725538

The Committee on Clinical Investigations and Use of Radioisotopes

hereby approves the program with the following title:

^{99m}Tc-S Colloid

Appl for TND 4172 made = colloid

CIRC # 15e has been assigned to this program.

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

REPOSITORY Records Holding Area Bldg. 494
COLLECTION Committee - Clinical Investigations and use of Radioisotopes
BOX No. 4
FOLDER CIRC # 15E

Harold Atkins, M.D., Chairman

Donald C. Borg, M.D.

Stanton Cohn, Ph.D.

Horton A. Johnson, M.D.

Kanti Rai, M.D.

Date: 2-16-1970

Place: Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Committee on Clinical Investigations and Uses of Radioisotopes

Approval Recommended ✓ Date 2-16-70

Disapproval _____ Date _____

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

20 Feb '70
Date

1179711

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: May 25, '71

TO: DR. Athins

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

SUBJECT: CIRC Proposal 15E

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 15E is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on Feb. 16 19 70. Do you wish to make any substantive changes in your proposal?_____

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office?_____. Please include the nature and frequency of such effects.

_____

_____

_____

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

The Sponsoring Physician on this proposal is_____. Has there been a change of Sponsoring Physician or Responsible Investigators?_____

_____

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its diliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER 15E IS: Continuing ☐

Inactive ☒

Signed Harold L. Athins May 25, 1970
Date

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

1179712

Clinical Investigation and Radioisotope Utilization Committee

Minutes of Meeting - February 16, 1970

The meeting was called to order at 1:35 P.M. Present were Drs. Atkins, Borg, Cohn, Johnson and Rai.

(A) CIRC #49 - $^{56}Mn\ SO_4$ Distribution in L-Dopa Treated Patients - Dr. Cotzias

The Committee approved this application with the suggestion that numerous typographical errors be corrected. These included:

page 1: $^{56}MnSO_4 \cdot H_2O$ wrongly typed

page 2: " " " "

page 2, line 3: ? 101.3 correct

page 2, 4th line from bottom: Millirad should not be capitalized

page 5: omit collimated from description of whole body counter

page 7: next to last line - nomogram

Reference #4: misspelled, Mean should be Mena

(B) CIRC #15e - ^{99m}Tc-Sulfur Colloid - Dr. Atkins

The Committee approved the application with the suggestion that a number of typographical errors be corrected.

Letter to FDA: change humans to man

Appendix 1, page 2, line 6: volume of $^{99m}TcO4$ in 2N Hcl

page 2, line 2: dolloid, should be colloid

page 3, line 3 below table: injested should be injected

page 3, next to last line: change humans to man

Appendix 2, page 4, line? dose should be site

page 4, B: add, Usual dose is 1 mCi in each foot

Appendix 3, page 4, line 5: change humans to man

Respectfully submitted,

Harold L. Atkins, M.D.

/bn

1179713

cc: Dr. Cotzias
Committee Members

Rec IND 4172 for enclosure of EIC transmittal 24 Feb 1970 of HLA addendum dated 19 Feb 1970

BNL 13905

Factors Affecting Distribution of Technetium-Sulfur Colloid[1]

H. L. Atkins W. Hauser, and P. Richards

Medical Research Center
and
Department of Applied Science
Brookhaven National Laboratory
Upton, L.I., N. Y. 11973

Running title: Distribution of Technetium Colloid.

[1]Research supported by the U.S. Atomic Energy Commission.

Proofs sent to:

H. L. Atkins, M.D.
Medical Physics Division
Medical Research Center
Upton, L.I., N. Y. 11973

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ABSTRACT

Technetium-99m sulfur colloid was prepared by two different methods: a) bubbling H_2S through an acid solution of pertechnetate, or (b) acid reduction of thiosulfate. The first method produces a colloid of smaller particle size which more readily concentrates in the bone marrow in comparison to the latter method. Distribution of colloidal material in the liver, spleen and bone marrow was studied in mice following I.V. administration. Marrow concentration is increased by the use of larger doses or pretreatment with "cold" H_2S colloid, gelatin, carbon or polystyrene latex particles. The effect of pretreatment with "cold" H_2S on distribution of thiosulfate colloid is to decrease marrow localization and increase the amount in the spleen. Apparently both particle size as well as number of particles administered affects distribution of colloid in the reticuloendothelial system.

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INTRODUCTION

The rate of removal and the distribution of colloidal particles introduced into the blood stream is dependent on blood flow to the reticuloendothelial organs and extraction efficiency of the phagocytic cells. Blood flow is affected by such factors as cirrhosis, vascular shunts, cardiac output and functional obstruction of blood vessels leading to the RE organs.

The extraction efficiency of the phagocytic cells is affected by a number of factors, some of them poorly understood. Among the factors discussed in the literature are particle size, number of particles injected, presence of carrier, stabilizer or competing substances, and the immunological competence of the subject (Dobson, 1957; Meredith, 1961; Meredith et al., 1962; Zilversmit et al., 1952; Dobson et al., 1949; Dobson and Jones, 1952; Scott et al., 1967; Neukomm et al., 1957; Benacerraf et al., 1957; Schapiro et al., 1966; Kampschmidt et al., 1966; Saba and Di Luzio, 1969). There is some confusion concerning the importance and mechanism of some of these factors. Many of the colloids are not homogeneous with regard to particle size, and in many studies the effects of carrier or stabilizer were overlooked. The effect of particle number was sometimes confused with particle size.

In our clinical studies with technetium-99m as the sulfur colloid, we have been interested in bone marrow scanning. We undertook these studies in order to ascertain what factors might be involved in concentrating the colloid in the marrow organ and to compare two different methods of technetium sulfur colloid formation in terms of tissue distribution.

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METHODS

Technetium-99m sulfur colloid was formed by two different methods. The first method (Atkins et al., 1966) (H_2S method) is as follows: To 4-5 ml pertechnetate solution add 0.5 ml conc. HCl and 50 mg gelatin dissolved in 1-2 ml warm H_2O. Bubble H_2S through solution for 5 min. Stir for 5 minutes and then bubble nitrogen through the solution for 5 min. The pH is adjusted to 5.5-6.5 with NaOH and the solution passed through a 0.3-μ sterile filter. The final volume is 8 ml.

Another method utilizes the acid reduction of thiosulfate (Stamm). To the pertechnetate solution is added 50 mg gelatin dissolved in 1-2 ml H_2O, 1 ml $Na_2S_2O_3$ solution (4 mg/ml) and 1 ml 1N HCl (dropwise in ~ 1 min). Stir in boiling H_2O bath for 8 min. Cool. Adjust pH to 5.5-6.0 with NaOH.

White mice weighing about 25 gm were injected via a tail vein with varying amounts of the colloids. The mice were sacrificed at 1-2 hours after colloid injection, and liver, spleen, both femurs and carcass activity determined by counting with a 2x2-in NaI (Th) crystal detector at 25-30 cm distance with a standard deviation in counts of ± 2% or less. The total counts obtained were assumed to be 100% of the injected dose, and this was confirmed by comparing one group of mice to an injection standard.

It had been previously determined that 6.0% of total marrow activity following administration of technetium sulfur colloid was in the two femurs (Carsten). Using this assumption in the various studies to be reported, it was possible to account for 88-99% of the total-body activity in the liver, spleen and bone marrow.

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In addition to determining the distribution with varying doses of colloid, the effect of pretreatment with several substances was studied. These were gelatin in 3% solution, polystyrene latex particles 0.088 μ in diameter, carbon particles 0.020 μ in diameter and "cold" technetium sulfur colloid. The formulation of the H_2S colloid was varied by increasing the amount of gelatin present during the H_2S bubbling procedure by factors of 2, 3 and 5.

RESULTS

The effect of increasing the dose of the H_2S colloid on liver and marrow concentration is seen in Fig. 1. About 84-87% of the activity was found in the liver and 0.45-0.50% in the femora with doses up to 0.005 ml/gm. Beyond this, up to 0.02 ml/gm, there was a steady decrease in liver concentration and an increase in femoral marrow concentration. The differences are statistically significant.* It was not possible to go to higher doses, since the animals could not tolerate them, due to the volume and pH change.

Increasing the amount of gelatin used as stabilizer also changed the organ concentration in a manner similar to increasing the dose of colloid. However, there was little effect beyond doubling the gelatin concentration. The results are shown in Fig. 2. With decreasing doses of colloid containing large amounts of stabilizer, the liver and femoral marrow concentrations approached the values obtained with the 0.6% gelatin.

Pretreatment with gelatin or "cold" H_2S colloid one-half hour before the dose of radioactive H_2S colloid also caused decreased liver uptake and increased marrow concentration (Fig. 3). The injection of

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*$p < 0.05$ by t test.

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2.24×10^{14} particles of 0.088 μ polystyrene latex particles (8.96×10^{15}/kg body weight) prior to injection of the H_2S colloid reduced liver concentration to 67.8 ± 12.7% of the activity while increasing the femoral marrow activity to 0.79 ± .09%. Carbon particles (3.44×10^{16}/kg body weight or 8.6×10^{14} particles total) in the form of India ink were also injected prior to the H_2S colloid and had a lesser but still definite effect. The liver activity was reduced to 72.5 ± 2.0%, while femoral marrow activity was increased to 0.69 ± 0.12%.

The influence of these various factors on splenic radioactivity was not consistent (Fig. 4). Certainly, varying the dose of colloid had little discernible effect. The effect of the R.E. blocking agents, such as gelatin, polystyrene latex particles and carbon was a tendency toward increased splenic localization, but the effect was not great.

The distribution of the thiosulfate colloid was similar to the H_2S colloid in small doses, but increasing the dose to a practical limit did not decrease the liver concentration or diminish marrow localization. The effect of pretreatment with gelatin, 0.09 mg/g body weight, was negligible. When "cold" H_2S colloid (0.012 ml/g body weight) was administered one half hour prior to injection of radioactive thiosulfate colloid, no effect on liver activity was noted. However, a significant increase in splenic radioactivity and a decrease in femoral activity was evident (Fig. 5).

DISCUSSION

The two colloids which we have studied differ both physically and biologically. The studies of Stern, McAfee and Subramanian (1966) with a thiosulfate colloid preparation indicate only 23% passing through a

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0.45-μ millipore filter, whereas more than 80% of the H_2S colloid will pass through a 0.45-0.3-μ millipore filter. In low doses the distribution of each in the reticuloendothelial system is the same but with larger doses relatively more of the H_2S colloid goes into the marrow and less to the liver.

The differences in behavior may be a function of particle size or number of particles injected. The gradually-increasing slope of the curve for relative marrow uptake as dose of H_2S colloid is increased is similar to the curves relating disappearance half-time to increased carrier (Meredith, 1961; Dobson and Jones, 1952), or to the number of particles per kilogram body weight (Cohen, et al., 1968). Why increased carrier or dosage should change the in-vivo distribution is not clear unless the efficiency for clearance of the blood stream by the R.E. cells in the various body sites differs from one site to another.

The effect of blocking agents on the two colloids is markedly different but may be a function of dose. The blocking agents such as gelatin, polystyrene latex and carbon definitely affected distribution of the rather large doses of H_2S colloid. The effect of "cold" H_2S colloid on the active material was the same as increasing the dose. Gelatin pretreatment had very little effect on the thiosulfate colloid distribution but presumably, if larger doses of colloid could have been given, there might have been an apparent effect.

Although some investigators have attributed much of the behavior of gelatin-stabilized colloids to the gelatin itself (Kampschmidt et al., 1966; Filkins and Di Luzio, 1966; Maurer, 1954; Murray, 1963; Koenig et al., 1965), this cannot account for all the observations, such as the effect of polystyrene latex or carbon particles. Especially interesting

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is the effect of a loading dose of "cold" H_2S colloid on the distribution of the thiosulfate colloid. Apparently there is a preference for the smaller H_2S colloid particles by the R.E. cells of the marrow, while the spleen took up the excess larger particles when the marrow sites were blocked. This effect cannot be ascribed to the gelatin stabilizer, since gelatin itself in larger doses did not produce the same changes.

We did not perform blood disappearance curves with these colloids, but if we assume that the change in distribution parallels the change in disappearance half-time as demonstrated by Cohen (1968) with increase in number of particles administered, then we can obtain some idea of the number of particles/ml. The assumption by Cohen is that a critical dose is 10^{13} particles/kg body weight, beyond which disappearance half-times from the blood and body distribution are affected. From our curves the dose of 0.005 ml/gm body weight corresponds to this point, i.e., there should be 10^{13} particles of the H_2S colloid in 5 ml or 2×10^{12} particles in a milliliter of the preparation.

The doses under discussion are not practical in considering human use. For a 70-kg man this would mean 350 ml of colloidal suspension to be administered, an impractical amount. However, the use of gelatin as a blocking agent is practical and has been used to measure reticuloendothelial function by others (Wagner and Iio, 1964). It may be possible to increase marrow deposition of technetium-99m sulfur colloid by pretreatment with gelatin.

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CONCLUSIONS AND SUMMARY

Technetium-sulfur colloid formed by bubbling H_2S through an acid pertechnetate solution in the presence of gelatin as a stabilizer is distributed primarily to the liver spleen and bone marrow following intravenous administration. Factors which tend to delay blood disappearance of colloids (increase in carrier, use of "blocking agents) also result in a change in relative distribution with less liver deposition and greater marrow concentration.

A similar colloid formed by acid reduction of sodium thiosulfate consists of larger particles which localize in the marrow to a lesser extent and, when in competition with the H_2S colloid, localize in the marrow in even smaller concentration and concentrate more readily in the spleen.

ACKNOWLEDGMENT

The technical assistance of Mr. W. Lehman is great appreciated.

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ILLUSTRATIONS

		Neg. No.
Fig. 1:	Effect of increasing the dose of technetium-sulfur colloid (H_2S method) on the concentration in liver and bone marrow.	4-123-69
Fig. 2:	Effect of changing the concentration of gelatin stabilizer on distribution of the technetium-sulfur colloid (H_2S method) in liver and bone marrow.	4-124-69
Fig. 3:	Changes in distribution of technetium-sulfur colloid (H_2S method) induced by pretreatment with gelatin and "cold" colloid. Also shown is the concentration in liver and bone marrow of two different doses of the colloid formed by the thiosulfate method.	4-125-69
Fig. 4:	Splenic concentration of radioactivity following administration of technetium-sulfur colloid prepared by two methods and the effect of pretreatment with gelatin and "cold" colloid.	5-1879-69
Fig. 5:	Splenic and marrow concentration of technetium-sulfur colloid (thiosulfate method) and the effect of pretreatment with "cold" H_2S colloid and gelatin.	5-1878-69

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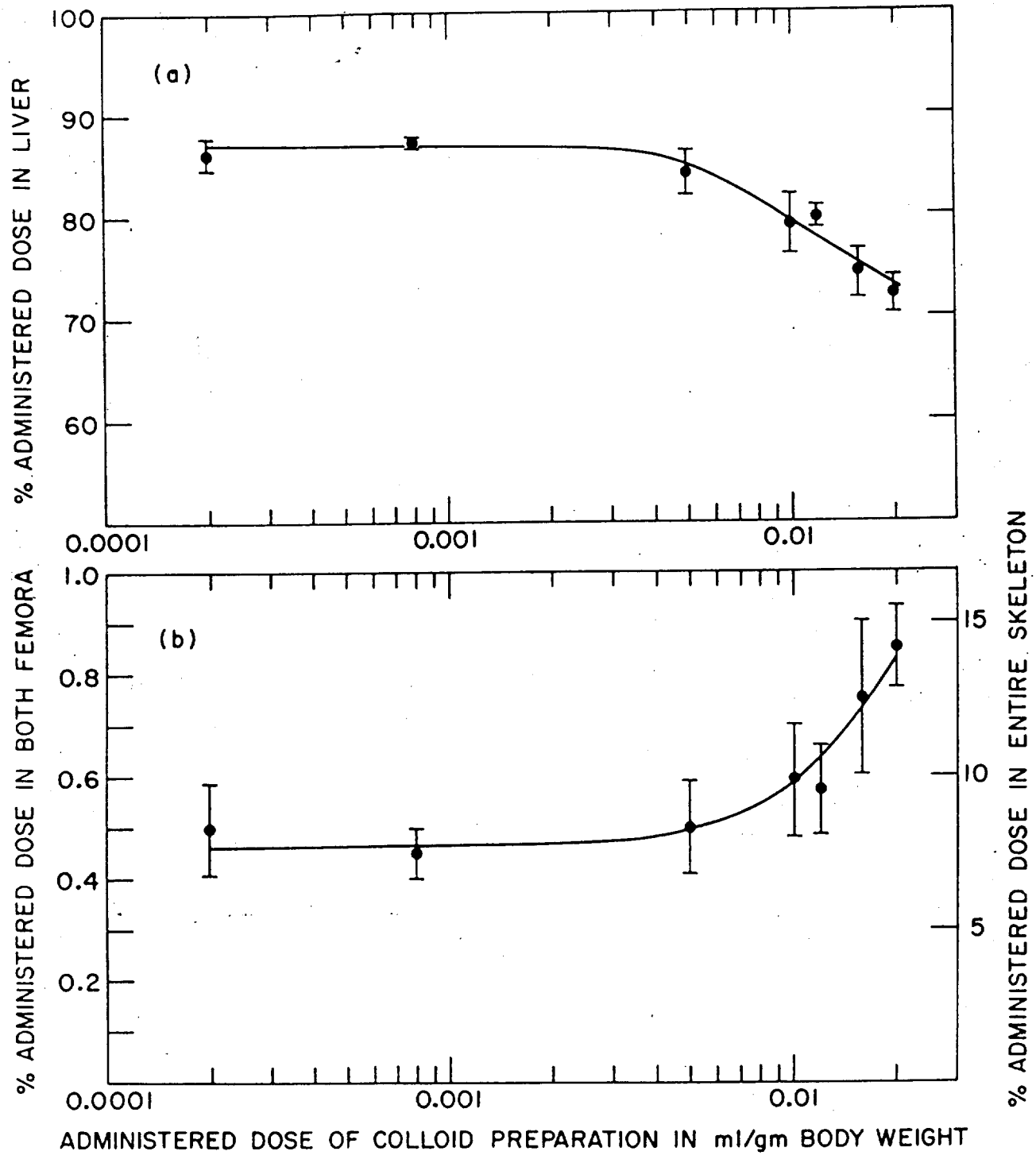

FIGURE 1

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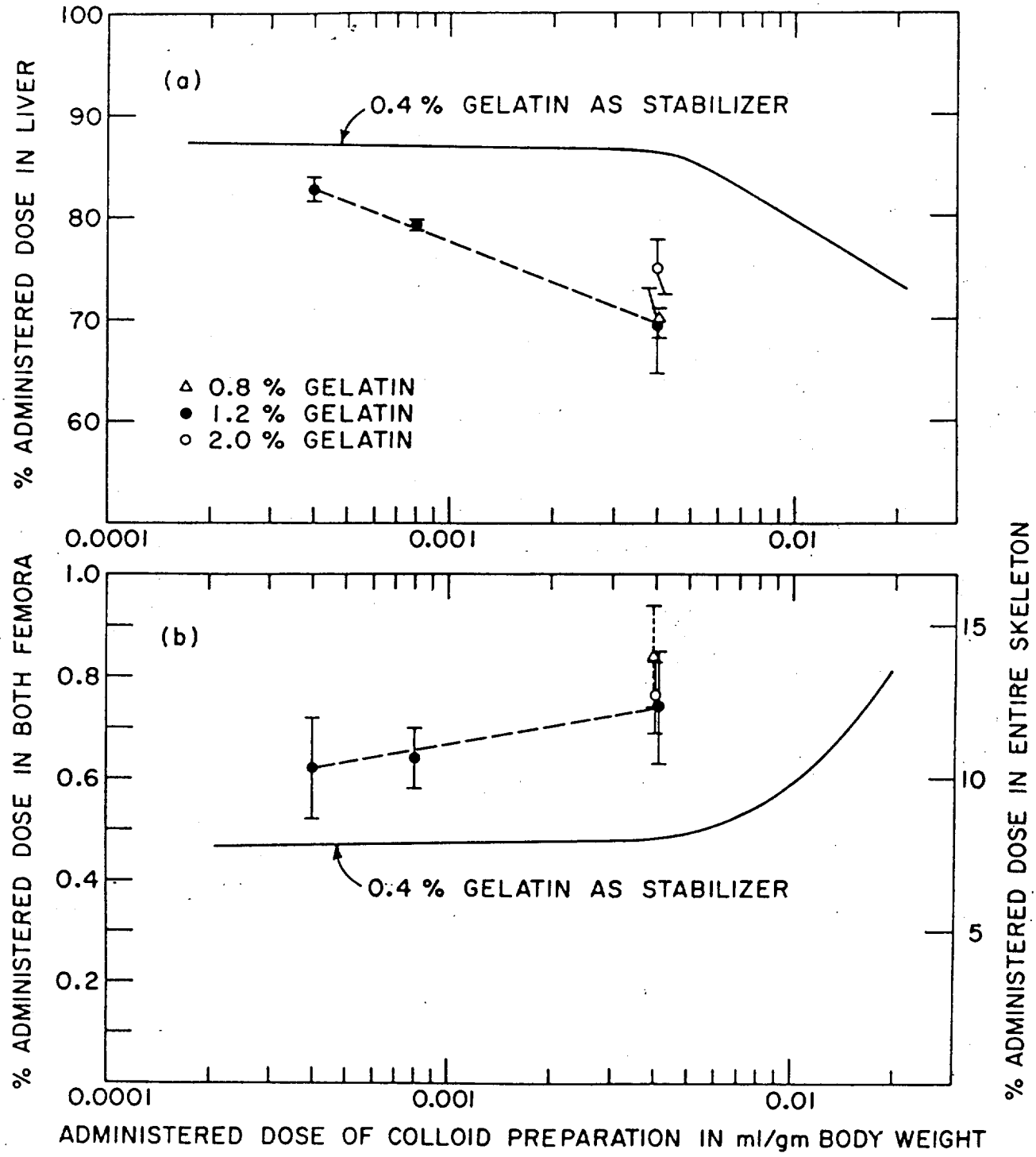

FIGURE 2

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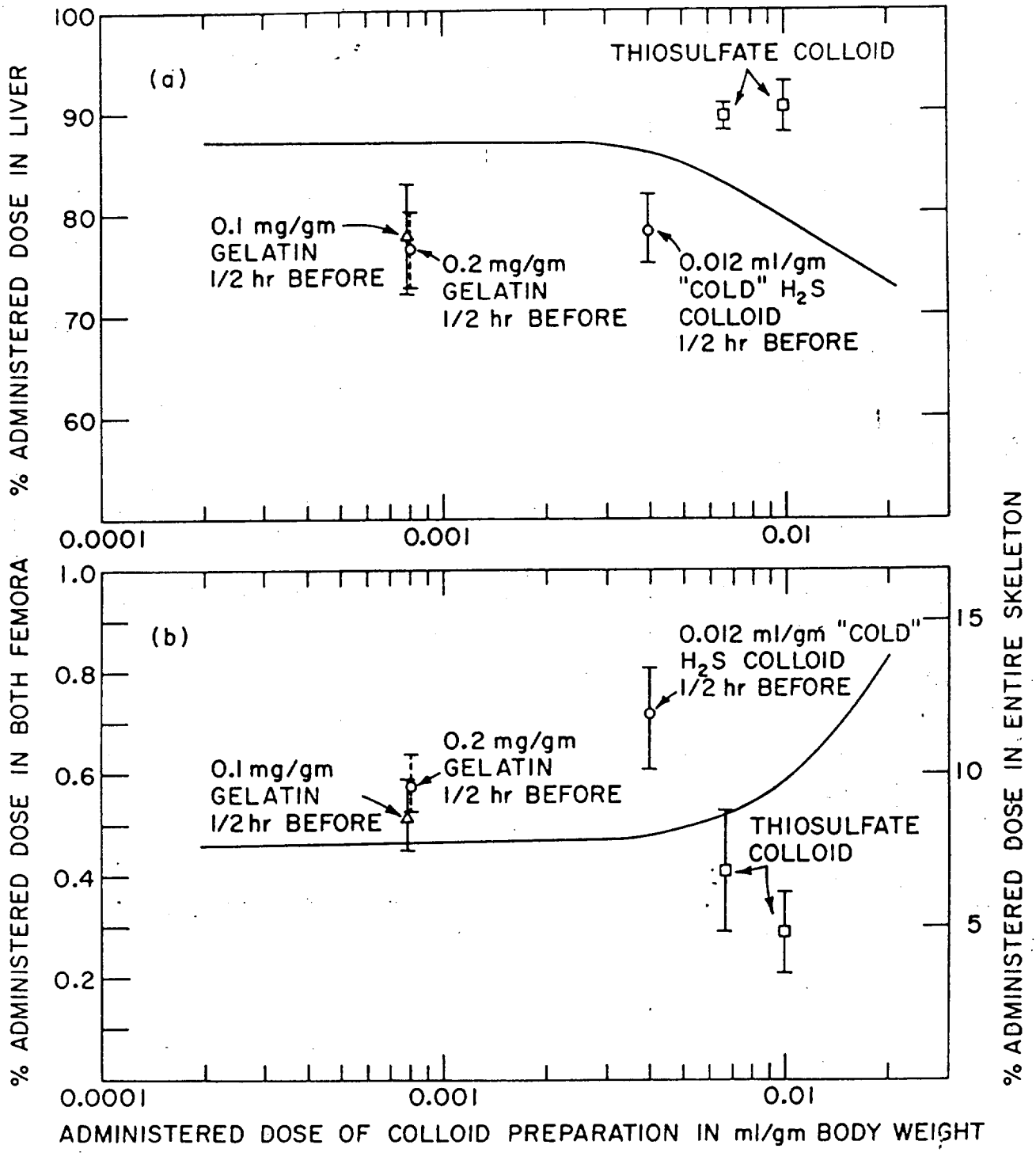

FIGURE 3

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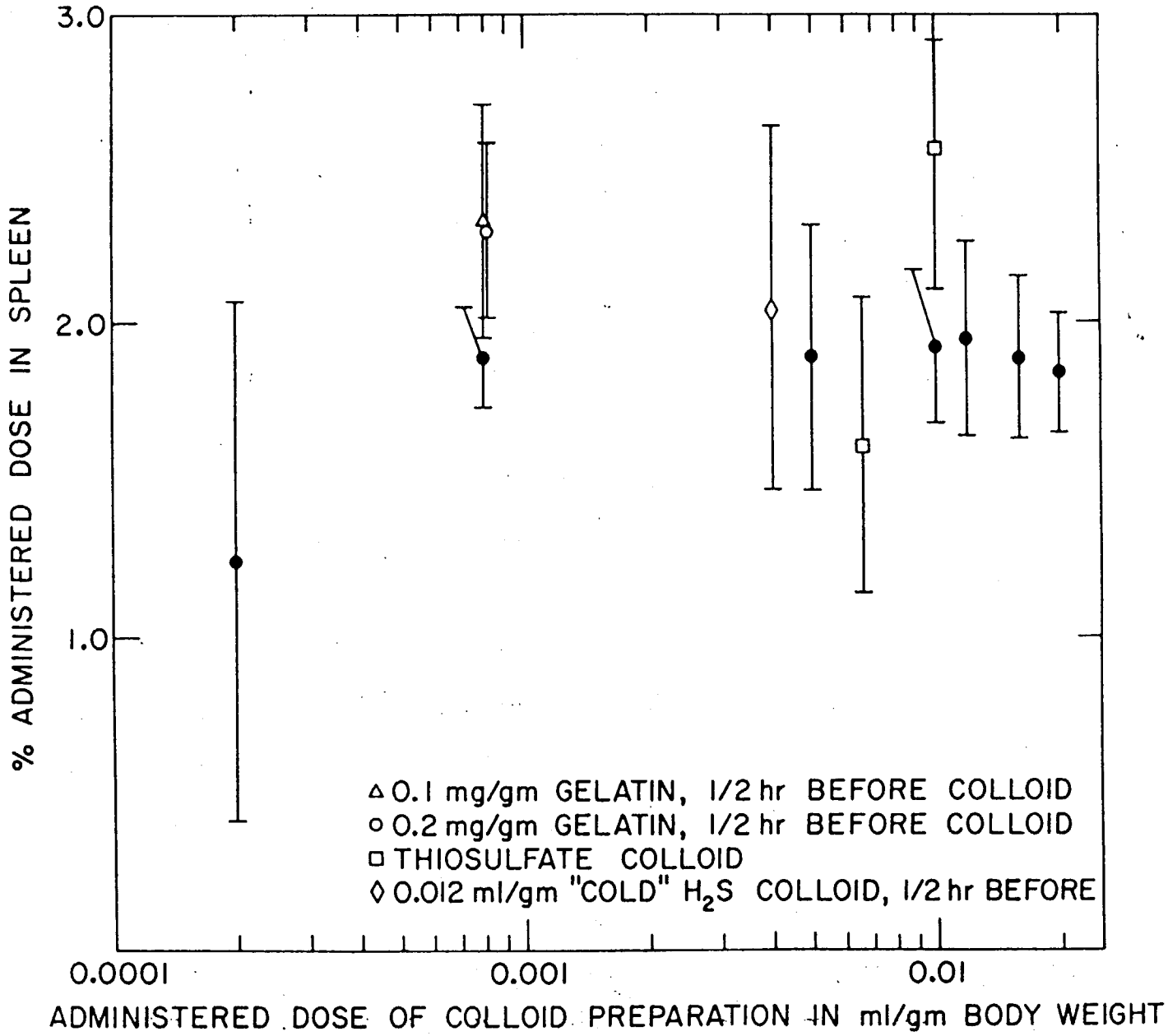

FIGURE 4

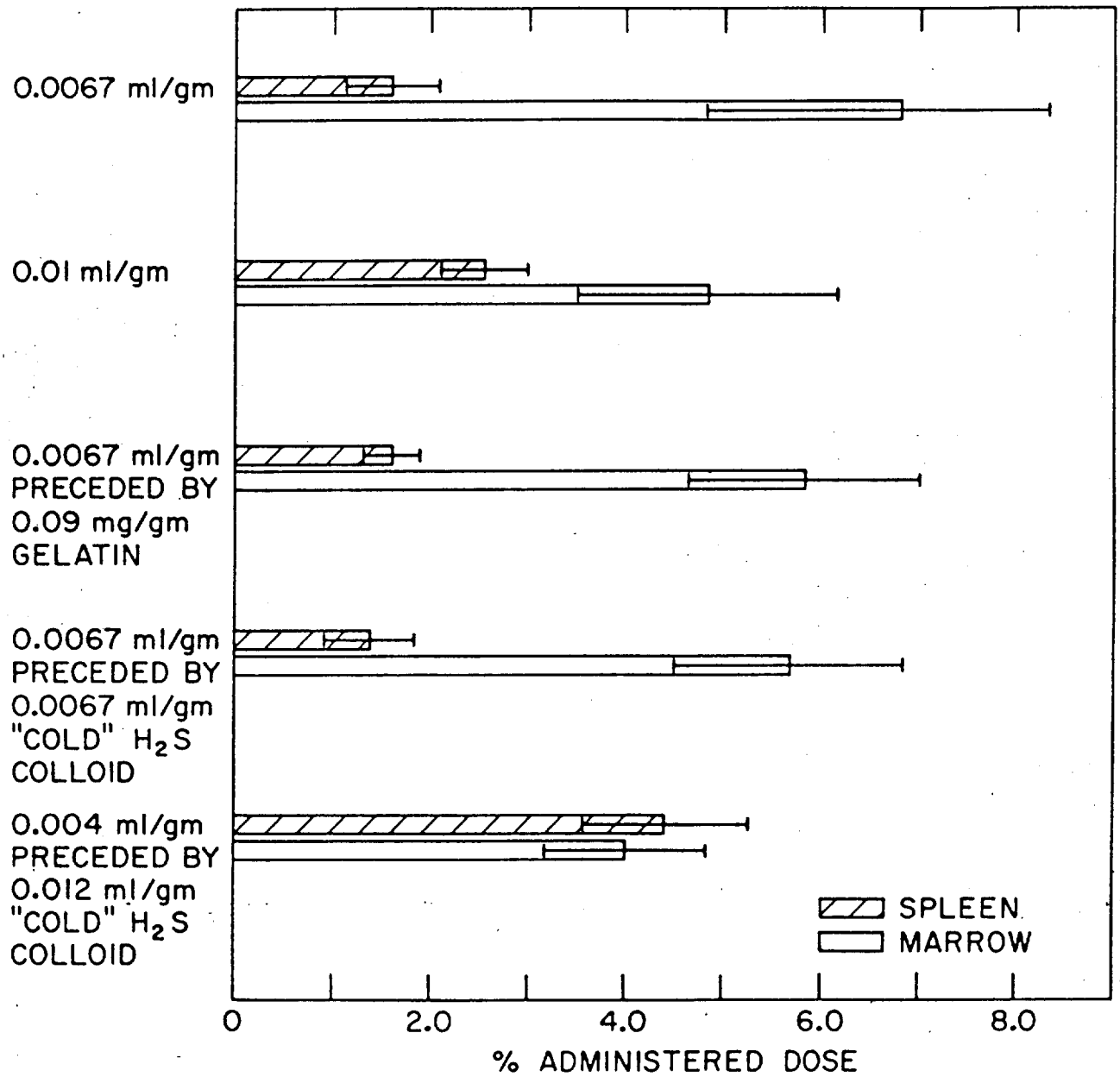

FIGURE 5

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BNL 14244

Five Years of Experience with ^{99m}Tc-Sulfur Colloid*

W. Hauser, M.D., H. L. Atkins, M.D., and P. Richards, B.S.

Medical Research Center
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Upton, L.I., N. Y. 11973

*Research supported by the U.S. Atomic Energy Commission.

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Scintigraphic examinations of the organs containing the bulk of the cells of the reticuloendothelial system can be carried out after the intravenous or subcutaneous injection of suitable radioactive colloidal substances. Since 1964 we have been using this approach and have been scanning liver, spleen, bone marrow and lymph nodes with technetium-99m-sulfur colloid. This approach is perhaps not the most refined when a scan of only one of these organs is wanted, but at the present time it is more practical than the use of any of the other radiopharmaceuticals specifically designed for either liver, spleen or bone marrow scans. From Table I it can be seen that the radiation dose absorbed from the high dose of ^{99m}Tc-S colloid (with a usable photon yield of 0.9/disintegration) compares favorably with that absorbed from the lower doses of the other scanning agents.

To take full advantage of the potential of ^{99m}Tc-S colloid it has been necessary to modify scanning equipment and technique. In this paper we want to summarize all the modifications we have introduced since 1964[1-5] and then give an evaluation of the results obtained with ^{99m}Tc-S colloid as a scanning agent.

Technetium-99m-sulfur colloid

Technetium was first suggested as a tracer for clinical studies by Richards in 1960.[6] Subsequently a technetium-99m-labeled sulfur colloid was developed at Brookhaven National Laboratory (H_2S method) and evaluated as a scanning agent at several institutions.[7-9] Since then other methods have utilized other sources of sulfur such as

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thiosulfate and antimony sulfide in order to simplify and speed up the procedure.[10,11] Not all colloidal forms of technetium have the same biological distribution, and each has certain advantages and disadvantages. We have, however, continued to use the originally-developed method with a few modifications. The currently-used method is:

A. Source of technetium.

1. Technetium-99m is obtained as pertechnetate from its parent molybdenum-99 by solvent extraction with methyl ethyl ketone.[8,12,13] The production of technetium by this method makes $^{99m}TcO_4^-$ available in any desired concentration and assures a low molybdenum contamination which is essential for the production of colloid by the H_2S method.
2. Molybdenum-99 contamination of the separated technetium-99m is determined by a recently-developed method using a commercially-available well-type ionization chamber and lead shield.[14]

B. Preparation of the colloid.

1. While stirring, ½ ml of conc. HCl (reagent grade) is added to ~ 5 ml of $^{99m}TcO_4^-$ in saline solution.
2. 100 mg of gelatin U.S.P. are dissolved in 1-2 ml of warm H_2O for injection U.S.P., and added to the solution.
3. H_2S (technical grade) is passed through a presterilized 0.45-μ filter and bubbled through the solution for ~ 5 min. The solution is then stirred for ~ 5 min.

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4. N_2 (prepurified grade) is passed through a presterilized 0.45-μ filter and bubbled through the solution to drive off excess H_2S until lead acetate paper is not darkened any longer.
5. The pH of the solution is then adjusted to 5.5-6.5 with NaOH (reagent grade).
6. Free $^{99m}TcO_4^-$ is removed by passing the solution through an anion exchange column.
7. The final product is sterilized by passing it through a presterilized 0.3-μ filter into a sterile multi-injection vial.

Although the use of gelatin in the production of technetium-sulfur colloid has recently been challenged,[15-17] we feel that sufficient information about the pharmacological use of gelatin has been accumulated[18,19] since the introduction of gelatin as plasma expander in 1915[20] to warrant its continued use.

Scanning procedure

For scans of liver and/or spleen, 3-5 mCi of ^{99m}Tc-S colloid are injected i.v.; ~ 12 mCi are used when bone marrow scans are desired in addition. For lymph node scans up to 2 mCi are injected s.c. into the drainage bed of the nodes to be examined.

The currently-used scanning procedure is the result of several studies[1,3,4,5] which were undertaken in an effort to obtain an optimum display on photoscans. Scanning is performed with a 5-inch diameter crystal rectilinear scanner which is equipped with a specially designed low-energy collimator system.[2] The scanning

speed is adjusted so that the following count densities are obtained over the area of the highest radiocolloid concentration: > 2,000 counts/cm^2 over liver and spleen, > 800 counts/cm^2 over a limited region of the bone marrow, 250 counts/cm^2 for the entire bone marrow, and 550 counts/cm^2 over lymph nodes. To obtain the best possible display on the photoscan, the following steps are taken:

1. The picture is recorded in one-quarter of the original size to aid visual perception.[5]
2. A large light spot (0.45 x 0.45 cm - corresponding to a 0.9 x 0.9 cm light spot in a 1:1 record) is used to avoid the introduction of statistical "noise" from a small light spot.[3,5]
3. The system of multiple overlapping with line spacing increments of 0.15 cm is employed in order to reduce the motion artifact[4] and to improve the visual display of scans.[3,5]

The use of an even smaller line spacing of 0.075 cm would be preferable[4] but would prolong the scanning procedure, since the scanner is usually already operating at its top speed of 500 cm/min with the presently-used technique. Only with attention to the details of recording, as described above, can an optimum resolution be achieved. We have also used a scintillation camera for studies with ^{99m}Tc-S colloid, but prefer the better resolution which can be obtained with a rectilinear scanner and a focusing collimator.[21] The only exception to this rule is in lymph node studies. In these the scintillation camera is used before the rectilinear scan for a rapid survey of the uptake of colloid in the various nodes. The improved diagnostic capability of this high resolution scanning system will be described below.

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Organ distribution

Exact quantitation of the relative organ distribution of the colloid has not been obtained. Our observations and those of others,[22] however, indicate that the distribution is very similar to that determined for colloidal radiogold in man (60-90% in liver; 5-16% each in spleen and red bone marrow).[23] Representative count rates with the same collimator are 250,000+ counts/minute over the liver, 200,000 counts per minute over the spleen and 15,000 counts per minute over the sacrum after i.v. injection of 12 mCi of ^{99m}Tc-S colloid. Twenty-four hours after injection the relative count rates remain unchanged. The actual count rates decrease only due to physical decay of technetium-99m.

The mean values that we obtained for half-times of blood clearance (2.65 min) and liver uptake (2.10 min) after intravenous injection were similar to those obtained by others with small doses of other colloids.[24,25] No characteristic pattern for any abnormality except cirrhosis was noted. In cirrhosis the half-times were increased.

Liver

Liver scanning is the best established of all scanning procedures that can be performed with ^{99m}Tc-S colloid. Routinely three views are taken, and the spleen is included in the anterior and posterior views, since a change in spleen size is not uncommon in liver disease. As with other scanning agents, position, size and shape of the liver and uneven distribution of the colloid due to cirrhosis or space-occupying lesions can be demonstrated. However,

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with the scanning procedure described, we have shown that the degradation of resolution by a factor of two or three due to respiratory motion[21] can be avoided,[4] and we have found it possible to unequivocally demonstrate dilated bile ducts in only slightly jaundiced patients with extrahepatic obstruction of the bile ducts.[26] Fig. 1 gives an illustration of the most common use of liver scans - the detection of space-occupying lesions (in this case due to metastatic carcinoma of the breast), and the evaluation of change during therapy (in this case Thio-TEPA i.v., i.p. and intrahepatically).

Spleen

The most common indication for a spleen scan is a left upper quadrant mass. Usually the posterior projection is best for small spleens or for visualization of the superior portion of the spleen. As spleens enlarge, they tend to extend anteriorly and are then best visualized on anterior scans. Best visualization is, of course, found in disorders in which the uptake of colloid in the spleen is enhanced. We have found this to be the case in patients with cirrhosis of the liver and in patients with myelogenous leukemia.

Seventy-eight of the patients we have examined have been scanned more than once, usually in order to get objective data on the change of spleen size in patients with leukemia undergoing treatment with extracorporeal irradiation of blood. In these patients a change of spleen size was found, usually an increase during the first week of treatment, followed by a subsequent decrease in size (Fig. 2)[27].

Next to splenomegaly the most common diagnosis made was splenic infarct. Indication for these scans was usually a complaint of pain

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in the left epigastric area. Serial scans show progression (Fig. 3), and in other patients gradual healing of the infarct.

Another indication for spleen scanning is the diagnosis of Hodgkin's disease in which an objective evaluation of spleen size may be helpful in the staging of the disease.[28,29]

Although there are theoretical disadvantages to the use of a colloid for delineation of the spleen, our practical experience has shown that spleen scanning with ^{99m}Tc-S colloid is a simple, rapid and reliable procedure.

Bone marrow

There has been interest in imaging the distribution of functioning bone marrow in the body for years.[30-32] Undoubtedly ^{52}Fe-citrate is the scanning agent of choice for outlining the erythropoietic component of the hemopoietic marrow. Its main disadvantages are expense and lack of availability. It was, therefore, quite obvious to try to label instead the reticuloendothelial component of the marrow and assess the results for clinical usefulness.[33] After more than five years of use of ^{99m}Tc-S colloid, the results can be best summarized in the statement that colloidal material is a good indicator of marrow hyperplasia (Fig. 4), while it cannot be used for the evaluation of erythropoietic marrow in patients with hypoplastic or aplastic anemia.

Since marrow hyperplasia can frequently be diagnosed by easier methods, the value of bone marrow scanning is then questioned. From our experience and that of others[35,36] it can be concluded that the main indications for bone marrow scans are the question of replacement of marrow by tumor (Fig. 5), and the detection of impaired vascular

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supply to bones with usually active hemopoietic marrow (lumbosacral spine, pelvis, proximal femur).[37] Similar to the experience with bone-scanning agents, tumor deposits have been detected before they were roentgenographically visible.[35,38]

In patients considered to have normal distribution, activity can generally be found in the sacrum, ilium, ischium, femoral neck and lumbar vertebral bodies. Scans of the dorsal spine are difficult to obtain because of the scattered radiation from the liver. Ribs can be seen on occasion. Normally, activity is also found in the acromion, the humeral head and in the cervical spine

We have found that in the majority of patients with various types of leukemia at various stages the distribution is essentially the same as that in healthy individuals. Occasionally hyperplasia is found in a patient with leukemia, but in the study of 86 patients with leukemia we have been unable to make any correlation with the type of leukemia.

Lymphnodes

After s.c. injection, ^{99m}Tc-S colloid is transported via lymphatics at a rate similar to that of ^{198}Au colloid.[39] In normal patients the inguinal and iliac lymphnodes can be demonstrated well, while only faint visualization of para-aortic lymphnodes is achieved. However, enhanced uptake of the colloid has been found in all abdominal nodes in patients with Hodgkin's disease in advanced stages, in which there is a generalized increase in phagocytic activity.[40,41]

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Adverse reactions

In the discussion above, the clinical usefulness of ^{99m}Tc-S colloid has been described. It is also important to establish that scanning with ^{99m}Tc-S colloid is a safe procedure. In our practice we have not encountered any untoward reactions. Generally the following undesired effects could be found from the use of radiopharmaceuticals: 1) pharmacological reaction, 2) toxic reaction, 3) hypersensitivity reaction, 4) reaction due to bacteria or pyrogens, and 5) reaction due to radiation. The kind of material and the amount of material used in the preparation of the ^{99m}Tc-S colloid is obviously too small to cause any reaction of the first two types. Antibody production after administration of gelatin has been described, but these antibodies are apparently of no clinical significance.[42] In 78 patients we have performed multiple studies, in 26 patients five or more, and in 3 patients 10 or more; no hypersensitivity reaction has been observed in any of these patients. Bacterial contamination could easily happen, since gelatin is a good culture medium for bacteria. This has been avoided by the fresh preparation of the gelatin solution daily immediately before the production of the colloid. Pyrogen reactions could be expected due to the protein nature of gelatin, and they have indeed been described when unprocessed gelatin was used in large amounts as a plasma expander.[43] With the small amount of gelatin (0.020-0.080g) injected with the colloid, we have not observed any pyrogen reaction nor are we aware of any such reaction observed by others. And, finally, the absorbed radiation dose, as shown in Table I, is comparable to that of diagnostic X-ray procedures and, again, no reactions are expected, nor have we observed any.

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Conclusion

From our experience over the past five years we would like to suggest that at the present stage of development ^{99m}Tc-S solloid can be considered the scanning agent of choice for liver, spleen, bone marrow and lymphnodes. The production of the colloid is not time-consuming and its use is safe. We have described a scanning method which best complements the use of technetium-99m. With this method it has been possible to extend the usefulness of ^{99m}Tc-S colloid to the diagnosis of dilated bile ducts on liver scans, infarcts on spleen scans, and to the demonstration of impaired vascular supply and replacement of marrow by tumor on bone marrow scans.

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TABLE I. Comparison of ^{99m}Tc-S colloid with organ-specific scanning agents

Scanning Agent	Administered Dose	Radiation Dose (in rads) Absorbed by			Remarks
		Liver	Spleen	Bone Marrow	
^{131}I rose bengal	150 μCi	0.35[44]			Change in count rate during scanning time
$Na_2{}^{51}Cr_2O_4$- "altered RBC"	400 μCi		16.0[45]		Low photon yield (.09/disintegration)
^{52}Fe-citrate	100 μCi			2.5[34]	Not commercially available
^{99m}Tc-S colloid	10 mCi	2.2[22]	1.6[22]	0.26[22]	Has to be produced on day of administration

INDEX WORDS

Radioisotope scanning

Technetium

Colloid

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ILLUSTRATIONS

		Neg. No.
Fig. 1:	Progression of metastatic disease of the liver during Thio-TEPA therapy.	11-597-69
Fig. 2:	Change of spleen size during extracorporeal irradiation of blood.	11-599-69
Fig. 3:	Splenic infarct.	11-771-69
Fig. 4:	Peripheral extension of functioning bone marrow in a patient with chronic myeloid leukemia.	12-823-65
Fig. 5:	Focal involvement of bone marrow by Hodgkin's disease.	10-837-69

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PRIVACY ACT MATERIAL REMOVED

70 a ♀

METASTATIC CARCINOMA OF BREAST

6-8-68

9-14-66

FIGURE 1

PRIVACY ACT MATERIAL REMOVED

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PRIVACY ACT MATERIAL REMOVED

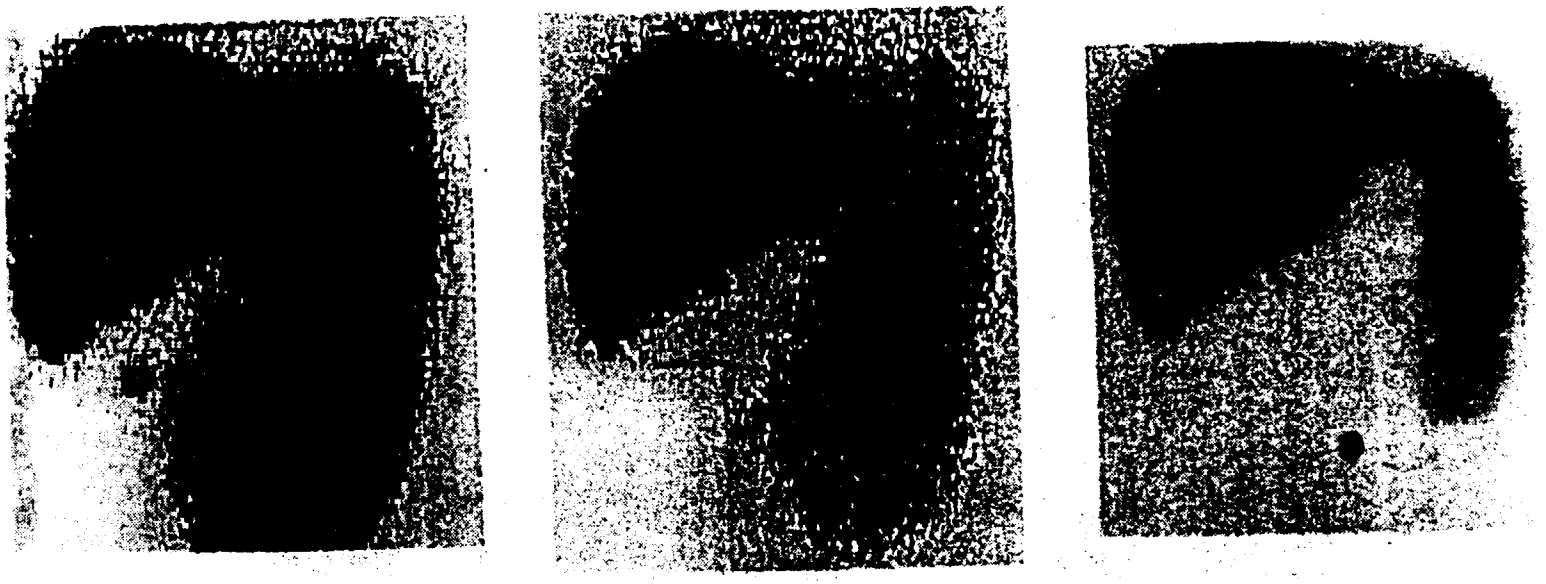
20 a ♀

CHRONIC MYELOID LEUKEMIA
ECIB

5-21-65

6-2-65

6-30-65



WBC 95,100/mm^3 43,500/mm^3 13,000/mm^3

PRIVACY ACT MATERIAL REMOVED

FIGURE 2

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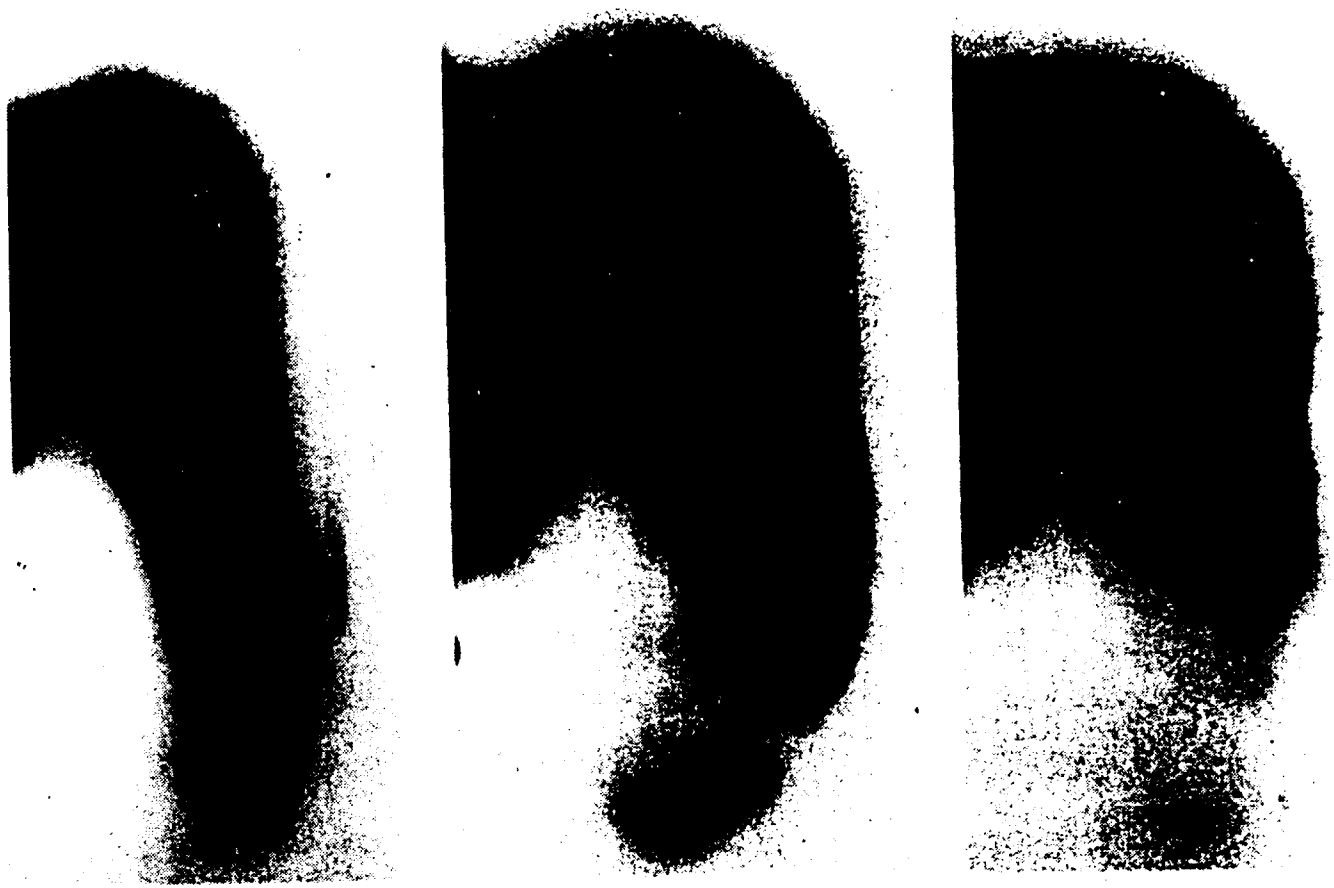
PRIVACY ACT MATERIAL REMOVED

52a ♀ CHRONIC MYELOID LEUKEMIA

8-8-65 8-25-65 9-28-65



PAIN ON LEFT SIDE OF CHEST, BACK AND UPPER ABDOMEN SINCE 8-1-65

FIGURE 3

PRIVACY ACT MATERIAL REMOVED

1119754

1197155

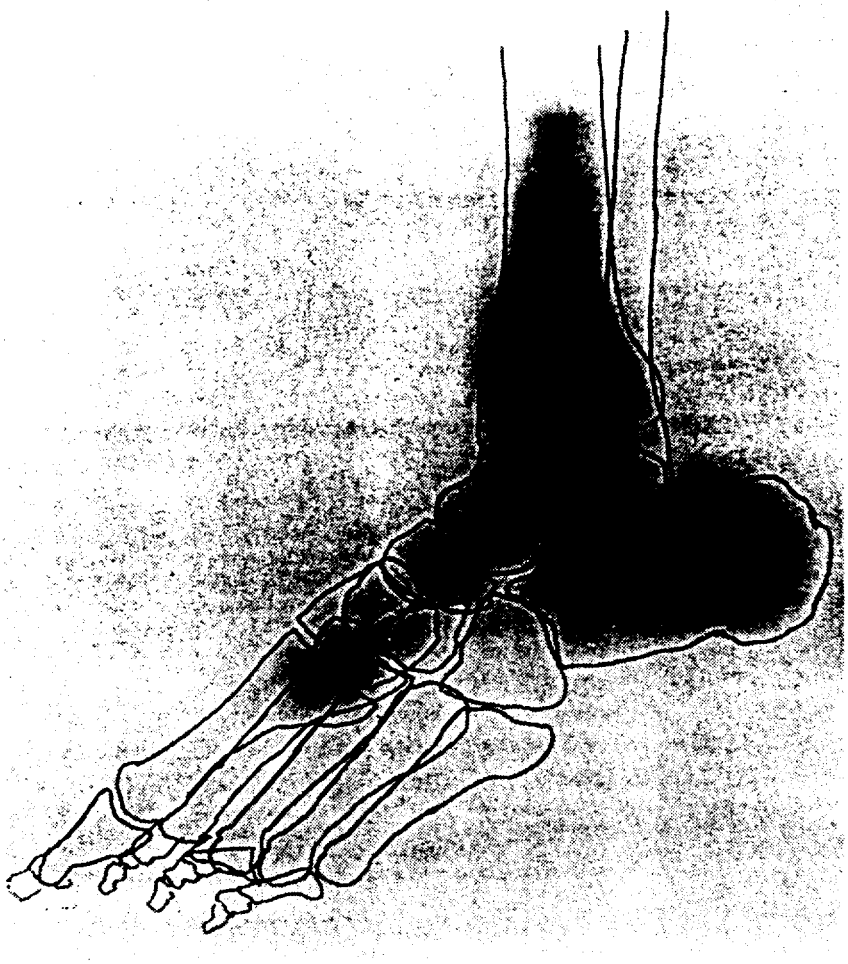


FIGURE 4

PRIVACY ACT MATERIAL REMOVED

31a ♂ HODGKIN'S DISEASE
WITH MARROW INVOLVEMENT

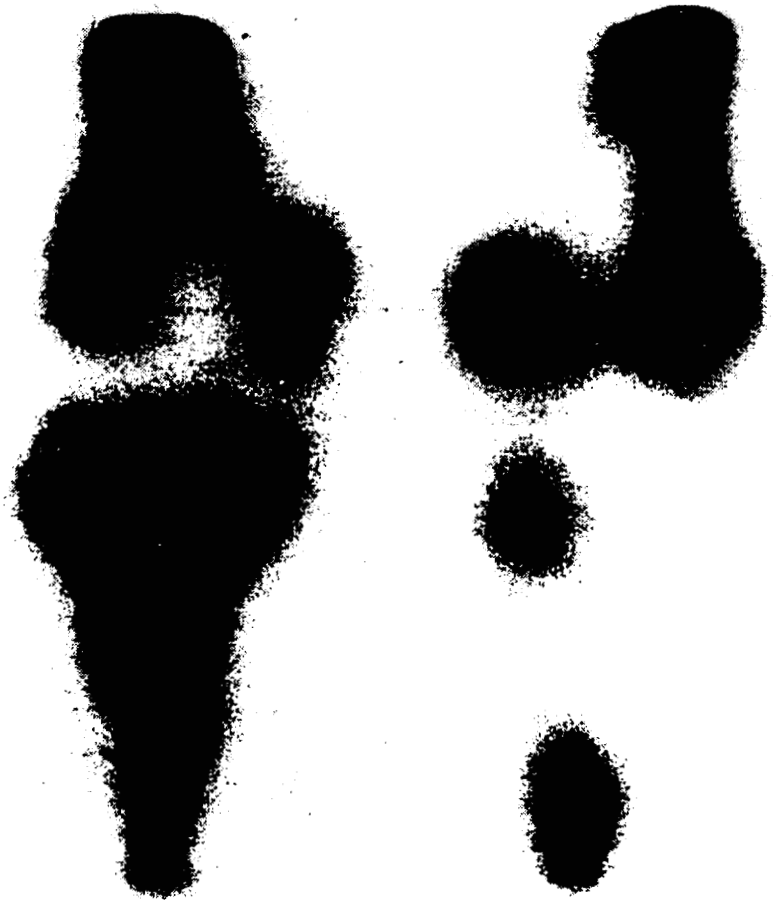


FIGURE 5

PRIVACY ACT MATERIAL REMOVED

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