RICKETS WITH ALKALINE PHOSPHATASE DEFICIENCY: AN OSTEOLASTIC DYSPLASIA

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Since the introduction of better diets with ample vitamin supplements by more enlightened mothers, and the virtual disappearance of infantile rickets due to lack of vitamin D, increased interest has been aroused in similar disorders of bone growth from other causes. In studying metabolic, biochemical and renal factors, which can all play a part, our knowledge has become clearer of physiological bone growth, the mechanism whereby calcium and phosphorus are maintained at a constant level in the blood, the part played by enzymes in calcification and of how deviation of these from the normal may be a feature of skeletal disorder.

Recently a girl of 7 months came under our care with hypercalcaemia, renal insufficiency and widespread radiological evidence of 'rachitic' osteoporosis, together with periosteal changes and bizarre bone formation. The diagnosis was very puzzling and no account of similar cases in this country could be found. Investigation showed a serum alkaline phosphatase far below the level associated with an abnormal and improperly calcified matrix. Eventually references were found in the American literature to a rare disorder of skeletal growth in which hypophosphatasia appeared to be a primary factor. Clinically our case seemed to fall into this group, and bone biopsy finally produced additional confirmatory evidence.

Case Reports

Case 1.* C.A., a girl and only child (no miscarriages), was first admitted at the age of 7½ months to the Kent and Canterbury Hospital under the care of Dr. Stanley Rodgers, to whom we are indebted for the early history. Following a normal delivery (birth weight 7 lb. 4 oz.) the baby seemed to thrive for a few weeks, but then began to vomit intermittently and ceased to gain weight regularly. Breast feeding was changed to dried milk at 3 months,

when cod liver oil was also introduced, but the symptoms gradually increased until she vomited all her feeds, became restless, then drowsy and so dehydrated that parenteral fluids were required (weight at 7½ months was only 10½ lb.). At no time was there any sign of infection and the stools were normal. Temperature was 100° to 103° F.

One of the most striking features was a widely open, tense, bulging anterior fontanelle, but the cerebrospinal fluid was not under pressure and quite normal. The skull circumference (16½ in.) was not increased. A subdural haematoma was suspected and it was at this stage that she was transferred under our care.

After an x-ray examination of the skull it was realized that some gross bone disorder was present. Obvious enlargement of the epiphyseal region of the wrists, knees and ankles, and 'beading' of the costochondral junctions suggested that the condition was some form of severe rickets, which was supported by further radiographs of the skeleton, although they were not entirely typical. Other clinical findings were rather blue sclerotics, prominent eyes and generalized mild pigmentation.

Radiological Report. Dr. L. G. Blair and Dr. G. N. Weber, reported as follows:

GENERAL. The skeleton was poorly developed for the age (7½ months); there was marked demineralization at the metaphyses and the growing margins of all the bones, producing an irregular, ill-defined margin and in many regions a faintly speckled ghost image of the subepiphyseal region, which was presumably poorly calcified osteoid tissue.

LONG BONES. The mid-shafts were normal. The metaphyses showed an irregular margin, distal to which was a zone of poorly calcified osteoid. In the femur these zones were sharply demarcated, but elsewhere this distinction was less marked. No cupping was present. The epiphyseal lines were irregularly widened. Epiphyseal development was slightly retarded. (Bone age at the wrist was 3 months.)

Epiphyseal calcification was irregular, being less dense centrally in most cases, but the cortex was affected in the same way. Early irregular periosteal new bone formation was seen along the shafts of several bones, particularly the tibiae and humeri (Fig. 1).

* This case was shown to a meeting of the Section of Paediatrics, Royal Society of Medicine, in January, 1954, and a brief description appeared in the *Proc. roy. Soc. Med.*, 1954, 47, 541.

FIG. 1.—Radiograph of the lower limbs of Case 1 at the age of 7½ months, showing irregular calcification of the metaphyses and epiphyses, zones of poorly calcified osteoid at the lower ends of the femora and early periosteal new bone formation along the shafts.

FIG. 3.—Radiograph of the lower limbs of Case 1 at 11 months, showing improved but still disordered ossification with cupping of the bone ends

FIG. 2.—Radiograph (ventriculograph) of the skull of Case 1 at the age of 8 months, showing widened sutures, a bulging anterior fontanelle and defective ossification.

FIG. 4.—Increasing but irregular calcification in Case 1 at just over 1 year of age, with striking periosteal new bone formation along the shafts.

FIG. 5.—The skull of Case 1 at 20 months is now well calcified, but there is premature closure of the sutures, producing abnormal growth of the vault.

FIG. 7.—The curious appearance of Case 1 at 14 months with deformity of the skull as a result of craniostenosis.

FIG. 6.—Diagram of the serological investigations over a period of 11 months.

RIBS. The rib ends, which were demineralized and ill defined, were slightly expanded.

SKULL. There was defective ossification throughout, resulting in widening of the sutures at the base and vault, and irregular growing margins of the flat bones. Scattered flecks of calcification in the suture lines were presumably attempts at ossification in the osteoid tissue. There was slight bulging of the enlarged anterior fontanelle (Fig. 2).

PELVIS, SCAPULAE, SPINE. Similar changes with fluffy bone margins and patchy mineralization were present throughout.

During the months of June, July and August, 1953, slowly increasing changes of patchy demineralization appeared at the bone ends, with extension of the periosteal thickening to most of the long bones. The epiphyses became less dense and one or two of the carpal centres had almost completely disappeared.

By September mineralization was improving throughout (Fig. 3). Periosteal thickening in the long bones and ribs had increased and ossification at the sutures had improved. The skull had a curious shape with bulging of the vertex and deficient growth of the frontal region, as the coronal and squamosal sutures were beginning to close.

In October there was further improvement (Fig. 4). There was now well-marked cupping of the bone ends, well seen in the knees and ribs.

On May 24, 1954, when the child was 20 months old, development was still retarded and there was considerable general porosis. The metaphyseal new bone was now consolidating. The metaphyses remained cupped and markedly irregular. Epiphyseal development was slightly retarded. (The bone age at the wrist was 15 months.)

The skull was well calcified; the anterior fontanelle and coronal and squamosal sutures had prematurely closed, causing restricted growth of the vault anteriorly and a prominence at the vertex (Fig. 5).

A trephine hole had been made in the right parietal region in the treatment of subdural haematoma on June 17, 1953. This measured 17 mm. across on films dated June 26, 1953, and had progressively increased in size to 23 mm. on the films of May 24, 1954. This is a reversal of the usual slow disappearance of a trephine hole.

Serological Investigations. These, over a period of 11 months, are presented in Fig. 6. The chief findings were a low serum alkaline phosphatase level, a raised serum calcium level falling to normal later, a low serum phosphorus level with a subsequent rise to normal and a persistently high blood urea concentration, with a normal cholesterol level. The serum protein was normal in total and albumin/globulin ratio, and electrophoresis produced a standard pattern. The acid-base balance was normal except for brief periods of acidosis. The blood Wassermann, P.P.R. and Kahn tests and the cerebrospinal fluid Wassermann reaction were negative.

Blood Counts. Blood counts revealed a severe normochromic anaemia (50% Hb) soon after admission to hospital, necessitating a blood transfusion; thereafter

there was a moderate anaemia (70% Hb), from which the infant eventually recovered. An initial leucocytosis (17,600 W.B.C. per c.mm.) with a normal differential count was present, but before long this disappeared.

Urine. Most specimens of urine contained some pus cells and a trace of albumin; usually they were sterile, but at times a light growth of *Bact. coli* was obtained. The reaction was on the whole acid; amino-aciduria and glycosuria were absent. Urea clearance at the age of 1 year in two successive specimens was 40.9% (standard clearance) and 56.2% (maximum clearance), which, together with the constantly raised blood urea and poor excretion of dye on pyelography, indicated renal impairment. There were no retinal changes at this period.

The urine was again examined by Dr. Charles Dent 22 months later, and he reported as follows:

'The standard chromatogram showed a rather weaker pattern than for the previous urine examined on January 25, 1953, as if to suggest that there was an increase in renal damage since that date. As far as we could see from this, however, the pattern was normal. In view of our findings with the urine from McCance's case we have done a further chromatogram, over-loaded five times, so as to show the weaker spots more easily. This now makes it quite clear that there is a definite abnormality in this urine, for the over-loaded chromatogram showed a good spot corresponding to ethanalamine phosphate, not very strong but nevertheless quite pathological. It is possible that this was present in the previous urine but was not detected as we only did a normal chromatogram.'

A positive calcium and phosphorus balance was demonstrated by Dr. Payne and Dr. Wilkinson (Table I),

TABLE I
CALCIUM AND PHOSPHORUS BALANCE

	Period = 3 days Calcium () = daily mg.	Phosphorus () = daily mg.
<i>Intake (by analysis)</i>		
Feeds	3,486 mg. (1,162)	3,087 mg. (1,029)
Rejects	439 mg.	455 mg.
	3,047 mg. (1,016)	2,632 mg. (877)
<i>Output</i>		
Faeces	2,026 mg. (675)	1,145 mg. (381)
Urine	268 mg. (89)	1,064 mg. (355)
	2,294 mg. (764)	2,209 mg. (736)
<i>Balance</i>		
Calcium	- 753 mg. (251)	Phosphorus - 423 mg. (141)

and the Sulkowitch test showed a normal precipitate, except after a three-month course of vitamin D in high dosage, when for a time there was evidence of excessive urinary calcium excretion, which soon reverted to normal when this treatment was stopped. It was at this time too that the only high blood inorganic phosphorus readings were obtained (6.7 and 6.2 mg. %), presumably due to renal insufficiency.

The early clinical picture was further complicated by the actual presence of a right-sided subdural haematoma. This diagnosis had been suspected originally, but rejected in view of a negative subdural tap and of all the other

FIG. 8.—Photomicrograph of biopsy from tibia on August 12, 1953 ($\times 60$, haematoxylin and eosin stain) to show the abnormal organic matrix at the margins of the bone trabeculae and the paucity of osteoblasts.

FIG. 9.—Photomicrograph of biopsy from tibia on December 2, 1953 ($\times 60$ haematoxylin and eosin stain) to show the bone trabeculae and the osteoblasts approaching normal. The seams of abnormal matrix have disappeared.

findings. When, however, left-sided fits suddenly arose, and a ventriculogram showed some displacement of the ventricular system, craniotomy was performed and a thin film of black blood clot was removed. It became clear nevertheless that the bulging fontanelle, which remained, had no connexion with this complication.

During the following six months of the child's stay in hospital progress was slow; she vomited at least one feed almost daily, anorexia was marked and gain in weight accordingly unsteady. Radiological examination failed to demonstrate any oesophageal lesion or delay in gastric emptying. The skull circumference showed little increase in size and at 14 months it still remained $17\frac{1}{2}$ in., growth taking place largely in a vertical direction in the posterior region, giving the child an oxycephalic appearance, further enhanced by rather prominent eyes (Fig. 7). The anterior fontanelle continued to bulge until it eventually closed at 16 months, and the same tenseness of the burr hole has continued throughout.

After the infant had been in hospital for three months it was decided to try the effect of vitamin D in high dosage, 10,000 units rising to 50,000 units daily. Improvement in her general condition appeared to coincide with this course; she became happier and more lively, a slightly better appetite developed, the vomiting eventually ceased and there was a steady gain in weight. At the same time the serum calcium fell to normal and calcification of the bones began to be more satisfactory. The treatment was stopped after about three months, as the serum calcium level showed signs of rising again and the serum phosphorus level was also noticed to be higher than normal.

The child has been examined periodically during the last year and has progressed slowly, but epiphyseal enlargement is still marked at the wrists and ankles, and a 'rosary' is palpable at the costochondral junctions.

Although she has now reached the age of 2 years, she cannot stand or bear any weight on her legs. On the other hand she has begun to talk, and she is an exceptionally bright and amiable little girl with fair intelligence. The blood pressure appears to be high, between 120 and 140 mm. Hg (systolic), and the blood urea level remains raised but is tending to fall towards normal (last record, 46 mg. per 100 ml.). For the last year the blood calcium level has been normal, but it rose again to 12.6 mg. per 100 ml. after a further course of vitamin D in high dosage (Fig. 6), when an increased excretion of calcium in the urine was also discovered. A low blood phosphatase level has persisted throughout. Radiological progress of bone growth has already been recorded.

Recently the child was again admitted to hospital for reassessment. Her general condition was good, but it was obvious from the increasing tension at the site of the old burr hole and the curious shape of the skull that craniostenosis had developed to a dangerous degree. The appearance of papilloedema confirmed this fear and a linear coronal craniotomy was successfully performed to relieve the increased intracranial pressure.

Meanwhile the mother was approaching term in her second pregnancy, but no radiological evidence of a similar bone disorder was found in the foetus.*

Final proof of lack of phosphatase was found at a bone biopsy, carried out on three occasions.

Bone Biopsy. The composite histological report of three biopsies of bone taken from the skull at 8 months and the upper end of right tibia at 10 and 14 months is as follows:

The first two biopsies from skull and right tibia, respectively, showed comparable features. The trabe-

* Post-natal progress is reported under 'Heredity' p. 275.

culae consisted of a slender central core of lamellar and woven bone and a conspicuous marginal zone of partially calcified connective tissue matrix, without any of the orderly architecture of osteoid seams. There was paucity of osteoblasts and osteoclasts at the margins of the trabeculae, and osteocytes too were only moderately well represented. The marrow showed no fibrosis (Fig. 8).

The third biopsy showed a greater approach to normal bone. The abnormal calcified connective tissue matrix had disappeared, the bone trabeculae were wider and rows of osteoblasts flanked the margins of the trabeculae. The uneven staining of the newly formed bone and the smaller size and number of osteoblasts were still somewhat abnormal features (Fig. 9).

Quantitative analysis of bone phosphatase was carried out by Dr. W. W. Payne and Dr. R. H. Wilkinson (Table 2).

TABLE 2
QUANTITATIVE ESTIMATION OF BONE PHOSPHATASE*

Case 1 (C.A.)	Normal Control (Necropsy)
Tibial cortex (quenched at -40° C.) 150 N.P.P. units/kg. wet tissue	530 N.P.P. units/kg. wet tissue
Calvarium Tibial periosteum 150 N.P.P. units/kg. wet tissue	560 N.P.P. units/kg. wet tissue

* Method of Bessey, Lowry and Brock (1946). *J. biol. Chem.*, 164, 321.

Histochemical preparations and biochemical estimations suggested a reduction in phosphatase activity in the excised bone and periosteum.

The changes observed indicated a defect in the process of ossification (dysostosis), manifesting itself in the production of an abnormal organic matrix and in quantitative and qualitative deficiency of osteoblasts.

The mother and father were investigated but no similar deficiency was found.

	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Alkaline Phosphatase (King-Armstrong units)
Mr. A. ..	10.4	3.8	5.7
Mrs. A. ..	9.9	1.9	5.6

About this time another case came to our notice under the care of Dr. R. L. Langley, to whom we are indebted for allowing us to include it in this report.

Case 2. S.H., a girl (birth weight 8 lb. 9 oz.), the first child of young healthy parents was brought to hospital at the age of 6 months because of vomiting and failure to thrive (weight at 6 months, 12 lb. 6 oz.). The infant had been breast fed with National dried milk complements until the age of 3 months, when she was weaned on to full-cream National dried milk, subsequently changed to Cow and Gate full-cream dried milk without any improvement in the vomiting, which was irregular and never immediately after feeds. Cod liver oil had been offered but refused, and no other vitamin D supplement

was given except the standard amount contained in the dried milk.

On examination, enlargement of the epiphyseal end of the forearms and the costochondral junctions suggested at once the presence of rickets. There was marked dorsal kyphoscoliosis and a tendency to calcaneo valgus. In addition certain other puzzling features were noticed. The anterior fontanelle was not only widely patent but was also remarkably tense (skull circumference 17 in. at 6 months). Since there was also unexplained fever for the first two weeks in hospital, ranging between 101° and 104° F., meningitis was suspected, but repeated lumbar punctures yielded a normal cerebrospinal fluid. The pyrexia did not respond to penicillin but appeared to subside fairly rapidly after chloramphenicol. Restlessness with a continual rotary movement of the hands and feet was another curious symptom. The radiological changes in the bones resembled closely those seen in Case 1.

Radiological Report. Dr. R. L. Hill reported as follows:

GENERAL. The skull showed defective ossification in

FIG. 10.—Radiograph of upper limbs of Case 2 at 6 months of age, showing the same ossification defects and deposition of periosteal new bone. Osteoporotic fractures are visible at the lower ends of both ulnae.

the base and vault. There were extensive bony changes throughout the skeleton, with profound disturbance of ossification in the metaphyses of the long bones and pelvis (Fig. 10). The ribs showed periosteal new bone. The metacarpals appeared normal. The appearances suggested a chondro-osteodystrophy with superadded rachitic changes.

SKULL. On June 12, 1953, when the baby was 8 months old, there was still defective ossification of the cranial vault, but considerable improvement since the previous examination.

LONG BONES. Marked improvement in bone detail was also seen at the left elbow, with ossification in the osteoid tissue in the metaphyses. The same could be said of the left knee and the general picture was that of healing rickets.

SKULL. On two occasions in July, 1953, when the baby was 9 months old, advancing calcification of the bones of the cranial vault was visible. There was, however, a generalized increase in the convoluted markings.

LONG BONES. In the long bones improvement at the left elbow continued and the bones were approaching normality.

In October of the same year improvement in ossification was maintained. The anterior fontanelle was still

very wide and the lacunar pattern in the skull persisted.

LONG BONES. On February 10, 1954, when the child was aged 15 months, there was further improvement; the bones of the upper limbs were now normal and those of the lower limbs were nearly so.

SKULL. The cranial vault had ossified further, but there was still a bulge in the region of the anterior fontanelle and increased lacunar markings. The base remained rather short and steep and there was a linear plaque of calcification in the suprasellar region.

On August 23, 1954, the child now being 21 months old, the appearance of the long bones was normal except at the lower femoral metaphyses, where there were well defined, elongated, translucent areas extending up the femoral shafts. The vault of the skull was asymmetrical, with relative flattening of the frontal and left parietal regions, where the convolutional markings were still prominent. There appeared to be partial fusion of the coronal sutures.

Serological Investigations. These gave the following results: a normal serum calcium level, 10.8 mg. per 100 ml., and blood inorganic phosphorus level, 4.8 mg. per 100 ml. The serum alkaline phosphatase, 7.3 King-Armstrong units per 100 ml., was low, considering the deficient calcification of the bones. Wassermann reactions of both parents and the child were negative. The urine was normal; there was no anaemia and the total and differential white cell counts were normal. During the infant's stay in hospital she had two infections, tonsillitis with otitis media and a right lower lobe pneumonia, which responded well to aureomycin.

Treatment adopted was 'radiostoleum' in moderately high dosage, 30 minims daily. On this regime progress was maintained, appetite improved on a mixed diet and a steady gain in weight was achieved (14 lb. at the age of 9 months). There was also radiological evidence of improved ossification. For a time the 'radiostoleum' was dropped to 20 minims daily. Within a fortnight clinical deterioration was noticed; general irritability with purposeless movement of the hands recurred and the baby was reluctant to sit up. When the original dose of vitamin D was resumed, these symptoms rapidly disappeared. Meanwhile, the anterior fontanelle was gradually becoming smaller, although it still felt rather tense, and the surrounding bones of the skull were raised and the area was rather like the crater of a volcano. At the age of 14 months the fontanelle was closed, the baby was sitting up well, trying to stand and the mentality was normal.

The child is now nearly 2 years old and her general condition is excellent; the blood urea is 28 mg. per 100 ml., serum phosphorus, 3.7 mg. per 100 ml., blood calcium, 10.7 mg. per 100 ml., but the serum alkaline phosphatase level remains low, 3 King-Armstrong units per 100 ml. Radiological progress of ossification has already been recorded in the series of x-ray reports.

A third case has since been brought to our notice by Sir Thomas Fairbank. She is under the care of Mr. J. S. Maxwell, and we are grateful to him for allowing us to include the case here.

FIG. 11.—Radiograph of the upper limbs of Case 3 at the age of 2 years, showing a wide zone of poorly mineralized osteoid and slight periosteal reaction over the shafts.

Case 3. M.M. was a girl, aged 2½ years. At the age of 2 years the parents first noticed that the legs were weak, and that she had knock knees. It had become worse when she began to walk at about this time. On examination the child was heavy, had a large globular head, poorly developed lower limbs and gross symmetrical genu valgum. She walked with difficulty and had a rolling gait. At the age of 2 years the serum calcium was raised to 12.1 mg. per 100 ml. and the serum phosphatase was low, 2.4 King-Armstrong units per 100 ml., and a month later 6.3 units, with a blood urea of 64 mg. per 100 ml. The Wassermann and Kahn reactions were negative. The urine was normal except for evidence of increased calcium excretion (Sulkowitch).

Radiological Report. The x-ray appearances were as follows:

LONG BONES. On September 15, 1953, when the child was 2 years 1 month old, slight general demineralization was present. The metaphyses showed a wide zone of poorly mineralized osteoid, fairly well-demarcated from the normal looking shaft by an irregular line of sclerosis. Slight cupping was visible with some periosteal reaction over the shafts of fibulae and ulnae. The epiphyses were poorly but evenly mineralized. Bone age was within the normal limits (Fig. 11).

SKULL. The vault was large and slightly thinned, with marked increase in convolutional markings throughout. The pituitary fossa was normal. A small prominence was present at the bregma. All vault sutures appeared fused (Fig. 12).

RIBS AND CHEST. On January 12, 1954, the child, now aged 2 years 5 months, the anterior ends of the ribs were poorly mineralized, ill defined and slightly cupped. Irregular mineralization of osteoid was seen at the growing points in the upper humeri and scapulae.

LONG BONES. By June 22, 1954, when the child was 2 years 10 months old, considerable growth had occurred at the bone ends. The metaphyses were better mineralized, but deep zones of irregular ossification

remained. There was still slight cupping at several of the metaphyses and also bilateral genu valgum deformity due to asymmetrical growth.

Bone age had not appreciably advanced since September 15, 1953.

SPINE AND PELVIS. The bone texture was mottled and the growing margins were fluffy at several points. The anterior ends of the ribs were slightly expanded and more cupped than previously, but now clearly defined.

The child's teeth are quite normal and she is above average in intelligence. Walking continues to be difficult. For the last eight months she has been on 50,000 units of vitamin D daily. There is one older brother aged 8 years, who is healthy and whose bones appear normal radiologically. His serum alkaline phosphatase level of 12.6 units per 100 ml. is normal. No other member of the family has suffered from any bone disease.

Two of these three cases are strikingly similar in the early onset of vomiting, their failure to thrive and anorexia, the clinical and radiological appearance of the bones, tense fontanelle and low alkaline phosphatase of the blood. Case 1 was apparently the severer of the two and was complicated by hypercalcaemia and renal damage. Case 2 improved fairly rapidly, and both clinically and radiologically was approaching normal when last examined. Case 1, on the other hand, still has radiological evidence of defective bone growth; the blood urea level remains high, although the serum calcium has dropped to normal apart from a fresh rise recently after further vitamin D therapy. Case 3 had no generalized symptoms during infancy, despite the slight rise of serum calcium recorded later, which seemed to be sufficient to cause some impairment of renal function. It was an orthopaedic disability that brought her to the doctor. She has shown some improvement, but bone growth has not yet become normal.

Fusion of the skull sutures and craniostenosis are a feature in all three and a persistent low alkaline phosphatase level appears to be a common defect.

Review of the Literature

Occasional reports of a disorder like the one described have appeared in the American medical journals. Rathbun (1948) first directed attention to an osteodystrophic condition in which serum alkaline phosphatase was deficient. This he found in a male infant of 3 weeks who died at the age of 1 year. Deformities of the wrists, bowing of the legs and beading of the costochondral junctions were present. The skull bones consisted merely of four rounded plaques in the frontal and parietal areas, and the remainder of the vault 'felt like a balloon filled with

FIG. 12.—Radiograph of the skull of Case 3 at 2 years of age, showing a thin vault with increased convolutional markings and fused sutures throughout.

water'. Serum calcium was raised at first (13.6 mg. per 100 ml.), later falling to a normal level, while the serum phosphorus remained high throughout (6.9 to 5.2 to 10.5 mg. per 100 ml.). The serum alkaline phosphatase was exceptionally low (0.0 to 0.7 Lowry-Bessey units or 0.0 to 5.1 King-Armstrong units), and at necropsy many tissues were found to have a greatly reduced alkaline phosphatase content as well. X-ray examination during life showed marked lack of calcification of the skull and vertebrae, and ossification defects with 'flaring' at the costochondral junctions and at the metaphyseal ends of the long bones. Fractures were also seen in the radius and ulna. Anaemia was present, necessitating a transfusion. Various forms of treatment were tried without avail, including vitamin D supplements, and the infant died after a series of convulsions.

The main findings at necropsy were tubular lesions in the kidneys with no evidence of calcinosis, suggesting a low-grade inflammatory reaction. Changes in the long bones resembled severe rickets. In the skull the framework appeared to be normally laid down in the form of osteoid tissue, periosteum, osteocytes, osteoblasts and organic intercellular material, but lacked calcification except in the four plaques previously mentioned.

Schneider and Corcoran (1950) described two brothers, aged 10 and 13 years, with bilateral genu valgum. Radiographs revealed increased density of the metaphyses with areas of rarefaction, irregular epiphyseal lines in the long bones and rarefaction in the scapulae. The serum calcium was raised and serum alkaline phosphatase less than 1 Bodansky unit (4 King-Armstrong units) in both patients. Both parents had low serum alkaline phosphatase levels.

Sobel, Clark, Fox and Robinow (1953) reported a further case, a girl of 19 months, who showed clinical and radiological evidence of rickets, premature loss of milk teeth and irregular calcification of the permanent teeth. The serum calcium and phosphorus levels were normal, but here again the serum alkaline phosphatase was abnormally low, 0.8 to 1.64 Lowry-Bessey units (5.8 to 11.97 King-Armstrong units). Biopsy of the liver and a rib also showed an alkaline phosphatase content far below normal. The father of this patient had a low serum alkaline phosphatase level, and two of the child's near relations had skeletal abnormalities described as dyschondroplasia.

The most hopeful line of treatment in this case seemed to have been high vitamin D dosage. This produced some improvement in bone calcification and a temporary rise of serum alkaline phosphatase to three times its former level, although it still

remained abnormally low. Nevertheless the treatment had to be abandoned when signs of calcium intoxication appeared—anorexia and vomiting—and the serum calcium rose to 17 mg. per 100 ml. Renal function was not impaired. General progress was reported as satisfactory, but the skeletal disorder continued.

The authors mention five other cases, including two siblings who died with the same disorder; in four, one or both parents had low serum alkaline phosphatase levels.

Other probable examples of this disease should be added. Anspach and Clifton (1939) published a case which they regarded as hyperparathyroidism. This was a girl of 4 years who at 3 months was suffering from anorexia, failure to gain weight, polyuria, tender limbs and swelling near the joints. The skull felt soft in the occipital region; the anterior fontanelle bulged markedly without other signs of increased intracranial pressure. At 9 months the sagittal suture became elevated into a ridge. The radiological changes were 'cupping' at the metaphyseal ends of the long bones, with imperfect ossification and a thin cortex. The bony tables of the skull were thin; digitations and many fracture lines were present.

The serum calcium was raised to 16.2-14.5 mg. per 100 ml., the phosphorus was low, 2.3-3.7 mg. per 100 ml., and the serum alkaline phosphatase was 12 units, falling later to 2 Bodansky units (8 King-Armstrong units). At 2 years the condition had deteriorated; the child only weighed 15 lb.; there was hypotonia, prominence of scalp veins and some proptosis. The head felt soft and nodular, the fontanelle was bluntly cone-shaped and calcification of the skull and long bones was grossly deficient. Renal function was not greatly impaired, although the blood urea was slightly raised (48.9 mg. per 100 ml.) and the blood cholesterol level was high (243 mg. per 100 ml.).

By the age of 4 years there was marked physical improvement, except for blindness which had developed, and the bones had almost completely become recalcified. The serum calcium and phosphorus had both reached a normal level but the alkaline phosphatase was still low, 1.5 Bodansky units (6 King-Armstrong units). The authors believed they had cured the condition by x-ray irradiation over the parathyroid region, but this seems very doubtful, and as operation had been refused, hyperparathyroidism was never established.

Chown (1936) described a case which he labelled 'renal rickets and dwarfism', in which the pituitary gland was thought to be implicated. Hypercalcaemia was present, but no mention is made

of the level of alkaline phosphatase. Radiologically all the bones of the skeleton showed evidence in varying degree of imperfect calcification, similar to the condition we are considering, and it may well have been another example.

The most recent reference to this disease is by Engfeldt and Zetterström (1954), who describe a fatal case at 10 months of age with marked renal impairment. She was the second child of healthy parents with no relevant family history. She was given 1,000 units of vitamin D from birth and progressed satisfactorily to the age of 3 months. At this stage anorexia and vomiting started, she became hypotonic and ceased to gain weight. At the age of 5 months she was found to have a skeletal disease resembling rickets with maximal involvement of the skull. Her systolic blood pressure was elevated. Investigations showed a reduced urinary concentration, a raised non-protein nitrogen level, mild hypercalcaemia and a lowered serum alkaline phosphatase. At 9 months a marked thoraco-lumbar kyphosis appeared.

There were repeated upper respiratory infections and at 10 months she died of pulmonary and cardiac failure.

The findings at necropsy were of a generalized retardation of growth of the skeleton, with inhibition of the remodelling of bone. There was abundant formation of an abnormal osteoid matrix and osteoblasts and osteoclasts were reduced in number. Alkaline phosphatase activity of the bone was low. There was also nephrocalcinosis with fibrosis.

Discussion

A fairly clear-cut syndrome emerges from a study of our three cases, comprising severe skeletal dysplasia associated with a low serum alkaline phosphatase. Hypercalcaemia is commonly present with a positive calcium and phosphorus balance. There may be impairment of renal function. Vomiting, anorexia, and failure to gain weight are the main features and sometimes fever, symptoms no doubt of the hypercalcaemia. Rickets is often suspected at first, but the early age of onset, the tense bulging fontanelle, atypical radiological changes, peculiar histological pattern and, above all, the low alkaline phosphatase level cannot be reconciled with this diagnosis. A hereditary factor seems to be present in some of the reported cases. The disorder can be expected to take a favourable course in most instances. Eventually bone calcifies, symptoms abate, and blood calcium and phosphorus levels return to normal. On the other hand, the serum alkaline phosphatase level remains low and there appears to be no guarantee that the kidneys will fully recover from any damage they may have

sustained. A fatal prognosis is usually associated with extremely low levels of serum alkaline phosphatase, hypercalcaemia with resulting severe renal damage and an advanced state of the disorder early in infancy. The condition has, in fact, been diagnosed radiologically before birth, when a previous sibling has had the disease and died from its effects. (McCance and Fairweather, 1954.) Early craniostenosis may also prove a real danger to sight.

In the differential diagnosis several disorders have to be considered which bear some resemblance to the condition we are discussing, although they show striking differences in their clinical behaviour and their biochemical, radiological and histological abnormalities. Somewhat similar bone lesions with periostitis are seen in congenital syphilis, but serological tests for this infection have been consistently negative. Hyperparathyroidism is a diagnosis readily advanced whenever some peculiar rarifying bone disease is associated with hypercalcaemia, but a high rather than a low serum alkaline phosphatase level would almost certainly be present, and there would also be evidence of increased phosphorus excretion in the urine.

The radiological appearances of dyschondroplasia (Ollier's disease) is hardly comparable and metaphyseal dysostosis is not associated with a low plasma phosphatase, though hypercalcaemia is present. The same can be said of leukaemia and myelomatosis, which in any case can be readily excluded by marrow puncture.

There are not many disorders in which the serum alkaline phosphatase level is reduced. It has been reported in scurvy (Smith, 1933; Schwachman, 1941), hypothyroidism (Talbot, Hoeffel, Shwachman and Tuohy, 1941) and rarely in achondroplasia, osteogenesis imperfecta (Hansen, 1934) and severe malnutrition (Talbot *et al.*, 1941). In all these conditions the deficiency is moderate, and in scurvy and hypothyroidism is rapidly overcome with appropriate treatment. Much lower levels are found in the syndrome we are describing and the deficiency may almost be complete as in Rathbun's case. No treatment has been found capable of reversing this apparent congenital defect.

Phosphatase and Ossification. The exact role played by alkaline phosphatase in bone formation is still uncertain, but there is little doubt that adequate amounts are essential to ensure normal skeletal development. Recent evidence suggests that phosphatase is more concerned with the production and maturation of the protein matrix of osseous tissue than with the precipitation or crystallization of bone salts in it (Bourne, 1943a and b, 1948; Siffert, 1951;

Pritchard, 1952). In mature bone phosphatase is found in the endosteum and in the inner layer of the periosteum. It is present in the superficial, osteocytes and in recently deposited bone matrix, but disappears from these regions as they grow older. The mesenchyme destined to form membranous bone in the developing embryo also contains phosphatase, but it only appears in cartilage just before ossification, first in the nuclei and then spreading to the cytoplasm and the matrix. Periosteal osteoblasts appear to go through a cycle of phosphatase activity in growing bone, which they retain when they become young osteocytes surrounded by bone matrix. As they become older they lose their phosphatase, but under certain circumstances, particularly in bone injuries and repair, they may show signs of renewed activity. Osteoclasts also contain phosphatase (Bourne, 1954).

The histology in Case 1 of the skeletal disorder we are now describing demonstrated a markedly defective bone matrix, which was represented by a disorderly architecture of fibrous tissue, few osteoblasts at the margins of the bone trabeculae and amorphous calcification. The histological features suggested a primary defect in the production of osteoblasts, with a resulting lack of sufficient phosphatase, which in turn prevented the formation of a proper template and matrix in which normal ossification could proceed. This theory appears to fit in best with the modern view of bone growth which has just been described.

Further evidence was provided by the behaviour of the trephine hole in the parietal region of the skull. Normal repair in this region depends on an adequate production of phosphatase, which first appears with large numbers of polymorphs and fibroblasts, and later in association with osteoblastic activity and the formation of calcified osteoid. In our case there was little sign of healing 14 months after the operation, and radiologically, in fact, the diameter of the burr hole had increased with growth of the skull.

Heredity. In the three cases we have studied the parents were healthy and in one (C.A.), where tests were possible, there was no suggestion of hypophosphatasemia in either the mother or father. All three were first children and C.A.'s unborn sibling appeared to have normal bone development on radiological examination. After birth, at 6 weeks of age, a radiograph of the long bones was normal, but the serum alkaline phosphatase was at the low level of 4.5 to 7.6 units per 100 ml., and Dr. Dent was able to demonstrate the same abnormal amino-acid, ethanolamine phosphate, in the urine as in the

affected sister. Serum calcium was 11.2 mg. per 100 ml.

The literature contains several accounts of the same disorder in other close members of the family, or a familial trait with low phosphatase blood levels (Schneider and Corcoran, 1950; Sobel *et al.*, 1953). Premature loss of teeth has been noted in some, but this was not a feature in our cases. No definite conclusions can yet be drawn on the genetics of the disorder.

There is no evidence of any teratogenic influences, either in the form of an infection, the action of a toxic agent or vitamin deficiency in the mother during pregnancy.

Radiology. The main defect appears to be abnormal patchy calcification at the metaphyses and growing edges of the bones, producing an irregular, ill-defined margin. This varies in degree; in some the whole skeleton is involved, in others certain regions which are not the growing points escape, as for example the upper end of the femur in Case 3. In the long bones the metaphyses are more severely involved than the epiphyses, but here as well calcification is abnormal. Bowing may be present and the rib ends are expanded, demineralized and ill defined. The periosteum is elevated due to early irregular formation of new bone. This and the absence of cupping at first at the growing ends of the bones give the x-ray picture a different appearance from that of rickets.

The Skull. Osteoporosis is particularly well marked in the skull. Calcification is so disorganized in this region that growth does not keep pace with that of the brain and the enlarged anterior fontanelle bulges. At first the sutures are widely separated, but later in the absence of normal growth at the margins, premature fusion of some of the sutures takes place, presumably due to amorphous calcification. This results in marked asymmetry of the skull with disproportionate growth, usually of the posterior part of the vertex, and a beaten silver appearance of the rest of the cranium. The anterior fontanelle finally closes later in a heaped-up prominence. It is interesting to note that craniostenosis has been reported in a case of vitamin D-resistant rickets (Coleman and Foote, 1954), possibly giving further support to the view that cessation of normal growth at the suture lines is the decisive factor.

Biochemical Changes. Deficient production of alkaline phosphatase, which is reflected by the low level in the blood, is not limited to the skeleton but is present in all tissues in which it is normally found

(Rathbun, 1948; Sobel *et al.*, 1953). No excessive loss has been discovered in the urine (Sobel *et al.*, 1953), nor has any increased excretion in the faeces or bile been established.

A raised serum calcium level was present in two of our cases (C.A. and M.M.) and in three of the four cases quoted in the literature in whom it was estimated. A possible explanation of the hypercalcaemia is that calcium is piling up in the blood because of the reduced ability of the skeleton to form normal bone salts.

There is little doubt that renal insufficiency, and the raised blood urea which resulted, were due to the hypercalcaemia, and Rathbun (1948) did in fact find plugging of the collecting tubules, with casts and a surrounding low-grade inflammatory reaction. It is also known that hypercalcaemia from any cause can result in renal damage.

Treatment and Prognosis. Various forms of therapy have been attempted. The only one which seems to be of any avail is vitamin D in high dosage. This seems to encourage calcification. Nevertheless the blood phosphatase level continues to remain low indefinitely, despite the fact that vitamin D₂ has been found to activate alkaline phosphatase (Zetterström and Ljunggren, 1951). This again may well be the result of a primary osteoblastic deficiency. Although bone growth improves, radiological abnormalities persist in some cases, and defective bone formation is well illustrated in cases where osteotomies have had to be performed later to correct orthopaedic deformities (Schneider and Corcoran, 1950). Whenever high vitamin D therapy is employed, careful watch must be kept for toxic reactions, which can easily develop and may call for reduction in dosage. The ultimate fate of the skull has already been recorded and the danger of craniostenosis impairing vision has been emphasized.

The prognosis seems to depend mainly on three factors: the age at onset of symptoms, the degree of

phosphatase deficiency and the severity of the associated renal lesion.

Summary

Three cases of a rare bone disorder are described in which calcification is defective. This has been proved to be associated with deficient production of alkaline phosphatase. It is suggested that the primary fault may be in osteoblast formation and that it would not be unreasonable to call this condition osteoblastic dysostosis. One of the main factors in the diagnosis is the discovery of hypophosphatasaemia, but hypercalcaemia is also present and may result in renal damage and nitrogen retention. This can prove fatal, but in less severe cases recovery can be expected and calcification of the affected bones ultimately takes place.

We are indebted to our colleagues both within and outside the hospital, already mentioned in the text, for their help and interest in the biochemical and radiological problems involved in these cases. Dr. Wilfrid Sheldon was one of the many physicians who examined the first case and it was he who directed our attention to this syndrome in the American literature. Dr. G. H. Bourne has been most generous in placing at our disposal the text of a book on the general subject of bone physiology and biochemistry, which has yet to appear in print.

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