PAGET'S DISEASE:

HISTORY & MANAGEMENT:

RECOGNITION & TREATMENT

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INTRODUCTION

OVER 100 YEARS AGO, Sir James Paget first recognized "Paget's Disease". Initially it was named Osteitis Deformans and thought to be due to an infectious process of bone. For years this disease remained a medical enigma which caused deformities specifically of long bones (mostly among older people). Recognition of this disease was rather incidental and treatment was almost nonexistent.

Abnormalities which were typically recognized in this disease arose gradually causing complications, such as pathological fractures and deafness. Some believe that compression of optic foramina and blindness results due to hypertrophy and thickening around the internal auditory meatus. This can result in deafness.

Recently specific methods of treatment have revived medical interest in this field. Previously, because of not having any definite treatment, there was no such incentive to make a definite diagnosis of Paget's Disease. However, these new treatments require that Pagetoid patients be recognized at any stage of the disease (especially early), so that treatment may be initiated as soon as possible.

Paget's Disease occurs in both sexes, and sometimes familial incidence takes place. Different countries have different incidences of Pagetoid people.

The disease may be caused by a slow growing virus. Inclusion bodies have been found in osteoclasts.

POSTMORTEM STUDIES

Postmortem and radiologic studies of Pagetic patients suggest that Paget's Disease may be present in at least 1 percent of the 50-60 year old population (the percentage increases with age). In fact, approximately 10 percent of the population over the age of 80 years may have the disease.

Although the precise number of patients with Paget's is unknown, the disease is widely spread throughout Europe. There may be 750,000 Pagetics in France, 700,000 in the United Kingdom, 250,000 in the Banalok Countries, 50,000 in Scandinavia and 800,000 in Germany. In the United States, there are 2 million patients with Paget's Disease (150,000 of which are known to be symptomatic).

The disease, seen primarily among the Anglo-Saxon race, is more rare in Africa and the Far East as compared with Europe and the United States. In the United Kingdom, the highest incidence of Paget's Disease occurs in Lancashire.

Based on these estimates, it is possible that general practitioners may have symptomatic Pagetics in different stages of disease development. A number of those symptomatic patients could benefit from treatment to help arrest or significantly impede the disease process. This emphasizes the importance of making an accurate early diagnosis.

AREAS OF INVOLVEMENT

Paget's Disease is known and found most frequently in the ilium, femur, lumbar spine, skull, sacrum, thoracic spine, tibia, humerus, and scapula. It is less commonly found in the hands and feet. Radiographs of long bones and the ilium demonstrate these findings.

PATHOLOGICAL STUDIES

Knowledge of the Pagetic process is made easier with fundamental understanding of normal bone formation. Adult bone is a highly organized structure, consisting of both inner cortical and spongy bone. Remodeling occurs continuously in both, due to the presence of two types of actively opposing cells: osteoclasts and osteoblasts.

Osteoclasts. These are basically giant cells which have been derived from monocytes of bone marrow. Osteoclasts are responsible for destroying bone tissue. During this process, minerals (including calcium) are dissolved. At the same time, collagen fibers from bone matrix are broken down. During such phenomena, amino acids are liberated and a particular hydroxyproline (from the breakdown of collagen) is released. This can be found in urine of patients with Paget's disease. Hence, twenty-four hour urine studies of hydroxyproline are most valuable in study of Paget's disease patients. Also obtainment of alkaline phosphatase is necessary.

Osteoblast. The osteoblast is a synthesizing cell which makes collagen fibers and the other components of bone matrix which contribute to the process of mineralization.

PROCESS OF BONE FORMATION

During the process of bone formation, osteoblasts release alkaline phosphatase into the blood system. This circulates throughout, initiating osteoblastic activities involving the entire skeleton. This process is similar in both cortical and trabecular bone.

Between bone resorption (osteoclastic activity) and bone formation (osteoblastic activity) destruction and reconstruction of bone is controlled by a complex process of remodeling. Osteoclastic resorption always precedes the formation of new bone laid down by osteoblasts.

When radiographic studies are done, one sees activity leading to loss of spongy formation. Also some loss of endosteal cortical bone can be noted.

In aging adults, this process produces small but gradual loss of bone, so that the final result in the Pagetic is always net gain of bone tissue. This results in positive bone balance. It also accounts for enlargement of bone and its typical osteoclastic appearance.

The primary disturbance in remodeling has been attributed to osteoclastic abnormalities. These cells are hypertrophied and increase many, many times, not only in number but also in size, producing erosion of irregular lacunar bone. It is during this process that hydroxyproline is freed into the system. Osteoclasts stimulate a reaction in osteoblasts causing them to increase in number, size and activity.

As a result, the process continues daily, producing twice the amount of matrix as normal. This matrix is laid rapidly in an abnormal, undisciplined fashion with such erraticism that bone loses its normal lamellar structure and organization.

A technique using Tetracycline may demonstrate osteoblastic overactivity. Two doses of Tetracycline are administered to the patient. Each is laid down selectively in bone. The distance between two fluorescent "Tetracycline" labels gives the amount of bone formed.

The final result of this remodeling disturbance is to produce dense bone whose microstructure is disorganized in such a fashion that the tissue thus formed becomes weak (despite the fact that it is dense).

DIAGNOSIS

The diagnosis of Paget's Disease is usually difficult to make in early stages since the process occurs over decades without any obvious symptoms that the patient can notice. When the process has progressed and the disease is evident, usually the first complaint of the patient is pain.

("Diagnosis of Paget's", Continues).

Initially pain is mild but it can become severe in joints. For example, if the femur is involved, pain is noted in the hip, knee, or low back. Pain occurs because:

1. Involvement of the shaft of long bones or skull.
2. Pain may arise from joint involvement. This causes early signs of deformity.
3. Bone pain may come from impaired joint movement. This leads to loss of articular cartilage.
4. Pain can arise from compression of neural tissues.

Complications may be due to diversion of blood supply to more highly vascular Pagetic bone. This causes a vascular steal effect. One may see warmth in the area of Pagetic disease.

Overall Pagetic pain is difficult to differentiate from other types of pain from other diseases. X-ray should help to differentiate from other problems.

The presence of increased alkaline phosphatase and urinary hydroxyproline are often necessary to assist the physician in making a definite and accurate diagnosis of Paget's disease. X-ray findings are sometimes diagnostic because of bone enlargement, striking facial features and thickening of the skull, vertebral bodies (both anterior and posterior directions), enlargement and bowing of femoral (or tibial) shafts, and enlargement of the ilium in all directions. Radius and ulnar involvement is less commonly seen.

The other specific radiological findings are osteoporosis, circumscript punched out lesions of the cranium, osteolytic lesions in long bones, as well as the irregular increased bone density.

BIOCHEMICAL CHANGES CAUSED BY PAGET'S DISEASE

Biochemical changes caused by Paget's disease usually reflect localized increased bone turnover occuring during the active part of the disease. Hydroxyproline often increases many times higher than normal. Increase in serum alkaline phosphatase usually reflects the severity of disease and can reach 10-20 times upper limits of normal.

Hydroxyproline and alkaline phosphatase levels also are a good means for monitoring treatment of the patient. If they decrease, the patient is certainly responding to medication. In fact, if during the process of treatment the medication is stopped, you can see alkaline phosphatase become higher.

There are many ways for establishing alkaline phosphatase levels of the blood in laboratories. Assays for urinary hydroxyproline are rather more difficult to obtain and difficult to evaluate. In regard to other chemicals, calcium has been known to remain at a normal level since there is usually a direct relationship between the amount of calcium entering and leaving bone.

BONE SCANNING

Bone scanning through cinematography, high resolution machines, and by isotopes are the most effective ways to detect signs of subclinical disease. Periodic scanning should also be done during therapy. It is best to limit radiographic study to those definitely known as Pagetic.

CLINICAL EXAMINATION

The obvious signs of Paget's disease are as follows:

1. Bony enlargement: femur, knee joint and skull.
2. Deformities: femoral, tibial or fibular bowing.
3. Pain: (may not be present), may be rheumatic rheumatoid-like, may be gouty. Headaches may be present due to platybasia.
4. Fractures: may be the first symptom. May be recurrent. Usually affect the long bones, but may not be painful. May result in complications such as: osteoarthritis or deafness.
5. Compression of spinal cord: This symptom is rare. May result from vertebral compression fracture. Patient may have mono- or paraplegia.
6. Sarcoma. Very rare (1:1000). Pain, loss of normal cortical definition and osteolysis are the findings of sarcomatous degeneration of Paget's.
7. Increased cardiac output: May lead to cardiac failure.
8. Urinary lithiasis: from increased serum calcium.

TREATMENT

The various modes of treatment are: drugs, physiotherapy, orthoses, corrective surgery and "others".

DRUG THERAPY

Specific treatment consists of drugs that influence osteoclastic activity. These include calcitonin and Didronel.

Calcitonin. This is a hypocalcemic hormone secreted by the parathyricular cells of the thyroid. Calcitonin works as an inhibitor of bone resorption. Several types of calcitonin are available, including those from salmon, human and pig.

Calcitonin is a 32-amino-acid peptide hormone secreted by the parathyricular C cells of the mammalian thyroid. The prime biological effect is inhibition of osteoclastic bone resorption.

Although it has been known to produce mild episodes of hypocalcemia, calcitonin regulates calcium levels in humans. It inhibits principal target cells -the osteoclasts. It has been proven useful in the treatment of Paget's disease.

Presently the only form of calcitonin that is widely available is synthetic salmon calcitonin (Calcimar -manufactured by USV Pharmaceuticals). Synthetic porcine and human calcitonin have also been used in the treatment of this disease. However, salmon calcitonin is considerably more potent than mammalian hormones (including human calcitonin). Cost of therapy with the salmon variety is much less than the others.

Calcitonin treatment of Paget's typically begins with 100 Medical

("Treatment", Continues):

Research Council (MRC) units a day, administered subcutaneously in the arms, legs and abdominal areas. Sometimes it is decreased to 50 MRC units three times a week; this occurs when the problem is alleviated. Once alkaline phosphatase decreases and hydroxyproline is absent, maintenance doses can be administered.

It has been noted that after discontinuation of calcitonin for several months, patients still continue to improve. Because of this, some physicians use intermittent treatment rather than daily therapy. Indeed, medication should be given every other day once the disease is completely under control.

Almost 80 percent of the patients respond to calcitonin. There is a decrease in pain, osteoarthosis, alkaline and hydroxyproline levels. Typically, all stabilize after two or three months at a third to half their pre-treatment values.

Improvement of bony lesions can be seen on serial x-rays. The patient may become sensitive to calcitonin therapy and develop allergies; at this stage other sources of calcitonin, such as human calcitonin or porcine, could be initiated.

Surprisingly, there are few side effects to injection of calcitonin (with the exception of mild nausea and flushing). Hypercalcemia may be induced and is also transient.

It is unfortunate that calcitonin has to be given by injection (either subcutaneous or intramuscular) and not by oral means.

Higher doses of calcitonin have proven to be effective in suppressing bone pain. Relapses may occur despite continuing treatment, and this resistance to treatment is associated with the development of antibodies to calcitonin.

Erythromycin. This is known to act on osteoclasts, but the later toxicity of the drug as well as resistance of the body to this agent has made it more advantageous to use calcitonin instead. In view of its toxicity to the liver, kidneys and bone marrow, the use of erythromycin is restricted to the exceptionally severe cases under hospital surveillance.

PHARMOLOGICAL DATA ON CALCIMAR

Calcitonin is a polypeptide of the hormone secreted by the parathyrcular cells (thyroid gland) in mammals and in the ultimobranchial gland of birds and fish. Calcimar is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula: Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

This product is provided in a sterile solution for subcutaneous or intramuscular injection, of which 1 mL contains 200 IU (MRC) of calcitonin-salmon (Armour), 5 mg. Phenol (as a preservative), with Sodium Chloride, Sodium Acetate, Acetic Acid, and Sodium Hydroxide to adjust toxicity and pH.

The activity of Calcimar is stated in International Units (equal to MRC or Medical Research Council) based on bioassay in comparison with the International Reference Preparation of Calcitonin, Salmon for Bioassay, distributed by National Institute for Biological Standards and Control, Holly Hill, London.

The main effect of calcitonin is on bone, but direct renal effect and action on gastrointestinal tracts are also recognized.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostasis regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibit bone resorption. This reduces transfer of calcium from bone to blood and tends to return blood calcium to normal levels.

The importance of this process in humans has not been determined. Salmon calcitonin, presumably by an initial block effect on bone resorption, causes a decreased rate of bone turnover with a resultant fall in serum alkaline phosphatase and hydroxyproline excretion in approximately two-thirds of patients treated.

Although parathyroid hormone levels do appear to rise transiently during each hypocalcemic response to calcitonin, most investigations have been unable to demonstrate persistent hypersecretion of parathyroid hormone in patients treated with calcitonin over long periods of time.

Circulating antibodies to calcitonin after 2 to 18 months of treatment have been reported in about half of the patients with Paget's disease in whom antibody studies were done, but calcitonin treatment remained effective in many of these cases. Occasionally patients with high antibody titers are found. These patients usually have suffered a biochemical relapse of Paget's disease and are unresponsive to acute hypocalcemic effects of calcitonin.

Also, calcitonin increased the excretion of filtered phosphate, calcium and sodium by decreasing their tubular resorption.

In some patients inhibition of bone resorption by calcitonin is of such magnitude that consequent reduction of filtered calcium load more than compensates for decrease in tubular resorption of calcium. The result in these patients is a decrease rather than an increase in urinary calcium.

In the gastrointestinal tract calcitonin has significant actions. Short-term administration results in marked transient decreases in volume of trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated.

Unfortunately, the metabolism of salmon calcitonin has not yet been studied clinically. Information from animal studies suggest that salmon calcitonin is rapidly metabolized by conversion to smaller inactive fragments, primarily in the kidneys, but also in blood and peripheral tissues. A small amount of unchanged hormone and its inactive metabolites are excreted in urine. Patients with increased cardiac output due to extensive Paget's disease had a measured decrease in cardiac output while receiving calcitonin.

WARNINGS

Allergic reactions are minimal and overlooked with the exception of rash and nausea. Certain precautions need to be taken after the administration of calitonin, with respect to the possibility of development of tetany (due to hypocalcemia). Laboratory studies should be carefully monitored. Also the injection site should be carefully cleaned prior to injection to prevent infection.

Calcitonin given during pregnancy of rabbits has been shown to decrease fetal birth weight. Nursing mothers should be aware of its excretion through their milk.

Calcitonin has not been advised for use in children.

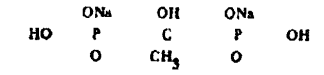
Nausea and rash can be treated symptomatically. An overdose of 100 I.U. (MRC) subcutaneously may produce nausea and vomiting. A dose of 32 units per kilogram per day for one or two days

("*Warnings*", *Continued*):

demonstrates no adverse effect. Dosage and administration should be 100 I.U. or MRC a day until alkaline phosphatase and serum hydroxyproline decrease to normal limits. At that time, calcitonin may be decreased to 50 I.U. (or MRC) per day. After several months this may be done QOD. The medication is supplied in a 2 ml. vial containing 200 I.U. (MRC) per millimeter and should be stored at 2 to 8 degrees C (or 36 to 46 degrees F).

DIDRONEL OR DIPHOSPHONATE COMPOUNDS

Didronel (etidronate disodium) is the disodium salt of (1-hydroxyethylidene) disphosphonic acid. Also referred to as EHDP or NAzEHDP, it is a white powder that is soluble in water with a molecular weight of 250 and the following structural formula:



Didronel is supplied in a rectangular white tablet containing 200 mg. of etidronate disodium for oral administration.

Clinical pharmacology. Didronel acts primarily on bone. It can modify crystal growth of calcium hydroxyapatite by chemisorption onto calcium phosphate surfaces. Inhibition of crystal resorption occurs at lower doses than those required to inhibit crystal growth.

Serum phosphate elevation has been observed with Didronel when it is administered in a daily dose of 10 mg. per kilogram per body weight per day. Occasionally at the level of 5 mg. per kilogram per day this has also been observed.

Didronel is not metabolized. The patient absorbs about 1 percent of an oral dose of 5 mg/kg/body weight/day, increasing with the dose level to about 2.5 percent at 10 mg/ kg/day and 6 percent at 20 mg/kg/day. Most of the absorbed drug is cleared from the blood within 6 hours, and within 24 hours almost one half of the absorbed dose is excreted in urine.

Indication and usage. Didronel can be used for treatment of symptomatic Pagetic disease of bone, and its effectiveness is demonstrated in patients with polyostatic Paget's who have pain. Clinically significant is Didronel's lowering of urinary hydroxyproline and serum alkaline phosphatase. In controlled studies, approximately 3 out of 5 patients experience decreased pain and improved mobility. About 2 of 5 patients in the placebo group experience similar improvement.

The medication has also been used in prevention and treatment of heterotopic ossification due to spinal cord injury or following total hip replacement. There have been no contraindications reported regarding Didronel treatment, although precautions have been discussed, suggesting that patients avoid over-treatment and adhere to the recommended dose.

Adverse reactions are mild. These are gastro-intestinal complaints, diarrhea, loose bowel movements and nausea. Adverse reactions occurred more frequently when patients used greater than usual dosages.

Didronel should be administered as a two-tablet, oral dose two hours from meals (for example, in the middle of the morning). It may be given with fruit juice or water. Food particularly high in calcium content (such as milk) may reduce intestinal absorption. Therefore, eating should be avoided for two hours before and after drug administration.

Initial treatment is 5 mg/kg per day and the treatment shouldn't exceed more than six months. After a period of rest the medication may be restarted, with urinary hydroxyproline excretion and serum alkaline phosphatase monitored periodically. It is suggested that retreatment be started with Didronel after three months to a year, although a premature retreatment should be avoided.

The medication is supplied as a white tablet containing 200 mg. etidronate disodium in a package of sixty. These diphosphanates closely resemble inorganic pyrophosphate.

History of development of diphosphanate. This goes back to 1961 with the discovery of inorganic pyrophosphate in biological fluid. The substance is probably responsible for controlling calcification of connective tissue under physiological conditions. This led to the idea of utilizing compounds of this type for prevention of abnormal calcification and ossification.

However, it became apparent that inorganic pyrophosphate could not itself be used because it was rapidly destroyed by alkaline phosphatase in the body. This instigated a search for an analogous compound which would be resistant to hydrolysis and led to the discovery of a new class of therapeutic agent, *i.e.*, the diphosphanates.

During experimental studies it became apparent that diphosphanate not only influenced calcification and ossification, but also had a powerful anti-osteoclastic effect. This stimulated research for treatment of osteoclastic disorders (such as Paget's disease).

Didronel EHDP or etidronate disodium was first used. It should be utilized for 6 months without interruption. In clinical trial, when Didronel at a dose of 5 mg/kg/day was compared with a placebo, a significant improvement in symptoms were found. When semi-quantitative methods are used for evaluating pain, significant pain relief is seen during treatment with Didronel. Improved mobility is frequently seen, and improvement is almost always accompanied by improvement in biochemical abnormalities.

The biochemical changes consist of an average falling alkaline phosphatase and hydroxyproline of 50 percent of their initial values. Treatment is accompanied by marked diminution in the number of the osteoclasts seen in bone.

Reduction in normal osteoclasts is accompanied by reduction in new bone formation at the recommended 5 mg/kg/day doses. The only side effect of Didronel is nausea or diarrhea in about 1 patient out of 15. This is usually mild and not persistent.

At the highest recommended Didronel dose, 20 mg/kg/day, normal mineralization of bone is inhibited. This is a dose and time dependent response and is reversible within three months of the end of treatment.

As a safety precaution, high dosage therapy should be limited to three months followed by a three month drug-free interval. Didronel has no contraindications.

The principal indication for use of Didronel is pain, decreased mobility, elevated urinary hydroxyproline, and elevated serum alkaline phosphatase level. Didronel therapy may also be warranted in an asymptomatic form of the disease where intensive involvement threatens irreversible damage to major joints or to weight bearing bones.

About 75 percent of all patients will require retreatment at some point. To determine which patients need this, regular three to six months followup visits should be scheduled.

("Use of Didronel", Continues):

Post-therapy. Biochemical values should be monitored as part of the follow-up if the disease is active. Courses of therapy should be separated by at least three months. One convenient treatment approach is a regular cycle regimen of six months on Didronel and six months off, as long as the disease is active. Didronel is a simple and effective oral treatment which is well tolerated. It suppresses the disease-process. This has been determined through several studies. Professor Russell and his colleagues published their early results concerning the effectiveness of EHDP in Paget's disease (Smith et al., 1971; Russell et al., 1974). Also such information has been obtained in the article by Canfield et al., in 1977. Long term maintenance therapy of the EHDP has also been suggested from 12 months to 24 and 36 months. This information can be obtained from the article written by E.S. Siris, R.E. Canfield, T.P. Jacobs, K.E. Stoddart and P.J. Spector, the title of which is "The Effect of Parathyroid Hormone in the Expression of Paget's Disease."

DISCUSSION

Paget's disease is a LOCALIZED disorder that is limited to bone. There is no primary hormonal abnormality shown to cause this disorder. Parathormone levels have been found to be within normal ranges in patients with the disease.

Parathormone levels in Paget's disease have been found to be within normal range (Burckhardt et al., 1973) or slightly above normal, in association with a minimal decrease in serum calcium (Rigga et al., 1971). In some patients it has been suggested that parathormone may play a role in the clinical expression of Paget's disease. Extensive work has been reported. Some state that parathyroid adenomata were found during surgery.

Abnormality in parathormone excretion in Paget's disease emerged from a study where patients were treated with Erythromycin. The induction of one alpha 25 (OH2D) secretion in response to erythromycin-induced hypocalcemia was done by Bilezikain et al. in 1978.

Indications for therapy. Finally, this depends on correct recognition of the disease, elevation of the hydroxyproline (and alkaline phosphatase), the presence of pain, the patient's history, physical findings, x-rays, biological studies, and progression of the disease.

The use of medication, corrective surgery, decompression, and other important data will be discussed later. ●

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