BONE CHANGES IN LEUKAEMIA*

PART I.—CLINICAL AND ROENTGENOLOGICAL

BY

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Skiagrams of children with leukaemia have revealed changes in the structure of the long bones. These were observed by us independently, but a search of the literature shows that similar changes have been reported by a few authors. The material for this report is obtained from skiagrams and

FIG. 1. Case 10.—A. Left wrist taken July 25, 1933, shows normal bone configuration. B. Taken Oct. 27, 1933, shows marked rarefaction particularly at the ends of the bones and periosteal elevation of radius and ulna. The same change was seen in the other long bones, particularly the humeri.

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Case	Age	Sex	History	Spleen and Glands	W.B.C.	Lymphoid. per cent.	Biopsy or P.M.	X-ray findings
1	2½ ⁶	F	Pallor, tiring easily	+	2,-20,000	84-90	+	Rarefaction at end of long bones adjacent to epiphyseal line
2	2½ ⁶	M	Anæmia, large abdomen	+	33,000	88	+	Same picture as above
3	3½ ⁶	M	Glandular enlargement	+	2,500-5,500	75-95	+	At first normal, later same as above
4	2	M	Swelling in neck	+	300,000	99	+	Same picture as above
5	4	F	Epistaxis	+	12,-50,000	60-97	-	Normal on admission, later same as above
6	3½ ⁶	M	Joint pains, swelling of joint, epistaxis	+	4,-17,000	92-97	-	Same picture as above
7	3½ ⁶	M	Weakness, fever, glandular swelling	+	1,900-6,500	95-100	-	Same picture as above
8	3½ ⁶	M	Glandular swelling, pallor, pain in extremities	+	2,-18,000	90-99	-	Same picture as above
9	6	F	Flitting joint pains, fever, twitching hands and face, pallor, irritability	+	3,500	98	+	Rarefaction at ends of bones, thinning of shaft, raising periosteum
10	2½ ⁶	M	Pains in joints recurring pallor, swelling of parotid gland	+	1,400-14,000	15-90	++	On admission normal, later same as Case 9
11	1½ ⁶	M	Swelling arms and legs, petechial hemorrhage	+	27,-30,000	86-96	+	Generalized marked change as in Case 9 + a spontaneous fracture of right femur
12	1½ ⁷	F	Pain and swelling of arms and legs	+	2,400-26,000	63-96	+	Marked change similar to Case 9

records of twelve cases of lymphatic leukaemia studied in the Hospital for Sick Children, Toronto. Only those details of the laboratory and clinical findings by which the diagnosis was established will be given and these are recorded in the table.

Each of these twelve cases of leukaemia at some stage showed bone changes. Eight showed only a rarefied area at the end of the bone; four showed a periosteal elevation as well. These are all the patients with leukaemia in which we have skiagrams of the bones in various stages of the disease. The age of all patients in this series is below six years, and for the most part, less than four years. Those showing periosteal elevation as well as two of the others, complained of pains in the extremities. The symptoms of this group simulated rheumatic fever, and, in the two younger

patients, scurvy and luetic bone change. The periosteal change might be confused with the picture of luetic bone disease.

Allison¹, in 1924, reported a case of chloroma in a three-year old girl in which there was a raising of the periosteum similar to that seen in congenital lues. The new bone was laid down parallel to the shaft except at the end where it was at right angles. Taylor², in 1926, reported a child of two and ten months with leukaemia, with pain and swelling of extremities. Skiagrams of long bones showed elevation of periosteum throughout. Karshner³ reported a similar case in a child of two years and nine months. Karelitz⁴ reports one case of leukaemia and one patient with neuroblastoma that had periosteal elevation.

Poynton and Moncrieff⁵ reported two cases of leukaemia which showed a rarefaction at the ends of the long bones, and later Poynton and Lightwood⁶ observed a patient who showed periosteal elevation.

FIG. 2. Case 11.—Both femora show marked rarefaction or decreased density throughout the shaft. There is a raising of the periosteum and a fracture of the left femur as a result of the pathological change.

The other diseases of the blood showing roentgen change in bone are: metastatic new growths with secondary anaemia, marble bones, Gaucher's disease, chloroma, haemophilia, von Jaksch's or erythroblastic anaemia^{3,4,6,7,8}.

Giles⁹ described the various types of non-luetic periosteal bone lesions, including fractures, following osteomyelitis, tuberculosis, typhoid, leprosy, pulmonary osteoarthropathy, osteitis deformans, rickets, scurvy and bone tumours. He did not mention leukaemia or chloroma.

The radiological examination of the long bones is of value in confirming the diagnosis of leukaemia. If a patient has a suggestive blood picture the examination of the bones may reveal the changes described above. In conditions where the patient has symptoms of rheumatic fever, examination of the blood and the bones are necessary to rule out leukaemia.

Osteomyelitis has also to be kept in mind in the differential diagnosis. One of the patients referred to in the bibliography was operated on as a case of osteomyelitis.

FIG. 3. Case 12.—Lower ends of humerus, radius and ulna on both sides show rarefaction of shaft more marked at ends of long bones and generalized periosteal elevation.

Summary.

The roentgen changes in the long bones of twelve cases of lymphatic leukaemia are given. In eight they consisted of rarefaction across the shaft just adjacent to the epiphyseal line. In four cases there was also a raising of the periosteum.

Flitting joint pains were noticed by six patients prior to admission. All the patients were less than six years of age.

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PART II.—PATHOLOGY

BY

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The purpose of this communication is to draw attention to the pathological changes which take place in bones in leukaemia, as the result of which the clinical and roentgenological picture as described by Snelling and Brown becomes apparent. While the roentgenological findings have been reported by several authors in recent years, comparatively little has appeared in the literature dealing with the underlying pathology. The subject is dealt with briefly by Smith¹, Taylor² and somewhat more fully by Petrassi³.

The material for this paper was obtained at post mortem from two cases of acute leukaemia dying in the Hospital for Sick Children. Case 1 (case 9 of the clinical series) is that of a girl who died with terminal septicaemia at the age of six years following an illness of nine weeks' duration, the outstanding symptoms of which were shifting joint pains, fever, twitching of hands and face, irritability and increasing pallor. Case 2 (case 10 of clinical series) is that of a boy of two-and-a-half years, who also died with terminal septicaemia, following an illness of six-and-a-half months' duration, in which the chief symptoms were recurring pains in the joints, pallor and swelling in the region of the parotid gland. These were the only cases in the series of twelve reported by Snelling and Brown in which autopsies were obtained. Instead of describing the details of these two cases individually, the findings in the bones in both cases will be grouped under various headings followed by a brief discussion of the relation of these lesions to symptoms.

Bone changes in leukaemia may be grouped under the following headings:—

1. Infiltration. 2. Rarefaction. 3. Proliferation. 4. Degeneration.
5. Haemorrhage.

One or more of these changes may be found in any case of leukaemia and in almost any bone in the body.

I. Infiltration.—By the use of this term in regard to bone changes, we mean simply the deposition of leukaemic cells in bone, be it in the marrow cavity, Haversian canals, or under the periosteum. We do not propose to discuss whether this infiltration is neoplastic or inflammatory, nor do we wish to discuss the question of the origin of these cells. Whatever may be the starting point of this disease, whether in the bone marrow, lymph glands or spleen, abnormal cells soon find their way into the blood stream and are distributed all over the body where they are deposited in various organs and

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where we have reason to believe they continue to multiply. Outside of the bones this infiltration is best seen in such organs as the liver, kidney, testicle, etc.

Wherever this infiltration takes place, these accumulations of cells tend to crowd out the original structures. In the kidney, for example, there may be compression atrophy of both tubules and glomeruli, the more highly specialized structures being damaged the most. The same is true of bone. These cells increase in number at the expense of the bone marrow, which gradually becomes crowded out (fig. 1) resulting in secondary anaemia, which

FIG. 1. Case 2.—Rib: extensive infiltration with leukaemic cells in marrow cavity. H. & E. $\times 60$.

is progressive. Not only do these infiltrating cells fill the marrow spaces, but they spread into the Haversian canals and ultimately may reach the periosteum. Here they may multiply between the periosteum and cortex of the bone, the periosteum becoming elevated as the cells increase in numbers.

2. Rarefaction.—As the process of infiltration increases, not only is the bone marrow crowded out, but many of the bone trabeculae also disappear. Whether this is simply a pressure atrophy caused by the marked increase in the numbers of leukaemic cells, or whether these cells produce an osteolytic enzyme, we are not prepared to say. At any rate, the trabeculae disappear at irregular intervals throughout the shaft of the long bones, and it is this

rarefaction which is one of the first evidences of pathological change to be visualized by x-ray. One common site for this rarefaction is at the epiphyseal line. Here, not only may the trabeculae disappear, but the normal architecture of the columns of cartilage cells is also greatly altered (fig. 2).

As the disease progresses and more and more cells invade the Haversian canals, these canals enlarge at the expense of the adjacent compact bone until there may remain only a shell of honeycombed bone between the periosteum

FIG. 2. Case 2.—Humerus at distal epiphyseal line. The normal architecture of both cartilage columns and bone trabeculae is greatly altered. Many of the latter have disappeared entirely. H. & E. $\times 36$.

and what was originally the marrow cavity (fig. 3). This process of rarefaction may progress to such an extent that spontaneous fracture may result as shown by Snelling and Brown. This, however, was the only case in the series in which this complication arose, and no such fracture has so far been observed at a post mortem in this department.

3. Proliferation.—While the processes of infiltration and rarefaction may occur in almost any bone, and at almost any site in the bone, the formation of new bone is apparently limited to the subperiosteal region. The stimulus responsible for this new bone formation seems to be the separation of the periosteum from the cortex of the bone by reason of the invasion of leukaemic cells underneath the periosteum, these cells having arrived there by way of the Haversian canals. It is not necessary to assume that these leukaemic cells possess any bone-forming stimulus themselves, since it is well known that such laying down of new bone may follow stripping up of the periosteum from any cause whatever. Familiar examples are seen

following subperiosteal haemorrhages in scurvy and cephalhaematomata, and and also following periosteal elevation in osteomyelitis. Another example less frequently seen is that of adrenal neuroblastoma with bone metastases. In a recent case (the details of which are shortly to be published), the periosteum of the skull was elevated in places to a distance of 5 cm. and in the underlying tumour mass were numerous spicules of bone radiating outward from the surface of the skull. A somewhat similar picture is described by Karelitz⁴ in discussing periosteal elevation. In leukaemia we have observed this new bone formation in the humerus, femur, fibula, ribs and sternum, although radiological evidence of such proliferation in other bones is by no means lacking.

FIG. 3. Case 2.—Humerus: widened Haversian canals filled with leukaemic cells. H. & E. $\times 36$.

In some instances the general tendency is for the trabeculae of new bone to lie perpendicular to the shaft, while in other instances, they appear to have no definite arrangement (fig. 4, 5).

Under the heading of proliferation, mention should also be made of the development of new bone marrow in some of the subperiosteal intertrabecular spaces. This was observed between the dura mater and skull in case 1 (fig. 6, 7; 8). Here the inner surface of the skull was traversed by numerous fine ridges of new bone, while the spaces or grooves between these ridges were filled with bone marrow. This extra-cortical bone marrow may represent a response to a demand for new blood-forming tissue in an attempt to replace that lost by the extensive infiltration by the leukaemic cells of the great bulk of the original marrow cavities of many of the bones.

4. **Degeneration.**—In some of the long bones the masses of leukaemic cells are prone to undergo degeneration. This is seen on gross examination in the form of yellowish foci of greater or less extent in the marrow cavities. Microscopically in these areas of degeneration the shadows of the cells can still frequently be discerned. The explanation of this degeneration probably lies in the interference with the blood supply as the result of pressure on blood vessels from the increasing number of leukaemic cells.

5. **Haemorrhage.**—Just as haemorrhage is prone to occur in other organs infiltrated with leukaemic cells, as for example, in the kidney, so it may occur in bone. It is the presence of these foci of haemorrhage alternating with yellowish areas of degeneration and reddish-grey areas of masses of living leukaemic cells that gives to the cut surface of the medullary cavity of a long bone the striking mottled appearance sometimes seen.

FIG. 4. Case 2.—Humerus: subperiosteal new bone. H. & E. $\times 36$.

Comment.

Of the changes described above, the most important from the clinician's point of view are the first three. The last two, namely degeneration and haemorrhage are of little clinical significance. Infiltration with leukaemic cells we believe to be of importance because of the relation which it probably bears to the symptom of pain in the extremities. Whether these cells are inflammatory or neoplastic, their presence in such enormous numbers must result in increased pressure within the bone, a condition somewhat akin to that of a tumour within the skull giving rise to headache. In this connection the clinical article illustrates the frequency with which the symptoms simulate those of acute rheumatic fever. Pain in the legs was also mentioned by

Karelitz⁴ in his case of neuroblastoma with metastases into the bones of the legs. Some idea of the extent to which leukaemic infiltration may progress may be obtained from our records of another case of leukaemia. This was that of a boy who died at four-years-and-nine months, after an illness of five-and-a-half months. In this case the combined weight of the kidneys was 1,124 gm., approximately ten times their normal size. All this increased weight was contained within the kidney capsule which had gradually stretched to accommodate the increase in leukaemic cells. On section of these kidneys there was marked eversion of the cut edges indicating increased tension on the capsule.

FIG. 5. Case 1.—Rib: the subperiosteal new bone is becoming more dense. H. & E. $\times 36$.

In bone, on the other hand, no such stretching is possible so that increased pressure must result. Whether this pressure is within the marrow cavity, the Haversian canals, or under the periosteum may matter little, except perhaps that in the latter situation the bones might be more tender on pressure. In any case pain in the extremities is a common complaint in cases of this type. That the symptom of pain may be referred to the joints without any evidence of pathological change within the joint itself may be explained on the basis of the close relationship between joint ligaments and periosteum.

The relation between replacement of bone marrow by leukaemic cells and the profound anaemia which is usually present requires little comment. Case 1 is of particular interest in view of the evidence of development of extra-medullary marrow between the dura mater and the inner table of the skull. This obviously represents an attempt to supply the demand for blood which is not being formed in its normal site.

While the process of infiltration we believe to be closely related to the symptom of pain, it cannot be visualized in the skiagrams. The changes which may thus be recognized are those of rarefaction on the one hand and

FIG. 6. Case 1.—Section through whole thickness of skull showing numerous ridges of new bone inside the inner table. The dura was stripped off in removing the calvarium. H. & E. $\times 2$.

FIG. 7.—Higher magnification of small area in fig. 6. $\times 36$.

subperiosteal proliferation of new bone on the other hand. Although we have had opportunity to study the tissues of only two such cases, nevertheless we believe that the process of rarefaction always precedes that of proliferation and for this reason it may be visible skiagraphically before there is any

evidence of new bone formation. As pointed out in the clinical paper, one common site for this rarefaction to make its appearance is at the epiphyseal line but it may be seen anywhere throughout the shafts of the long bones.

FIG. 8. Case 1.—Section of dura showing ridges of new bone marrow. These lay between the bony ridges shown in fig. 7. H. & E. $\times 30$.

Summary.

The changes in bone in acute leukaemia in childhood may be grouped under the following headings: Infiltration, rarefaction, proliferation, degeneration, haemorrhage. These changes are illustrated by two cases of leukaemia, one, a girl, dying at the age of six years, the other, a boy, dying at the age of two-and-a-half years.

Infiltration with leukaemic cells may occur in bone as it does in the liver and kidney or elsewhere and may involve the marrow cavity, Haversian canals or subperiosteal region. By replacing bone marrow it may give rise to profound anaemia. It is not visible on x-ray examination.

Rarefaction occurs chiefly towards the ends of the long bones, but may occur anywhere along the shaft and involve both cancellous and compact bone. Spontaneous fractures may result.

Proliferation of new bone occurs underneath the periosteum following elevation of the periosteum by infiltrating leukaemic cells. This new bone is demonstrable by x-ray examination as are also the areas of rarefaction.

Degeneration of masses of leukaemic cells, as well as haemorrhage into the marrow cavity may occur in the course of the disease, but these changes are of little clinical significance, except perhaps to add to symptoms of toxæmia.

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For further literature see references in Part I.