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 50-80 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 Balkan 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 these 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, parietal, 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 hydroxy-

proline are most valuable in study of Paget's disease patients. Also, determination 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 sponginess formation. Also some loss of endosteal cortical bone can be noted.

In aging adults, this process produces slow 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 usual 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 laminar structure and organization.

A technique using Tetracycline may demonstrate osteoclastic 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 facts 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,
BONE SCANNING

Bone scanning through cinematography, high resolution machines, and by isotope 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:

2. Deformities: femoral, talibial or cubital bowing.
3. Pain: may not be present, may be rheumatic rheumatoid-like, may be gouty. Headaches may be present due to pathway.
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 Didronex.

Calcitonin. This is a hypocalcemic hormone secreted by the parathyroid 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 parathyroid 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 L'Oréal 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). Case of therapy with the salmon variety is much less than the others.

Calcitonin treatment of Paget's typically begins with 100 Medical
"Treatment". Continued:

Research Council (NRC) units a day, administered subcutaneously in the arms, legs and abdominal areas. Sometimes it is increased to 50 NRC units three times a week; this occurs when the problem is severe. Once calciuria phosphaturic decreases and hypocalcemia is evident, maintenance doses can be administered.

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

Almost 60 percent of the patients respond to calciurin. There is a decrease in pain, excessive, diaphoretic, and headaches; levels. Typically, all patients after two or three months as a third to half their pre-treatment values.

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

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

It is uncertain that calciurin has to be given by injection (either subcutaneous or intravenous) and not by oral means. Higher doses of calciurin have proven to be effective in suppressing bone pain. Relapses may occur during continuous treatment, and the recurrence to treatment is associated with the development of antibodies to calciurin.

Erythromycin. This is known to act on osteoclasts, but the later study of the drug as well as resistance of the body to this agent has made it more advantageous to use calciurin instead. In view of the fact that calciurin is administered to the exceptionally severe cases under hospital surveillance.

PHARMACOLOGICAL DATA ON CALCMIAR

Calcunin is a polypeptide of the hormone secreted by the parathyreoptic gland in mammoths and in the aluminoblastic gland of birds and fish. Calcunin is a synthetic polypeptide of 32 amino acids in the same form as bovine parathyreoptic hormone is in the molecule of molecular weight 3,500. This is shown by the following graphic formula: Cys-Pro-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Glu-Glu-Leu-Lys-Leu-Val-Thr-Pro-Arg-The-Ar-Ar-Thr-Lys-Leu-Leu-Ser-The.

This product is provided in a sterile solution for subcutaneous or intramuscular injection, of which 1 ml contains 200 IU (NRC) of calciunin. It consists of Sodium Chloride, Sodium Acetate, and Sodium Hydroxide to adjust uniformity and pH.

The activity of Calciun is stated in International Units (equal to NRC or Medical Research Council) based on its ability to cause an increment in the serum calcium level of the reaction mixture, determined by a colorimetric technique of reference. Preparations of Calciun, available from Biomass, distributed by National Institute for Biological Standards and Control, Hove SE5, London.

The main effect of calciurin is bone, but direct renal effect is also noted and on gastrointestinal tract is also recognized.

Animal studies indicate that endogenous calciurin, primarily through its action on bone, participates with parathyroid hormone in the maintenance regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calciurin which, in turn, inhibits 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, but calciurin, presumably by an initial block effect on bone resorption, causes a decrease in the number of bone cells with a resultant fall in serum alkaline phosphatase and hydroxyproline excretion in approximately two-thirds of patients tested.

Although parathyroid hormone levels do appear to rise uncoordinately, these hypocalcemic response to calciurin, these investigations have been unable to demonstrate persistent hypocalcemia of parathyroid hormone in patients treated with calciurin over long periods of time.

Calcium and calciurin after 2 to 10 months of treatment have been reported in about half of the patients with Paget's disease in whom nobody found was done, but calcium treatment remained effective in many of these cases. Occasionally patients with high antibody titers are found. These patients usually have a biochemical relapse of Paget's disease and are uropathetic to some hyperparathyroidism of calcium.

Also, calciurin increased the excretion of filtered phosphatase, calcium and sodium by decreasing their tubular reabsorption.

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

Warnings

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

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

Calcium has not been afforded for use in children.

Nausea and rash can be provoked symptomatically. An average of 100 IU (NRC) subcutaneously may produce nausea and vomiting. A dose of 32 units per kilogram per day for one or two days
DIDRONEL OR DIPHOSPHONATE COMPOUNDS

DIDRONEL (edinonate disodium) is the diaminonitrile salt of 1-hydroxy-
ethylene-1,1-diphosphonic acid. Also referred to as EHDP or NADEHP, it is a white powder that is soluble in water with a
molecular weight of 250 and the following structural formula:

\[
\text{ONa} \quad \text{OH} \quad \text{ONa}
\]

\[
\text{HO} \quad \text{P} \quad \text{C} \quad \text{P} \quad \text{OH}
\]

\[
\text{O} \quad \text{CH}_2 \quad \text{O}
\]

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

Clinical pharmacology. DIDRONEL acts primarily on bone. It can
modify crystal growth of calcium hydroxyapatite by chemisorp-
tion onto calcium phosphate surfaces. Inhibition of crystal recryst-
allization 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 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
50 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 Paget's disease of bone, and its effectiveness is
demonstrated in patients with polyostotic Paget's who have pain.
Clinically significant is DIDRONEL's lowering of urinary uric acid.
protein, and serum alkaline phosphatase. In controlled studies,
approximately 3 out of 5 patients experience decreased pain and
improved mobility. About 2 out of 5 patients in the placebo group
experience similar improvement.

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

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

DIDRONEL should be administered as a mouthtablet after two
hours from meals (for example, in the middle of the morning). It
may be given with fresh parts of water. DIDRONEL is particularly
held 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 medica-
tion may be repeated, with urinary hydroxyproline excretion and
serum alkaline phosphatase monitored periodically. It is suggested
that rest periods be started with DIDRONEL after three months to a
year, although a premature rest period should be avoided.

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

History of development of diphosphonates. 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 components 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 initiated 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 diphosphonates.

During experimental studies it became apparent that diphospho-
ates not only influenced calcification and ossification, but also had
a powerful anti-osteoclastic effect. This stimulated research for
administration of osteoclastic disorders (such as Paget's disease). DIDRONEL is not effective in these disorders.

DIDRONEL is edinonate disodium formed in the year 1961. It should be
used for 6 months without interruption. In clinical trials, when
DIDRONEL at a dose of 5 mg/kg/day was compared with a placebo,
no significant improvement in symptoms was found. When some
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 25 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 as the recommended 5 mg/kg/day doses. The
only side effect of DIDRONEL is nausea or diarrhea in about 1
percent of patients, but 15. This is usually mild and not persistent.

At the highest recommended DIDRONEL dose, 50 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 dose 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 parenteral
administration, elevated urinary hydroxyproline, and elevated serum
alkaline phosphatase level. DIDRONEL therapy may also be advanta-
ged in an asympstomatic form of the disease where excessive involve-
ment threatens irreversible damage to major joints or to weight
bearing bones.

About 15 percent of all patients will require retreatment at some
point. To determine which patients need this, regular three to six
months follow-up visits should be scheduled.
Posttherapy. Biochemical values should be monitored as part of the follow-up if the disease is active. Course of therapy should be separated by at least three months. One convenient treatment approach is a regular cycle regimen of six months on Didroflo and six months off, as long as the disease is active. Didroflo 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). Additional 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. Siru, E.L. Canfield, T.P. Jacobs, R.E. Stoddart and P.J. Sporer, 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 disease. 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., 1975) or slightly above normal, in association with a minimal decrease in serum calcium (Kiegs 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 parathormone adenomas were found during surgery.

Abnormality in parathormone excretion in Paget's disease emerged from a study where patients were treated with EHDP. The induction of one alpha 2S (osteocalcin) secretion in response to parathormone-induced hypocalcemia was done by Bielik 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.

**REFERENCES**


("References", Continu).


