OSTEOSPATHYROSIS (Lobstein’s Disease)

A CRITICAL REVIEW

BY

CONSTANCE M. OTTLEY, F.R.C.S.,
Assistant Surgeon, New Sussex Hospital, Brighton.

The disease of which an illustrative case is reported below was first described in 1833 by Lobstein, who gave it the name of ‘osteospathyrosis’ (ὀρτίον = a bone, ἕφθυρον = friable). According to his original description it is characterized by the appearance in certain families of cases of undue fragility of the bones. This fragility manifests itself in a tendency, of the bones to break as the result of slight violence. On the other hand, repair of the fractures takes place not less rapidly than in normal bones.

Since the publication of Lobstein’s work many other cases of the disease have been recorded, and a clinical picture has gradually emerged in which fragility of the bones appears as one of a group of associated abnormalities. Many of these are exemplified in the case now to be described.

Case report.

The patient, a married woman of 35, came to the New Sussex Hospital complaining of curvature of the spine, present since the age of 10 years, and of pain in the back for the last few months. She stated that since the birth of her only child, 5 years ago, she has noticed that her eyes were getting blue. This blueness is said by her sister, however, to have been present for at least 8 or 10 years. Four years ago she began to be deaf in the right ear, as the result, she thought, of a cold. She was treated by politzerization but the deafness was not relieved. It grew gradually worse, and the left ear began to be affected. Ringing noises were noticed, first in the right ear and later in the left ear also. She broke her left humerus at the age of 12 years, from a fall while jumping at school, and shortly afterwards broke the left ulna twice in succession from falls in the school playground.

Physical examination.—Patient is a small woman (about 5 ft. in height), healthy looking and (for her size) of fair muscular development. She is so deaf that the voice must be raised in speaking to her. The sclerae are of a moderately deep indigo blue colour, and each cornea shows a well-marked arcus senilis. The upper teeth are false. The lower incisors are small and thin, and the enamel worn away towards the free edge, which has a mouse-eaten appearance. The remaining teeth appear normal. There is a severe structural scoliosis (single curve, convex to the left, apex at the 10th-11th dorsal vertebra). The limbs are of normal length and the long bones show no abnormal curvature. The shape of the skull is not suggestive of ‘crâne à rebord.’ There is slight hyperextensibility of the fingers. Routine examination of chest and abdomen reveals nothing abnormal.

X-ray Examination.—The following bones were examined: skull, spine, pelvis and the long bones of both upper and both lower limbs. The vertebrae show the ordinary sciotic changes. There is a slight irregularity of the lower end of the left humerus, at the site of the former fracture. An exostosis is present at the upper end of the right fibula. With these exceptions the bones, which are of slender build, show nothing abnormal in form or structure. There is no evidence of otosclerosis in the plates of the skull, nor of arteriosclerosis in any of the plates. There is well-marked calcification of the laryngeal cartilages.
HEARING.—Otological examination by Mrs. Logan yielded the following results:—


512 D.V. " 60 sec.

Mastoid: 256 D.V. indistinguishable from own tinnitus.

512 D.V. minus 15 sec.

Mixed deafness, but tending to be more labyrinthine than obstructive.

L. ear: Rinné positive/negative. Meatus: 256 D.V. minus 20 sec.

512 D.V. " 10 sec.

Mastoid: 256 D.V. " 50 sec.

512 D.V. " 10 sec.

Meatal hearing and mastoid hearing are equally impaired.

BLOOD.—Calcium content of serum 10-2 mgrm. per cent. Wassermann reaction negative.

FAMILY HISTORY.—The patient states that 'blue eyes' have occurred frequently in her family on the mother's side. The earliest case known to her is that of her mother's mother, who was also deaf. This grandmother was the second child in a family of three. The eldest (♀) also showed 'blue eyes' and deafness, and the youngest (♂) was deaf. None of these people is known to have had a fracture.

The grandmother had two children. The elder, the patient's mother (now dead), had very marked blueness of the scleræ, was deaf, and is known to have had one fracture (toe). The younger (♂) showed none of the family peculiarities.

The patient's mother had four children. The eldest (♀), aged 40, shows no sign of the disease. The second (♂) died in infancy from an unknown cause, and so far as is known the disease did not appear in him. The third (♀), aged 36, has blue scleræ, is deaf and has had one fracture (rib). The patient herself is the youngest child.

The patient's eldest sister, who has been twice married, has two children, both boys, one by each husband. In the elder, aged 15, it has recently been noticed that his 'eyes are turning blue.' Neither is deaf and neither has had a fracture.

The second sister has had ten children, two of whom died in infancy. Of the survivors, the eldest and the youngest are girls aged 14 and 2½ years respectively, the others are boys ranging from 12 to 5 years of age. The eldest has blue scleræ, has once fractured a bone (clavicle), and though not deaf, has complained of noises in the head. The six boys all show the blue coloration of the scleræ except one, the youngest but one, aged 7 years. None of them are deaf and no fractures have occurred in them. The youngest has very marked blueness of the scleræ and has recently broken her leg by falling off a chair.

The patient herself has one child (♀) aged 5 years. This child has 'blue eyes' but does not appear to be deaf. She had an acute otitis media at the age of 2. She has never had a fracture. She walked at a normal age and appears healthy.

The writer has had the opportunity of seeing the following members of the patient's family:—

1. The eldest sister who shows no sign of the disease.

2. The second sister. In this case the scleræ are of a deep blue colour, and a very well-marked arcus senilis is present in each cornea. She is not so hard of hearing as her younger sister.

3. The patient's daughter who has slightly blue scleræ.

4. The eldest sister's 'blue-eyed' son. The blue tint is very slight but definite. It is more marked close to the cornea, and gradually shades off towards the outer part of the eyeball.

5. The two eldest of the younger sister's children. In both of them the blueness of the scleræ is very striking.

None of the children as yet shows the arcus senilis. All appear healthy and well grown. The genealogical table opposite shows these relationships.
Genealogical Table.

B = blue sclera.  D = deafness.  F = fractures (number in brackets).
Discussion.

This case displays a number of the features which are now recognized as those of Lobstein's disease. Fragility of bone is not in itself pathognomonic, occurring in connexion with various other conditions, such as rickets, senile atrophy, etc. Apert\textsuperscript{1} gives the following list of characteristics which, occurring in combination, constitute Lobstein's disease:—

(1) Fragility of the bones.
(2) Peculiar conformation and structure of the bones.
(3) Peculiar shape of the skull.
(4) Laxity of ligaments, leading to excessive mobility of the joints and in some cases to repeated dislocations.
(5) Blue coloration of the sclerae.
(6) Deafness.
(7) Abnormal electrical reaction of the muscles.
(8) Other miscellaneous abnormalities, more rarely seen: unusually fine hair, white patches in the nails, deficiency of the teeth in enamel. The subjects of Lobstein's disease have been stated to show a special liability to migraine and various vasomotor disturbances.
(9) The familial character of the disease.

Functional and structural abnormality of the bones.—The fragility of the bones may become manifest at any time after birth, sometimes not for a number of years. It expresses itself in a tendency to repeated fractures, often the result of very trivial violence, and often, therefore, subperiosteal and associated with but little displacement. On the other hand, if the fracturing force is more considerable, comminution is more apt to occur than in a normal bone. The fractures heal readily in the usual way. The long bones are slender, often curved, the cortex very thin. The bones are unduly transparent to the X-rays. The chemical composition appears to be normal. Lobstein believed that the medulla of the bones is primarily affected in these cases, and that the essential lesion is an expansion of the medullary cavity at the expense of the cortical part of the bone, as the result of the primary pathological change in the medulla.

Schuchardt\textsuperscript{16} suggested that the cause of the condition is to be found not in an affection of the medulla but in a dysplasia of the periosteum. This view met with considerable opposition. Rebbeling\textsuperscript{2} pointed out that resorption of callus by the periosteal cells, following a fracture, is more than usually rapid in these cases; and Döering\textsuperscript{13} argued that the cellular proliferation seen in the periosteum excluded any atrophy of the latter.
Osteopsathyrosis

Looser\textsuperscript{28}, on the histological examination of cases of osteopsathyrosis, found evidence of deficient function on the part of the osteogenetic cells of both marrow and periosteum, and of increased osteoclastic activity. Looser's observations and conclusions received support from Schmorl\textsuperscript{32}, Fowler\textsuperscript{16}, Lovett and Nichols\textsuperscript{29}, Fuchs\textsuperscript{20} and others. Some authors, however, maintain that the osteoclasts are not in excess of normal. It appears to be agreed that the outstanding histological feature is the relatively small amount of ground substance as compared with the number of osteoblasts present. The periosteum is thin, the marrow and epiphyseal cartilages normal.

Shape of skull.—The cranium appears flattened from above downwards and expanded in its other diameters (\textquoteleft crâne à rebord \textquoteright). There is thus an abnormal prominence of the occipital and temporal regions. In the latter situation especially the bulging may be so marked that the upper part of the pinna is pushed outwards and folded upon the lower part. Arlabosse\textsuperscript{2} records a case where the cranial abnormality was well marked.

Blue scleræ.—Spurway\textsuperscript{38} seems to have been the first to draw attention to the fact that blue coloration of the scleræ is present in typical cases of Lobstein's disease. Eddowes\textsuperscript{14}, who also reported a case of blue scleræ, suggested that the disease represents an abnormality of the supporting tissues of the body. Buchanan\textsuperscript{11} found on histological examination that the scleræ are abnormally thin, allowing the uveal pigment to show through. Bronson, on the other hand, found the scleræ to be of normal thickness, but deficient in calcium, and hence unduly transparent. Apart from the blue coloration of the scleræ, other ocular abnormalities appear to be fairly common. Peters\textsuperscript{21} and others have noted the premature development of arcus senilis. Congenital defects such as cataract, coloboma, etc., have also been reported.

Deafness.—Van den Hoeve and de Kleyn\textsuperscript{21} observed several cases, in some of which the deafness was the result of otosclerosis. It may be noted that Dighton\textsuperscript{12} had previously published a case as one of nerve deafness. The type of deafness varies. In some of the published cases it has been of middle ear type, in others labyrinthine, while in some it has partaken of the characters of both, as in a case recorded by Friedberg\textsuperscript{19}. In Dighton's case the deafness was labyrinthine. In van den Hoeve and de Kleyn's second case there was no proof of otosclerosis. Voorhoeve's\textsuperscript{39} four cases had labyrinthine deafness. Of Ruttin's\textsuperscript{34} cases, in three the deafness was labyrinthine origin, in three otosclerotic. Kompanejetz\textsuperscript{25} reported three cases with labyrinthine deafness, with or without otosclerosis in addition. Bigler\textsuperscript{9} described a family of which one member had otosclerosis, another labyrinthine disease. Apert\textsuperscript{1} regards the deafness as due to abnormal thinness of the tympanic membrane and laxity of the ligaments attached to the ossicles.
Abnormal electrical reaction of the muscles.—This has been noted by several observers, including Larat and Bolton. The response to faradic stimulation is weak, and with the galvanic current there is a greatly diminished response and the rapidity of both contraction and relaxation is much below normal, so that the form of contraction resembles that characteristic of smooth muscle. In effect, there is an incomplete reaction of degeneration. All the muscles are alike involved, not only those attached to the affected bones.

Hereditary.—Of the hereditary character of osteopsathyrosis there can be no doubt. Among the reported cases in which the hereditary factor is well marked, those of Spurway, in which four generations of one family were involved, and of Holcomb, in which five generations were affected, are especially noteworthy. As regards the exact mechanism concerned, the evidence is conflicting. Bauer and Stein maintain that the deafness is associated with two recessive Mendelian factors, while other authors (e.g., Apert, Holcomb) have found evidence of a dominant factor. The question is further discussed by Aschner and Engelmann. Individual cases of osteopsathyrosis display the distinctive features of the disease in varying combination: a given case may exhibit any or all of them. Blue sclera, for instance, may be the only apparent abnormality (J. Bauer). Apert maintains that in any given family the combination of symptoms remains constant, though some abnormalities may be less well developed than others. That the various characteristics may occur in different degrees of development is clear from the recorded cases. In those described by Voorhoeve, for instance, the blue coloration of the sclera was much more marked in some than in others. Thus the deafness or the fragility of bone or any of the other features of the disease may be inconspicuous or absent in any individual case. Francke expresses the opinion that the complete syndrome (blue sclera, deafness, fragile bones) is found only in people whose parents have also shown it.

Aetiology and pathology.—The question has been much discussed, what relation (if any) Lobstein’s disease bears to the condition known as congenital osteogenesis imperfecta. Despite the fact that many cases of each disease have been investigated, this problem has not yet been solved. It remains uncertain whether the two conditions represent, as many authors hold, two different aspects of the same abnormality; or if, as others assert, they are unrelated maladies bearing merely a superficial resemblance to one another.

Congenital osteogenesis imperfecta was first described by Vrolick in 1845. Its chief clinical characteristic is undue fragility of the bones. This may first manifest itself in intra-uterine life, and results in multiple fractures.

* H. A. T. Fairbank (Proc. R. Soc. Med., Lond., 1930, XXIII, 1263, Child. Sect. 77) is of opinion that both ante-natal and post-natal cases are of intra-uterine origin, the date of the first fracture depending on the severity of the affection in a given case.
OSTEOPSATHYROSIS

The children are often stillborn, and if they survive continue to suffer from frequent fractures occurring as the result of trivial causes. The bones may be either short and thick or long and slender in form, and are very poorly calcified. Heredity is sometimes a marked factor. The majority (about 80 per cent.) of the recorded cases have been in the female sex. Associated with the fragility of the bones there may be other abnormalities, such as imperfect ossification of the cranial bones with non-closure of the sutures, ' crâne à rebord ' and blueness of the sclerae: Bentivoglio and others have reported cases in which muscular hypotonia, with histological changes in the muscles, has been present. Since the disease so often results in the child being stillborn, many opportunities for post-mortem examination have arisen, in contrast to Lobstein's disease, in which material for pathological examination has been chiefly obtained, so far, from osteotomy operations. The chief anatomical peculiarities found on autopsy are defective ossification of the bones and imperfect development of the teeth. Jeckeln has recently published a detailed account of the histological appearances. He describes a disturbance of the normal process of ossification. Changes, according to him, are first apparent in the zone of cartilage-cell columns; they include deviations from the normal longitudinal arrangement of the cell columns and disturbance of the normal relationship between the size of the cells and the amount of intercellular material, the latter being considerably reduced. In the ossifying zone trabeculae are laid down but remain chiefly cellular; very little ground-substance is produced and calcification takes place most irregularly, some trabecule staining normally with haematoxylin-eosin, others showing little or no evidence of calcification. There is, in fact, evidence that the function of the osteoblasts is imperfectly carried out. According to Jeckeln the number of osteoclasts present is not in excess of the normal.

As regards the tooth-germs Jeckeln describes enamel formation as proceeding normally. Abnormal conditions, however, obtain in the pulp. The odontoblasts in the early stages appear normal, but soon begin to show retrogressive changes, with the result that both the formation and calcification of the dentine are imperfect.

Although many authors maintain that the cause of osteogenesis imperfecta is deficient osteoblastic function, some have stated that it is to be found in abnormal activity of the osteoclasts. They point out that rapid healing of the fractures, with exuberant callus-formation, is usual. Harbitz, Buday and others claim to have shown that the osteoclasts are increased both in numbers and in functional activity, resulting in expansion of medullary cavity. Jeckeln's case furnishes evidence against the view that the osteoclasts are responsible for the condition. Frontali has reported a case where there was complete absence of compact substance in the tubular bones, while the cancellous substance was of fibrous structure and there was no formation of lamellae or Haversian canals; in this case also, histological examination revealed very few osteoclasts, and the osteoblasts were few in number and abnormal in appearance.
Those who maintain that osteopsathyrosis and osteogenesis imperfecta are merely two aspects of the same condition base their contention upon the similarity of the structural changes in the bones and of the clinical features; and, in particular, upon the occurrence of both types in the same family, several examples of which have been reported. For instance, Tillaye (quoted by Sorrentino) has described a family of five children all subjects of fragility of the bones, in whom the first fracture to be noted occurred at the ages of 29 years, 20 years, 2 months, 6 weeks, and 8 days respectively: Lovett and Nichols have recorded the occurrence of osteopsathyrosis in the parent and osteogenesis imperfecta in the child. In this connexion, however, it should be borne in mind that a fracture in very early life may easily be overlooked. Blueness of the sclera may occur in either disease. There would appear clinically to be no sharp line of demarcation between osteogenesis imperfecta and osteopsathyrosis; the distinction is to be found in the time of onset, in ante-natal life in the former, after birth in the latter. As regards the histological changes, Looser found that those presented by his cases of osteopsathyrosis corresponded to those described in the published cases of osteogenesis imperfecta. Both showed evidence of deficient osteoblastic function, while the epiphyseal cartilage, preliminary calcification of cartilage and resorption of bone appeared normal. The relatively large numbers of cells present, and the rapid formation of callus which follows a fracture are similar in both diseases. Looser therefore made the suggestion that the essential unity of the two conditions should be recognized by giving to osteopsathyrosis the name of osteogenesis imperfecta tarda. Neither name can be regarded as satisfactory, since neither takes into account all the varied features of the disease. It is perhaps best, at the present time, to use the non-committal name of Lobstein’s disease in referring to the condition, although Lobstein’s own account of it was very incomplete.

Much discussion has taken place as to the essential nature and causation of these diseases. Hildebrand, in 1899, suggested that osteogenesis imperfecta is due to the injurious action of some toxin upon the osteoblasts. Biebl amplified this hypothesis, the results of his work on the teeth leading him to suggest a toxæmia of pregnancy as the cause. Fahr and others have postulated an endocrine origin. Changes have been described in the thymus, thyroid, pituitary, etc. Macciotta suggests that the condition is due to an anomaly of cholesterol metabolism (reduction of the amount of cholesterol present in the blood) associated with changes in the suprarenal cortex. Kraus, on the other hand, brings evidence against the theory of an endocrine deficiency or dysfunction. Vitamin deficiency has also been held responsible. Stress has been laid on the anatomical resemblance between osteogenesis imperfecta and scurvy, but it now appears that in the former disease the marrow is at first unaffected, only later showing secondary changes. As regards Lobstein’s disease, Axhausen has expressed the opinion that the disease is akin to osteomalacia, and this view has been
supported by Recklinghausen\textsuperscript{33}. Others have suggested disease of the spinal cord, others again syphilis as the cause.

It is clear that as regards osteopsathyrosis none of these hypotheses can stand against the weight of evidence that has accumulated to show that the disease arises by hereditary transmission. If we accept the view that osteogenesis imperfecta is merely the pre-natal form of osteopsathyrosis, it is necessary to find some explanation which will cover both diseases. The most important hypothesis at present put forward is that of an inherited anomaly of certain tissues of the body of which the cause, like that of other congenital defects, is unknown. This view has been expanded by various authors, especially by Hoffmann\textsuperscript{22}, more recently by K. H. Bauer\textsuperscript{7}. Bauer bases his conclusions chiefly upon the pathological findings in one case, a seven months’ foetus (female) with osteogenesis imperfecta, and upon the clinical features of a case of osteopsathyrosis in a boy of eleven. Like Looser, Bauer regards the two diseases as identical. In the former case post-mortem examination revealed changes in the bones, teeth and connective tissues, together with excessive development of the lymphatic tissues (status lymphaticus), calcification of the intima of the arteries and the presence of eosinophil leucocytes in the lymphatic glands, thymus, pituitary and spleen. In his case of osteopsathyrosis Bauer also found enlarged tonsils and adenoids.

On this evidence Bauer concluded, in his first paper, that osteogenesis imperfecta is a disorder affecting the connective tissues as a whole, manifesting itself as a dysfunction of all matrix-forming cells. In his second paper he went further, and expressed the view that osteogenesis imperfecta and osteopsathyrosis are the result of an inherited constitutional anomaly (inferiority or deficiency) of the tissues derived from the mesoderm, or more precisely from the mesenchyme. His suggestion is that while all tissues of mesenchymal origin are involved, the more highly organized tissues (bone, cartilage, pulp of teeth) are chiefly affected. He failed to discover any changes in the muscles (striated and unstriated), the urinary or genital organs or the suprarenal cortex, whence he concluded that only the mesenchymal part of the primitive mesoderm is involved. Cell-formation is not necessarily deficient (as exemplified by a case reported by Buday, where osteoblasts were present in great numbers and were of normal structure), but the matrix-forming function is always impaired.

Later cases of osteogenesis imperfecta reported by Fahr\textsuperscript{15} and by Kraus\textsuperscript{26} failed to confirm Bauer’s mesenchymal theory. Fahr, moreover, found evidence of excessive development of the thyroid and thymus (derived from the entoderm), pituitary and suprarenal medulla (derived from the ectoderm), but again only in one unconfirmed case.

Since the publication of Bauer’s hypothesis, various observers have described changes in other tissues of mesodermal origin: such as the muscular
hypotonia and structural changes already alluded to (Bentivoglio and others), and excess of lymphocytes in the blood (Frontali, Macciotta and others). General oedema has been described in some of the recorded cases, and has been accounted for in terms of the mesenchymal deficiency hypothesis, by assuming that it is due to primary insufficiency of the vessel walls. Against this view it has been urged that oedema is a common symptom of children's ailments, especially those of the bones, and may in these cases also be merely symptomatic. Recent work has tended to cast doubt upon Bauer's hypothesis. Friedberg\textsuperscript{14}, for instance, holds that the evidence of changes in other mesodermal tissues (subcutaneous connective tissue, tendons, ligaments, the capsules and interstitial connective tissue of the internal organs, the blood and blood-vessels, lymphatics and glands, muscles and urogenital organs) is inconclusive, and points out that abnormalities have been found in tissues of other than mesodermal origin. Fahr, as already mentioned, describes changes in the endocrine glands derived both from the ectoderm and the entoderm. In the case of osteopsathyrosis reported by Blegvad and Haxthausen\textsuperscript{10} there was zonular cataract as well as blue discoloration of the sclæ. In other reported cases the blue sclæ have been accompanied by delayed development of the teeth, cleft palate and syndactyly. Further, as already seen, the deafness may be due to a lesion of the labyrinth: the degeneration of the auditory nerve underlying this type of hereditary deafness cannot be reconciled with the mesodermal deficiency hypothesis. It would appear that in osteogenesis imperfecta, using the term in its widest sense, we are dealing not with a system-disease of the mesoderm or mesenchyme, but with a connected group of constitutional anomalies. Such a condition might be due either to a primary failure of development, or as Jeckeln\textsuperscript{24} suggests, to interruption of the normal progress of development. This author, from the results of his observations on dentine formation in a case of congenital osteogenesis imperfecta, postulates a condition of progressive exhaustion of osteoblastic function, with intervals of remission. He suggests that this hypothesis would throw light upon the essential nature of osteopsathyrosis (osteogenesis imperfecta tarda).

**General conclusions.**

In the case of Lobstein's disease described above, the familial aspect is well marked, cases having occurred in four generations. The inheritance has been direct from mother to child, except in one instance, that of the patient's eldest sister's son, who has the blue sclæ and whose mother has shown no signs of the disease. The direct character of the inheritance, the number of members of the family showing the peculiarity and the constancy with which the disease has appeared in each generation would seem to point to a Mendelian dominant factor being concerned. The case of the boy just mentioned is difficult to reconcile with the others. There are four possibilities: (1) The father (now dead) might have belonged to a family in which the disease was present. This is denied; and the father himself, who was in
no way related to the mother, is said to have shown no sign of the disease. (2) The mother may later develop signs of the disease, the taint being as yet latent in her. (3) The factor concerned may not be a dominant one. (4) The case may not be a genuine one of Lobstein’s disease.

In this family fragility of bone has been but little in evidence; fractures have been few. It is possible that in the case of the patient herself the scoliosis (see below) is caused by some defect of ossification of the vertebrae; or that it is due to muscular hypotonia, which again may be a manifestation of the disease. It may, however, be merely coincident.

Another point in connection with this family is the more marked incidence of the disease among female members. No fracture is known to have occurred in any of the males of the family, and the complete triad of symptoms (blue sclerae, deafness, fractures) has only appeared in the females.

As in many other of the recorded examples, the anomaly in the instance here reported appears to involve certain tissues of epiblastic origin (enamel, auditory nerve) as well as tissues derived from the mesoderm; the case thus according with the view that Bauer’s hypothesis of mesenchymal deficiency is not a true explanation of Lobstein’s disease.

**REFERENCES.**

36. Schuchardt, K., *Deutsche Chir.*, Stuttgart, 1899, XXVIII.