Depression in children

Until recently most doctors have ignored or denied the possibility of depressive disorder in prepubertal children.1 2 Those who acknowledged it were either overinclusive3 or suggested that it was masked by other symptoms,4 thus enabling society and its psychiatrists to continue to disillusion that children could be depressed. The same happened with infantile sexuality. In the past 10 years research has shown that prepubertal depression is a reality and may continue to become an adult depressive disorder.

Two factors have made these advances possible: firstly, developmental psychopathology has led to an understanding of normal and deviant development of affective expression;5 and, secondly, operational definitions of psychiatric disorders have been introduced.6 7 A depressive disorder may be diagnosed if the child has had a depressed mood for at least four weeks and if he or she has two or more of the following symptoms: anxiety, sleep disturbance, irritability, suicidal thoughts, eating disturbances, school refusal, phobias, all-
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 osteoclastogenesis 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 osteostatic 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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