Acta orthop. scandinav. 38, 280–290, 1967.

From the Orthopaedic Hospital of the Invalid Foundation.
(Head: Professor A. Langenskiöld, M.D.) Helsinki, Finland.

HYPERPLASTIC CALLUS FORMATION IN OSTEOGENESIS IMPERFECTA

Report of a case simulating sarcoma.

By

L. E. LAURENT & P. SALENIUS

Received 27.ii.67

Hyperplastic callus formation in osteogenesis imperfecta is rare. *Strach* (1953) stated that fifteen cases had been described in the literature. The pathology was described by *Baker* (1946) and the clinical picture by *Fairbank & Baker* (1948). Early in the course of the disease, particularly, the clinical picture and the radiological findings resemble those of sarcoma. At least two cases have been described in the literature in which amputation was carried out, but the subsequent course showed that the condition had been due to hyperplastic callus formation. We therefore feel justified in reporting a further case.

CASE REPORT

The boy born in 1954 was first seen at the age of three years. There was a history of fracture of the right femur at birth. Later there had been fractures of the ribs and the right tibia. No family history. The patient had not blue sclerae. No gross, deformities, the patient was able to walk. In 1959, the radiograms showed typical platyspondylia with codfish vertebrae; there were fractures of the left tibia and the right fibula. The right femur was very slender. There was thickening of the distal part of the left femur (Figure 1). The patient was no longer able to walk.

In 1962 the patient was admitted to the hospital. During the preceding year he had fractured both tibiae. Severe antecurvatum and valgus deformity of both legs had developed. The spine was kyphotic and the thorax deformed. The upper extremities looked almost normal. In both hips there was severe flexion contracture. A two stage release operation with fasciotomy at the anterosuperior iliac spine was carried out on both sides.

Two weeks after the last operation the patient had fever lasting for two months. The sedimentation rate rose to 65 and the Hb fell to 9.1 g. The calcium and phosphorus values were normal, and the alkaline phosphatase rose to 13 Bodansky

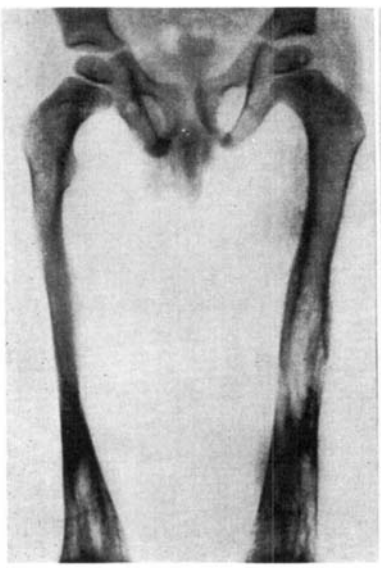

Figure 1. *Figure 2.*

Figure 1. Radiograph in 1959, when the patient was five years old. The right femur is slender, the left thickened. The hip joints appear normal.

Figure 2. Radiograph in 1962 after bilateral release operation for hip contracture. There is a considerable callus formation at the lateral border of the left acetabular roof.

units/ml. The condition was interpreted as a streptococcal infection (AST 2300) and the symptoms gradually subsided under antibiotic treatment. A radiogram two months after the operations showed considerable callus formation in the area of the left hip and slight callus formation above the right hip joint (Figure 2). Continuous therapy with anabolic hormone was instituted (dianabol 1 mg×3), dosage periods of two weeks alternating with intervals of two weeks.

Nine months later, in February 1963, the patient was readmitted. He had had fever for two weeks and progressive swelling of the left thigh. Remitting diagnosis osteomyelitis femoris sin. The left thigh was swollen and hot, and the skin reddish with dilated veins. The clinical appearance is seen in Figure 3.

Sedimentation rate 42, Hb 9.7 g. Alkaline phosphatases 5 Bodansky units. One month later the phosphatase value had risen to 13. Radiogram (April 5, 1963) (Figure 5), showed slight callus formation and extensive infiltration of the soft tissues of the left femur, but no fracture. Since clinically and radiologically there was a suspicion of sarcoma, biopsy was carried out on April 16, 1963. Microscopic examination showed undeveloped cartilage cells which did not form an organized structure. The cells were in places spindle-shaped, resembling myxoma cells. The stroma was loose. No mitoses. Histologically the tumour was benign. PAD: Chondro-myxo-fibroma (Figure 4).

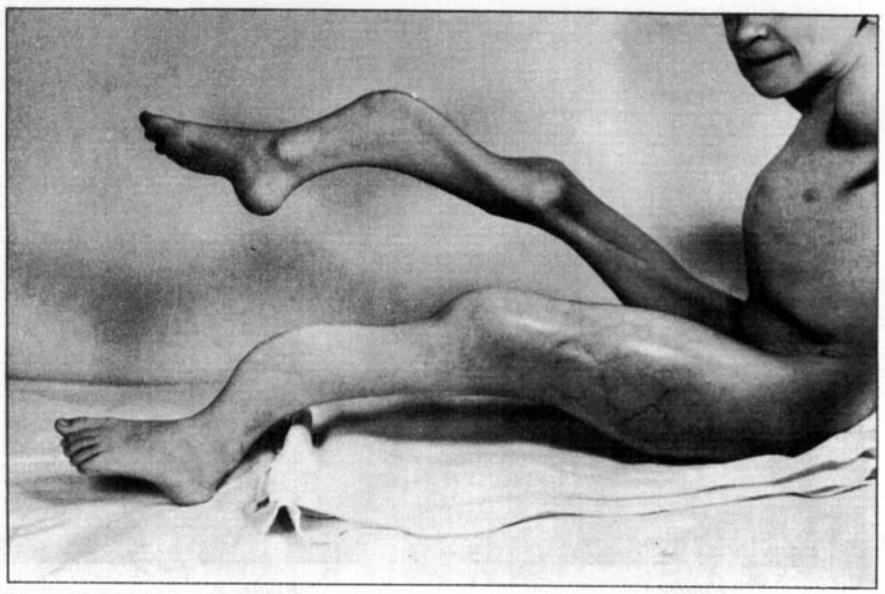

Figure 3. The appearance of the patient on 4.4.1963 when a callus tumour had developed in the left thigh, which was swollen, reddish and hot. Severe ante-curvatum deformity of both tibiae.

The patient was sent to another hospital for radiotherapy. For a period of three weeks he was given 2300 r into the tumour, and there was evident regression. Biopsy was again carried out on May 11, 1963, four weeks after the earlier biopsy, four different pathologists being consulted. At this stage the patho-anatomical diagnosis was callus tissue. Radiogram of June 14, 1963, shows hyperplastic callus (Figure 6). The condition normalized about one month later, although there was still considerable thickness of the proximal part of the left femur.

The patient returned to the hospital 3½ years later, in December 1966. He had been to a school for crippled children since autumn 1963, sitting in a wheel-chair. There was severe deformity of the lower extremities. Both tibiae were sabre-shaped. There was marked flexion contracture in the hip and knee joints. Mobility in the hip joints was insignificant, and in the knee joints very limited. As a result of platyspondylia there was a marked gibbus, and the chest was sagittally compressed. The cranial bones were thin but otherwise the head was normal and the teeth good. There were no significant deformities in the upper extremities and their function was satisfactory. Radiograms of the forearms showed bilateral bony excrescences on the interosseous border of radius and ulna. The patient had had no fractures since 1962, since when anabolic hormone had been continuously administered.

For the past month the patient had had pain in his right thigh in which a diffuse induration could be felt. The sedimentation rate was increased, 33, but there were no other inflammatory symptoms. The left femur was proximally thickened as

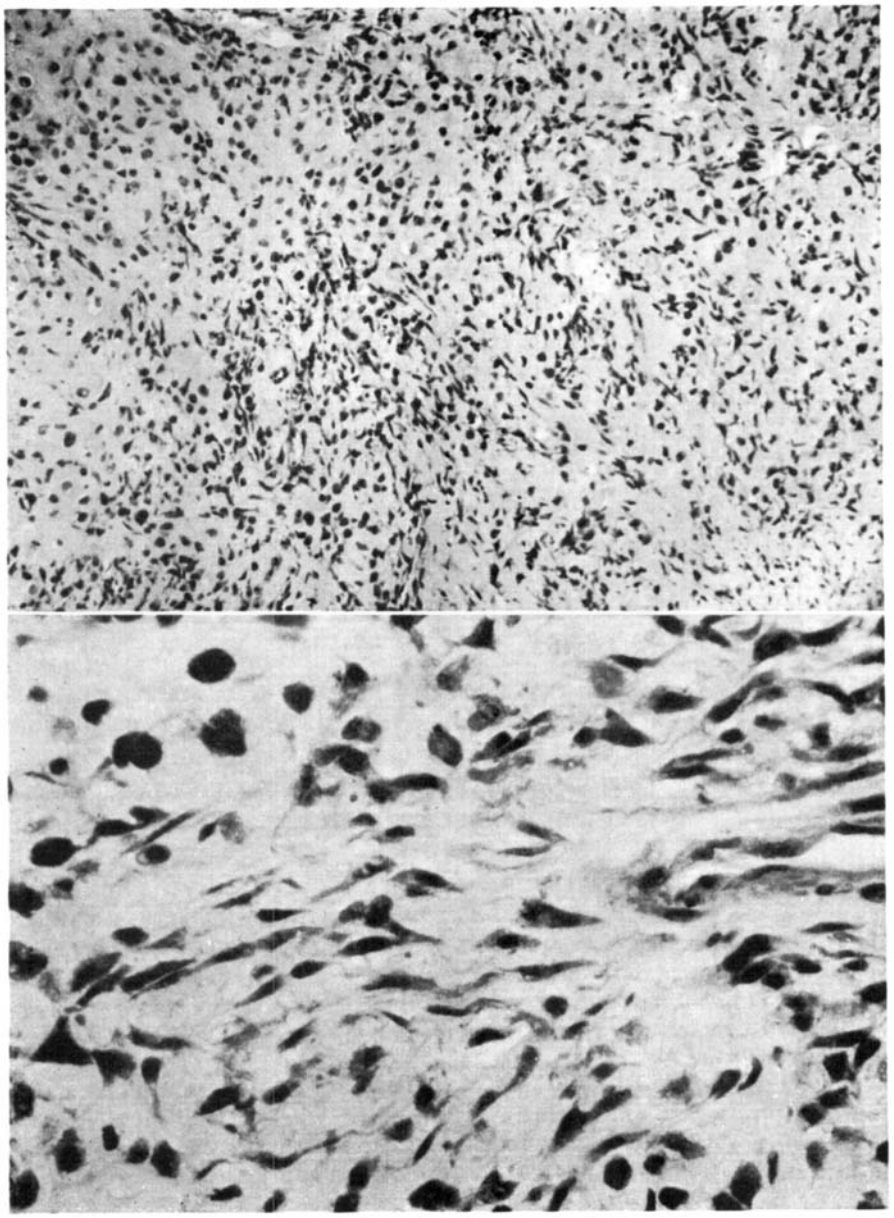

Figure 4 A and B. Micrographs of section of biopsy specimen of the callus tumour taken 16.4.1963. Nuclear pleomorphism and hyperchromasia are seen in tissue containing fibroblasts and chondrocytes. (A × 80, B × 267, HE).

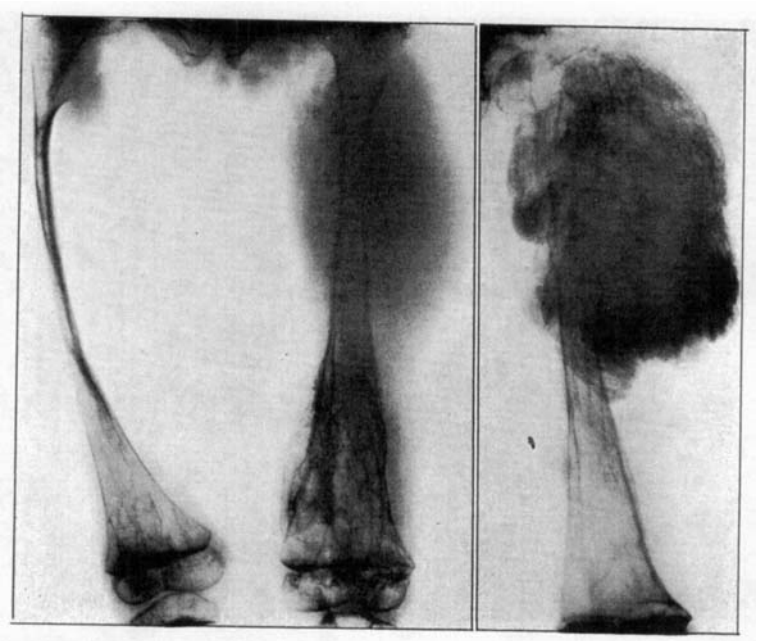

Figure 5. *Figure 6.*

Figure 5. Radiograph on 5.4.1963. Slight callus formation is seen on the lateral side of the proximal part of the left femur and an extensive infiltration of the soft parts. No fracture visible.

Figure 6. Radiograph on 14.6.1963 shows abundant callus formation in the proximal part of the left femur.

a result of the earlier hyperplastic callus formation. Radiographic examination of the right femur on Dec. 2, 1966 (Figure 8) showed slight callus formation but no fracture. The patient was discharged for Christmas and readmitted one month later. He had had fever for two weeks. The right femur was now very swollen, red and inflamed, the clinical picture being similar to that of the left thigh 3½ years previously (Figure 7).

Radiogram of the right thigh on Jan. 16, 1967 (Figure 9) showed massive callus formation. Radiogram of the left femur (Figure 10) revealed extensive calcification in the proximal part as a result of the process in 1963. The bony formation overbridges the hip joint. Sedimentation rate 65, Hb 8.3 g, Er: 3500, leuk. 10700. Alkaline phosphatase 13.2 Bodansky units. WaR–. Radiotherapy was commenced and the general condition improved. Regression of the tumour cannot so far be observed but the pain has been considerably alleviated.

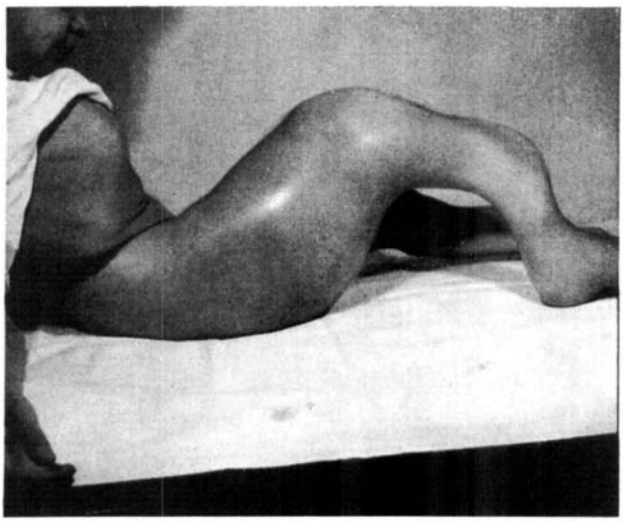

Figure 7. Appearance of the patient in January, 1967, when a callus tumour developed in the right thigh, which was swollen, hot and tender.

Figure 8. Radiograph on 2.12.1966 shows callus formation on the medial side of the distal part of the right femur. No fracture visible.

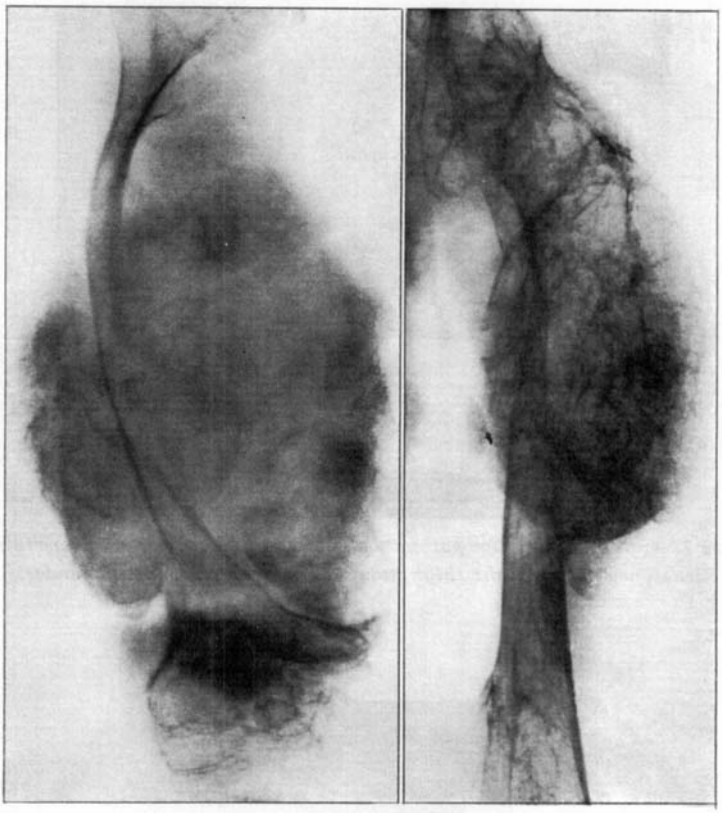

Figure 9. *Figure 10.*

Figure 9. Radiograph on 16.1.1967. There is massive callus formation around the right femur. X-ray treatment was instituted.

Figure 10. Radiograph on 16.1.1967 of the left femur shows an extensive callus formation as a result of the process in 1963. The bony formation overbridges the hip joint.

COMMENTS

The patient's skeleton showed clear signs of osteogenesis imperfecta. Before the age of eight, he had had at least seven fractures in the lower extremities and also fractures of ribs. When the patient was eight years old, continuous treatment with anabolic hormone with intervals of two weeks was instituted. During a subsequent follow-up period of four years, the patient had not had additional demonstrable fractures, but there had been three episodes with formation of hyperplastic callus without fracture.

In connexion with a release operation for flexion contracture of the hips, there was a long period of fever which was interpreted as a streptococcal infection. After this period the radiogram showed considerable persistent callus formation in the region of the left hip joint. To what extent the operative trauma contributed to this callus formation cannot be decided.

Nine months later there was marked swelling of the left thigh. Fever, increased sedimentation rate and anaemia were present. Since, both clinically and radiologically, the process strongly resembled sarcoma, biopsy was carried out. Histological examination revealed undifferentiated chondroid (*Baker*) tissue, the diagnosis of the pathologist being chondro-myxo-fibroma. Biopsy was repeated one month later when histological examination revealed callus tissue. The patient was given radiological treatment, 2300 r, after which there was evident regression of the process. A thickening of the proximal part of the left femur persisted, however, after the inflammatory symptoms had ceased. No fracture was observed.

A similar process occurred in the right femur 3½ years later. There was no fracture but massive callus formation took place, simulating sarcoma clinically and radiologically. Radiological treatment was instituted with evident amelioration of the patient's pain.

This case resembles those described by *Strach* and *Koskinen*, and two of *Fairbank* and *Baker*'s cases. Since the disease is extremely rare, it is natural that the clinician primarily suspects sarcoma. In the beginning of the process in particular, the histological picture is one of unorganized chondroid tissue which may mislead even the pathologist. The most peripheral part of the process, from which the sample is as a rule taken, shows undifferentiated tissue, while the central part shows callus tissue. This has been demonstrated in *Baker*'s and *Strach*'s cases, among others.

As in *Strach*'s case, radiological treatment had an evident effect. *Strach* points out that treatment must be instituted at an early stage when the process is progressing. When more differentiated callus tissue is present, the effect of radiological treatment is probably insignificant.

There were severe inflammatory symptoms in the present case, as also in he cases reported in the literature. The calcium and phosphorus values were normal, the alkaline phosphatases rising during the initial stage of the process.

In one of *Brailsford's* cases, sarcoma developed in a patient who

had previously had hyperplastic callus formation. Sarcoma in osteogenesis imperfecta has been reported by *Jewell & Lofstrom* and by *Werner,* among others.

In osteogenesis imperfecta there is normal chondroblast activity while the osteoblast activity is reduced (*McKusick*, and others). In the present stage it is not possible to state what metabolic activity of the osteoblasts is injured (*Caniggia et al.*) Employing a tetracycline technique, *Ramser & Frost* demonstrated faulty periosteal ossification in osteogenesis imperfecta in an adult woman. After fractures, however, the osseous tissue responds with good callus formation and pseudarthroses are rare. According to *McKusick, Follis*, and others, osteogenesis imperfecta is a heritable disorder of the connective tissue which manifests itself in various ways. *McKusick* points out that a tendency to hypertrophic scars, as reported by *Scott & Stiris* in osteogenesis imperfecta, can be compared with the manner in which osseous tissue reacts with hyperplastic callus in certain cases. *Johansson* and *Sundberg* described severe calcification of the vessels of the extremities in osteogenesis imperfecta in the newborn.

On the basis of investigations with microradiography, polarized light microscopy and X-ray diffraction *Engfelt et al.* point out that the immature fibrillary bone normally seen in foetus and newborn infant resembles in several ways the tissue found in osteogenesis imperfecta. Normally the primary bone is replaced by secondary bone after birth, but in osteogenesis imperfecta this secundary bone is not found. It is also a well known fact that fractures in the newborn heal with extensive callus formation, partly, perhaps, because of faulty immobilization.

Without greater knowledge of the factors which control osteoblast activity, the delayed bone formation in osteogenesis imperfecta cannot be explained, nor why there is hyperplastic callus formation in certain cases.

SUMMARY

A case of osteogenesis imperfecta in an 8-year-old boy is described, in which hyperplastic callus formation simulating osteogenic sarcoma developed in the left femur without fracture. The inflammatory signs were striking, with prolonged fever, elevated sedimentation rate and anaemia. The alkaline phosphatases were increased. After X-ray treatment there was evident regression. A similar process developed in the right femur 3½ years later, also without signs of fracture. The

pathology of the condition is briefly discussed. The importance of recognising the true nature of the disease is stressed.

RESUME

Un cas d'ostéogénèse imparfaite chez un garçon âgé de 8 ans est décrit. Il y avait dans ce cas une formation hyperplastique d'un cal simulant un sarcome ostéogénique qui s'était développé dans le fémur gauche sans fracture. Les signes d'inflammation étaient nets, avec état fiévreux prolongé, élévation du taux de la sédimentation et anémie. Les phosphatases alcalines avaient augmenté. Aprés un traitement aux rayons X, on constata une régression marquée. Un processus similaire s'est développé dans le fémur droit trois ans et demi plus tard, aussi sans signe de fracture. Il est discuté brièvement de la pathologie de cet état. L'importance qu'il y a à reconnaître la vraie nature de la maladie est soulignée.

ZUSAMMENFASSUNG

In dem linken Femur eines 8 Jahre alten Junges, der von Osteogenesis imperfecta leidete, entwickelte sich eine sarkomähnliche hyperplastische Callusbildung ohne Fraktur. Die inflammatorischen Symptome waren ausgeprägt. Der Patient hatte prolongierter Fieber, gesteigerte Senkungsreaktion und Anemie. Die alkalischen Phosphatase waren gesteigert. Während Röntgenbehandlung trat eine deutliche Regression ein. Ein ähnlicher Prozess entwickelte sich 3½ Jahren später in dem rechten Femur auch ohne Fraktur. Die Pathologie des Zustandes wurde kurz beschrieben. Die Verfassern pointieren die Wichtigkeit des Feststellens der richtigen Artdiagnose des Zustandes.

REFERENCES

Baker, S. L. (1946) Hyperplastic callus simulating sarcoma in two cases of fragilitas ossium. *J. Path. Bact.* **58**, 609.

Battle, W. H. & Shattock, S. G. (1908) A remarkable case of diffuse cancellous osteoma of the femur following a fracture, in which similar growths afterwards developed in connection with other bones. *Proc. roy. Soc. Med.* **1**, 83.

Brailsford, J. F. (1943) Osteogenesis imperfecta. *Brit. J. Radiol.* **16**, 129.

Caniggia, A., Stuart, C. & Guideri, R. (1958) Fragilitas ossium hereditaria tarda. Ekman-Lobstein disease. *Acta med. scand.* **162**, suppl. 340.

Engfelt, B., Engström, A. & Zetterström, R. (1954) Biophysical studies of the bone tissue in osteogenesis imperfecta. *J. Bone Jt Surg.* **36**-B, 654.

Fairbank, H. A. T. & Baker, S. L. (1948) Hyperplastic callus formation, with or without evidence of a fracture, in osteogenesis imperfecta. *Brit. J. Surg.* **36**, 1.

Follis, R. H. Jr. (1952) Osteogenesis imperfecta congenita; a connective tissue diathesis. *J. Pediat.* **41**, 713.

Jewell, F. C. & Lofstrom, L. E. (1940) Osteogenic sarcoma occuring in fragilitas ossium. *Radiology* **34**, 741.

Johansson, S. (1921–22) Ein Fall von Osteogenesis imperfecta mit verbreiteten Gefässverkalkungen. *Acta radiol.* **1**, 17.

Koskinen, E. V. S. (1958) Hyperplastic callus formation simulating osteogenic sarcoma in osteogenesis imperfecta. *Ann. Chir. Gynaec. Fenn.* **47**, 257.

McKusick, V. A. (1956) Heritable disorders of connective tissue. V. Osteogenesis imperfecta. *J. chron. Dis.* **3**, 180.

Ramser, J. R. & Frost, H. M. (1966) The study of a rib biopsy from a patient with osteogenesis imperfecta. *Acta orthop. scand.* **37**, 229.

Scott, D. & Stiris, G. (1953) Osteogenesis imperfecta tarda. A study of three families with special reference to scar formation. *Acta med. scand.* **145**, 237.

Strach, E. H. (1953) Hyperplastic callus formation in osteogenesis imperfecta; report of a case and review of the literature. *J. Bone Jt Surg.* **35**-B, 417.

Sundberg, C. G. (1939) Discussion of paper by G. Zander. *Nord. Med.* **1**, 802.

Werner, R. (1940) Mehrfaches Vorkommen einer Neigung zu Knochenbrüchen und Sarkomenentwicklung in einer Familie. *Z. Krebsforsch.* **32**, 40.