A MOUNT SINAI HOSPITAL MONOGRAPH ON

# *Bone Changes in Hematologic Disorders*

## (*Roentgen Aspects*)

*By*

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GRUNE & STRATTON New York and London 1963

Library of Congress Catalog Card No. 63-12179



Printed and bound in the United States (WP-B)

# Bone Changes in Hematologic Disorders

# Preface

This monograph consists of a series of articles on the bone changes in hematologic disorders published in the *Journal of the Mount Sinai Hospital* between 1959 and 1962. A discussion of the bone changes in osteopetrosis and a short concluding commentary have been added. Otherwise, only a few minor changes have been made.

The remarkable developments which have been taking place in the field of hematology in the past decade have prompted this review. The application of physicochemical, genetic, immunologic and anthropologic technics to the study of hematologic disorders has led to some stunning revelations regarding the basic nature of these conditions and, at the same time, has posed new problems for investigation and solution. These new technics have made possible diagnostic refinements which are only now beginning to come into general use. Some refinements in the roentgen diagnosis of the skeletal manifestations of these disorders are also evolving. It was considered that there may be some value, at this time, in bringing together our current knowledge regarding the bone changes in hematologic diseases in one central source. To this body of information some personal observations have been added and some lingering misconceptions have been pointed out.

The value of analysis of these bone changes should not be underestimated. Study of these osseous abnormalities has already played an important part in our understanding of the pathologic physiology and genetics of several of these conditions and further roentgen study of the skeleton in the light of continuing important developments in hematology is certain to be rewarding. The diagnostic significance of the various patterns of bone change in these disorders is not always fully appreciated. In some instances a correct diagnosis can be made on the basis of the roentgen findings alone. In others the particular pattern of bone abnormality will indicate the direction in which clinical and laboratory investigations should be pursued. Indeed, the finding of certain lesions may be the first clue of any kind to the hematologic nature of the patient's complaint. Furthermore, under certain circumstances (e.g., in hemophilia) the roentgen examination provides invaluable information for guidance in orthopedic rehabilitation.

The roentgen images cast by the various pathologic processes in the bones are discussed in detail and the diagnostic importance of these abnormal bone patterns is indicated. The most accurate evaluation of these osseous defects, however, can be achieved, in most instances, only by careful correlation of the roentgen findings with the available clinical and pathologic data. The pertinent clinical and pathologic features of the diseases under discussion, therefore, are included.

Although it is hoped that this monograph will have general value, it is addressed primarily to radiologists. For this reason every effort has been made to present illustrations, the relevant details of which can be clearly seen and readily appreciated. In this connection all thanks are due to Mr. Robert W. Carlin,

medical photographer of New York City, whose excellent photo-electronic prints reveal details of roentgen pathology with remarkable clarity.

An expression of sincere gratitude is also extended to Dr. Bernard S. Wolf, Director of the Department of Radiology at The Mount Sinai Hospital, for the encouragement he has given to this project and for his consistently brilliant analyses of roentgen pathology which have been a source of inspiration, as well as instruction, to all members of his staff. Thanks are also due to Dr. Herman Zuckerman who shares our interest in the radiology of bones and from whose many discussions much has been learned. The willing cooperation of the staff of The Mount Sinai Hospital Library is deeply appreciated and the invaluable assistance offered by the editorial staff of the *Journal of the Mount Sinai Hospital* is gratefully acknowledged. For the typing of the manuscripts an expression of sincere thanks goes to our most cooperative and uncomplaining secretary, Mrs. Mary Pitts Jones.

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# I. The Anemias

## CONGENITAL APLASTIC ANEMIA WITH MULTIPLE CONGENITAL ANOMALIES

### (Fanconi Syndrome)

In recent years there has been an increasing interest in the hereditary and fetal environmental factors which may result in congenital anomalies. The hematopoietic system is not uncommonly affected by these factors. In addition to the well-known hereditary blood diseases there is an interesting group of hematologic disorders which occur in association with congenital anomalies of other systems. Those that are perhaps best known include congenital leukemia and mongolism, congenital aplastic anemia with multiple congenital anomalies (Fanconi syndrome), congenital spherocytosis associated with congenital hypoplastic thrombocytopenia and malformations and congenital labile factor deficiency with syndactylism. In these conditions bone abnormalities are not the result of the blood dyscrasia but coexist with it. From the point of view of roentgen diagnosis the most important of these is the Fanconi syndrome. In this condition certain bone anomalies occur with sufficient frequency to arouse suspicion of the disorder when they are observed. Added importance may be attributed to these bone defects since the hematologic manifestations of the syndrome do not appear until some years after birth.

The congenital aplastic anemias are divided into two distinct syndromes. In one, the Fanconi syndrome, the idiopathic aplastic anemia is associated with multiple congenital malformations. In the other, there are no associated congenital anomalies. Fanconi's syndrome is characterized by pancytopenia, bone marrow hypoplasia and a variety of congenital anomalies and is the more frequently occurring of the two syndromes. The exact etiology of the condition is unknown but it is generally considered to be hereditary and transmitted by an autosomal recessive gene with variable penetrance. Sporadic cases are seen and at present are thought to be due to spontaneous gene mutation. There is a high familial incidence, several siblings being affected in a number of instances. Fanconi (1) originally described the syndrome in three brothers. On some occasions siblings of patients with the complete syndrome have had congenital anomalies without the hematologic disorder. There does not appear to be any racial or geographic preponderance. The anemia is normocytic and slightly macrocytic and coexists with leukopenia and thrombocytopenia. The leukopenia

is usually due to neutropenia but in some instances all varieties of leukocytes may be affected equally. As in patients with aplastic anemia, the bone marrow varies from acellular to hypercellular.

The number and severity of associated congenital anomalies vary considerably. The most frequent abnormalities encountered are a patchy brown pig-

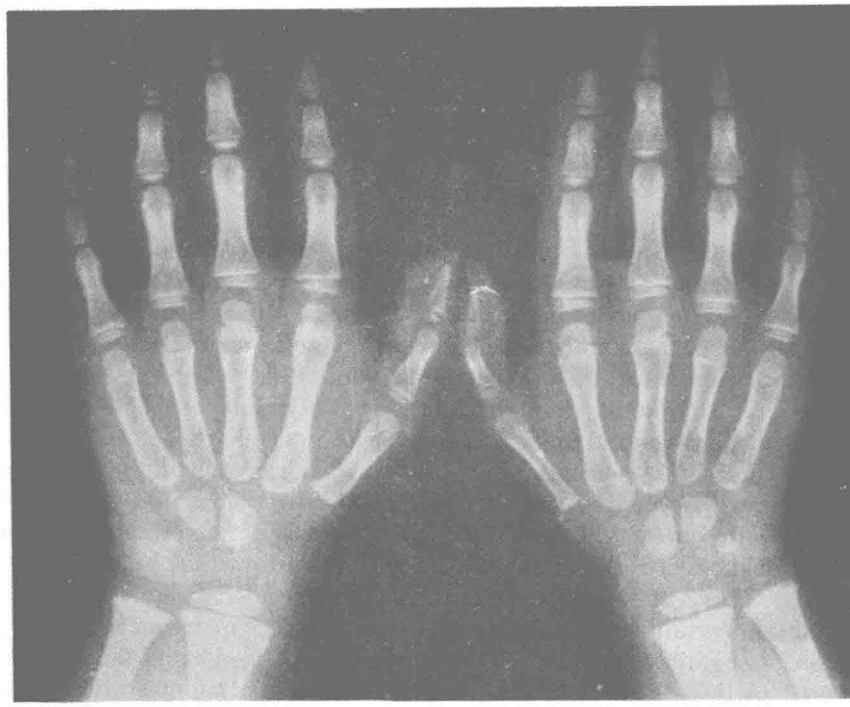

FIG. 1. Fanconi syndrome. Hands of 4 year old male with aplastic anemia (pancytopenia) of one month's duration. The patient was small in stature, with a small head and microphthalmia. The testicles were unusually small and there was ptosis of the left kidney. While he was under observation in the hospital, numerous areas of brown pigmentation of the skin developed. There was webbing of the second and third toes bilaterally. Skeletal survey showed hypoplasia of the phalanges of both thumbs and of both first metacarpals. There was a congenital dislocation of the left hip.

mentation of the skin due to a depostion of melanin, dwarfism, hypogenitalism, microcephaly, strabismus, mental retardation, renal and skeletal anomalies.

Skeletal anomalies may be quite prominent in Fanconi's syndrome and outstanding among these are anomalies of the thumbs, first metacarpals and radii. These may vary from complete absence to various degrees of hypoplasia (Fig. 1). Other skeletal abnormalities which have been observed in this syndrome include syndactyly, club foot, congenital dislocation of the hip (Fig. 2) and deformities of various long bones. A variety of other anomalies may be found *but the occurrence of anomalies of the thumb, first metacarpal or radius in conjunction with several other congenital defects of the soft and bony parts should arouse suspicion of Fanconi's syndrome.*

Of considerable interest in this disorder is the fact that hematologic abnormalities are not usually detected until the patient is several years old (2). In most of the reported cases the initial hematologic manifestations occurred between four and twelve years of age. One case has been reported in which the onset was observed to be at thirteen months of age and in two brothers symptoms of a blood disorder appeared at the ages of 19 and 20 years respectively (3). Rare cases have been described of a congenital hypoplastic thrombocytopenia with skeletal and cardiac anomalies. These patients usually die within

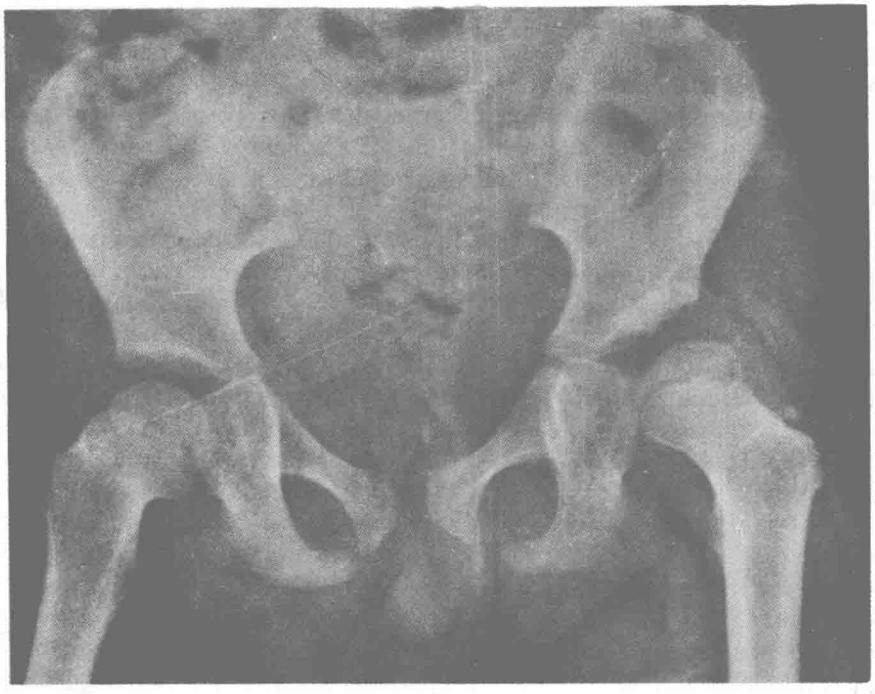

FIG. 2. Fanconi syndrome. This is the patient shown in Fig. 1. There is a congenital dislocation of the left hip.

the first weeks or months of life. They may be considered as neonatal equivalents of the Fanconi syndrome (4). A rather high incidence of leukemia in the families of patients with Fanconi's syndrome has been noted (5).

## IRON DEFICIENCY ANEMIA

Every so often a significant new finding is reported in a common, much studied disease and one is left wondering why such an observation was not made long before. A recent excellent example of this interesting phenomenon is the detection of skull changes in iron deficiency anemia in infants and children. Although this disorder has been long and extensively studied throughout the world it was not until 1958 that Lie-Injo Luan Eng (6), an Indonesian investigator, first described bone changes in the skull of a 12 year old Indo-

nesian girl who suffered from chronic iron deficiency anemia. The skull changes were similar to those which may be found in the congenital hemolytic anemias as a result of marrow hyperplasia. Although Lie-Injo Luan Eng's communication was the first documented report with illustrations of the bone abnormality, Caffey (7) had already called attention to the occurrence of these bone changes in his classic paper on Cooley's anemia which appeared in 1957. Shahidi and Diamond (8) reported skull changes in three white infants with iron deficiency anemia in 1960 and Britton, Canby and Kohler (9) added a report of five white children with similar findings. In 1961 Moseley (10) reported skull changes in a Puerto Rican boy and later the same year Burko, Mellins and Watson (11) described similar skull lesions in seven Negro children. No doubt numerous similar reports will follow.

In the newborn infant, following an initial stationary period of about a week or ten days, there is a gradual decline in the hemoglobin and red cells in the peripheral blood. This is the result of normal or slightly increased red cell destruction accompanied by relatively inactive erythropoiesis. The drop in the hemoglobin and red cell levels reaches a maximum at about seven weeks in the premature infant and at about two to three months in the full term infant. The period of diminishing blood levels is referred to as physiologic anemia of the newborn (12). When minimum levels are reached, the relative hypoxia and other stimuli initiate active erythropoiesis. Hemoglobin regeneration is accomplished through re-utilization of iron released from destroyed red cells and stored in the tissues during the postnatal drop in hemoglobin. Such regeneration depends primarily, therefore, upon the hemoglobin concentration and hemoglobin mass available at birth. With growth the supply of stored iron is depleted and the infant is exposed to an iron deficiency anemia if the supply is not replenished by an adequate diet. The more rapidly the infant grows, the greater is the strain on the iron supply. According to Smith (12) the most important causative factors in iron deficiency anemia in infants and children are: 1) inadequate iron stores at birth which may result from premature, twin or multiple births, severe iron deficiency in the mother or fetal blood loss at or before delivery; 2) inadequate intake due to a deficient diet; 3) impaired absorption due to gastrointestinal disorders and 4) excessive demands for iron, such as may result from blood loss during infancy or failure to meet increased demands for growth. The factors of inadequate supply and excessive demand for iron tend to be interdependent and overlapping. In the presence of anemia the erythropoietic response is exaggerated and the overactive erythropoiesis is manifested mainly as marrow hyperplasia.

### *Bone Changes in Iron Deficiency Anemia*

The skull changes which may be radiographically demonstrated in some cases of iron deficiency anemia in infants and children are similar to those which occur in the congenital hemolytic anemias and are similarly due to erythroid hyperplasia of the diploic marrow between the tables of the skull. The diploic space is widened. The outer table is displaced externally and is often thinned

(Figs. 3–5). In some cases it may be completely atrophied. Occasionally the diploic trabeculae assume a position perpendicular to the inner table presenting a radial pattern which when advanced is referred to as a hair-standing-on-end appearance. Caffey (7) has called attention to the usual absence of involvement

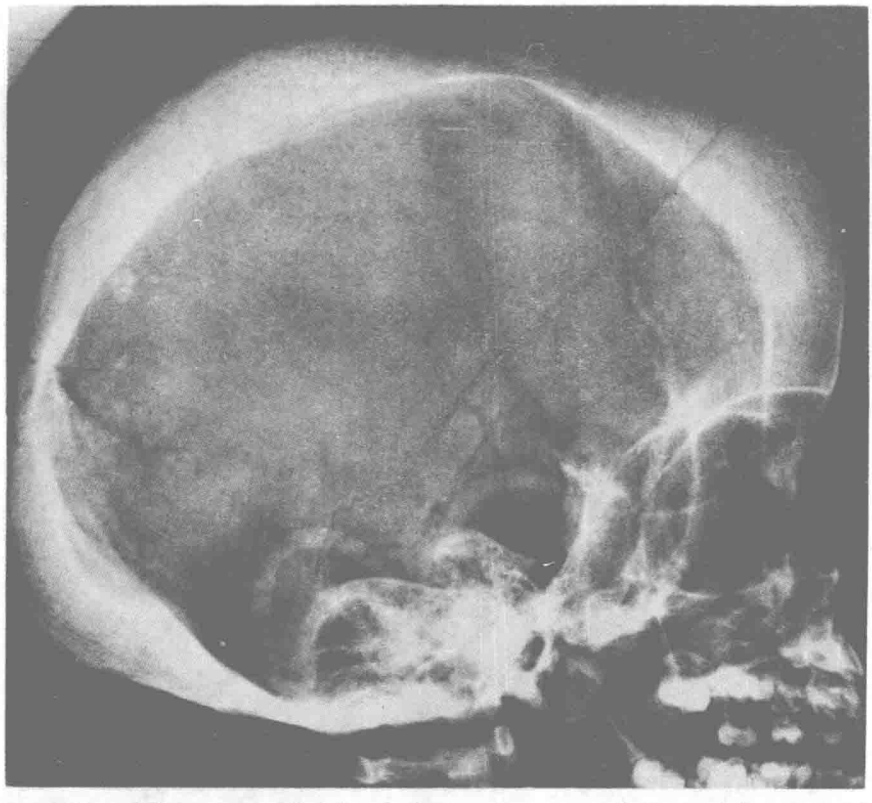

FIG. 3. Iron deficiency anemia. The skull of a three year old Puerto Rican male shows widening of the diploic space. The parietal trabeculae show an early fine radial pattern. The outer table is atrophic in some areas and there is a generalized granular osteoporosis. The frontal, parietal and occipital bones are all affected but the occipital squamosa inferior to the internal occipital protuberance is uninvolved, probably because there is normally no marrow in this portion of the bone. This patient was born at term with multiple cutaneous hemangiomata and cerebral vascular anomalies. He was mentally retarded and would take no solid foods. His diet consisted almost solely of milk. There was a prompt response of the anemia to iron therapy. (Moseley, J. E.: Am. J. Roentgenol. & Rad. Therapy, 8: 649, 1961.)

of the occipital squamosa inferior to the internal occipital protuberance in cases of hemolytic anemia and this appears to be so in iron deficiency anemia as well. It is presumably due to a normal absence of marrow in this portion of the bone. None of the cases of iron deficiency anemia so far reported have shown swelling of the facial bones with retardation of pneumatization of the maxillary sinuses as occurs in severe Cooley's anemia and no roentgen evidence of marrow hyperplasia has been reported in the long bones. In Cooley's anemia roentgen evidence of marrow hyperplasia is consistently found

in the long and short tubular bones, particularly the metacarpals and distal femora. Changes are often manifest in the extremities when none are present in the skull but skull changes in the absence of tubular bone alterations are not seen in infants and young children. After puberty, when the lesions in the tubular bones regress, involvement of the central skeletal segments, including the skull may persist and increase. On the

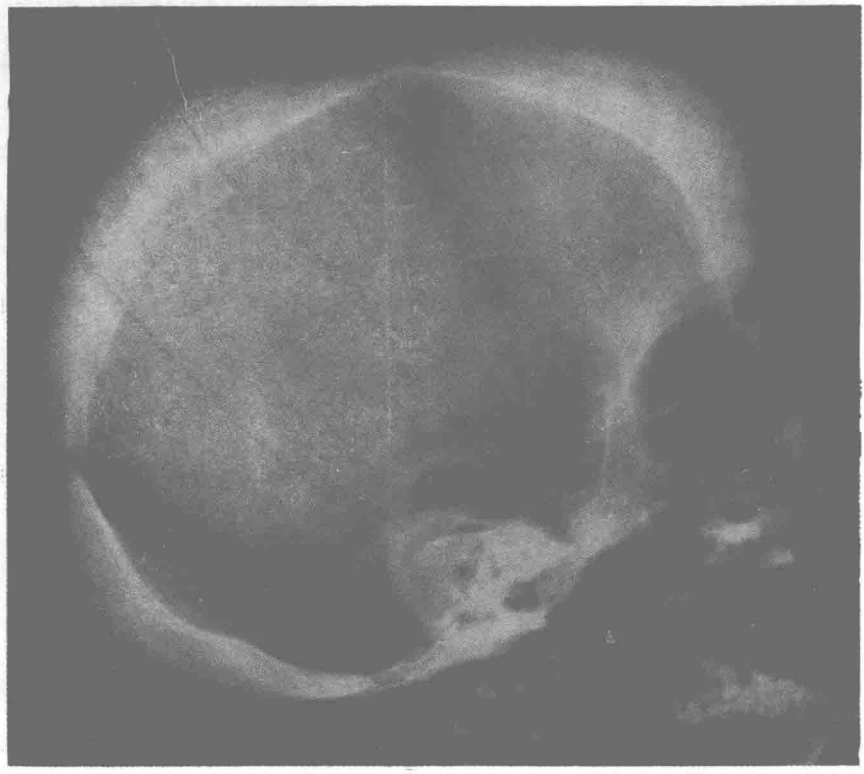

FIG. 4. Iron deficiency anemia. Same patient at age 2½ years. The diploic space is widened but radial striation of the trabeculae is not yet apparent. There is no swelling of the facial bones. (Moseley, J. E.: Am. J. Roentgenol. & Rad. Therapy, 8: 649, 1961.)

basis of our experience and the descriptions of all cases published to date *the absence of facial bone involvement* and, more particularly, *the absence of long bone changes differentiate the roentgen bone changes of iron deficiency anemia from those of severe Cooley's anemia in infants and young children.*

As in the chronic hemolytic anemias there is marked variation in the roentgen findings in the skulls of patients with iron deficiency anemia. Patients of the same age with similar clinical and hematologic findings may show marked differences in the roentgen appearance of the skull. Siblings with iron deficiency anemia as severe or more severe than those with skull changes may show no

cranial bone abnormalities whatsoever. In both chronic hemolytic anemia and in chronic iron deficiency anemia the skull is an unpredictable and unreliable index of the severity of anemia (11).

Of the reported children with iron deficiency anemia and skull changes a large number have been born prematurely or were born with a twin. Many of those born at term were considerably less than average in birth weight. Most of the patients suffered from poor diets which consisted mainly of milk. The 12 year old girl reported by Lie-Injo Luan Eng was said to have had an adequate

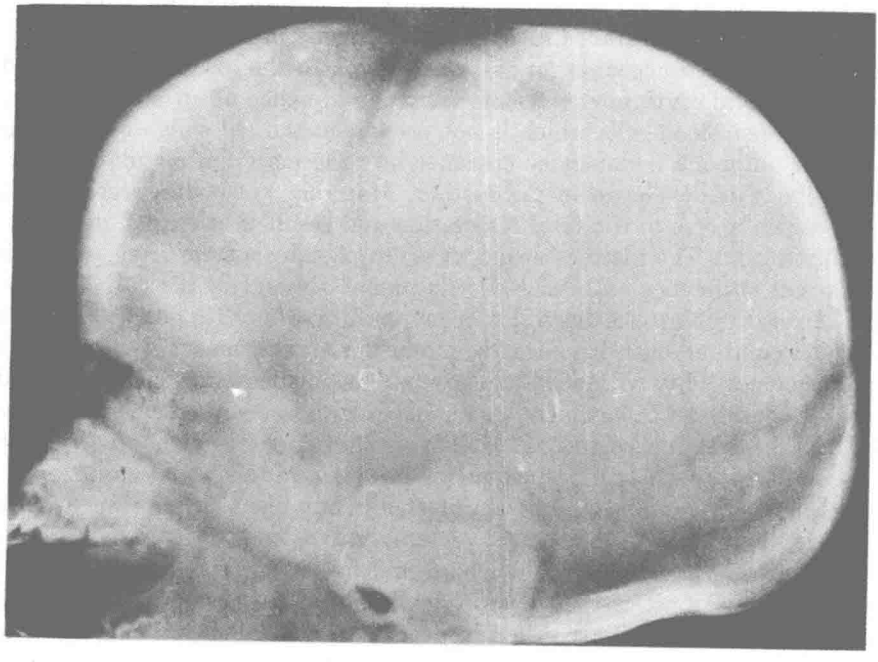

FIG. 5. Iron deficiency anemia. Skull of same patient taken at 3 months of age. Early changes are already apparent in the frontal bone. (Moseley, J. E.: Am. J. Roentgenol. & Rad. Therapy, 8: 649, 1961.)

diet and the anemia was believed to have resulted from chronic blood loss from the intestinal tract due to hookworm infestation.

Skull changes similar to those occurring in the congenital hemolytic anemias and in iron deficiency anemia have also been reported in other conditions accompanied by erythroid hyperplasia. Ascenzi and Marinozzi (13) have described such skull findings in two girls, age 3½ and 6 years, with cyanotic congenital heart disease and secondary polycythemia. In the 3½ year old child the cardiac malformation was that of pulmonary atresia with an interatrial septal defect. In the 6 year old girl there was a tetralogy of Fallot. At autopsy both skulls showed marked erythroid hyperplasia of the marrow with widening of the diploic space similar to that seen in Cooley's anemia, sickle cell disease, familial hemolytic icterus and iron deficiency anemia. Erythroid hyperplasia

in cyanotic congenital heart disease is due to hypoxemia resulting from the circulatory shunts. Dykstra and Halbertsma (14) have reported skull changes of the same kind in a 12 year old patient with polycythemia vera.

## ERYTHROBLASTOSIS FETALIS

### (Hemolytic Anemia of the Newborn)

Erythroblastosis fetalis is a hematologic disorder which occurs in the fetus and newborn as a result of excessive destruction of the erythrocytes. Excessive hemolysis leads to active erythropoiesis in the liver, spleen and bone marrow with the frequent appearance of nucleated red cells in the peripheral blood, a circumstance which accounts for the name given to the disease. Excessive destruction of fetal erythrocytes results from the presence of an antigenic factor in the fetal red blood cells which is not present in the red cells of the mother. When this antigenic factor gains entrance into the maternal circulation a specific antibody is developed in the mother. Maternal antibodies recrossing the placenta gain access to the fetal circulation and result in excessive destruction of fetal red cells. The manifestations of erythroblastosis stem from this action of maternal antibodies on fetal red cells prenatally and in the early neonatal period. In erythroblastosis due to Rh incompatibility, fetal Rh positive blood enters the circulation of an Rh negative mother. A similar mechanism may occur due to incompatibility within the ABO groups. The incidence of Rh negative individuals is considered to be much less among Negroes and when erythroblastosis occurs in the Negro, ABO incompatibility is the more common cause. Rh incompatibility is not distinctly uncommon, however, in this racial group.

Erythroblastosis fetalis may be manifested in any one of three clinical forms. These are: 1) congenital anemia; 2) icterus gravis and 3) fetal hydrops. So-called congenital anemia of the newborn and icterus gravis account for about seventy per cent of all cases of hemolytic disease in the newborn. The designations, however, indicate only different degrees of the same pathologic process. Congenital anemia of the newborn is a mild form of the condition in which pallor becomes apparent as jaundice recedes in the first week of life. In icterus gravis neonatorum the disease is more severe and there is progressive anemia and jaundice. In fetal hydrops there is a massive edema of the fetus which is usually stillborn and premature. All three conditions represent different degrees of severity of the hemolytic process.

#### *Bone Changes in Erythroblastosis Fetalis*

Nonspecific bone changes may occur in all forms of this hemolytic disorder. Their incidence tends to increase with the severity of the disease. In many cases of both mild and severe disease no bone changes can be demonstrated. The bone lesions are hardly of any real diagnostic significance, however, since they may occur in numerous other disorders of the mother, fetus or infant. When skeletal alterations are demonstrable they consist of transverse bands of diminished and increased density at the metaphyseal ends of long bones, ad-

jacent to the zone of provisional calcification (Fig. 6). These result from interference with prenatal endochondral bone formation and are in no way different from similar bands which may be seen in premature infants, infants born after

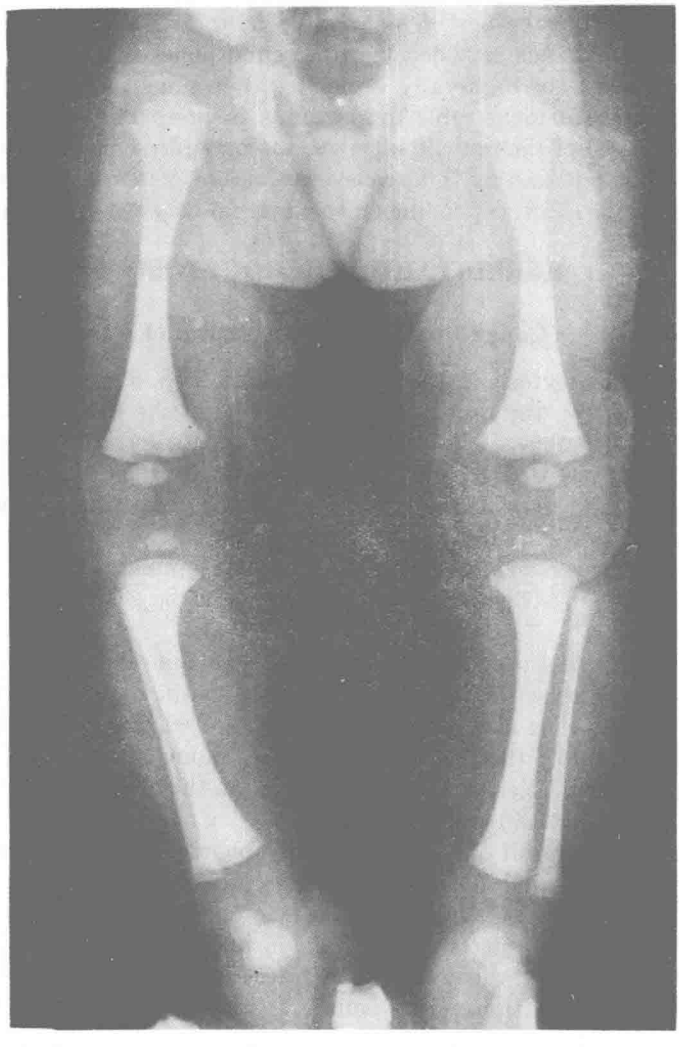

FIG. 6. Erythroblastosis fetalis. There are transverse bands of radiolucency at the ends of the long bones adjacent to the zones of provisional calcification. Adjacent to these are bands of increased density. Similar zones are noted in the round bones of the feet. (Courtesy of Dr. David Baker, New York, N. Y.)

a pregnancy in which there was significant maternal illness, fetal diseases such as congenital syphilis or acute and chronic diseases of infancy. Follis and his associates (15) reported a diffuse sclerosis of the long bones with narrowing of the medullary cavities in this condition in 1942 and many present-day descrip-

tions of erythroblastosis continue to perpetuate this belief (16). Thick cortices with narrow medullary cavities are frequently seen, however, in premature and normal full term newborns and are of no radiologic significance. When present the metaphyseal bands tend to occur most frequently at the sites of most active bone growth and may be best demonstrated at the wrists, knees and ankles. Analogous lines or bands may occur in the round bones and epiphyses as well. These lesions tend to be bilaterally symmetrical and in some cases may be distinct enough to be demonstrable in the fetus *in utero* on films made of the maternal abdomen. If the patient survives, the metaphyseal bands tend to disappear and to be replaced by thin transverse lines of increased density (growth lines) deeper in the shaft, depending on the interval between examinations (17).

## HEREDITARY SPHEROCYTOSIS

### (Congenital Hemolytic Jaundice)

Hereditary spherocytosis is a genetically determined, chronic hemolytic disease characterized by the presence of spherocytes in the peripheral blood, increased osmotic fragility of the red cells and, commonly, an enlarged spleen. The defect is transmitted by either parent as an autosomal dominant characteristic, males and females being equally affected. Some discrepancies in the hereditary transmission of the disorder have been observed and have been tentatively ascribed to spontaneous mutation or incomplete expressivity of the responsible gene (18). The disease is considered to be relatively rare among Negroes (19).

The genetic defect is responsible for an intrinsic anomaly of the red cell which accounts for its globular shape and increased susceptibility to hemolysis. These spherically shaped cells of abnormal thickness are trapped in the spleen and destroyed more rapidly than normal cells. Splenectomy corrects the anemia in these patients but spherical red cells persist as do their increased osmotic and mechanical fragilities (20).

The clinical manifestations of hereditary spherocytosis vary considerably both in regard to the time of onset and their intensity. They are usually first recognized in childhood or adolescence but the onset may occur in infancy or as late as middle age. Jaundice is uncommon in infancy and early childhood but may be present when the disease is manifest in the newborn. In these latter circumstances the condition may simulate erythroblastosis. Jaundice is more apt to appear in late childhood and becomes more pronounced in the young adult. Although the degree of anemia varies, it is seldom severe.

#### *Bone Changes in Hereditary Spherocytosis*

The bone changes which may occur in spherocytic anemia are due to the premature destruction of abnormal red cells. Compensatory erythropoiesis results in marrow hyperplasia. Overgrowth of marrow is manifested as expansion of the medullary spaces and atrophy of the spongiosa and cortex. In this disorder,