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MCP:DSZ

Oak Ridge, Tennessee 37830
March 14, 1966

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee

BEST COPY AVAILABLE

Attention: Dr. William G. Pollard

Subject: A DIAGNOSTIC METHOD FOR THE DETECTION OF BONE LESIONS IN HUMANS USING ^{68}GALLIUM WITH ADDED CARRIER GALLIUM

Gentlemen:

Thank you for forwarding the report of the above invention by Messrs. M. L. Hayes, C. L. Edwards and J. Ahumada. The invention was of interest to the Commission for possible patenting.

We regret to advise you that because of the publication of data indicating that adequate scans could be made in rats in your Annual Report for 1964, the subsequent extrapolation to humans cannot be patented.

It is hoped that in the future we may be able to detect inventions of patent interest prior to publication of such preliminary data in order that appropriate patent credit may be achieved for your worthwhile discoveries.

Thank you for the assistance of Mr. Koons and Medical Division personnel who reported this invention.

Very truly yours,

D. S. Zachry, Chief
Oak Ridge Patent Group
Oak Ridge Operations

CC: H. M. Roth

Zachry/dys

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OPTIONAL FORM NO. 10
MAY 1962 EDITION
GSA GEN. REG. NO. 27
5010-107

UNITED STATES GOVERNMENT

Memorandum

TO : D. S. Zachry, Chief
Oak Ridge Patent Group

DATE: March 9, 1966

FROM : Roland A. Anderson, Assistant
General Counsel for Patents

SUBJECT: AEC CASE S-34,023

GCP:RAA

This case has been reviewed. We are disposed to agree with your recommendation to inactivate this case based on the prior publication of December 31, 1964 as well as the lack of use envisioned by the inventors.

This case is therefore being closed and will be filed with those cases not to be prosecuted.

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1185023

R. A. Anderson, Assistant General Counsel for Patents, Germantown

February 4, 1966

D. S. Zachry, Chief,
Oak Ridge Patent Group

S-34,023 - CONTRACT AT-(40-1)-GEN-33, ORAU

MCP:DSZ

Enclosed are a Record of Invention and its attachment in the above case. The invention reported is the discovery that by administering ^{68}Gallium citrate together with 2-4 mg of Gallium per kilogram of body weight as a carrier, scans of osteogenically active portions of the bone may be obtained. Lesions not visible with standard X-ray can be detected with ^{68}Gallium.

Preliminary investigations in this field were published in report ORINS-49, Annual Report for the Year Ending December 31, 1964, page 79. It is reported "adequate scans of the skeleton of the rat can be made at levels of 1 to 10 mg/kg of gallium carrier". The subsequent extrapolation to humans and the limitation of the carrier from 2-4 mg/kg is not considered to be patentable in view of the prior publication of the rat data. It is also reported by the inventors that certain other radioisotopes provide scans that are more sensitive to lesions than X-rays, so that such property is not unique or unexpected.

Accordingly, inactivation is recommended with priority P-0.

D. S. Zachry

Enclosure:
Record of Invention w/attach.

Zachry/dys

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FORM AEC-213
(3-48)

UNITED STATES
ATOMIC ENERGY COMMISSION
PATENT BRANCH

RECORD OF INVENTION

This Record of Invention is an important legal document and proper care in its early and complete preparation will save important time and inconvenience in the future. The Instructions* on the back should be read carefully before filling in the data.

AEC CASE NO. S 34,023

(A) INVENTOR (1) NAME(S): (1) R. L. Hayes (2) C. L. Edwards, (3) J. Ahumada

(2) TITLE OR POSITION: (1) Senior Scientist (2) Chief Clinician (3) Resident in Clinical Investigation

(3) EMPLOYED BY:

(4) PERMANENT ADDRESS: (1&2) Box 117, Oak Ridge, Tenn. (3) Radioisotope Dept., Instituto Nacional de Bogota, Columbia, S. America / Cancerologia

(B) TITLE OF INVENTION (*1) A Diagnostic Method for the Detection of Bone Lesions in Humans using ^{68}Gallium with added Carrier Gallium.

(C) DESCRIPTION OF INVENTION (*2) By administering ^{68}Gallium in the citrate form together with inactive gallium citrate (2-4 mg gallium/kilogram of body weight) it is possible to obtain radioisotopic scans of the osteogenically active portions of the human skeleton within 1 to 2 hours after administration. Bone lesions that are not visible by standard X-ray techniques can often be detected. The addition of gallium to the preparation enhances the preferential localization of the ^{68}gallium in active bone. (see attachment)

(D) DATES AND PLACES OF INVENTIONS:

(1) CONCEPTION BY INVENTOR (*3) Fall 1962 AT Medical Div., ORINS, Oak Ridge, Tenn.

(2) FIRST SKETCH OR DRAWING Does not apply AT ..... IN WORKBOOK ..... PAGE .....

(3) FIRST WRITTEN DESCRIPTION Med. Div. Research Report for 1963, ORINS-43, page 68 AT MED-ORINS IN WORKBOOK ..... PAGE .....

(4) DISCLOSURE TO OTHERS (*4) not applicable AT .....

(a) ..... 19 AT .....

(b) ..... 19 AT .....

(5) COMPLETION OF MODEL OR FULL SIZE DEVICE Does not apply AT .....

(6) FIRST TEST OR OPERATION OF INVENTION June 4, 1965, patient No. 511640 AT MED-ORINS

(E) RESULTS OF TESTS, AND EXTENT OF USE OF INVENTION (*5) Gallium-68 citrate has been employed as an agent for scanning in 41 patients with known or suspected bone lesions. (See attachment)

(F) NAMES OF ALL PERSONS HAVING KNOWLEDGE OF FACTS STATED UNDER (D) AND (E): Not applicable

(G) PERTINENT REPORTS (*6):

(H) OTHER CLOSELY RELATED PUBLICATIONS, PATENTS, AND PATENT APPLICATIONS (*7): Journal of Nuclear Medicine 6: 605, (1965)

(I) RIGHTS OF U. S. GOVERNMENT: Entire rights, title and interests

(J) LICENSES OR ASSIGNMENTS: None

(K) CONTRACTS INVOLVED: ORAU

CONTRACTOR AND ADDRESS: Box 117, Oak Ridge, Tennessee

CONTRACT NO: AT-(40-1)-GEN-33 DATE: 3/18/47

TYPE OF CONTRACT: X UNCLASSIFIED | RESTRICTED | CONFIDENTIAL | SECRET

(L) SIGNATURE OF WITNESS: DATE:

SIGNATURE OF INVENTOR(S): DATE:

FORWARDED BY (*8)— DATE

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(OVER)

16—57445-2

ATTACHMENT TO SECTION C, FORM AEC-213

Historical Developments

Dudley, as the result of studies on the toxicity of gallium, first suggested that gallium might be a "new tool for the study of bone metabolism" (Journal of Pharmacology and Experimental Therapeutics 96: 135 (1949)), and later proposed the use of radioactive isotopes of gallium in the therapy and diagnosis of bone lesions (J. Pharmacol. and Exper. Therapeutics 96: 224 (1949); Radiology 55: 571, (1950)). Extensive diagnostic and therapeutic clinical trials of ^{72}gallium were carried out at the Medical Division (ORINS) and elsewhere, without significant positive results (Radiology 61: 534, (1953)). Toward the end of the investigation of gallium at this installation work carried out with ^{67}gallium indicated the existence of a pronounced effect on tissue distribution produced by the amount of stable gallium carrier administered (see Section G). Recently a nuclide generator for the production of ^{68}gallium has been developed elsewhere (International Journal of Applied Radiation and Isotopes 12: 62, (1961)). The availability of this short-lived radioisotope of gallium (half-life 68 min) and the considerable advances that had taken place in diagnostic scanning raised the question of the possible use of this radioisotope in the diagnostic detection of bone lesions. It appeared on the basis of a report by Dudley (J. Pharmacol. and Exper. Therapeutics 98: 105, (1950)) and work at the Medical Division (see Section G) that close attention to the level of carrier gallium administered might make it possible to achieve rapid bone localization coupled with equally rapid clearance from other tissues. Accordingly, a gallium-68 generator was ordered from Brookhaven National Laboratory on October 30, 1962 (Req. No. 40456; received February 8, 1963) and studies were started in early 1963.

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Gallium-68 as an agent for bone scanning

Gallium is not unique in its tendencies to localize in bone lesions. Such behavior is a general characteristic of bone-seeking elements such as calcium, strontium, and fluorine. The finding that gallium-68, when suitably prepared, can be used to detect bone lesions before standard X-ray techniques make them visible is predated by similar findings with other radioisotopes (for example, ^{85}strontium) and is thus an extension of a known diagnostic technique using a new agent. The main advantages associated with the use of ^{68}gallium in such diagnostic tests are:

1. The short half-life of ^{68}gallium (68 min) and the resulting decrease in dose to the patient or increase in detection sensitivity or suitable combination of both.
2. The long half-life of its ^{68}germanium parent (280 days) resulting in a very long useful life for the generator system.

The one unique characteristic of gallium is the fact that the distribution pattern can be markedly controlled by the amount of gallium administered and that preferential localization in active bone occurs within a short period of time after administration at high levels of gallium administration rather than at low levels.

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ATTACHMENT TO SECTION E, FORM AEC-213

E. Results of Tests, and Extent of Use of Invention (continued)

Known metastatic malignant lesions have been consistently detected as areas of increased density on the scans. As with other bone scanning agents, these lesions can occasionally be detected by scanning before they are visible on roentgenograms. One possibly false positive scan has been obtained. Other bone lesions which are detected include recent fractures, degenerative arthritis, and myelofibrosis with osteosclerosis. With the same preparation using sufficient stable carrier (4 mg/kilogram), very good kidney scans can be obtained.

1185028

MCP:DSZ

Oak Ridge, Tennessee 37831
December 22, 1965

Oak Ridge Institute of
Nuclear Studies
Post Office Box 117
Oak Ridge, Tennessee

Attention: Dr. William O. Pollard

Subject: "BONE SCANNING WITH GALLIUM-68 CITRATE"

Gentlemen:

In my letter of September 16, 1965, I requested an invention disclosure giving full details of the work which was reported briefly in the subject abstract. To date the disclosure has not been received.

Since evaluation of the invention for patentability requires submission to AEC Headquarters and often requires several months before a decision as to patentability is reached, we would appreciate receiving the disclosure at a reasonably early date. If we can be of assistance in this matter please do not hesitate to call us.

Thank you for your assistance.

Very truly yours,

D. S. Zachry, Chief
Oak Ridge Patent Group
Oak Ridge Operations

CC: Herman H. Roth

Zachry/cjl

1185029

Jan. Korno

RADIOISOTOPES OF GALLIUM

R. L. Hayes

Medical Division, Oak Ridge Institute of Nuclear Studies, an operating unit of Oak Ridge Associated Universities, Inc., Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission.

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Of the radioactive isotopes of gallium only three, ^{67}Ga, ^{68}Ga, and ^{72}Ga, are apt to be of any medical interest either because of production limitations or half-life considerations or both. Pinajian[1] has recently reviewed production methods for these radionuclides and compiled a bibliography of their medical uses.

The medical use of gallium radionuclides dates back to the suggestion by Dudley[2,3] that ^{72}Ga might be of use in the diagnosis and treatment of osteogenic sarcoma and metastatic bone lesions. This was the result of observations made during toxicological studies related to the possible use of gallium as a reactor coolant. He reported an elevated deposition of gallium in animals at sites of osteogenic activity when gallium was given in the lactate or citrate form. Early reports on clinical trials of ^{72}Ga[4,5] were encouraging but subsequent investigations reported by Brucer,[6] King,[7,8] and van der Werff[9](who used a mixture of ^{66}Ga and ^{67}Ga) in general failed to yield favorable therapeutic or diagnostic results. Only a few reports on the use of gallium radionuclides as bone-seeking agents have appeared since then.[10-12] It should be emphasized in connection with the earlier diagnostic trials that the instrumentation available during this active period of investigation, coupled with the decay characteristics of ^{72}Ga, made for a difficult task indeed. All the gamma emissions associated with the decay of ^{72}Ga have energies above 0.6 Mev with 40% above 1.0 Mev and 30% above 2.0 Mev.

In 1960 Gleason[13] suggested the generator production of 68-min ^{68}Ga from the long-lived parent, ^{68}Ge ($T_{1/2}$ = 280 days). His method was modified in 1961 by Greene and Tucker[14] resulting in the Brookhaven alumina generator for this isotope. Gallium-68 decays mainly by positron emission with associated 0.51 Mev annihilation radiation. Although some high-energy gamma rays are emitted these amount to only 4% of the output. Gallium-68 is thus a much more

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satisfactory radionuclide from a gamma-ray energy standpoint than ^{72}Ga. In addition it has the advantage of positron capability for coincidence detection. The advantages of its short half-life for diagnostic use are the same as those of other short-lived radionuclides and will not be detailed. The unusually long half-life of the ^{68}Ga parent, ^{68}Ge ($T_{1/2}$ = 280 days), is of course a distinct advantage since the generator will thus have a long useful life.

Gallium-68 ethylenediaminetetraacetic acid (EDTA), the form in which the radionuclide is milked from the generator, has been used by Anger and Gottschalk[15] and Shealy, Aronow, and Brownell[16] as a brain-scanning agent. We believed that ^{68}Ga in the citrate form might possibly be used as a bone-scanning agent and the major portion of this paper will be devoted to a discussion of this use.

Toward the end of the investigation of ^{72}Ga citrate by the Medical Division of the Oak Ridge Institute of Nuclear Studies (ORINS), animal studies of the distribution of carrier-free ^{67}Ga citrate were carried out. A considerable discrepancy between the distribution of the two isotopes was observed. Since this observation is quite pertinent to the use of ^{68}Ga in bone scanning, a brief discussion of these studies is desirable.

Table 1 shows a comparison of some of the animal distribution data obtained during these studies of ^{72}Ga and ^{67}Ga. The times of sacrifice and dose levels do not exactly correspond because the data are taken from several different studies as indicated at the bottom of the table. The word carrier-free is in quotes because some carrier gallium was undoubtedly present in the preparation although it could not be detected spectroscopically. Gallium-67 was produced by proton bombardment of zinc. The difference between the tissue concentrations in liver and spleen for ^{72}Ga (necessarily administered with carrier since it was reactor produced from natural gallium) (column 1) and

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the carrier-free ^{67}Ga (column 2) are quite striking. As shown in column 3 the addition of carrier gallium to the ^{67}Ga preparation resulted in a distribution that was approximately the same as that obtained with ^{72}Ga. The decrease in the skeletal content shown in column 3 probably arises from the fact that the bone is approaching a saturation level.[17] These studies of ^{67}Ga by Bruner and co-workers[18] showed that bone deposition of gallium was directly proportional to the dose administered over a wide range of gallium dose levels. More important, it was also observed that the concentration in other tissues tended to decrease with increasing stable gallium above a level of approximately 0.25 mg gallium per kilogram. This carrier effect can be of considerable importance in the use of gallium radionuclides as bone seekers.

Gallium-68 as obtained from the Greene and Tucker Brookhaven generator[14] is in a carrier-free EDTA chelate form. If it is to be used as a bone-seeking agent, it should be freed from EDTA and converted into a suitable form, such as the citrate. In view of the carrier effect seen with ^{67}Ga, it is apparent that the effective use of ^{68}Ga in bone scanning may necessarily involve the addition of some stable carrier gallium to the ^{68}Ga bone-scanning preparation. Because of its short half-life a further and even more important requirement for practical bone scanning with ^{68}Ga is that of rapid localization in bone coupled with an equally rapid clearance from other tissues after administration. In the original ORINS Medical Division study of gallium citrate, no animal distribution studies were carried out at less than 6 hr after administration. On the other hand Dudley[19] in an earlier communication on the distribution of gallium in animals, presented evidence that localization in bone was quite rapid. In attempting to assess the feasibility of using ^{68}Ga for bone scanning, we have studied the distribution of gallium as a function of stable gallium dose during the first few hours after administration.[20] Table 2 shows some of

the results of this study. Gallium-68 with and without carrier was administered intravenously in the citrate form. In going from carrier-free to high levels of gallium the percentage in the bone increased, while, with the exception of the kidney, percentages in the other tissues decreased strikingly. In this study, except for the carrier-free preparation, the molar ratio of citrate to gallium was held at 2:1. In another study, in which the gallium dose was kept constant at 5 mg/kg and the citrate-gallium ratio was varied, some decrease in the kidney concentration occurred with increasing citrate, but otherwise the concentration in other tissues remained approximately constant up to a citrate to gallium ratio of 5:1.

Figure 1 shows the distribution of ^{68}Ga in the rat with time at a 5 mg/kg level and a 3:1 molar citrate to gallium ratio for selected tissues; distributions beyond 3 hr were carried out with ^{72}Ga as the tracer. The concentrations in the bone are the average of the rib, femur, and calvaria. There was a rapid deposition of gallium in bone coupled with a pronounced drop in the level in the blood and muscle. At 2 hr after administration the ratio of blood concentration to bone concentration was approximately 25 and that of bone to muscle approximately 100. The vascular compartment contained 2% of the administered dose. Approximately 40% of the dose had been excreted via the urine and of this 80% was excreted in the first 1/2 hour.

The next three figures show some scans made with ^{68}Ga citrate. Figure 2 shows the rather dramatic effect of the presence of stable carrier on the distribution of ^{68}Ga citrate in the rat. In both scans the animals were killed at 1 hr and scanned by identical techniques. Notice the more or less diffuse distribution in the carrier-free animal while the deposition in the animal receiving carrier is mainly confined to the skeleton, kidney, and urinary bladder.

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Figure 3 shows a 2-hr ^{68}Ga citrate scan of a rabbit given a carrier dose of 5 mg stable gallium per kilogram. Here the definition is even more pronounced. The area of apparent uptake on the left foreleg is an artifact due to a leakage from the injection site in the ear. Again the areas of pronounced uptake are the skeleton, kidneys, and urinary bladder.

Figure 4 is an example of the type of scans that have been obtained in our clinical program with ^{68}Ga citrate. The subject was considered to have a normal skeleton. Notice on the right side of the illustration the early visualization of both bone and kidney. Thirty-six patients have been studied to date. As with other bone-scanning agents, bone lesions have been detected with ^{68}Ga citrate before they were roentgenographically visible. Based on our studies in rats the estimated radiation dose to the bone and kidney is of the order of 400 millirads per millicurie. The average whole-body dose is estimated to be approximately 76 millirads per millicurie.

In the animal studies of ^{68}Ga citrate distribution, it was necessary to separate ^{68}Ga from the EDTA milking before its preparation in the citrate form. Gallium-68 in the EDTA form does not localize in the skeleton. This separation was accomplished by acidifying the EDTA eluant with hydrochloric acid and extracting with isopropyl ether.[20] When sufficient carrier gallium is involved in the dose preparation, as it normally is in preparations for use in humans, the added carrier gallium can mask the presence of EDTA in the milking, if exchange occurs between ^{68}Ga EDTA and ionic gallium or gallium citrate. For example, for a 70-kg subject dosed at a level of 2 mg Ga/kg only 5% of the ^{68}Ga dose would be present in the EDTA form if complete exchange occurs (20 ml of 0.005 M EDTA used as eluant). The remaining 95% would be in the citrate form and available for bone localization. This method of dose preparation would eliminate the necessity for a separation step.

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If this procedure is to be adopted it is of upmost importance that adequate measures be taken to insure that exchange takes place during the preparation of the ^{68}Ga citrate dose. Saito and Tsuchimoto[21] have reported that the rate of exchange between ionic gallium and gallium EDTA is immeasurably slow from pH 7 down to pH 1.5. Table 3 illustrates the rather disastrous results that can occur if steps are not taken to promote exchange when preparing ^{68}Ga-labeled gallium citrate from ^{68}Ga EDTA. Column 1 shows the distribution obtained with a carrier dose of 5 mg gallium per kilogram where the ^{68}Ga was obtained by the extraction procedure previously mentioned. The results shown in column 2 were obtained when the appropriate amount of a generator milking that would give a 5% ^{68}Ga EDTA contamination of the ^{68}Ga citrate preparation, assuming complete exchange, was added to a neutralized preparation of stable gallium citrate. The preparation remained at room temperature for up to 30 min. There was practically no ^{68}Ga deposition in the bone. The results in column 3 were obtained when appropriate steps were taken to produce exchange before the preparation was neutralized. The distribution is similar to that in column 1. The procedure indicated in column 3 is the method now being used to prepare doses for administration to humans.

The distribution shown in column 2 of Table 3 is similar to that obtained with ^{68}Ga EDTA. Gallium-68 EDTA does not deposit in the bone and is very rapidly excreted via the urine. The initial half-disappearance-time from the blood in rats is approximately 10 min. Rat distribution data from some of our studies of ^{68}Ga EDTA are shown in Table 4. The high concentration of ^{68}Ga in the spleen (column 2) is of interest but probably not of practical importance. Column 3 shows that this high spleen concentration disappears when carrier gallium EDTA is added to the preparation. Figure 5 shows a series of ^{68}Ga EDTA scans made on two rats. The scans show that the rate of passage through the

kidneys to the bladder is quite rapid even in the dehydrated animal.

Myers[22] has proposed the use of ^{51}Cr EDTA for in vivo dynamic physiologic studies. Gallium-68 EDTA appears to be a good candidate for this type of study because it can be obtained directly from a generator, is rapidly excreted, and can be used in large amounts in scanning procedures without undue radiation exposure. With camera or rapid scanning equipment, dynamic studies should be practical. As an example, Fig. 6 shows a set of ^{68}Ga EDTA kidney scans on a patient from our clinical program. This subject had moderate partial bilateral kidney obstruction. Since the scan speed was only 0.3 in./sec admittedly the definition obtained in this series of scans was due in large part to the delayed passage of urine from the kidney; however, with rapid scanning or camera instrumentation "^{68}Ga EDTA pyelograms" might be readily obtained even on normal subjects.

From a purely physical standpoint ^{68}Ga also appears to be an excellent radionuclide for scanning of the reticuloendothelial system. Its short half-life is a distinct advantage. Use of ^{68}Ga in this type of scanning would require that it be administered in a colloidal form, but because of its short half-life, rapid removal from the blood would also have to occur. On the other hand, long-term retention of ^{68}Ga by the colloid would not be of importance beyond the useful decay period of ^{68}Ga.

Ferric hydroxide has long been used as a scavenging agent for various radionuclides. A method for the concentration of micro amounts of stable gallium is based on this property.[23] Colloidal hydrous ferric oxide is readily prepared by the hydrolysis of dilute solutions of ferric salts. Its preparation is a well-known and convenient laboratory exercise. In recent preliminary studies we have found that colloid preparations of hydrous ferric oxide labeled with gallium rapidly localize in the reticuloendothelial system

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of test animals without any apparent loss of activity to bone during the first hour after administration.

Table 5 shows the results of a preliminary study of the distribution of this type of preparation in the rabbit. For convenience ^{72}Ga was used as the tracer. The data show bone marrow to bone and bone marrow to liver concentration ratios of 50 and 0.8.

Figure 7 shows a scan of a rabbit killed 1 hr after administration of ^{68}Ga-labeled hydrous ferric oxide colloid. Bone marrow, liver, and spleen are clearly defined. On autopsy the distribution in this animal was found to be similar to that shown in Table 5. The effect on distribution of variations in the method of colloid production are under study at the present time. The localization seen in animal studies, of course, is no guarantee that similar results will be obtained in man, but the prospect that such might occur certainl merits further investigation.

In summary, of the radionuclides of gallium of possible interest in medicine, ^{68}Ga appears to offer the best qualifications for diagnostic use. Gallium-67 might in turn be considered as a therapeutic agent where ^{68}Ga studie show sufficient localization. Gallium-68 appears to be useful in the following ways:

1. In an EDTA chelate form as an agent for brain scanning and possibly also as an agent for in vivo dynamic physiologic studies.
2. In the citrate form, with proper attention to carrier effects, as a rapid localizing agent for bone scanning.
3. Incorporated in a hydrous ferric oxide colloid as a potential scanning agent for the reticuloendothelial system.

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ACKNOWLEDGMENTS

The author wishes to acknowledge the competent technical assistance of J. E. Carlton and B. L. Byrd and to express his appreciation to Patricia Dalton and Roger Cloutier for the calculation of ^{68}Ga absorbed dose estimates.

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LEGENDS

Fig. 1. Gallium (citrate form) distribution in the rat as a function of time. Gallium citrate was administered intravenously at a level of 5 mg gallium per kilogram; the molar ratio of citrate to gallium was 3:1. Each point is the average of 5 determinations or more with the exception of the 6-hr points (3 animals each). Measurements beyond 3 hr were made with ^{72}Ga as the tracer; in all others ^{68}Ga was used.

Fig. 2. Gallium-68 scans of rats administered equal amounts of ^{68}Ga citrate, one with and one without stable gallium carrier. Both animals were killed 1 hr after intravenous administration and scanned by identical procedures. Notice the clear definition of the skeleton, kidneys, and urinary bladder in the animal given the carrier preparation.

Fig. 3. Two-hour ^{68}Ga (citrate form) scan of a rabbit. The animal received 5 mg carrier gallium per kilogram; the citrate to gallium ratio was 3:1. Note the excellent skeletal definition. The active area in the left foreleg is an artifact due to a faulty ear vein injection.

Fig. 4. Gallium-68 (citrate form) scans of a human with normal skeletal deposition. Notice the early uptake of ^{68}Ga in both bone and kidney.

Fig. 5. Serial ^{68}Ga EDTA scans of a dehydrated (24-hr withdrawal) and a hydrated rat. Notice the rapid passage through the kidneys. The scans required approximately 10 min each.

Fig. 6. Serial ^{68}Ga EDTA scans of a patient with moderate partial bilateral kidney obstruction.Scans required approximately 25 min each. Scan speed was 0.3 in./sec.

Fig. 7. Scan of a rabbit made 1 hr after intravenous administration of hydrous ferric oxide colloid labeled with ^{68}Ga. Notice the excellent visualization of the bone marrow, spleen, and liver.

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Table 1 - CARRIER EFFECT ON GALLIUM CITRATE

DISTRIBUTION IN THE RAT

Organ	Percent administered dose		
Liver	0.91*	5.81†	0.98†
Spleen	0.07	1.66	0.13
Skeleton	20.90	21.60	15.70
Blood	0.14	0.23	0.07
Conditions			
Mg Ga/kg	26	C.F.‡	25
Day sacrificed	4	5	5
Isotope	^{72}Ga	^{67}Ga	^{67}Ga
Animals	5	4	4

* Data from H. D. Bruner, J. D. Perkinson, Jr., E. R. King, G. A. Andrews, J. B. Nash, and M. Brucer, A Study of Gallium^{72}, V, Distribution Studies on Gallium^{72} in Rats, Radiology, 61: 555-570 (1953).

† Data from H. D. Bruner, R. L. Hayes, and J. D. Perkinson, Jr., A Study of Gallium^{72}, X, Preliminary Data on Gallium^{67}, Radiology, 602-612 (1953).

‡ "Carrier-free"

1185043

Table 2 - EFFECT OF CARRIER ON TWO HOUR GALLIUM CITRATE DISTRIBUTION IN THE RAT

Tissue	mg Ga/kg body weight		
	C.F.*	1.0	10.0
	% admin. dose/g (250-g rat)		
Blood	1.33	0.59	0.10
Muscle	0.21	0.07	0.01
Kidney	0.42	1.51	4.27
Rib	1.61	2.96	3.35
Femur	1.20	2.15	2.41
Calvaria	0.65	1.28	1.50
Liver	0.29	0.21	0.08
Spleen	0.35	0.18	0.05
Lung	0.56	0.36	0.09
Animals	5	5	5

*Carrier-free ^{68}Ga containing 1 mg citric acid; other doses, 2:1 molar citrate/Ga ratio.

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Table 3 - EXCHANGE OF ^{68}GA EDTA-GA(III) IN GALLIUM CITRATE DOSE PREPARATION

Tissue	Extracted $^{68}GaCl_3$ + citrate, OH^-	^{68}Ga EDTA + neutral Ga citrate	^{68}Ga EDTA + Ga^{+++}, H^+ (0.5N), heat + citrate, OH^-
	% admin. dose/g tissue (250-g rat)		
Blood	0.12	0.01	0.11
Muscle	0.02	0.004	0.02
Kidney	1.46	0.32	0.58
Rib	3.92	0.06	3.48
Femur	2.69	0.07	2.57
Calvaria	1.68	0.04	1.41
Liver	0.08	0.01	0.07
Spleen	0.05	0.01	0.04
Lung	0.08	0.02	0.06
Animals	9	5	5

5 mg Ga/kg; 3:1 molar citrate/Ga ratio; killed 2 hr

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Table 4 - DISTRIBUTION OF ^{68}GA EDTA IN THE RAT

Tissue	0.5 h	2.0 h	Carrier* 2.0 h
	% administered dose/g tissue (250-g rat)		
Liver	0.10	0.08	0.02
Spleen	0.16	0.35	0.02
Kidney	1.12	0.40	0.33
Lung	0.14	0.03	0.03
Muscle	0.04	0.02	0.01
Femur	0.09	0.04	0.03
Blood	0.19	0.04	0.03
Animals	5	15	4

*5 mg Ga/kg; 1.5 molar EDTA/Ga ratio

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Table 5 - TISSUE DISTRIBUTION OF GALLIUM-LABELED HYDROUS FERRIC OXIDE COLLOID

Tissue	Dose per gram % injected
Liver	0.76
Spleen	1.97
Bone Marrow	0.61
Femur	0.01
Lung	0.07
Blood	0.01
Muscle	0.002
Kidney	0.01

Six 2.5-kg rabbits; 2.5 mg Fe/kg; killed 1 hr

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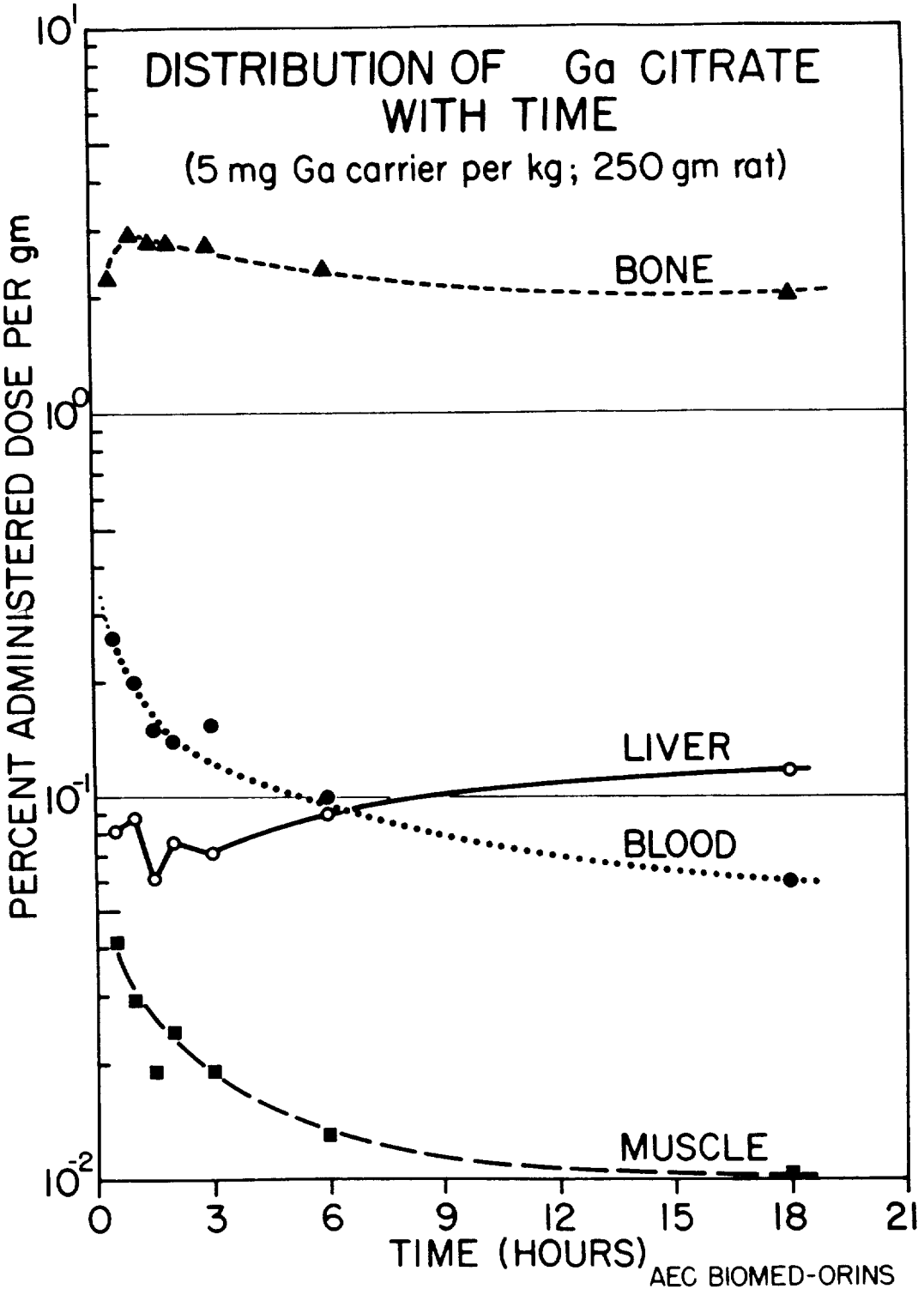
DISTRIBUTION OF Ga CITRATE WITH TIME
(5 mg Ga carrier per kg; 250 gm rat)
PERCENT ADMINISTERED DOSE PER gm
10^1
10^0
10^{-1}
10^{-2}
BONE
LIVER
BLOOD
MUSCLE
0
3
6
9
12
15
18
21
TIME (HOURS)
AEC BIOMED-ORINS

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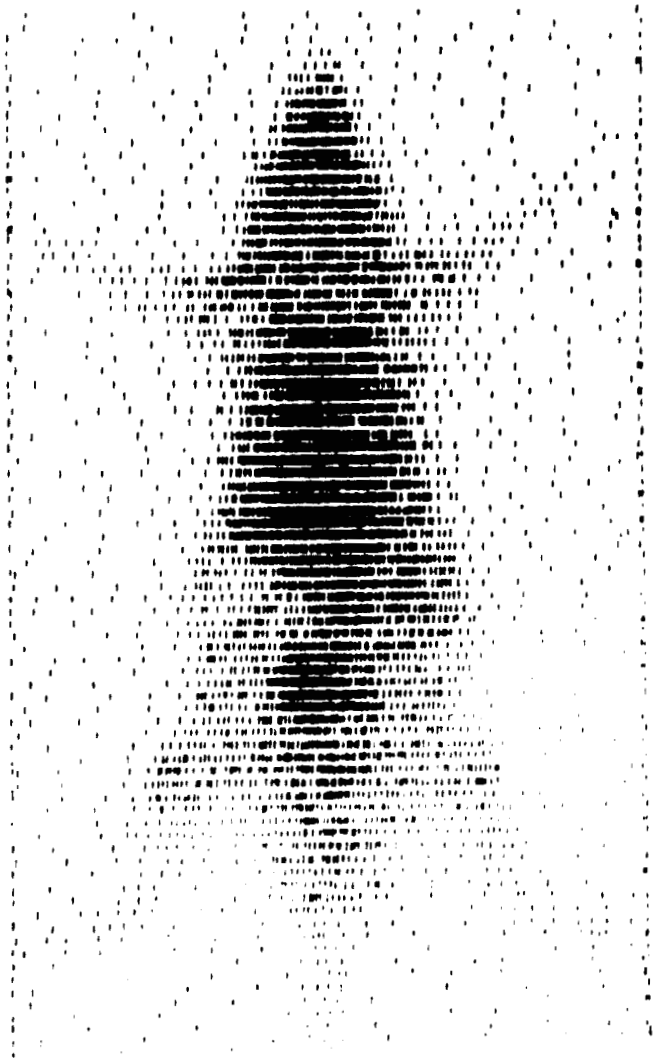
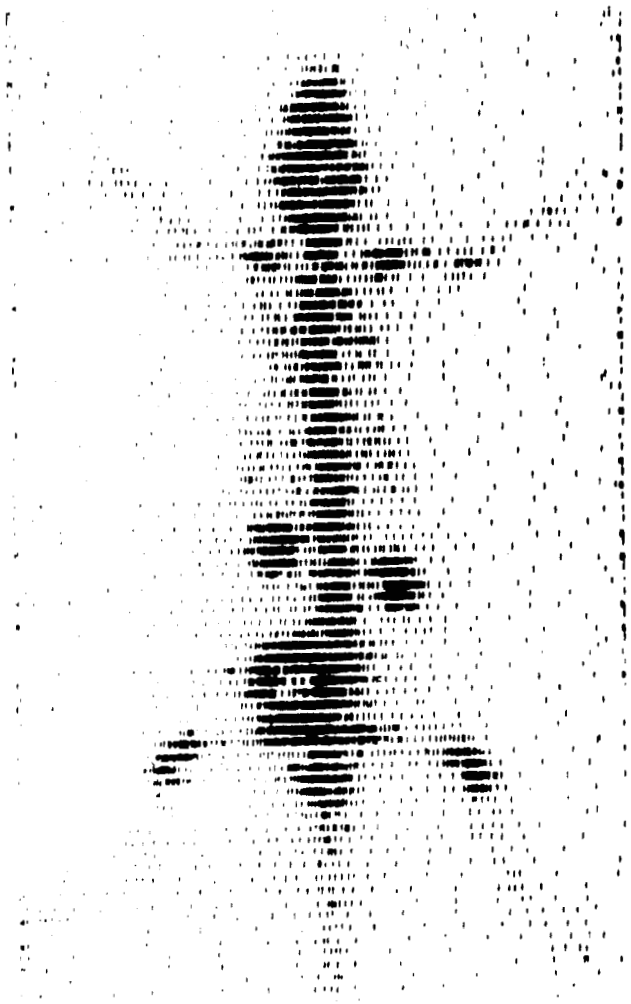
^{68}Ga CITRATE

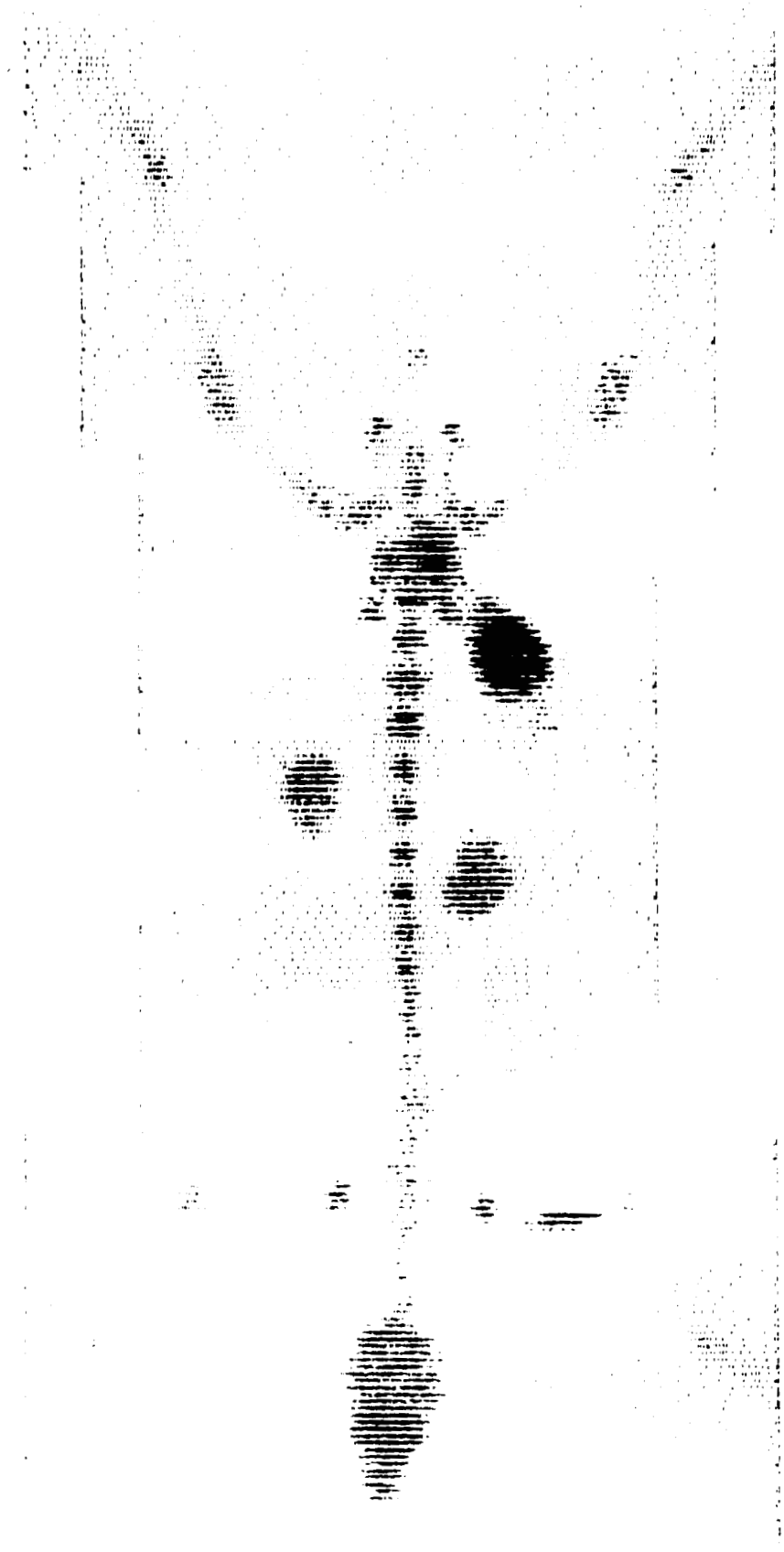


CARRIER-FREE



5 mg Ga/kg

AEC BIOMED-ORINS



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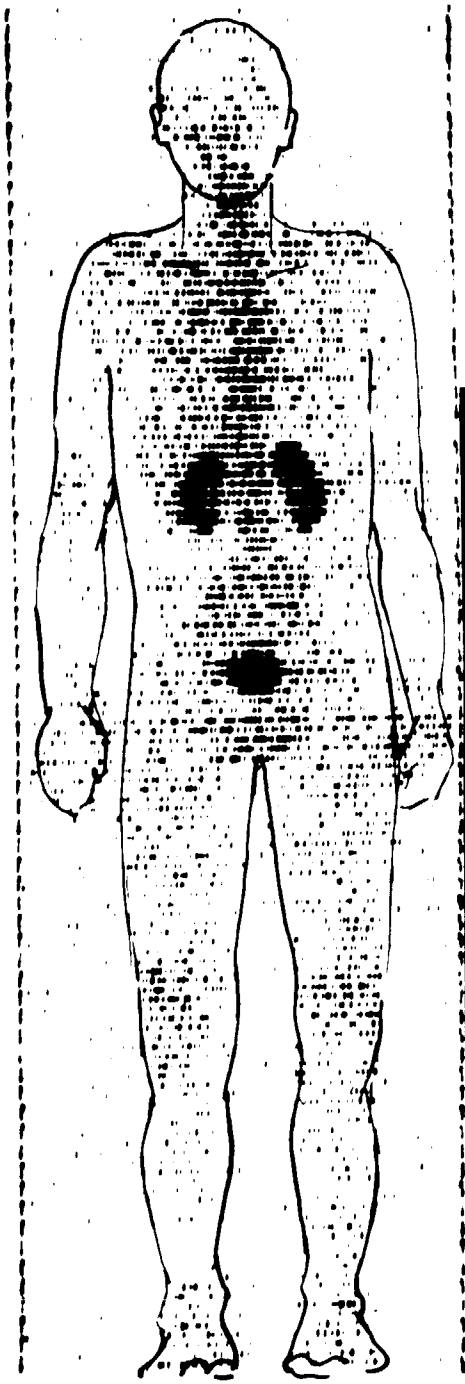
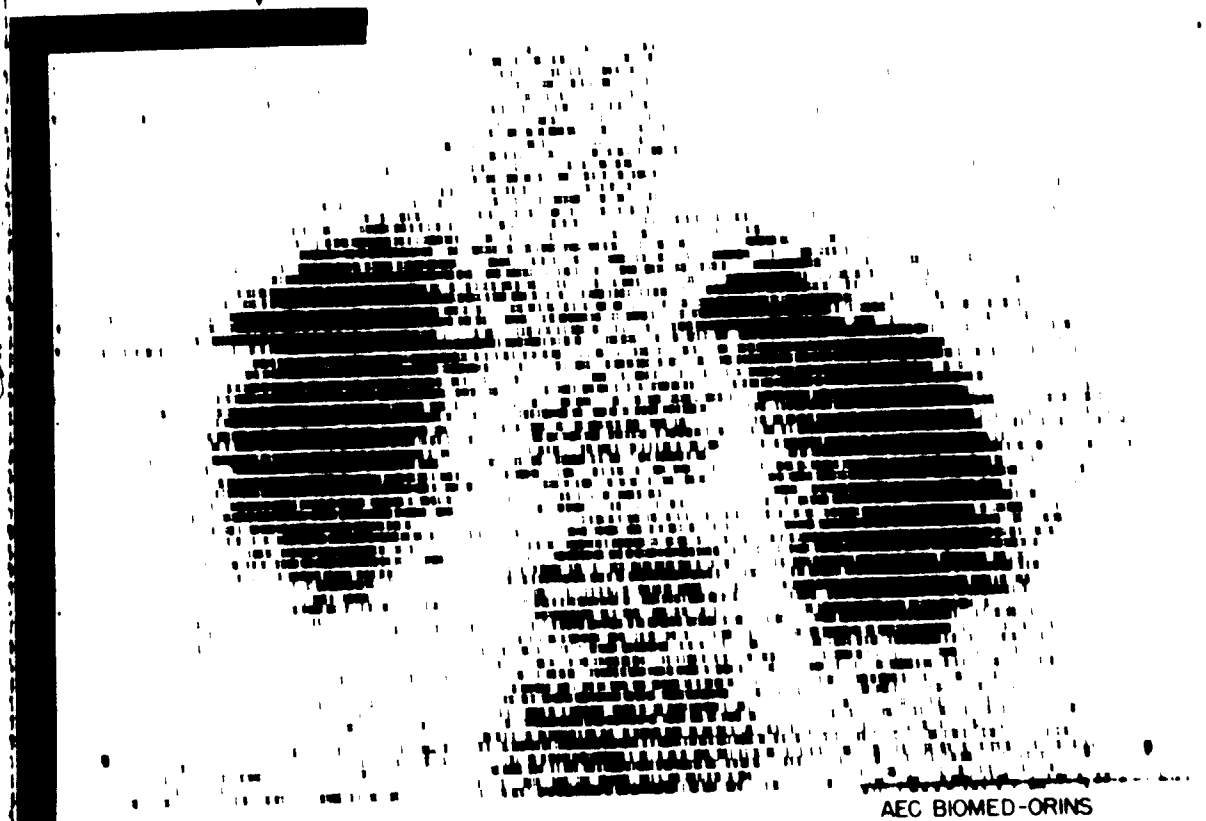


Aug. 16, 1965
^{68}Ga 7.4 mc I.V.
Carrier Ga^{+++} 4 mg/kg
Time Intervals:
← 2¼ hours ↓35 min



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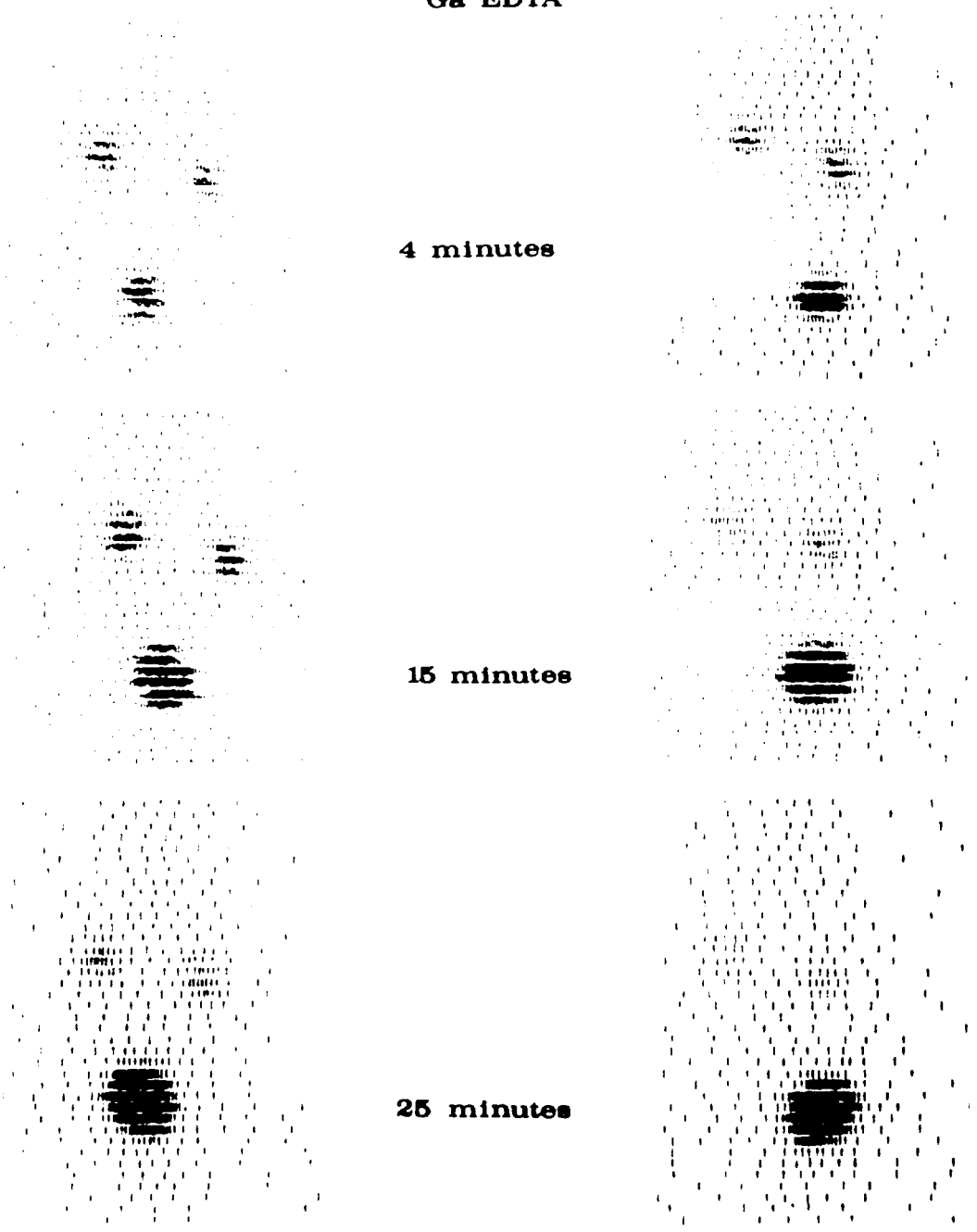
^{68}Ga EDTA



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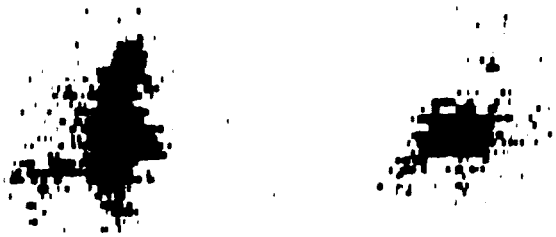
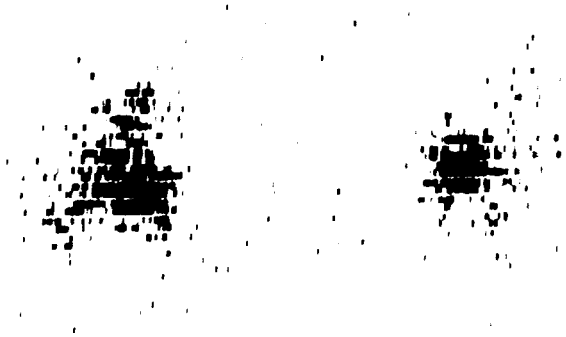
GALLIUM-68 EDTA

15 MINUTES

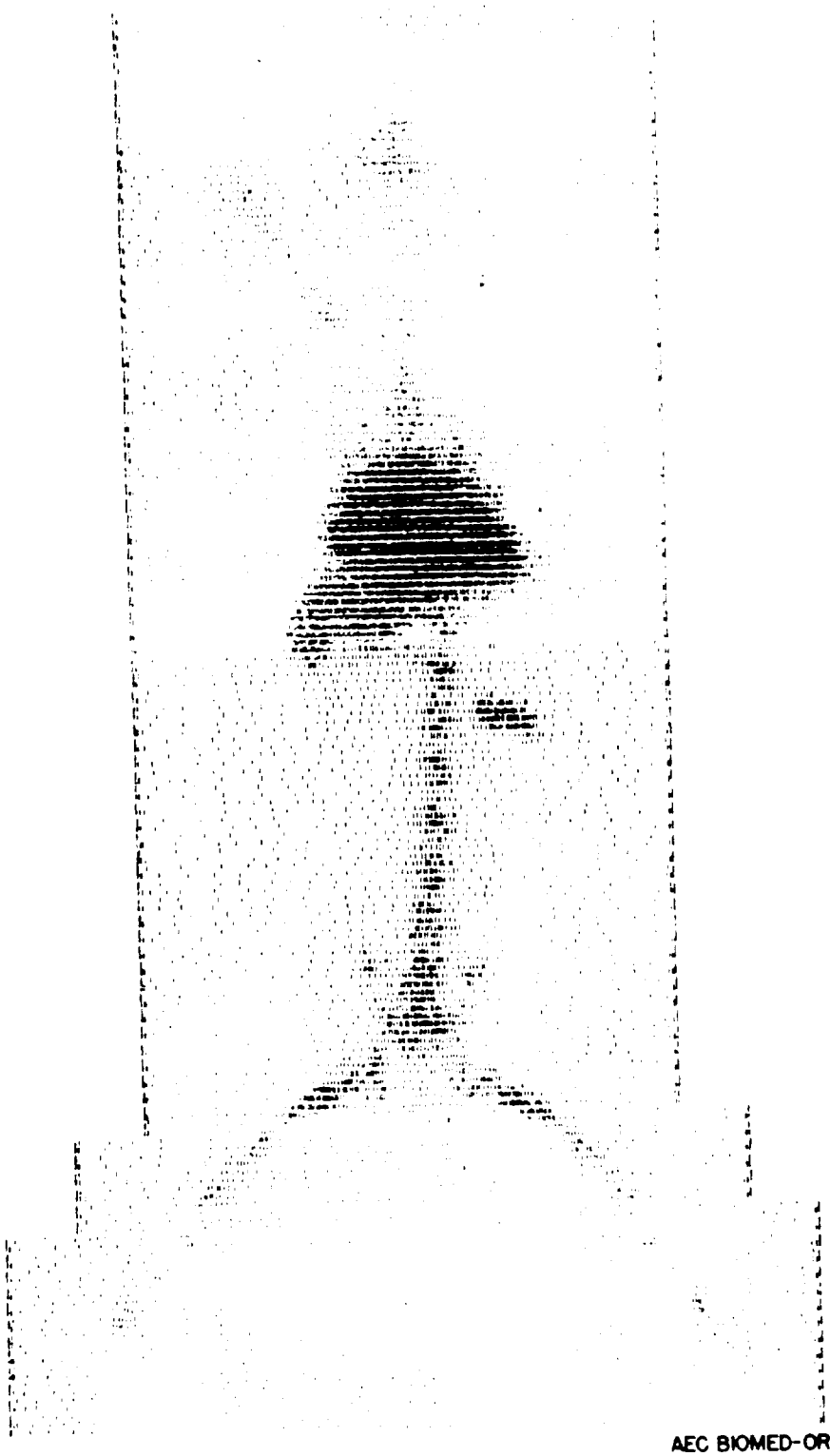


50 MINUTES



No. 610616 85 MINUTES AEC BIOMED-ORINS

1185053



AEC BIOMED-ORINS

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