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A study of osteopoikilosis

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The first case of osteopoikilosis on record was published by Albers-Schönberg (1915). Roentgen examination of a 23 year old man with pain of the shoulders and feet revealed numerous round to oval densities in the skeleton. The densities, which were 2 to 50 mm in largest diameter, were oriented in the longitudinal direction of the bone trabeculae of the spongiosa. They did not occur in compact bone. They were most abundant in the pelvis and the shoulder girdle, and in the epiphyses and metaphyses of the long shaft bones, but also in the diaphyses. The foci appeared dense, but the degree of condensation was sometimes less marked in the centres.

More than 150 cases of osteopoikilosis are now on record. The name of the disease was coined by Ledoux-Lebard et al. (1916). The condition is also called: osteopatia condensans generalisata, osteosclerosis disseminata, osteosclerosis familiaris disseminata, spotted bones, and osteosclerosis fragilitas disseminata. The changes show a predilection for areas described by Albers-Schönberg, but have also been seen in other parts of the skeleton (Fig. 1).

Voorhoeve (1924) described a case of striated osteopoikilosis in a 14 year old boy. In various parts of the skeleton the patient showed distinct 1 mm wide, parallel lines of densification. They extended from the epiphyseal line down into the diaphyses and even to the cortex, which might have been elevated. In the pelvis the striae tended to radiate. The sites of the changes corresponded to those seen in osteopoikilosis of oval type. Voorhoeve found the same type of changes in the patient's sister, while the father was found to have skeletal lesions of the type seen in oval osteopoikilosis. Further cases of the striated form (osteopatia striata) as well as mixed striated and oval form have been described. Both are probably manifestations of one and the same fundamental disease.

Buschke and Ollendorff (1928) reported a 41-year old, mentally deficient woman with osteopoikilosis with the oval type of skin changes, which they called dermatofibrosis lenticularis disseminata. The changes consisted of a network of slightly elevated, clearly outlined efflorescenses, localized, above all, to the back, upper arms and trunk. Histologically, these efflorescenses proved to consist of diffusely outlined, fibromatous thickenings of the cutis without the true character of tumour and without destruction of the elastic fibres. In addition, the patient showed abundant striae.

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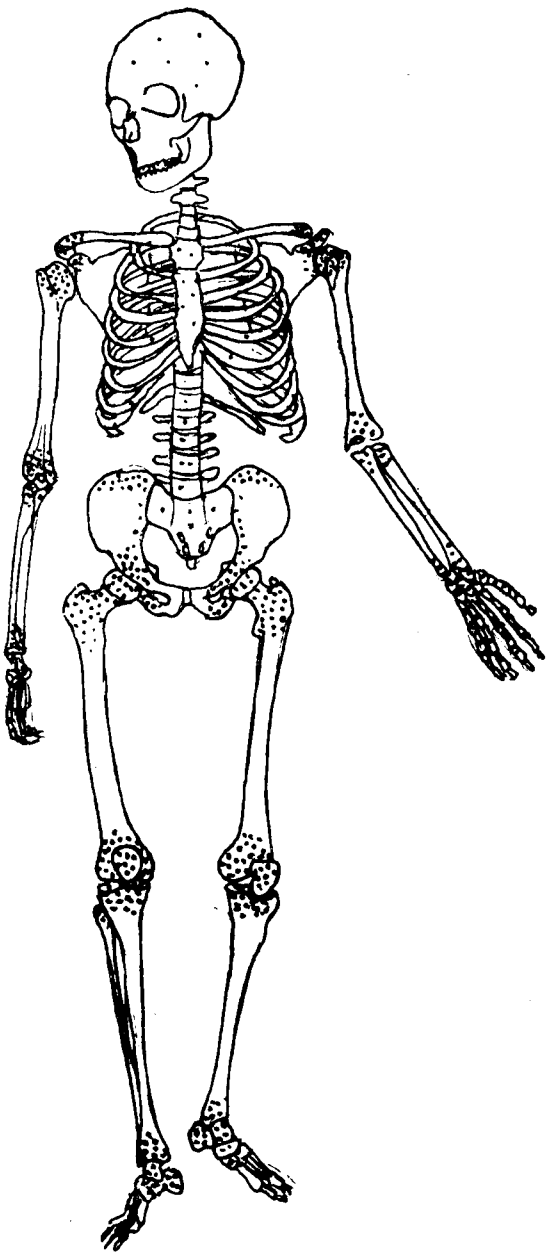

Fig. 1. Osteopoikilosis, sites of predilection

Since the two rare conditions, osteopoikilosis and dermatofibrosis lenticularis disseminata, were seen in one and the same patient, and since these conditions resembled one another in several respects (disseminated, symmetrically distributed, oval and distinct) it was assumed that both were of common origin.

Several cases of osteopoikilosis of the oval or striated form have since been described in combination with dermatofibrosis lenticularis disseminata (Lindblom, 1942, Fairbank, 1950).

Only few histological descriptions have been published of the lesions and then only of the oval form (Schmorl, 1931, Windholz, 1932, Uebelhart, Hinderling and Voellmy, 1958). Schmorl (1931) reported a 14-year old boy who died with ostemyelitis and with roentgenological evidence of osteopoikilosis. Macerated preparations and sawn slices of some bones showed dense foci of irregular, somewhat angular, homogenous, yellow surfaces.

Microscopically, the changes consisted of centrally tapering bone trabeculae. The trabeculae were arranged in a network, whose meshes contained fatty marrow without cartilage. The osseous foci which appeared as densities in the roentgenogram, thus consisted of dense layers of spongiosa. Uebelhart, Hinderling and Voellmy (1958) found corresponding changes in a biopsy specimen of the greater trochanter. The spongiosa showed radiating bone trabeculae consisting of lamellated " osteons ". In some areas the

lamellae were situated concentrically around blood vessels. Since no cartilage could be demonstrated, it was thought that the foci were not endochondral.

The diagnosis osteopoikilosis is made roentgenologically. The changes are of characteristic appearance and generally offer no differential-diagnostic difficulties. The disease does not produce any symtoms or increased brittleness of the bones (Buschke, Ollendorff, 1928, Schinz et al. 1950, Serowy, 1958). A search of the literature failed to reveal any descriptions of fractures of bone affected by osteopoikilosis. No regular changes of the blood composition have been described either, especially not of the blood calcium and phosphorus.

A number of coexisting conditions have been described in patiens with osteopoikilosis, such as malformation of the vertebrae, cryptorchism, mental deficiency, impaired growth, cleft palate, leontiasis ossea, impairment of hearing and hypopituitarism. But in no instance has any causal relationship been proved.

According to some authors (Albers-Schönberg, 1915, Buschke and Ollendorff, 1928), joint pain is common.

Osteopoikilosis has been found twice as often in males as in females. This can probably be explained by the fact that the frequency of roentgen examination of the skeleton is higher among males than females owing to accidents, and that most publications are based on single patients and not supported by familial investigations.

The condition has been described in patiens of all ages. The foci in young patients vary in size, new foci appear, and others disappear during the course of some years (Holly, 1936), but long follow-ups (4-7 years) of adults have shown that the changes later became stationary (Newcomet, 1929, Nichols and Shiflet, 1934).

The relation between osteopoikilosis and so-called solitary compact islets is obscure. The latter are often seen at the same sites as the osteopoikolitic foci. They are said to occur in up to 40% of normal calcanei and are often seen also in the region of the hips. They have the same roentgenographic appearance as osteopoikolitic foci, and Windholtz (1932) has shown that their histological structure is unique. Since the sites of predilections of both conditions are the same they have been believed to be of the same origin (Schinz et al. 1950), but Busch (1936), who was unable to show any intermediate forms in his large series, claimed the conditions to be fundamentally different entities.

The etiology and pathogenesis of the condition are obscure. Infections (tuberculosis, syphilis, dysentery, typhoid and scarlet fever) have been suggested as possible causes, but no evidence has been produced in support of such an assumption.

Hormonal disorders such as hypopituitarism (Nichols and Shiflet, 1934) and Cushingoid habitus (Uebelhart, Hinderling and Voellmy, 1958) have been described in a few cases.

Since the condition has now often been seen in otherwise healthy persons, members of the same family, it is now regarded as a benign, constitutional anomaly.

Case report

The patient was an 18-year old glass-blower. Delivery had been normal after uncomplicated pregnancy. The patient's development and growth was normal apart from a congenital hydrocephalus, which did not progress after 1 year of age. The cause of his hydrocephalus is unknown.

Since the age of 11 years, the patient had had impaired vision, for which he had been examined on several occasions at the Eye Clinic, where myopia and weakness of the left eye with amblyopia had been diagnosed. He had no history of liver disease and no joint pain. He had been admitted twice to the Department of Medicine, Central Hospital, Växjö, because of hydrocephalus and gastritis. On those two occations, he had had several sudden attacks of palpitation, sweat and breathlessness. No explanation could be offered for these attacks. He had no convulsions. He otherwise felt well and had not had any fractures, and he showed no skin changes.

On March 12, 1962, the patient fell from a cycle and sustained a medial fracture of the neck of the left femur.

Examination showed hydrocephalus (circumference of head 68 cm) and strikingly small hands and feet. There were no skin changes and he appeared to be mentally normal. Physical examination of the heart, lungs and abdomen revealed nothing of interest. Blood pressure 150/85 mm Hg. Neither did he show any neurological abnormalities.

Roentgen examination revealed that fracture passed through an area of widespread osteosclerotic changes of the same typical appearance as those seen in the oval form of osteopoikilosis. On further roentgen examination of the skeleton corresponding changes were also found round the other hip joint, as well as in the pelvis, knee, foot and elbow joints.

Skull X-ray showed a strikingly large calotte, but no destructions, no osteopoikilotic foci and no intracranial pathological calcifications. The sella turcica was normal. There was no widening of the sutures. Roentgen examination of the chest as well as previous roentgen examination of the digestive tract showed no signs of a pathological condition.

Ophthalmological status was as previously. Otological status was normal. Electrocardiography showed no abnormalities.

The following laboratory studies showed nothing remarkable: Hb, erythrocyte count, thrombocyte count, serum transferrin, serum iron, leucocyte count, differential count, total number of eosinophilic cells, MCV, MCHC, haematocrit, alkaline phosphatase, total acid phosphatases, tartrate-inhibited acid phosphatases, urinary sediment, urine sugar, urine protein, standard bicarbonate, Cl, Na, K, Ca in serum (repeated tests), prothrombin index, E.S.R., ASTA, ASL, agglutination of sensitized sheep blood cells, Widal'test, Wassermann's test, Meinicke's test, serum electrophoresis, serum creatinine, electrophoresis of urine, serum haptoglobin.

The following laboratory values were found to be abnormal: serum bilirubin

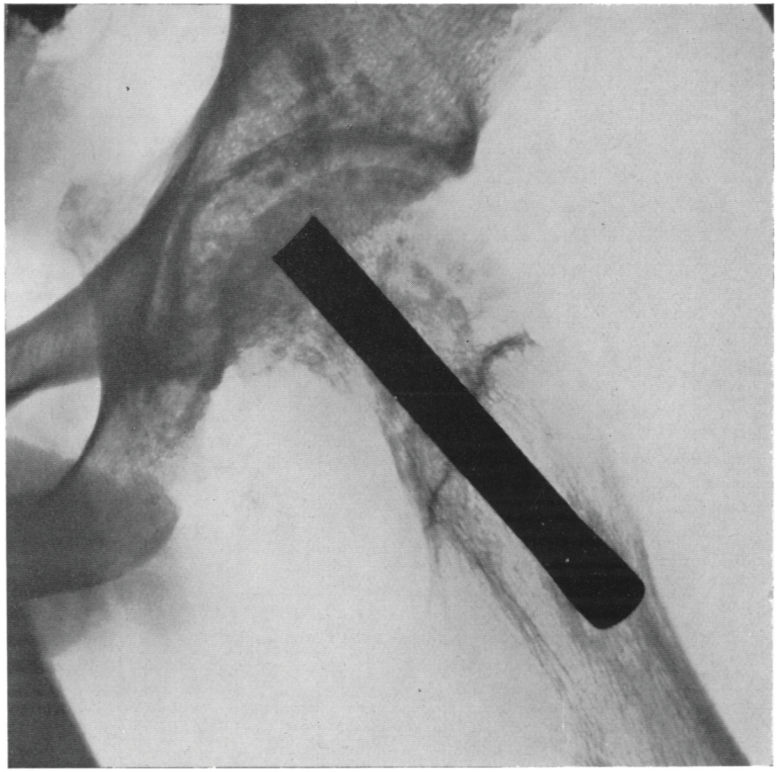

Fig. 2. Male, aged 18, with osteopoikilosis

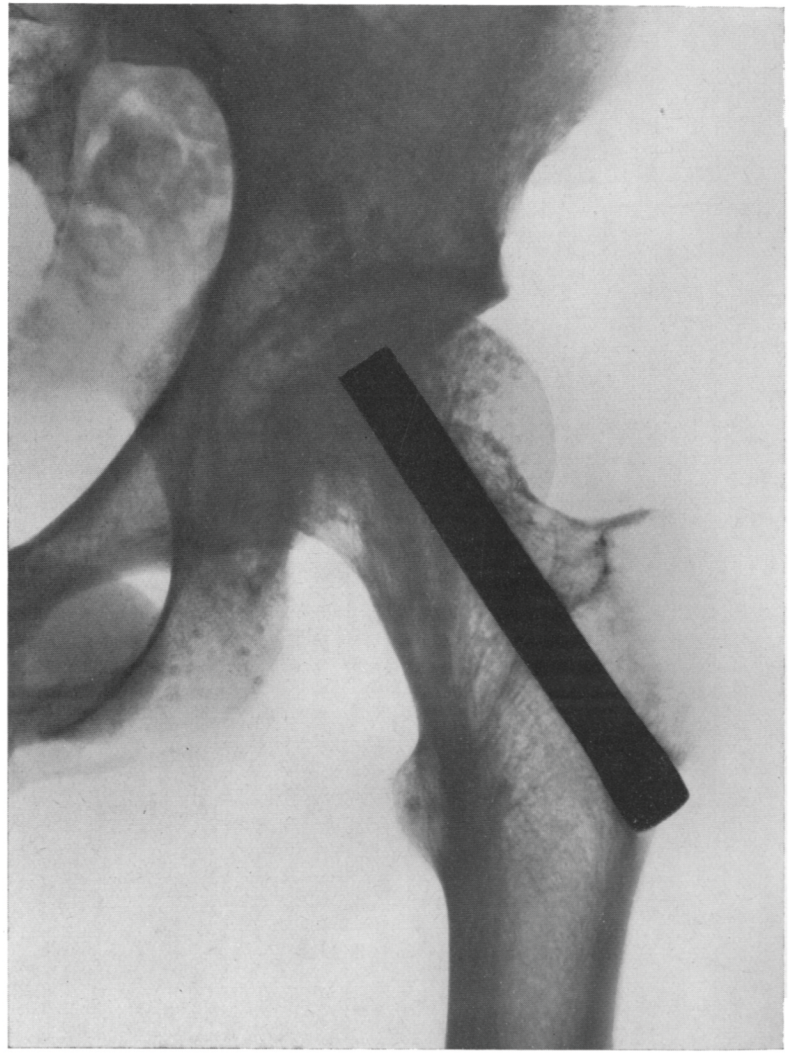

Fig. 3. Male, aged 18, with osteopoikilosis

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(2.3 mg/100 ml. with negative direct reaction), P in serum (4.6-5.1 mg/100 ml.), N.P.N. (40 mg/100 ml.).

The test for Toxoplasma was slightly positive (Sabin-Feldman 1/50 and KBR 1/7.5).

Cerebrospinal fluid: no cells, total protein 94 mg/100 ml.

Check examination in February 1963 gave the following values: Serum bilirubin 2.6 mg/100 ml. with negative direct reaction. GPT 54-50 U., GOT 41-33 U., P in serum 4.5 mg/100 ml., Ca in serum 9.5 mg/100 ml., and N.P.N. 37 mg/100 ml.

The pathological findings in this patient thus consisted not only of osteopoikolitic foci but also of hydrocephalus, small hands and feet, positive titre against toxoplasma, increased values for serum phosphorus, GPT, GOT and cerebrospinal fluid protein, and high values for serum bilirubin and N.P.N. There was also a refraction anomaly.

At operation on March 16, 1962, osteosynthesis was done *ad modum* Sven Johansson with a 3-flanged vitallium nail (Figs. 2-3). A piece of cortex and a piece of spongiosa were removed for microscopic examination. The patient was discharged from hospital symptom free on March 28, 1962, and has since been examined on several occations. On April 10, 1962, he showed signs of incipient callus formation, and on May 28, 1962, a good filling of the fracture with callus was noted. Since the middle of July, 1962, he has shown no further roentgenological changes in the arrangement and thickness of the bone trabeculae. On the other hand, during the healing period (4 and 7 months after the accident) a number of foci close to the fracture appeared less dense. In roentgenograms taken in January 1963 (10 months after the accident) these foci reappeared in the same size and density as at the time of the accident (Fig. 4-5).

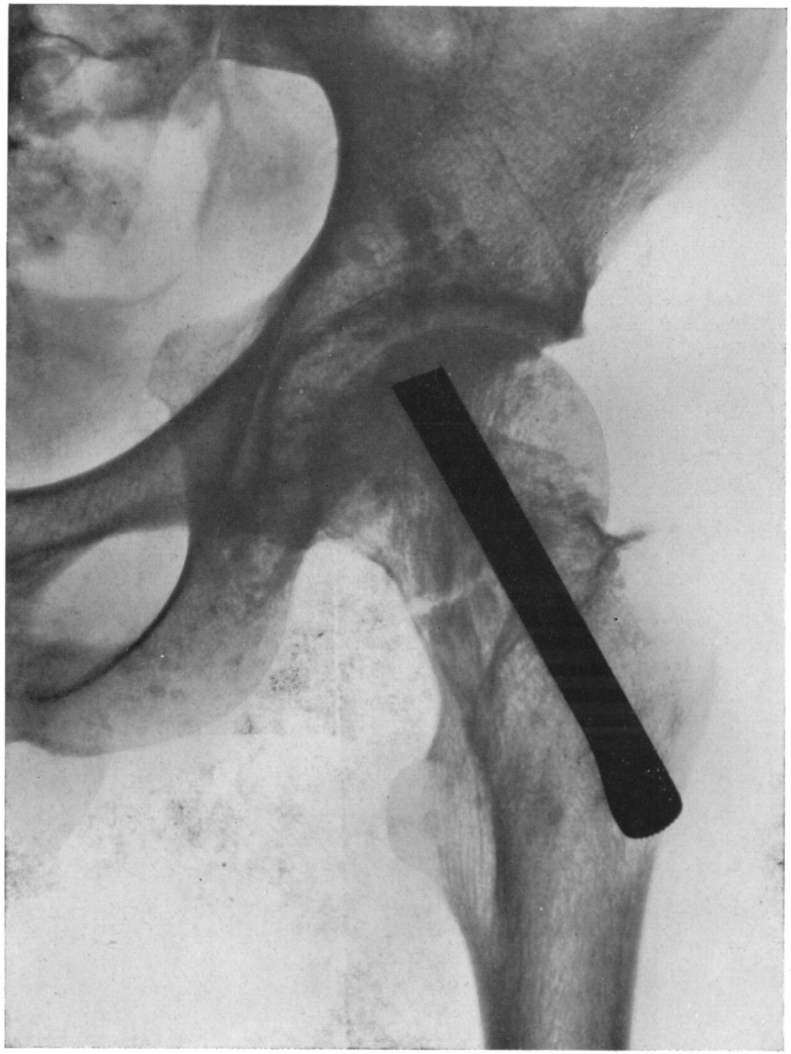
In 1956 the patient injured his knee, and the knee joint was examined roentgenologically. On re-examination of the films, foci of distinct osteopoikolitic appearance were seen. In films, from 1962 the changes could be recognized at these sites which were, however, larger and more dense. In addition, some 30 further foci have appeared.

Microscopic examination T. 2830/62, Pathol. Inst., Malmö (M. D., G. Östberg) (Fig. 6). Compact bone fragments of the cortex and fragments of thin spongiosa trabeculae with remainders of blood- forming marrow or fatty marrow. A few more dense foci composed of layers of coarse bone trabeculae often arranged concentrically around the vessels. In some areas the bone trabeculae are broken without distinct comenting lines. The spaces between the trabeculae are filled with fibrous tissue or fatty marrow. Thin spongiosa trabeculae are seen in the periphery.

The picture appears to fit in with that described by Schmorl (1931) for osteopoikilosis.

Genetic analysis

Twenty-four of the proband's relatives were examined roentgenographically; frontal films were taken of their pelves, hips, knees and elbows. It was found that



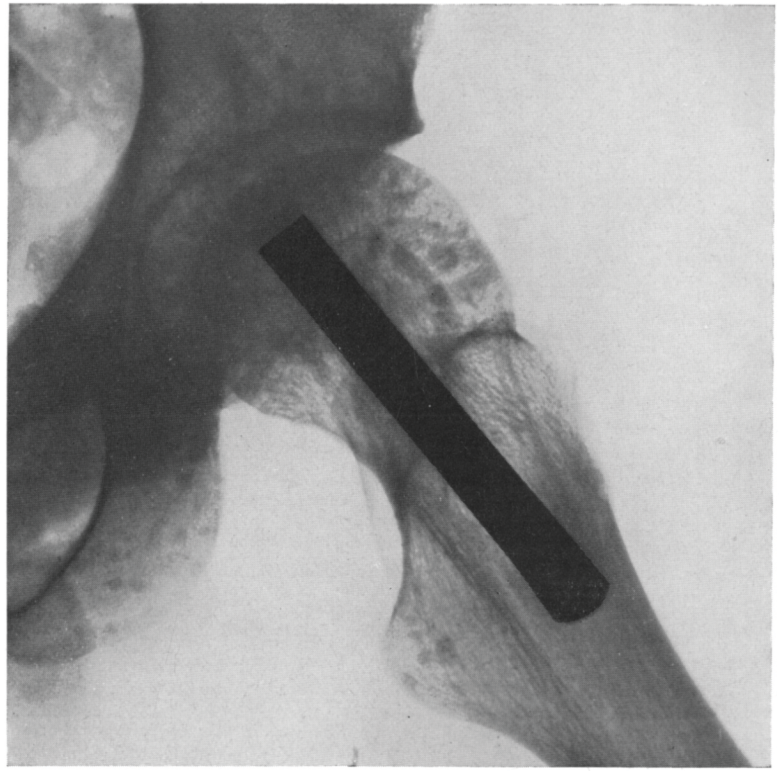


Fig. 5. Male, aged 18, with osteopoikilosis

Fig. 4. Male, aged 18, with osteopoikilosis

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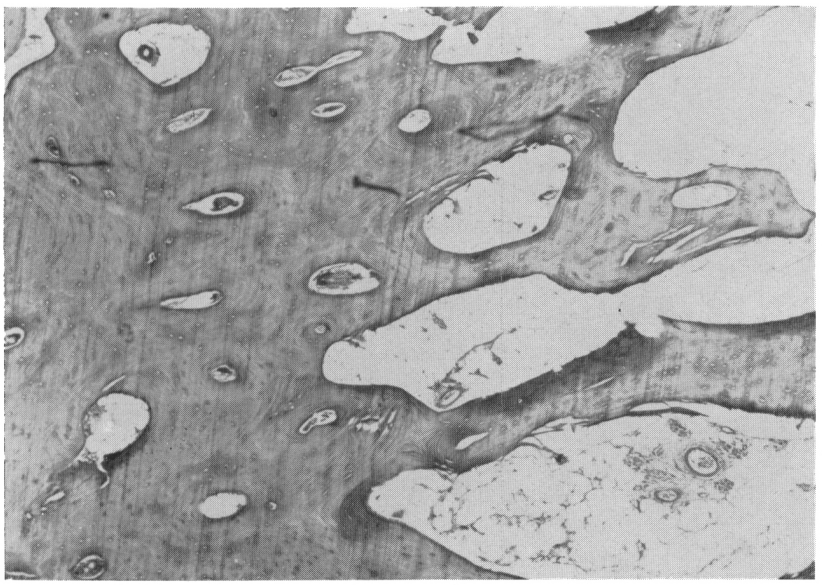

Fig. 6. Histological picture of osteopoikilosis. The microscopic picture shows to the left a focus consisting of coarse, lamellar bone trabeculae. They are partly arranged concentrically around narrow cavities containing fatty marrow or fibrous tissue with thin vessels. Thinner spongiosa trabeculae to the right merge with denser structures of the focus (Haematoxylin-cosin 31 ×)

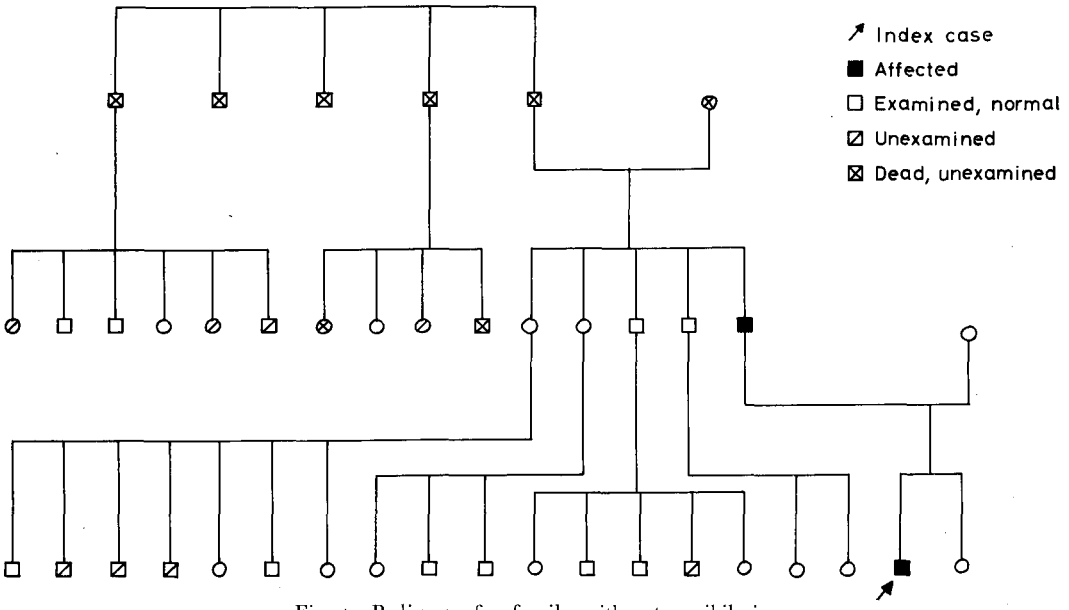

Fig. 7. Pedigree of a family with osteopoikilosis

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the father of the proband also had osteopoikilosis; the other 23 relatives had normal films (Fig. 7). The parents of the proband were not related.

The father showed less advanced roentgenologic abnormalities than the son, but ones of the same type (fig. 8). He was now 51, and had been healthy all his life; he

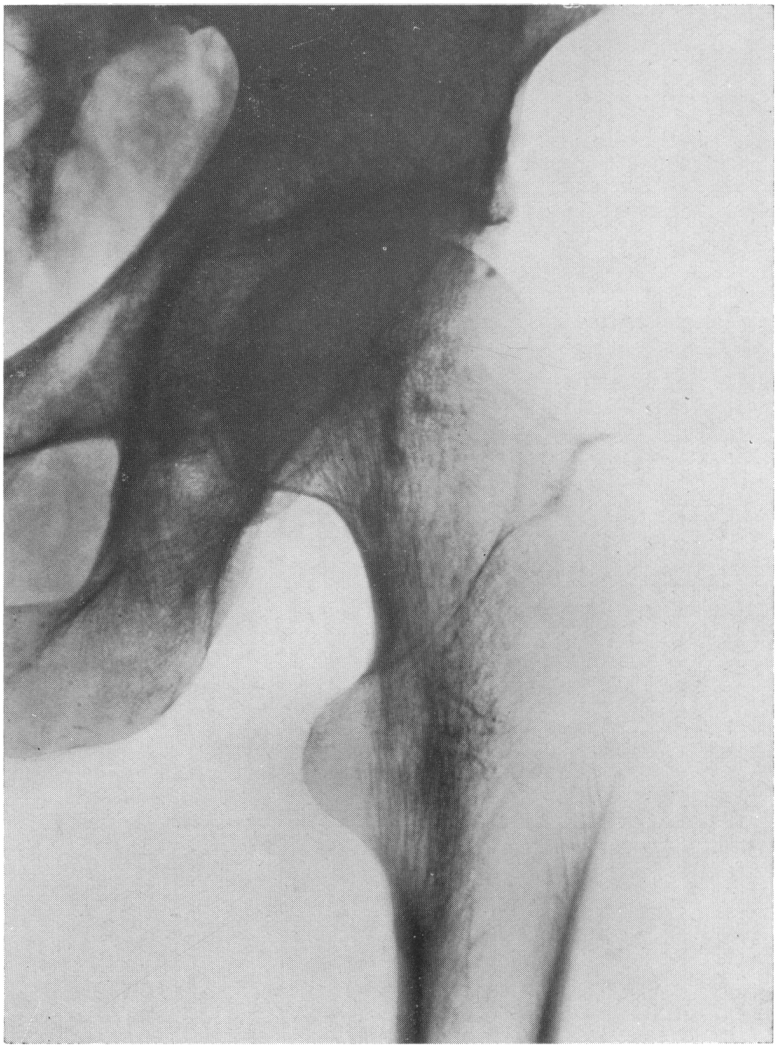

Fig. 8. Male, aged 51, with osteopoikilosis, father of the proband

had never had any joint trouble or any fractures. He had normal values for serum bilirubin (direct reaction), N.P.N., serum calcium and phosphorus, GPT, and GOT; the mother and sister of the proband were also normal in these respects.

Since these observations did not permit us to form a hypothesis on how osteopoikilosis is transmitted, we collected family data from the literature. The reports in the literature, however, often have a selective nature that bias the data pooled from them. Moreover, many authors leave out important family data.

Sixteen families with affected children in which both parents were roentgenographed are described in the literature. In 14 of these, one of the parents proved to have the disease; in only 2 neither parent was affected. In one family the disease was found in three generations.

As osteopoikilosis causes no clinical symptoms, and is only discovered incidentally on roentgenography, it may be assumed that each family or set of siblings described contained only one proband. Unfortunately the authors seldom say which person was the proband, or wether the disease was first discovered in a parent or a child.

Twenty-three families with one affected parent are described (table 1). These

Tab. 1. Families with one affected parent distributed by number of affected children they contained

Number of children in family	Number of children affected							Number of families
	0	1	2	3	4	5	6	
1	8	1						9
2	2	1	4					7
3		1	1	2				4
4				1				1
6					2			2
Total observed	10	3	5	3	2			23
Total expected (a)*		6.5	4.3	1.4	0.6	0.2	0.0	13.0
(b)*	6.8	10.0	4.1	1.4	0.5	0.2	0.0	23.0

* See text

families contained 51 children, and 30 of these had the disease. In 13 families, the disease occurred in both parents and children. These 13 contained 39 children, and not less than 30 of these 39 had the disease. This is a ratio of 0.8 – an unlikely figure considering that osteopoikilosis is an extremely rare disease (In rare dominant diseases, the affected parent can be assumed to be a heterozygote). Ovbiously, the families we collected from the literature were not representative of families with this disease.

Table 1 shows that they contain a disproportionately large number of families with many affected children, and also of families with no affected children. If it is assumed that osteopokilosis is inherited as a dominant, non-sex-linked disease possessing fully penetrance, one can test how representative the families are by comparing the expected number of affected children per family with the observed number. We compared these two figures first assuming (*a*) that an affected child was the proband

in the 13 families with affected children, and then (*b*) that one of the parents was the proband in all the 23 families; both these hypothesis are plausible.

The last two lines of table 1 show these two expected distributions. Working with the first hypothesis (*a*), comparison between the observed and expected distributions of affected children showed that there were too many families with three or more affected children in the material; the disproportion was statistically significant ($0.02 < P < 0.05$).

Working with the second hypothesis (*b*), it appeared that there were too many families with no children affected and also too many with most children affected. Here again the disproportion was significant ($P < 0.01$).

The cases of osteopoikilosis contained in the literature up to now have probably been mainly reported for one of two reasons; either because the authors were interested in the clinical features of the disease, or because they were interested in the genetic aspects of the disease. The first category of authors would tend to lead to a disproportionate number of families with no affected children being described, and the second to a disproportionate number with many affected children.

One often has to fall back on data in the literature when one is interested in the way a rare disease is transmitted. The difficulties which are then encountered are clearly illustrated by this attempt to analyze osteopoikilosis. Nevertheless, it should be possible to assume from the family data published to date that osteopoikilosis is caused by a gene difference of the autosomal dominant type.

Summary

The clinical and histologic observations in an 18-year old male with osteopoikilosis are described. Twenty-four of the proband's relatives were roentgenographed; films were taken of their pelves, hips, knees and elbows. The father was found to have osteopoikilosis, but none of the others were affected.

It has been attempted to figure out how osteopoikilosis is transmitted by a study of the family data given in the literature. Though it is realized that these data are biased because of their selective nature, it is suggested that osteopoikilosis is inherited as an autosomal dominant disease.

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RIASSUNTO

Vengono riportate le osservazioni cliniche ed istologiche effettuate in un individuo di 18 anni affetto da osteopoichilosi. In 24 parenti del probando sono stati esaminati radiologicamente pelvi, anche, ginocchi e gomiti, ma solo il padre risultò affetto da osteopoichilosi. Si è cercato di immaginare il meccanismo di trasmissione dell'osteopoichilosi mediante uno studio dei dati familiari indicati dalla letteratura; ci si è resi conto, tuttavia, che tali dati sono soggetti a fonte di errore, a causa della loro natura selettiva, e si suggerisce l'ipotesi che l'osteopoichilosi venga trasmessa con meccanismo autosomico dominante.

RÉSUMÉ

Les Auteurs rapportent les observations cliniques et histologiques effectuées chez un individu de 18 ans avec ostéopoïkilose. Vingt-quatre parents du propositus ont été examinés radiologiquement, notamment en ce qui concerne le bassin, la hanche, les jenoux et les coudes, mais seulement le père présentait l'ostéopoïkilose. L'on a cherché de se figurer comment l'ostéopoïkilose, se transmet, moyennant une étude des données de la littérature, mais ces données sont biaisées, étant donnée leur nature sélective et l'on ne peut qu'avancer l'hypothèse d'un mécanisme autosomique dominant.

ZUSAMMENFASSUNG

Es werden die klinischen und histologischen Beobachtungen bei einem 18-jährigen beschrieben, der an Osteopoikilosis leidet. Von 24 Angehörigen des Probanden wurden Röntgenaufnahmen des Beckens, der Hürten, Kniegelenke und Ellenbogen gemacht. Es stellte sich heraus, dass der Vater eine Osteopoikilosis hatte, aber keiner der anderen Angehörigen.

Es wurde versucht, den Erbgang der Osteopoikilosis mit Hilfe der Suppenerhebungen im Schrifttum festzustellen. Man ist sich zwar darüber klar, dass diese Erhebungen nicht objektiv bewertet werden können, da es sich dabei um eine Auslese handelt; doch ist daraus anzunehmen, dass sich die Osteopoikilosis als autosom dominante Krankheit vererbt.

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