# SKELETAL CHANGES ASSOCIATED WITH DISEASES OF THE BLOOD*†

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*Wesley M. Carpenter Lecture*

IT has not been easy to prepare a talk being conscious always of the august tradition of this Lecture which honors Dr. Wesley M. Carpenter. My predecessors have set high standards which I cannot hope to emulate. My briefing instructions were to present the significant advances in the subject of skeletal lesions associated with diseases of the blood. Time requires that I limit my discussion to the changes in leukemia, in myelosclerosis and in the chronic familial and racial anemias. I shall review the roentgen appearance of these bone changes, but I hasten to say that, although through the kindness of radiologists in many parts of the United States, I have been privileged to study a large amount of radiographic material, I have nothing to add to the descriptions you will find in many textbooks. During the past two years, however, it has become apparent that in certain instances of these incurable diseases, the bone lesions may be altered and the bone structure return to a near-normal appearance. These findings, and other recent literature, justify speculation regarding the pathogenesis of the bone changes which I propose to do even though there may be many in this audience whose wider experience will find what I have to say unacceptable.

## LEUKEMIA

The bone changes in leukemia are not uniform but perhaps that is, in part, a reflection of the fact that leukemia is not in the biological sense a uniform disease. For example, acute leukemia generally occurs in children. Acute cases also occur in elderly adults but it is thought by some

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that they are acute exacerbations of chronic disease. Chronic lymphocytic leukemia usually appears over the age of fifty years. The age spread in acute and chronic myeloid leukemia is somewhat more uniform but the acute disease usually occurs in the first decade. There are other significant biologic differences between lymphocytic and myelocytic leukemia and between the acute and chronic diseases which are reflected in such biochemical features as the beta-glucuronidase level of the buffy coat,[1] the total blood histamine levels[2] and the carbonic anhydrase activity of the peripheral leukocytes.[3] The response of individual cases to various drugs is not uniform and we shall have occasion to speak more of this later.

In acute leukemia, the growing skeleton is affected in nearly all cases unless early death supervenes.[4] Skeletal changes are demonstrable radiographically in more than one-half of leukemic children.[5, 6] Four types of roentgen change are seen.[5] Most often, there are transverse bands of diminished density in the metaphyses of the long bones, sometimes sharply defined, sometimes indefinite and merging with normal bone. The knees are the most convenient area to look for these changes. Occasionally a uniform transverse band progresses into a grossly irregular and apparently osteolytic lesion but the transition is not a sharp one. It is not unusual for both types of lesions to be present in the same case. Osteolysis may be both focal and diffuse. The focal form is characterized by areas of translucency in the spongiosa which may be confluent. The involved bone may appear motheaten and suggests destruction of both the spongy and compact bone. Not infrequently there are spontaneous fractures. Rarely there is a generalized decalcification of the entire skeleton.

Osteosclerosis is not uncommon occurring in about 10 per cent of the acute leukemics. The endosteal new bone formation is thought to be due to overproduction of cancellous bone rather than to thickening of the cortex. Often there are patchy conglomerate areas of increased density which may be quite marked. Lifting of the periosteum, periosteal thickening and irregular new bone formation is more frequent and is found in perhaps one-fifth of the acute cases. Cortical thickening has been observed in all of the major long bones, less frequently in the ribs and the small tubular bones of the hands and feet. In advanced cases, spotty destruction is visible in the larger epiphyseal ossification centers and in the flat bones of the calvarium, shoulder girdle and pelvic girdle. When an

epiphysis and juxta-epiphyseal portion of a bone are involved, aseptic necrosis may be simulated.

In chloroma, localized masses are found most often in relation to the periosteum and ligamentous structures particularly of the skull, paranasal sinuses, orbits, spine, ribs and sacrum. Periosteal changes are found in addition to those in the medulla.

In chronic leukemia, occurring in the adult, the lesions usually appear destructive although an occasional example of osteosclerosis has been reported (I am excluding for the moment the cases of myelosclerosis who die with leukemia). By the time the patient is subjected to radiographic examination, the lesions are usually multiple. Discrete or confluent areas of rarefaction are found, resulting in a motheaten appearance. Vertebral compression is a relatively frequent finding. Innumerable areas of osteolysis in the skull involving the diploe or diploe and cortex are not infrequent. Periosteal elevation is fairly common. The most frequent sites of involvement are the femurs and humeri as well as the pelvis and spine. Radiographic abnormalities are said to be present in about 8-10 per cent of chronic leukemics[7] but this figure may be misleading because many patients are not referred for roentgen examination.

*Pathology:* I am not competent to discuss in any detail the pathology of leukemia. You know that both myelocytic and lymphocytic varieties involve the bone marrow, lymph nodes, spleen and other pre-existing lymphoid tissues. Heterotopic growths of lymphoid tissue appear in the liver, kidney, lung, skin, serous membranes and many other organs. Of particular interest, however, is the fact that in most cases, the aggressive quality of cancer is lacking, as Ewing[8] points out in the following words: "In the bone marrow, the process begins in multiple hyperplastic foci which enlarge, coalesce and eventually extend the limits of lymphoid marrow throughout all portions of the skeleton. At the height of the process the new tissue is firm, light-colored, opaque or pyoid, or beset with foci of infarction, necrosis, hemorrhage or mucoid softening . . . the spongy trabeculae are often absorbed and even the shafts may be thinned but a distinctly aggressive destruction of bone as in true tumor is missing. . . . In acute febrile leukemia, local aggressive properties are almost entirely wanting, the infiltrating cells show a great respect for the invaded tissues, the lymph node lesions may be very moderate, local lymphomas may be scanty, and any neoplastic quality present is confined to the simple multiplication of atypical cells, while an acute toxic

process is prominent. In chloroma, on the other hand, a very different grade of neoplastic properties is present, and the effects are so different that it seems unwarranted to exactly identify the two processes."

It would seem then that the bone rarefaction which we see in leukemia is not ordinarily explained by an aggressive destruction of bone. We can account for thinning and destruction of bone trabeculae in many cases by pressure, hemorrhage, necrosis and infarction, resulting from crowding of the closed marrow spaces with leukocyte-forming tissue.[9] This has been suggested as the reason the roentgen changes in adults are less pronounced than in children. The bone marrow space in infants and children is completely or largely occupied by hematopoietic tissue, whereas in adults, much of the marrow has become fatty and there is room for expansion. However, this mechanical theory fails to explain many of the roentgen and correlated pathological features. The following are some of these discrepancies.

(a) There is general agreement that the transverse metaphyseal zone of diminished density is not seen exclusively in leukemia. It is found in a variety of conditions and in apparently normal children. It was observed in Nagasaki where it was thought to be due to radiation and malnutrition.[10]

(b) The skeletal lesions appear and disappear rapidly. X-ray evidence of bone involvement may appear within four to ten weeks after the onset of symptoms. This perhaps is not surprising when it is recalled that a transition from a completely fatty to a solidly cellular marrow has been seen under experimental conditions within two days.[11] However, the speedy reossification which may follow the administration of folic acid antagonists in acute leukemia is less readily explained on purely morphologic grounds. Karpinski[12] refers to a case in which there is evident beginning reossification of osteolytic areas in the shaft of the radius six days after instituting treatment. This change was apparent in the "destroyed" compacts as well as in the cancellous portion. Transverse metaphyseal bands of diminished density were observed by Silverman[13] to disappear within four to six weeks of this therapy. The rarefied zone is replaced first by a fine line of increased density which, in time, presents as a heavy transverse band. Dr. Silverman has been kind enough to let me see his cases but I can add nothing to his description as follows: "as this band widens, it loses some of its density between the epiphyseal and diaphyseal faces of the band. Gradually two parallel lines are

formed, one deep in the shaft, the other at the epiphyseal plate. The line in the shaft becomes more deeply buried as longitudinal growth of the bone carries the epiphyseal plate away from the region, and the epiphyseal plate again widens and undergoes the same cycle of change." Histologic examination of the bone in such cases demonstrates "an increase in the number and thickness of trabeculae in the region of the transverse line and a persistence of a homogenous gray-blue-staining material as a central core beneath the newly formed bone." There are many well-documented instances, some in my collection, of the disappearance of the transverse bands and other apparently osteolytic lesions during spontaneous clinical remission. It is curious, however, that I have been unable to find any reference to similar alterations following treatment with nitrogen mustard, urethane or other presumably cytotoxic drugs. If any have occurred, they must be few. This is due, at least in part, to the fact that these drugs are not ordinarily clinically effective and are now seldom used in acute leukemia. ACTH, however, is said to produce clinical remissions in a few instances,[14] but I have found no reference to the regression of a bone lesion. I found only one mention[15] of this result following a systemic agent other than a folic acid antagonist, namely "in a case of acute leukemia, the roentgen appearance of lumbar and dorsal vertebral destruction was improved after $P_{32}$ therapy." Local roentgen therapy to an involved bone in chronic leukemia may result in repair of the lesion but precise information about the mechanism is not available.

(c) In twelve patients of the series reported by Karpinski and Martin,[15] there were chest lesions, including hilar adenopathy, pleural effuson and parenchymal disease, none of which was influenced by aminopterin. However, some of these children exhibited bone lesions which did respond. I interpret this to indicate that the bone changes may have a unique pathogenesis, although other explanations are possible.

(d) The use of folic acid antagonists in the treatment of leukemia followed the observation that folic acid seemed to stimulate the leukemic process.[16] There can be little doubt that both folic acid and its antagonists have a profound effect both on the leukemic process and on normal tissue, but whether the difference is qualitative or quantitative is not yet clear. However, the fact that aminopterin therapy has resulted in the disappearance of bone rarefaction in 20-30 per cent of cases of acute leukemia suggests that not only is the leukemic process modified

but also bone formation. This assumption is strengthened by the finding that areas of bone rarefaction which reossified during a clinical remission induced by aminopterin, reappeared during the continued administration of this drug even though there was no change in the clinical and hematologic status.[15, 17]

The discrepancies have led me to a hypothesis regarding the pathogenesis of at least some of the skeletal lesions which I will present to you even though I have no corroborative experimental data of my own. Published data suggest that the rapidly growing immature granulocytes are capable of fixing or utilizing an excessive amount of folic acid.* I suggest that there is created thereby a relative deficiency of this substance in other metabolic functions. There is no direct proof of this theory but it would provide a satisfactory explanation of the macrocytosis which is found in some cases of leukemia and which heretofore has been assumed to be due to a mechanical or toxic factor.[19]

When aminopterin is administered, it may be accepted by the rapidly metabolizing leukemic cells in place of folic acid. There is experimental evidence supporting this thought.[20] The folic acid freed from utilization by the leukemic cells might now be available to correct the deficiency which I assumed to be present in other tissues. With continued therapy, the increased leukemic requirements being met by aminopterin are reduced as the number of immature cells is reduced. Part of the administered aminopterin is now freed and enters successfully into competition in the enzyme systems of normal tissue. It is important to recall in this respect that the basic feature of the action of competitive antagonists is that the velocity of the enzymatic reaction is proportional to the ratio of the concentrations of metabolite and antagonist rather than to the concentration of one alone.[21]

I do not know what part, if any, folic acid plays in bone metabolism. It is said to be essential to the normal functioning of all cells. However, it might be significant that vitamin $B_{12}$, which appears to be closely related to folinic acid in its actions, apparently is involved in the methylation of hemocystine to methionine and in the reduction of cystine to cysteine.[22] These are "free" essential amino acids of which there are no reserve stores in the body. In their absence, a deficiency in a particular one cannot be corrected from the protein stores themselves. These

* Folic acid is used to mean the acid itself or a utilizable derivative. Folinic acid might be more properly used since this is now thought to be the utilizable form of folic acid, and folic acid antagonists may operate by interfering with the conversion of folic acid to folinic acid.[18]

amino acids are essential for growth and are intimately involved in the protein substrate of maturing bone but whether their deficiency creates a specific lesion or the non-specific lesion of malnutrition is not known. Malnutrition is known to interfere with osteogenesis. The epiphyseal cartilage stops proliferating and bone growth ceases at the cartilage shaft junction and in the shaft as well.[23] However, Silverman noted that there is no significant retardation of longitudinal growth during aminopterin therapy.[13] Another possible link is the finding that the excretion of folinic acid in humans depends on the ascorbic acid levels.[18] Furthermore, Hagtvet[24] found low, almost undetectable levels of ascorbic acid in the serum of leukemics. The latter finding, however, may be a nonspecific result of a febrile disease.[2] Dr. E. Neuhauser whose data I have quoted,[17] wrote me that he believes that there is an antagonistic action of the aminopterin with some substance that has to do with intercellular cement formation or matrix formation. Perhaps he is wise to venture no further than this in speculating on mechanisms.

A discussion of leukemia would be incomplete without some reference to multiple myeloma. It is possible, perhaps, probable, that this disease is a variant of plasmocytic leukemia such as lymphosarcoma is thought by many to be of lymphocytic leukemia. Snapper[25] cites excellent reasons in support of this view. Wintrobe[26] also quotes pertinent cases. However, because our time is limited and because, in spite of marked clinical palliation which may follow treatment with stilbamidine and urethane, there have been few reports describing an alteration in the skeletal lesions, the subject will not be discussed in the present review.

## Myelosclerosis with Leukoerythroblastic Anemia

Diffuse fibrosis of the bone marrow is an unusual progressive condition which sometimes follows a known disease or intoxication but often develops without known cause. Occasionally, there is in addition proliferation of cancellous bone but, as far as can be determined, this is not the result of a fundamental difference in the two processes. Clinically, the syndrome is that of myelophthisic anemia. There may be a leukoerythroblastic peripheral blood picture but more often there is leukopenia. Preterminally, a marked increase in the number of granulocytes may be found.

At autopsy, myeloid proliferation characterized by the predomin-

ance of megakaryocytes, is present in the spleen and to a less extent in the liver. The bone marrow of long bones, skull, vertebrae, pelvis, ribs and sternum shows a uniform change. Early, all of the marrow may be deep red, moist and succulent; it appears markedly hyperplastic. Later, the bones are uniformly dense, grey-white and hard without any well-defined marrow spaces, or may show scattered foci of red or yellow marrow.[27] In the early stages, both the myelopoietic and erythropoietic elements are increased. Eosinophilic myelocytes as well as mature and immature megakaryocytes stand out and appear to be increased in number. There are also cells which seem to correspond to stem cells of undetermined nature. There is evidence of necrobiosis of many immature cells which lie in the midst of visible marrow. The marrow reticulum cells are increased in size and number and form complete septations.[27]

Later in the disease, marrow atrophy appears. The marrow reticulum is more prominent and islands of active blood cell formation are few. The loose network of reticulum is filled by a finely granular or vacuolated material resembling coagulated protein-containing fluid; at other times, collagen formation is simulated. There are numerous dilated empty vessels surrounded by small groups of bizarre megakaryocytes or small hematopoietic cells. The end stage in a certain number of cases involves a distinct type of new bone formation[27] which is of particular interest in our present discussion. There are first focal granular deposits of calcium in the eosinophilic matrix where reticulum cell nuclei lie parallel and close to a trabecular surface. After the matrix is calcified, bone is deposited in a layer about part or all of the old trabecular surfaces. Prominent cement lines permanently demarcate the margins of the original trabeculae. This process becomes generalized but irregular and the eventual trabecular pattern is quite tortuous with jutting, rounded thickenings of spongy bone. Ultimately, completely new bone trabeculae, which are irregular in thickness and direction, are formed in the marrow spaces by precipitation of calcium in the fluid or gelatinous reticular matrix, with an intermediate osteoid stage.[27]

In this later stage, roentgenologically, the usually sharply defined trabecular structure gives way to an overall ground glass appearance. There may be a uniform increase in density or more patchy areas of condensation. Not infrequently, scattered more or less uniformly through the dense bone are small, rounded areas of relatively diminished density. The cancellous bone appears particularly to be affected. The

compacta may be broadened but is not as dense; it sometimes seems relatively porotic. The distribution of lesions radiographically corresponds to that described pathologically. The changes are not pathognomonic but when found in association with a very large spleen, will permit the roentgenologist to suggest the diagnosis.

Fibrosis and even sclerosis of bone marrow with myeloid metaplasia in spleen and liver is found in many conditions including such varied diseases as marble bone disease, acute tuberculosis[28] and metastatic carcinoma. The relation to certain other coincident or antecedent diseases particularly leukemia has been the subject of considerable debate. Occasionally the myelosclerotic patient dies with what competent pathologists consider to be true leukemia.[25] Two of my cases were in this category.[29] Custer[11] refers to a characteristic case with early bone marrow hyperplasia and typical granulocytic leukemia. Two years later, there was bone proliferation and partial fibrosis of the marrow. Seven years later, at autopsy, all bones were densely sclerotic. Other reports, however, state unequivocally that "myeloid metaplasia . . . is of a fundamentally different nature than leukemia."[30] Leukemia cannot be excluded in the individual case except at autopsy and even then the diagnosis often rests on a personal interpretation of the morphology. There is unfortunately no biologic test for the disease. Perhaps the observation that the total blood histamine is elevated in chronic granulocytic leukemia and is normal in physiologic leukocytosis and leukemoid reactions[2] will provide useful additional data.

Many cases of myelosclerosis follow "burnt out" polycythemia. The bone marrow picture in this disease is complicated by the fact that the patients have almost always been subjected to irradiation, phlebotomies and later, transfusions. Some authors believe that at least some instances of polycythemia represent a response to early leukemic infiltration of bone marrow. An interesting observation in this connection is the finding that the total blood histamine is elevated in chronic myelocytic leukemia and in polycythemia.[2] A recent review of the literature emphasizes the significant result that with one exception, all cases of polycythemia which become leukemic had been exposed to some form of irradiation.[31] The observation that a sustained increase in erythrocyte counts occurs in patients treated for more than two weeks with ACTH or cortisone led Thorn[32] to suggest a possible role of cortisone-like hormones in the pathogenesis of polycythemia. Should this theory prove to

have merit, the delayed and inconstant appearance of myelosclerosis in this disease might be related to the protective action of hyperadrenal corticoidism on connective tissue.[33]

It is evident that there is little precise information regarding the pathogenesis of this skeletal abnormality. The fact that the disease is known by so many names expresses the confusion regarding its fundamental nature. It is unlikely that mechanical limitation of hematopoietic tissue is a primary factor since, as Vaughan pointed out, the total quantity of red marrow is often quite in excess of the amount normally present.[34] It is not clear whether osteosclerosis is the result of a simultaneous stimulation of derivatives of the primitive mesenchyme reticulum cell—osteoblasts, fibroblasts, hematocytoblasts and megakaryocytes —or is secondary to another disease. Wyatt and Somers[27] for example discussing chronic marrow failure implicate as etiologic factors, exogenous toxic chemicals, endocrine abnormalities, blood loss or destruction and cardiovascular disease. They suggest that pathogenesis is by way of liver dysfunction which results in protracted marrow exposure to certain substances normally conjugated rapidly in the liver and excreted. Others regard myeloid metaplasia as a non-specific response of immature multipotent cells of the liver and spleen to a wide variety of stimuli,[30] and osteosclerosis as a further secondary phenomenon.

It seems to me significant that unusual numbers of osteoblasts or osteoclasts are not present in the osteosclerotic marrow. This might suggest that primarily there is a physico-chemical change in the protein substrate of bone with altered conditions for the precipitation of calcium. If my discussion of the pathogenesis of the leukemic bone changes merits consideration, there is the possibility of applying a similar analysis to our present problem. We have seen that the continued administration of a folic acid antagonist to a leukemic in clinical and hematologic remission results in the reappearance of rarefaction in the metaphysis. It is also reported that in leukemic marrows, a diffuse fine fibrosis results from chronic exposure to folic acid blocking agents.[35] Although myelosclerosis is the characteristic bone change in myeloid metaplasia extensive decalcification has been noted in a medullary form of aleukemic myelosis described by Bouchut, Levrat and Guichard.[25] In this syndrome there is a proliferation of erythroblasts, myeloblasts and megakaryocytes which is strictly limited to the bone marrow. In the parts of the skeleton where the marrow shows abnormal proliferation the cortex of the bone is

thinned and is porotic. It is not too difficult to imagine that in the usual case of myelosclerosis, similar alterations take place in the bone matrix but with physicochemical conditions such that excess rather than less calcium is precipitated.

## Chronic Familial and Racial Anemias

This group of anemias includes those diseases in which there is a congenital dystrophy of erythropoiesis. There is an excessive destruction of red blood cells but to a varying degree in the different diseases. The present discussion will be limited to familial hemolytic jaundice, sickle cell anemia and familial erythroblastic anemia. All of these conditions are transmitted as a mendelian dominant trait, appearing in a major form when homozygous. The trait is present at birth but may never become clinically evident. On the other hand, active manifestations may appear at any age. Common to all three conditions is a markedly hyperplastic marrow.

There are skeletal changes which ordinarily are thought to result from the overgrowth of the marrow causing dilatation of the medullary cavity and pressure atrophy of the spongiosa and corticalis.[4] The radiographic appearance suggests to me that there is a preservation and exaggeration of the fetal type of bone formation but proof is lacking. Developmental anomalies also appear. These bone changes are frequent in the erythroblastic anemia of childhood, less common in sickle cell anemia and relatively uncommon in hemolytic jaundice. No basic difference in the patterns has been described. The variation between the bone lesions in the three diseases seems to be one of frequency, severity, extent and distribution. On the other hand, in a given disease there is no absolute correlation between the degree of skeletal abnormality and clinical severity. Excellent descriptions of the x-ray changes have been given by Snapper[25] and Caffey.[4] The following is in general a summary of their chapters.

In Cooley's anemia, there is a generalized spongy osteoporosis. The proliferation of the marrow first involves the cancellous bone, then the cortex. In the calvarium, the tables are more widely separated than normal due to broadening of the diploic space. The outer table in particular becomes atrophic but the total thickness of the bone is increased. Later bone trabeculae develop at right angles to the tables and perforate the outer table giving rise to the hair-on-end appearance.

Caffey considers that the radial appearance is probably a compensatory arrangement to support the diploic space in the presence of a weakened atrophic outer table. The frontal bones thicken first; the process then spreads to the parietal and lastly to the occipital bones. Even when the skull is markedly thickened and striated, the nasal process and the lower portion of the frontal bone remain free of striation. The air spaces in the temporal bone and the paranasal sinuses are encroached upon by the swollen contiguous bones and may be obliterated. Swelling of the zygomas makes the cheek bones stand out giving an appearance of mongoloid facies. Expansion of the upper and lower maxillas may cause malposition of the teeth and malocclusion of the jaws. The roentgen changes in the skull are not necessarily proportional to those in the long bones.

In the long bones, the narrow cavity is widened, the cortex is thinned and atrophic, the spongiosa is deformed and partially destroyed, and the marrow cavity is crossed by irregular and distorted trabeculae, which may enclose cyst-like areas. Frequently there are heavy horizontal striations near the ends of the diaphyses of the long bones which are distinctly suggestive of irregular "growth lines." The bones are increased in diameter and the ends are more rectangular than usual, so that the lower ends of the femurs, for example, show an Erlenmeyer flask deformity, and the normally concave borders of the metacarpals become convex. Sometimes, the spongiosa is almost completely destroyed and the bones have a swollen, ground-glass appearance in contrast to the usual coarse trabeculated pattern. The appearance in such short bones as the metacarpals matches those in the flat bones. Exaggerated trabecular markings are found in the ilia and scapulas. The ribs are widened. The vertebral bodies are cupped; they are relatively shortened in vertical height and are widened.

Bone changes may be evident by the end of the first year of life. They are usually progressive in the growing child. However, in those individuals who live beyond adolescence, some irregular sclerosis is found, probably due to thromboses with infarction. There may be patchy cortical thickening, narrowing of the medullary cavity, loss of bone tissue and periosteal reaction.[36] Translucent areas ringed by sclerotic bone may be seen resembling the bone infarcts of caisson disease. In several cases, there is retardation of growth and infantilism.

The bone changes in sickle cell anemia are usually less marked than in Cooley's, but on occasion there is little difference between the two.

In sickle cell disease, the parietal bone is more likely to be involved than the frontal. The calvarium is increased in diameter and the tables are thinned. Because the disease appears symptomatically at a later age than Cooley's and because even the severely affected patients live much longer hemorrhage and fibrosis are more prominent. Bone infarction and patchy sclerosis is more often seen in the long bones and spine. Bone deformities such as kyphosis, scoliosis and saber shins are frequent as is oxycephaly.

In congenital hemolytic jaundice, bone lesions are still less frequent. However, a very few cases show bone lesions as extensive as in Cooley's anemia. Developmental anomalies, however, seem to be more common. Oxycephaly has been described by many authors. Less frequently, prominent eyes, epicanthus, an abnormally wide nasal root, persistence of deciduous teeth, absence of incisors, fanglike canines, polydactylism and brachydactyly have been observed. Growth may be impaired. It is significant that similar developmental anomalies have been described in other dystrophic disturbances such as hereditary non-spherocytic hemolytic anemia,[37] and erythroblastosis fetalis.[4] Bone decalcification on a familial basis has also been related to achylia gastrica of the pernicious anemia type.[38]

The alteration in bone structure in these diseases is so striking that one would anticipate a well-defined pathogenesis, but so far as I know, none has been described. The statement that the hyperplastic marrow is responsible tells little about how and why. The basic abnormality in these dystrophies apparently is in the erythrocyte. Recent studies suggest that in the abnormal-shaped red blood cells the hemoglobin molecule differs physically from the normal, and that the configuration of the molecule may be different for each of the diseases.[39] Studies on zinc concentration and carbonic anhydrase activity in the sickling phenomenon suggest a role of this enzyme, but other reports challenge these data.[3, 32, 40, 41] In thalassemia some have thought the essential lesion depends on defective porphyrin synthesis.[9] While these data cannot be applied immediately to the elucidation of the pathogenesis of the bone changes, it is evident that powerful and ubiquitous mechanisms are disturbed.

Attention is drawn to the possibility that the adrenocorticosteroids will provide a means of investigating the subject further. In a recent report[3] there is reference to two cases of acquired idiopathic hemolytic

jaundice which showed striking hematologic improvement under therapy. Treatment of a case of pernicious anemia suggested that ACTH favors release of preformed elements from the bone marrow and may increase the rate of maturation but is not capable of inducing bone marrow regeneration. A case of Cooley's anemia in a severe crisis was treated recently with ACTH by Dr. M. J. Whitelaw of Phoenix. There was a satisfactory clinical response but the patient also received transfusions and it is difficult to evaluate the contribution of the ACTH to the improvement. There has been no distinct hematologic improvement. At the end of four months, the therapy being continued, there has been no striking change in the bones but there is a suggestion of new bone formation in the diploe between the two tables of the calvarium and perhaps slightly sharper trabeculae in the long bones. It would be most interesting should a definite change in the bone become apparent, since it would then be likely that when adrenal hypercorticoidism is induced, the bone matrix is protected from the changes following defective erythropoiesis[33] and more normal bone is found in spite of the negative calcium balance.

## Conclusions

I have reviewed what I consider to be the significant recent advances in the study of the skeletal lesions found in certain diseases of the blood. These new data suggest to me that, in the primary blood disorders, there is a change in the metabolic and enzyme systems, qualitatively and/or quantitatively specific for such disease, which alters the protein substrate available for bone formation and the physicochemical conditions for calcium precipitation. I suggest that the bone changes may, in certain cases, be a secondary tissue reaction based on these physicochemical alterations rather than a purely local cellular response to the adjacent disease process.*

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