Introduction

Biology of Bone Healing

Various bone disorders can affect the ability of bone cells to structure organic and inorganic components. Avascularity can cause osteonecrosis, with death of haematopoietic cells, lipocytes and endothelial cells. Repair of osteonecrosis is the time needed for the process to replace necrotic bone. Callous fracture healing is a regenerative process consisting of three stages of inflammation: development of soft callus, of hard callus and remodelling [1, 2]. During inflammation, new blood vessels are induced, enhancing angiogenesis, which can be investigated by Doppler ultrasound. Following inflammation, fibrous and cartilaginous tissue known as soft callus develops, which can be observed by grey-scale ultrasound. In the hard callus stage, cartilaginous tissue converts to woven bone, which will finally be remodelled to lamellar bone.

In primary bone healing under rigid plate fixation creeping substitution can be observed histologically after 4 weeks. Following the Haversian system, osteoclast activities are first necessary to enable cone formations and ingrowth of bridging osteoblasts. This remodelling takes time and weakens the bone for 1–2 years. In the remaining tiny gaps, blood vessels and osteoblasts grow in within the first 2 weeks, forming a lamellar bone that is osteoconductive and bridged at week 4.

Healing of Bone Grafts

Healing of nonvascularised autologous, cancellous and cortical bone shows inflammatory response with vascular ingrowth. With increase of fibrous granulation, in 2 weeks, repair of cancellous grafts differs as osteoblastic new bone is apposed onto necrotic trabeculae, correlating radiographically with an increase in radiodensity. At month 6, this graft is completely repaired, with the necrotic trabeculae resorbed by osteoclasts. The osteoinductive and osteoconductive graft is initially stronger due to apposition of new bone, but strength declines to normal when the necrotic bone is resorbed.

Nonvascularized autologous cortical grafts are incorporated by creeping substitution at a lower rate due to the greater amount of osteonecrosis. In humans, graft healing is prolonged, with loss of 50% graft strength within the first 6 months, maintaining this strength for another 6 months. Radiographically, density is reduced due to bone porosity. Graft strength can be regained up to the second year. In humans, fatigue failures occur between month 6 and 18 [3]. The osteoconductive graft is not completely substituted but remains as a mixture of necrotic donor bone and new host bone. Healing of the osteoconductive graft depends on compression and oxygenation, which can be improved by vascularisation. Such vascularised autologous cortical grafts contain less necrotic bone and show the identical pattern of repair. Strength and stiff-
ness, however, were found to be accelerated, making them superior to nonvascularised grafts [4].

**Allogeneic Bone Grafting**

In nonvascularised allogeneic cancellous bone, incorporation lasts longer, with increase of vascular response and with the granulation tissue becoming loosely structured. This web is filled with inflammatory cells rather than with fibroblasts and blood vessels. Bone resorption and bone formation are delayed, and the graft may incorporate incompletely.

Nonvascularised allogeneic cortical grafts are osteoconductive and show creeping substitution to be markedly prolonged. Allografts differ from autografts, as vascular penetration and bone formation are slower and resorptive activity is more extensive. Primary lymphocytes dominate, and fibrous tissue encapsulates the graft. The inflammation can either disappear or become chronic. The initially vascular network around the graft becomes occluded, leading to periosteal necrosis and thereby prohibiting appositional bone healing, with more necrotic bone existing than new bone to be formed.

**Immunological Response to Allogeneic Structured Bone Grafts**

There is much evidence that bone is immunogenetic. The marrow contained in bone, endosteal and periosteal cell-surface antigens as well as bone matrix have been suggested to be responsible for immunogenicity [5]. Cell-mediated immunity is considered to play a minor role in rejection of composite tissue allografts and of bone alone as compared with antibody-mediated response. There is some evidence that cytotoxic antibodies directed against bone allografts do, indeed, appear and may coincide with cellular immunity although they seem to not be directly involved in the rejection process. Bone healing after allotransplantation may proceed normally. Chronic repair is characterised by greater incidence of nonunion or delayed union, peripheral resorption or loss of graft size. In some cases, the graft can be resorbed completely [1].

**Vascularized Allogeneic Cortical Grafts Under Immunosuppression**

In contrast to avascular allografts, primary vascularisation of limb-tissue allograft is reported to change the pattern of rejection into considerable humeral response early after transplantation [6]. The various components interact with the host immune system in a complex pattern, eliciting less immune response than an individual tissue allograft. Radiographs and histology can be indistinguishable from autograft healing as long as sufficient immunosuppressive drugs are taken. After withdrawal of the immunosuppression, both vascularised and nonvascularised allografts can be rejected quickly [7]. In experimental studies with vascularised bone marrow transplantation, stromal and marrow cells act early after transplantation, circulate to the lymphopoietic system of the recipient and are reported to generate tolerance in long-term survival [8]. Factors affecting chimerism in bone allotransplantation are still unclear. Allogeneic vascularised knee joints have been transplanted under immunosuppression with cyclosporine and azathioprine and corticosteroids with good early results [9].

**Biomechanical Properties of Bone Grafts**

Incorporation of cancellous bone grafts with new bone formation upon necrotic trabeculae results in early graft strength. In cortical bone grafts, initial graft resorption causes graft porosity with reduced strength, which only slowly improves. It is suggested that human segmental cortical bone grafts lose almost half of their biomechanical strength within the first 6 months and remain weakened for another 6 months. This hypothesis is supported by the high number of graft failures between 6 and 8 months after transplantation. Creeping substitution is significantly prolonged in allografts, with fracture of