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RÉSUMÉ

Chez les individus exposés quotidiennement à la lumière intense, notamment chez les aviateurs, la vascularisation cornéenne est d'observation très fréquente; il en est de même des signes attribués à la carence de vitamine B_2: larmoiement, fatigue oculaire, fatigabilité à la lecture, céphalée et vertiges. La riboflavine (B_2) donnée à forte dose (9.9 mgm p.j.) pendant 2 mois a amené chez un groupe de sujets une diminution progressive de la vascularisation dans environ 70% des cas, et la disparition des autres signes de la carence dans 95%. Chez un second groupe, la même dose donnée pendant un mois a diminué la vascularisation à un degré moindre mais a enrayé les symptômes concomitants de façon au si efficace qu'avec le traitement de 2 mois. La recherche photographique de cette vascularisation cornéenne auprès du personnel civil et militaire de la R.C.A.F. a démontré que celle-ci était très fréquente. Les régions où la R.C.A.F. est bien pourvue en lait sont celles où l'avitaminose B_2 est la plus légère. JEAN SAUCIER

PAGET'S DISEASE OF BONE

(With Report of a Case)

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THERE is a curious and interesting paradox about osteitis deformans (Paget's disease), for it is both rare and comparatively common. In his first paper, read before the Royal Medico-Chirurgical Society of London, Paget[6] says "I have looked for records of cases similar to these in nearly every work that seemed likely to contain them, but in vain. I have found only three cases and the first two of these are doubtful." During the ten years that I was a member of the Deutsche Pathologische Gesellschaft (1904-14) only two cases were presented to the society, and the German pathologist being what he is, or was, one can be fairly certain that few if any fully worked out cases with autopsy findings were missed during that period. On the other hand, G. Schmorl,[7] of Dresden, gives details of 138 cases which came to autopsy during a period of thirty years and were observed by himself.

The fact is that there appear to be two forms of the disease, one common and involving one bone of the skeleton (monostotic), the other rare, involving several bones or the greater part of the skeleton (polyostotic). If the monostotic or subclinical variety be included it is estimated (Jaffe[3]) that the disease occurs in 3% of persons over the age of forty years. Whether these are actually two forms of the same disease or different and related conditions is uncertain. A point in favour of their being different in origin is the fact that the monostotic variety is most common in the tibia while the polyostotic favours the sacrum and the vertebræ, although it also may implicate the femur and the other bones of the extremities.

Without knowledge of the cause and with some uncertainty as to the pathology of the condition, it is probable that several anomalies are included under the heading, Paget's disease of bone. The original term suggested by Paget, osteitis deformans, is almost certainly wrong, for the pathological changes do not suggest inflammation of bone. The name leontiasis ossea, introduced by Virchow, is merely descriptive of the gross appearances of the patient suffering from the very rare type affecting the bones of the face. Recently the term osteodystrophia deformans (δυς, difficult, and τροφε, nourishment) has been suggested. It is non-committal but clumsy. In view of our uncertainty as to causation, however, the term "Paget's disease" is probably the best. It should be emphasized that it is necessary to add "of bone" because Paget's disease of the nipple is a totally different condition and the etiology has been worked out by Robert Muir as being essentially malignant and associated with the presence of an underlying duct carcinoma.

Regarding related bone disease, that which most closely resembles Paget's disease is osteitis fibrosa cystica (Recklinghausen's disease). Indeed, G. Schmorl at the Freiburg meeting of the Deutsche Pathologische Gesellschaft in 1926 fell into the error of regarding the two as manifestations of one and the same disease. At the time he was either unaware of or had ignored the work of Askanazy, Mandle and others which linked Recklinghausen's disease definitely with hyperpituitarism. In consequence Schmorl had to appear at the 1930 meeting of the Society more or less in sackcloth and ashes and withdraw his previous statement. Rickets and osteomalacia, which were originally regarded as factors in the differential diagnosis, have, of course, been placed among the deficiency diseases, due to lack of vitamin D. With the etiology in obscurity and the pathogenesis vague, the factors which have some bearing upon the condition assume importance.

As regards *age,* the disease is one of later middle life. Most cases begin to show signs over the age of forty years, although instances have been described in children and adolescents (Kerr[4]).

Sex seems to play some part. Paget believed the condition to be more common in males, and statistics including large numbers of cases bear this out. Kerr, analyzing 439 cases in which sex is reported, finds 60% in males and 40% in females. Schmorl, in his 138 cases, found the distribution between the sexes to be 57.9% males, 42.1% females.

As regards *race* and *climate,* Kerr mentions that in America nearly all the cases were reported from the more northern states. Of the 208 cases in the United States in which race is mentioned 101 were Caucasians, 9 Negroes, and one occurred in an individual of mixed Indian, French and Anglo-Saxon origin. Cases have been reported from most of the European countries, and the condition does not appear to be more common in one than in others. It is probable that race is not a factor of any importance. In this relation it is interesting that instances of a disease similar in gross and microscopic appearances have been reported in apes (Max Koch[5]) as well as in horses, goats, swine and several of the smaller domestic animals (Aschoff[1]).

Heredity.—Paget stated that no hereditary tendency was to be found in his series of cases. Kerr says that in 22 of his American cases there was an hereditary element, more than one member of the family being affected. De Costa mentions four instances in which other members of the same family were affected. In the case now presented the disease appeared to show a family distribution.

Insanity.—Paget makes the point that the disease is not associated with mental trouble, a matter of some importance in the differential diagnosis. The case cited below was under treatment in a mental hospital, but her condition was probably due more to arteriosclerosis than anything else.

Endocrines.—There is no known connection between pathological changes in any of the endocrines and Paget's disease of bone. Some degree of hypertrophy of the parathyroids has been described in some cases and in one an adenoma of the parathyroid was found, but this was probably an instance of mistaken diagnosis (Kerr).

PATHOLOGICAL FINDINGS

According to Paget the disease affects most frequently the long bones of the lower extremity and the skull, and the changes are usually symmetrical. As already stated, a distinction has to be made between the monostotic type in which the tibia is the bone most frequently affected (Bell[2]) and the polyostotic with involvement of many bones. Schmorl, in his series of 138 cases, found the frequency to be: sacrum, vertebræ, right femur, skull, sternum, pelvis, left femur, clavicle, tibia, ribs, humerus, in that order. The hands and feet are least commonly affected and the bones of the face, very rarely (leontiasis ossea). The bones increase in length and thickness. They are heavier than normal, but this is due to there being more bone, not to increase in weight of bone. The bone is more vascular, more porous and softer, so that not infrequently it can be cut with a knife. The distinction between compact and spongy bone is lost (Fig. 1). Necrotic and eventually cystic areas appear. The consequent weakening of the bone results frequently in spontaneous fracture.

Microscopically the earliest change to be observed is, according to Schmorl, the appearance of osteoclasts or multinucleated bone cells, which hollow out and remove the normal bone. Howship's lacunæ appear at the margins of the bony trabeculæ as seen in Fig. 2. As the bone is removed, both it and the intervening marrow are replaced by a well formed fibrous tissue without exudation or inflammatory cell infiltration. While some bony trabeculæ are being removed by the osteoclasts new ones are being laid down by osteoblasts. This new bone exhibits alternate denser and less dense layers, the dense being narrow and staining deeply with hæmatoxylin, giving a mosaic-like structure somewhat similar to the rings seen on a cross-section of a tree trunk. This mosaic structure was first described by Schmorl and is regarded by him as characteristic of Paget's disease. It is found in no other bone condition. Later on local necrosis of bone occurs with subsequent liquefaction and formation of cysts (Fig. 3). It may be, as is suggested below, that this is consequent on narrowing of vessels from arteriosclerosis.

The *x-ray findings* are in conformity with the above bony changes. In the early stage there is absorption of bone (osteoporosis) with, later on, the appearance of new bone replacing the old. Of this new bone the radiologists (Shanks,

Kerley and Twining[8]) distinguish two forms called spongy and amorphous. Both forms may be present in the same patient, although the spongy form is more common. It consists of coarse, irregular striæ arranged either as parallel trabeculæ or running in the direction of the normal lamellæ of a cancellous bone. The amorphous form is a generalized opaque deposit producing a granular mortar-like appearance in the skiagram.

ASSOCIATED CONDITIONS

The most constant of these is arteriosclerosis. This is usually of the Mönckeberg type, with calcareous deposit in the middle coat of the vessels. There is also thickening of the intima with consequent narrowing of the media. Sequelæ of this arteriosclerosis are to be found in various organs, heart, kidney and brain, and, as has already been mentioned, there is some reason to believe that the necrotic cysts of the bone may be due in part to the resulting interference with vascular supply (Fig. 3). The calcareous deposit in the vessel walls of the lower limb especially is often visible in the skiagram.

In his original paper Paget drew attention to the frequent association of "cancer" with this disease. Out of his first series of five cases he found cancer in three. In the first case of all, described in great detail by him, a cancerous growth appeared in the upper third of the left radius within a month or two of death and at the autopsy cancerous deposits were found in both lungs. So far as one can gather from a study of the illustrative drawings of the tumour, the growth was probably a carcinoma originating in the lung with a metastasis in the left radius. Another of the Paget cases showed

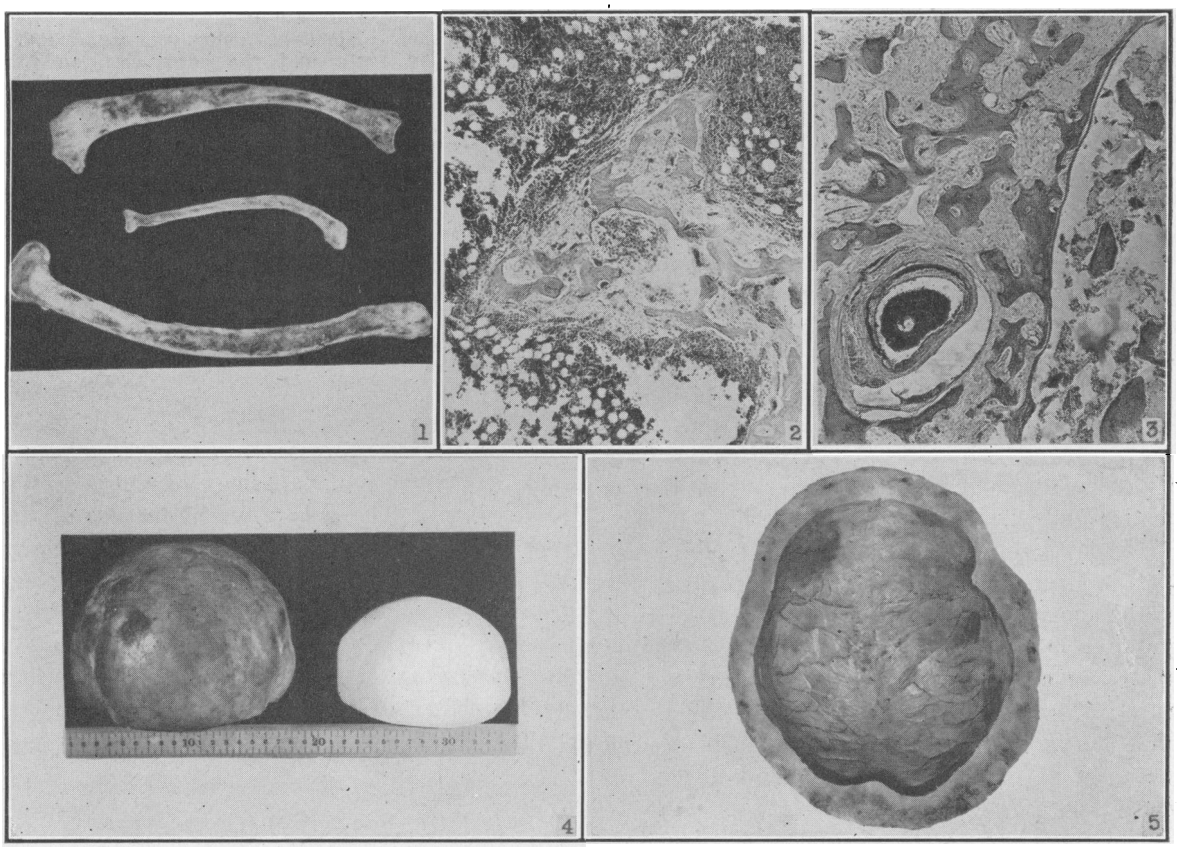

Fig. 1.—Tibia, radius and femur from case, showing thickening and bending of the bones, loss of distinction between compact and spongy bone with areas of vascular marrow interspersed amongst new bony trabeculæ. **Fig. 2.**—Early bone lesion in Paget's disease. Removal of bone by osteoclasts (large dark cells) and replacement of bone and marrow by fibrous tissue. **Fig. 3.**—Advanced lesion of bone with well-defined cyst containing necrotic bone and debris, right. Bony trabeculæ showing mosaic structure and connective tissue filling intervening spaces, also thickened vessel with calcareous deposit in media to the left. **Fig. 4.** — Anterior view of calvarium contrasted with calvarium of normal female. The latter has of course been macerated. The vascularity and roughness of the former is seen. A dark area in the frontal lobe was soft enough to be pierced with a knife. **Fig. 5.**—Section of calvarium viewed from below. Note the great thickness of the bone, the disappearance of the distinction between outer and inner tables and diploë; also soft vascular areas, dark in appearance, particularly the one in the frontal bone seen above and to the left.

what he calls an epithelioma of the arachnoid surface of the dura mater of the brain, which was probably a meningioma (psammoma), and, therefore, not malignant. It is interesting that in the case described below there were two tumours, a carcinoma of the pyloric end of the stomach and a small meningioma of the cerebral dura mater. In several of the cases in literature which have come to autopsy cancerous growths and simple tumours (Sternberg[9]) have been recorded. There is a further association between sarcoma and Paget's disease. Jaffe states that about one in ten of the more diffuse forms of the disease shows complications with sarcoma. This sarcoma is often widespread in the bones. From the other standpoint, in 71 cases of osteogenic sarcoma (Shanks, Kerley and Twining[8]) osteitis deformans was present in 28%. Further, in all of these cases the bone disease preceded the development of the sarcoma by ten or fifteen years. There appears, therefore, to be a definite association between Paget's disease and malignant neoplasia, the bone dystrophy being the earlier condition.

Blood chemistry.—Jaffe[3] states that the only chemical test of any value is the serum phosphatase. This test frequently shows high values, sometimes up to twenty times the normal. Further, the more severe and widespread the case the higher the value. The explanation of this high serum phosphatase is not clear. It is probably associated with the formation of new bone rather than destruction of the old. The test, however, is not specific. High values have also been reported in generalized osteitis fibrosa cystica and in rickets.

The levels of serum calcium and serum phosphorus are normal, which is remarkable in view of the considerable destruction of bone which is going on, and in view of the deposit of calcium in the arterial walls. In contrast to this, in osteitis fibrosa cystica and in rickets the serum phosphorus is lowered, while the serum calcium is raised in the former disease and normal in the latter.

The following is the new case brought forward. For the notes I am indebted to Dr. C. M. Crawford and the staff of the Ontario Hospital, Kingston.

The patient, E.S., was born in the south of England in 1870. She was a widow and previous to marriage worked as a weaver. She was a member of a family of six, four girls and two boys. There is no record that either of the parents suffered from bone disease, but all four sisters have developed symptoms suggestive of Paget's disease; and one, who is resident in Canada, has distortion of most of the bones of the body and has had repeated spontaneous fractures. There are no precise data as to the onset of the disease in the patient, but it was apparently well marked in 1928. She was admitted to Rockwood Mental Hospital in 1940 and died in March, 1942. The diagnosis in her case was senile psychosis with simple deterioration. Clinical pathological observations carried out during hospitalization were as follows: serum calcium 10.2 mgm.; blood urea 24 mgm.; hæmoglobin 60%; red blood cells, 2,580,000, leukocytes 5,760. The Wassermann test was negative. No observations were made on the serum phosphorus or serum phosphatase.

The relevant autopsy findings were as follows: The calvarium was enormously enlarged, measuring 63.5 cm. in circumference. When removed, it weighed 1,740 grm. It varied in thickness from 1 to 3 cm. (Figs. 4 and 5). The distinction between diploë and outer and inner tables had disappeared, the whole bone being transformed into soft osteoid material, red in colour and easily cut with the saw, and some parts with the knife. The spine showed well marked kyphosis in the dorsal region. The long bones—radius, ulna, femur and tibia — were bent, thickened and softened, and the marrow of the shafts was red and partially occupied by soft bone (Fig. 1). The stomach showed a large ulcerating carcinoma in the region of the pylorus and there was a small rounded meningioma attached to the dura mater over the left frontal area 3 cm. from the middle line. There was atheromatous change in the aorta and the coronaries, and the arteries generally, especially those of the lower limbs, were extensively calcified. In regard to the endocrine glands, the adrenals were large, but normal, and the pituitary was flattened, as was also the brain, by a projection upwards of the base of the skull; the thyroid was small and showed nothing of note microscopically; the parathyroids were dissected out and found to be normal as regards gross and microscopic appearances.

Microscopically, the bony changes were in conformity with those usually found in Paget's disease, the only unusual feature being well marked calcification of the media of the arterioles in the substance of the bone itself.

SUMMARY

A case of Paget's disease of bone is presented and the nature and pathology of the condition is discussed. The only unusual feature of this case was the occurrence of an osteodystrophy, apparently of a similar nature, in several members of the same family. A point not hitherto observed in such cases is the association of arterial disease in the bones with the necrosis and cyst-formation which commonly occur.

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