

OSTEOGENESIS IMPERFECTA CONGENITA *

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This condition was first described by Vorlik in 1849. Up to 1906, 140 cases had been reported. So many names have been used in the description of bone abnormalities in infants that an uncertainty remains as to just what is meant in some of these descriptions. For example, Lovett and Nichols,¹ after a careful study of all the case reports, conclude that only fourteen of these are true cases of osteogenesis imperfecta congenita. Since the introduction of the roentgen ray the descriptions have been more accurate. Valuable articles on the subject have also recently been contributed by Schwartz and Bass,² Griffith,³ Hess,⁴ Bookman⁵ and Mixsell.⁶

Two types are recognized, namely: osteogenesis imperfecta congenita and osteogenesis imperfecta tarda. Authors are convinced that there is a clearly defined distinction between these two types. It is a rare systemic disease of unknown etiology, characterized by imperfect development of bone, numerous fractures and excessive callus formation.

The condition has been described in textbooks under a variety of names as follows: Osteomalacia congenita; rachitis foetalis annularis; malacia myeloplastica; periosteal dysplasia; dystrophia periostale; osteitis parenchymatosa chronica; micromelia annularis; osteoporosis congenita; fragilitas ossium.

Some authors (Griffith,³ Schwartz and Bass⁴) uphold the theory of an hereditary tendency; others, however, find no familial influences. A study of the recent literature would indicate that syphilis is not a cause. There is no evidence of a disturbance of the endocrine glands, and environment is not a factor.

Opinion differs as to the process of bone formation in this condition. Axhausen says that there is a deficiency in periosteal bone formation due to the lowered function of the osteoblasts, but that the preparatory calcification of cartilage and the absorption of bone are normal. According to Sigowa, the pathologic process consists in a

* Read before the American Pediatric Society, June, 1919.

1. Lovett and Nichols: Brit. M. J. **2**:915, 1906.

2. Schwartz and Bass: Am. J. Dis. Child. **5**:131 (Feb.) 1913.

3. Griffith: Am. J. M. Sc. **113**: 1897.

4. Hess: Arch. Int. Med. **19**:163 (Feb.) 1917.

5. Bookman: Am. J. Dis. Child. **7**:436 (June) 1914.

6. Mixsell: Arch. Pediat. **34**:756 (Oct.) 1917.

disproportion in the building up and breaking down leading to osteoporosis. Whatever the theory, the fact is that bone formation from periosteum remains in a primary fibrous state. Osteoporosis is a secondary result from the excessive formation of medullary spaces, due to deficient development of bony substance and increased absorption. In the congenital type of case, such as the one described, a more remote cause is embryonal failure of the periosteum and endosteum at the time when ossification should begin, so that the lime salts are deposited in small amounts.

The study of the bone in this case shows evidence that the osteoblasts rising from vascular fibrous bone marrow, because of insufficient nourishment or some toxic influence, did not develop properly, but remained polygonal and later underwent metaplasia into osteoclasts.

REPORT OF CASE

Baby L., male, was admitted to University of Nebraska Hospital, Oct. 1, 1918, aged 3 months. Breast fed up to the time of admission.

History.—Parents in good health. Two older children living and well. No miscarriages. Pregnancy normal and full term. Labor normal. Deformity was apparent at birth. Infant had several fractures, including forearm, thighs and legs. Masses in shafts of long bones easily felt. Head was large and soft. Cry had always been feeble; nursed readily; bowels regular and of yellow color; urine free.

Condition on Admission.—The infant lay on a cot, with thighs flexed on body, seldom moving unless disturbed. The cutaneous reflexes were normal. The abdomen was large, with an umbilical hernia. Spleen and liver were normal. Arms and legs were bent and deformed. Masses of callus could be palpated in the shafts of the humeri, femora and tibiae. Ribs felt soft and pliable, with no discernible fractures. Head felt like a membranous bag with small islands of bone here and there. The skin was soft; the eyes followed objects; no exophthalmos. Heart and lungs were normal; weight 7 pounds and 2 ounces. The mother was certain that the baby had grown, but it was not weighed at birth. Wassermann was negative; von Pirquet tuberculin test was negative. Urine: specific gravity, 1.008; albumin, negative. diacetic acid, negative; acetone, negative; indican, positive; microscopic examination negative.

Blood: Hemoglobin, 70 per cent.; red blood cells, 3,640,000; leukocytes, 18,700. Differential leukocyte count: polymorphonuclears, 56 per cent.; lymphocytes, 40 per cent.; eosinophils, 2 per cent.; special forms, 2 per cent.

As the mother did not remain with the infant, it was placed on a modified milk mixture. The child remained in the hospital from Oct. 1 to Nov. 16, 1918. During the first two weeks of its stay it made a gain of 10 ounces in weight; the next two weeks it lost 8 ounces, due to indigestion and withdrawal of food. For the next three weeks it lost 4 ounces. During the last three days of life, while acutely ill it lost 17 ounces of weight. Ten days before death there developed numerous small furuncles over the body. A culture of the pus revealed *Staphylococcus aureus* in pure culture. While in the hospital, the temperature varied between 99 and 102 F. The bowels were normal, except on two occasions. The urine was free and did not stain. He constantly remained very quiet. The arms were placed in light splints at right angles to the body; the legs were constantly flexed. No attempt was made to apply splints to the legs. November 14, he developed a temperature of 105.6 F. with cough and dyspnea. Respirations were from 60 to 90. The temperature ranged from 103 to 105 F. during entire period of sickness. Examination of

the chest revealed fine râles over the posterior chest with small areas of dulness on percussion. During the last twenty-four hours of life there were frequent attacks of cyanosis, and for the last twelve hours of life there was a constant expiratory grunt. Death from exhaustion, November 18, with a loss in weight of 17 ounces, during this period. As far as can be ascertained from the literature, this is the youngest case with a fatal issue which has been reported in which a careful histologic study has been made.

The conclusions of Professor Willard agree very closely with those recorded by Nichols on an infant dying at the age of 10 months, the youngest previously reported.

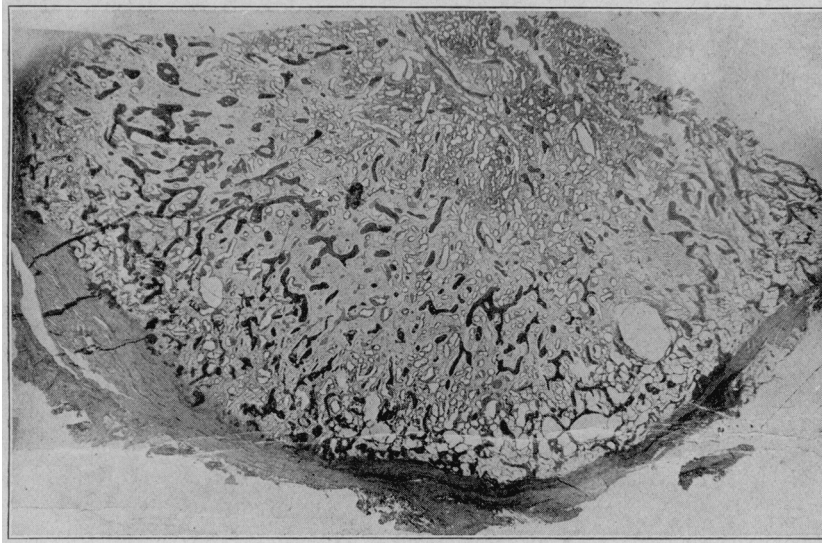


Fig. 1.—Half of transverse section of diaphysis of left femur. Decalcified in nitric acid and formol. Doubly embedded in celloiden and paraffin. Section cut 10 microns thick. Stained in hematoxylin and eosin. Photomicrograph shows an enlargement of 10 diameters. The partially ossified trabeculae are shown black. They are less numerous near the center of the shaft and extend slightly into the periosteum at the periphery. The periosteum is much thicker than normal. It reacts to fracture of the bone by still further thickening, as indicated on the left side of the section. Note the absence of a wall of compact subperiosteal bone which in the normal would extend half way to the center of the diaphysis although the total diameter of the normal is less than half that represented in this case. The blood sinuses of the marrow are the numerous smaller open spaces. Blood cells are adherent to their endothelial walls showing as a darker border to the spaces. The larger spaces in the periphery are possibly shrinkage spaces in the mucoid-like marrow. Blood forming marrow cells are abundant only in the center of the bone where they give a darker appearance to the section.

The apparent shortening and bending of the legs are believed to be due to the pull of the muscles. The relative shortening of the legs and the long body would suggest achondroplasia. However, in the latter condition there is interference with the proliferation of car-

tilaginous cells in the zone between the shaft and epiphysis, resulting in shortening and premature ossification of the long bones. There is also a premature ossification of the sphenoid and the sphenoidal processes of the occipital bone which lead to skull clavis. Both of these conditions are absent, as shown by the roentgenogram and the microscopic studies of the epiphyses. The thickening of the bone is due to increased deposition of cartilaginous cells.

The soft condition of the bone, the multiple fractures and the excessive callus formation combine to make the diagnosis of osteogenesis imperfecta congenita.

REPORT ON NECROPSY

A postmortem examination was made five hours after death by Dr. J. A. Wineberg.

Inspection: Small furuncles were scattered discretely over the head, trunk and extremities. The face was that of an "old man"; the body was emaciated; weight, 5 pounds 15 ounces; the head was large, easily compressed; the arms and legs were short and curved. Callus masses were readily palpated.

Abdomen: No gross changes noted in intestines, liver, spleen or kidneys. No excess of free fluid.

Chest: Both lungs show patches of consolidation with small areas of hemorrhagic infarctions on section. Pleura shows no adhesions. Thymus and thyroid normal. Suprarenals normal. Brain not examined.

Bones: Long bones show multiple fractures with false joints in right tibia and left humerus. Periosteum not ruptured, except on the humerus and on the tibia. On removal of the bones, the left humerus was broken in being dissected out. The bones have a grayish appearance; are easily bent; are soft and pliable. A number of callus rings were present on the site of former fractures.

Microscopic Examination.—The spleen shows congestion. Large areas of necrotic tissue are present in the lungs similar to other postmortem findings in influenzal pneumonia. Kidneys show parenchymatous degeneration. Liver, thyroid, thymus and suprarenals normal. The histologic examination of the bone was made by Dr. Willard.

As the name indicates, this case is one of imperfect development of bone. The interest in the histologic side of the question centers chiefly in the attempt to discover in what way the normal process has been arrested or diverted. This is not easy to do in the absence of stages in the process, the normal of which is an extremely complex and imperfectly understood subject.

However, the outstanding features of normal bone development are well known, involving as they do the early development of an embryonic cartilaginous skeleton which in fetal life is largely replaced by bone and to which are added other bones developed in fibrous tissue and known embryologically as membrane bones.

The histologic structure of all bone tissue is the same regardless of origin, owing to the fact that it is always formed by accretion or deposit of osseous matrix through the combined activity of certain cells derived from embryonic connective tissue. It is thus formed

locally wherever these osteoblasts are active, and when once formed, is fixed, unless absorbed. Such absorption or destruction of bone is a normal part of bone growth and is supposed to be accomplished by large multinucleate cells known as osteoclasts. If this is true, the form and architecture of a bone depends on the balanced interplay of osteoblasts and osteoclasts. The cause behind this is unknown, and must be answered before a real explanation of osteogenesis imperfecta can be advanced.

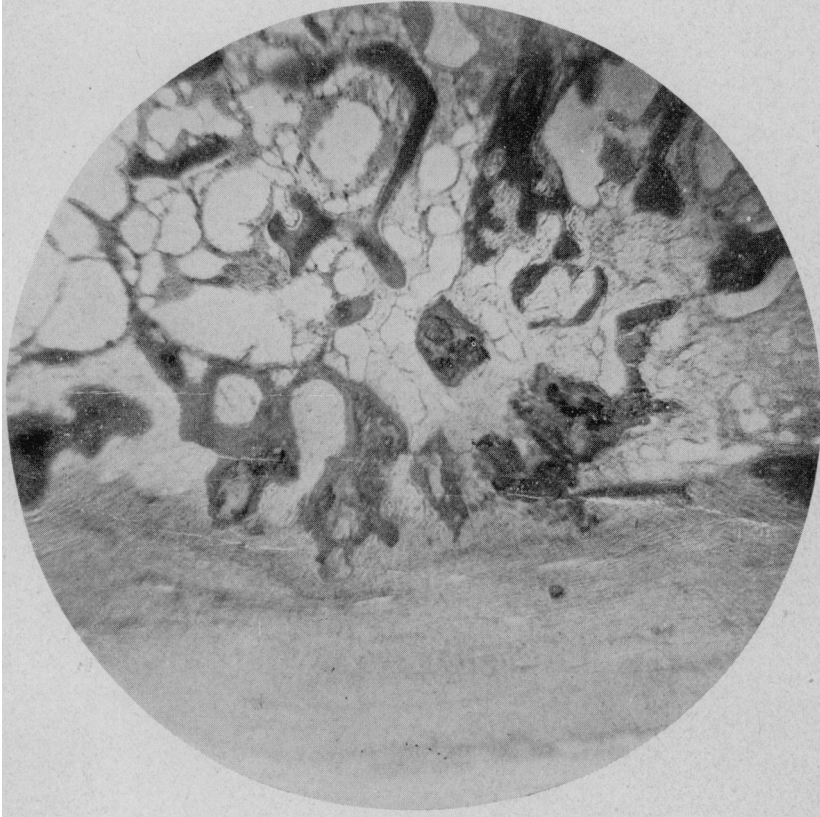


Fig. 2.—Detail from Figure 1. Magnification, 50 diameters. The full thickness of the periosteum with some adjacent bony trabeculae are shown. The darker central areas of the trabeculae are cartilage which has been formed from the periosteum.

Previous investigations on osteogenesis imperfecta indicate that all the bones of the body show much the same changes. We may, then, take the features presented by sections of the femur as typical of this condition. The sections shown in Figures 1, 2 and 3 are from the middle of the shaft or diaphysis of the bone, but they can only be fully understood through a consideration of the bone as a whole. First,

consider the condition of a normal long bone in the new-born child. The shaft is slender but composed of an outer shell of compact bone, which in the case of the humerus is one fourth the total diameter. The marrow cavity is traversed by strong trabeculae entirely of bone. The cartilage of embryonic days has long since been absorbed and no new cartilage is formed. The epiphysis, on the other hand, is composed entirely of hyalin cartilage. The ossification centers that will appear later are preceded at this stage by a vascularization. The region where

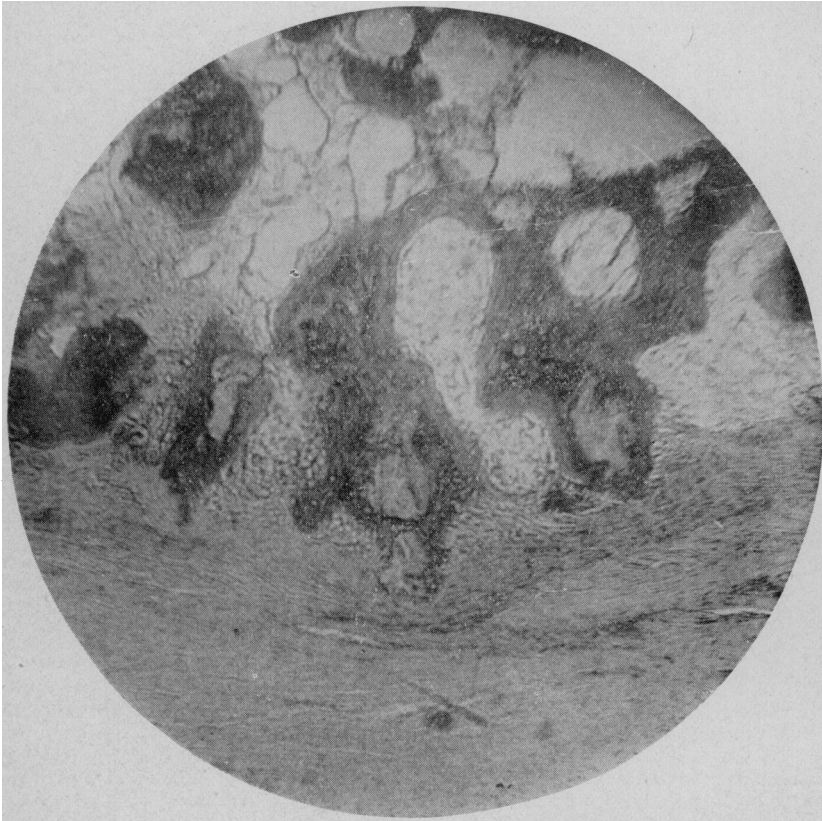


Fig. 3.—Small portion of the field shown in Figure 2. Magnification, 100 diameters. This shows the transformation of periosteal tissue into trabeculae. The encapsulated cartilage cells shown at the left represent the first stage in this process.

the cartilage abuts on the marrow cavity of the shaft is the zone of cartilage absorption and spongy bone formation. As long as the bone is capable of growing in length this zone persists. The increase in length depending directly on a process of cartilage formation in this zone between the epiphysis and the shaft of the bone. Keeping pace

with this cartilage formation on the side of the epiphysis, cartilage absorption is going on next the marrow cavity. This absorption is incomplete in that slender remnants are left which offer the scaffolding on which the osteoblasts of the marrow begin the deposit of bone, thus building up bony trabeculae and contributing the necessary strength to the shaft until the sides of the shaft shall have been strengthened through the formation of a wall of compact bone laid down underneath the periosteum. With the normal growth at the ends of the bone but with the absence of periosteal bone formation at the sides, there would be formed a shaft consisting of a fibrous periosteum enclosing marrow tissue through which anastomosing bony trabeculae would run. If the actual formation of bony tissue around the trabeculae should be still further reduced, they would consist of little more than cartilage remnants with one or two lamellae of bone tissue covering them. If, along with this reduced activity on the part of the osteoblasts or bone forming cells there exists increased or even normal activity on the part of the osteoclasts or bone absorbing cells, there is nothing left in the process to result in bone of any strength whatever.

REPORT OF HISTOLOGIC EXAMINATION OF BONE

A study of the sections in this case of osteogenesis imperfecta shows evidence that the normal processes of bone growth have been diverted in all these ways. All accounts seem to agree that cartilage is formed in the normal way and that the vacuolization of the cartilage leading to the formation of the primary marrow spaces in ossification centers occurs normally but that this process is not met by an immediate and active formation of bony tissue on the part of the osteoblasts. The cartilaginous epiphyses are normal in size and character in this specimen, but the section through the diaphysis as shown in Figure 1 shows complete absence of periosteal bone formation. The periosteum is abnormally thick but there is no bony wall underlying it. The trabeculae scattered through the marrow are slender, and section shows them to be poor in bone tissue. They all show cartilage remnants indicating that bone development has not gone beyond the initial stage. On the other hand, the actual size of the shaft is three times that of normal. Comparison shows that a normal humerus of a new-born child has a slender shaft about 5 mm. in diameter with an enlarged epiphysis of 15 mm. In this case, the shaft of the humerus has a diameter of 14 mm. while the epiphyses corresponds to that of the normal at birth. It should further be stated, that the normal shows a marrow cavity of less than 3 mm. surrounded by a wall of compact bone more than 1 mm. in thickness. The thick stocky form of the bones in osteogenesis imperfecta may be explained as the result of muscle pull on a shaft that has no supporting walls, but histologic study of the periosteum indicates that there is also a process of transformation of subperiosteal tissue into certain constituents of the marrow. This would contribute to the process that widens the marrow cavity. This subperiosteal zone is the one region where abnormal process seems to be an active one. The osteogenic layer of the periosteum, instead of forming orderly circumferential layers of bone, expresses itself in this abnormal condition through the formation of poorly developed type of cartilage. This arises in localized areas and pushing out into the marrow cavity form trabeculae which may become slightly bony as in the case of the other trabeculae. One may recognize in Figures 2 and 3 showing detail of this

region groups of encapsulated cells resembling embryonic cartilage. Between the bases of these trabeculae which extend in from the periosteum multinucleate cell masses often appear. These have the structure of osteoclasts and transitional forms trace their origin to the deeper cell layer of the periosteum. Similar masses are smaller and less numerous throughout the rest of the marrow.

The marrow and its vascularization is strikingly different from the normal. The delicate reticular tissue of normal marrow is replaced by a mucoid-like ground substance containing relatively few cells. Many of these being large fibroblasts, giving tissue a distinctly embryonic appearance. Throughout the marrow are large sinusoidal blood vessels with distinct endothelial lining. The characteristic marrow cells of blood-forming function were found in abundance only in the central part of the section. Careful analysis of these cells could not be made from the material thus far studied, but typical myelocytes, nucleated red cells and megakaryocytes (giant marrow cells) were prominent.

In the foregoing general account there has been no attempt to discuss the literature bearing on the microscopic study of the bones in cases of osteogenesis imperfecta. This will be left to a later study of the cellular elements. This case, as far as presented, agrees in essentials with the description by Michel and others.