Bone marrow transplantation in precocious osteopetrosis

Osteopetrosis is a rare disease of bone characterised by a densely sclerotic skeleton and was first described by a radiologist, Albers-Schönberg. Since then many sporadic cases have been reported and collected in useful reviews. Osteopetrosis also occurs in animals, and rodents carrying the gene for osteopetrosis have been invaluable in elucidating the origin and function of the osteoclast, the cell that is deficient in this disease. Indeed, study of experimental osteopetrosis has been responsible for important therapeutic advances in man.

The condition occurs in two main forms, although intermediate varieties have been described. The benign autosomal dominant type, referred to as Albers-Schönberg's or marble bone disease, is usually a chance finding on radiological examination. Life expectancy is normal, and no treatment is needed. The autosomal recessive type is a lethal disease recognisable at or soon after birth, and until recently no affected child had survived the first decade. Not only are the medullary cavities of shaft bones obliterated by unresorbed juvenile bone but they are also misshapen, stunting growth. Encroachment on neural foraminae by bone causes blindness, deafness, and facial paralysis. Anaemia is severe and compensated for by hepatosplenomegaly. Death occurs from anaemia, haemorrhage, or infection. The intermediate forms of osteopetrosis are associated with rickets, renal tubular acidosis, and deficiency of the enzyme carbonic anhydrase II. The latter is important because it offers a means for genetic counselling. Accurate diagnosis is important not only because specific treatment is now available but also because the battered child syndrome has been mistaken for a form of bone dysplasia.

As osteopetrosis is caused by a failure of osteoclastopoeisis a hormonal defect was suspected. Yet giving parathyroid hormone, vitamin D metabolites, and adrenal corticosteroids and manipulating calcium metabolism were all without much effect. Haematological features were temporarily improved by blood transfusion, splenectomy, and treatment with iron. Then Reeves et al in 1979 correctly postulated a generalised inherited abnormality of phagocytes and even osteoclasts, which was unlikely to be influenced by such treatments.

Osteopetrosis also occurs widely in animals, and Walker was the first to use transplantation—parabiosis and bone marrow—in osteopetrotic rodents to show failed bony resorption because of a stem cell and not a hormonal defect. Skeletal sclerosis in the treated mutants disappeared, showing that an osteostastic stem cell or precursor in the haematopoietic tissue was conveyed by the blood stream to sites needing bony resorption. Once the stem cell deficiency was confirmed it was a small step to clinical application. Further research with osteopetrotic rodents carrying cellular markers showed that in syngeneic bone marrow grafts (comparable to grafts from one identical twin to another) donation of a few stem cells was enough to maintain bony resorption. Immunosuppression was needed if there were greater antigenic differences between donors and recipients.

The first report of human osteopetrosis treated with cellular infusions without immunosuppression produced results that might have been predicted from the experimental findings. Of four children, one benefited by a marrow graft from her HLA identical sister, but the others did not because the graft failed to take. Thymic cells were also given in the belief that the thymus was important in bone resorption, but this has since been disproved. Three reports have described successful treatment of human autosomal recessive osteopetrosis with bone marrow transplants from matched sibling donors and with varying immunosuppressive regimens. A review of 14 children shows that six have been successfully treated, a considerable achievement in a disease that used to be always fatal.

Study of osteopetrosis in animals and man has helped our understanding of osteogenesis and led to the disease being included among those that may be helped by bone marrow transplantation. The search for the primordial stem cell for the osteoclast continues.

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Should general practitioners be able to prescribe orthopaedic appliances?

Why should general practitioners not be allowed to order lumbosacral corsets for their patients with backache when they can prescribe drugs which may be both expensive and dangerous?

In the days when tuberculosis and poliomyelitis were common orthopaedic surgeons became expert in making and fitting various appliances used to support the halt and the lame. In many cases they set up special workshops in their hospitals to supply this need. When the National Health Service was introduced in 1948 it may well have seemed natural that hospitals should be the source of the appliances to be provided for patients. During the next 10 years orthopaedic practice altered as social changes and the Salk vaccine reduced, and almost eliminated, these two diseases. The need for calipers and braces diminished; but an increasing number of patients with backache came to orthopaedic clinics. The demand for simple back supports also increased, and these were mostly prescribed by orthopaedic surgeons.

In more recent years rheumatologists have undertaken a share of this work. A new specialty of orthotics and prosthetics has now developed to prescribe and make more complicated appliances and artificial limbs.

So what is special about the ordering of corsets that it cannot be done by general practitioners? Or can they get round the regulations which state: "A hospital may order and provide an appliance for a patient only if the patient has been examined and the appliance prescribed by or under the direction of a consultant, either at a hospital or clinic, or on the occasion of a domiciliary visit."

An inquiry to orthopaedic surgeons throughout England, Scotland, and Northern Ireland suggests that the rules are not being broken: in no area are general practitioners ordering corsets. Most of those questioned thought that general practitioners should be allowed to do so, but there were some reservations. The cost of a custom made corset is £50-£60, and there was concern about the possibility of overprescription; but this is largely a matter of education. Orthopaedic surgery and rheumatology are squeezed into the small corner of the curriculum in many medical schools, so a student may never be taught about corsets. It would take a long time to correct this failing, but surely a postgraduate seminar lasting a day or half a day would be a remedy.

All this is written on the assumption that a corset is useful in relieving backache. Many doctors believe this to be true. Certainly a multicentre study on the treatment of low back pain concluded that "a corset was as effective as the other treatments, and it is certainly less expensive than manipulation or physiotherapy and safer than drugs."

This was written in 1975, and no new miracle cure for backache has been found since then.

I am heartened to learn that open access to orthopaedic appliances (mainly corsets and collars) now exists in Clwyd (p 000). A clinic is run by a nursing sister from orthopaedic outpatients and was begun as a local response to the Dutch report, which encouraged such an arrangement in an attempt to reduce pressure on consultant orthopaedic clinics. The Clwyd venture has been successful, since the average waiting time for an orthopaedic appointment was 5 to 6 months (regrettably this is not uncommon in Britain) and most patients were seen in the appliance clinic within five weeks of referral.

The matter could be dealt with centrally by putting corsets on the drug tariff, which is not as odd as it might seem since the tariff now includes trusses and elastic stockings. But this might well take a long time, and a lot of argument, before it could be achieved. Clearly it is open for local groups of interested doctors to get together to make the arrangements that answer the needs in their own area. What can be done in north Wales can be done elsewhere. Why wait?

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