Section for the Study of Disease in Children

President—F. C. PYBUS, M.S.

[*May* 25, 1934, *continued*]

Osteopetrosis

(*Marble Bones; Albers-Schönberg's Disease; Osteosclerosis Fragilis Generalisata; Congenital Osteosclerosis*)

By R. W. B. ELLIS, M.D.

SINCE Albers-Schönberg's original description, in 1904, of a young man suffering from this rare bone disease, rather less than forty examples of the condition have been reported.

The radiological appearances of the bones are characteristic. Symmetrically arranged areas of greatly increased density are seen involving both the membrane and cartilage bones; the base of the skull, the bodies of the vertebræ, and the long bones are those generally most affected. The carpal bones often appear "ringed" with a dark shadow. The dense, compact bone encroaches on the medullary cavity, which may ultimately become almost entirely obliterated. These areas of sclerosis appear in some instances to be of uniform density throughout, or may show transverse lines of rarefaction. The parts of the skeleton unaffected by the sclerosis also usually show some degree of osteoporosis, and the cortex of the long bones may be considerably reduced in thickness until the sclerosis spreads throughout their length. Brailsford has recently drawn attention to the occurrence of vertical cracks in the lower ends of the phalangeal diaphyses (which were themselves the site of dense sclerosis), in the case of an adolescent girl. Unlike the appearance seen in (melo) rheostosis Léri (in which irregular sclerotic lesions extend to form excrescences on the surface of the bone), the contour of the bone in osteopetrosis is not altered by the sclerosis, although clubbing of the posterior clinoid process and of the ends of the long bones (particularly of the lower ends of the femur and the radius) occurs sufficiently often to be regarded as the rule rather than the exception. That this clubbing is not directly due to the sclerosis is well seen in the two cases reported below, in which the main area of sclerosis occurs in the middle third of the shaft of the long bones and completely outside the area of clubbing. Nor can the clubbing be regarded as secondary enlargement to compensate for the area encroached on, since in these cases the area of encroachment is still relatively small. It may be pointed out here that the site of sclerosis within the bone shows considerable variation in different cases, and although several authors have insisted on its appearance at the *ends* of the long bones, these present cases (which show several characteristic features confirming the diagnosis) prove that this distribution is not essential. It is interesting that the skiagrams published by Ghormley of his two cases, a father and son, also show an identical distribution of the sclerosis in the middle third of the shaft of the phalanges. It appears, therefore, that different family groups (see below) present variations of the condition which are, however, constant within the particular group.

The nature of the areas of increased density observed radiologically has given rise to considerable difference of opinion, which is reflected in the number of names that have been applied to the condition. The early description "Marble Bones" has largely been abandoned, since it was found that, in spite of the increased deposition of calcium the bones were abnormally liable to fracture. Karshner suggested the name osteopetrosis, implying limestone rather than marble, and Pirie that of "chalky bones," since he found that the bones could be drilled and broken as readily as chalk. Dupont, on the other hand, from the autopsy findings in a case originally reported by Péhu, Policard and Dufourt, insists that the sclerosed bone is abnormally hard, with areas of rarefaction interposed. He claims that it is through these lines of rarefaction that fractures occur.

Inheritance.—The condition occurs in either sex, and is frequently familial. As mentioned above, the features of the disease may vary somewhat in different family groups. In a few instances it has been directly inherited from an affected parent, either the mother (Pirie), or the father (Ghormley). It is possible that direct inheritance may prove more frequent than at present suspected if the parents of all patients are examined radiologically, since the father of Ghormley's patient was entirely free from symptoms, and his condition only detected when examined in this way. Consanguinity of the parents has been recorded in several instances, to which may be added the two cases reported here, whose parents were second cousins. Considering the cases of direct inheritance from affected parents, however, it is most unlikely that the condition is inherited as a Mendelian recessive character.

Clinical features.—The disease may be manifest at birth, or symptoms may not appear until later life. In general, the condition is progressive, and the prognosis worst in those patients in whom evidence of sclerosis could be detected in early childhood. Although the clubbing of the long bones has frequently caused the condition to be mistaken for rickets, the bony deformities are seldom such as to cause disability. Multiple fractures are frequent in the later stages of the disease, but generally unite readily without an abnormal formation of callus (Kudrjawtzawa). Delayed eruption of the teeth, defective "chalky" calcification, and dental caries are common.

The most striking symptoms, however, and those for which advice is usually sought, arise from the secondary involvement of the hæmatopoietic and nervous systems. Thus, the progressive sclerosis of the long bones gradually reduces the medullary cavity and bone-marrow to a degree incompatible with normal blood formation. Anæmia of myelophthisic type occurs (Boyd); over-activity of the residual bone-marrow at first results in an increase of reticulocytes and nucleated red cells in the peripheral circulation, and is followed by a true aplastic anæmia as further reduction of the bone-marrow takes place. In attempted compensation, there is enlargement of the liver, spleen, and lymphatic glands throughout the body. The severity of the anæmia has caused a number of these cases to be reported as examples of aplastic anæmia, atypical leukæmia, etc., without the primary nature of the bone changes being recognized, and this makes it almost impossible to estimate at all accurately the number of cases in the literature. Goodall's case of "acute myelocythæmia associated with osteosclerosis and other unusual features occurring in an infant," and Hueck's "zwei Fälle von Leukämie mit eigenthümlichem Blut- resp. Knochenmarksbefund" are probably examples.

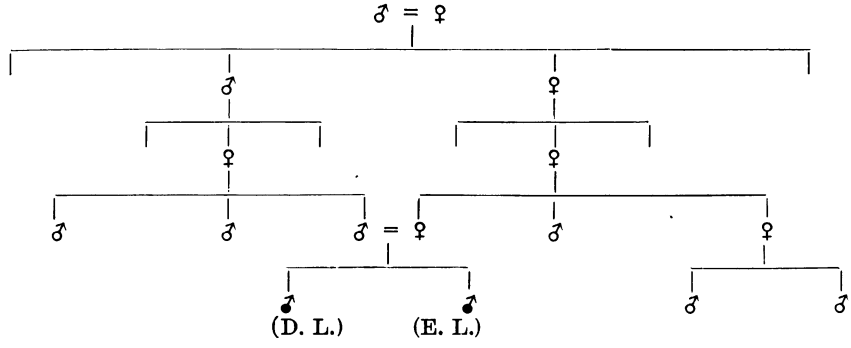
The deposition of dense bone at the base of the skull results in a variety of neurological symptoms, including hydrocephalus and pressure on cranial nerves in their exit from the cranial cavity. Amongst the most common findings are optic atrophy, ocular and facial palsies, and nystagmus. There is frequently clubbing of the posterior clinoid process, and some reduction in size of the sella turcica. It is possible that some of the cases of delayed growth and development have therefore a pituitary origin.

The following two cases are of interest in that they show an early stage of the disease, in which encroachment on the medullary cavity is insufficient to cause anæmia, and an unusual distribution of the sclerosis. They appear to be the third and fourth cases (with the possible exception of Goodall's) to be reported clinically in this country, although skiagrams of other cases have been shown. Wakeley reported a somewhat atypical case (which Brailsford is inclined, on radiological grounds, to regard as more akin to rheostosis Léri) before the Clinical Section of this Society, and Parsons has given brief particulars of a second case. The two cases of "Albers-Schönberg's Disease" reported recently by West are examples of a second and distinct bone-disease described by Albers-Schönberg in 1915 (osteopoikilie or osteopathia condensans disseminata), probably bearing no relation to osteopetrosis.

Case Reports.

Derek L., aged 2 years and 10 months, and Edward L., aged 1 year and 6 months. The patients are brothers.

Family history.—No other children; no miscarriages. The parents are both well and are English. They are second cousins, the relationship being as follows :—



No other relatives known to be affected. Skiagrams of right hand of both parents showed no abnormality.

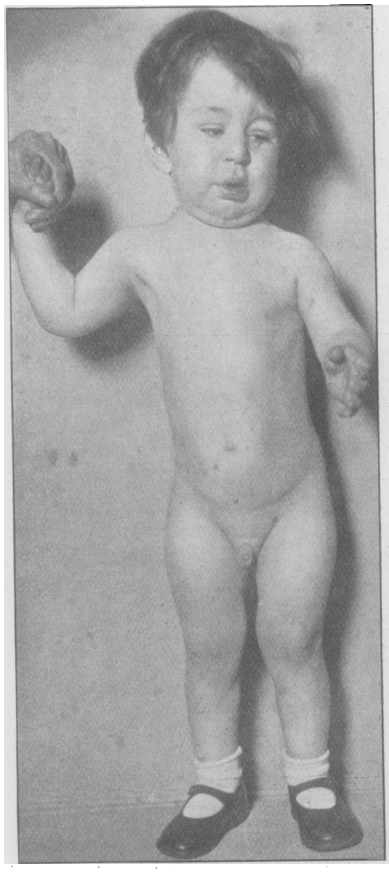
Derek L. (fig. 1), full term, instrumental delivery, birth weight 8¼ lb. Breast fed for nine months, then a mixed diet, including green vegetables, bone broth, gravy and potatoes. He has had three or four teaspoonfuls of Scott's emulsion regularly since he was 12 months old. He appeared well until 6 months old, when he had a prolonged convulsion at the onset of bronchopneumonia. General health has been moderately good. He sat up at 11 months, stood at 13 months, walked at 18 months; now talks normally for his age and does not seem mentally backward. The eyesight has been thought to be defective since about 6 months of age, and recently the pupils have been constantly dilated.

On examination.—Moderately well-developed boy, height 36 in., weight 30 lb. Circumference of head 20½ in.; intermeatal measurement (over vertex) 13½ in. The face appears rather flattened, and there is moderate frontal and very marked parietal bossing, with a horizontal ridge in the temporo-parietal region comparable to that seen in fragilitas ossium. Below this there is a hollow in the occipital region. The anterior fontanelle is patent. The chest is relatively narrow, and considerable bending of the ribs occurs during respiration. There is no beading or disproportion between the length of limbs and trunk, but there is considerable expansion of the ends of the long bones. Macular atrophy of skin of abdominal wall; no enlargement of lymph-glands, liver, or spleen. All the teeth are defectively calcified and

appear chalky, but have erupted normally. The finger-nails show platyonychia. Pupils dilated, reacting poorly to light. Bilateral weakness of sixth cranial nerve.

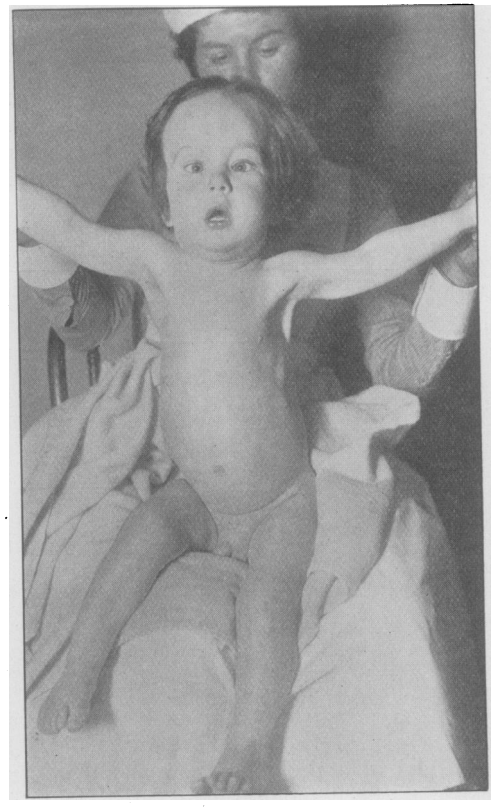
Ophthalmic report (Mr. G. G. Penman): "Primary optic atrophy, right and left."

Radiological report (Dr. Bertram Shires): "Skull shows delay in closure of anterior fontanelle and prominent coronal sutures; relative increase in size of cranial



Derek

FIG. 1.



Edward

FIG. 2.

vault. Long bones show greatly expanded ends of diaphyses with cortical thickening, apparently encroaching on medullary cavity in centre of shaft."

Wassermann reaction negative.

Biochemical investigation (26.6.34).—Serum calcium 8·9 mgm.%. Inorganic blood phosphorus 3·39%. Blood phosphatase 12·5 units (normal 10 to 20 units). Blood cholesterol 157 mgm. per 100 c.c. Blood-urea 31 mgm. per 100 c.c.

Blood-count (22.6.34).—R.B.C. 5,113,000 per c.mm.; Hb. 74%; C.I. 0·72; W.B.C. 8,850; Polys. 63%; small lymphos. 23%; large lymphos. 8%; monos. 5%; plasma. 1%.

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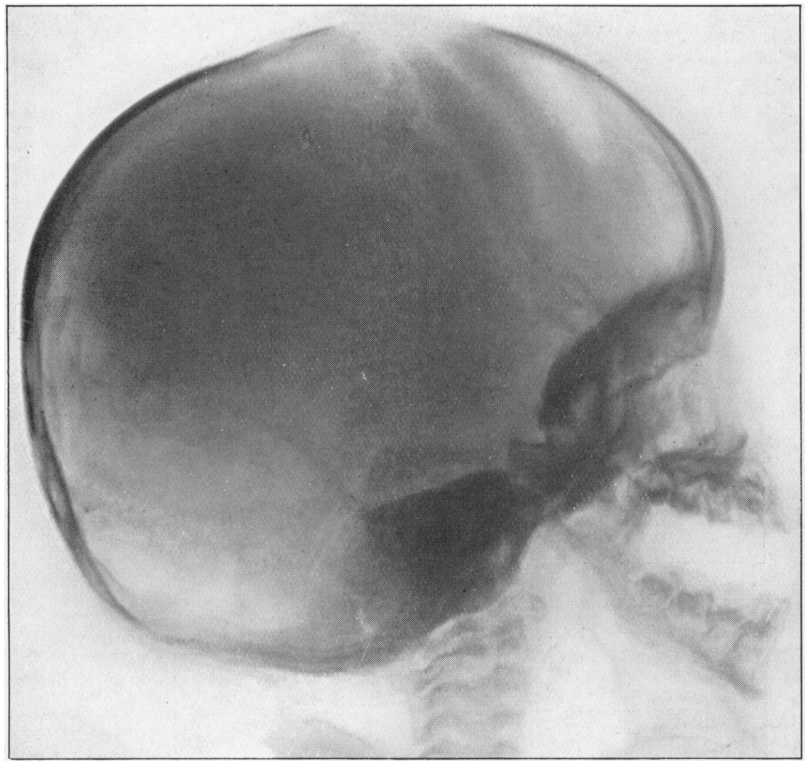
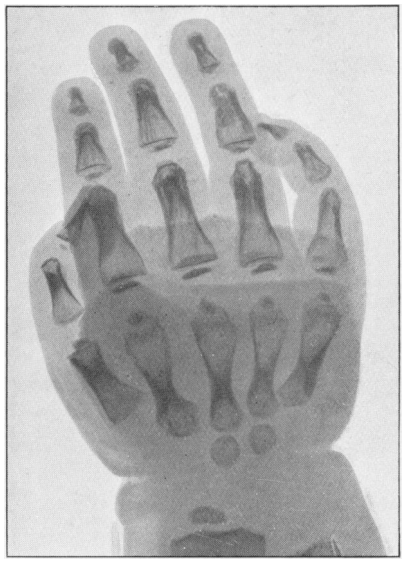
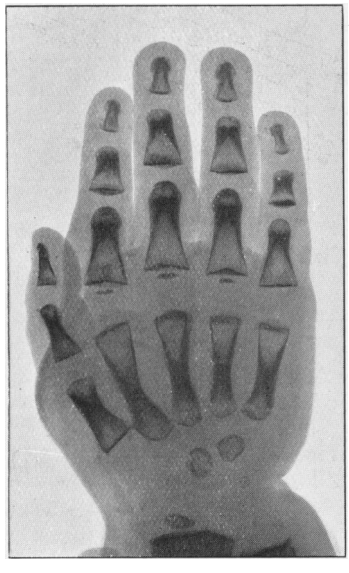
PLATE I



Edward: Skull showing patent fontanelle and dense bone at base.



Derek



Edward

ELLIS: Osteopetrosis (Marble Bones; Albers-Schönberg's Disease; Osteosclerosis Fragilis Generalisata; Congenital Osteosclerosis).

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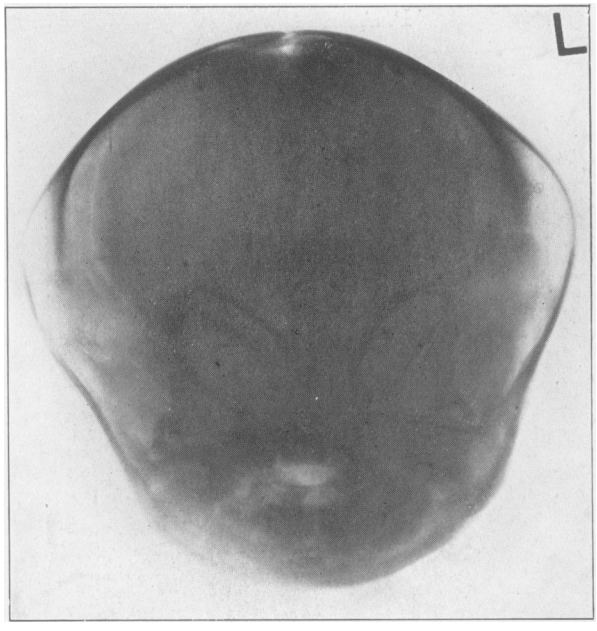
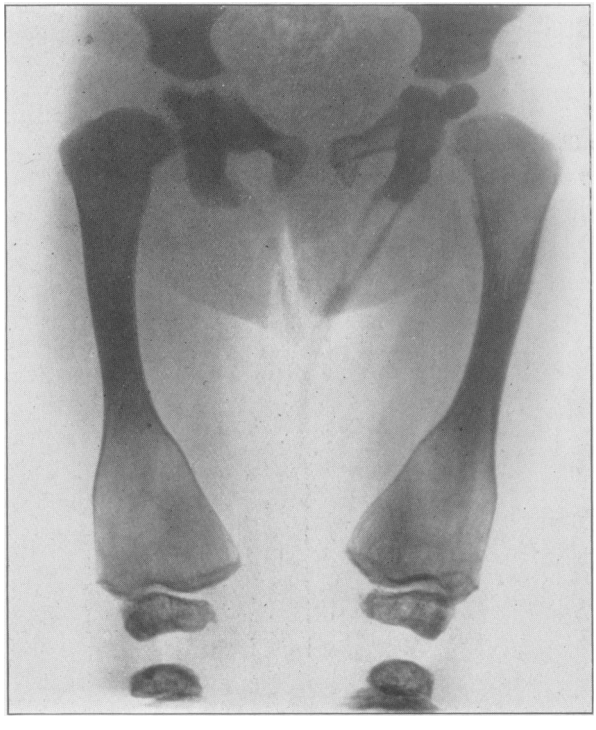
PLATE II



Edward: Skull showing lateral ridging.



Derek: Increased density in middle third of shaft of femora (with obliteration of medullary canal), and in a narrow band at lower end of expanded shaft; stippled and "ringed" appearance of epiphyses.

ELLIS: Osteopetrosis (Marble Bones; Albers-Schönberg's Disease; Osteosclerosis Fragilis Generalisata; Congenital Osteosclerosis).

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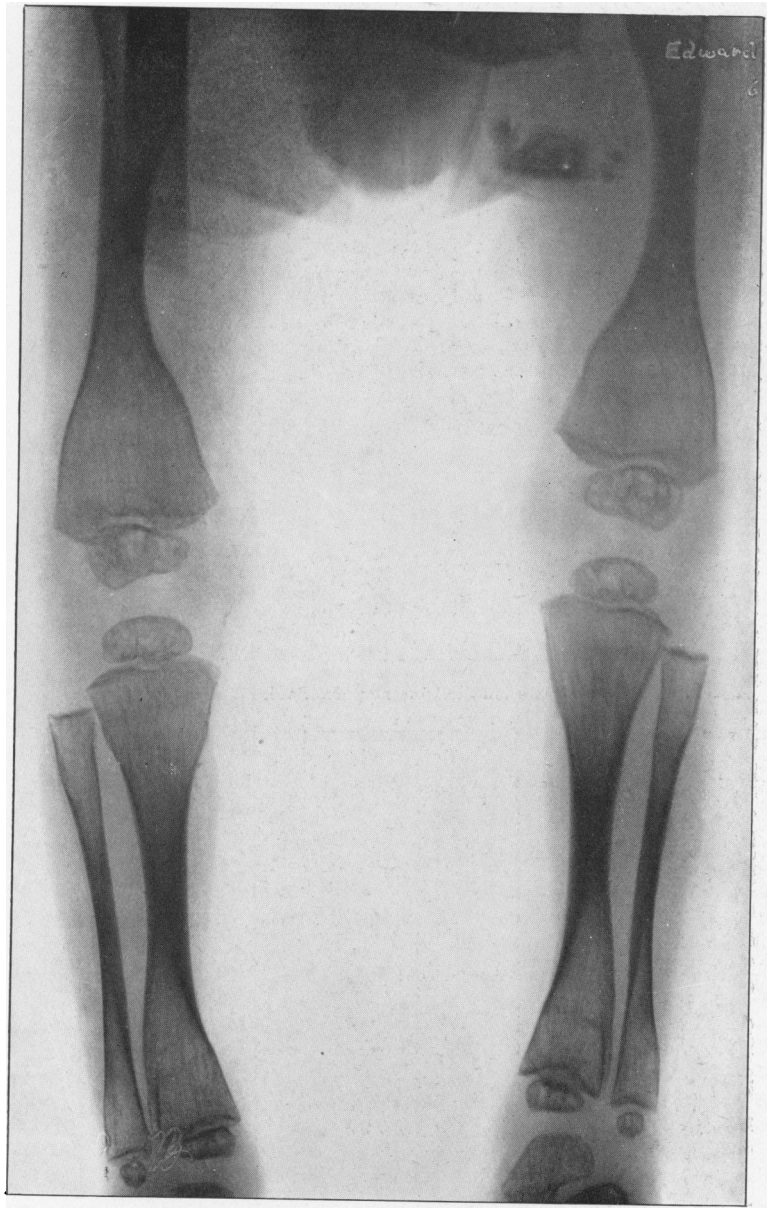
PLATE III



Edward

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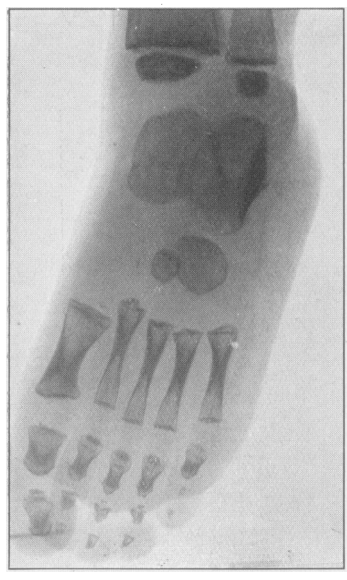
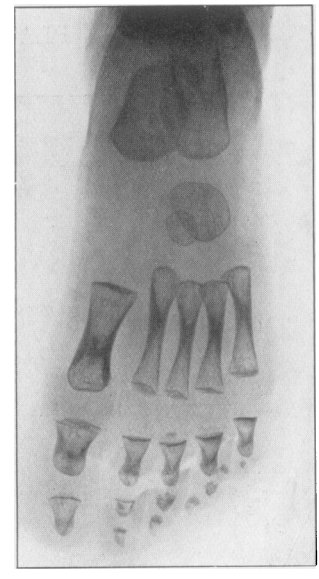
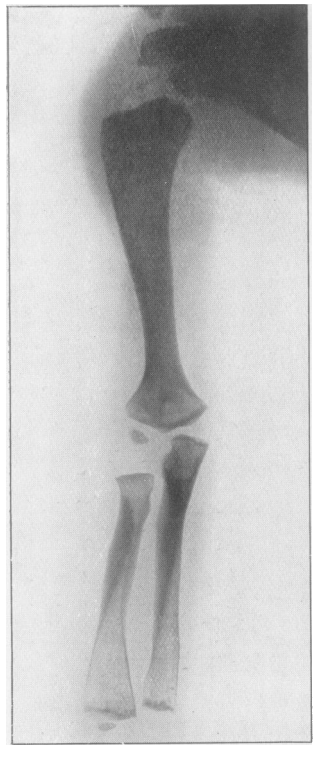
PLATE IV



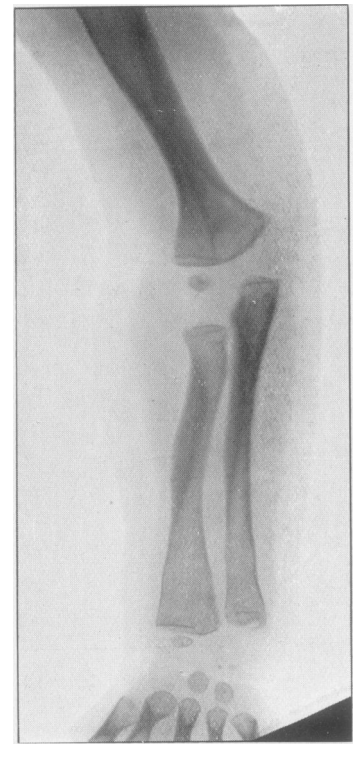
Derek



Edward



Derek



Edward

ELLIS : Osteopetrosis (Marble Bones ; Albers-Schönberg's Disease ; Osteosclerosis Fragilis Generalisata ; Congenital Osteosclerosis).

Edward L. (fig. 2). Full term, forceps delivery, birth weight 8½ lb. Breast fed 3 months, then Robinson's patent barley and cow's milk followed by mixed soft solids at 11 months. Scott's emulsion regularly since 11 months old. Started to cut teeth at 5 months, sat up at 13 months, beginning to stand at 17 months. Admitted to hospital at this time on account of tonsillitis and cervical adenitis.

On examination.—Rather feeble infant, making little effort to stand unsupported. Weight 22 lb. Length 27 in. Massive skull, with frontal and parietal bossing, and wide anterior fontanelle. A narrow central bony ridge runs from the anterior fontanelle to the nasion, and temporo-parietal ridging and occipital hollows are present, as in the case of the brother. Circumference of head 20 in.; intermeatal measurement 13 in. Pigeon-breast deformity of chest with some flaring and beading of ribs. Limbs not abnormally short; expansion of ends of long bones, especially at wrists. Heart, lungs and abdomen normal. Bilateral internal strabismus. Deep reflexes present. The pupils are generally dilated, but react to strong light. Bilateral enlargement of cervical glands. Nails show platyonychia. 14 teeth; incisors defectively calcified.

Ophthalmic report (Mr. G. G. Penman).—"Primary optic atrophy, right and left."

Radiological report (Dr. Bertram Shires).—"Skull: enlarged cranial vault, with large fontanelle and wide sutures. Abnormal shape of skull with bossing. No evidence of rickets. Long bones show expanded diaphyses, with thickening of cortex, especially in centre of shafts, and stippling of epiphyses. Appearance almost identical with that of brother."

Biochemical investigations (9.5.34) (Dr. Payne).—Serum calcium 9·97 mgm. %. Inorganic blood phosphorus 4·4 mgm. %. Blood phosphatase 9·6 units (normal 10 to 20 units). Blood-urea 31 mgm. per 100 c.c. Blood cholesterol 170 mgm. per 100 c.c. Wassermann reaction negative.

Blood-count (14.5.34).—R.B.C. 4,200,000 per c.m.m.; Hb. 62%; C.I. 0·73; W.B.C. 14,000. *Differential*: Polys. 50%; small lymphos. 17%; large lymphos. 26%; monos. 2%; eosinos. 3%; Türk 2%.

There was no clinical evidence in either case of thyroid or parathyroid enlargement.

Comment

These two children illustrate several of the classical features of the disease, and show the somewhat peculiar distribution of the sclerosis referred to above. The familial incidence of the condition, and the fact that both children present an almost identical appearance clinically and radiologically (allowing for the slightly more advanced stage in the elder child) emphasize the uniformity within the family group. Thus the peculiar facies and cranial conformation make it obvious that these two children are suffering from the same condition, although they do not correspond closely to the appearance in other family groups. The clubbing of the long bones (without clubbing of the posterior clinoid process), and the neurological symptoms (optic atrophy and bilateral sixth-nerve palsy) are also identical in both cases.

Whilst the occurrence of sclerosis in the middle-third rather than at the ends of the long bones is admittedly atypical of the majority of the reported cases, it undoubtedly represents a familial variation of osteopetrosis and not a distinct disease. Indeed, the elder boy is beginning to show the appearance of a narrow transverse line of increased density at the lower end of the femur, which has been regarded as characteristic of the first stage of the disease. The clubbing of the long bones and the deposition of dense bone at the base of the skull with secondary neurological signs confirm the diagnosis.

Ætiology.—A number of theories of ætiology have been advanced, the majority with little evidence to support them, or general applicability. Thus Robertson has drawn attention to the high vitamin-D content of the diet of his own case, but this factor does not appear to have figured at all prominently in others. From the

familial incidence of the disease, an hereditary factor is clearly operative in at least many of the cases, whilst the nature of the bone changes indicates a disturbance of calcium metabolism. That this disturbance may occasionally extend beyond the osseous system is seen from the case reports of Péhu *et al.* (who recorded the presence of large calculi within the renal pelves), of Schulze, who found deposits of calcium in the tendons, myocardium, etc., and of Alexander, who described calcification of the vessels, tendons, and skin, in a boy aged 11. The few authors who have estimated the serum calcium have obtained normal values, with the exception of Schulze, whose case showed extreme hypercalcæmia and Kopylow and Runowa who recorded a single reading of 13·1 mgm.%. Raised inorganic blood-phosphorus values have also been recorded in one or two instances, Kopylow and Runowa's patient showing 7 mgm.% on two occasions.

The theory for which there appears to be most support is that put forward by Dupont, who regards the primary condition as being parathyroid hyperactivity. Whilst it is now well recognized that parathyroid tumours are liable to result in mobilization of calcium from the bones, with consequent osteoporosis, it has also been claimed that under certain circumstances the local increase in the concentration of calcium may result in a secondary excessive deposition. Dupont based his views on the finding of a parathyroid adenoma in Péhu, Policard, and Dufourt's case at autopsy, and he also drew particular attention to the areas of rarefaction found within the sclerosed bone. These he regarded as the primary result of parathyroid hyperactivity.

Since the publication of Dupont's thesis, certain experimental observations have been made which are at least consistent with a parathyroid ætiology. Pugsley found that in rats the daily injection of parathyroid hormone at first resulted in an increased calcium excretion lasting approximately four days, which was subsequently followed by a normal or subnormal excretion. This acquired resistance to experimental hyperparathyroidism was explained by Selye as due to a proliferation of osteoblasts, which resulted in a condition closely resembling marble bones if the administration of parathyroid hormone was continued. In a recent paper, these two authors have shown that the osteoclastic reaction (osteitis fibrosa) changed over to an osteoblastic one (marble-bone formation) at the same time as the increased calcium excretion and hypercalcæmia returned to normal levels.

In the two cases reported here, the effect of daily injections of parathyroid hormone on the serum calcium and inorganic blood phosphorus was investigated. It was thought that if calcium could be mobilized from the bones by this means, it might be possible to reduce to some extent the degree of the osteopetrosis. For this purpose an initial dose of 5 units of parathormone, followed by daily doses of 10 units, were given subcutaneously in each instance. The effect on the serum calcium and inorganic blood phosphorus is shown in Charts I and II.

The blood phosphatase values (normal 10 to 20 units) were as follows :—

Edward.				Derek.			
Date			Phosphatase (units)	Date			Phosphatase (units)
9.5.34	...	...	9·6	26.6.34	...	...	12·5
12.6.34	...	...	12·7	13.7.34	...	...	11·3
20.6.34	...	...	10·6	23.7.34	...	...	10·9
26.6.34	...	...	14·2	31.7.34	...	...	10·6
23.7.34	...	...	11·8	7.8.34	...	...	8·6
31.7.34	...	...	9·8				
7.8.34	...	...	8·6				
16.8.34	...	...	12·0				

The above figures show the somewhat surprising result that the phosphatase remained within normal limits during the injection of parathormone, although there were considerable variations in the serum calcium values.

From Charts I and II it is seen that in each case there was an immediate rise in serum calcium during parathormone injection, which reached a maximum in ten

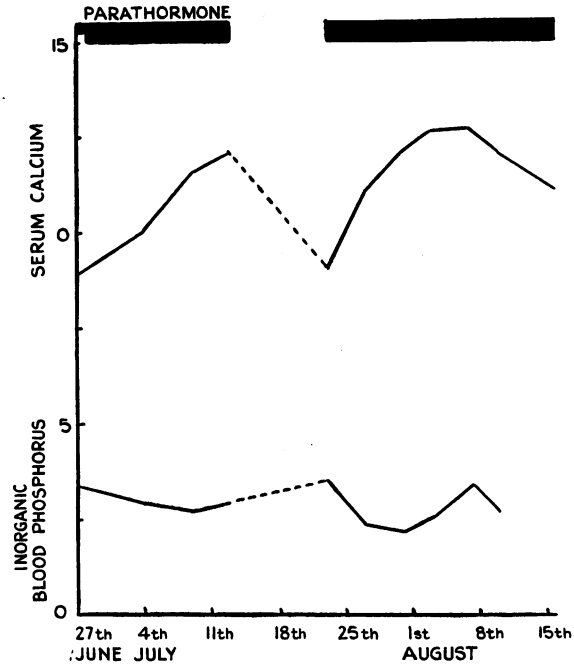


CHART I.—Effect of parathormone administration on inorganic blood-phosphorus and serum calcium (Derek).

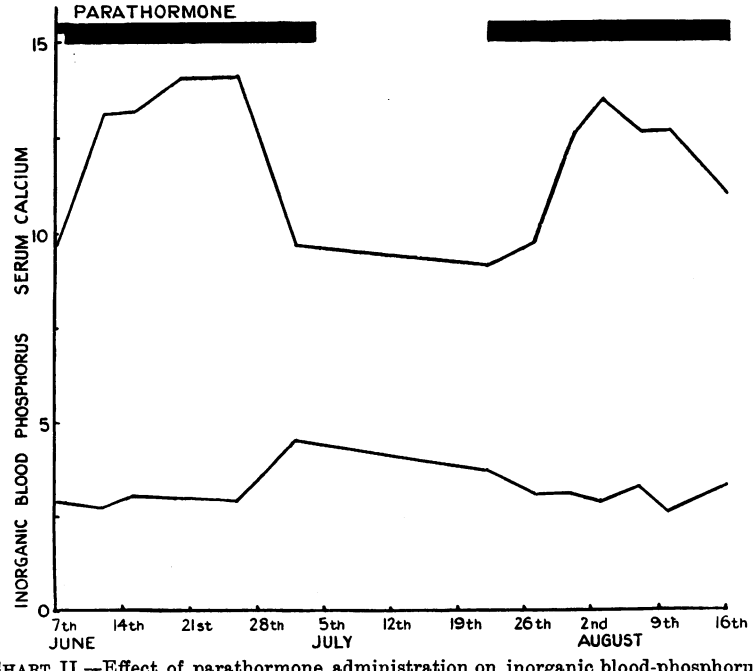


CHART II.—Effect of parathormone administration on inorganic blood-phosphorus and serum calcium (Edward).

to nineteen days, and was followed by a rapid fall, although the dosage of parathormone was kept constant. (This general form of curve corresponds with that described by Pugsley and Selye in adult rats, although the maximum rise, with a larger dose of parathormone, was reached in their experiments in a shorter period.) Although Hunter and Aub have shown that increased calcium excretion following parathyroid hormone injection is not necessarily associated with a corresponding rise in serum calcium, it was assumed from the experimental work referred to above that the fall in serum calcium in these children would be associated with a diminished calcium excretion. Parathormone administration was therefore discontinued when the serum calcium fell, since continuance beyond this point might be expected to result in increased deposition. The same effect was, however, obtained a second time in the case of Edward after a period of eighteen days, and in Derek (in whom owing to contagion the original dosage had been discontinued before the spontaneous fall in serum calcium had occurred) after a period of ten days. It appears, therefore, to judge from the serum calcium, that an acquired immunity to the injection of parathormone is produced, which is lost within a period of eighteen days if the injections are discontinued. The blood phosphorus (which was rather low at the beginning of the experiments) showed a tendency to fall as the calcium rose, and to rise as the latter fell.

It seems probable that these curves are to be regarded as a normal response to prolonged parathormone injection, since acquired immunity of this type has been described in animals.

(A control investigation at present being carried out on a mentally defective child of 1 year 11 months, with no evidence of rickets, gives the following figures:—

Date	Serum calcium (mgm. %)	Inorganic blood phosphorus (mgm. %)	Plasma phosphatase (units)
11.9.34	8·3	3·5	9·1
18.9.34	9·4	2·9	7·8
21.9.34	10·4	3·0	5·8
24.9.34	11·3	2·5	6·2
26.9.34	9·8	3·2	8·4
2.10.34	9·86	3·25	7·2
3.10.34	Parathormone stopped.		

The first estimations (11.9.34) was carried out before parathormone administration was started; it will be seen that the serum calcium was at the lower limit of normal, so that the level subsequently reached represents a considerable rise. Five units of parathormone were injected on 11.9.34, and ten units on each day following throughout the experiment.).

It is somewhat difficult to reconcile the osteopetrosis charts with an existing condition of parathyroid hyperactivity, since if the osteopetrosis were due to the patients being in an "osteoblastic" stage of hyperparathyroidism (i.e. when the activity of the parathyroids was causing deposition rather than mobilization of calcium), it would seem most probable that parathormone injection would tend to cause further deposition immediately rather than an initial *rise* in serum calcium. However, it is quite possible that a condition of hyperparathyroidism may be intermittent rather than continuously operative. This is seen in conditions of hyperinsulinism and hyperthyroidism, and appears likely in view of the alternation of transverse bands of dense sclerosis with lines of rarefaction at the ends of the long bones in many of the advanced cases of osteopetrosis, suggesting periods of varying activity. If, therefore, the patients were in a period of remission when the investigations were carried out, a normal response to parathyroid injection might be expected.

At present the most one can say is that the balance of evidence appears definitely in favour of a parathyroid origin of the disease.

I wish to thank Drs. Hutchison, Cockayne, and Donald Paterson for permission to report these cases, and Drs. Shires and Payne for the radiological and biochemical investigations respectively.

REFERENCES

ALBERS-SCHÖNBERG, H. (*Aerzt. Verein.*, Hamburg, Feb. 9, 1904), *Münch. med. Wochenschr.*, 1904, li, 365.
ALEXANDER, W. G. (with Review), *Amer. Journ. Roent. and Rad. Ther.*, 1923, x, 280.
BOYD, W., "The pathology of internal diseases," London, 1931, 571.
BRAILSFORD, J. F., "The radiology of bones and joints," London, 1934.
DUPONT, J., "L'Ostéopétrose" (*Thèse*), Lyon, 1930.
GHORMLEY, R. K., *Bull. Johns Hopkins Hosp.*, 1922, xxxiii, 444.
GOODALL, A., *Edin. Med. Journ.*, 1912, viii, 500.
HUECK, G., *Arch. f. path. Anat. u. Phys. u.f. klin. Med.* (Virchow), 1879, lxxviii, 475.
HUNTER, D., and AUB, J. C., *Quart. Journ. Med.*, 1926, xx, 123.
KARSHNER, R. G. (with Review), *Amer. Journ. Roent. and Rad. Ther.*, 1926, xvi, 405.
KOPYLOW, M. B., and RUNOWA, M. F., *Fortschr. Röntgenstr.*, 1929, xl, 1042.
KUDRJAWTZAWA, N., *Arch. f. klin. Chir.*, 1930, xlix, 658
LÉRI, A., and JOANNY, *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1922, xlvi, 1141.
PARSONS, L. G., "Diseases of infancy and childhood," London, 1933, 1560.
PÉHU, M., POLICARD, A., and DUFOURT, A., *Presse Méd.*, 1931, xxxix, 999.
PIRIE, A. H., *Amer. Journ. Roent. and Rad. Ther.*, 1930, xxiv, 147.
PUGSLEY, L. I., *Journ. Physiol.*, 1932, lxxvi, 315.
PUGSLEY, L. I., and SELYE, H., *Journ. Physiol.*, 1933, lxxix, 113.
ROBERTSON, G. E., *Journ. Ped.*, 1933, iii, 439.
SCHULZE, F., *Arch. f. klin. Chir.*, 1921, cxviii, 411.
SELYE, H., "Endocrinology," 1932, xvi, 547, and *Journ. Amer. Med. Assoc.*, 1932, xcix, 108.
WAKELEY, C. P. G., *Proc. Roy. Soc. Med.*, 1931, xxv, 145.
WEST, J. W., *Proc. Roy. Soc. Med.*, 1934, xxvii, 1269.