x-ray exposures and the Japanese atomic bomb experience, and need not apply to radioisotopes, where the rate of radiation is much lower. They are also based on a linear extrapolation to low doses. Since the average dose of radioactive iodine for the treatment of thyrotoxicosis gives approximately 10 rads of whole-body radiation, one might expect one excess case of leukemia in subsequent years per 5,000 persons treated in this way. Therefore, it is not surprising that earlier studies in England (*28*) and the cooperative thyrotoxicosis therapy followup study failed to show an increase in leukemia in patients treated for thyrotoxicosis with radioactive iodine (*29*) because if these figures are valid, only three cases of leukemia would have occurred above the expected number in the latter study. Furthermore, since 1 rad of whole-body radiation permits quite a large dose of the usual radioisotopes used in metabolic experiments, the probability of causing leukemia in the course of a radioisotope study can be placed at less than 1 in 50,000. One could do 500 such studies and still have a less than 1% risk of generating one case of leukemia. One may worry as much as he likes about that one case of leukemia, but this may only lead him into the philosophical problem of statistical morality. Society regularly asks individuals to mine coal, build bridges and do countless other tasks where there is a perfectly clear and ascertainable risk to life (*30*).

THYROID CANCER

The thyroid gland shares with other tissues a susceptibility to radiation damage and may have an additional risk because of its architectural peculiarity. Most of the interesting evidence comes from the studies of the Rongelap islanders (*31,32*). Eighty-four percent of the children exposed before the age of 10 to doses between 700 and 1,400 rads of internal and 175 rads of external radiation have

developed thyroid nodules. The relationship of thyroid adenomas and carcinomas to irradiation in early childhood is well established (*33–36*). Winship and Rosvoll (*37*) found that approximately 80% of children with thyroid carcinomas had received radiotherapy into the neck region at an early age. They calculated that 1 rad of radiation to the thyroid carries a risk of thyroid cancer of 1 in a million persons per year, while Dolphin (*38*) finds the risk to be about five times this value. Hempelmann (*36*) has found as little as 20 rads of external radiation associated with nodules of the thyroid in early childhood. The Hiroshima experience has provided confirming information. Diffusely enlarged thyroids, single nodules, multinodular goiter and a few carcinomas appeared in excess frequency among those patients subjected to high flash radiation exposure (*39*). A recent study from Japan reports a 16% incidence of microcarcinomas in routine autopsy material from subjects not exposed at the time of the explosions in 1945 but a 6% higher incidence in those who received more than 50 rads (*40*). It is perhaps conceivable that multifocal microcarcinomas are much more common than we have considered and that they are held in check by the immune apparatus which is damaged by radiation of the thymus in early life.

It is interesting that cancer of the thyroid has not proved to be a problem in patients treated for thyrotoxicosis with radioactive iodine. The doses delivered to the gland are larger than those from external sources which have caused troublesome and serious changes in organ architecture. Dose rate may be one major factor; age at time of delivery of radiation is certainly another. It has also been suggested that the doses are so large that malignant change cannot occur, and there are experimental observations to support this theory.

Also, extensive experience with the investigative use of radioisotopes of iodine in the thyroid has so far failed to indicate that there is significant risk of malignant degeneration in adults. There would appear, accordingly, to be little reason for dose limitation in the course of experiments with radioiodine on the thyroid of adult man on the basis of damage to the gland itself.

THE GENETIC RISK

The most serious indictment of radioisotopes relates to genetic risk. Radiation has been recognized as an effective mutagen since the classic experiments of Muller (*41*) more than 40 years ago. Molecular biology has provided a clear analysis of the way in which changes induced by radiation in the base sequences of DNA cause changes in the structural proteins and enzymatic machinery of the cell. These effects of radiation must be considered against a background mutation rate caused by natural radiation, dietary mutagens and copying errors (*42*). While genetic loci vary and in some instances vary widely in natural mutation rate, the risk of mutation at any one locus is approximately one per 100,000 per generation. Most mutations are recessive and are not seen until the carrier crosses with one who has a similar recessive gene, and then one quarter of the progeny will be homozygous for the mutant gene. While it is clear that most recessive mutations are damaging in the long run, it must be kept in mind that hybrid vigor does indeed exist, and that many mutations which are deadly in the homozygous form may be highly advantageous to the heterozygote: witness the success of the heterozygote for hemoglobin "S" in struggling with falciparum malaria, a circumstance which permits the development of a 40% carrier rate for the abnormal gene in certain regions where malignant tertian malaria might otherwise decimate the population (*43*). This should not imply that one is hospitable to more radiation and more mutations; quite the contrary. The purpose is only to reinforce the point that the matter is not as simple as it appears at first glance.

It is difficult indeed to estimate the risk of a given dose of radiation to the gonads. The risk is real but our information is not adequate to give a true estimate of the impact of a given dose on human fitness. It may be pointed out that Green (*44*) has irradiated successive generations of male mice with 100 rads of radiation and has detected no increase in phenotypic abnormalities by the 20th generation, and Russell (*7*) has found no mutations at specific loci after irradiating female mice with 63 rads if given 6 weeks before conception. These reassuring experiments clearly indicate that, at least in the mouse, processes of repair of radiation damage on the one hand and elimination of damaged gametes, zygotes and embryos on the other, are remarkably effective. Nevertheless one must remember that chromosomal changes have been seen in man after no more than 12 rads of diagnostic x-ray (*45*), and in radiation workers exposed to an average of 1.4 rem/year (*46*).

EXPOSURE STANDARDS

Users of radioisotopes are obliged to be concerned with standards of radiation safety because of the demonstrated hazards of ionizing radiation. Dermatitis from x-ray exposure was recognized within a few months of the discovery of the roentgen ray on 18 December 1895 (*47*). Perhaps the first at-

by Rollins (*48*) 6 years later. He suggested that radiation would not be harmful if it failed to fog a photographic plate in 7 min. This was probably 10–20 R/day of soft x-rays. In the intervening years several national and international committees have developed standards of radiation safety, and maximal permitted doses have been repeatedly lowered.

In 1952 when the Advisory Committee on X-Ray and Radiation Protection of the Bureau of Standards lowered the upper limit for radiation workers below the previously permitted 0.1 R/day, they wrote that,

> "It is well to state explicitly that the recommended reduction in the permissible dose for the blood-forming organs is not based on definite knowledge that 0.1 R per day is too high. There is actually no direct information indicating that 0.1 R per day is too high. . . . The general impression among radiologists is that no harmful effects result from whole body exposure at these levels. Nevertheless in the absence of long term experience backed by various statistical data it is desirable to be on the safe side" (*49*).

In 1959 the same Advisory Committee recommended that the permissible dose be reduced and integrated on a quarterly basis. There are currently efforts to lower these limits even further. Generally the maximum permissible dose for nonradiation workers has been set at approximately one-tenth of the dose permitted radiation workers. Nonradiation workers were given this safety factor because of the difficulty of knowing the precise dose to people living in the vicinity of radiation installations, and because some of them would be children and others, pregnant women. Current federal regulations (*50*), and those in my own institution, for radiation workers are set at 1.25 rads per quarter for whole body, lens of eye and gonads. Limits for nonradiation workers are one-tenth those for radiation workers.

THE ETHICAL DILEMMA

Radiation protection committees charged with setting safety standards in human experimentation have had the difficult task of balancing the needs of investigators against the conjectural risks of radiation. They have had to make their decisions when the benefit of the investigation to the patient and its relevance to his therapy were at best uncertain. They have been forced to decide whether the risk of radiation exposure to an individual would outweigh the benefit which the new information might have for society. Usually these committees have been guided by the standards established for radiation workers or they have taken the position that the dose is at the discretion of the investigator and his individual conscience as a physician. No one could be entirely happy with either solution.

Recently the Medical Research Council of Great Britain has issued a document entitled "Responsibility in Investigations on Human Subjects" (*51*). It is an attempt to define the responsibility of the physician in clinical investigations. A distinction is drawn between procedures contributing to the benefit of the individual, that is, of patients with particular disturbances wherein the investigation is intended for the benefit of the individual whether directed to treatment, to prevention or to *assessment*, and to other patients or subjects who are to be classified as volunteers. In the first category the propriety of procedures is considered to be determined by the same considerations as govern the care of patients. In general the fact that the patient has put himself in the physician's care allows the physician to assume that consent has been given to the same extent as he would were the procedure entirely established. The report continues to a consideration of procedures not of direct benefit to the individual, that is, on volunteers, and it is clear that additional restraints must apply to this group.

Radiation protection committees have often made a similar distinction in setting limits for radiation dose for human subjects and have permitted larger doses of radioisotopes for studies in patients than in volunteers. But a subtle ambiguity often arises when a procedure might be considered "assessment" from one point of view, and from another an undertaking "not of direct benefit to the individual." What is meant by "assessment?" For example, given a patient with gout: a determination of the metabolic products of an administered dose of carbon-labeled glycine could be called "assessment"; this would put the subject in one dose category. The procedure could hardly be construed as being of direct benefit to the individual, and this would put him in a category restricting the dose to a much lower level, so low perhaps as to make a significant observation impossible.

One may venture the opinion that for patients with a disease being studied, there need be no stricture imposed by a lack of immediate and direct benefit to the patient, but rather that the term "assessment" as used by the MRC should be understood to encompass full investigation of the disease process exhibited by the patient. This is the crucial point. Of course, the investigation must be directly related to the illness exhibited by the particular patient.

Any consideration of the maximum permissible dose of radiation in clinical investigation in man must take into account the information which is

available on biological effects at low dose levels, and here at once one is confronted by many uncertainties. For example, is there a threshold dose for carcinogenesis, and genetic and other effects? There is impressive evidence which indicates that in many situations there is. For example, survival curves after radiation almost always show a relatively lessened effect in the low dose range (*52*), and there is evidence for a threshold dose for radium and related bone-seeking nuclides in the production of bone cancer (*53*). Russell (*54*) has found that the mutation rate in mice is proportionally lower at low doses of radiation than at high doses. There is also impressive evidence in favor of a no-threshold position. Indeed, support for virtually any position on the risks of radiation can be found in the endless literature of this field. It is obvious that there is a pressing need for more innovative research in low-dose radiobiology.

After reviewing the evidence, there appears to be little reason for apprehension about either genetic or somatic effects from a few rads of whole-body radiation, except in the first few years of life or in the pregnant female. There also seems to be little reason for concern even for a few hundred rads of radiation to the thyroid from isotopes of iodine, provided again that this is restricted to subjects who have reached their adolescent years. In other situatons where there might be selective localization of an isotope in vulnerable tissue, such as possibly ^{90}Sr in the chromosomes (*55*), individual considerations apply, but so often the necessary information is not available.

PROPOSED GUIDELINES

It is clear that available information is insufficient for rational formulation of the maximal permissible doses of radioisotopes in the course of studies on man, and indeed this may be impossible for a long time to come. One must be content with a set of principles for guidance which seem intuitively acceptable and not at variance with present knowledge. One such set follows:

1. Radiation in any dose is not desirable; neither is it desirable that knowledge be restricted nor access to it be made impossible through unreasonable restrictions in the permissible doses of radioisotopes.
2. No experiment should be performed on man unless there is reason to believe that within the permitted dose a definitive answer can be obtained.
3. Experiments should only be performed when they conform to established ethical and legal standards and when the experiment gives promise of providing *new* information.
4. Whenever possible, subjects should be chosen who, on the basis of age or physical fitness, are least likely to contribute to the genetic pool in the future.
5. The investigator must continually endeavor to keep the total radiation dose at the lowest possible level by continuing attention to experimental design and instrumentation.
6. The validity of the research and, particularly in this context, its use of radioisotopes must be under surveillance of a review committee of experts not involved in the experiments.
7. In view of the many uncertainties regarding radiation effects there is a sound basis for a first approximation to relate maximal permissible doses in clinical research to the radiation worker protection guidelines which have been established. These guidelines must be flexible in order to take into account individual circumstances such as the number of patients involved, sex, age, life-expectancy, reproductive potential and the importance of the information. This flexibility must extend—with obvious constraints—to true volunteers, who may be as crucial to the experiments as the patients are.

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A Primer On New Drug Development

by Wayne L. Pines

The development of a new drug product is a long, complex process that can begin in many places—a drug manufacturer's laboratory, a chemical company, research at the National Institutes of Health—and that hopefully will end with benefits to the public.

By the time a new medicine becomes available to the general public, it has been thoroughly tested in both animals and humans under carefully controlled circumstances, and information has been approved for physicians to help them prescribe the drug correctly.

The Food and Drug Administration is responsible for approving the marketing of all new drugs that are sold in the United States, and for monitoring their use after approval.

This primer provides a simplified view of how a new drug is developed and approved for general marketing. Much of this applies only to prescription drugs, although some parts could apply to nonprescription medicines.

The First Step

The first step in the development of a new drug is research into the chemistry or anatomy of a disease, or the discovery of possible drug effects for a chemical. Recently, most drugs have been developed in the laboratories of pharmaceutical companies.

The chemical is subjected to screening tests and to testing in animals. Initial animal studies are performed to see whether the chemical has any desired drug effects. If it does, additional testing is done to determine what effects it might have, what dosage levels are poisonous, what the safe dosage range might be for humans, and whether there is a reason for testing the chemical in humans.

FDA initially requires that sufficient animal studies be performed to show it is reasonably safe to begin human testing. Additional animal tests are required as the human tests progress.

FDA does not monitor animal tests. But if they indicate the drug can be safely tested in man and that the chemical may be useful therapeutically, the drug sponsor will then proceed to the next step, which does involve FDA. This step makes the drug an Investigational New Drug (IND), which means the sponsor wants to test it in humans.

Before human tests can start, the sponsor must submit to FDA a form known as a "Notice of Claimed Investigational Exemption for a New Drug." The sponsor must tell FDA the complete composition of the drug, its source, and how it is made.

In addition, the sponsor must submit the results of all animal studies to document that enough testing has been performed in animals to indicate that the drug shows promise of being useful in humans and that no test subject will be exposed to an unreasonable risk.

The IND also contains a detailed outline, called a protocol, describing the planned testing in humans. The sponsor must wait 30 days after submitting the IND to enable FDA to review the materials to make sure patients are not being subjected to unwarranted risks.

Before testing is done on humans, FDA requires that, at the institution where the drug is to be tested, a committee composed of a broad spectrum of disciplines such as physicians and clergymen review the protocol to assure that patients' rights are adequately protected.

Human testing is divided into three phases.

Phase I

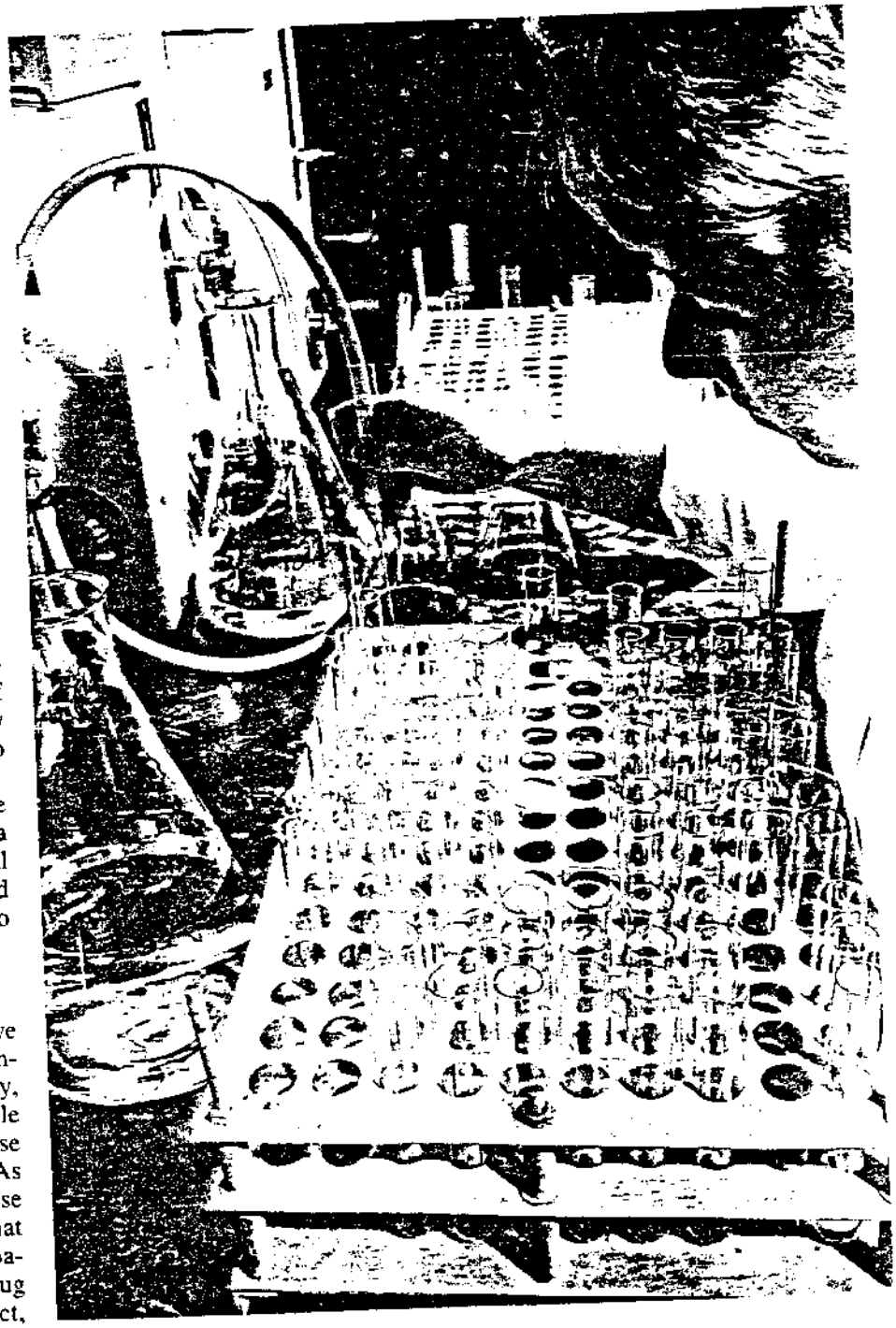
The first phase of human testing is directed at determining what chemical actions a drug has, how it is absorbed into the body, how it should be given (by mouth or injection, for example), and what the safe dosage range is. These tests involve a small number of patients—usually fewer than 10.

The basic approach during Phase I is to begin with doses one-tenth or less of what might be expected to be useful, and gradually increase the dose with the patient carefully watched. Much of this testing is done in normal, healthy volunteers.

The safety record of such research is excellent. FDA knows of no volunteer patient who has been

permanently harmed as a result of Phase I testing of hundreds of new compounds under the FDA procedures established in 1962. Some patients do become ill as the dosage is increased.

The main things investigators are looking for during Phase I studies are to see that the chemical does act in the body, that it is safe, and that further testing can continue. Once Phase I studies are completed successfully, Phase II studies can start.



Phase II

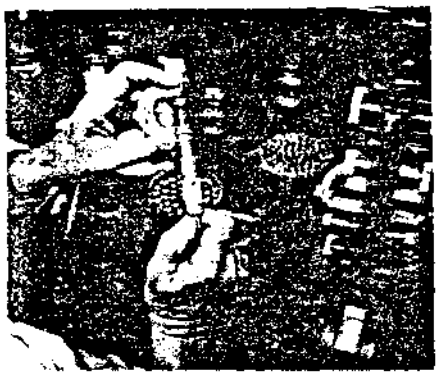
Phase II studies involve human testing on a limited number of patients for treatment or prevention of a specific disease. The number of patients depends on the nature of the drug.

This is the time when investigators evaluate the effectiveness of the drug. Additional testing usually continues on humans or animals to indicate the drug's safety.

If the Phase II tests show the drug may be useful in treating a disease and the long-term animal testing indicates no unwarranted harm, then the sponsor proceeds to Phase III.

Phase III

This is by far the most extensive testing. Phase III studies are intended to assess the drug's safety, effectiveness, and most desirable dosage in treating a specific disease in a large number of patients. As with earlier human studies, these tests are carefully controlled—that is, the investigator must have a basis for determining that the drug itself is causing the desired effect,



"No matter what system we set up, as technical knowledge grows, presently acceptable procedures and systems will appear inadequate. This is part of scientific progress."

rather than other variables or chance.

In Phase III, the drug is used the way it would be administered when marketed. Once Phase III is completed and the sponsor believes the drug is safe and effective under specified conditions, the sponsor applies to FDA for approval to market the drug. This application is called a New Drug Application (NDA).

The New Drug Application

By the time an NDA is submitted, a drug usually has been studied in several hundred to several thousand patients. An NDA contains all the information the sponsor knows about the drug. Often the NDA runs into thousands of pages.

The NDA is reviewed by the division in FDA's Bureau of Drugs responsible for evaluating that category of drug. There are six divisions: cardiopulmonary-renal, neuropharmacological, metabolic-endocrine, anti-infective, oncology-radiopharmaceutical, and surgical-dental.

Each division is composed of physicians, pharmacists, chemists, and other professionals experienced in evaluating new drugs. FDA makes extensive use of advisory committees composed of experts from outside the Agency.

The NDA is reviewed by a team who determine whether the drug is safe and effective and whether the drug sponsor can manufacture the drug properly and consistently, batch after batch.

Among the information submitted in the NDA are: chemical structure of the drug, scientific rationale and purpose the drug is to serve, all animal or laboratory studies, and all tests in humans.

FDA reviews the entire NDA to determine whether the benefits of the drug when used properly outweigh the risks. This is the crucial determination in evaluating a new drug.

If a drug is indicated for a cancer patient, for example, a relatively high degree of risk and adverse reactions may be tolerated if some benefit may ensue, because the alternative to use of the drug might be death. If a drug is used as a minor tranquilizer, then a much lesser degree of risk would be acceptable.

The benefit-risk judgment that goes into approval of a new drug is one of the hardest anyone can make. It involves not only medical but also societal considerations. How much risk is the public willing to take to obtain the benefits of a new drug, when no drug is completely free from risks?

Very often manufacturers of drugs —who may have spent considerable sums to develop a drug—complain that the review process for an NDA takes longer than it should. Legally, once an application is filed, FDA has 180 days to review it. In many cases, the application is not approved in the initial review, and the review period is extended.

The reason for most delays in the past has been that the data submitted to FDA were inadequate. Studies were not well controlled or there were not enough. In a large number of cases there was inadequate information about the manufacturing and quality control.

In making an important decision such as authorizing the sale to the public of a potent new chemical, it is imperative that FDA make sure the drug's benefits outweigh the risks and that the product will be made properly.

In the past, too, there may have been some unnecessary delays in the approval of a new drug. The Bureau of Drugs has taken steps, such as computerization, the use of project officers, and the use of advisory committees, to try to reduce the time delay. All the problems have not been solved, but the Bureau is working on them.

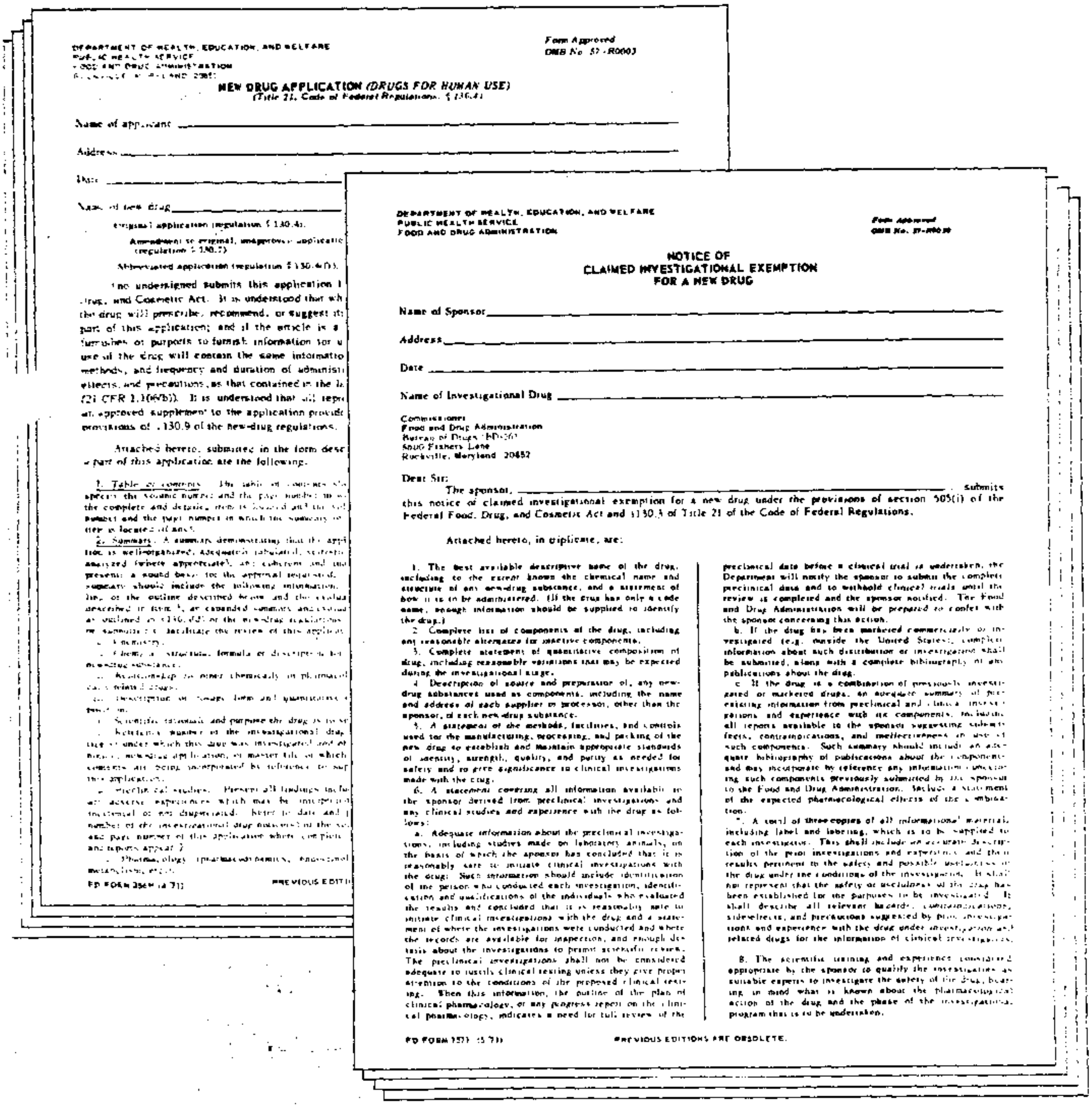
One of the final steps in the approval of an NDA is the review of the package insert or labeling. This is a detailed explanation of what the drug is, how it works, what it has been proven useful for, adverse reactions, means of administration, dosages, and other pertinent information.

The package insert must accompany the drug whenever it is shipped in interstate commerce. It also serves as the basis for all information on the drug disseminated by the manufacturer. The company may not make any claim for the drug which is not in the approved labeling.

A summary of many package inserts appears in the Physician's Desk Reference, a widely distributed book to which physicians often turn for information about prescription drugs.

Once an NDA is approved, the company is required to keep records relating to production methods for the drug and its safety and effectiveness. Any information in-

These are the forms that sponsors estigational New Drug (IND) .ew Drug Applications (NDA) must fill out. The forms explain what types of information are required for each application. The information submitted in support of the application is considerably longer.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION (DRUGS FOR HUMAN USE)
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant ____

Address ____

Date ____

Name of new drug ____

Original application (regulation § 130.4).

Amendment to original, unapproved application (regulation § 130.7)

Abbreviated application (regulation § 130.4(f)).

The undersigned submits this application [illegible]

Attached hereto, submitted in the form desc[illegible] a part of this application are the following:

1. Table of contents. [illegible]

2. Summary. [illegible]

FD FORM 356H (4/71) PREVIOUS EDITI[illegible]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF
CLAIMED INVESTIGATIONAL EXEMPTION
FOR A NEW DRUG

Name of Sponsor ____

Address ____

Date ____

Name of Investigational Drug ____

Commissioner
Food and Drug Administration
Bureau of Drugs (BD-20)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, ____, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug. Such information should include identification of the person who conducted each investigation, identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection, and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of three copies of all informational material, including label and labeling, which is to be supplied to each investigator. This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

FD FORM 1571 (5/71) PREVIOUS EDITIONS ARE OBSOLETE.

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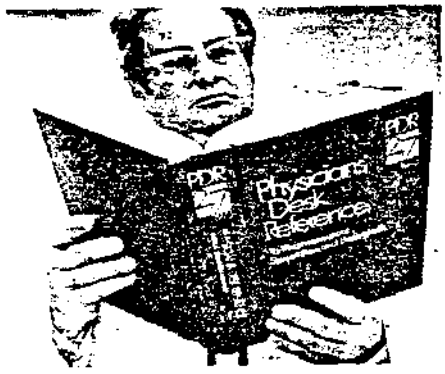


A summary of many package inserts appears in the Physician's Desk Reference, a widely distributed book to which physicians often turn for information about prescription drugs.

dicating that the drug may pose an unexpected hazard must be reported.

A manufacturer must report to FDA every 3 months during the first year after approval, every 6 months in the second year, and once a year after that. Immediate reports are required in cases of drug mixups or contamination, or when unusual or especially severe adverse reactions are reported.

For some drugs, FDA requires more than recordkeeping. FDA can require additional studies to test the long-term effects of the drug. For example, FDA is requiring long-term studies for levo-dopa, a new and powerful drug used for Parkinson's disease.

"Me-Too"

If a drug has previously been marketed, another company's version is called a "me-too" drug. In some cases, it is unnecessary for a company wanting to market a "me-too" drug to go through the same type of extensive testing required of the original drug. FDA therefore has established an Abbreviated New Drug Application (ANDA). Depending on the nature of the drug, FDA requires varying amounts of information from a manufacturer who wants to make the drug.

In the same vein, it is important to note that FDA does not issue patents for drugs. They are issued by the U.S. Patent Office and last for 17 years. If a firm develops a new drug, it can get a patent and take legal action against any company that tries to market the identical drug during the 17-year period. Once the original patent expires, any other company can market a "me-too" version of the drug under its "generic" name or under a new trade name if the drug meets all the requirements of the law.

Changes in the NDA

Whenever a company wants to change any part of the procedure for making a drug, it must seek FDA approval. This is because even what appears to be a minor change in the manufacturing process can affect the final product. This type of approval, which is sought frequently, is called a supplemental New Drug Application.

The same applies to labeling. Very often after a drug has been in use for some time, new information develops about it. Perhaps there are new purposes for which it can be prescribed, or new warnings that need to be included. Any change must be approved by FDA.

Withdrawing NDA Approval

If an approved drug is found to produce an unexpected side effect or to be less safe or effective than anticipated, FDA can seek to withdraw approval. FDA gives the firm an opportunity to present its views. In some cases, this may involve a hearing.

In landmark rulings in five "drug effectiveness" cases June 18, 1973, the U.S. Supreme Court supported FDA's authority to be the final judge of whether a drug is safe and effective, and to deny a hearing to a company that cannot show that significant facts are at issue.

Labeling for Patients

In 1970, FDA took a major step to provide information about prescription drugs directly to patients. The Agency decided that manufacturers of oral contraceptives—"The Pill"—must include in all packages received by patients a statement summarizing the potential risks of the drug. Physicians were provided with brochures listing the benefits and risks of the drug in greater detail.

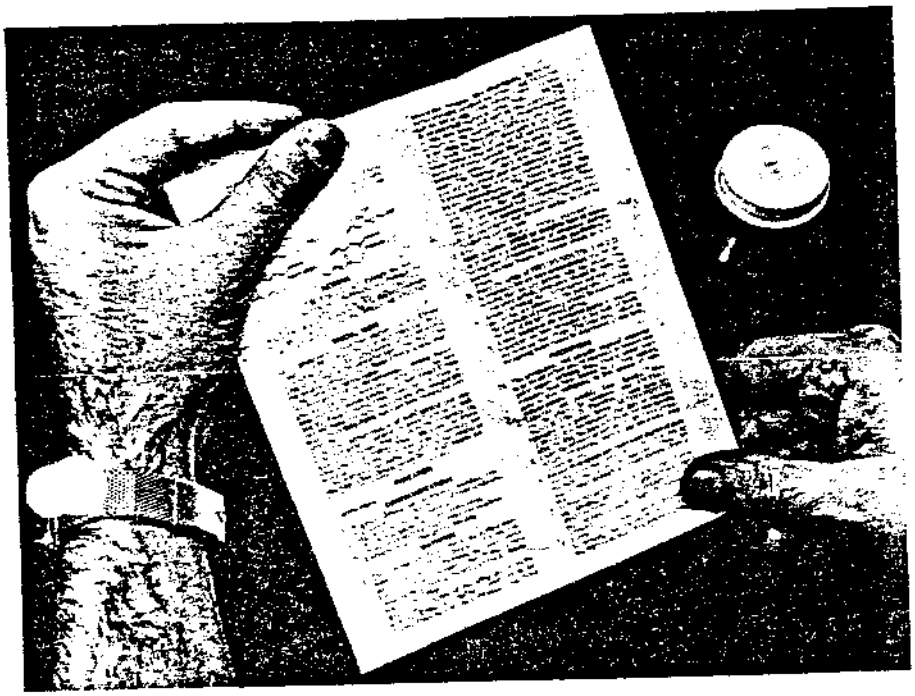
The reason for this decision was that FDA believed women should participate in the decision on whether to take "The Pill." Drugs used for contraception are different from others in that they are given to healthy women, not to treat disease, and there are nonchemical alternatives.

In 1973, FDA decided that information should be provided directly to patients on two other contraceptive drugs, diethylstilbestrol (DES) as a "morning after" pill and Depo-Provera as a long-acting injectable contraceptive. Information may be provided directly to patients on other prescription drugs in the future.

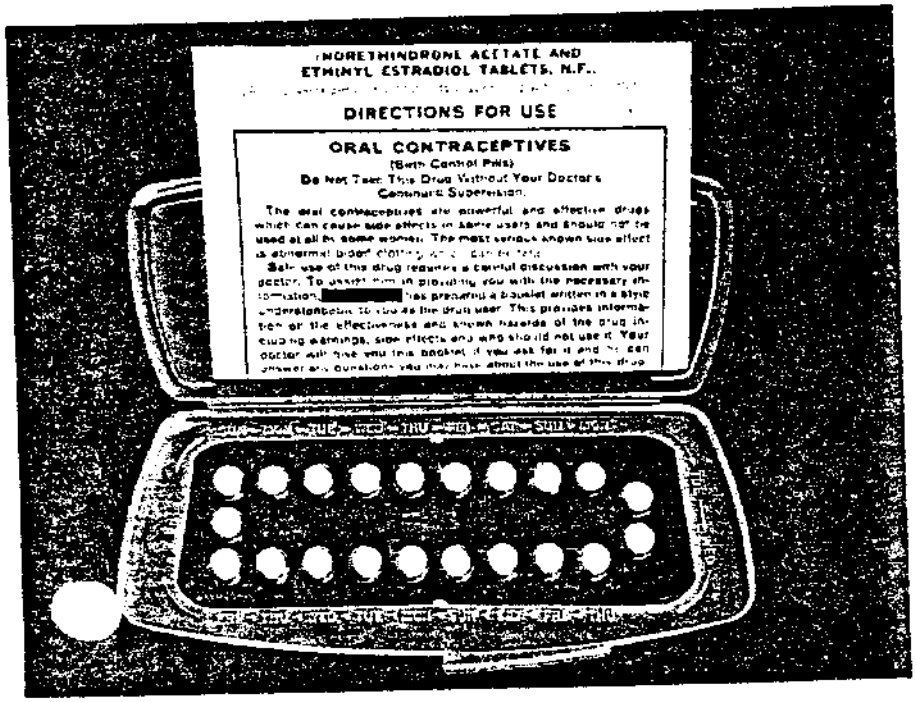
Patient Consent

Increasing concern has been expressed in recent years about the use of prisoners and other institutionalized people for drug studies. People in institutions are the most convenient volunteers for some studies because they are in controlled environments.

However, FDA does not believe that any person should be required to participate in a study involving investigational drugs, or duped into taking a drug he does not need. The law requires that before using investigational drugs on humans,



The package insert must accompany the drug whenever it is shipped in interstate commerce. It also serves as the basis for all information on the drug disseminated by the manufacturer.



In 1970, FDA decided that manufacturers of oral contraceptives must include in all packages received by patients a statement summarizing the potential risks of the drug. This has become known as a "patient package insert."

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To help improve medical communications, FDA publishes a Drug Bulletin for all physicians, dentists, pharmacists, and other health professionals.

the physician must obtain the person's consent. That consent must be informed—that is, the patient must know what the risks are. The only exception is when consent is not feasible or when in the physician's judgment it is contrary to the best interests of the person.

Drugs for Pregnant Women and For Children

FDA is concerned about the use of drugs by all persons, but especially about drugs being taken by pregnant women and by children. A drug can have a very different effect on the fetus than on the mother, since the fetus is particularly sensitive to biological change.

Investigators who believe a drug may be useful in pregnant women have to be extra careful in testing them. Most drugs have not been tested in pregnant women, and the labeling is required to indicate that. However, extensive testing is required in pregnant animals.

Thus, many physicians know which drugs pass through the placenta to the fetus. In treating a pregnant woman, physicians have to make a delicate benefit-risk decision.

The same problem applies to drugs for children. Many drugs available for adults are also prescribed for children. Some labeling and standard charts provide guidance for the physician.

However, FDA believes that drugs to be used in children should be tested in them under very carefully controlled circumstances. The only children who would ever receive a drug in a test situation are those who need it for a disease. This area is now receiving considerable attention at FDA.

Certification

The law provides that two types of drugs—antibiotics and insulin—must not only be approved generally for marketing by FDA, but must be certified batch-by-batch. The manufacturers pay for this service. FDA tests random samples from each batch for purity and potency. The manufacturer may not release the batch until FDA certifies it.

Advertising

One of the most significant sources of information about prescription drugs is information supplied by the drug manufacturers to physicians, through advertising in medical journals, direct mail, or salesmen known as "detailmen."

The law requires that information supplied to physicians about prescription drugs be truthful, fully informative, and fairly balanced. Claims for a drug's effectiveness must be balanced with information on its side effects.

FDA extensively regulates prescription drug advertising and mail promotion. Whenever material is found misleading, FDA can seek to seize the drug on the grounds that it is "mislabeled." In virtually all cases, however, FDA seeks alternatives that have proven more effective. Among these are remedial ads required by FDA to be placed by the drug company in the journals in which a misleading ad appeared, or remedial letters sent to physicians.

It is generally acknowledged that the prescription drug information system in the United States needs improvement, so that physicians are assured of having accurate and complete information. FDA publishes a Drug Bulletin for all physicians, dentists, pharmacists, and other health professionals which reports significant new regulatory developments. FDA is developing further systems to try to provide physicians with the best information about drugs.

What Consumers Can Expect

The system of new drug development and control in the United States is far from perfect. Admittedly, improvements are needed.

No matter what system we set up, as technical knowledge grows, presently acceptable procedures and systems will appear inadequate. This is part of scientific progress.

But despite the defects in the system, consumer exposure in the United States to drug products of unproven safety and effectiveness is minimal. This does not mean that patients are never exposed to unnecessary hazards from prescription drugs. All medicines have the potential to harm as well as benefit, and despite all precautions, prescription medicines at times are misused or misunderstood.

Looking beyond FDA's responsibilities in the regulation of drugs, ultimately it is up to the "three P's"—physicians, pharmacists, and patients—to make sure that drugs are used wisely and that FDA's regulatory efforts result in true benefits to the public.

Wayne L. Pines is editor of FDA CONSUMER.

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FORM FD-1571 (4/67)
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

Form Approved
Budget Bureau No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor Gould A. Andrews, M.D., Chairman, The Medical Division

Address Oak Ridge Associated Universities, Oak Ridge, Tennessee 37830

Date July 10, 1972

Name of Investigational Drug Strontium -85 m

To the Secretary of Health, Education, and Welfare
For the Commissioner of Food and Drugs
Washington, D.C. 20204

Dear Sir:

The sponsor, Gould A. Andrews, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of five copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

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9. The names and a summary of training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and ...ating the evidence of safety and effectiveness of the ... as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of claimed investigational exemption for a new drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the ...cal trial, phase 3. The first two phases may overlap when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. *Clinical trial.* This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. It is understood that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. It is understood that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

Very truly yours,

Oak Ridge Associated Universities, Medical Division
(Sponsor)

Per S/
Gould A. Andrews, M.D.

Chairman, The Medical Division
(Indicate authority)

, notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. ress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

Form Approved
Budget Bureau No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

ame of applicant _____

Address _____

Date _____

Name of new drug _____

☐ Original application (regulation §130.4).
☐ Amendment to original, unapproved application (regulation §130.7).
☐ Supplement to an approved application (regulation §130.9).
☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology, and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

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8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. *a.* An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C. 20204), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

_____

(Applicant)

Per _____

(Responsible official or agent)

_____

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

STATEMENT OF INVESTIGATOR
(Clinical Pharmacology)

Form Approved
Budget Bureau No. 85-R0064

TO SUPPLIER OF THE DRUG *(Name and Address)*

Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37830
C.L. Edwards, Principal Investigator

NAME OF INVESTIGATOR *(Print or Type)*
S.J. Adelstein, M.D., Ph.D.

DATE
April 13, 1971

NAME OF DRUG
Gallium-67 citrate (IND No. 5489)

Dear Sir:

The undersigned, S.J. Adelstein, M.D., Ph.D., submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.

1. A STATEMENT OF THE EDUCATION AND TRAINING THAT QUALIFIES ME FOR CLINICAL PHARMACOLOGY

B.S., M.S. Mass. Institute of Technology 1949
M.D. Harvard University 1953
Ph.D. Mass. Institute of Technology 1957
(Biophysics)
House officer, senior resident physician and chief resident physician, Peter Bent Brigham Hospital, Boston, Mass. 1953-1954,1957-1958,1959-1960
Mosely Traveling Fellow of Harvard University to the Department of Radiotherapeutics, Cambridge University, 1958-1959
Fellow in the Division of Nuclear Medicine, Johns Hopkins Hospital, 1968. Course in radiochemistry and radiopharmaceutical chemistry with Dr. H. Stern
Director, Division of Nuclear Medicine, Peter Bent Brigham Hospital, 1968- , Chief Division of Nuclear Medicine, Children's Hospital Medical Center, Boston, Mass., 1970- , Associate Professor of Radiology, Harvard Medical School, 1968- .

2. THE NAME AND ADDRESS OF THE MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL PHARMACOLOGY WILL BE CONDUCTED

r Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115

3. THE EXPERT COMMITTEES OR PANELS RESPONSIBLE FOR APPROVING THE EXPERIMENTAL PROJECT

Isotopes Committee, Peter Bent Brigham Hospital
Pharmacy Committee, Peter Bent Brigham Hospital
Committee on Human Studies, Peter Bent Brigham Hospital

4. THE ESTIMATED DURATION OF THE PROJECT, AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED

1 year
Maximum number of subjects - 25

5. A GENERAL OUTLINE OF THE PROJECT TO BE UNDERTAKEN *(Modification is permitted on the basis of experience gained without advance submission of amendments to the general outline.)*

Gallium-67 will be purchased from the Isotopes Development Center of the Oak Ridge National Laboratory and compounded into Gallium citrate according to the method specified under paragraph IIIA of Dr. Ralph M. Kniseley's memorandum, dated Dec. 15, 1970 seeking joint support from the USAEC and NCI to study Gallium-67 in lymphoma and lung cancer. The agent will be prepared by Dr. M.A. Davis, Chief Radiopharmaceutical Chemist to the Joint Program in Nuclear Medicine, Children's Hospital Medical Center/Peter Bent Brigham Hospital. The agent will be administered only to patients with microscopic evidence of lymphoma and cancer in accordance to the protocol outlined in Dr. Kniseley's memorandum. Consent will be obtained from patients in accordance with the guidelines of the Committee on Human Studies, Peter Bent Brigham Hospital.

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6. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE GOVERN HIS RECEIPT AND USE OF THIS INVESTIGATIONAL DRUG

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended or terminated to return to the sponsor any unused supply of the drug.

c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.

d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effect which may reasonably be regarded as caused by, or is probably caused by, the new-drug shall be reported to the sponsor promptly; and if the adverse effect is alarming it shall be reported immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.

e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date the new-drug application is approved for the drug; or if no application is to be filed or is approved until 2 years after the investigation is discontinued and the Food and Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him,

B.L. Holman, M.D.
D.E. Drum, M.D.
S. Treves, M.D.

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any patients or any persons used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

S. A. Adelstein
(Name of Investigator)

Peter Bent Brigham Hospital
(Address)

Boston, Massachusetts 02115

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