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Patterns of Marrow Hypertrophy and Atrophy in Man

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The development of the positron camera has made it possible to record the distribution of erythropoietic marrow in human subjects, using a dose of ^{52}Fe that is within that permitted for diagnostic purposes (1). From such studies it has become apparent that wide variations in the distribution of marrow occur and that expansion and atrophy of the marrow may be classified into several characteristic patterns. Since the pattern of distribution bears a relationship to diseases involving bone marrow, it is useful to characterize the major types of marrow distribution patterns encountered.

MATERIALS AND METHODS

The positron camera (2) and the method for the preparation of the 8-hour positron-emitting isotope ^{52}Fe (3) have been described previously, as have the techniques used for obtaining positron scintiphotos of the distribution of ^{52}Fe in the marrow (1). In brief, an intravenous injection of 100 μc of ^{52}Fe is given and positron pictures of its distribution are taken 16 hours later when uptake by the marrow is maximum. A series of pictures are taken, each requiring 5-10 minutes exposure and showing the marrow distribution within a 9-inch diameter area. Complete iron kinetics studies (4) were done whenever possible to provide a basis for interpretation of the pictures.

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RESULTS

Positron camera pictures of the distribution of erythropoietic marrow in a 69-year-old normal male are shown in Fig. 1. Studies of normal subjects, 29, 40, and 69-years of age, showed similar gross distribution patterns. The pattern in a 40-year-old normal subject has been published previously (1-Fig. 2).

Fig. 2 shows the pattern of marrow distribution in a 22-year-old woman with polycythemia of unknown etiology. The picture shows a normal gross distribution of erythropoietic marrow. Another example of increased red cell production secondary to congenital cyanotic heart disease with a normal marrow distribution pattern has been published previously (1-Fig. 3).

Distribution of marrow in the active phase of primary polycythemia is shown in Fig. 3. Marrow was present in the normal sites and there was also extension of marrow down the shaft of the femur. This pattern of marrow distribution has been seen in two patients in the active phase of primary polycythemia. The same distribution has been seen in a patient with polycythemia secondary to congenital cyanotic heart disease, a patient with moderately severe chronic blood loss, a patient with multiple myeloma, and a patient with drug-induced hypoplastic anemia which responded to testosterone therapy.

The distribution of marrow in a patient with severe hemolytic anemia of three years duration is shown in Fig. 4. The marrow extended peripherally into the ankle and elbow, and heavy concentrations of marrow were found in the knee. Another example of this type of marrow distribution in a patient with polycythemia secondary to severe congenital cyanotic heart disease has been published previously (1-Fig. 4). Alfrey *et al* (5) have described a similar distribution in patients with "polycythemia in relapse".

Erythropoietic marrow distribution in a patient with severe hemolytic anemia is shown in Fig. 5. The distribution in the extremities was similar to that shown in Fig. 4, except that the normal concentration in the lumbar spine was absent and some of the ^{52}Fe was concentrated by the enlarged spleen. Iron kinetics measurements in this patient demonstrated rapid initial accumulation of ^{59}Fe is sacral marrow, but none was detected in the liver or spleen. Subsequently, there was a rapid release of radioiron from the sacral marrow and marked secondary accumulation of radioiron in the spleen. No secondary accumulation occurred in the liver. Furthermore, the iron kinetics study showed that the red cell survival time was approximately 1/20 normal. This was due to extremely rapid splenic sequestration and destruction of erythrocytes. Hemoglobin synthesis was 10 times normal. Another example of this type of erythropoietic marrow distribution in a patient with severe chronic hemorrhage has been published previously (6).

The distribution of marrow in the "burned out" or myelofibrotic phase of polycythemia vera is shown in Fig. 6. Erythropoietic marrow had disappeared from most of the normal sites. Only small amounts were present in the shoulder, knees, and ankles. The spleen took up most of the ^{52}Fe. Iron kinetic studies demonstrated that erythropoiesis was occurring almost exclusively in the spleen. Red

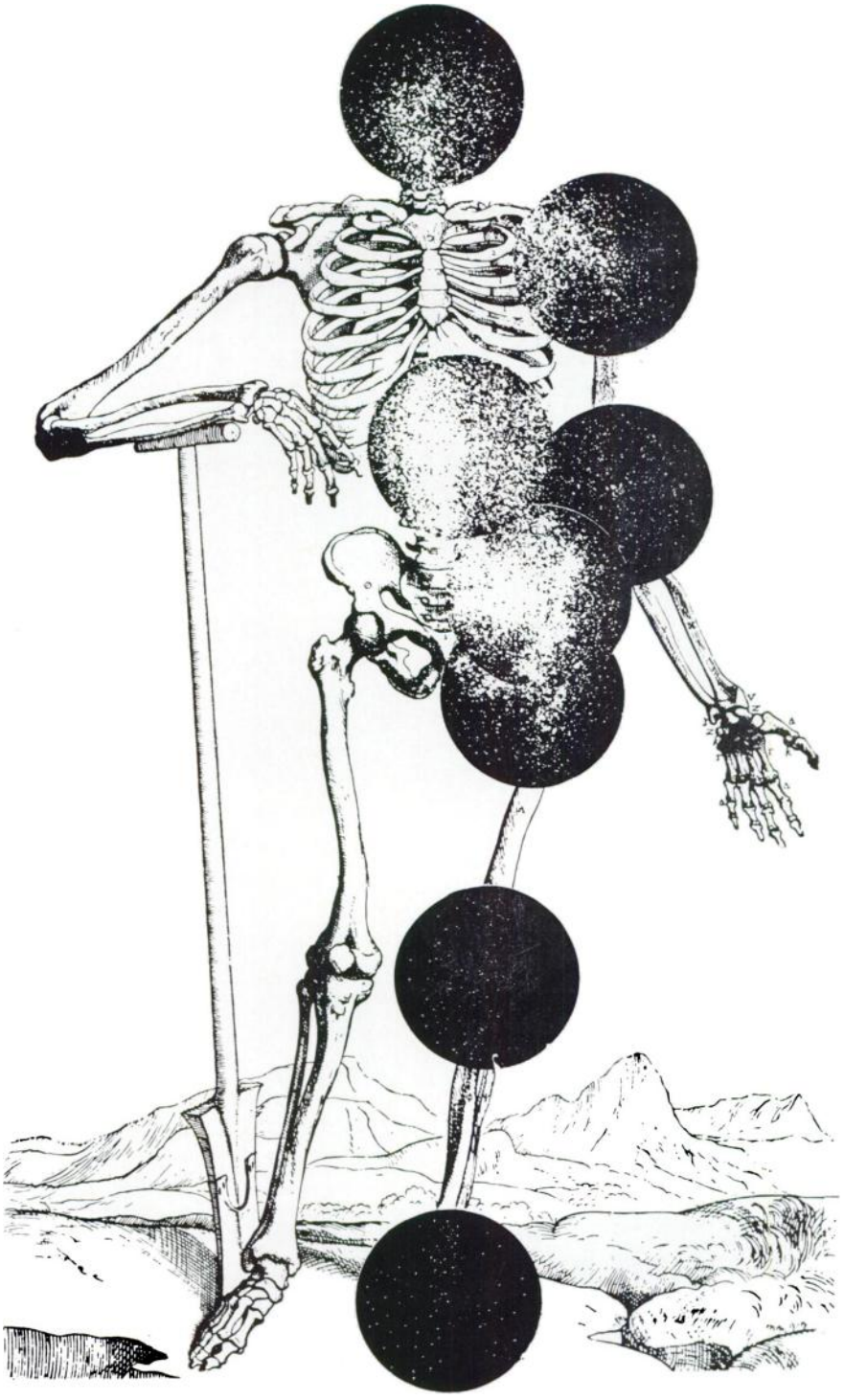

Fig. 1. Erythropoietic marrow distribution in 69-year-old normal subject.

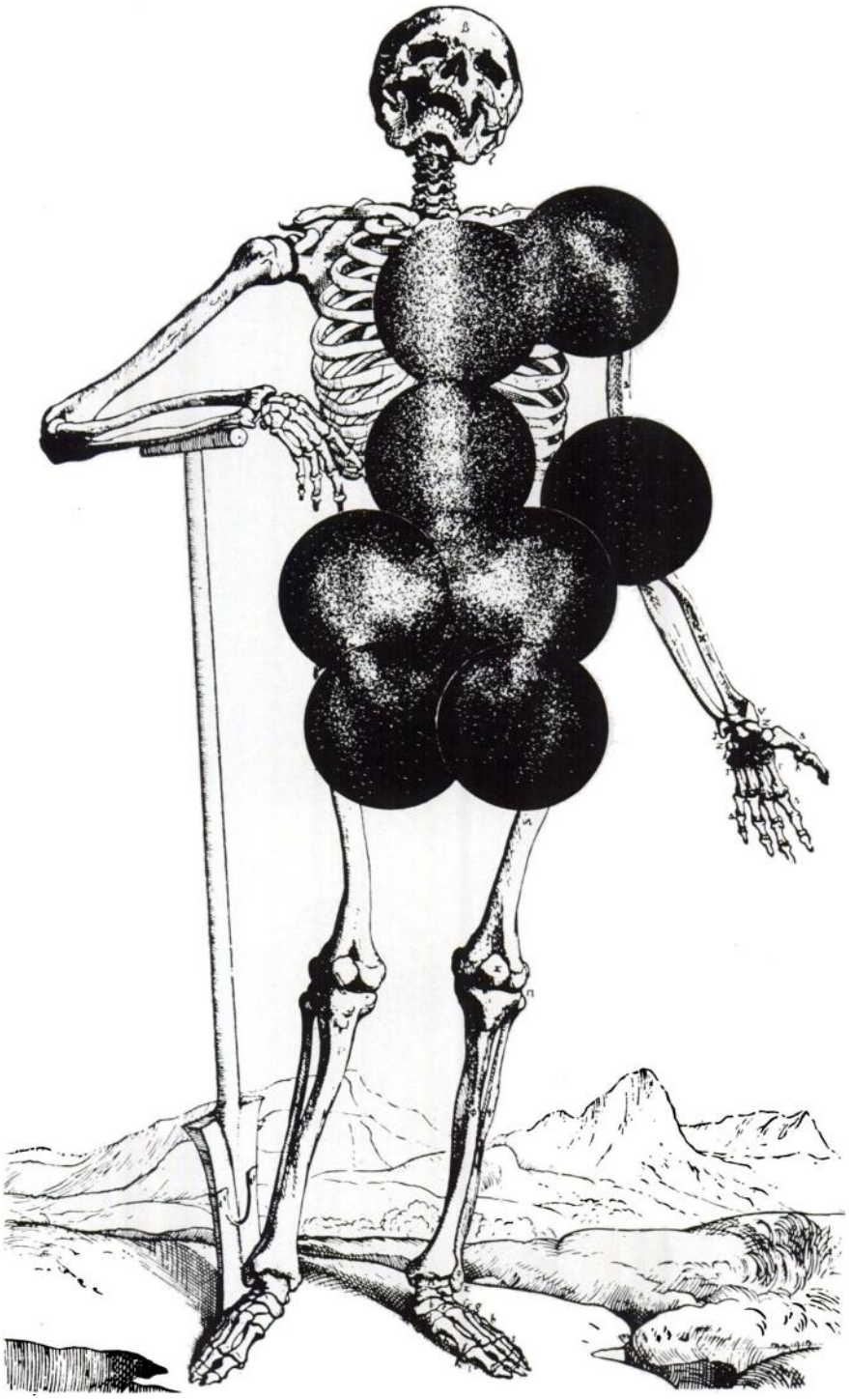

Fig. 2. Pattern of marrow distribution in 22-year-old woman with mild secondary polycythemia.

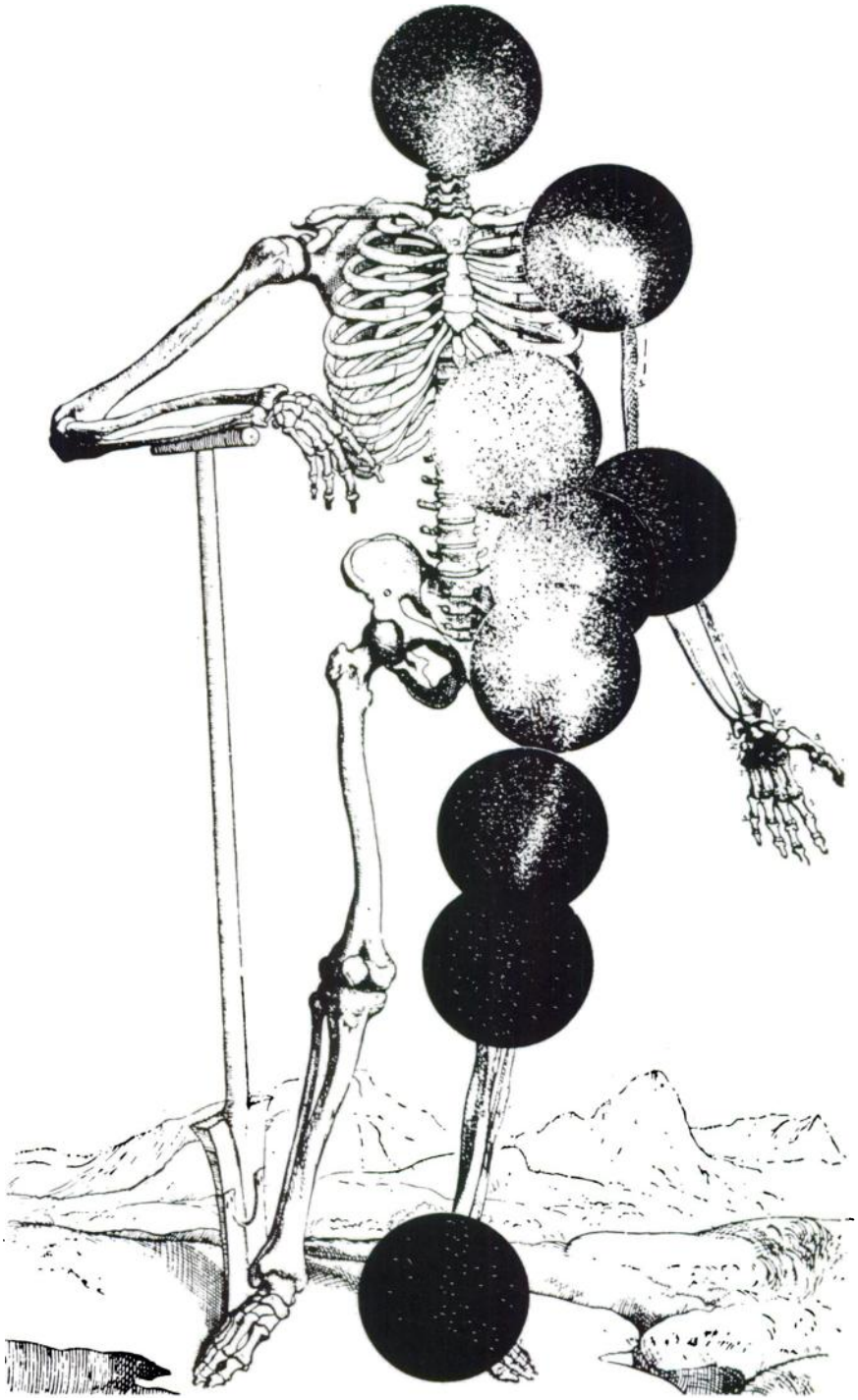

Fig. 3. Abnormal extension of marrow down shaft of femur in patient in active phase of polycythemia vera.

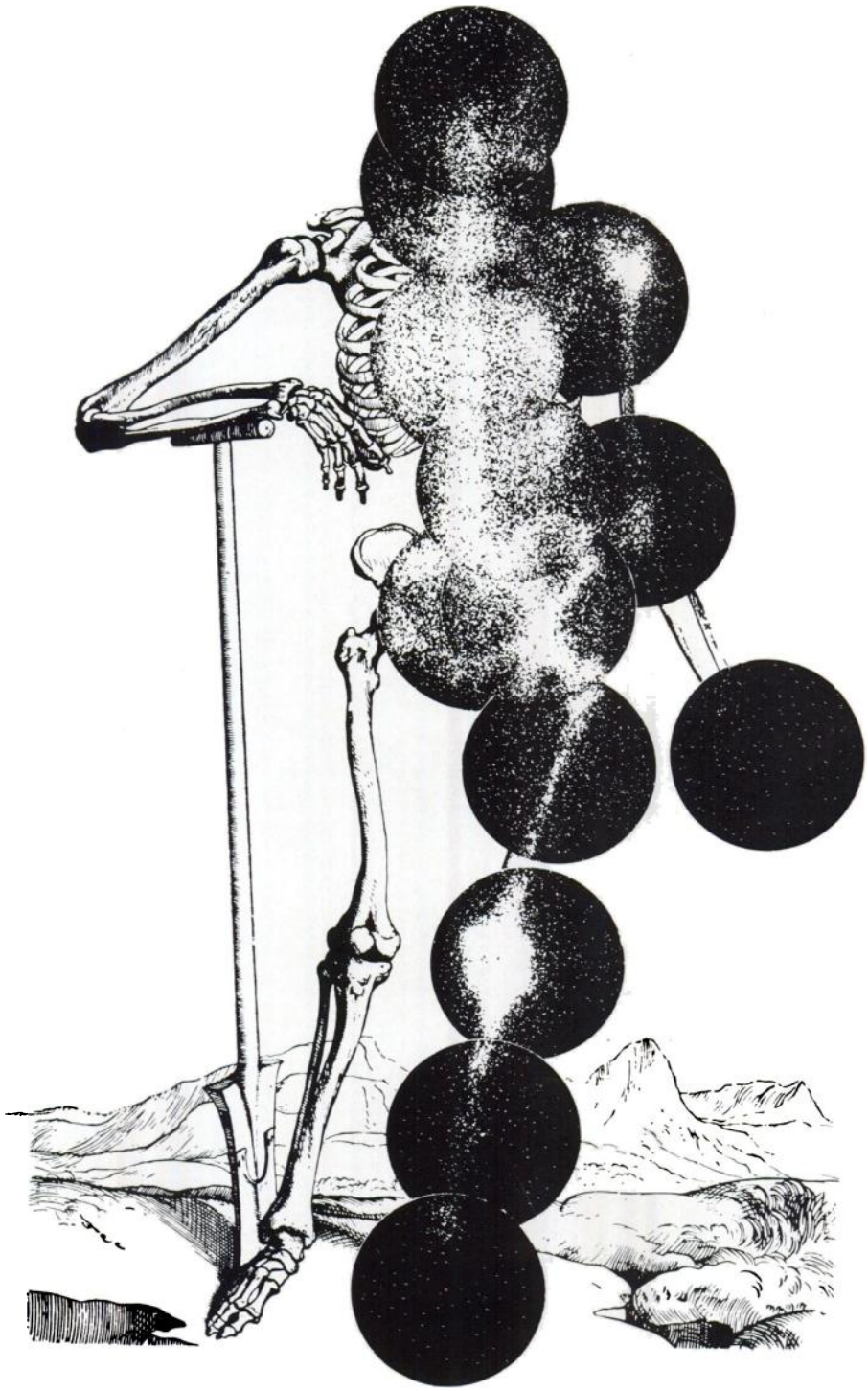

Fig. 4. Extension of marrow into knee, ankle and elbow in patient with severe hemolytic anemia of three years' duration.

cell survival was less than ¼ normal as a result of splenic sequestration and destruction of erythrocytes. Erythropoiesis was approximately three times normal, thereby largely compensating for the hemolytic process.

Pictures of a patient with active extramedullary erythropoiesis in the spleen and virtually no erythropoiesis demonstrable in the skeleton are shown in Fig. 7. Bone marrow aspiration revealed a fibrotic marrow containing few erythroid elements, resulting in a diagnosis of myelofibrosis.

The distribution of iron in a patient with complete red cell aplasia is shown in Fig. 8. Iron accumulated primarily in the liver and to some extent in the spleen.

DISCUSSION

In the normal adult human being, marrow is concentrated in the spine, pelvis, sternum, ribs, and proximal portion of the extremities. There are also variable amounts in the skull (7). The normal adult distribution of erythropoietic marrow we have called Type I. The changing pattern during maturation has not yet been studied.

When the marrow of the human being is called upon to produce red cells at a rate somewhat in excess of normal, hypertrophy of erythroid marrow occurs at the expense of fat within those areas of the skeleton that contain marrow normally (7). Under such circumstances the gross distribution of erythroid marrow remains normal, as shown in Fig. 2.

When the need for hypertrophy is greater than can be accommodated by replacement of fat, or when the usual sites are occupied by other elements, such as tumor or fibrous tissue, marrow expands into the bones of the extremities. When expansion is limited to the proximal portion of the humerus and femur, as shown in Fig. 3, we classify the marrow distribution as Type II. When, under extreme conditions of erythropoietic demand, the marrow extends into the tibia and elbow, as shown in Fig. 4, we call this Type III.

In the patients studied to date, marrow may extend into the ankle and wrist before significant extramedullary erythropoiesis occurs. Expansion of marrow into the extremities, loss of marrow from part or all of the usual sites in the skeleton, and extramedullary erythropoiesis in the spleen, as shown in Figs. 5 and 6, we call Type IV.

When medullary erythropoiesis fails completely and erythropoiesis is found only in extramedullary sites, as shown in Fig. 7, we call the distribution Type V. When erythropoiesis is absent in both medullary and extramedullary sites, the administered radioiron goes to storage in the liver and spleen, as shown in Fig. 8.

The above classification is not expected to accommodate all pathological situations, particularly those in which the disease process is localized in portions of the skeleton. For example, the distribution of erythropoietic marrow in Paget's disease has been found to correspond to the distribution of bone involvement. Edwards *et al* (8) have demonstrated the lack of recovery of the phagocytic activity of the marrow at sites of previous radiation therapy for carcinoma of the bladder. In our series a patient with Hodgkin's disease, who had complete hemopoietic recovery one year following large doses of radiation to the entire torso,

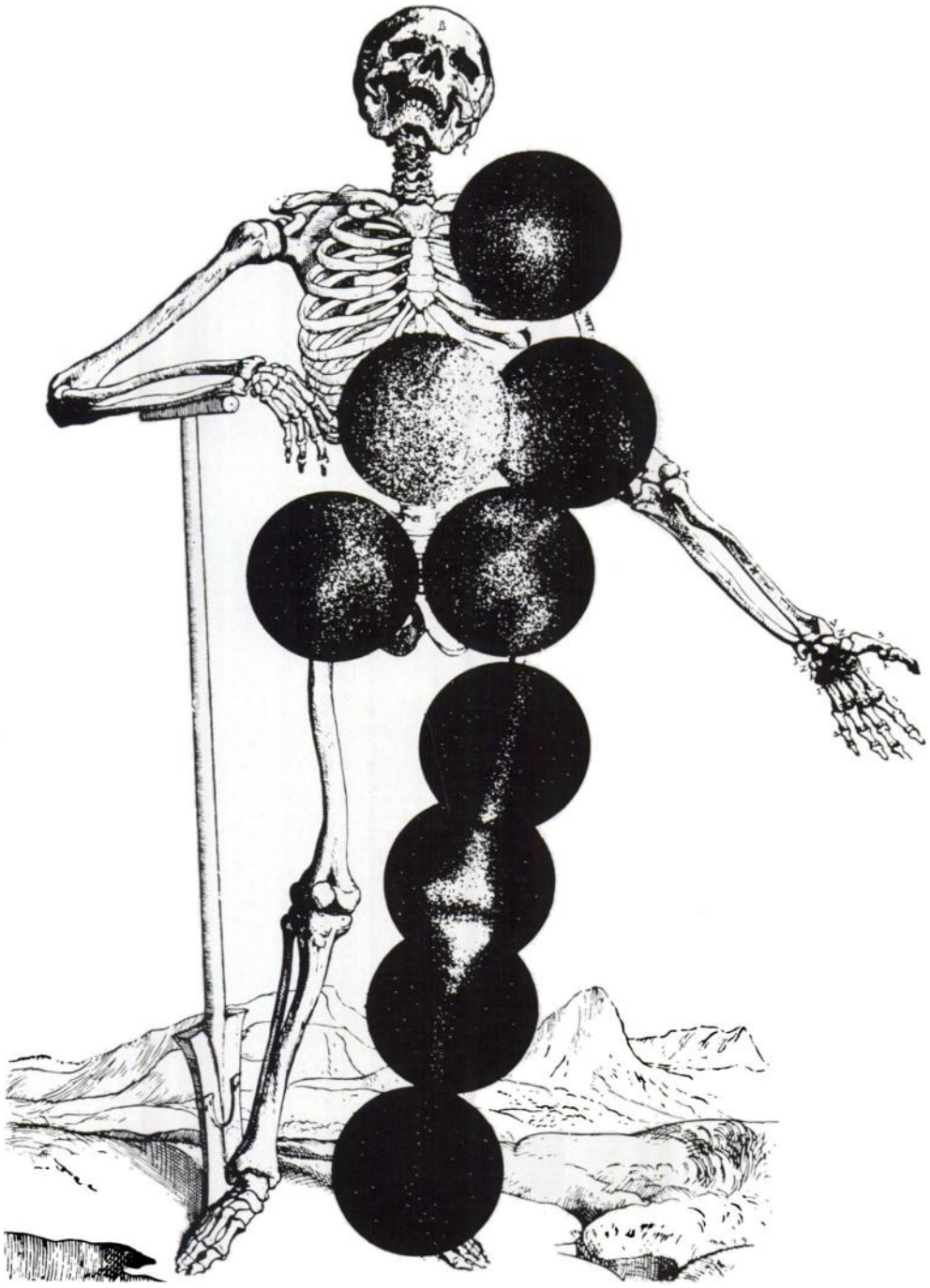

Fig. 5. Erythropoietic marrow distribution in hemolytic anemia. Marrow extends into humerus and tibia with loss of marrow in spine. There was extremely rapid splenic sequestration of erythrocytes.

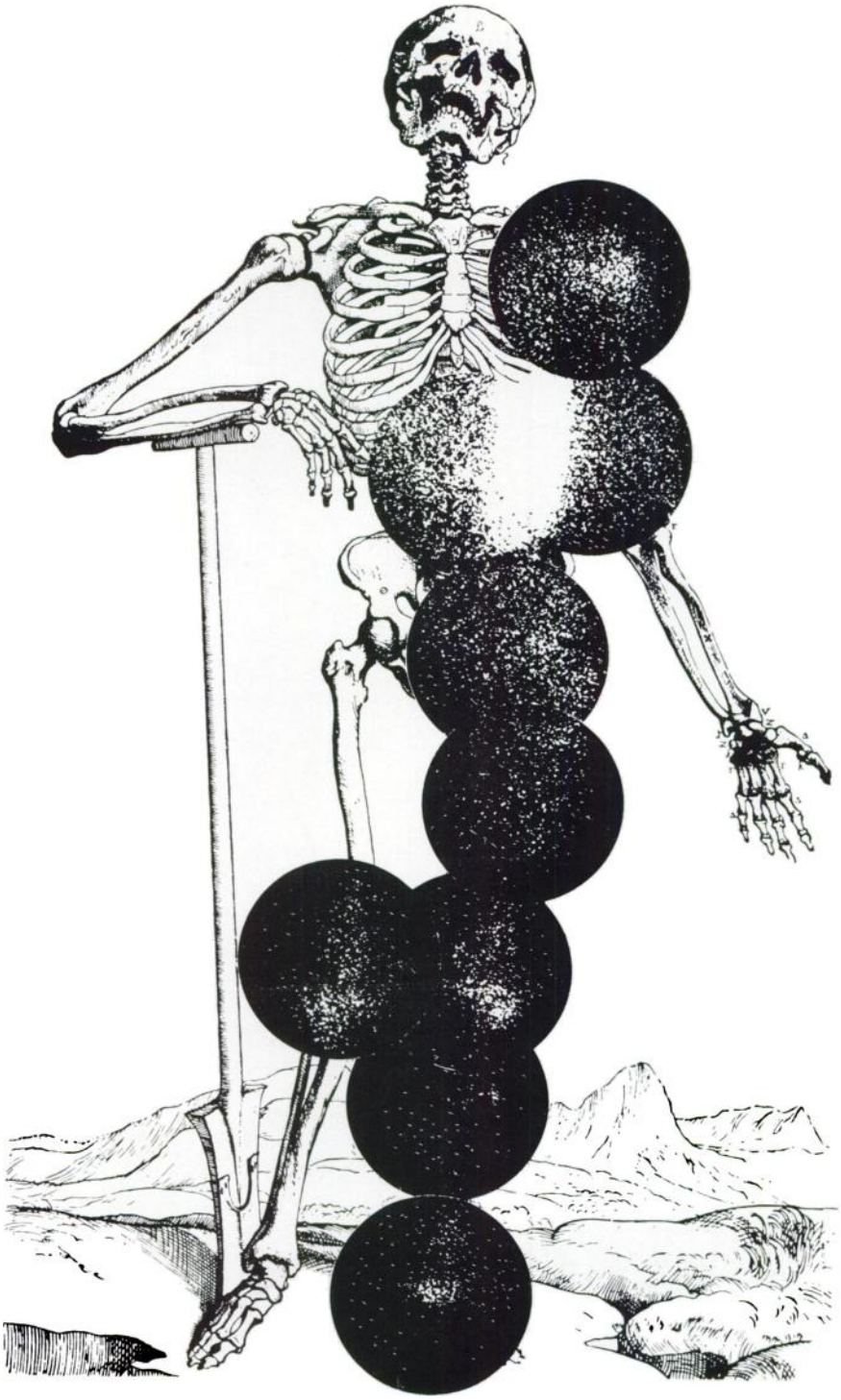

Fig. 6. Erythropoietic marrow distribution in patient in "burned out" stage of polycythemia vera, showing loss of marrow in all normal sites except shoulder, peripheral development in knee and ankle, and marked extramedullary erythropoiesis in spleen.

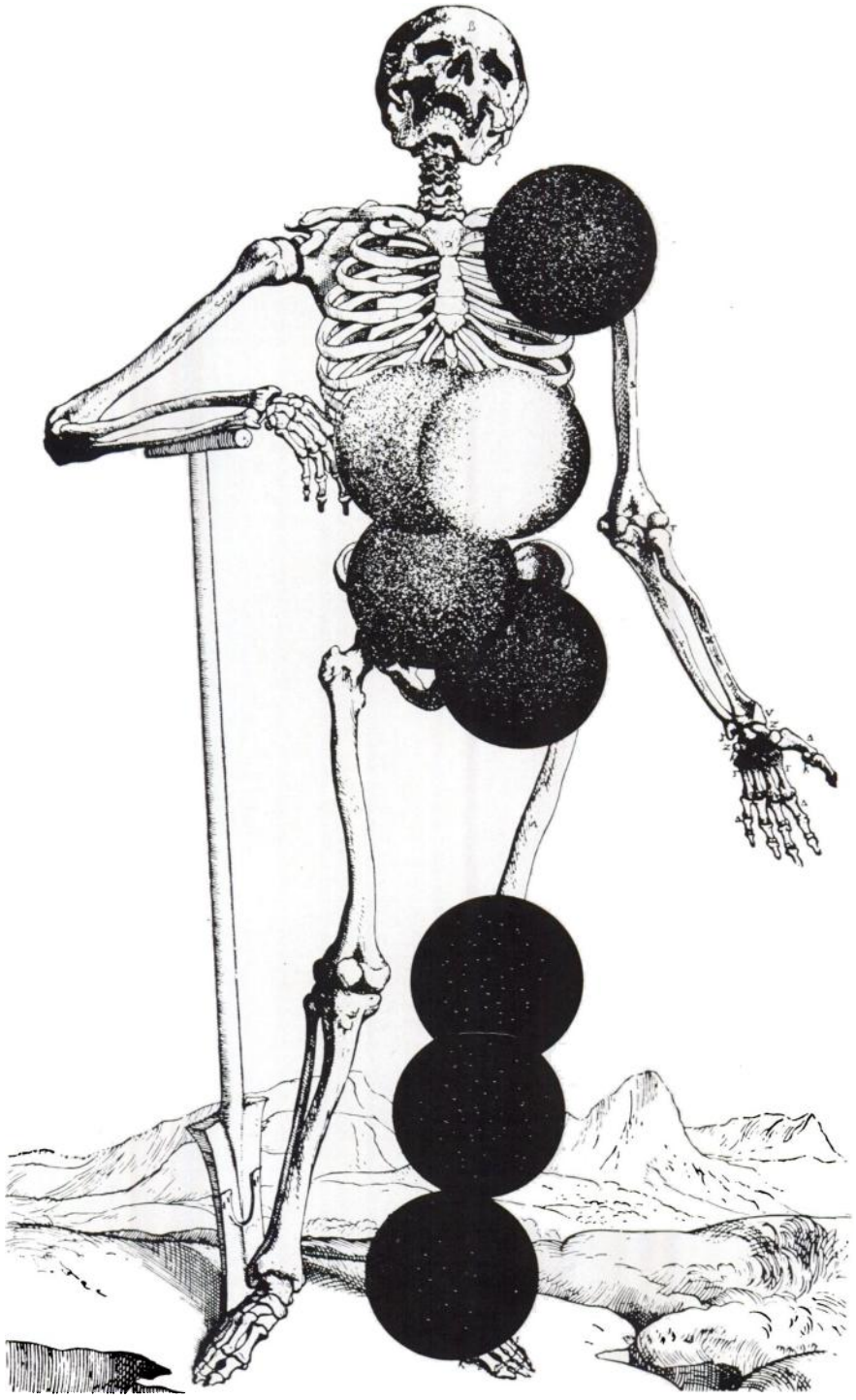

Fig. 7. Almost complete failure of medullary erythropoiesis in patient with myelofibrosis. Extramedullary erythropoiesis is shown in spleen.

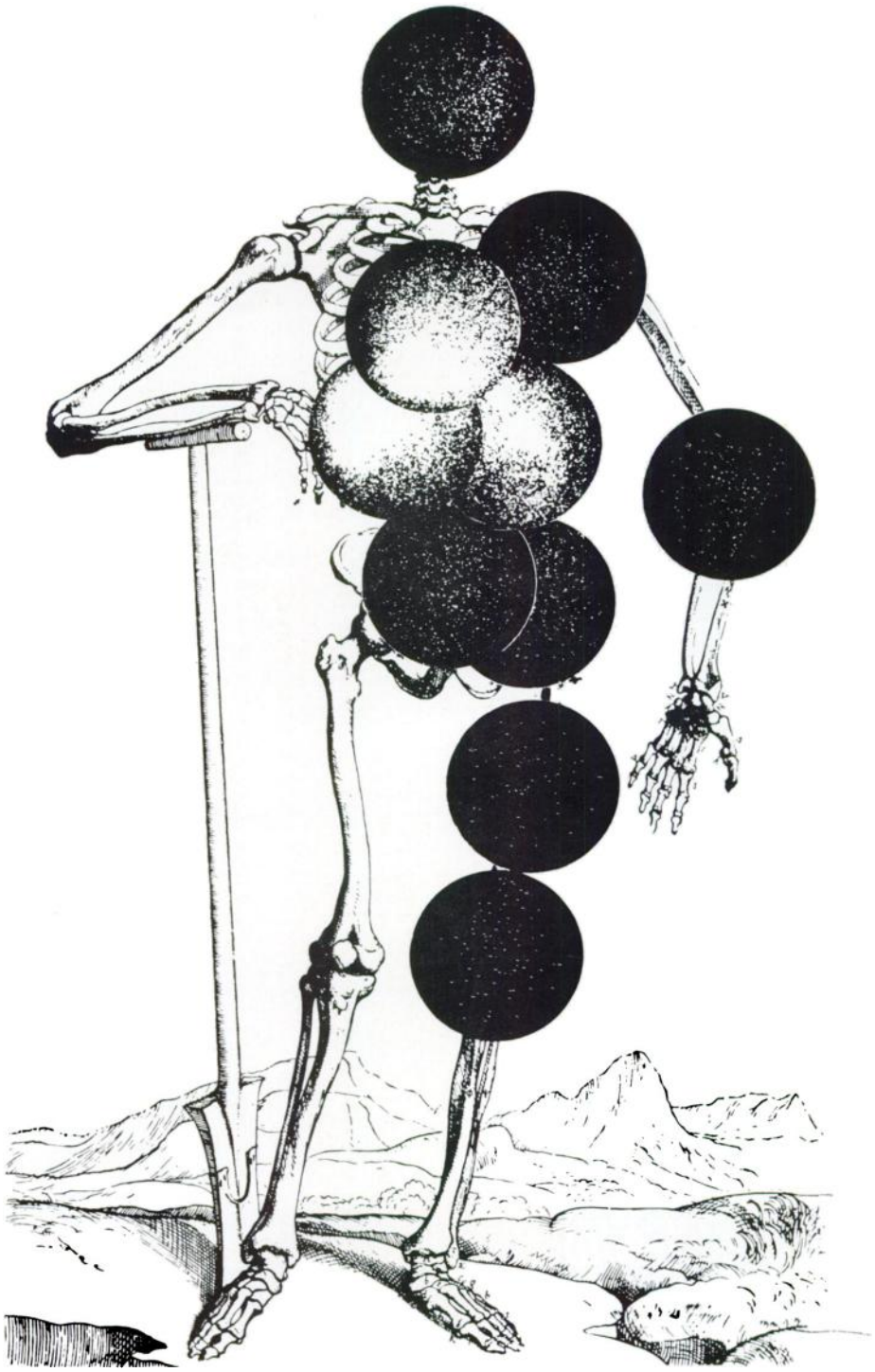

Fig. 8. Absence of both medullary and extramedullary erythropoiesis in patient with aplastic anemia. The administered ^{52}Fe was stored in liver and spleen.

was found to have nearly all of his marrow in the sternum, shoulder, and humerus. There was none in the lower extremities and almost complete loss from the spine and pelvis.

In our only case of multiple myeloma, the erythropoietic marrow distribution was Type II. In two cases of multiple myeloma studied by Edwards *et al* (8) the phagocytic marrow distribution corresponded to Type IV of our classification.

In diseases causing hypertrophy of the erythropoietic marrow, such as chronic blood loss, hemolytic anemia, and cyanotic heart disease, the pattern of marrow expansion consists of a progressive extension into the bones of the extremities. When a disease results in atrophy of the marrow, the process of expansion is not reversed as might be expected. Atrophy begins centrally in the spine and pelvis and extends peripherally. This conclusion is made from single observations on different patients in various stages of marrow failure. We do not know whether marrow failure without previous hypertrophy follows this pattern, because such patients have not been studied during the development of their disease.

SUMMARY

From positron camera studies of the gross distribution of erythropoietic marrow in patients with various hematologic diseases, it has become apparent that hypertrophy and atrophy of the marrow tend to follow a characteristic pattern. Both hypertrophy and atrophy frequently begin centrally and extend outward to the periphery of the skeleton. A classification of patterns based on three major stages of hypertrophy and three stages of atrophy is proposed.

ACKNOWLEDGEMENT

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