OSTEOPETROSIS

BY

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The condition about to be described is known under an imposing array of names, among which osteosclerosis, osteosclerosis fragilis generalisata, marble bone or Albers-Schönberg's disease are perhaps the most familiar. The now commonly accepted name of osteopetrosis was proposed in 1926 by Karschner and means literally 'stony or petrified bones.'

The name of Albers-Schönberg is attached to this disease because he was the first to discover it radiologically in 1904. His patient was a man of twenty-four who was subsequently followed up till his death at the age of forty-nine. Similar examples were noted, however, prior to Albers-Schönberg's first description (1904) and usually labelled as leukaemia or pseudoleukaemia (Hueck, 1879; Neumann, 1880; von Jaksch, 1901). Most of the accounts of osteopetrosis appeared hitherto either in the German or American literature. One of the earliest reviews of the condition was made in 1926 by Karschner (1926), who gave a brief account of the findings in eighteen instances and added four of his own cases. Karschner's list was slightly amplified by McCune and Bradley, who published in 1934 an excellent summary of sixty-nine records including one of their own. In 1937 Harnapp produced the latest comprehensive review showing a total of seventy-nine cases, but he left out several of the less well-authenticated ones which were accepted by other authors. I was able to collect a total of 112 cases and a table of those not quoted by either McCune and Bradley or by Harnapp is given in an appendix (see p. 172).

Case record

HISTORY.—The patient, a male, aged three years and three months, is an only child of first cousins. He weighed 8 lb. 8 oz. at birth, and is supposed to have been a fortnight overdue. He sat up between six and seven months, stood up at ten months, and began to walk at fourteen months. Until about nine months the child was fed on boiled milk without the addition of any form of vitamin D; later he was given usual mixed diet, including porridge, bone and vegetable broth, gravy and potatoes. At the age of eighteen months he was referred to me from the Ear, Nose and Throat Department, where he
attended for nasal obstruction and enlarged tonsils. At that time the boy showed somewhat enlarged epiphyses and beading of ribs with marked inspiratory indrawing of lower intercostal spaces. The tibiae were slightly curved, the skull showed marked bossing, and no teeth had yet come through. The first x-ray, although suggestive of rickets, was unusual, but in view of the findings and the history, a diagnosis of vitamin D deficiency was made. Radi-

![Image](http://adc.bmj.com/Arch Dis Child: first published as 10.1136/adc.13.74.161 on 1 June 1938. Downloaded from http://adc.bmj.com/)

Fig. 1.—R. P. at the age of 2 years and 10 months.

ostoleum 10 minims thrice daily was ordered, and after two months there appeared to be some improvement. The epiphyses were less widened and there was less indrawing of lower ribs, but the anterior fontanelle was as widely open as before. After another two months (July, 1936) the epiphyses felt quite normal and he cut two upper incisors. In October, 1936, he was considered fit enough for the removal of tonsils and adenoids. Following this
Fig. 2.—Skull showing enormous thickening of the base and some clubbing of posterior clinoid processes. Anterior fontanelle still open at 2 years and 10 months.

Fig. 3.—Uniform density of the whole thoracic cage. Upper ends of humeri and clubbed and an old fracture of the right clavicle can be seen.
the snuffles became less marked but he developed discharging ears for a short time.

A blood count, done on October 27, 1936, showed: 
Hb, 65 per cent.; 
R.B.C., 4,520,000 per c.mm.; 
C.I., 0.7; 
leucocytes, 23,100; 
polymorphs, 28 per cent.; 
lymphocytes, 54 per cent.; 
hyalines, 8 per cent.; 
eosinophils, 2 per cent.; 
basophils, 4 per cent.; 
myelocytes, 4 per cent. 
The film showed 
anisocytosis, poikilocytosis and 1 megaloblast per 100 white cells.

In spite of the fact that adequate dosage of radiostoleum was kept up, he failed to cut any more teeth, and the fontanelle remained open as before.
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Repeated x-ray examinations of the wrist showed no further evidence of rickets, and the peculiar density at the end of the bones remained unaltered. On March 20, 1937, the serum calcium was 10.5 mgm. per cent. and phosphorus 3.9 mgm. per cent.

FIG. 5.—There is clubbing and accentuation of density at the ends of the long bones, especially femora. Relatively less dense transverse bands can be seen. There is a healed fracture at the upper end of the right fibula.

He was quite normal and bright mentally and was able to say a few words before two years old. In May, 1937, his mother reported that he could only see straight in front of him and that for any outside objects he had to feel. At that time nystagmus was noted. The anterior fontanelle had been diminishing
in size gradually, and at the beginning of September, 1937, admitted only the tip of one finger. He still had only two teeth and it was thought advisable to x-ray the skull again and also the rest of the skeleton. This revealed the marked deposition of calcium in all the bones, and the diagnosis of osteopetrosis was then made.

Lately (October, 1937) the child was readmitted to hospital because of a fall since when he has been limping with the left leg. X-ray examination revealed no fracture in the hip region, but marked flexor spasm of the thigh persists.

Examination on October 20, 1937, at the age of two years and ten months,

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RADIOGRAPHIC REPORT: Typical case of osteopetrosis with extensive changes in the whole skeleton. Evidence of three fractures, one in right fibula, the other in right clavicle and third in right ulna.

OTHER INVESTIGATIONS: Wassermann reaction, negative. Serum calcium, 9.7 mgm. per cent. Inorganic blood phosphorus, 2.7 mgm. per cent. Blood phosphatase, 9.5 units (normal 3.5–8). Blood urea, 21 mgm. per cent. Blood count: Hb, 60 per cent.; R.B.C., 3,440,000 per c.mm.; W.B.C., 11,200; polymorphs, 38 per cent.; lymphocytes, 59 per cent.; hyalines, 3 per cent.; anisocytosis and poikilocytosis.

He was re-examined recently, shortly after his third birthday, and the condition is still appreciably the same.

Etiology

The numerous theories about the cause of the disease include suggestions of polyglandular dyscrasia—especially a disturbance of parathyroid function—of poisoning with phosphorus or fluorine and of chronic bone infection. Many authors (Nadolny, 1924; Llado, 1931; Kopylow and Runowa, 1929) conclude that the disturbance is one of calcium metabolism, but the evidence incriminating the parathyroid for this (Péhu, 1931; Ellis, 1934) is not at all clear. There remain the undisputed facts of the frequency with which parental consanguinity has been noted in osteopetrosis and the tendency for familial incidence in this disease. Many authors comment also on the large number of miscarriages preceding or following the birth of an affected individual and on the high mortality rate among the sibs.

It is interesting to note that both parents of Kudrjawtzewa’s (1930) patients had been married before and that the father had three normal children by the first marriage and the mother one. By their consanguineous union they had five children, two of whom died in infancy and three had typical osteopetrosis. D’Istria (1928) noted a similar occurrence, the father having had three normal children by his first marriage, whereas his union with a first cousin resulted in five children, three of whom died in infancy, one was mentally defective and one had osteopetrosis. Up to date there appear to be recorded 112 cases (including that here described) and in those consanguinity was noted in twenty-three instances. Of the fourteen marriages covering these twenty-three cases eight (ten cases) were between first cousins. Consanguinity was specifically denied in twenty patients (eleven families) and no record was made in sixty-nine instances (forty-nine families). The above points taken in conjunction with the early lethal outcome of the disease lead to the conclusion that osteopetrosis is an inherited recessive defect.

Against this are the records of seven families embracing twenty-six affected individuals in whom the disease was handed down directly from generation to generation. In six instances (Ghormley, 1922; Lautenburg, 1926; Pirie, 1930; Zaleski, 1932; Pagenstecher, 1935; and Harnapp, 1937) two generations were affected and in one (McPeak, 1936) mention is made of a woman aged seventy, her two daughters, and five grandchildren who were involved. It is unlikely that inbreeding would wholly explain this occurrence, because the disease is so rare, and it is safer to assume that there is also a type of osteopetrosis which is handed down as a simple dominant. Deducting the above twenty-six cases from the total of 112 leaves eighty-six, 11.7 per cent. of which were born to first cousins. The 10 per cent. incidence of first-cousin marriages would probably be greater had the majority of authors made a statement about
consanguinity, but in any case it is significant because the normal rate in the general population is estimated to lie between 0.5 and 1 per cent.

The segregation of osteopetrosis into recessive and dominant would coincide with the suggestion of Harnapp (1937) and McPeak (1936), who divide the cases into the more or less severe or 'malignant' and the relatively mild or 'benign,' and would be parallel to a condition known as epidermolysis bullosa dystrophica, the severe form of which is a homozygous recessive and the less severe a heterozygous dominant. It is certainly more than a coincidence that all the cases in which direct inheritance can be traced fall into the benign group and that the evidence of consanguinity occurs only in the first or malignant group.

Osteopetrosis is pre-eminent a disease of childhood and early adolescence. It has been diagnosed as early as in utero (Pirie, 1930) and as late as at the age of seventy (McPeak, 1936). Of the 112 cases eighty-one were under and twenty-nine over twenty-one years of age; in two the age was not mentioned. Sex plays no obvious rôle, because of the 110 instances in which it was stated fifty-eight were male and fifty-two female. No special tendency could be traced in the sibships for those affected to be of one sex and those unaffected to be of the other. Race does not appear to be a factor, because cases have been recorded in many countries, including one in a negro in U.S.A. and another in a Japanese.

Pathology

The essential feature of the disease is the great increase in thickness and density of the cortical and spongy portions of the skeleton and a variable degree of decrease in the space occupied by the bone marrow. Most authors assume that this encroachment of bone on the medullary cavity is responsible for the myelophyseal type of anaemia met with in the severe type of osteopetrosis. The occasional changes in the peripheral blood resembling leukaemia, and the more rare attempts at vicarious haemopoiesis in enlarged liver, spleen and lymph glands are taken to be natural consequences of the same process. It is tempting to explain the anaemia on this simple quantitative basis, but it is equally possible that the changes in the blood-forming elements are primary and that the excessive deposition of bone is a replacement phenomenon. If it is agreed that the condition is an inherited dyscrasia of the mesenchymal tissues responsible for the formation of both the bone and the marrow it can be accepted that the two processes may go on side by side without influencing each other unduly. In favour of this supposition is the fact that great increase in density of bones has often been observed, particularly in those who inherited the disease as a dominant, together with slight or even no anaemia. On the occasions on which the bone marrow was examined (Assmann, 1907; Schmidt, 1907; Goodall, 1912) it was found to be healthy, although in parts it may be replaced by fibrous tissue. The sclerosing process usually begins near the epiphyseal lines, and opinions differ as to which bones are first affected. In flat bones like the ileum concentric arcs of dense material represent the initial stage, whereas in small bones of hands and feet early condensation produces a ring-like appearance. In long bones there is a tendency for the sclerosis to occur in bands at right angles to their long axis. These bands alternating with the less dense portions give a striped appearance on cross-section. Both the
cortex and the individual trabeculae of the medulla are reported to be thickened and extra bone may also be deposited in longitudinal ridges beneath the periosteum, thus producing a fluted contour. The ends of the long bones are frequently clubbed.

The departure from normal in the affected portions of bones is due, according to most authors who made a study of it (Pirie, 1930; Nadolny, 1924; Alter, 1931; Laubmann, 1934), to a disturbance in endochondral formation of bone which allows the cartilagenous basis to persist. In the skull the distinction between the cortex and diploe is obliterated, the basal bones are greatly thickened and the posterior clinoid processes often clubbed. The meninges may be thickened and on occasions pachymeningitis interna haemorrhagica has been observed (Kraus and Walter, 1925; Lorey and Rye, 1923). Hydrocephalus is common and is possibly explained by the obstruction to venous return through the narrowed foramina at the base of the skull. The bones may show evidence of many fractures, particularly in the 'malignant' type of disease. Most of these fractures are pathological, and it is not certain whether they are liable to occur through the dense or relatively rarefied areas.

Pirie (1930) stated that the dense portions of the skeleton are soft and friable, but he stands alone in this respect, because the consensus of other opinion (Clairmont and Schintz, 1924; Alexander, 1923; Lautenburg, 1928; Parkinson, 1928; and Harnapp, 1937) is that the sclerosed bone is abnormally hard. Nearly all chemical analyses of affected bones gave results within normal limits (Pirie, 1930; Kopylow, 1929; Kudrjawtzewa, 1930; Péhu, Policard and Dufort, 1931; and Lautenburg, 1928).

Clinical features

The condition of osteopetrosis is most commonly discovered accidentally when the patients are brought up on account of fractures, apparent rickets, necrosis of jaw bones, severe anaemia or failing sight. This and the ensuing description applies to the severe or 'malignant' type, which, it is suggested, is inherited in the form of an autosomal recessive defect. Retardation in growth is common and is more marked in those cases in which the disease is fully established early in life. On account of the frequent combination of hydrocephalus and marked bossing of the skull bones the head assumes a characteristic appearance. The veins on the scalp are dilated. The closing of the anterior fontanelle is usually much delayed. The teeth are often late in erupting, defective in quality and decay early. Dental caries combined with compression of nutrient foramina of the jaw bones may result in necrosis of the mandible. Fractures, usually provoked by trivial violence, are common and many of them, by escaping notice at the time, lead to deformities. Callus formation and healing of bones appears to be normal. The encroachment on the foramina at the base of the skull produces optic atrophy which shows itself clinically in defective vision, nystagmus and eventually blindness. Occasionally other cranial nerves are similarly affected leading to lower motor neuron lesions. In younger patients enlargement of lymph glands, spleen and
liver may be found. Despite the disabilities, such as poor vision and anaemia, intelligence is not appreciably impaired.

In the 'benign' form of osteopetrosis the general condition of the patient is usually not affected and fractures are relatively rare. Here recognition is always accidental, usually when the patients are X-rayed because of trauma.

X-ray appearances are characteristic and apply to both types of the disease. There are symmetrically arranged areas in both the cartilage and membrane bones where dense, rather fuzzy-looking bone appears to encroach and obliterate the medullary cavity. The base of the skull, the long bones and bodies of vertebrae are most prominently involved. The long bones may show alternating transverse bands of more and less opaque areas and clubbing at the ends, corresponding to the pathological findings. As a rule centres of ossification appear at normal times and fusion of epiphyses and shafts are not delayed.

Blood picture.—In the 'benign' osteopetrosis this is usually normal. In nearly all other cases there is anaemia, most frequently of the hypochromic kind. Immature red cells such as normoblasts or rarely megaloblasts may be present in the peripheral circulation. In infants the blood often shows an increase in white cells, some of which may be immature, but in adolescents and adults this is rare. There are recorded instances in which the disturbance in the blood picture was more severe than radiological appearance of the bones would suggest, but the opposite is even more common.

Chemical analysis of the blood.—Normal values were found in nearly every instance in which the serum calcium and phosphorus were analysed. Notable exceptions were the patient of Schultze (1921) who showed extensive calcification of soft tissues with a blood calcium 'double its normal value' and the one of Flood (1929) whose serum calcium ranged from 14.6 to 16.6 mgm. per 100 c.c.

Diagnosis

The complete picture of osteopetrosis, especially in its severe form, is so characteristic that it can hardly be confused with any other condition. The x-ray appearance of the skeleton is, of course, the most striking feature, and this is found in both types of the disease. In the differential diagnosis of 'malignant' osteopetrosis the elimination of leukaemia may prove a difficulty on account of some resemblance in the blood pictures, but in leukaemia the occasional involvement of the bones is more in the nature of invasion and destruction rather than of the excessive deposition of bone as in osteosclerosis. The presence of nucleated red cells in the peripheral blood may suggest Cooley's erythroblastic anaemia, but the x-ray appearances of the bones, especially those of the skull, are entirely different. Increase in density of single bones has been described under the titles of 'ivory vertebra' and eburnising osteitis, but besides this there is no other point of resemblance to osteopetrosis. Melorheostosis (Léri) is another condition in which there is only a localized increased density of one or more bones of an extremity. Secondary deposits of malignant disease, quite apart from the different age incidence, give an entirely different
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x-ray picture. The history would help to eliminate chronic lead, phosphorus or fluorine poisoning which sometimes gives rise to diffuse bone changes. Paget's disease, though bearing some superficial radiological resemblance, has again a different age incidence and a characteristic distribution of bony changes. Pathological fractures may occur in fragilitas osseum, but here there is usually a decrease and never an increase in density of bones.

Prognosis

The 'benign' form may show a slight increase in tendency to fractures, but apart from that it does not appear to shorten or otherwise appreciably affect the life of the individual. The 'malignant' form is usually fatal early in life either from anaemia or intercurrent infection. The earlier the disease is fully established the worse the prognosis. Some of the less severe cases may drag out a rather subnormal existence well past adolescence.

Treatment

In the light of present knowledge this can only be symptomatic. Correction of deformities due to fractures may be required, osteomyelitis when it occurs will have to be dealt with, and in a desperate case blood transfusion may stave off the inevitable end.

Summary and conclusions

(1) The condition of osteopetrosis is briefly reviewed.
(2) The hereditary aspect of the disease is stressed and evidence brought forward in support of dividing it into two forms, the benign, which is inherited as a dominant, and the malignant, which is handed down as a recessive.
(3) A personally observed patient is described and a list of cases not included in previous reviews is appended.

Thanks are due to Dr. E. A. Cockayne for his helpful criticism of the section dealing with the etiology.

REFERENCES

ARCHIVES OF DISEASE IN CHILDHOOD


**APPENDIX**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>AUTHOR</th>
<th>AGE YEARS</th>
<th>SEX</th>
<th>BLOOD RELATIONSHIP OF PARENTS</th>
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