

## PAGET'S DISEASE\*

KAZEM FATHIE, M.D., FAANAOS-C, FACS  
Chief FAANAOS College of Neurological Research

An autopsy performed several years after his death revealed that Beethoven's skull cortex was thickened and highly vascular<sup>1</sup> (a classic finding of Paget's disease of the skull). Therefore, it is probable that his deafness was due to the skull changes of this most interesting disease.

### HISTORY

**P**AGET'S DISEASE WAS RECOGNIZED BY Sir James Paget approximately over 100 years ago. Initially it was a rather mysterious disease, which caused a variety of deformities as well as fractures (which could heal quite rapidly). Besides this problem, Osteitis Deformans (as it was called by Sir James), could cause a variety of neurological disorders such as visual problems, deafness, etc.

It should be emphasized that there was no reason for recognizing the disease by physicians since there was no way to cure the problem at that time. Recently, however, with the degree of availability of calcitonin and Didronel (etidronate disodium), the disease must be recognized as early as possible to reverse its course.

Paget's disease has been observed in both sexes, and evidence suggests that it may be familial. The incidence of the disease does vary with geographic locations in sundry countries. Significant differences have even been noticed between cities.

The etiology and incidence. It is known that the disease is caused by a slow virus infection. Characteristic inclusion bodies are seen in osteoclast formation in Paget's disease.

Some radiological surveys and pathological studies suggest that Paget's disease may be present in almost 1 percent of the population age 50 and over. With increasing age the problem reaches almost 10 percent of the population after the age of 80.

The disease has been seen throughout Europe. Since Paget's disease has been identified, 750,000 patients have been recognized in France, 700,000 in the United Kingdom, 250,000 in the Banalok countries, 800,000 in Germany, and 50,000 in Scandinavia. In the United States, there are 2 million patients with Paget's disease (150,000 of whom are asymptomatic).

This unique disease has been observed in Anglo-Saxon areas, as well as in Africa. The highest incidence of the disorder has been annotated in England (in the area of Lancashire).

**Clinical findings.** Paget's disease is most frequently seen in the ilium, femur, lumbar spine, tibia, humerus, and the scapula respectively. It is least commonly found in the hands and the feet. The x-ray findings have demonstrated the predominancy of this lesion affecting the long bones of the patient (femur). With the exception of the deformities that have been noticeable in this disease, it is of interest to recognize what happens in the bone itself.

**Pathogenesis of Paget's disease.** Within adult bone there is a highly organized osseous structure consisting of both cortical and spongy bone where remodeling occurs continuously. This is due to the presence of two cell types with opposing actions (the osteoclast and osteoblast).

Osteoclasts are giant cells derived from monocytes of bone marrow. Osteoclasts are responsible for destroying bone tissue. During this process the minerals (which include calcium) are dissolved. At the same time collagen fibers from bone matrix are broken down. As a result, amino acids and hydroxyproline (which is derived from the breakdown of collagen) is liberated. Traces of hydroxyproline can be found in the urine of the patient with Paget's disease.

The osteoblast is a synthesizing cell which makes collagen fibers and other components of bone matrix. Furthermore, osteoblasts contribute to the process of mineralization, causing an overproduction of alkaline phosphatase.

The process that is observed during the production of cortical bone is also similar to that which occurs in the remodeling of trabecular tissue.

Bone resorption is brought about by the osteoclast. Bone formation occurs from the osteoblast. In the adult, this activity normally leads to a small loss of spongy bone (from the endosteal surfaces of cortical bone).

The final result of osteoblast and osteoclast activity in the aging adult is therefore to produce a small, but gradual loss of bone. It is just this process in the patient with Paget's disease which results in the creation of osseous enlargement and osteosclerosis.

It should be mentioned that primary remodeling disturbances in patients with Paget's disease seem to occur at the osteoclastic level. The cells are increased in number and in size. This leads to irregular lacunar cavitation in the affected bone, during which process increased amounts of hydroxyproline are liberated.

This osteoclastic overactivity stimulates osteoblastic formation, so that they also increase in number and activity. As a result, the osteoblast makes about twice the normal amount of bone matrix on a daily basis.

Because matrix is layed down so rapidly it becomes abnormal, in an undisciplined fashion. Pagetoid bone loses its normal organized shape, form, and structure.

**Labeling with Tetracycline.** Osteoblastic overactivity can be demonstrated by labeling bone with Tetracycline. First, two doses of Tetracycline are given. Then a measure of the amount of bone deposited between the two doses is taken.

The final result of this remodeling disturbance is to produce a dense bone whose cortical and trabecular microstructure is weak, despite being dense.

**The diagnosis.** In terms of making a diagnosis, it is important to recognize that Paget's disease can progress for decades in the affected patient without any obvious symptom. When the disease does become evident, it is usually causes the patient to have pain (in the specific bone(s) involved).

Pain of Paget's disease frequently comes from the shaft of the long bones or the skull. However, the pain can arise from an affected joint due to actual enlargement. This can lead to deformities and impaired movement. Ultimately the joint loses its articular cartilage and osteoarthritis results.

Pain can also arise as a result of compression of the spinal cord or spinal nerve root due to hypertrophy and enlargement of osseous structures about them.

**Vascular problems.** Complications caused by the diversion of blood supply to the more highly vascular diseased Pagetoid bone, somehow produce the vascular steal effect. In addition, the patient's overlying skin is warmer. Oftentimes this increased blood supply which overlies Pagetoid bone can be recognized indirectly, through the presence of engorged vessels (in the temporal region, for example).

**X-ray changes.** Besides measuring serum alkaline phosphatase and urinary hydroxyproline, radiographs should be obtained of the affected patient. Bone enlargement can be striking radiographic findings. Characteristics include thickening of the involved bone (with increase in size of the cranial cavity), enlargement of vertebrae bodies (anteriorly and posteriorly), increased iliac bone, with deviation, deformity, elongation and bowing of long bones.

**Laboratory findings.** Increased serum alkaline phosphatase and urinary hydroxyproline reflect the severity of the patient's underlying disease. Measuring alkaline phosphatase is easy, but assays for urinary hydroxyproline are quite difficult to obtain.

Blood calcium levels remain normal at all times in

Paget's disease (since there are parallel increased amounts of calcium entering and leaving the bone).

Bone scanning is very remarkable and valuable since it will pick up almost all the lesions which are active. Even with all these diagnostic adjuncts, oftentimes the diagnosis of Paget's disease is quite difficult. It is particularly important to remember that whenever the patient complains of musculo-skeletal pain in and around a joint, then Paget's disease should be suspected.

**Complications of Paget's disease.** With the exception of deformities, there are bone fragility with fracture, as well as compression of vital organs (such as the auditory nerves). These fractures are quick to heal and oftentimes are the first sign of the disease.

**Neurological complications of the disease.** Besides deafness, spinal cord compression can occur which leads to walking difficulties with paraplegia. If the optic foramina are compressed, blindness may result. In addition, a varying degree of obstruction may be seen on myelography.

Vascular insufficiency also may play a major role in producing spinal cord dysfunction.

**Other complications of Paget's disease.** Sarcoma is one of the worst complications, but fortunately is rare (about 1 in 1,000). Characteristic features are intense pain, with an x-ray showing osteolysis and loss of normal cortical definition. Other conditions have been reported to be more common as a result of the extreme vascularity of bone. For example an increase of cardiac output may occur, leading to cardiac failure.

### TREATMENT

**Calcitonin.**<sup>2</sup> Specific treatment consists of drugs which influence osteoclastic activity. Calcitonin is a hypocalcemic hormone secreted by the thyroid. It works by inhibiting bone resorption. Several types of calcitonin are available. These include natural hormones (extracted from the thyroid) or synthetic calcitonin (from salmon or eel). In certain countries, synthetic human calcitonin is also available.<sup>3</sup>

Calcitonin has to be given by injection (intramuscular or subcutaneous). Low doses are ineffective. In the higher doses, calcitonin can suppress bone pain and reduce alkaline phosphatase and hydroxyproline levels by one-half. However, calcitonin has to be given continuously otherwise a relapse may occur.

**Side effects of Calcitonin.** The use of calcitonin is frequently associated with nausea or flushing of the face (about one-fourth of the patients). Relapses may occur despite continued treatment. This resistance to treatment is sometimes associated with development of calcitonin antibodies.

**Mithramycin.**<sup>4</sup> This also acts on the osteoclast, but this medication has not been used extensively because of liver and kidney toxicity. The theory of its use is that Paget's disease is considered to be a low-grade neoplastic process.<sup>6</sup> Mithramycin is primarily toxic to osteoclasts.

**Didronel (etidronate disodium).**<sup>5</sup> Didronel has been given orally producing effects on patients with Paget's disease which are similar to those which come from calcitonin. The recommended dosage for Didronel (EHDP) is 5 mg. per kilogram of body weight per day. Didronel should not be taken with milk, milk products or anti-acids; they interfere with the intestinal absorption of the medication. The length of treatment should be six months without interruption. Improvement is usually accompanied by decreased alkaline phosphatase and hydroxyproline levels (to about one-half of their initial values).

These suppressed biochemical changes may persist for months or even years beyond the end of the period of treatment. Didronel and calcitonin therefore ameliorate pain in Paget's disease and effect laboratory decreases of alkaline phosphatase and hydroxyproline. Didronel may be used prophylactically in asymptomatic forms of the disease.

### SUMMARY

Paget's disease affects 2 million Americans, but only 150,000 are symptomatic. Musculoskeletal pain, with or without deformity should cause one to suspect Paget's disease, especially if the patient's serum alkaline phosphatase and urinary hydroxyproline levels are abnormally high.

Spinal cord and cauda equina compression, deafness, and high-output cardiac failure are some of the more unusual complications of Paget's disease. Sarcomatous degeneration is quite rare.

The advent of the 32 amino acid polypeptide known as Calcitonin (produced by the thyroid gland) and Didronel (etidronate disodium) have altered the clinical course of this once incurable disease. ●

(References: ) →

## BIBLIOGRAPHY

1. NAIKEN, V.D.: "Did Beethoven Have Paget's Disease of Bone?". *Ann. Intern. Med.* 74: 995, 1971.
2. AVRAMIDES, A.: "Salmon and Porcine Calcitonin Treatment of Paget's Disease of Bone". *Clin. Orthop.* 127: 78-85, 1977.
3. SINGER, F.R.: "Human Calcitonin Treatment of Paget's Disease of Bone". *Clin. Orthop.* 127: 86-93, 1977.
4. JAFFE, H.L.: "Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints". Lea & Febiger, Philadelphia 1972, pp. 240-271.
5. KHAIRI, M.R.A. and JOHNSTON, C.C.: "Treatment of Paget's Disease of Bone (Osteitis Deformans) with Sodium Etidronate (EHDP)". *Clin. Orthop.* 127: 94-105, 1977.
6. RYAN, W.G.: "Treatment of Paget's Disease of Bone with Mithramycin". *Clin. Orthop.* 127: 106-110, 1977.
7. SCHMIDEK, H.H.: "Neurologic and Neurosurgical Sequels of Paget's Disease of Bone". *Clin. Orthop.* 127: 70-77, 1977.
8. PAGET, J.: "Osteitis Deformans". *Royal Med. & Chir. Soc. of London* 66: 37, 1877. ■