OSTEOGENESIS IMPERFECTA
and
Osteogenesis Imperfecta Cystica

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Osteogenesis imperfecta (synonyms: fragilitas ossium, idiopathic osteopothyrosis, periosteal dysplasia) is characterised by fragility of skeletal bones. The cause is unknown. Cases may be grouped as pre-natal and post-natal, but there is no clear-cut distinction between the two groups except in the date of the first fracture which depends upon the severity of the disorder. Pre-natal cases are on the average decidedly more severe; many die at birth or survive only a few days or weeks. The exact proportion of surviving to fatal cases is unknown. A child may sometimes survive several months despite birth fractures of many ribs. Osteogenesis imperfecta tarda is the term often applied when there is delay in occurrence of the first fracture; for example, a girl with intensely blue sclerotics sustained the first of many fractures at the age of seven.

Hereditary and familial influences are apparent in a minority of both groups, but more often in the post-natal group. The disorder may be inherited through either parent. Many family trees have been published, some covering four generations, with certain members marked as having blue sclerotics, some also with bone fragility, but others without (50 per cent., Fraser, 1934).

Sex—Both sexes are affected, females more frequently than males; of thirty-five cases known to the writer nineteen were females.

Blue sclerotics, fairly deep indigo and not just blue as may often be seen in normal babies, may be present in both groups of cases but more frequently in the post-natal group. The depth of colour sometimes fades with age.

Otosclerosis may occur in those who live till the third decade, but deafness has twice been reported as early as the thirteenth year. (Cleminson, 1926, and Bigler, 1923.) Bickel et al (1943), analysing a series of forty patients found deafness in 45.5 per cent. of the hereditary and only in 17.3 per cent. of the non-hereditary cases. Of adults with blue sclerotics 60 per cent. are said to develop otosclerosis with or without evidence of bone fragility (Rodger, 1936). Osseous fragility, blue sclerotics, and deafness constitute Van der Hoeve’s syndrome.

Laxity of joints with susceptibility to strain and dislocation is not uncommon in families afflicted with one or more elements of the syndrome.

Osteomalacia—An osteomalacic element (molлитies), i.e., softening leading to bending, may be present in addition to fragility of bone and this contributes to the development of deformities, particularly in pre-natal cases. This feature is strikingly displayed in the pelvis which is indented and tri-radiate in 25 per cent. of all patients.

Fractures—The number of fractures varies enormously. In severe cases fractures are spontaneous and cause little if any pain. A newly born child may exhibit as many as 100 fractures, many involving the ribs. One patient with rather less severe manifestation of the disorder, but nevertheless of the pre-natal type and with blue sclerotics, died at the age of eight having sustained ninety-eight fractures. One bone is often fractured repeatedly; for example, a child sustained twenty-three fractures of only three bones. Refracture may of course be favoured by the additional osteoporosis which results from immobilisation of the first fracture, or by persistent angulation of the fragments, or by both these factors.

Dwarfing—Most severe cases are dwarfed. Dwarfing is accentuated, or indeed largely accounted for, by deformities of the limbs and curvature of the spine. Scoliosis is often severe and is present in at least a quarter of the cases. In pre-natal cases the limbs may be relatively short, sometimes to a striking degree.
Skull—The typical skull is broad, with prominent parietal and occipital bones (crâne à rebord); the ears are directed downwards as well as outwards. In some familial and hereditary cases the skull has prominent frontal and occipital regions with no bulge or ridge in the temporal region.

Teeth—The milk teeth are poorly calcified and semi-translucent or waxy. The permanent teeth are better calcified, even in post-natal cases, and they are usually normal in appearance.

Intelligence is at least up to the average.

The musculature is extremely feeble in all but milder cases, this hypotonicity being no doubt secondary to fractures and deformities.

Blood chemistry varies but is usually within normal limits, and is of no diagnostic value.

Clinical progress—A tendency towards improvement is often evident. This is seen most frequently in mild pre-natal and in post-natal cases. A few patients, in spite of severity of the disorder survive for many years; for example, a boy, a pre-natal case, was alive at the age of nineteen though bedridden since birth. Another pre-natal case, only slightly less severe and markedly dwarfed is still able to earn her living as a secretary at the age of twenty-nine.

Pathology—The essential pathology is imperfect formation and imperfect calcification of bone trabeculae. Islands of cartilage are seen, notably under the periosteum, with chondroid or incompletely calcified osteoid trabeculae taking the place of properly calcified bone. The periosteum is thickened, and there is failure to form a normal shell of cortical bone beneath it. The bone is discontinuous and fragmentary. The medullary contents may be in part fibroid, lymphoid, or fatty. Deficiency in numbers of osteoblasts has been stressed as an essential factor (Knaggs, 1924), but histological study of nine cases has shown great variation. In some, the number of osteoblasts was quite numerous although the formation of bone was deficient.

Radiographic appearances—Three groups of cases may be defined:

Type 1—Thick bone type (Fairbank, 1930)—These are severe pre-natal cases, born with limbs which are stunted as in achondroplasia and with numerous fractures, notably in the ribs. The major long bones are short; they are usually broad and thick, and show one or more fractures with ample callus. The proximal segments of the limbs, the femora and humeri, are most severely affected, but the tibiae may also be enlarged. The appearance of the bones suggests that the thickening is not due entirely to callus formation following recent or remote fractures. It may be seen up to three months after birth but is seldom met with later. Other bones show general osteoporosis and are similar to those seen in Type 2.

Type 2—Slender, fragile bone type—This condition is seen in pre-natal cases which survive more than a few months, and in all post-natal cases. The skeleton as a whole is osteoporotic and the long bones are usually slender. The cortex is characteristically thin and of deficient density. The extremities of the bone often appear large, and in older children they may show varying degrees of honeycombing. Occasionally the shafts of some long bones, perhaps after repeated fracture, may be slender and yet surprisingly dense as compared with the ends of the bones. Deformities due to fracture or bending are common. Transverse lines of dense bone, straight or wavy, often mark the ends of the metaphyses. In one ante-natal case, at the age of fourteen years, many rings of dense bone were seen in the epiphyseal lines in the region of the knee joint. The fibulae may be reduced to little more than faint lines. The skull is thin and Wormian bones may be present. The pituitary fossa is normal. The petrous bone may show excessive density. The vertebral bodies are translucent, shallow, spread, and biconcave, the intervertebral discs being biconvex.

Type 3—Osteogenesis imperfecta cystica—This name was suggested in 1935 for cases with pronounced honeycombing of bones. It is extremely rare. Only two living patients and one post-mortem skeleton are included in this series. The condition dates from birth. It is definitely progressive. Cystic changes which are more pronounced in the lower than in the
upper limbs become increasingly evident with advancing years. During the first few years of life the upper limbs may show no more than simple osteoporosis. Deformity due to fracture and bending of bone is progressive. Hereditary and familial influences are not in evidence. In the two cases here recorded the sclerotics were not blue. The condition differs from multiple diffuse fibrosis of bone in that bone change occurs much earlier; the radiographic appearances are not really similar and the histological appearances are quite different.

REFERENCES

The writer is greatly indebted to his many friends who have supplied him with clinical details of cases under their care. Figs. 1, 5, 6, and 24 are reproduced by courtesy of the British Journal of Surgery.

CASE I—OSTEGENESIS IMPERFECTA—Thick Bone Type—Pre-natal
(Figs. 1–4.) Male. Lived three days. Third child—others healthy. No history of bone fragility in family. Ossification of skull very imperfect and patchy. Very large fontanelle. Bossing of parietal bones. Numerous fractures including most of the ribs (under Dr G. F. Still).

![Fig. 1](image-url)

Case 1. Greatly thickened cylindrical femora with multiple fractures; the thickening is not entirely due to callus. Upper ends of tibiae somewhat enlarged.
Case I. Note that there are fractures of all long bones including the clavicles, which show some relative thickening; also fractures of most of the ribs.

Fig. 2

Fig. 3
Case I. Note the relative shortness of limbs suggesting achondroplasia.

Fig. 4
Case I. Section of femoral shaft. Fragmentary bone formation; complete absence of continuous cortical layer beneath thickened periosteum; in this case marked deficiency of osteoblasts.
CASE 2  OSTEOGENESIS IMPERFECTA—Thick Bone Type—Pre-natal

(Figs. 5-6.) Female. Lived ten weeks. Seventh child. Mother very poorly nourished during pregnancy. Other children healthy. Skull very imperfectly ossified. Serum calcium low—5·45 mg. per cent. (Under Dr F. J. Poynton.)

Fig. 5
Case 2. Note the short, thickened humerus with fracture and callus formation. The radius and ulna are not generally thickened, but are poorly calcified with thin, translucent cortices and somewhat bulbous extremities.

Fig. 6
Case 2. The tibiae as well as the femora are affected by the general thickening which is apparently not due to callus.

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CASE 3—OSTEOGENESIS IMPERFECTA—Slender Bone Type

(Figs. 7–8.) Girl aged six years. History imperfect but almost certainly pre-natal in origin. Only child. Dwarfed. Has had many fractures. Sclerotics blue, but not markedly so.

Case 3. Femora show very slender shafts with much deformity due mostly to mal-union of fractures. Typical osteoporosis of the ends of the bones and the epiphyses. Pelvis slightly deformed.

Case 3. Typical slender, imperfectly ossified tibia and fibula with marked deformity, apparently due more to bending (mollities) than to fractures. Bones of foot show similar fragile appearance. Note the poor cortex of tarsal bones which do not show the "pencilled outline" seen when translucency is due to simple atrophy.
CASE 4—OSTEOGENESIS IMPERFECTA—Ante-natal (Brother of Case 5)

(Figs. 9-10.) First fracture at six months, though disease certainly ante-natal. Severe case. Has never walked though aged eleven years when last seen. Scleroties not noticeably blue. Elder sister also affected (Case 5) but a brother and sister, the first and third children of the family, are normal. No known hereditary influence. Died when aged nineteen years.

![Image](9)

Case 4. Tibia when aged 5 years (Fig. 9) shows extremely slender, fragile bones, with one fracture. When aged 8½ years (Fig. 10) extremities of femur show typically poor ossification. Central portion of shaft, slender but sclerosed. Ununited fracture with persistent tendency to angulation.

CASE 5 OSTEOGENESIS IMPERFECTA—Ante-natal (Sister of Case 4)

![Image](10)

Case 5 at 12 years of age. Slender femora with coxa vara. Tri-radiate pelvis and scoliosis. Shaft of left femur fractured.
CASE 5—OSTEOGENESIS IMPERFECTA—Ante-natal (Sister of Case 4)

(Figs. 11–13.) Born with fractured humerus. First seen at age twelve years. Sclerotics not blue. Has shown some tendency towards improvement. Angular deformity of right tibia and left femur resulted in very delayed union of fractures of these bones with a strong tendency to refracture. Was able to walk with appliances for various periods between fractures. Dwarfed—not entirely by fractures. Severe scoliosis. Tri-radiate pelvis—bones are therefore soft as well as fragile. At age twenty-nine years is able to walk, and work as a secretary.

Fig. 12
Case 5 at 16 years of age. Note the slenderness of right femur and marked shortening of left femur due mostly to anterior bowing.

Fig. 13
Case 5 at 19 years of age. Left femur shows gross anterior bowing, the result of repeated fractures, one incompletely united after many months.
CASE 6--OSTEOGENESIS IMPERFECTA
Ante-natal (Fig. 14.) Male aged seventeen years. Born with one leg fractured. History of at least seventeen fractures. Sclerotics markedly blue. Half-sister (same mother), has blue sclerotics but no fragility. Tri-radiate pelvis. Scoliosis.

Case 6. Note the unusual general cancellous appearance with poorly defined cortex and general osteoporosis. The deformity suggests bending of the bones rather than malunion of fractures, but the leg has been fractured at least once.

CASE 7--OSTEOGENESIS IMPERFECTA
Post-natal (Fig. 15.) One of twin girls aged seven years. Both were affected and both showed blue sclerotics. The onset was post-natal. There were familial and hereditary factors. A comparatively mild case.

Case 7. This leg has been fractured nine times, the last a year ago. Shows typical slender, fragile type of bones, with imperfectly united fractures, very easily refractured. Child was walking. Deformity corrected by open operation.
CASE 8—OSTEOGENESIS IMPERFECTA—Ante-natal

(Figs. 16–17.) Female baby aged nine months. Born two months prematurely with a leg broken. The head was markedly flattened antero-posteriorly. A very severe case with multiple fractures of nearly all ribs, both thighs, both legs, both arms, and both forearms, and with gross deformities of the limbs.

Case 8. Note that nearly all the ribs are fractured; some are broken in two or three places. Nevertheless the child was alive nine months after birth. The upper limb is typical of the condition, with multiple fractures and gross deformity.
Case 8. Severe ante-natal case (aged nine months) with multiple fractures of many ribs (Fig. 16) and of all four limbs (Fig. 17). Exceptionally marked fragility with gross deformity of all long bones of the lower limbs.
CASE 9—OSTEOGENESIS IMPERFECTA—Mild Post-natal Case

(Fig. 18.) Male aged seven years. The patient’s father broke his leg three times between the ages of fourteen and sixteen, but has not blue sclerotics. No other fractures in family. The child’s sclerotics are rather blue. Only three fractures to date.

Fig. 18

Case 9. Spine shows osteoporosis with very shallow biconcave vertebral bodies and deep biconvex discs.
CASE 10—OSTEOGENESIS IMPERFECTA

(Figs. 19-22.) Male aged nine years. Very numerous fractures dating from birth. Scoliosis and tri-radiate pelvis. Circumference of head twenty-two and a half inches—of abdomen twenty-three inches. Has never walked. Sclerotica not blue. When sitting, height was seventeen inches. Blood chemistry shows no striking abnormality. Was still alive at the age of nineteen years. (Under Mr H. Tyrrell-Gray.)

![Fig. 19](image)

Case 10. Note the absence of cortex and the suggestion of honeycombing of the bones.

![Fig. 20](image)

Case 10. The bones are grossly deformed and there is almost complete absence of cortex.
Case 10. Radiographs of lower limbs show gross deformity with irregular density, both the result—at least in part—of multiple fractures.

**Fig. 21**
Case 10. Male aged 9 years with very numerous fractures dating from birth. Note the characteristic bulge in the temporal regions. The circumference of the head was twenty-two and a half inches; the circumference of the abdomen twenty-three inches; the sitting height seventeen inches. Calcification of the teeth is not bad.
CASE 11—OSTEOGENESIS IMPERFECTA

(Fig. 23.) Girl aged fourteen years. Pre-natal onset. No hereditary or familial influence. Temporary teeth were markedly translucent. Sclerotics not blue. Many fractures had been sustained—fourteen in the first three years of life.

Fig. 23

Case 11. Curious multiple circular opacities or rings in the metaphyses and epiphyses of the femora and tibiae adjacent to the two knee joints. Comparable changes were not seen elsewhere in the skeleton.
CASE 12—OSTEOGENESIS IMPERFECTA CYSTICA

(Figs. 24-33.) Girl, seen at the age of five years, and again when eleven years of age.

Family history—Father normal. Mother, and several members of the mother’s family, including her father, were said to have bluish sclerotics, but there was no history of bone fragility. The patient was the third of five children; two have blue sclerotics without bone fragility, and the others are normal.

Clinical history—History of many fractures; the condition was said to be congenital. She was not deaf. The sclerotics were not unusually blue. The head was not of typical shape; there was no bulging in the temporal regions. There was scoliosis. Deformity of the pelvis was severe and apparently responsible for faecal obstruction when she was in hospital. She could not walk but made good use of her arms.

Blood examination—Red cells, 3.6 million. White cells, 84 thousand. Lymphocytes, 60.5 per cent. Wassermann reaction negative. Slight trace of albumin in urine but blood urea within normal limits. Serum calcium normal (complete investigation of calcium metabolism was impossible). Phosphatase raised (1.42 units—normal 0.1 to 0.2).

Radiographic examination—Honeycombing was distributed throughout the whole skeleton but not in a uniform manner. In the lower limbs it was fairly general, but in the upper limbs (at the age of five years) only the metaphyses were cystic. This was strikingly so in the radius and ulna. By the age of eleven years, when the condition appeared to have increased in severity, this distinction was much less obvious.

Microscopic examination of bone—Microscopic sections of bone from the tibia show medullary spaces filled with loose vascular fibrous tissue.

Subsequent history—By the time the child was eleven years old the deformities had become much more accentuated. At the age of eighteen years the bone changes were universal, even the skull showing changes. The girl died when aged twenty-three years.
Case 12. Radiograph of femora and pelvis at the age of 5 years shows almost general cystic condition. There is marked deformity of the pelvis. The inset (Fig. 26) is a microscopic section of a fragment of tibia, showing the medullary spaces filled with loose vascular fibrous tissue.
Case 12. The grossly deformed child when aged 11 years.

Fig. 27
Case 12. Aged 11 years. The whole of the shafts of radius and ulna, and the bones of the hand, are now affected.
FIG. 29

Case 12. Aged 18 years. The upper limbs show generalised cystic changes in all bones, with old and recent fractures.
Case 12. Aged 18 years. The hand shows almost universal changes.

Fig. 30

Case 12. Aged 18 years. The lower limbs show gross cystic changes, particularly marked at the extremities of the bones.

Fig. 31
Case 12. Aged 18 years. Foot showing general changes.

Case 12. Aged 18 years. Skull showing irregular hyperostosis affecting both tables of the skull in the frontal and parietal regions.
CASE 13  OSTEOSTENESIS IMPERFECTA CYSTICA

Radiograph of part of a skeleton in the museum of King's College Hospital. The history is unknown. Apparently of adolescent age. Multiple fractures, scoliosis, and deformity of the pelvis are seen. The marked cystic structure of the bones seems to justify inclusion in the cystic class of osteogenesis imperfecta.

Footnote—Attention has been called by Professor S. L. Baker to a very rare complication of osteogenesis imperfecta, namely Hyperplastic Callus Simulating Sarcoma (Journal of Pathology and Bacteriology 1946, 58, 609).