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POLYOSTOTIC FIBROUS DYSPLASIA—A FORM OF XANTHOMATOSIS?

By

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Albright and later *Lichtenstein* and *Jaffe* were among the first to draw attention to the disease now usually known as polyostotic fibrous dysplasia. In recent years case reports and surveys of the condition have been published with increasing frequency. The aetiology and pathogenesis of the changes are still obscure. Many theories have been put forward, but none provide a satisfactory explanation. The pathologic-anatomic picture gives no definite clue to the fundamental nature of the disease. *McCune & Burch* (1937) and then *Snapper* assumed the changes to be a form of xanthomatosis, an assumption rejected by *Lichtenstein* and *Jaffe* in particular, who expressed the view that the demonstrated foam cells were only degenerative manifestations and therefore provide no evidence arguing in favour of the disturbance being some kind of lipoidosis. However, foam cells have been demonstrated in an increasing number of cases (e.g. *Russel & Candler, Valls et al., Sanchez-Lucas & Freixa*).

In 1938 the writer described a typical case of the disease as a form of xanthomatosis in a patient who was observed for 2 years and in whose skeleton considerable xanthomatous deposits were seen[1]. It was also shown that the cholesterol and esters found in the foci had a ratio differing from the normal range and from that usually recorded in Hand-Schüller-Christian's disease. Now, 17 years later and after a recent review of the patient, the writer has considered himself justified in presenting the findings made at the initial and at subsequent examinations and in discussing some of the data apparently arguing in favour of the xanthomatosis theory.

That the patient under consideration had typical polyostotic fibrous

[1] A further analysis of the case was presented later in connection with a survey of earlier case reports of bone xanthomatosis. Readers interested in a detailed description are referred to Acta orthop. Scand. 11, 70, 1940.

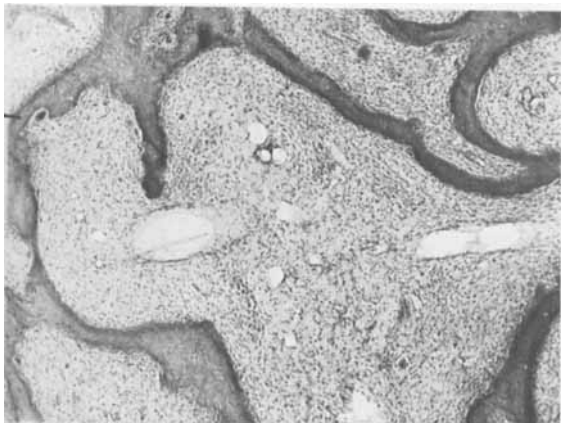

Fig. 1.
Abundant fibrous tissue and scattered foam cells.
The trabeculae are thin and show signs of lacunar absorption.

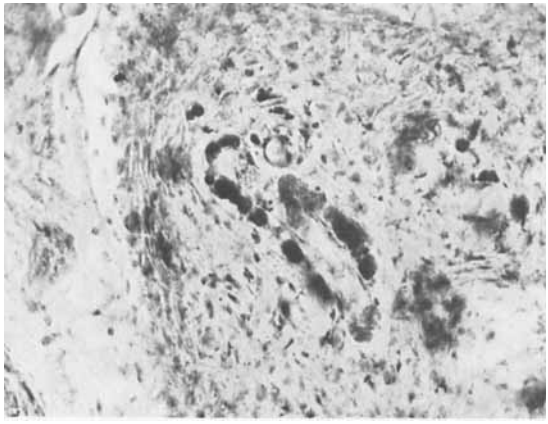

Fig. 2.
Fibrous foci with perivascular xanthoma cells (lipid staining).

dysplasia is beyond doubt. Thus, typical skeletal changes, hyperostosis of the skull, patchy pigmentation and slight hyperthyreoidism were observed. Histologic examination of biopsy specimens showed typical fibrous foci in some parts of the skeleton, while in other parts similar foci were seen but with considerable accumulations of foam cells.

Several observations argue in favour of the xanthomatous nature of the picture in this case.

1) As mentioned above, the histologic examination showed features typical of fibrous dysplasia in some of the bone lesions, in other parts of the skeleton slight accumulations of foam cells were seen, usually

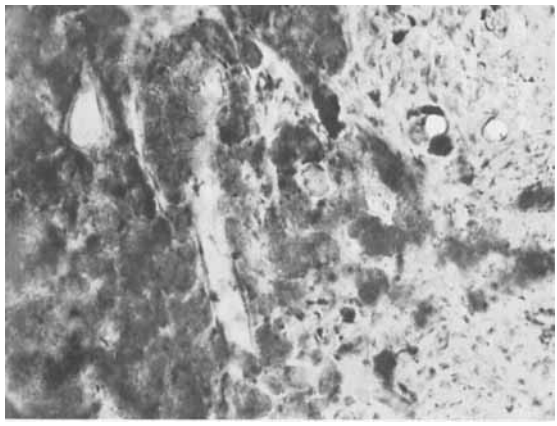

Fig. 3.
Abundant, diffuse infiltration of xanthoma cells (lipid staining).

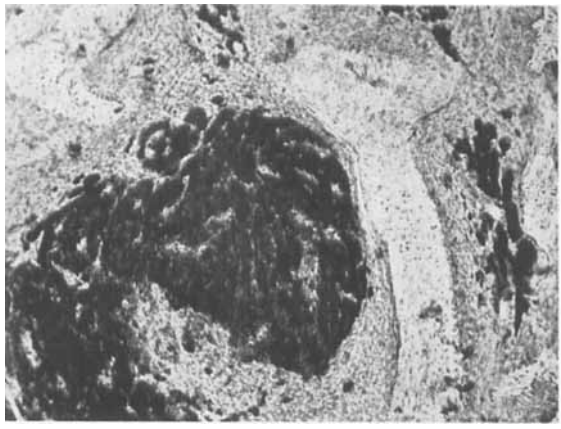

Fig. 4.
Circumscribed accumulation of xanthoma cells (lipid staining).

perivascularly, but other lesions showed a considerable accumulation of foam cells, which dominated the picture (Figs. 1–4). It is known that such lesions can change in appearance and that such changes reveal the different development stages of the local lesion (cf. *Bogart & Imler, Fairbank* and others) and that the older these lesions are, the poorer they seem to be in cells. *Snapper* believes that it is in the early lesions that we see the foam cells, because he was unable to trace any such cells in the old lesions. Thus, a biopsy specimen taken purely from one single part or region does not give adequate information about the condition of the lesions elsewhere in the skeleton: there-

fore the investigation should preferably be complemented by radiography, a method which often reveals the state of the different lesions in the various parts of the body (erosion of the cortex from the endosteum and sclerosis, etc.). Thus, the absence of lipid deposits in lesions in one part of the body does not permit one to exclude the presence of such deposits in other lesions. In the case under discussion, for instance, the first examination offered only the picture of what is now generally described as fibrous dysplasia (Fig. 5). However, fat staining immediately afterwards cleared up the nature of the disease. Judging by the literature, fat staining has not frequently been used in the study or investigation of the disease. Such small accumulations of cholesterol as that illustrated in Fig. 2, for example, can readily escape attention unless use is made of lipid stains.

In the present case the xanthomatous changes were too considerably massive to be classed as insignificant. The number of cells round these lesions was such as to indicate that the processes were in a state of proliferation. In long-standing lesions, on the other hand, the cells were not so numerous and the foam cells were also much more infrequent (Fig. 6).

2) A biopsy specimen of mainly compact bone from the femur was submitted for chemical analysis. The most remarkable observation was that the amount of free cholesterol exceeded that of the esters, so that the ratio between the free cholesterol and the esters was 4.4: 1, as against a normal ration of 1: 3, and in Hand-Schüller-Christian's disease usually 1: 4–5. *This abnormal ratio suggests a general or local disturbance in the cholesterol metabolism.* Diseases in which free cholesterol is preponderant in the local lesions have been described before, e.g. in the skin by *Bogaert et al.* and by *Epstein & Lorenz* in cases of xanthomatosis. In the blood of patients with diabetes, liver or renal diseases similar values can be demonstrated. In the present case careful examination revealed no signs of diabetes, liver or renal disease. Neither were any xanthomatous lesions found outside the skeleton. Nor was any cholesterol present in a biopsy specimen from one of the pigmented patches.

The total plasma cholesterol value repeatedly amounted to about 190 mg./100 ml.[1], as measured by the Hoppe-Seyler-Authenrieth method, hardly an abnormal value. Recent analysis showed a total plasma cholesterol value of 198 mg./100 ml. of which 56 mg./100 ml. consisted of free cholesterol (ref. Schoenheimer-Sperry method).

The ratio between the free and the esterified cholesterol was thus 1: 3.9 and the blood cholesterol concentrations were thus normal. The

[1] The total blood cholesterol value rose after roentgen irradiation. See below.

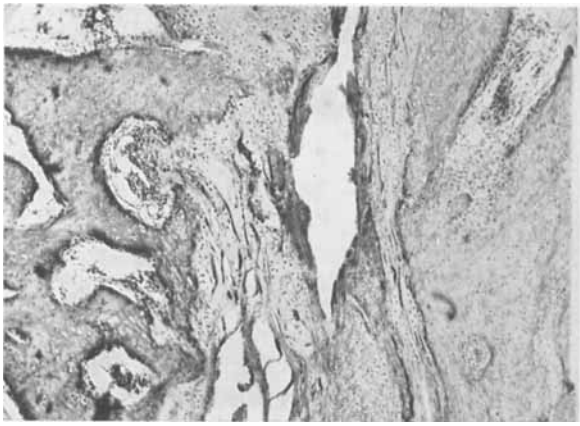

Fig. 5.
Fibrous focus with pronounced lacunar absorption of bone and cartilaginous islands.

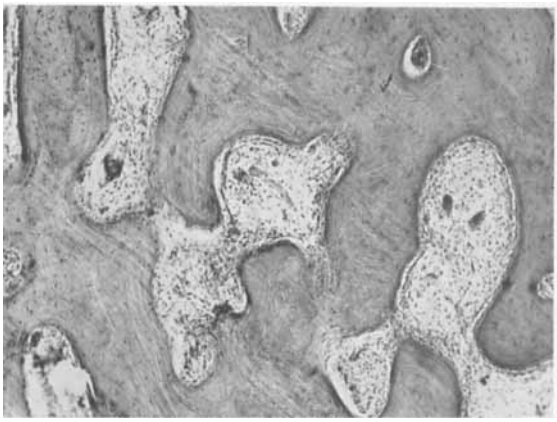

Fig. 6.
Bone from a densified area. Note the sparsity of the cells and the almost complete absence of foam cells.

total of plasma fat was 920 mg./100 ml. and the concentration of the plasma phospholipids 243 mg./100 ml., thus both within the normal range.

3) Another observation supporting the xanthomatosis theory was provided by the response to roentgen irradiation. It was found that the irradiation of one femur increased the serum cholesterol within a few days from 186 mg./100 ml. to 223 mg./100 ml. It afterwards returned to its former level. A similar effect was produced by irradiation of one of the arms: the value rose from 194 mg./100 ml. to

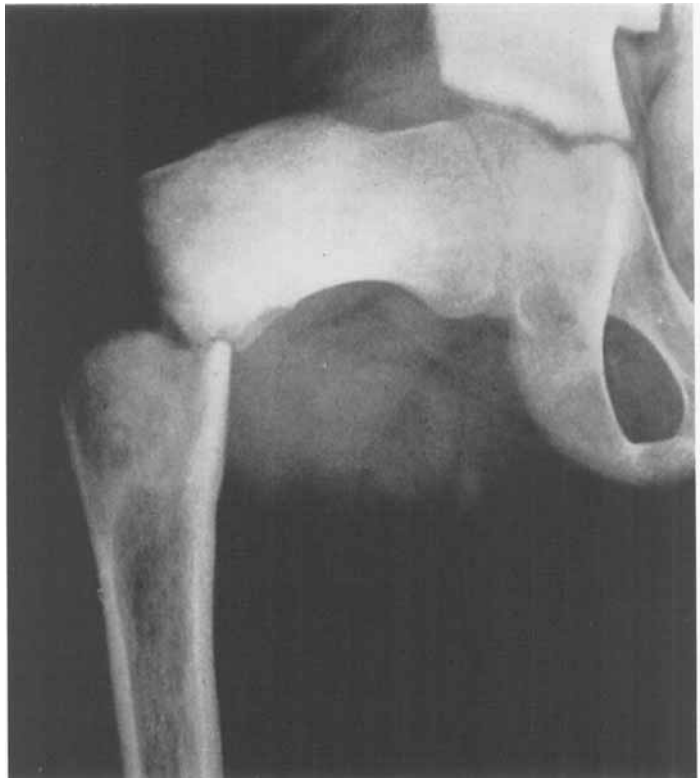

Fig. 7.
Right femur in 1933.

228 mg./100 ml. The figures suggest that large quantities of cholesterol were thrown off into the blood. *Sosman* and others made similar observations during the treatment of Hand-Schüller-Christian's disease by roentgen irradiation. In my opinion it would be of value to test the effect of irradiation in other cases of fibrous dysplasia. This would provide a simple test for assessing the presence of cholesterol in the lesions.

DISCUSSION

In the clear-cut case of polyostotic fibrous dysplasia under discussion considerable amounts of cholesterol were demonstrated in several of the lesions. In many of the lesions the accumulation of foam cells dominated the histological picture. The most striking observation was, however, the ratio between the free and the esterified cholesterol found on analysis of a specimen of mainly compact bone removed from the femur. The free cholesterol was distinctly

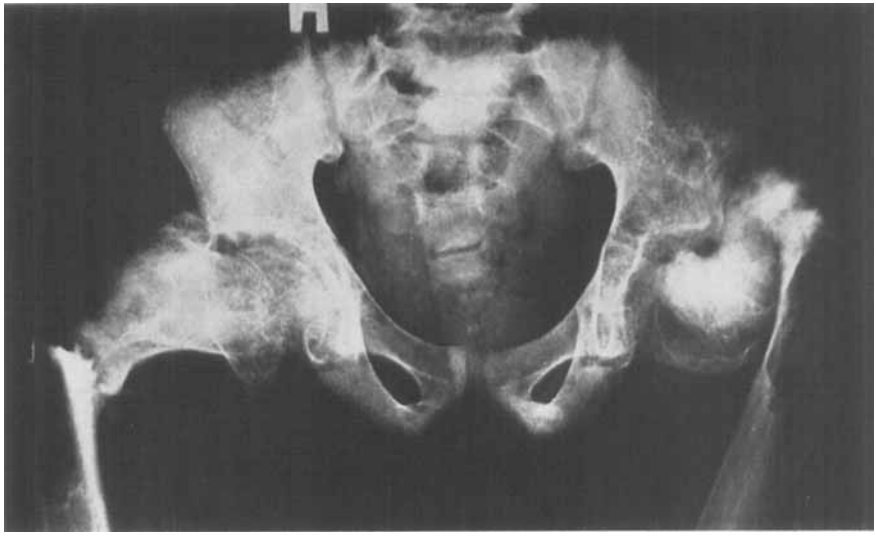

Fig. 8.
Roentgenogram taken in 1937 (11 months after osteotomy).

predominant (ratio between the free cholesterol and the cholesterol esters 4.4: 1). The values thus differed from those normally seen and from those seen in Hand-Schüller-Christian's disease. This suggests a disturbance of the cholesterol metabolism. But as the blood cholesterol values were normal, the disturbance must presumably be located in the actual tissues. If so, this disturbance of the local cholesterol metabolism by a local storage would be classed as some form of multiple reticulosis. The underlying mechanism is, of course, obscure, and it is also difficult to explain the frequently observed unilateral localisation of the changes. The endocrinic disorders seen in Albright's syndrome may be assumed to be secondary to the xanthomatous changes, but on the other hand the great importance of the sterols for the activity of the sex glands and of the adrenals should be borne in mind.

Finally, it may be useful once more to stress the value of the roentgen irradiation test, which should be tried in all cases of fibrous dysplasia and to emphasise that such irradiation should not be restricted to one part of the skeleton only.

CASE REPORT

The patient, a male, is now 32 years old. Inquiry into the personal history revealed no signs of heredity. At the age of 6 he sustained a subtrochanteric

Fig. 9.
Right femur in 1953.

fracture. This fracture healed, but 5 years later (1933) he fractured the same bone on the other side when kicking a ball, and very soon afterwards there occurred a spontaneous subtrochanteric fracture on the other side (Fig. 7). Roentgenographic examination showed skeletal changes in some respects resembling those seen in osteitis fibrosa generalisata. Both femora gradually underwent deformation and as the patient found walking difficult, a subtrochanteric wedge osteotomy was performed in 1936. The patient was then 15 years old and the picture presented was roughly as follows.

The boy was small and fairly thick-set with large patches of pigmentation on the trunk and arms. The genital organs and the secondary sex characteristics were poorly developed. The thigh bones were considerably deformed (see roentgenographic appearance in Fig. 8) and the cranium was hyperostotic and asymmetric. The blood serum calcium level was 11–11.7 mg./100 ml. The urinary calcium level and excretion were normal. Bence-Jones reaction was negative. The erythrocyte sedimentation rate was less than 5 mm. The total plasma cholesterol was 186 mg./100 ml. The B.M.B. varied between +26 and +42 per cent. Liver function tests showed no signs of a pathologic condition. Blood eosinophilia of 5–10 per cent, which had been followed for 2 years, still persisted. Blood sugar values were within a normal range. Wasserman's test was negative. Operative exposure revealed no adenoma of the parathyroid glands. A specimen of the bone resected from the femur and a specimen of a cyst-like rarefied region in the left radius and an

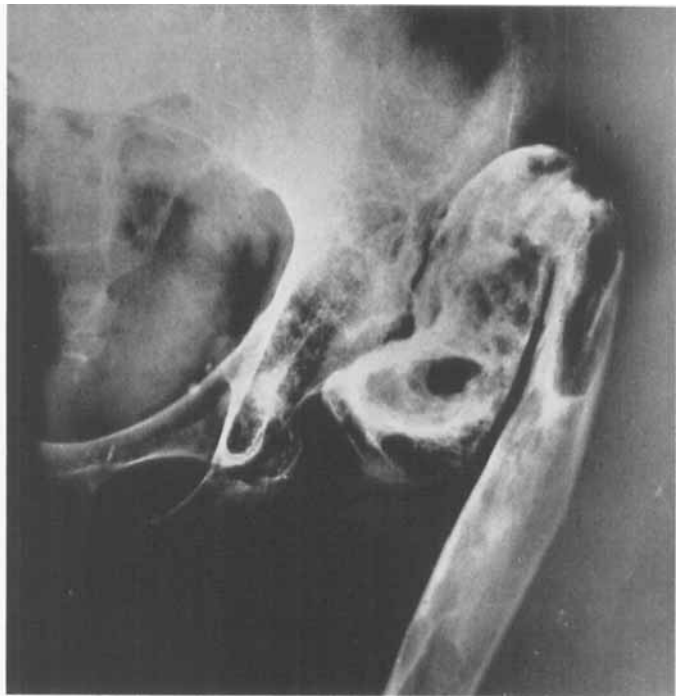

Fig. 10.
Left femur in 1953.

enostosis-like region in a metatarsal bone were examined histologically. The specimen from the femur showed an irregularly arranged bone structure with plexiform, thin trabeculae showing signs of destructive processes and of repair. The bone marrow had been replaced by vascularised fibrous tissue rich in collagenous fibres, some of which extended at right angles from the bone. No osteoid was seen. Another part of the same specimen showed a different picture. Here the bone was undergoing a lively transformation. The marrow spaces were filled with richly cellular fibrous tissue extending from the centre and destroying the cortex. In the region of the fracture which the patient had sustained 3 years earlier cartilage and osteoid tissue were noted. The specimen contained a number of lesions showing the normal perivascular pattern of foam cells and in other areas, considerable accumulations of foam cells, and in these fat staining revealed considerable amounts of lipids. On examination under polarised light, features typical of cholesterol were observed. The accumulations were largest in the central parts of the bone: in the compacta the foam cells were less frequent. The specimen from the radius showed a similar picture, while the preparation from the sclerotic region of the metatarsal bone showed marrow poor in cells, signs of degeneration and only a few perivascular foam cells.

Since 1938 no further fractures have occurred, the disease has given the patient no trouble and he has felt well. The genital organs and the secondary sex characteristics have been normal. On a check-up in 1953 further deformation of

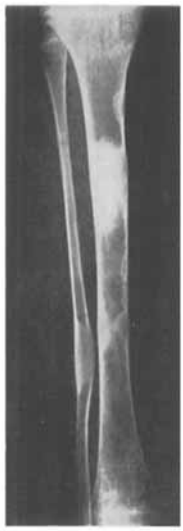

Fig. 11.
Right lower leg
in 1937.

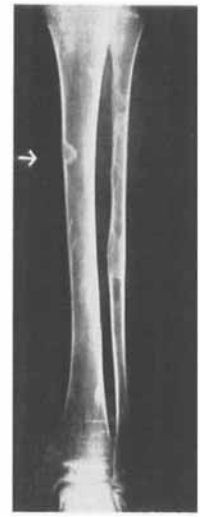

Fig. 12.
Left lower leg
in 1937.

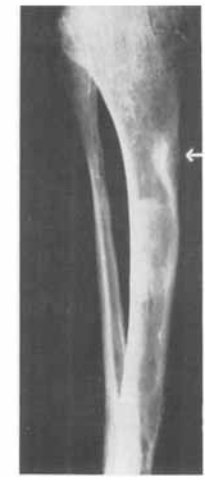

Fig. 13.
Right lower leg
in 1953
(↑ Infraction).

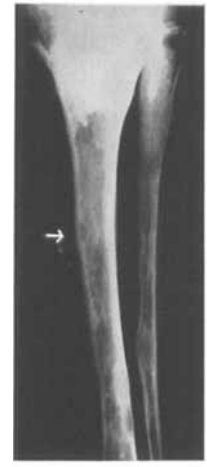

Fig. 14.
Left lower leg. (Compare with Fig. 12). The density seen in 1937 is now replaced by rarefaction and erosion of the cortex. This suggests the possibility of a fluctuating course of the lesion.

the bones was observed. The blood picture was normal. Sedimentation rate 5 mm. Serum calcium 11.2 mg./100 ml. Phosphatases 13.7 U. Total blood fat 920 mg./100 ml. Total serum cholesterol 198 mg./100 ml., of which 56 mg./100 ml. was free cholesterol and 243 mg./ml. phospholipids.

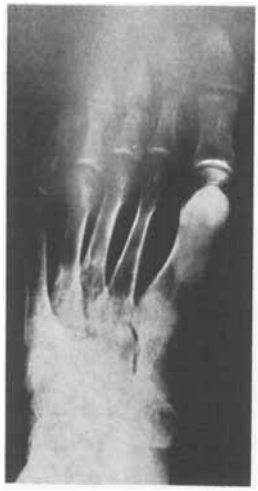

Fig. 15.
Right foot in 1953.

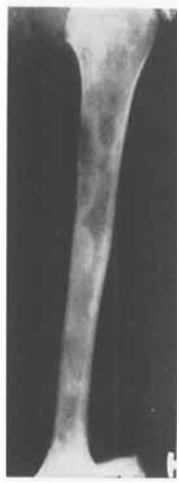

Fig. 16.
Right upper arm in 1953.

The roentgenograms show some interesting features. Comparison of the films (Figs. 7–14) shows the development of the deformative changes over 20 years. The subtrochanteric lesions have not healed. Some of the skeletal changes have regressed, e.g. the enostosis-like formations in the hands, which were observed in 1936. However, some of the lesions have progressed, e.g. in the lower legs where new lesions have appeared. Both the cyst-like rarefactions and densities are still persistent and the former suggest that the pathologic process is still active. On examination in 1938 certain signs of general atrophy were observed in the extremities, but not in the vertebrae or pelvis. This atrophy was then less striking. When last reviewed in 1953, no signs of such atrophy were seen in the pelvis or elsewhere in the skeleton. The hyperostosis seen in the skull in 1938 had increased. Earlier, bone repair appeared to be poor and the bones seemed to be fragile. However, no further fractures have occurred since adolescence, but the roentgenogram now shows signs of infraction of the right tibia (Fig. 13).

It is generally believed that polyostotic fibrous dysplasia heals after puberty. In this case, the patient is now 32 years old and the lesions demonstrated 20 years ago have not yet healed. The disease has possibly passed into a less active stage, as suggested by the decreased tendency to spontaneous fractures. The cortex in general is now thicker and does not seem to be so severely eroded. That the disease has not yet healed is obvious from the appearance of new cyst-like foci.

SUMMARY

An account is given of a case of clear-cut polyostotic fibrous dysplasia (Albright's type) that has been followed for 20 years and which was described by the writer in 1938 as a special case of bone xanthomatosis. Like *Snapper* and others, the author is of the opinion that the disease is a xanthomatosis. This assumption is based on the following observations from a detailed analysis of the case.

1) Considerable accumulations of cholesterol were seen in some of the lesions, where they often dominated the histological picture, while in other lesions such accumulations were only small or absent.

2) The ratio between the free and the esterified cholesterol in these bone lesions differed widely from what is normal and from that usually found in Hand-Schüller-Christian's syndrome.

3) Roentgen irradiation of different parts of the skeleton caused the repeated passage of cholesterol into the bloodstream.

4) The serum cholesterol values were normal and there is some reason for presupposing a disturbance of the cholesterol metabolism in the bone tissue (multiple reticulosis).

When the patient was reviewed 17 years later (he was then 32 years old) it was observed that the disease had not healed. The healing tendency of the fractured bones was also obviously impaired.

RÉSUMÉ

L'auteur rend compte d'un cas certain de dysplasie fibreuse polyostéotique (type Albright) qui a pu être suivi pendant 20 ans et qui avait été décrit en 1938 par l'auteur comme un case spécial de xanthomatose osseuse. L'auteur estime, d'accord en cela avec Snapper et d'autres, que la maladie est une forme de xanthomatose.

Voici les faits présentés à l'appui de cette thèse et ressortant de l'analyse detaillée de ce cas faite en 1938:

1) Importantes stratifications de cholesterine qui dominent souvent sur les images histologiques. Elles existent dans certains foyers, tandis que dans d'autres elles font totalement ou partiellement défaut.

2) Le rapport entre la cholestérine libre et la cholestérine fixée dans ces foyers osseux est totalement divergent de celui qui existe dans les maladies de type normal et de Hand-Schüller-Christians.

3) Par irradiation de differentes parties osseuses, on a obtenu des formations répétées de dépôts de cholestérine dans le sang.

4) La maladie comporte une normocholestérinémie. Il doit s'agir vraisemblablement d'une perturbation du métabolisme du cholestérol dans le tissu osseux (réticulose multiple).

Après l'étude de ce cas qui a porté sur 17 années (le sujet a aujourd'hui 32 ans), il a pu être constaté que la guérison n'était pas complète. En outre on doit signaler dans ce cas une durée sérieusement plus longue de la consolidation de la fracture.

ZUSAMMENFASSUNG

Ein sicherer Fall von polyostotischer fibröser Dysplasie wird beschrieben. Der Fall ist 20 Jahre lang verfolgt und vom Verfasser 1938 als eine spezielle Art der Knochenxanthomatose publiziert worden. Wie Snapper u. a. ist der Verfasser der Ansicht, dass die Krankheit eine Xanthomatose sei. Zum Beweis wird eine eingehende Analyse angeführt und folgende Fakta werden vorgelegt:

1) Bedeutende Cholesteroleinlagerungen, die oft das histologische Bild beherrschen, wurden in mehreren Herden gefunden, während andere Herde zum Teil oder ganz lipoidfrei waren.

2) Der Knochen zeigte einen vom Normalen und vom Morbus Hand-Schüller-Christian abweichenden Cholesterol-Cholesterolester-Quotient.

3) Während der Röntgenbestrahlung verschiedener Knochengebiete wurden wiederholt Erhöhung des Cholesterols im Blutserum gefunden.

4) Die Krankheit zeigt normale Cholesterolwerte im Blut, und wahrscheinlich handelt es sich um eine lokale Störung des Cholesterolstoffwechsels (multiple Reticulose).

Bei einer Untersuchung nach 17 Jahren (der Patient ist jetzt 32 Jahre alt) wurde konstatiert, dass die Krankheit noch nicht ausgeheilt war. Ausserdem wurde eine auffallend verlangsamte Frakturheilung beobachtet.

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