Bone and Joint Diseases

Paget's disease of bone, osteogenesis imperfecta, and fibrous dysplasia

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These disorders are seen both by physicians and by orthopaedic surgeons, and each may have a different view of them. The physician may be interested in Paget's disease because of its biochemical changes and the possibility of altering them, whereas the orthopaedic surgeon may regard it as a common disorder of bone that makes surgery difficult. The physician finds interest in osteogenesis imperfecta because it is an inherited metabolic disorder; the surgeon because of the deformities and surgical problems it produces. Fibrous dysplasia means to the physician the rare multisystemic polyostotic disease with pigmentation and sexual precocity (Albright's syndrome); the orthopaedic surgeon thinks of the commoner monostotic form apparently limited to bone. The most recent advances have been in the first two disorders; to understand them it is helpful to have some idea of collagen chemistry.

Collagen

Collagen is the main extracellular protein in the body.^{1 2} More than half of it is bone matrix. It is metabolically active and provides the organic support on which bone mineral is deposited. Extracellular collagen consists of fibres made of organised chains of cross-linked collagen molecules. These chemical cross-links give collagen its characteristic physical strength. Each molecule is composed of three helical polypeptide (alpha) chains wound round each other and linked mainly near the ends of these chains. These chains are synthesised within the fibroblast or osteoblast and undergo several changes before export from the cell. Errors in these synthetic steps may give rise to recognisable disorders.

For our purposes, two points are relevant. Firstly, collagen contains two unusual amino-acids, hydroxyproline and hydroxylysine, formed by hydroxylation of proline and lysine residues after the peptide chain is synthesised: because of this, they are not reincorporated (as are other amino-acids) when the chains are broken down. Their excretion in the urine, mainly in peptide form, can thus provide a readily measured index of collagen turnover. Secondly, different connective tissues contain collagen molecules that are genetically distinct³—for instance, skin contains collagens known as type I and type III, whereas cartilage contains type II.

Paget's disease

It is the centenary of the first description of this common disease, but its cause remains unknown, and only recently

has it been the focus of much research. This has been concerned with the biochemical changes that the overactive bone produces, and their modification by treatment. The effect of such treatment on present symptoms and future complications is not fully established. The following comments deal with some current problems.

CAUSE

There are some clues as to the cause. Since Paget's disease occurs with increasing frequency in later life, this may be a slow neoplasm or virus, or both; and some evidence exists of virus-like particles in the bone. The considerable geographical differences and occasional familial incidence are compatible with this. Analysis of skin collagen suggests an abnormality of connective tissue.

INCIDENCE

The accepted incidence of about 3% in people over 40 falsely suggests that this disease is not seen in the 20s and 30s, but most investigators have patients in these earlier decades. So-called juvenile Paget's disease is excessively rare and similar to recessively inherited idiopathic hyperphosphatasia. An important unsolved question is how many of the half a million or so patients with Paget's disease in Britain have symptoms that can be attributed to it, or require treatment.

PATHOLOGY

The Pagetic bone is busy and disorganised. There is excessive futile osteoclastic and osteoblastic activity and marrow fibrosis. Resorption may predominate, and this is said to be a feature of early disease; later more bone may be formed than resorbed. As in normal bone, resorption and formation appear to be closely linked.

SYMPTOMS AND SIGNS

The symptoms and signs are pain, deformity, fracture, nerve compression, sarcoma, and heart failure, of which the commonest are probably pain and deformity. Uncomplicated Paget's disease may itself be painful, although some consider that Pagetic bone is painful only when partly or completely fractured or when complicated by sarcoma. Since degenerative hip disease and Paget's disease are both common, hip pain in association with a Pagetic femur is likely to be caused by osteoarthritis. This is important in assessing treatment.

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NATURAL HISTORY

There are two unsolved and related problems—firstly, whether there is a real difference between the apparently localised and the generalised forms of the disease. This is important to the patient with monostotic Paget's disease who wishes to know if in future other bones, such as the skull, will be affected; and secondly, which patient with Paget's disease will subsequently develop complications, and what effect treatment might have on them.

BIOCHEMISTRY

The histological appearances explain the biochemical findings. The increased alkaline phosphatase concentration in the plasma is caused by excessive osteoblastic activity. It correlates well with the raised urinary excretion of total hydroxyproline, attributable to osteoclastic bone resorption and increased bone collagen turnover. In the plasma there is an increase of the non-protein-bound hydroxyproline and also of an enzyme responsible for the later stages of collagen breakdown.

RADIOLOGY

The many different radiographic appearances in bone may record past events rather than present activity, and are less useful than biochemistry in assessing treatment.

TREATMENT

The main advance in treatment has been the investigation of agents that can specifically suppress the excessive activity of Pagetic bone. This does not eliminate the need for established analgesics and for the treatment of complications; but in practice it does mean that we must consider specific treatment for an increasing number of patients, particularly in an attempt to prevent progression of their disorder. Especially in the under-50s, Paget's disease should no longer be considered as a disorder about which nothing can (or should) be done. Of the four agents used, mithramycin is a potentially toxic antimitotic agent with only temporary effect that has to be given intravenously; glucagon also has side effects and requires intravenous administration. Both the calcitonins and diphosphonates, however, produce predictable and similar biochemical suppression, and current therapeutic research centres on their effects.

Injected calcitonin rapidly inhibits osteoclastic activity. The most effective commercially available form is salmon calcitonin (Calsynar); much research has also been done with human calcitonin. Calcitonins need repeated injection (in a daily dose of about 12.5 µg (50 MRC units) for Calsynar); pain is said to be improved, and bone structure tends to become normal, but biochemical suppression may not persist, and calcitonin antibodies may develop. There is no double-blind trial of the effect of calcitonin on pain attributed to Paget's disease compared with a placebo. Reports conflict on the effect of calcitonin on complications.

Diphosphonates¹ are only available for research. They contain a P-C-P bond resistant to the effect of naturally occurring phosphatases and pyrophosphatases that degrade the P-O-P bond present in pyrophosphate itself. They are effective by mouth but their exact mode of action is not known. In Paget's disease they produce similar biochemical effects to calcitonin; however, the suppression is maintained during and after phosphonate treatment. The correct dose of the phosphonate used disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP) has yet to be established, and the larger doses cause defective mineralisation. It appears to relieve pain better than a placebo, but (as for calcitonin) there is no convincing evidence that it prevents complications. Calcitonin and EHDP, together or consecutively, may be more effective than either alone.³

Treatment should be considered in young patients, in those with pain directly attributable to Paget's disease, and those with complications. Response should be measured biochemically as well as clinically, with the help of a specialist centre. It is useless, and expensive, to continue calcitonin injections without evidence of continuing suppression of bone overactivity.

Osteogenesis imperfecta

In contrast to Paget's disease, osteogenesis imperfecta (OI), which affects mainly the young, is as rare as haemophilia. Nevertheless, it deserves our attention as a cause of lifelong crippling. The classic features of brittle bones and blue sclerae suggest a single disease, but this may be an oversimplification. Opinions differ about its classification, cause, pathology, biochemistry, and treatment.

CLASSIFICATION

A considerable difference exists between those who have fractures at birth, with no family history, who may die early, who are deformed, and may never walk, and those who fracture during childhood, in whom there is a strong family history, and who walk without difficulty or deformity. The established classification of OI into "congenita" and "tarda" forms recognises this difference but overemphasises the lethal outcome in the first group, since infants born with fractures may live to adulthood. Recent clinical studies⁶⁻⁷ define severe and mild groups roughly equivalent to OI congenita and tarda respectively but based on the degree of bone deformity, and emphasise its clinical heterogeneity. Subgroups include patients with severe bone disease and white sclerae; with severe bone disease, excessive callus, and dominant inheritance; and severe disease in siblings, which suggest a recessively inherited defect. Brittle bones, like anaemia, may only be a sign of many distinct disorders.

CAUSE

The clinically affected tissues of patients with OI, such as the bones, sclerae, and teeth, all have collagen as their major structural component, which suggests that this protein may be abnormal. Most studies to establish this have been on the skin, a readily accessible source of collagen, on the assumption that the supposed defect is generalised. Thus the skin of patients with mild OI contains less collagen than normal. Extracted cross-linked skin collagen from patients with severe OI may be less stable than from matched controls, which implies defective cross linking. If the same is so in bone its fragility might be partly explained. Skin contains two types of collagen (I and III), however, whose proportions change with age, whereas bone contains only type I. Skin fibroblasts from some patients with OI produce less type I collagen than normal relative to type III, and tissue analysis may show the same. Finally, controlled hydrolysis of OI skin may give an abnormal peptide pattern.

Even if a collagen defect is eventually shown in OI, there is also evidence that non-collagen proteins of bone are defective. Biochemical changes described in OI that fit less well into the clinical picture are those concerned with pyrophosphate, white cell biochemistry, and metabolic rate. Recent reports of controversies may be found in the *Lancet*.⁸⁻¹²

CLINICAL FEATURES, DIAGNOSIS, PROGNOSIS, AND GENETICS

The clinical features are well described.¹³ Some features, however, that are regarded as classical, such as blue sclerae, are not always present. In the severe form, the sclerae of adults may be a normal colour (the sclerae of normal infants tend to be blue); scoliosis and dentinogenesis imperfecta are common in those who survive; deafness is not. In mild OI, blue sclerae may be the main feature and the main clue to the diagnosis. At birth severe bone disease may be mimicked by hypophosphatasia. In childhood OI may closely resemble idiopathic juvenile osteoporosis. In all forms of OI the increased number

of fractures may lead to suspicion of "baby battering." Since it may be impossible to exclude OI, legal difficulties may arise.

It is important to give some idea of prognosis. The parents of an infant with intrauterine and neonatal fractures should not be given too gloomy an outlook, since survival to adult life with normal intelligence is possible. Early death from respiratory infection, however, is common. The legs are often deformed and unassisted walking cannot be expected. Children with mild OI may have numerous fractures, but most heal well without deformity, and their frequency decreases in adult life.

The genetic advice given to patients with OI or their relatives must depend on the family history and the type of disorder. When clinically normal parents have a severely affected infant (OI congenita) there is a negligible risk of further children being affected. Adults with OI are likely to have the mild form that is dominantly inherited; thus if one parent is affected the likelihood of having affected children is 50%, but it is not possible to forecast accurately the severity of the disease in an individual child. There is insufficient information to predict the outcome when both parents have mild OI or one parent has severe OI.

PATHOLOGY

The bone of severely affected infants is immature with a woven collagen matrix. It is difficult to interpret the cellular appearances in this type of bone, but probably faulty to consider that it has a high turnover with excessive resorption. In mild OI the bone is osteoporotic. The appearances on electron microscopy support the early idea of a primary reduction in osteoblast activity. The skin may contain less collagen, and the collagen of the sclerae may appear disorganised.¹¹ In the teeth the defective dentine leaves the enamel unsupported.

BIOCHEMISTRY

Many biochemical abnormalities have been described, but none confirmed. The hydroxyproline-containing fractions in blood and urine are probably normal. An increase in the pyrophosphate concentration in the serum and urine has been reported.

RADIOLOGY

Radiology shows many different appearances, which vary from almost normal bones to the bizarre changes that develop in the useless legs of severely affected patients.¹⁵

TREATMENT

In a crippling disease of childhood, there is a natural wish to try any form of treatment that might be useful. It is also important, however, to protect the patients (and their parents) from measures that have no scientific basis. Severely affected patients should be assessed at a specialist rehabilitation centre and provided with aids and advice that enable the disabled child to survive in an adult environment. Despite their dwarfism and deformity, such children are of normal intelligence and should be properly educated. Societies exist in Britain (Brittle Bone Society)¹⁶ and the USA that can provide useful information for OI patients and their families.

Measures intended to improve the bone disease include various diets, oral magnesium oxide, and calcitonin injections. None are of proved effectiveness. Orthopaedic treatment includes frequent attention to fractures, and the attempted correction of deformity (particularly of the leg bones) with intramedullary rods, which may increase the mobility of severely affected patients. The selection of the appropriate patients for this latter procedure and prediction of its outcome are difficult.

FIBROUS DYSPLASIA

The cause of the rare disease fibrous dysplasia, in which areas of bone are replaced by fibrous tissue, is not known. Monostotic and polyostotic forms are recognised; the first is probably more frequent, but the second has been more widely studied, because of its mysterious extraskeletal associations. The disorder usually presents by early adult life.

In the monostotic form the commonest first symptom is a fracture, often of the upper end of the femur. Other long bones and the ribs and facial bones may also be affected. An isolated lesion in the ribs may be asymptomatic for many years. Management of the fractured femur may be difficult, since the fibrous dysplasia may extend a long way down the shaft. Studies of the natural history¹⁷ do not suggest that the monostotic lesion progresses rapidly or becomes polyostotic, but sarcomatous change may occur.

The polyostotic form may be a different disease. Here there is bone deformity, such as "shepherd's crook" femur, and leontiasis of the facial bones. Bone lesions tend to be unilateral and with time extend to other bones. Skin pigmentation (if present) tends to be on the same side. Skin pigmentation, unilateral bone disease, and sexual precocity are the features of Albright's syndrome. Much discussion has centred on the cause of the associated sexual precocity.¹⁸ Thyrotoxicosis, acromegaly, and Cushing's syndrome may also be associated. The clinical problems presented by this syndrome are thus not exclusively orthopaedic and may require the attention of an expert endocrinologist. It has been suggested that these endocrine manifestations are the result of a generalised increased sensitivity of end organs to trophic hormones; it may also be that the rarely associated hypophosphataemic osteomalacia is an effect of the abnormal fibrous tissue,¹⁹ and that calcitonin is an appropriate treatment when there is excessive bone turnover in this condition. It will require much more work to establish these points, and it is difficult to envisage a single defect that may cause changes in bone structure, skin pigmentation, and hormonal function.

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Have there been any reports of addiction to sodium cromoglycate?

I have not heard of any reports of addiction to sodium cromoglycate, and I am unaware of this being the case with any of my patients. The method of administration is rather tiresome, and patients are only too anxious to reduce the dose. Furthermore, there is no pharmacological reason why such addiction should occur.