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APPLICATIONS OF RADIOISOTOPES AND RADIATION IN THE LIFE SCIENCES

HEARINGS
 BEFORE THE
 SUBCOMMITTEE ON
 RESEARCH, DEVELOPMENT, AND RADIATION
 OF THE
 JOINT COMMITTEE ON ATOMIC ENERGY
 CONGRESS OF THE UNITED STATES
 EIGHTY-SEVENTH CONGRESS
 FIRST SESSION
 ON
 APPLICATIONS OF RADIOISOTOPES AND RADIATION IN THE
 LIFE SCIENCES

MARCH 27, 28, 29, AND 30, 1961

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Dr. ARMSTRONG. Yes. Fluoride in large amounts is toxic. There is a confusion about toxicity. Actually, of course, there is no substance that is uniquely toxic. We always have to state the amount of a substance to define its toxicity.

Representative PRICE. What about chlorine, is it toxic in any way? Could it be?

Dr. ARMSTRONG. It could be, if you inhale large quantities of chlorine. It was used as a war gas in World War I.

Representative PRICE. So the safety has resulted from years of research in that field to get the proper formula?

Dr. ARMSTRONG. That is right.

Representative PRICE. Can the radioisotope research results help in educating the public in the use of fluoride?

Dr. ARMSTRONG. I believe so, if we can some way find some avenue to bring these results to the public. So far they are published only in scientific communications. What they do is to demonstrate the remarkable ability of the body to regulate the fluoride concentration of the body fluids. There is a general principle of homeostasis in that in the extracellular fluid, which is a kind of portable seed that we carry with us, most substances are maintained at a constant concentration in the blood and extracellular fluid chiefly by the operation of kidneys. In the case of fluoride this is a remarkably well-regulated process, in spite of large variations of fluid intake—for example, we find that the blood fluoride content of people who drink water containing 0.15 parts per million is the same as those who drink water containing 2½ parts per million of fluoride. The persons who drink the water with the larger fluoride content simply excrete it in the urine.

Representative PRICE. Thank you very much, Dr. Armstrong. We appreciate having your wise statement.

Dr. ARMSTRONG. Thank you.

Representative PRICE. The next witness will be Dr. C. C. Lushbaugh, Los Angeles Scientific Laboratory, who will present the paper on the "Use of Radioisotopes and Radiation in the Diagnosis of Diseases."

STATEMENT OF C. C. LUSHBAUGH,* M.D., LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA, LOS ALAMOS, N. MEX.

Dr. LUSHBAUGH. Thank you, Mr. Price.

May I have a lantern slide projector to show my slides?

Representative PRICE. Yes. Would you proceed, please.

Dr. LUSHBAUGH. The assignment I was given, the uses of radioisotopes and radiation in the diagnosis of diseases, I would like to limit to the developing, new technique of whole body counting and

*Born in [redacted] in [redacted]. His main fields of research and practice involve pathologic histology, clinical pathologic diagnosis, medicolegal problems in pathology, cancer detection (cytologic and chemical), damage from ionizing radiation, and chemical toxicology and diagnostic radiology. He received three degrees from the [redacted]: a B.S. in anatomy in [redacted], a Ph. D. in pathology in [redacted] and an M.D. in [redacted]. He joined the staff of the biomedical research group of the Los Alamos Scientific Laboratory in the spring of 1949. He is a member of the American Association for the Advancement of Science, American Association for Cancer Research, American Medical Association, American Society for Experimental Pathology, Radiation Research Society, and the Society for Experimental Biology and Medicine.

its application to diagnosis. When I say new, I realize very well that whole body counting was started long before I was in this field, and much of it rests today upon the basic work of Dr. Marinelli of the Argonne National Laboratory. At Los Alamos we have been since 1955 experimenting with a device called a liquid scintillator, and I would like to tell you about it and what we feel are coming applications in this field.

The Los Alamos liquid scintillation counters, known as whole body or human counters because they are more than large enough to scan an entire adult man within them, have recently been shown to have clinical diagnostic applications that promise to facilitate and simplify radioisotopic diagnosis in the future. These counters were designed by my colleagues E. C. Anderson, W. H. Langham, F. N. Hayes, and R. L. Schuch. They were constructed in order to detect and measure minute amounts of gamma radioactivity in the biosphere. They were used first by E. C. Anderson to investigate the possible contamination of milk and other foodstuffs by Cs^{137} from atomic fallout.

Mr. RAMEY. We had testimony on that in our fallout hearings several years ago.

Dr. LUSHBAUGH. If we could have the first slide which shows the original human counter known as Humco I.

It was found through their use that man himself also contained such radioactivity, which could be quantitated in relation to his K^{40} content. These machines and techniques were largely responsible for determining that biologic contamination by radioactive fallout had not reached alarming or even potentially serious levels in man and his biosphere. When the atom bomb testing program was curtailed, the subsequent decline in this activity has been easily followed with these devices.

The original human counter (Humco I) is a 140-gallon tank of liquid scintillator solution which surrounds a horizontal well 18 inches in diameter and 72 inches in length (exhibit 1, p. 28). Scintillations caused by penetration of the tank by radioactivity from the subject in the well are recorded by one hundred and eight 2-inch photomultiplier tubes and the usual amplifying and scaling circuits (exhibits 2, 3, 4, pp. 29-31). Here is the tank pulled out from its lead shield showing some of the photomultiplier tubes. A person is inserted into the well of that tank and his entire body is counted. The next slide (p. 30) shows an artist's conception of how a person looks in the tank. You can see that the scintillation solution surrounded him entirely, and he is shielded from outside radiation by this lead shield. The next slide (p. 3) shows a person in the sling being motor driven into the tank for counting purposes. The persons in the far corner show the injection of the radioisotope into an arm.

A second such counter was made for the research unit of Walter Reed Hospital where it has been in active use since 1957. The first extensive modification of this counter, known as the Geneva counter, because it was demonstrated at the second International Atoms for Peace Conference in Geneva in 1958, by my colleagues, Dr. Hayes and Dr. Hiebert, consisted essentially of a vertical tank of scintillator solution. The next slide (p. 32), which I forgot about, shows our smallest subject; her mother received radioactive iron 2 months previously to this child's birth. Following its birth we were able to see

whether or not iron actually passed this woman's placenta and whether the baby had taken up any. We tried to get at the problem of the baby's need of the maternally ingested iron. We were able to find it very easily with this machine. The next picture is the Geneva counter (p. 33). It shows the man standing with his back to the liquid scintillation tank. This had six 18-inch-diameter photomultiplier tubes monitoring the tank and proved so sensitive that a second modification has been made recently with twenty-four 18-inch photomultiplier tubes placed in a steel room.

The next photo (p. 34) shows an artists' conception of this counter, known now as Humco II. It has the same motor-driven sling. A person is placed into the tank by this. The drawing is cut away to show how the tubes look through this tank of liquid.

The next picture (p. 35) shows this device as it actually exists in Los Alamos today, with the door open at one side allowing you to see the large photomultiplier tubes which make this so sensitive. In experiments which are as yet still incomplete as much as a 30-fold increase in sensitivity has been obtained, promising here long-term tracer studies in man, with less than a tenth of a microcurie of radioactivity, doses which are less than one-thousandth of doses used clinically today. Paralleling this series of large counters is a group of smaller scintillation tank counters known locally as arm counters or small animal whole-body counters.

The next picture (p. 36) shows the prototype of these. These counters were developed by my colleagues, Dr. Robert Schuch and Harry Foreman, under the direction of Wright Langham, and they have been used in research with animals. The well is only large enough to accommodate the forearm of a man or a quart ice cream carton which contains a mouse, rat, or samples of blood, feces, or urine. Many tests have been found applicable to these devices.

The next picture (p. 36) shows a man lying with his arm in this tank, which is shielded by 900 pounds of liquid mercury from outside radiation. He has in that picture a scintillation probe pointed at his liver, doing a Rose Bengal liver function test.

The next picture (p. 38) shows our most modern version of this device which is now shielded by disused naval armor plate. The woman there is about to do a whole-body count on a rat.

Shortly after the instruments became operational a program was initiated in Los Alamos to determine their clinical applicability. Since the thyroid uptake test is the most common, and is the only one that gives some money back to the isotopologist, this measurement was one of the first to be studied with the whole-body counting technique.

The concept that is basic to this technique is the now well-established fact that animals excrete important materials at rates that stress the turnover kinetics of the organs and systems that are utilizing these materials. On this basis it has been proven previously that it is possible to determine the thyroid uptake iodine 131 by measurement of the urinary excretion of this substance. The whole-body counter technique determines such excretion rates by measuring the retention of the administered isotopes, or in other words, by measuring the amount of radioisotope which has not yet been excreted by the person.

The resulting whole-body retention curves are thus the sum of two or more exponentially excreting metabolic compartments which are easily determined by simple mathematical analysis.

In the next picture (pp. 39 and 41) we show several thyroid uptake tests done by this method. Instead of seeing here the amount of iodine which is picked up by the thyroid and kept in it as one does with a sodium iodide probe, one sees here the final retention of iodide in the body which is the NaI-131. Here are three examples: One a hyperthyroid man, with very high retention; a woman that was thought to be euthyroid; and a man whose gland was completely removed for thyroid cancer, according to his surgeon. Following this test it was obvious that the surgery had not been quite complete and some thyroid gland had been left behind, as shown by the flattening of the curve.

The next slide (p. 42) shows how we do iron retention studies with this device. This was an experimental slide and today we give the person a dose of oral iron on one day and a week later after he has passed fecally all of the iron that he has not absorbed, we then do another body count which takes about a hundred seconds and determine the amount of iron that is left in him.

In this example here one sees the retention of a normal man, which is about 4 percent, and then after we had determined this uptake for a normal man, which is gastrointestinal absorption of iron, we had this man donate 500 cc.'s of blood to the local blood bank, and we did it again. We can see that his uptake has increased threefold and he then took up 12 percent of the iron.

This device which is so sensitive that we can only use six-tenths of microcurie of radioactive iron, has enabled us to make some studies on the pregnant woman, the heavily menstruating young woman, and the iron deficient child. There are two examples here. One is the commonly seen anemic woman where the physician wonders whether or not this woman will absorb iron. You can see she has absorbed 30 percent of the dose given to her on that day. The iron deficient child in this case has received only milk in the first year of its life. You can see that the line turns up at 70 percent, so this child by this test is shown to be extremely iron deficient. At the same time the test shows that the child would absorb iron if it were given it.

The next slide (p. 44) shows the type of test one obtains by the use of the arm counter. The arm counter enables us to study the clearance of the blood by various radioactive dyes. Here iodine labeled Rose Bengal was placed in a person's arm while the other arm was in the arm counter. Then the arm counter recorded the disappearance of the dye from his blood as his liver took it up. We found (in the upper graph) that our normal persons have the (dotted line) same liver uptake rate as our abnormal or sick persons, but because the livers of the sick persons are functionally smaller, much less dye is removed from the blood and one can see increased retention of dye much as in the ordinary bromsulfalein test. Similarly one can test kidney function by the use of radioactive Mioran. We can test for iron by the injecting iron. And also test for the disappearance of vitamin B₁₂ label with cobalt.

In our opinion, the numerous clinical applications described here do not exhaust the possibilities and potentialities for these measuring

devices in clinical medicine, and diagnosis. But their potential usefulness in clinical and experimental research seems to be limited only by the number of processes and diseases that can be studied with such radioactive materials. Their increasing use in these fields seems to us to be assured because of the simplicity and the facility of their operation and because of the great sensitivity of these machines and their counting precision.

That is the end of my statement.

Representative PRICE. Thank you very much, Doctor. I do not think you followed your statement exactly.

Dr. LUSHBAUGH. No, sir; I did not.

Representative PRICE. Therefore it will be included in the record at this point.

(The statement referred to follows:)

USE OF RADIOISOTOPES AND RADIATION IN THE DIAGNOSIS OF DISEASES: WHOLE-BODY COUNTING¹

(By C. C. Lushbaugh, M.D., Los Alamos Scientific Laboratory, University of California, Los Alamos, N. Mex.)

The Los Alamos liquid scintillation counters, known as "wholebody" or "human" counters because they are more than large enough to scan an entire adult man within them, have recently been shown to have clinical diagnostic applications that promise to facilitate and simplify radioisotopic diagnosis in the future. These counters were designed by my colleagues, E. C. Anderson, W. H. Langham, F. N. Hayes, and R. L. Schuch. They were constructed in order to detect and measure minute amounts of gamma radioactivity in the biosphere. They were used first by E. C. Anderson to investigate the possible contamination of milk and other foodstuffs by Cs^{137} from atomic fallout. It was found through their use that man himself also contained such radioactivity, which could be quantitated in relation to his K^{40} content. These machines and techniques were largely responsible for determining that biologic contamination by radioactive fallout had not reached alarming or even potentially serious levels in man and his biosphere. When the atom bomb testing program was curtailed, the subsequent decline in this activity has been easily followed with these devices.

The original human counter (Humco I) is a 140-gallon tank of liquid scintillator solution which surrounds a horizontal well 18 inches in diameter and 72 inches in length (exhibit 1). Scintillations caused by penetration of the tank by radioactivity from the subject in the well are recorded by 108 2-inch photomultiplier tubes and the usual amplifying and scaling circuits (exhibits 2, 3, 4, and 5). A second such counter was made for the Research Unit at Walter Reed Hospital in 1957. The first extensive modification of this counter, known as the Geneva counter, was demonstrated at the second International Atoms for Peace Conference in Geneva in 1958 by my colleagues, F. N. Hayes and R. D. Hiebert. It consisted essentially of a vertical tank of scintillation liquid against which the subject stood in a conchlike shell of lead (exhibit 6). The six 18-inch diameter photomultiplier tubes that monitored this tank proved so sensitive that a second modification was made recently with 24 18-inch photomultiplier tubes in a steel room (Humco II) in order to determine the maximum sensitivity of such devices (exhibits 7 and 8). In experiments, which are yet still incomplete, as much as a thirtyfold increase in sensitivity has been obtained, promising long-term tracer studies in man with less than 0.1 μc of radioactivity—doses less than one one-thousandth of dose used clinically today.

Paralleling this series of large counters is a group of smaller scintillation tank counters known locally as "arm" or "small-animal whole-body" counters (exhibits 9, 10, and 11). These counters were developed by R. L. Schuch with H. Foreman, under the direction of W. H. Langham. They have been used exclusively by my associates, C. R. Richmond and J. E. Furchner, in research with animals.

¹Work performed under the auspices of the U.S. Atomic Energy Commission.

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EXHIBIT 1.—Humco I, a liquid scintillation counter, shown with well open. Patients get into the loading sling by the ramp

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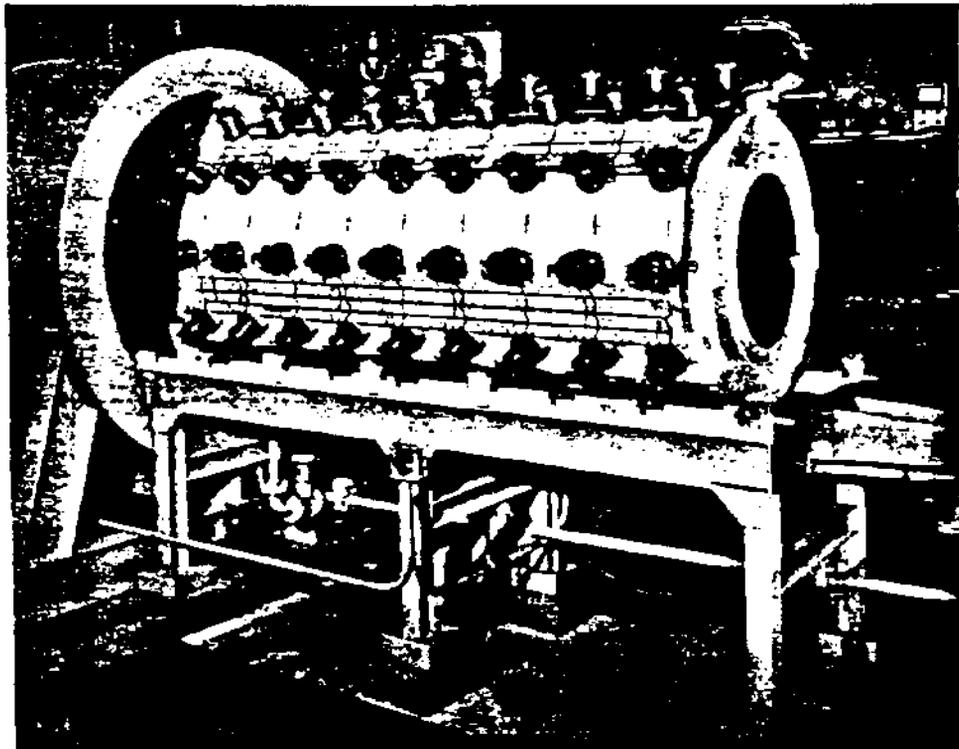


EXHIBIT 2.—The tank and phototubes of Humco I are shown drawn out from the circular lead shield for maintenance

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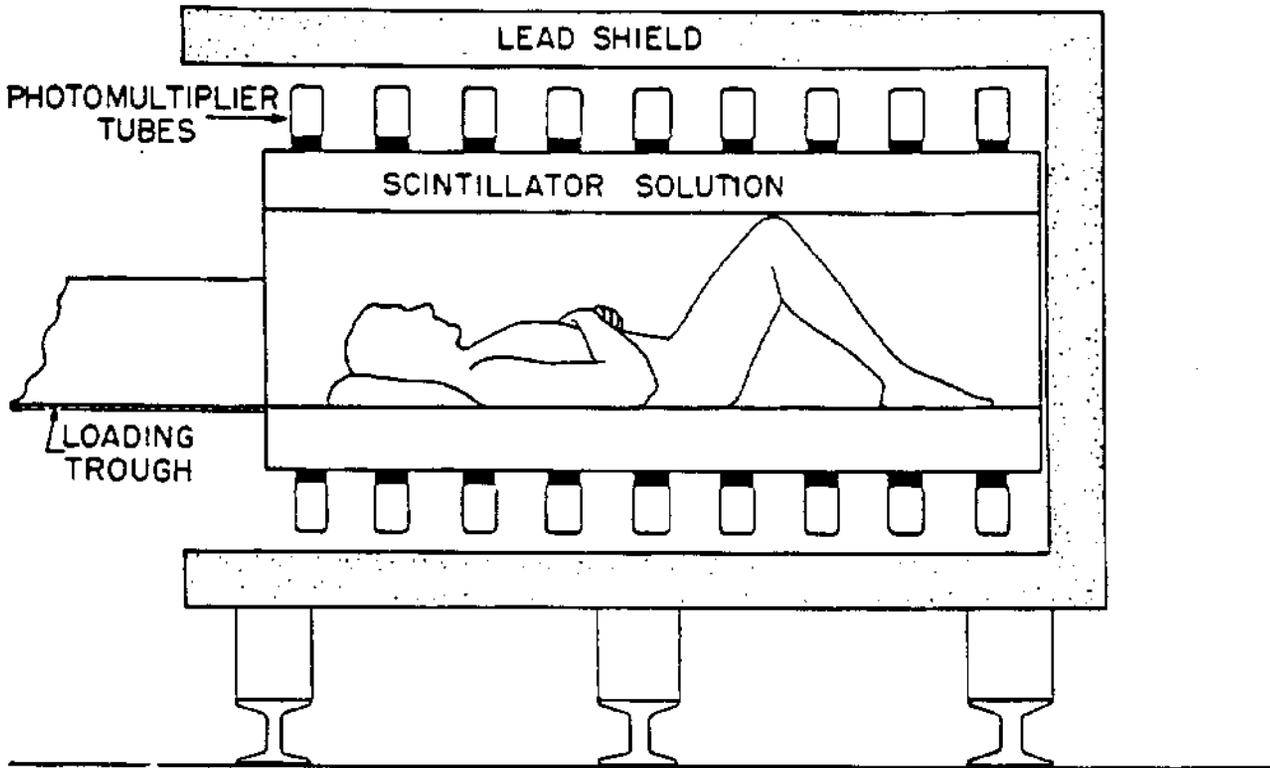


EXHIBIT 3.—Artist's diagram of a patient in position to be counted within Humco I.

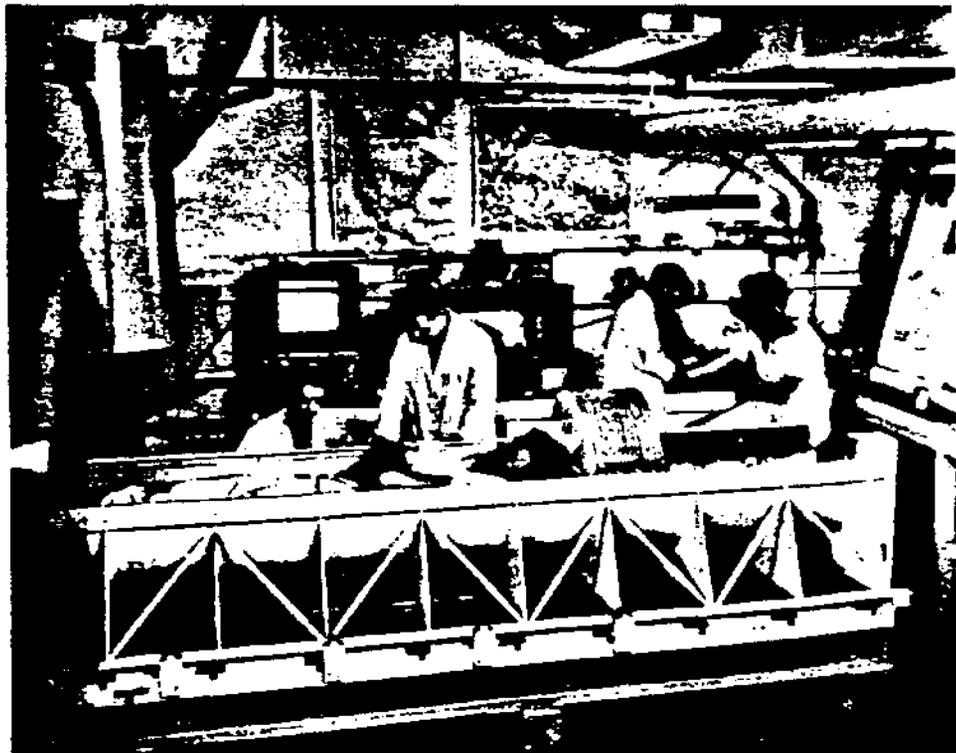


EXHIBIT 4.—Subject in loading sling being carried into the counting tank for clinical 500133574.008

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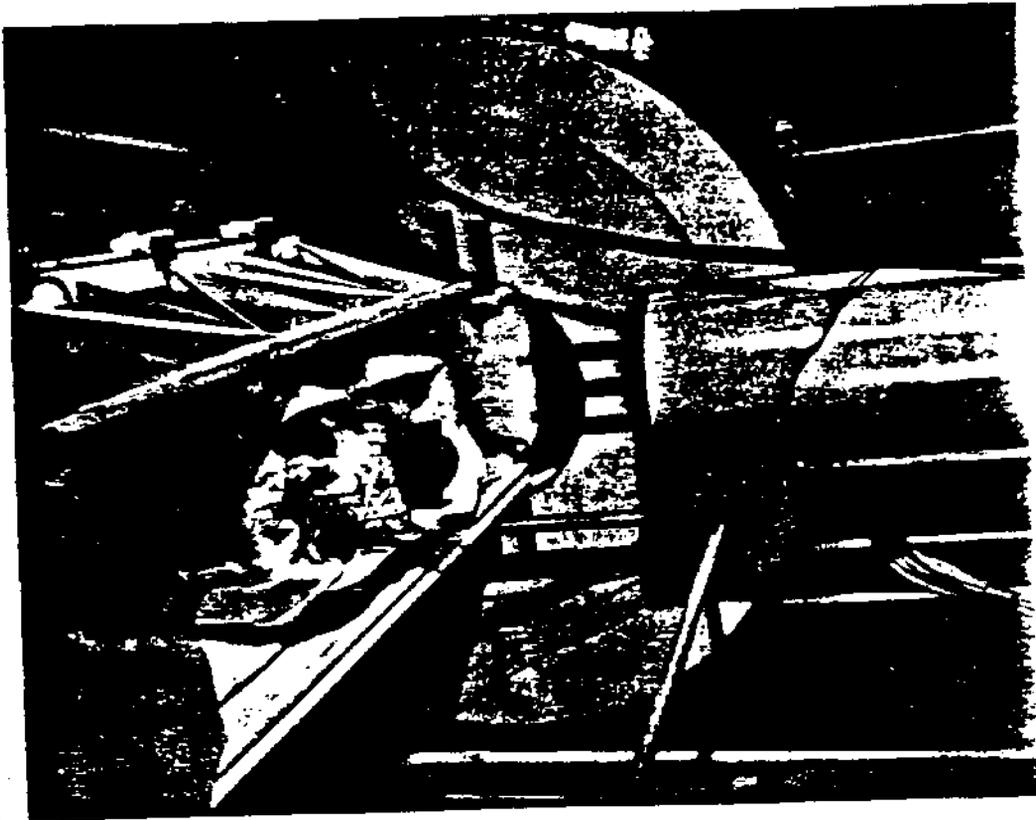


EXHIBIT 5.—Another view of Jimmie I, showing a new-born infant about to be assayed for radioactive iron which had been fed to his mother 2 months before his birth.

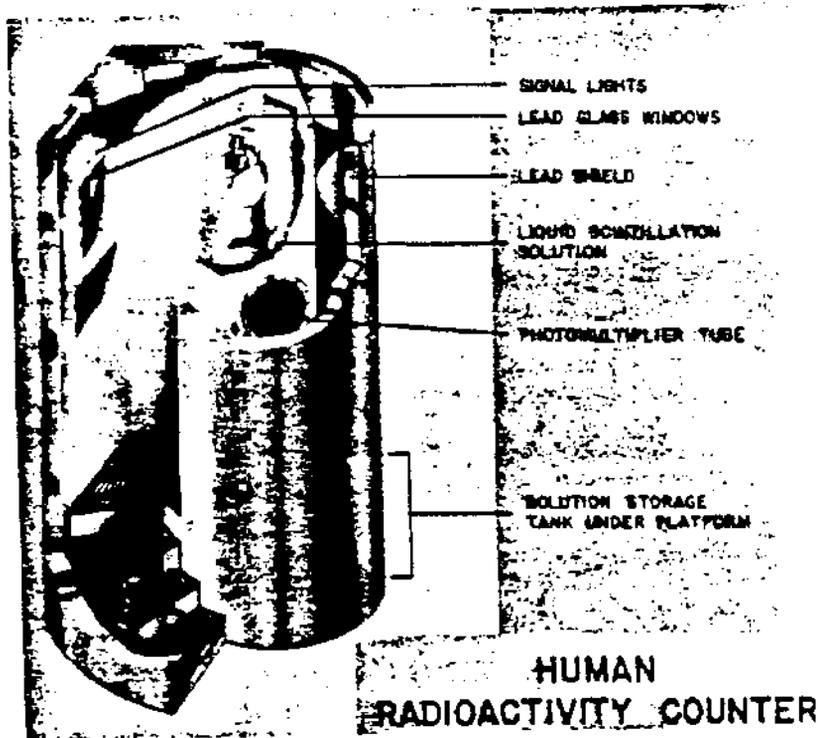
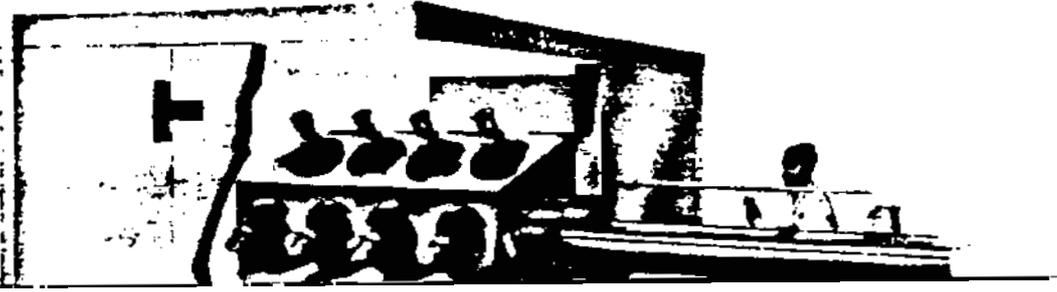


EXHIBIT 6.—Drawing of the Geneva Human Radioactivity Counter showing subject standing against a vertical tank of scintillator solution, monitored by six 18-in. photomultiplier tubes.



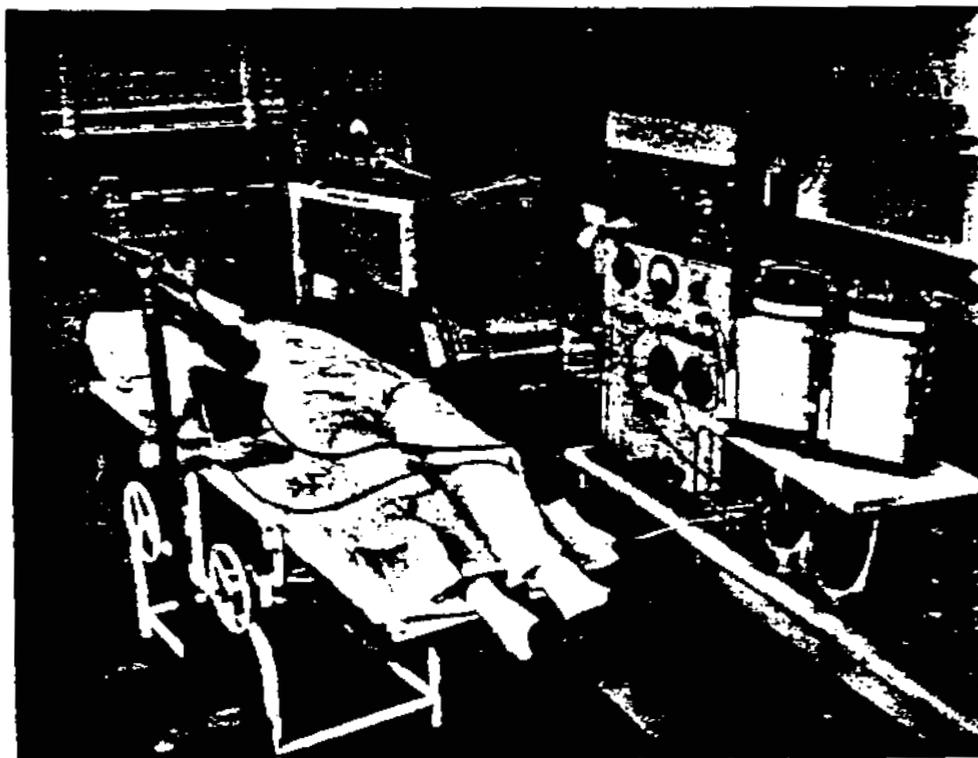


EXHIBIT 10.—A subject with his left arm in the Arm Counter and a collimated sodium iodide crystal scintillometer scanning his liver during a Rose Bengal-¹³¹I liver function test.

The well in these machines accommodates only the forearm of a man or a girl, ice-cream carton containing mice, a rat, or samples of blood, feces, or urine. Many diagnostic clinical tests have been found applicable also to these well-type devices.

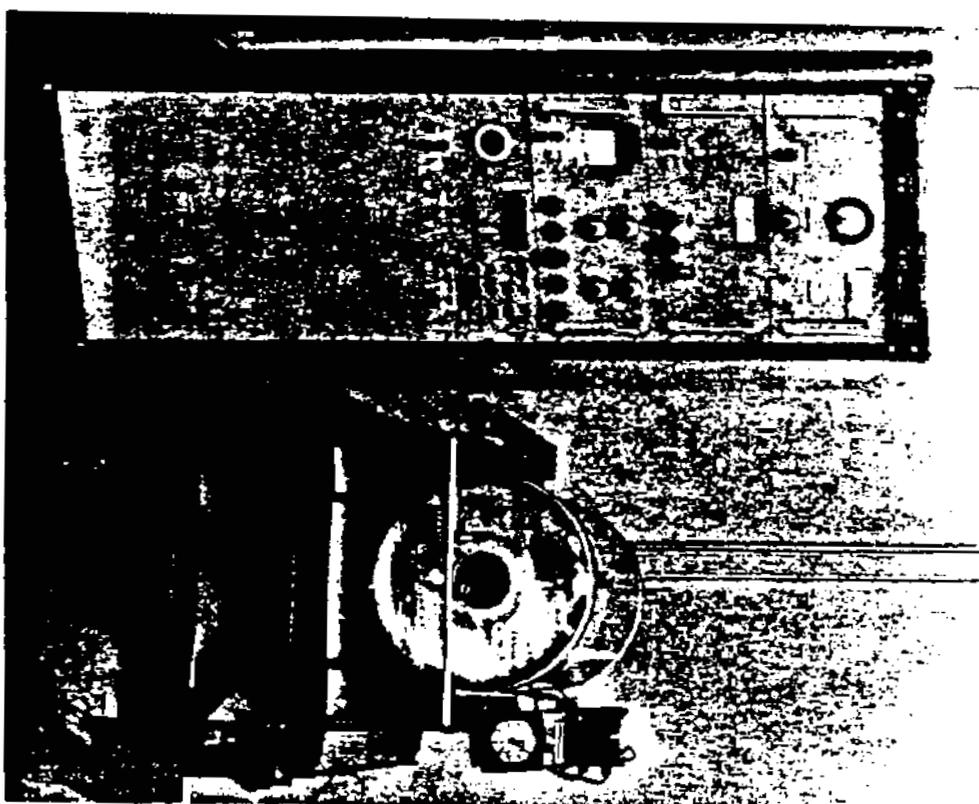


EXHIBIT 9.—Original Lee Almas Arm Counter with electronic scaling units. The tank of liquid scintillator is shielded by tanks of mercury, weighing about 500 pounds.

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EXHIBIT 11.—Most recent version of the Los Alamos Arm Counter, shielded with turret armor plate, being used to perform a whole-body retention study of a radioisotope in a rat.

Shortly after these instruments became operational, a program was initiated at Los Alamos to determine their clinical applicability. Since the radiiodine thyroid uptake test is the most commonly done radioisotopic test (and the only actual moneymaker), this measurement was one of the first to be studied with the whole-body counting technique. The concept basic to this technique is the now well-established fact that animals excrete metabolically important materials at rates that express the turnover kinetics of the organs and systems that utilize these materials. On this basis, it had been proven previously that it was possible to determine the thyroid uptake of I^{131} by measurement of daily urinary excretion of I^{131} . The whole-body counter technique determines such excretion rates by measuring the retention of an administered isotope or, in other words,

by measuring the amount of radioisotope which has not yet been excreted. The resulting whole-body retention curves are the sum of two or more exponentially excreting metabolic compartments, which are easily determined by simple mathematical analysis (exhibit 12).

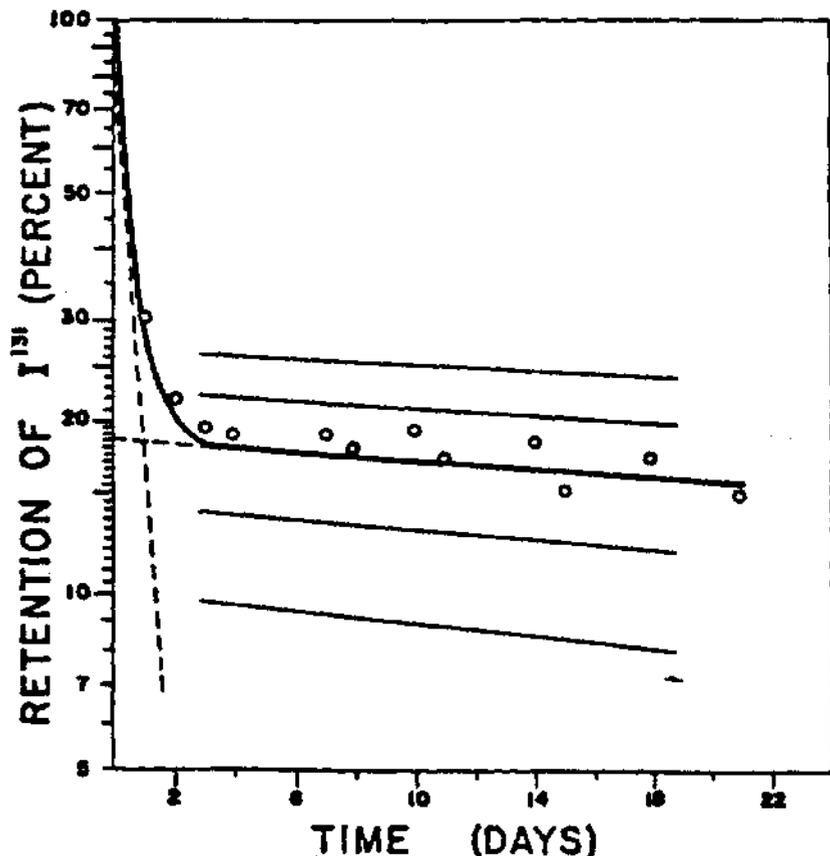


EXHIBIT 12.—Composite graph of whole-body retention of NaI^{131} in normal persons as determined with Humco I, showing the fiducial limits of the data and the two exponential urinary excretion rates of unbound and thyroid-bound iodine.

For example, following the oral administration of NaI^{131} , the iodide is absorbed totally from the intestine and excreted by the kidneys from two metabolic compartments, each with a characteristic rate. The first compartment comprises the unbound iodide in the body fluids and has, in a normal person, a rapid 8- to 9-hour half-time excretion rate. The second compartment is the thyroid-bound iodide and has a slow excretion half time of 90 days. A successful thyroid uptake study depends upon the accurate measurement of the metabolic size of this second compartment, which actually is the amount of the tracer dose taken up by the thyroid gland. The common technique of measuring the gland itself by the 2-inch-in-diameter sodium iodide crystal scintillometer often fails because of its comparative low sensitivity and difficulty in reproducing the relationship of the gland to the crystal because of patient movement and technician error. The whole-body counter technique has proved very efficacious in this regard because no alignment of the scanner and thyroid gland is required, since the whole patient is counted and patient movement does

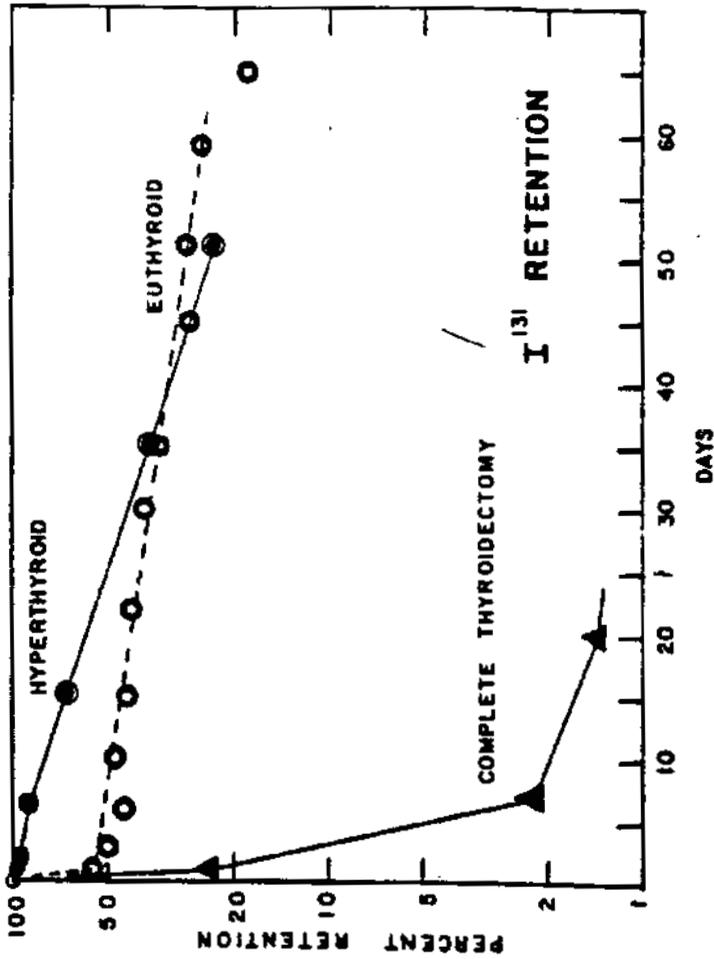


EXHIBIT 13.—Diagnostic whole-body retention studies using NaI^{131} in a hyperthyroid boy, a questionably normal woman, and a man whose thyroid was thought to have been completely removed for cancer. The curving upwards of the last line, in this case, was due to residual thyroid tissue.

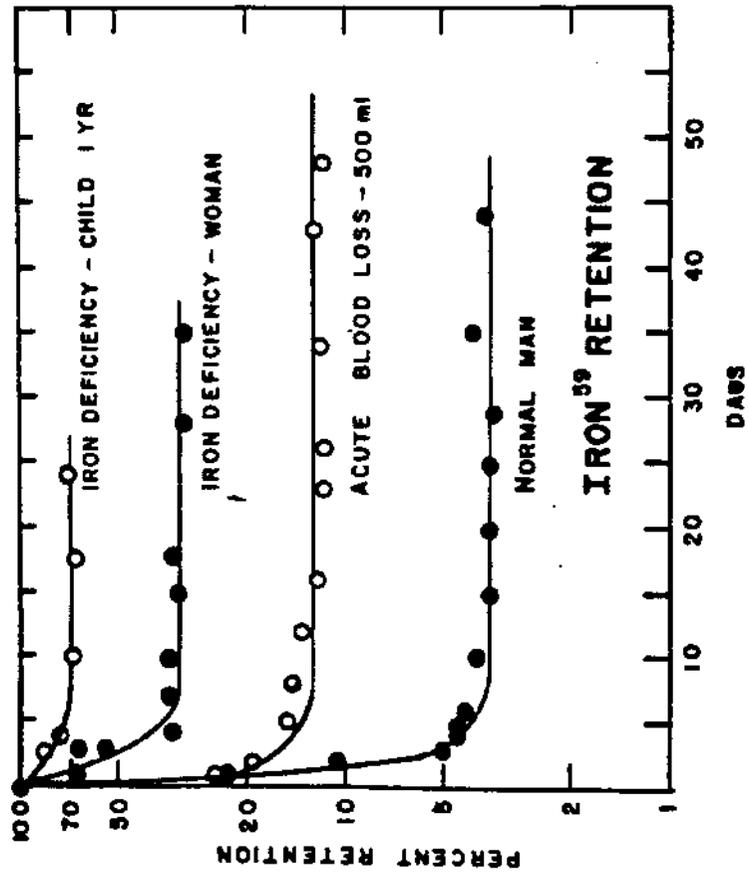


EXHIBIT 14.—The retention of orally administered radioactive iron in a normal man before and after a blood donation, a heavily menstruating young woman, and a 1-year-old child fed milk exclusively for the first year of his life.

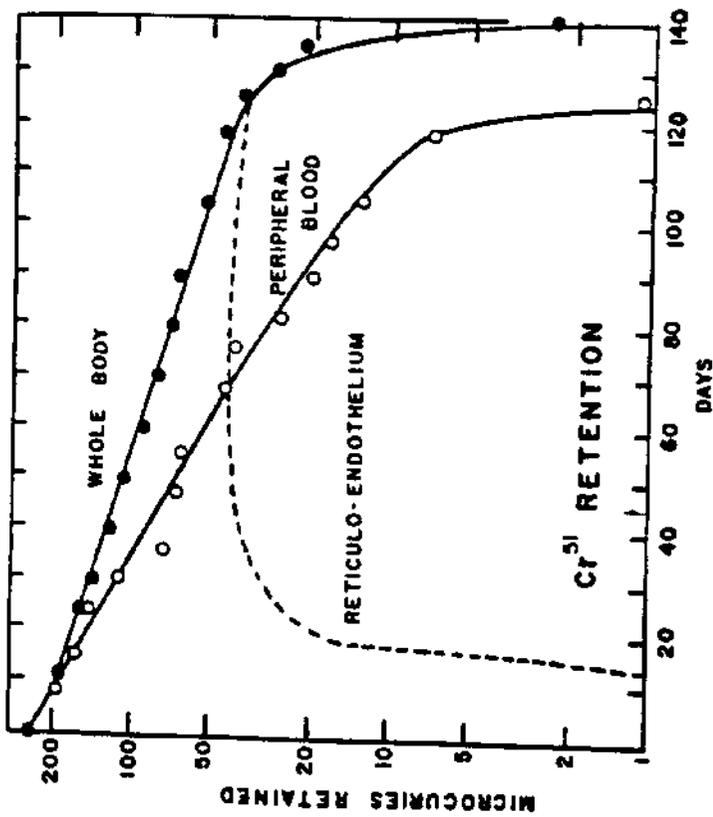


EXHIBIT 15.—Whole-body and peripheral blood retention curves of a Cr^{51} -label or normal human red blood cells. The dotted line represents the difference between the amount of labeled blood in the whole body and in the circulating blood. This line represents blood sequestered in such deep-seated organs as the spleen and bone marrow.

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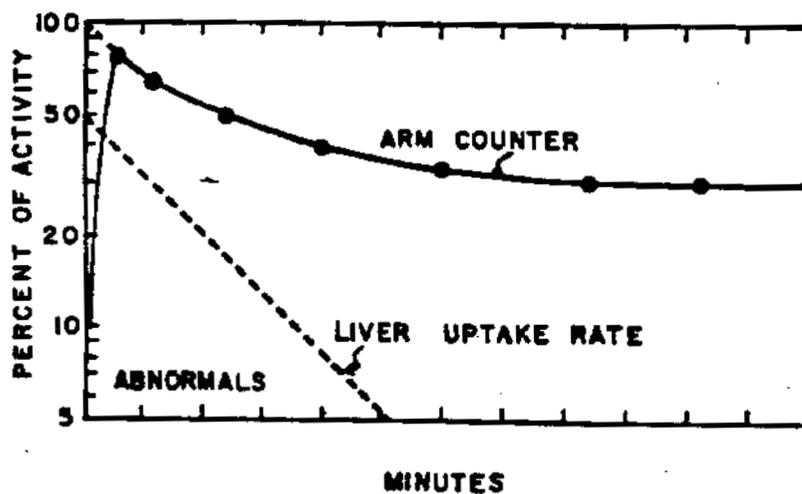
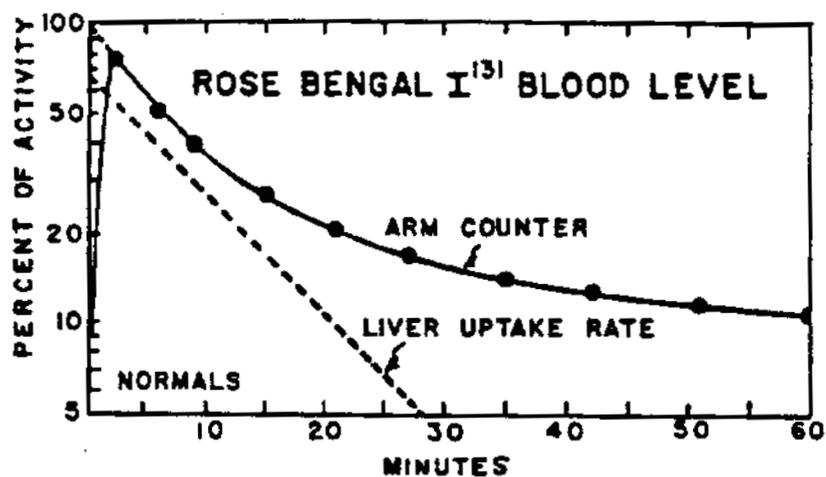


EXHIBIT 16.—Typical changes in blood concentration of Rose Bengal-I¹³¹ in normal persons and in patients with known hepatic disease. It is to be noted that, while the liver uptake rates of the dye are the same in the two groups of persons, the injured livers fail to clear as much dye from the blood, and the residual radioactivity is higher than in the normal group.

In addition to this, they have also been investigating what I think is a very interesting subject: How often can an Army man be used as a blood donor without altering his avidity for iron or depleting him so badly in iron storage that he is no longer usable to them as a soldier? There are obviously many such problems which are applicable to their own operations which I know are underway, but I do not know about them in detail.

Representative PRICE. Would these machines be valuable if used in the various medical centers that are springing up in the country, or are they too expensive for such use?

Dr. LUSHBAUGH. I think it is true that these machines will be expensive. We do not know exactly how much the development of these machines costs us.

Representative PRICE. Are you able to put a cost on them right now?

Dr. LUSHBAUGH. We think it is of the order of \$50,000 apiece. We think at the present time they can be made less expensive if one uses different types of shielding materials. But we also feel that these are such labor-saving devices and that they are so easily operated that the \$50,000 initial cost can be easily defrayed by their operation at capacity. Such a machine, for example, does a thyroid uptake test actually in 400 seconds, roughly about 6 minutes. This test can be done without a physician having to locate the person's thyroid gland, or having to aim a sodium iodide crystal at a talkative nervous woman's neck. The person is placed in the tank and immediately measured by technical personnel rather than professional personnel. There is a large labor-saving possibility there.

The usual price for such a test varies but I would imagine is about \$15. Six minutes of counting time for \$15 in an 8-hour day can, you see, defray a large initial price for equipment.

Representative PRICE. Mr. Ramey.

Mr. RAMEY. One of the unsolved problems brought out in our 1959 fallout hearings was the problem of short-lived radioisotopes, including iodine 131. Have you used these machines in any of that kind of research?

Dr. LUSHBAUGH. In one of our accidents a year ago, for instance, this machine as well as the whole body counter in our steel room with the large crystal was used to determine the amount of neutrons that this injured man had received. Not only were we able to establish his dose of radiation by this device, but we were also able to screen the five security police who were also thought to have been exposed and the several men who also worked in the room with him. In a matter of 15 minutes we had shown that only one other man had received any neutrons but had so little sodium 23 activation that we did not have to worry about him. We were able, therefore, to put his mind at rest at once. We have done work with sodium 23 as an example of a short-lived radioisotope. We have also tried iodine 132 which is a shorter one.

Representative PRICE. If there are no further questions, thank you very much, Doctor. We are pleased to have your statement.

Dr. LUSHBAUGH. Thank you.