

PAGET'S DISEASE OF BONE (OSTEITIS DEFORMANS)

A Review of 48 Cases

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It is now more than sixty years since Sir James Paget¹ described the bone disease which bears his name. He advocated the term "osteitis deformans", but this would seem to be a misnomer. We do not believe infection to be concerned in the cause, and we know that in many cases there is no skeletal deformity. Therefore, we prefer to designate it "Paget's disease". A summary of the salient features encountered and the present-day concepts of the disease, together with a review of 48 cases recorded at the Cleveland Clinic, are presented.

The advanced stages present a striking picture of skeletal changes, and the classic cases with the massive but well-formed head, reduced stature with marked kyphosis, the great anterior bowing of the legs and the pendulous abdomen present no difficulty in diagnosis. These cases are uncommon and the frequently diagnosed ones are much less advanced, perhaps involving but one bone. It is in these early or localized lesions that the differential diagnosis becomes more formidable and important.

INCIDENCE AND DISTRIBUTION

Paget's disease is frequently recognized now. Brailsford² was able to collect only 300 cases which had been recorded prior to 1926. He added 154 cases of his own in 1936 and since that time many others have been reported. Forty-eight cases have been diagnosed and recorded at the Cleveland Clinic.

Paget's disease is essentially a disease of late life, perhaps later than the average carcinoma age, although in most cases the disease has been present some years before it is recognized. The average age in our series was about 60 years; the youngest was 32 and the oldest was 88 years of age (Table 1). No important difference in sex incidence was shown, this series consisting of 15 women and 33 men. All were white, although the disease may occur in Negroes. One patient reported two siblings with a definite diagnosis of Paget's disease, a familial tendency that has been seen frequently. Several cases have been described in children, but they do not seem to be well authenticated.

TABLE 1
Age Distribution

30-40	40-50	50-60	60-70	70-80	81	88
2	6	18	18	2	1	1

Schmorl³, in the course of his work on intervertebral discs, became interested in Paget's disease and made complete skeletal examinations on 4,600 persons. He made a diagnosis of Paget's disease in 138 of these cases, an incidence of 3 per cent in persons past 40 years of age. The greatest number of lesions was in the spine, including the sacrum. However, many of the lesions were local, some being almost microscopic and obviously nonclinical. Thus, the relative distribution in the skeletal system seems to depend somewhat upon the method of diagnosis used.

It has long been said that the skull and femur are the sites of greatest predilection; however, later authors place the spine and pelvis first. Table 2 lists the frequency with which various bones were involved, as well as the number of times that the involved bone was radiographed in the series. Some patients had only one or two bones radiographed so that involvement elsewhere can only be conjectured. In other cases only portions of the spine were examined. Obviously, full skeleton radiographs of each patient would be required to determine the true distribution. The tendency for routine abdominal radiographs on gastrointestinal and genitourinary cases probably has led to the finding of a disproportionate incidence in the pelvis and lower spine, although Schmorl reported a similar incidence.

TABLE 2

	<i>Frequency of bone involvement (by radiograph)</i>	<i>Number of times radiographed (all or part)</i>
Skull	18	27
Spine (or portion)	16	39
Pelvis	35	39
Femur	18	27
Tibia	11	13
Forearm	3	4
Humerus	5	6
Metacarpal	1	1
Scapula	1	1

A correct clinical diagnosis was made on the basis of the history and physical findings in 15 of the cases. In 9 others the radiologic findings of Paget's bones apparently were related to the presenting symptoms;

in the remaining 24 cases the diagnosis was made incidentally from changes seen in roentgenograms taken to investigate complaints aside from the skeletal system. There was no obvious constancy to this group of complaints. The typical symptom of the disease was pain in the back and legs, present for several years, with no particular aggravating or alleviating factors. When the tibia had been involved, many patients noticed anterior bowing of the leg. Only a few of the 17 cases with skull involvement had noticed enlargement of the head. One case with multiple involvement but normal skull radiographs complained of increasing hat size. Two cases presented themselves with fractures of involved bone.

ETIOLOGY

No theory of the cause of this enigmatic disease thus far advanced has gained wide acceptance. Paget considered it an inflammation of bone, but this idea is thought to be untenable at present. Moller⁴ pointed out the similarity of chronic fluoride intoxication, but important differences are present. In fluoride poisoning the bone changes are symmetrical, universal, and slowly but surely progressive, while Paget's bones are asymmetrical and unpredictable in their progression.

Great efforts have been made in the past to incriminate endocrine factors, particularly dysfunction of the parathyroid glands. This view has been partially abandoned and, according to Jaffe⁵, no case of a parathyroid adenoma associated with Paget's disease has been reported since 1926. Three of our cases had parathyroidectomies. All had normal glands and had only temporary relief of symptoms. Adrenal cortical extract has been reported as a successful therapeutic agent, although there is no obvious logical basis for it⁶. Jaffe believes that this is not a systemic disease and therefore is less apt to be a metabolic disease. He feels that it may be a breakdown of the normal mechanism for replacement of bone.

Moehlig and associates⁷ pointed out a familial tendency to obesity, tallness, and diabetes in a series of their patients. These cases showed an elevation of the glucose tolerance curve and a high carbohydrate diet with insulin relieved their pain. One of our cases had a diagnosis of chronic hypoglycemia, but no diabetic cases were encountered.

Trauma has been cited as a factor. However, in at least some of these cases bone changes were shown to be present before the trauma. European writers speak of "pagetoid" bone disease following trauma. With a typical monostotic lesion this terminology would seem more discreet. One of our monostotic cases gave a history of trauma, and the roentgenologic changes were typical.

In our cases both serum phosphorus and calcium levels were at the upper limit of normal. The mean serum calcium reading was 10.8 mg.

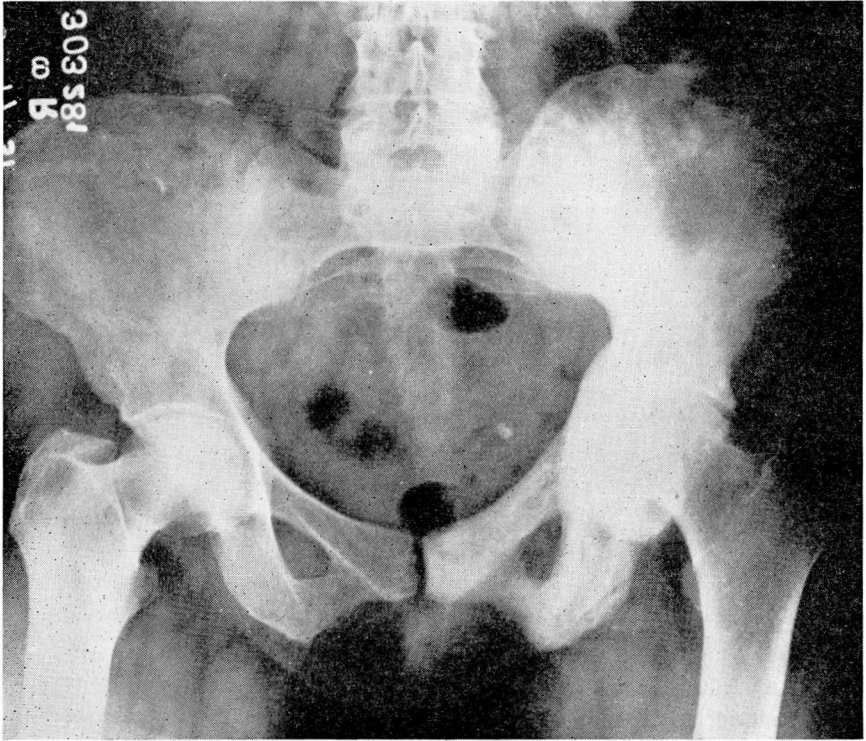


FIGURE 1: Paget's osteitis deformans with typical thickening and sclerosis, and with unilateral distribution.

per cent, with normal figures being 9 to 11. The average serum phosphorus was 3.7 mg. per cent, and normal is 2 to 4.0. The highest calcium reading was 11.7 except in a case which was suspected but not proved to also have hyperparathyroidism, and the highest phosphorus, 4.2. The literature indicates that the serum calcium usually is somewhat low, but such was not the case in our group. In osteitis fibrosa cystica the serum calcium is definitely elevated and the serum low.

The only constant laboratory finding is the marked elevation of serum phosphatase activity, which reaches its highest levels in Paget's Disease. It may rise to 80 units or more as contrasted with a normal maximum of 4.0 by the Bodansky method. There is some correlation between the activity and extent of the disease and the phosphatase level. Certain other diseases give moderate phosphatase elevations. These include osteitis fibrosa cystica, rickets, bone metastases from carcinoma of the prostate⁸, and certain liver diseases with jaundice. Destructive bone lesions are less apt to have elevated serum phosphatase values.

Thus far we have discussed the commonly employed "alkaline" serum phosphatase determinations. Kutscher⁹ has described phosphatase

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readings done on acidified serum in which by far the highest levels are found in patients with bone metastases from carcinoma of the prostate. He calls this substance prostatophosphatase. Gutman⁸ finds that in Paget's disease this "acid" phosphatase is normal in nearly all early and moderately advanced cases. This may represent a valuable differential procedure in certain cases.

PATHOLOGY

The sequence of pathological changes in the bone in Paget's disease has been well determined. There is primarily a progressive absorption of bone with accompanying osteoporosis and vascular changes, followed by the laying down of new bone, or one might better say osteoid tissue because little attempt is made to reproduce normal bone structure. Early in the disease the bone is quite soft, and it is at this stage that bowing of the long bones begins, due probably to muscle pull. With expansion of the bone this may continue, especially in the leg and forearm, because of inequality of length when the adjoining bone remains normal. A considerable amount of fibrous tissue is formed, which may almost obliterate the marrow cavity. This tissue is vascular and osteoblastic. Most of the bone is deposited from the periosteum.

The typical end picture is a longer bone, laid down on a more porous plan. The trabeculae are coarse and the fragments of lamellar



FIGURE 2: A. Involvement of left ulna, right first metacarpal and right radius showing varied distribution of Paget's disease in the long bones.

B. Thirty-nine year old woman with bowing and enlargement of leg following trauma, with characteristic changes.

bone are laid down as an irregular mosaic with little evidence of re-creation of the haversian systems. This distinguishes the disease pathologically from any other bone disease. The irregular mosaic pattern was Schmorl's criterion for the diagnosis of Paget's disease.

Vascular changes are seen particularly in the skull. The vessels show thrombosis, congestion, hemorrhage, and edema. Some feel that it is primarily a vascular disease. Large areas of hemorrhage or anemia with necrosis result in the appearance of pseudocysts which are frequent. The varied pictures seen roentgenographically depend upon the stage of absorption and redeposition of calcium at the time. This process characteristically may be arrested in any stage with minimal involvement, or it may "spread" to involve many bones.

ROENTGENOLOGIC FINDINGS

The well known typical roentgenologic picture is one of altered density in bone. There is first a porosis with the resorption of bone, followed by a widespread sclerosis and increase in bone size, with loss of the normal structure. This may vary, depending upon the type of bone involved. The shaft of the long bones often is curved and the entire bone becomes greater in diameter. There is loss of normal cortex shadows and the appearance of a much thickened, not entirely regular cortex, less dense in some regions and more dense than normal in others. There may be small areas of decreased density suggestive of cysts. The entire bone usually is not involved, and the demarcation between normal and diseased bone is fairly sharp and often V-shaped. The epiphysis offers no barrier, a fact which is a valuable differential point. The marrow cavity is narrowed, and the trabeculae, especially at the ends, are thickened and irregular. The bone as a whole is less dense than normal until late in the disease and may have the appearance of cotton wool.

The skull is thickened, and the tables are not distinguishable. There are very typical mixed areas of porosis, with numerous small circular areas of greatly increased density representing localized sclerosis. The outer table and diploe show the first and greatest involvement. Some early cases show large well-defined areas of uniformly decreased density which is termed *osteoporosis circumscripta*, and which has been described by Kasabach and Dyke¹⁰ and others as a progenitor of Paget's disease with the usual train of Paget's changes following it. We have not recognized a true *osteoporosis circumscripta*.

When the pelvis is involved the radiographic picture is often one of widespread, dense, but not uniform sclerosis with some areas of decreased density. The increase in diameter aids to differentiate it from osteoblastic metastases, such as from carcinoma of the prostate. The uniformity of the lesion in metastases is also notable.

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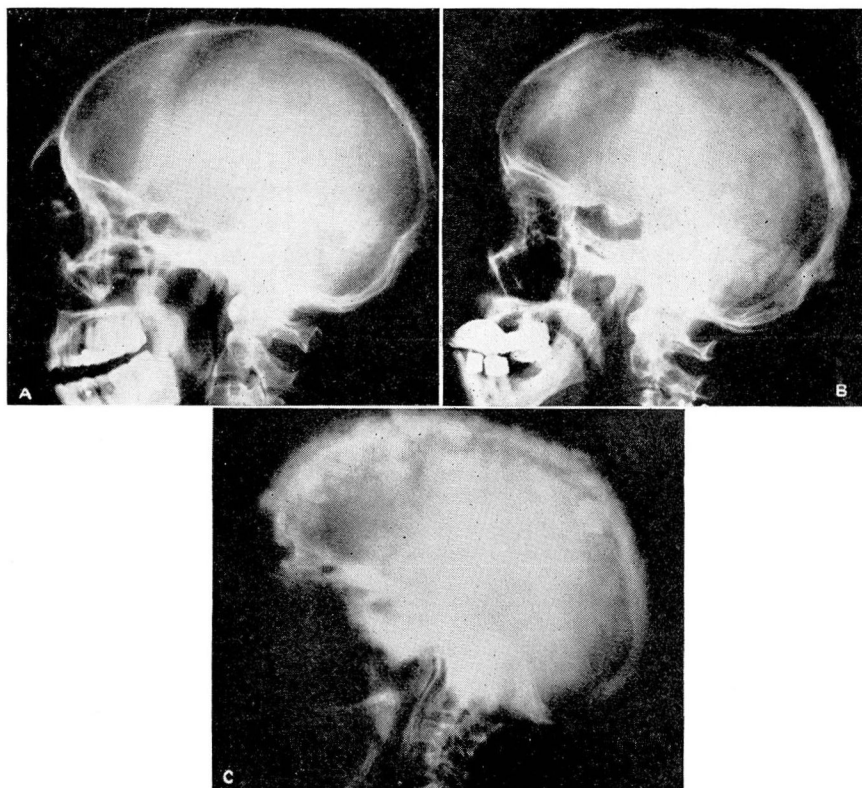


FIGURE 3: We believe these three cases represent stages in the development of Paget's disease.

A. Early changes with osteoporosis and thickening of the calvarium. The pelvis showed typical findings.

B. There is extensive involvement with mottling, thickening, and osteoporosis. There was no increase in hat size.

C. Typical advanced changes.

The spine usually shows dense, irregular, wavy trabeculae. The vertebral bodies may cause cord compression by collapse or increase in size. Usually the entire vertebral body is more or less evenly involved, and one or several may be affected. If more than one is involved, they are usually adjoining ones. The increase in width may extend out beyond the intervertebral cartilages, and bony union may then occur.

Joints are involved rarely, but there may be apparent irregular superficial defects in the periosteum. Often an adjoining ilium and femur will be involved in unilateral disease without evidence of joint disturbance.

COMPLICATIONS

In Paget's bones there is a definite tendency toward the occurrence of fractures with minor trauma. These usually are transverse and are relatively painless¹¹. A callus appears early and prompt healing occurs. Multiple transverse fissure fractures in long bones involved with Paget's disease have been described as possibly antecedent to complete fractures. Two of our cases were first seen because of fractures; one was of the forearm which occurred while driving a car, and one was of the scapula which resulted from a fall from a porch.

The relationship of malignant tumors of bone to this disease was noted by Paget in his first article, in which he described three bone tumors in his 7 cases. While the incidence is not nearly so high, there is an apparent connection between the two diseases. Coley and Sharp¹², in reviewing the osteogenic sarcomas listed in the American Registry of Bone Sarcomas, found that in 71 cases over 50 years of age, 28 per cent were in association with Paget's disease. In this group of cases the usual sites of predilection were involved, and in every instance the tumor was located in bone already the site of Paget's disease. Several had multiple points of origin, and the lesions were less radio-sensitive than in patients without Paget's disease. The newly formed osteoblastic marrow connective tissue seems to originate the tumor. In none of our cases was there an osteogenic sarcoma, and a review of all of our cases of osteogenic sarcomas in adults has shown no case of Paget's disease.

The occurrence of neurologic symptoms as a direct result of the bone changes in the skull is not well established. The auditory nerve in particular is thought to be encroached upon frequently. Several of our patients had varying degrees of deafness, and two had diagnoses of trigeminal neuralgia. Headache was a frequent symptom. Several cases of compression of the spinal cord occurring as a complication of Paget's disease in the spine and being relieved by laminectomy have been reported. Schwarz and Reback¹³ reported this complication, showing how the increased size of the vertebral body encroaches upon the spinal canal and cord. These lesions are most often in the thoracic region, where the interpedicular measurements are smallest.

THERAPY

The wide range of therapeutic measures advocated by different workers bespeaks their lack of specificity. No clinical or roentgenologic cures have been reported, but symptomatic relief has been claimed from many measures.

Roentgen irradiation for pain, particularly of the long bones and spine, has been used frequently, and good symptomatic results have been reported¹⁴.

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Both parathyroid and adrenal extracts have been advised on empirical grounds. Watson⁶ is especially optimistic about the use of adrenal cortical extract. We have used parathyroid extracts with doubtful benefit.

A high carbohydrate diet with insulin has been recommended⁷.

Lineal osteotomy of long bones is said to be efficacious for intractable pain. Most logical is support or splinting, especially if the tibia is involved.

CONCLUSIONS

1. An analysis of 48 cases of Paget's disease of bone is presented.
2. No conclusions as to etiology have been reached.
3. Studies of serum calcium and phosphorus are mentioned, and the use of "acid" phosphatase activity measurements to differentiate metastasis from prostatic malignancy is suggested.
4. Roentgenographic differentiation between these two lesions can usually be readily made by the coarse mottling of the bone with alternate areas of increased and diminished density, increased size of the bone and bowing in Paget's disease. On the other hand metastatic prostatic lesions do not enlarge the bone but only show islands of increased density giving a mottled appearance of the bone. The location of the metastases usually is confined to the pelvis and lumbar spine, although occasionally other bones may be involved.

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