HYPOPHOSPHATASIA
A METABOLIC DISEASE WITH IMPORTANT DENTAL MANIFESTATIONS

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Hypophosphatasia may be described briefly as a condition mostly occurring in infants and children, in which there are rachitic bone changes with a variable degree of hypercalcaemia, and a lowered serum alkaline phosphatase (normal levels, adults 3-7-13-1 K.A. units/100 ml., children 15-20 K.A. units/100 ml.). Urine analysis by paper chromatography shows the presence of a spot corresponding to phosphoethanolamine, which is excreted in small amounts and is considered pathognomonic.

While the bone lesions in hypophosphatasia have been extensively studied, the dental changes, which are equally striking, have been less so. We present here our conclusions from having observed 10 cases of hypophosphatasia, studied with particular reference to the teeth, of which 4 illustrative cases are briefly described.

Case Reports

Case 1. (A.H.). This boy was first investigated when 2½ years old for bony deformities which had been present since birth. He had also had bouts of vomiting which occurred after meals, lasted two day and recurred at six-weekly intervals, and were accompanied by extreme fatigue. At this time he was able to walk, but with a pronounced roll and tended to drag his toes. Both arms and legs had been short since birth and both femora were bowed, the knees were not fully extended, and he had short Trident hands. There was lordosis of the lower spine and sulci on either side of the sternum at the costochondral junction. The face was asymmetrical with left-sided proptosis, and the deciduous incisor teeth were reported lost. The coronal sutures of the skull were heaped up.

Radiographs showed the cortices of the bones to be very thin and several long bones showed evidence of old fractures.

Plasma alkaline phosphatase, 2-8 K.A. units/100 ml. Serum calcium, normal. Paper chromatography of urine showed a large excretion of phosphoethanolamine.

Family History. Both parents were alive and well, and were not related. The mother's alkaline phosphatase level was low, 2-9 K.A. units/100 ml., and urinary chromatogram revealed a definite slight excess of phosphoethanolamine. The father's alkaline phosphatase level was also low, 3-8 K.A. units/100 ml., and his urine contained a small amount of phosphoethanolamine. Both parents were, therefore, considered to be heterozygotes for the defect under discussion.

There was one sib, a brother 6 years older than the patient who now at the age of 8 years was well, though at the age of 2 years he had had for six months had intermittent bouts of vomiting. Clinically and radiographically his bones were normal, but his alkaline phosphatase level was low, 8-3 K.A. units/100 ml., and his urine contained considerable amounts of phosphoethanolamine.

At 7 years the patient was referred for dental opinion with this typical history of infantile hypophosphatasia. He was now a small child for his age, with some frontal bossing. He was unable to run much, suffering pains in feet and legs. The alkaline phosphatase level, which had fallen to 0-7 units at the age of 5½ years, had risen but was still at a low level, 2 K.A. units/100 ml.

On examination the following teeth were present:

6 E D S D E 6
6 E D 1 1 E 6

The first permanent molars were hypocalcified and carious and the second deciduous molars were also hypoplastic and showed extensive attrition. The midline supernumerary was conical, loose, and tilted labially.

Radiographic examination showed the presence of a second midline supernumerary, and all the permanent teeth were present, but the enamel was very thin in both primary and secondary dentitions and showed gross hypoplasia. The alveolar bone appeared atrophic. The following teeth were removed under general anaesthesia:

6 5 5 6
6 D 6

At 8 years the following teeth were present:

E D 1 E
E 2 1 12 E

All these deciduous teeth and the permanent upper left central incisor were a little loose. The permanent incisors were hypoplastic and radiographically the upper right incisors appeared near to eruption. At 9 years
HYPOPHOSPHATASIA WITH DENTAL MANIFESTATIONS

Fig. 1.—Case 1 at 9 years: intraoral radiographs show IJ is not covered by bone but is unerupted. All the teeth have hypoplastic enamel especially the developing premolars. The erupted teeth have large pulps and thin roots.

(Fig. 1) the following teeth were present, all of which were a little loose: E 6 D 1, and the phosphatase level had risen to 3·2 K.A. units. Radiographically there had been practically no growth of the dental tissues in the past year.

At 9\frac{1}{2} years this child's height was 45\frac{1}{2} inches (115 cm.) and weight 49\frac{1}{4} lb. (22·4 kg.). He was attending a normal school and played football. The following teeth were present: E D 2 1 4 5 8.

The deciduous teeth were very loose and the incisors were grossly hypoplastic but fairly firm.

The patient has been provided with partial dentures overlaying the deciduous molars, providing a larger occlusal table and preventing overclosure of the bite with further loosening of the incisors by occlusal trauma (Fig. 2).

Case 2. (C.N.) This girl presented at 3 months with bowed legs and varus feet which required splinting.

Radiographs showed no evidence of bone disease in the skull or ribs, but some of the lower thoracic and lumbar vertebrae were rather beak-shaped. There was periostitis and metaphysitis of the long bones with bowing, especially of the femora.

At 18 months it was noted that her teeth were falling out and that she had already lost A A and B A B were very loose. B D were erupting, and there appeared to be some recession of the gums. There was considerable alveolar resorption in the upper incisor region radiographically, but the bone structure of the long bones had improved and there appeared to be less bowing. A provisional diagnosis of rickets was made.

The serum alkaline phosphatase was 5·3 K.A. units: serum calcium and phosphorus normal.

Before the age of 2 years all the primary incisors had been lost except the lower laterals which were loose as were the upper canines.

By 4 years all the incisors and canines had been lost and the deciduous upper right first molar was loose. There was, however, no evidence of the permanent dentition. Radiographically the bone was approaching normal compared with the coarse trabecular pattern suggestive of an earlier generalized decalcification which had been present a year before.

At 5 years, though small, height 36\frac{1}{2} in. (91·5 cm.), weight 24\frac{1}{2} lb. (11·2 kg.), the child was fit and well but...
still had a deformity of the right foot. The alkaline phosphatase level had risen to 10 K.A. units/100 ml. Urine chromatography confirmed the diagnosis of hypophosphatasia, by showing a phosphoethanolamine spot.

Radiographically there were deep indentations in the iliac crests with areas of defective ossification in the outer aspects of the femoral necks. There was no abnormality of the skull other than brachycephaly, and the sutures were patent. Only the deciduous second molars were present, and these showed extensive cervical resorption.

At 6 years the lower first permanent molars were erupted, they were firm but hypoplastic. The serum alkaline phosphatase had now risen to 15 K.A. units.

At 6½ years the lower central incisors were not present and both the upper deciduous second molars were loose. At 8 years all the incisors were erupted, except the upper laterals, and there was a large diastema between the upper centrals. The following teeth were present but loose and carious: E D D E.

No further tooth eruption took place in the following year but the diastema was slowly closing.

At 9 years and 5 months, when the serum alkaline phosphatase level was 6 K.A. units/100 ml., dental development was normal, the following teeth being present: 6 4 2 1 12 4 6.

The first molars had early caries and the lowers had early lingual decalcifications. 1 1 were proclined with an increased overbite and central diastema, 1 1 were slightly retroclined. The tooth/bone ratio was high (Fig. 3).

The patient continued fit and well, but at 11 years and 4 months it was noticed that the upper incisors were loose, and required splinting with a bite plane plate and labial bow wire. During the following 9 months these teeth became firmer but there were intermittent periods of loosening. Radiographically these teeth were vital but there was little alveolar bone; 1 which clinically was the loosest tooth appeared a little extruded from the socket and apically slightly resorbed. This tooth was dislodged and lost by a light blow on the mouth.

At 13 years the patient still wore the splint, and 6 6 were both carious. Radiographically 6 6 showed gross resorption, the second premolars were submerged and there was marked thinning of the lamina dura in both upper and lower incisor and canine regions with recession of the alveolar bone. Enamel on the incisors and the roots of all the teeth appeared thin. The four first molars were extracted at which time it was noted that the mesial root of 6 and the mesiobuccal root of 6 had been completely resorbed away and the pulp chambers exposed. There was considerable resorption on the mesial aspect of 6 with near exposure of the pulp. The roots of these teeth were both short and rather thin. The tips of all the cusps were hypoplastic, and all these teeth had occlusal fillings (Fig. 4).

At 13 years the patient continues well with a normal growth rate, though she is very small for her age. The following teeth are present: 7 4 3 2 1 2 3 4 7, but the upper incisors are a little loose and the splint is still worn.

Case 3. (S.L.) At birth it was noted that the girl had short arms and legs with bowing of the long bones, and dimples of each limb, but was otherwise normal. Later she refused feeds and had occasional bouts of vomiting; there was a tendency to constipation and she failed to thrive. Cranio-facial development was small but of normal ratio, the thoracic cage was small with palpable enlargements of the costochondral junctions.

The serum alkaline phosphatase was 7 6 K.A. units/100 ml., and the urine chromatogram had a hypophosphatasia pattern. Radiographically, a generalized upset in bone formation at the growing ends of the long bones with sites of multiple healed old fractures was seen.

At 2 years, marked bulging of the anterior fontanelle with premature synostosis was present. All the deciduous incisor teeth had been lost, with no evidence of radicular resorption.

At 3 years bilateral papilloedema necessitated bilateral coronal craniectomy. The serum alkaline phosphatase at this time was 5·9 K.A. units.

Case 4. (M.M.) At 15 months it was noticed that this little girl had a peculiarly shaped skull, and by 2 years had genu valgum. The serum alkaline phosphatase level was 2·4 K.A. units/100 ml.

All the deciduous incisors had been lost by the age of 4 years (Fig. 5).

A year later papilloedema resulting from craniostenosis necessitated bilateral coronal cranioplasties. That condition, however, continued to worsen, and going into renal failure she died before her sixth birthday.
Dental Radiographic Findings

Most cases exhibit early resorption and loss of the deciduous teeth especially the deciduous incisors, but there is no compensatory early eruption of the permanent teeth, nor is there any constant delay in eruption. Not infrequently deciduous teeth are exfoliated with very little evidence of resorption. The pulp cavities in the deciduous teeth appear considerably larger than normal and those in the permanent teeth also seem slightly larger.

Thickness and density of the lamina dura and the width of the periodontal space appear to be normal in most cases, but the layer of cementum on the permanent teeth is thin.

Hyoplasia of the deciduous teeth, the permanent incisors, and first molars is a constant finding and

Fig. 4.—Case 2 at 13 years: there is extensive alveolar resorption especially in the incisor region and the roots of the lower incisors are very thin, the \( J \) is elevated in the socket, the second premolars are impacted, and there is considerable resorption of the roots of the first permanent molars.
the dentine had a typical scalloped edge corresponding to the amelodentinal junction, the tubules appeared swollen coronally and stained densely. There was considerable occlusion of the pulp by normal secondary dentine. The cementum was practically non existent and there was no evidence of resorption.

3. (Case S.H.). Microradiographic section of a deciduous canine which was normally shed, but again lost early, on examination showed evidence of only a small amount of resorption. The enamel was slightly hypoplastic and most had been shattered and lost in sectioning. There was a well-defined granular layer of Tomes in the radicular dentine just below the crown, and the coronal pulp had been occluded by secondary dentine. The radicular pulp chamber was still wide with a bar of calcified tissue across the apex where some resorption had taken place. The layer of cementum was thin, with patches of resorption where the cementum has been completely lost together with a small amount of dentine. There were scattered patches of calcified tissue in the root canal and a shadow corresponding to the predentine.

Function of Alkaline Phosphatase in Development and Formation of Teeth

In the developing tooth germ alkaline phosphatase first appears in the differentiating stellate reticulum: this was considered by De Fazio (1954) to be associated with mineralization. Symons (1954) suggested that mineralization occurred later in development and that the enzyme reflected active cellular differentiation. This was not supported by earlier work of Morse and Greep (1947) who found little or no phosphatase activity in various sites of proliferation in the rodent tooth germ or in the epiphyseal plate of growing bones.

The presence of alkaline phosphatase in the stellate reticulum is believed to be important for the liberation of the carbohydrate radicle from hexosephosphate and its synthesis to mucopolysaccharides (Moog and Wenger, 1952; Kroon, 1952). According to Butler (1956) and Ten Cate (1957) acid mucopolysaccharide produced by the reticulum cells of the stellate reticulum assists in the determining of crown pattern. Phosphatase activity also occurs in the external enamel epithelium and is presumed to be associated with the transfer of phosphorylated glucose across the cellular barrier. Alkaline phosphatase is most active in all parts of the enamel organ when the matrix is being laid down, that is when the ameloblasts are most active and nutrient transfer greatest (Johnson and Bevelander, 1954). However, there is no evidence of phosphatase activity within the ameloblasts in the human tooth germ up to and including enamel matrix formation (Ten Cate, 1962; Chèvremont and Firket, 1953).

Similarly the absence of cytoplasmic alkaline

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**Dental Histology**

Three typical examples are described.

1. (Case S.H.). A slightly carious deciduous lower second molar, which had been exfoliated early, was decalcified, stained with haematoxylin and eosin, and sectioned mesiodistally.

The dentine appeared normal and the pulp chamber was largely occluded by secondary dentine, the remaining space being occupied by strands of degenerative pulp tissue. A small amount of resorption had taken place at the apex of the roots and there was evidence of earlier resorption. Cellular secondary cementum was confined to the apical third of the root.

A ground section of the deciduous upper lateral incisor which was also exfoliated early, with little evidence of resorption, showed that the enamel and dentine were normal though the incremental lines in the dentine were accentuated. The cellular cementum was confined to the radicular apex and there were only a few Howship's lacunae present, showing that there had been practically no resorption.

2. (Case S.L.). A lower lateral incisor which had been shed early: there was no apparent resorption of the root and the apex was wide open and the enamel appeared normal. A mesiodistal decalcified section showed that

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**Fig. 5.—Case 4 at 5 years: early loss of the anterior deciduous teeth, large dental pulps, thin roots in the erupted teeth, and hypoplasia of the developing teeth.**
phosphatase activity has been reported during
dentinogenesis in human odontoblasts (Ten Cate,
1962). Since both ameloblasts and odontoblasts
produce a calcified tissue and are devoid of alkaline
phosphatase and since both are related to a cell layer
rich in phosphatase in the stratum intermediate and
the subodontoblastic zone respectively, it is reasonable
to suppose that both these enzyme-rich structures are
associated with the production of a calcified tissue.

Three possible functions of alkaline phosphatase
in relation to calcified tissues have been postulated by
Bourne (1956): it may (a) assist in the formation of
an organic matrix, (b) provide a phosphate ester
template for the crystallization of bone salt, or (c)
keep the surface of bone crystals free of ester
phosphatase for the continued growth of crystals.
The two latter postulates are not supported by the
work of Lefkowitz, Bodecker, and Shapiro (1944)
and Barnum and Armstrong (1941).

Phosphatase is associated with the production of
mucopolysaccharide which is linked to both fibrillo-
genesis (Gersh and Catchpole, 1949; Curran, 1953;
Buck, 1953) and the formation of collagen (Bourne,
1943: Buck, 1953).

It is not known whether the enzyme plays a direct
or indirect role in the formation of collagen, but
sulphated mucopolysaccharide, the ground substance
of the dentine, is elaborated by the pulp (Bevelander
and Johnson, 1955), and the intense enzyme activity
in the subodontoblastic area may be associated
directly with this, or indirectly with fibrillogenesis.

A fibrillar ground structure at the beginning of
enamel matrix formation has been demonstrated
(Nylen and Scott, 1958; Scott and Nylen, 1960).

Fearnhead (1960) demonstrated a granular
precursor in the ameloblasts, which was passed
through the cell wall in the terminal bar region and
became orientated as definite fibres.

The function of alkaline phosphatase in the
stratum intermedium is believed to be associated
with the elaboration of mucopolysaccharide which passes
between the ameloblasts and forms a template for the

It is now believed that alkaline phosphatase plays
no direct part in the precipitation of mineral salts.

**Treatment**

At the present time there is no satisfactory medical
treatment for this disease. Vitamin D has been
tried in varying doses, but some authorities have
claimed that on occasions this has aggravated the
condition. A low calcium diet, however, is generally
favoured. If the child survives, the general clinical
condition slowly improves but may deteriorate later
in middle age (Bethune and Dent, 1960).

Hypoplastic teeth should be protected by strict
oral hygiene and attention to dietary habits and the
use of fluoride compounds. Prophylactic odonto-
tomy and shell crown coverage should be considered
where applicable. Dentures should be provided to
prevent overloading the teeth when few are standing,
and to splint and support those that are loose.

In view of the high tooth/bone ratio, it may be
advisable, in treating the overcrowding, to remove
the first permanent molars, which are usually hypo-
plastic and prone to caries.

**Conclusions**

Hypophosphatasia of severe intensity, occurring
during the time when dental tissues are being formed,
results in hypoplastic deficiency and reduction in the
thickness of enamel. Many deciduous teeth are lost
very early, especially the incisors, and they are often
lost with very little resorption of the roots. There is
no compensatory early eruption of the permanent
teeth and the incisors and first molars are often
hypoplastic.

The permanent incisors, especially the uppers,
become loose early and suffer periods of looseness
and relative firmness. The cementum layer is rather
thin and the loosening of these teeth is probably
associated with the breakdown of the periodontal
attachment under normal function. Splinting the
teeth after loosening has occurred has no real long-
term effect. These observations tend to reinforce
the view that alkaline phosphatase is, among other
functions, associated with the production of the
organic matrix for enamel formation and with the
production of collagen.

The jaws of these patients tend to be small, so that
a high tooth/bone ratio results. Early loss of the
hypoplastic first permanent molars due to caries often
results in collapse of the bite.

**Summary**

Ten cases of hypophosphatasia have been studied
with particular reference to the dental lesions.

Dental lesions are prominent in this disease, and
consist of hypoplastic deformity, with crowding and
early loss of the teeth in both dentitions.

The role of phosphatase in the development of the
teeth is discussed.

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BIBLIOGRAPHY

Barnum, C., and Armstrong, W. D. (1941). *In vitro and in vivo*
exchange of phosphorus by enamel and dentin. *J. dent. Res.*, 20,
232.

Bethune, J. E., and Dent, C. E. (1960). Hyponphosphatasia in the

Bevelander, G., and Johnson, P. L. (1955). The localization of

Bourne, G. H. (1943). Some experiments on the possible relationship
between vitamin C and calciumification. *J. Physiol. (Lond.)*, 102, 319.

— (1956). Phosphatase and bone. In *The Biochemistry and
Physiology of Bone*, ed. G. H. Bourne, p. 251. Academic Press,
New York.

Bruckner, R. J. (1949). Alkaline phosphatase in pulpal tissue of


40.


Curran, R. C. (1953). Observations on the formation of collagen in

Currario, G., Neuhauser, E. B. D., Reversbach, G. C., and Sobel,

De Fazio, E. (1954). L’attività fosfatasi nella odontogenesi

Engel, M. B., and Furuta, W. (1942). Histochemical studies of
phosphatase distribution in developing teeth of albino rat.

(Lond.)*, 188, 509.


Gersh, I., and Catchpole, H. R. (1949). The organization of ground
substances and basement membrane and its significance in tissue

Glasestone, S. (1958). The distribution of alkaline phosphatase in

19, 197.

Harris, E. S. (1950). The sites of alkaline phosphatase in

Harris, H., and Robson, E. B. (1959). A genetical study of ethanol-
amine phosphatase excretion in hypophosphatasia. *Ann. hum.
Genet.*, 22, 421.

Illingworth, R. S., and Gardiner, J. H. (1955). Premature loss of

Johnson, P. L., and Bevelander, G. (1954). The localization and
interrelation of nucleic acids and alkaline phosphatase in the
developing tooth of *dent. Res.*, 33, 128.

Kroon, D. B. (1952). Phosphatase and the formation of protein-

Experimental paraplecomy. Part II. *Histological study of *J. dent.

McCance, R. A., Fairweather, D. V. I., Barrett, A. M., and Morrison,
A. B. (1956). Genetic, clinical, biochemical, and pathological
features of hypophosphatasia, based on the study of a family.
*Quart. J. Med.*, 25, 523.

—, Morrison, A. B., and Dent, C. E. (1955). The excretion of

Meyer, K. (1947). The biological significance of hyaluronic acid

*Connective Tissues: Transactions of the First Conference*, pp. 88-

mucopolysaccharide at sites of high alkaline phosphatase activity.
*Amer. J. Anat.*, 90, 339.

Morse, A., and Greep, R. O. (1947). Alkaline glycerophosphatase in


Rathbun, J. C. (1948). 'Hypophosphatasia': a new developmental

—, MacDonald, J. W., Robinson, H. M. C., and Wanklin, J. M.
540.

Robison, R. (1923). The possible significance of hexosephosphoric

Sasso, W. S., and Castro, N. M. (1957). Histochemical study of

alkaline phosphatase deficiency: an osteoblastic dysplasia.


Rickets, deficiency of ‘alkaline’ phosphatase activity and

Symons, N. B. B. (1954). Alkaline phosphatase activity in the

Ten Cate, A. R. (1957). Histochemical investigations on the stellate
reticulum of human foetal teeth. *ibid.*, 91, 609.

— (1962). The distribution of alkaline phosphatase in the human
tooth germ. *Arch. oral. Biol.*, 7, 195.

*ibid.*, 1, 259.
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