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Delineation of Active Marrow by Whole-Body Scanning with Radioactive Colloids[1]

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The bone-marrow organ is difficult to delineate. Although kinetic aspects of hematopoiesis have been clarified by a variety of valuable studies, until recently, the clinical determination of marrow size and location in diseases affecting hematopoiesis has been limited to local sampling by aspiration or biopsy.

The bone-marrow distribution now can be detected by radioisotopic scanning techniques. We have in earlier papers (1, 2) demonstrated marrow patterns using intravenous colloidal gold-198 and a research scanner with a gold-tungsten collimator, confirming and extending the observations of Engstedt (3), *et al* and Larsson (4), *et al.* Although the uptake of the colloid is by reticuloendothelial cells, we and others (3) have observed that correlation exists in the bone marrow between reticuloendothelial function and hematopoiesis, and this method has proved of value in studying marrow distribution. In this paper, marrow described as "functioning," or "active," refers to reticuloendothelial activity.

The present report covers recent work in which we have explored improvements in instrumentation, searched for colloids having more favorable physical and biologic characteristics, and it summarizes our experience in scanning active marrow.

MATERIALS AND METHODS

Instrumentation. The area scanner limits views to 14 × 17 inches and requires approximately one hour for each scan. To survey the total bone-marrow organ, we have developed, in collaboration with Oak Ridge National Laboratory, a whole-body scanner (5), which uses a moving detector beneath the patient ac-

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cording to established principles of rectilinear area scanning. The display is either by a mechanical mark pattern or by photoscan recording, and each can be recorded either life size or at a reduction of 5:1. The 5½-inch, 88-hole, 4-inch focal-length lead collimator (6) for the 5- × 4-inch NaI crystal gives excellent resolution, but sensitivity suffers. A shorter 3¾-inch version of this collimator with ^{198}Au improves the sensitivity about four times, but with some loss in resolution. A whole-body scan can be obtained in about 80 minutes. Additional collimator-detector combinations are under construction that will be more sensitive and more appropriate for lower energy emissions.

Test Compounds. Until now most of the scans have been made after intravenous colloidal ^{198}Au* given in doses of 1 to 2 millicuries. Recently, pilot studies have been performed with ^{159}Gd hydroxycitrate, since animal experiments show this material to behave like a colloid after intravenous injection (7) when given with a suitable amount of stable carrier. The preparations used had 6-to-7 mg of gadolinium per millicurie, and for adult patients, 2-to-4 millicuries were given. Also, scans have been made with ^{99m}Tc sulfur sol colloid prepared by the method of Richards (8).

Patients. Our experience includes 109 sets of scans on 89 patients, most of whom had serious hematologic disorders or some malignant neoplasm.

RESULTS

Instrumentation. The whole-body scanner has provided a reasonably rapid and complete method of showing in a single view all the functioning bone marrow, except that obscured by liver and spleen (Fig. 1). Previously similar information required correlation of multiple views of smaller areas with linear (profile) scans. Because we have chosen to have the patient routinely lie on his back with the detector passing beneath him, the collimator focus is in a plane posterior to the midpoint of the body; anterior areas of marrow are, therefore, seen less well. Compared with area scans (1, 2) detail has been sacrificed somewhat because of the less sharply focused collimation.

Test Compounds. The initial trials with ^{159}Gd hydroxycitrate show that it clears from the blood less rapidly than colloidal gold, although physically it appears to have larger colloidal size (Fig. 2). The scans show a pattern resembling that observed with gold-198. We have also been able to delineate functioning reticuloendothelial activity with the sulfur colloid of ^{99m}Tc, and its distribution corresponds with that observed with gadolinium and gold colloid. Our initial results with ^{99m}Tc indicate that for whole-body scanning, difficulties caused by scatter characteristics of the 140-keV energy emission are encountered (Fig. 3, 4). Considerations of this problem are being reported separately.

Clinical Findings. We have obtained one or several sets of bone-marrow scans in 20 cases of acute leukemia and find no consistent pattern of decreased, normal, or expanded marrow typical for this disorder. Not surprisingly, some of the patients show uptake of the colloid only in the liver and spleen with no delineation of the reticuloendothelial tissue of the bone (Fig. 5). However, some children

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with acute leukemia show a marrow uptake resembling the peripheral skeletal pattern of a normal child. This same wide range of uptake has also been observed in the adults that we have examined (Fig. 2).

The scans of four patients with chronic granulocytic leukemia have all shown some expanded marrow with extension into the extremities (Fig. 6).

In chronic lymphocytic leukemia we have seen a range of results, including decreased, patchy uptake, approximately normal distribution, and distinct expansion of the marrow.

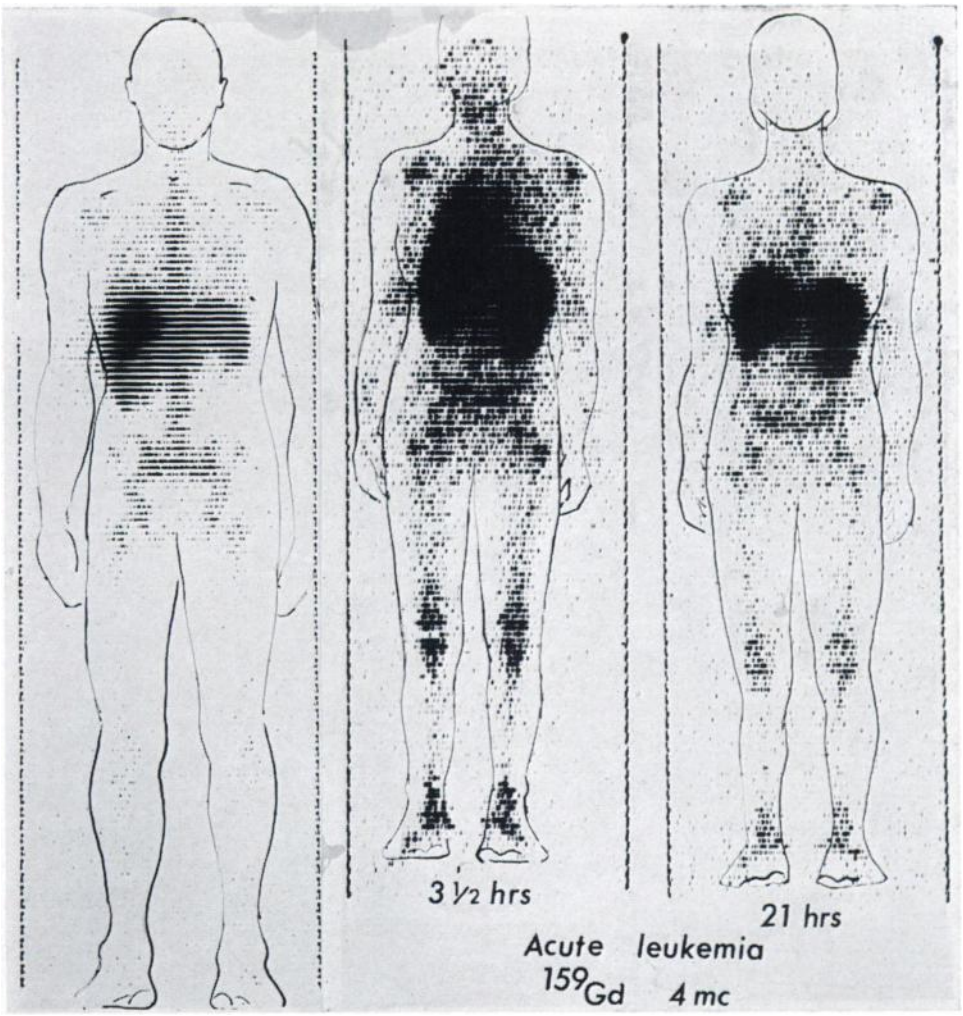

Fig. 1 *Left:* **Typical whole-body scan with intravenous colloidal ^{198}Au. This man, age 28, had a metastatic soft-tissue tumor, with no known bone involvement. Distribution of functioning marrow is essentially normal.**

Fig. 2 *Middle and Right:* **A woman, age 44, with acute granulocytic leukemia. After intravenous ^{159}Gd hydroxycitrate. The scan on the left, taken at 3½ hours, shows lung activity, less on the left side where there was a pleural effusion. Improved marrow delineation was obtained at 21 hours. Note pronounced marrow expansion into the lower extremities.**

In polycythemia vera the degree of uptake correlates rather well with the state of progression of the disease. An asymmetrical expansion of the marrow clearly seen in one patient is unexplained. Other patients with myelofibrosis complicating polycythemia vera show a pattern that also is characteristic of four other patients with idiopathic myelofibrosis in which the liver and an enlarged spleen are visualized and without visualization of the marrow in the skeleton.

In four patients with multiple myeloma, destruction of the marrow of the trunk has been accompanied by some evidence of functioning marrow in the extremities.

Local bone-marrow lesions have been delineated, and small defects can be detected under optimal scanning conditions. Scans of marrow within the field of previous radiotherapy easily demonstrated decreased or absent uptake of the radioisotope sometimes for months or years after the radiation.

The response that might be anticipated in some disorders is not always found. One patient with an active acquired hemolytic anemia showed less than the anticipated marrow expansion. Another patient, who had recurring, extensive blood loss caused by hereditary telangiectasis and had been treated with iron, failed to demonstrate the marrow expansion that would be predicted.

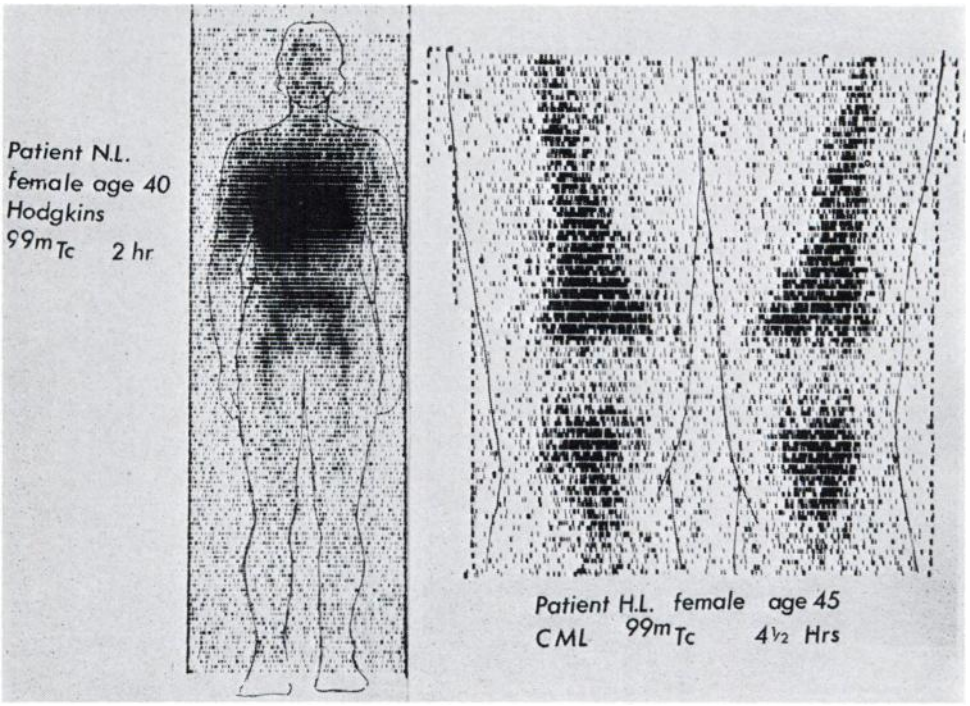

Fig. 3 *Left:* **A woman, age 40, with Hodgkin's disease, was scanned 4½ hours after 4 millicuries of ^{99m}Tc. The spectrometer was set at 125 keV base with a 100 keV window, yet scatter in the trunk and especially in the arms, from the high liver activity, is significant.**

Fig. 4 *Right:* **Scan of the knees after ^{99m}Tc colloid (research area scanner) in a patient with chronic granulocytic leukemia whose whole-body scan showed marrow expansion. The detail is good and scatter effects are absent.**

DISCUSSION

Even at the present stage of development, bone-marrow scanning is a useful adjunct to understanding the patient's hematopoietic status. Responses to destruction of the marrow, the patterns of extension of the active marrow into the extremities, the delineation of local lesions, the hyperplasia seen in some anemias can be shown, and sometimes in dramatic detail.

For hematologic diagnosis, the ideal tracer would demonstrate erythropoiesis, granulopoiesis, and thrombopoiesis, preferably distinguishing each of these cell lines. Practically the only technique that partially fulfills this requirement employs ^{52}Fe, which has been very skillfully studied by the group at Donner Labora-

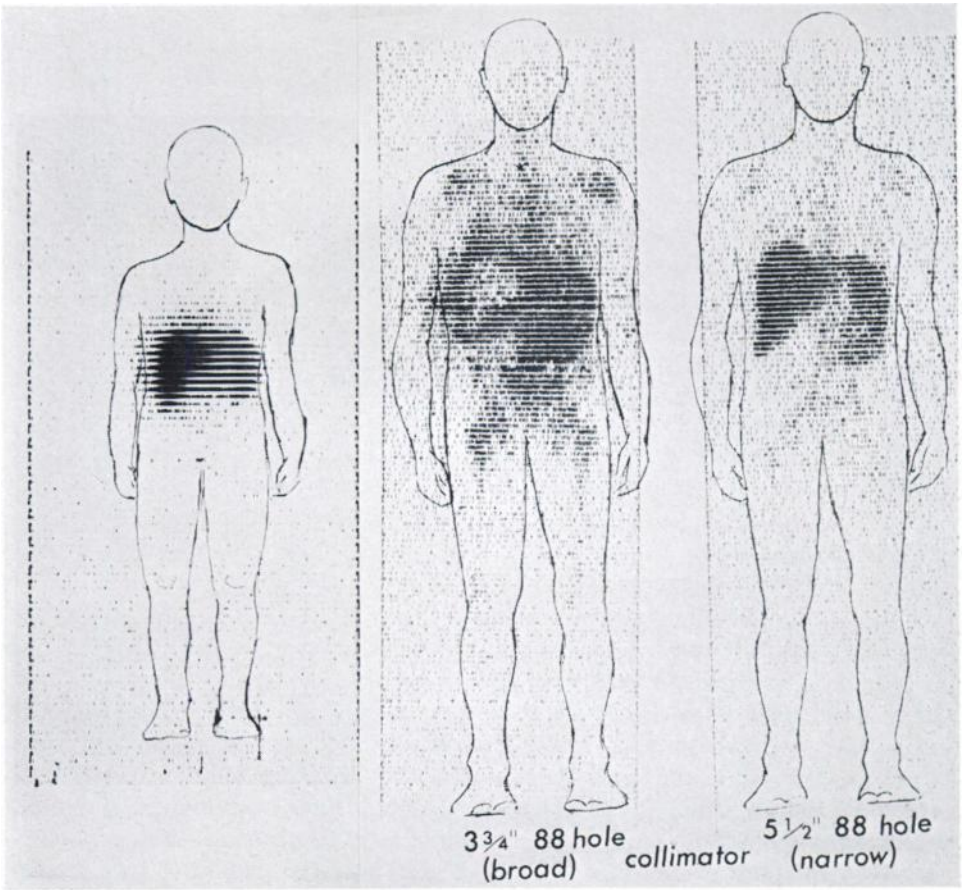

Fig. 5 *Left:* **Boy, age 4 years, with acute lymphoblastic leukemia in relapse. Scan 18½ hours after intravenous colloidal ^{198}Au. Note absence of marrow uptake.**

Fig. 6 *Middle and Right:* **Scans obtained after colloidal ^{198}Au in a patient with chronic granulocytic leukemia. Care in interpretation is necessary: although marrow expansion is obvious with the "broad" collimator, the "narrow" collimator less readily shows this alteration. These are mechanical dot scans, and the hole in the midportion of the liver is overload freezing of the tapper.**

tory (9, 10). One of the virtues of this isotope is its short half-life, which allows use of large doses without excessive radiation. Those authors have not detected any evidence that the daughter ^{52m}Mn leaves the vicinity where it was formed by ^{52}Fe decay. In its favor is the positron emission, theoretically an advantage for electronic localization. Iron-52 is limited to those laboratories close to special cyclotron facilities and there is at present no promise of its practical availability for wide clinical use.

Radioactive colloids distribute in the reticuloendothelial elements of bone marrow that are usually in close association with the developing blood cell precursors. But colloids have the disadvantage that only a minor portion deposits in the marrow. The larger share, going to the liver and spleen, obscures the view of the marrow in the midtrunk, and gives a significant radiation dose to these organs. Furthermore, alterations in the blood supply of liver and spleen affect the amount reaching the marrow and complicate quantitative evaluation of the marrow uptake.

The interpretation of the patterns involves a number of considerations, some of which are assumptions that are not well based yet or adequately established. Fatty or fibrous marrow, or that replaced by tumor, has consistently failed to take up the colloid; normal and hyperplastic marrow has never failed to do so. Leukemic marrow has given extremely variable results, which may prove of clinical value but are not yet well understood. The leukemic patient in Figure 2, for instance, had little erythropoietic or granulopoietic activity as judged by the marrow specimen, but marrow uptake was extensive. Various approaches are being taken to study the significance of scan findings and their relation to the actual *in vivo* bone-marrow activity. When ^{52}Fe becomes available we intend to do the obvious experiment of comparing directly in the same patient scans made with radioiron and with radioactive colloids. Evaluations have been made in the light of general hematologic findings, results of multiple marrow aspirations, history of local radiation, radiographic findings, and autopsy studies in which many marrow sites are examined. Additional experience should enhance the ability to interpret the records.

To produce better marrow scans, improved radioactive colloids are needed. Clearly both particle size and chemical properties of particle surfaces are important, and a material that would concentrate more in the marrow and less in the liver and spleen would be desirable. The enormous amount of published work on behavior of colloids in experimental animals has not been fully evaluated yet for this clinical application. Present choices of colloids have been influenced by availability, and by half-life and gamma energy of a convenient radioactive label. One of the main needs is to reduce the radiation dose to the patient so that the diagnostic test can be performed without concern, even in patients without serious diseases.

In a previous report we mentioned the possible use of colloidal ^{199}Au and ^{131}I-labeled albumin (1). The former has had very limited trials, but its theoretical advantages over ^{198}Au are not great. The albumin preparation has the disadvantage of early release of the ^{131}I label, leading to circulating radioactivity and concentration in the bladder where it interferes with the view of the pelvis. Gado-

linium-159 and ^{99m}Tc both have the advantage of much shorter half-lives than ^{198}Au, and thus they largely solve the problem of radiation dose to the patient. Table I summarizes the physical aspects of these three preparations. Not shown is the estimated dose to bone marrow. Smith (11) has calculated this to be 2.8–7.2 rads per mC administered for ^{198}Au, and 0.026-to-0.34 rads per mC of ^{99m}Tc administered. The liver receives the highest radiation dose, but because of its greater radiosensitivity the marrow is believed to be the more critical organ for acute radiation effects.

The gadolinium isotope is inexpensive to produce. Animal studies have shown a relatively high concentration in the marrow. If it can be shown for the human, this may be an important asset. This has not been reflected yet in improved clinical scans, and the early concentration in the lung, along with the slow removal from the blood stream, suggests that its colloidal properties may not be uniform or ideal with the present methods of preparation and amounts of carrier.

The preparation of ^{99m}Tc has not been extensively studied for colloidal properties, and its particle size is not known. The currently available methods of colloid preparation are probably not optimum. A compound of uniform particle size and completely free of pertechnetate ion is needed. In spite of difficulties, scans of good quality have been produced (12). However, this isotope, because of its low energy, will not lend itself to quantitation *in vivo* because of variations in attenuation by tissue. Even higher energy emissions, such as the ^{198}Au (410 keV) are attenuated, and the variability in tissue thickness in different parts of the marrow organ have prevented quantitations by linear scanning. The problem of scattering of the low-energy gamma emissions of ^{99m}Tc is serious and should receive further attention.

The instrumentation problems for bone-marrow scanning are more complex than for scanning of any other organ, especially because of the variable depth of the marrow from the surface of the body. The depth of the collimator focus is critically important, and factors of scatter and attenuation are significant also.

TABLE I

CHARACTERISTICS OF THREE ISOTOPES USED FOR MARROW SCANNING

	^{198}Au	^{99m}Tc	^{159}Gd
Half-time	2.67 days	6 hours	18 hours
Emissions	γ0.41; β0.97	γ0.14; β0.014	γ0.37, 0.057; β0.95
Production	^{197}Au (n,γ)	^{99}Mo generator	enriched ^{158}Gd (n,γ)
Daughter	^{198}Hg (stable)	^{99}Tc (stable)	^{159}Tb (stable)
Rads to liver/mC	32—42	0.2—0.3	10—13

Based on one millicurie given intravenously with 70-to-90% concentration in liver, remaining till complete decay.

SUMMARY

Radioisotopic scanning has been successfully applied to the evaluation of the hematopoietic organ. The objective is to delineate, with radioisotopic compounds, the size and location of functioning marrow, and to quantitate, if possible, the extent of abnormalities produced by marrow disorders or responses to various stresses. We have used intravenously administered radioactive colloids for this purpose. Improved isotopic labels and improved colloidal properties promise lower radiation exposures and more favorable marrow localizations. A whole-body scanner with a five-inch sodium iodide crystal and a 5:1 reduction scan of the patient's body has facilitated the procedure. Patterns of marrow alteration have been collected and analyzed in patients with acute leukemia, chronic leukemia, multiple myeloma, lymphoma, hemolytic anemia, polycythemia vera, and in patients with local marrow lesions. Multiple factors involving instrumentation, characteristics of the test compounds, and other clinical findings are needed for interpretation of the scans.

ACKNOWLEDGMENTS

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