In type-III OI spinal deformity can be very severe. Finidori (Paris) regards spinal fusion as mandatory, often preceded by halocranial traction. No form of surgery corrects the severe shortening, including that of the upper segment, in type-III and type-IV OI. Growth hormone produced a sustained increase in linear growth rate in some children with type-IV OI (Marini, NIH, Bethesda), but it is too early to draw any conclusions from this study and work from Australia (Sillence) and Italy.

Since sodium fluoride stimulates osteoblasts it is an obvious therapeutic candidate in OI; however, in a double-blind placebo-controlled randomised study pulsed sodium fluoride was found to be ineffective in children with OI (Whyte, St Louis).

In contrast, bisphosphonates selectively reduce bone resorption. Intermittent pamidronate (APD; an amino bisphosphonate) produces dense lines in the growing skeleton. In eight children with type-III or type-IV OI intravenous APD given at four- to six-month intervals increased bone mineral content and density, reduced bone resorption (assessed biochemically) and improved symptoms (Glorieux, Montreal).

Potentially, the most dramatic form of treatment in OI is gene replacement (Prockop, Philadelphia). In type-I OI this could involve stimulation of type-I collagen synthesis and in types II, III and IV replacement of the gene. The ethical and technical problems of correcting type-II OI and in types II, III and IV replacement of the gene. This could involve stimulation of type-I collagen synthesis (Memphis) described the infusion of normal bone marrow into infants with severe type-III OI after previous ablation chemotherapy. If such normal stromal cells do engraft in the marrow, it is not known whether they will alter the phenotype. Where should we go from here? The excitement of mutation discovery has declined and gene therapy seems far ahead. Many new osteotropic agents are now being developed, some as a spin-off from research on osteoporosis, and these may increase bone mass and possibly strength. We can no longer delay in assessing their effectiveness in OI by properly conducted clinical trials. Since OI is so phenotypically variable this is not easy and never will be.

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Bone allograft: a cause for concern?

Skeletal allograft is now widely used to restore bone stock especially during joint reconstruction and for limb salvage after tumour resection. Many patients have benefited and there is now a shortage of allograft in parts of the UK. Despite this popularity, a number of issues regarding its biology, processing and safety remain unresolved. Reports of graft-related failure and of complications such as infection, fracture and nonunion are relatively common.

Deep infecction in an allograft is usually disastrous. Its occurrence has been shown to increase with the size of the graft and may be seen in over 10% of massive allografts. It appears to be unrelated to preoperative contamination of the graft, and probably results from the complexity of the procedure and poor incorporation with dead bone behaving like a sequestrum. The incorporation process also appears to weaken the bone, predisposing to fracture. In a large series of massive allografts, Mankin and his co-workers reported an overall fracture rate of 19%. Without incorporation, allografts are essentially bony endoprostheses. The aim is peripheral union, but radiological nonunion can be expected in about 17%. Union is difficult to assess reliably on radiographs; postmortem analyses of acetabular structural grafts have shown little evidence of histological...
union, despite the appearance of radiological union.\textsuperscript{3} Acetabular reconstruction using solid allograft became popular after good early results\textsuperscript{4,5} had been reported, but eventual failure follows in up to 54\% after the use of femoral heads.\textsuperscript{6,7} Single photon-emission CT (SPECT) has provided evidence of incorporation in only about two-thirds of such grafts.\textsuperscript{8} The results may be better than this when male femoral heads or cadaver bones are used, because of their better initial strength,\textsuperscript{9} but care must be taken to avoid reliance on the graft for mechanical support.\textsuperscript{10}

The more recent technique using impaction of morselised allograft has provided encouraging early results with few complications,\textsuperscript{11,12} and this is now widely used to restore bone stock during revision of hip replacements. Its application is restricted to situations in which it can be contained and impacted although, even then, the stability of the impacted bone has been questioned.\textsuperscript{13} Significant early migration has been reported,\textsuperscript{14} and it is likely that surgical technique, graft composition\textsuperscript{15} and choice of prosthesis\textsuperscript{16} are important. A number of animal and clinical biopsy specimens have suggested that incorporation is quite consistent.\textsuperscript{17-19}

Complete incorporation of bone allograft in a manner similar to autograft is clearly possible,\textsuperscript{20} but in practice the degree of incorporation is quite unpredictable.\textsuperscript{21,22} This variation may be related to antigenic disparity, notably between the cell-surface antigens of the major histocompatibility complex, although there is no clear clinical correlation,\textsuperscript{22} and many grafts are essentially acellular. The links between the antigen in the bone and the biological responses to it are not known.\textsuperscript{20} The resorption of a graft is sometimes dramatic; this may well be due to an immune response.\textsuperscript{21} Less aggressive resorption is a normal biological reaction to bone graft and is part of neovascularisation,\textsuperscript{22} but in allografts it probably contributes to fracture formation.\textsuperscript{23} Tissue typing to try to reduce resorption and fracture is of uncertain value\textsuperscript{21} and would be very difficult to implement.

In the UK, the supply of allograft relies heavily on femoral heads obtained during primary hip replacement and the most common indication for its use is revision surgery, many bone banks have difficulty in meeting demand. Cadaver donation is becoming a more important source of bone, and the harvesting of such bone is subject to similar guidelines as those for live bone.\textsuperscript{25,26} Live donors are requested to attend for second HIV and HCV antibody tests at 180 days after donation. Cadaver donors cannot do this, and screening therefore relies on a single test and an interview with the relatives, often under difficult circumstances. A recent survey of routine blood samples taken in London hospitals has shown an HIV carriage rate of 1 in 120 for men and 1 in 440 for women,\textsuperscript{27} and the transmission of viral and other diseases must remain a cause for concern.\textsuperscript{28,29} Bacterial contamination is also common, especially during cadaver harvesting, which is not always performed under the aseptic conditions of operating theatres.\textsuperscript{30}

Sterilisation of grafts is therefore frequently used. The most popular method is gamma irradiation, in keeping with methods for other medical devices and equipment. The effective dose of radiation is that which will inactivate HIV, since lower doses are required for bacteria and other common viruses. Prions,\textsuperscript{31} some viruses and other potential, but as yet unknown, infective agents may be more resistant to irradiation. A dose of 25 kGy is probably the minimum required to inactivate HIV,\textsuperscript{32} but more than 30 kGy are recommended for its complete eradication.\textsuperscript{33} The adverse effects of such high doses of radiation on bone graft are well-established with respect to mechanical performance\textsuperscript{34} and osteoinductivity.\textsuperscript{35}

Ethylene oxide sterilisation is not a popular alternative because residual gas may remain within the transplanted tissue and cause irritation.\textsuperscript{36} Pasteurisation is used by some centres. It is probably effective against HIV,\textsuperscript{37} but falls short of sterilisation. Autoclaving, boiling and other methods damage the graft and are not suitable.

Reliance on terminal sterilisation does not obviate the need to reduce contamination, and also raises concerns about the implantation of dead bacteria and altered viral particles with the graft. Careful donor selection and safeguards to cover harvesting, processing and handling may be more appropriate,\textsuperscript{38} but the variation in present methods used by bone banks has implications for graft safety, graft function and the comparison of results.

Most published reports on this subject are from centres with many years of experience of bone allografting and can be expected to show the best results. Yet they reveal that allograft is somewhat unpredictable even in these units. Despite this, and concerns about its safety, the growing use of allograft for the restoration of skeletal tissue has been virtually unchallenged. If adequate and safe supplies can be maintained this is likely to be continued until alternative methods are found.

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