Introduction
Loss of mechanical continuity in a bone that leads to pathological mobility between the broken ends of a bone generally heals through a regenerative biological process that is termed “fracture healing”. Several aspects of embryological skeletal tissue formation are replicated during this process that involves interplay between cells and their growth factors resulting in reformation of bone. Key to completion of the healing process is the presence or restoration of a degree of stability between the fractured ends of the bone that helps formation and preserves an osteo-conductive scaffold over which the bone forming cells can lay bone. We discuss the types of fracture healing, the concepts described to understand how this occurs and the various cellular and non-cellular factors essential for fracture healing.

Macroscopic changes
A key process in fracture healing is the establishment of a bony bridge between the fracture fragments. The bridge then can hypertrophy and remodel to enable bone to regain its normal shape and strength. At a macroscopic level, as seen on radiographs, this bridging bone is formed on the external surface of the bone, the internal or medullary surface of the bone and directly between the fractured ends of the bone which are termed “external callus”, “medullary callus” and “primary bone union” respectively. The amount of external callus formed (Figure 1) is related to the degree of mobility between the fractured bone ends and is not seen in case of immobilisation with absolute stability. Its presence in the
Microscopic changes

At a cellular level, following the fracture, there is formation of a haematoma at the fracture site following bleeding from the torn blood vessels and bone ends. In the initial stages there is local vasodialatation with exudation of leucocytes along with plasma. This initial stage is termed “the inflammatory phase”. Later on during this phase clearing up of the debris commences with the local accumulation of cells including histiocytes and mast cells. It is important to note that the ends of the bone do not directly participate in the healing process as it is comprised of dead tissue and the healing process commences in the tissues around the fracture site including blood vessels and periosteum. Fracture mobility is reduced in this stage by pain felt by the individual and the hydrostatic pressure exerted by the fracture haematoma.

The second stage of fracture healing “the reparative phase” commences within a few days overlapping with the inflammatory phase. Pluripotent mesenchymal cells form fibroblasts, chondroblasts and osteoblasts. The source of these cells are a combination of local cells including the cellular layer of the periosteum which is a two layered structure, the outer fibrous and the inner cellular layer, and cells which have migrated to the fracture site along blood vessels. The local environment which was acidic and hypoxic during the inflammatory phase gradually turns neutral and slightly alkaline to enable optimal action of alkaline phosphatase and bone mineralisation. Reparative bone can be formed either directly from precursor cells close the fracture ends without an intermediate cartilage formation termed intramembranous ossification or there can be chondrogenesis the periphery with gradual endochondral calcification where the cartilage matrix is degraded and mineralised reducing the mobility at the fracture site and then allowing vascular proliferation, increased oxygen tension invasion of osteoblasts and laying down of primary spongiosa (woven bone) similar to the sequence of events at the growth plate.

Presence of internal fixation was once considered a failure of fixation. Similar to the external callus bony bridging is seen on the medullary surface as a callus and this is less dependent on fracture mobility. Primary bone healing occurs between rigidly fixed bone ends where dead ends of the cortical bone are recanalised by new Haversian systems with resultant obliteration of the fracture line (Figure 2). A final phase in fracture healing is the remodelling of bone which is an extension of the normal turnover process within the bone but where the resorption of bone and laying down of bone occurs in an organised fashion chiefly aimed at restoring normal physical and mechanical properties of the bone.

Figure 1a & 1b: Forearm fracture in a child (a) treated with a plaster cast that allows mobility at the fracture site resulting in external callus formation (b).

Figure 2a & 2b: Fracture of radius (a) treated with rigid internal fixation and absolute stability resulting in primary bone union (b).
FOLLOWING A FRACTURE VARIOUS GENES ARE SWITCHED ON AND OFF DURING THE DIFFERENT PHASES OF FRACTURE HEALING. DURING THE INFLAMMATORY PHASE PLATELETS INVOLVED IN THE CLOTTING CASCADE ALONG WITH POLYMORPHONUCLEAR LEUCOCYTES, LYMHPOCYTES, MONOCYTES AND MACROPHAGES RELEASE CYTOKINES THAT STIMULATE ANGIOGENESIS.

The final phase of fracture healing is the remodelling phase where the woven bone is replaced by lamellar bone. Moreover the extra callus is gradually resorbed and the architecture of the bone is restored as close as possible to its preinjury level with osteoclastic bone resorption and formation of bone along lines of stress the process occurring over a period of many months.

In rigidly immobilised fractures healing occurs by primary healing in two ways, gap healing and contact healing. In gap healing woven bone is directly laid in the fracture gap that is then replaced by lamellar bone, the orientation of which is initially transverse to that of the original lamellar bone orientation. Subsequently this is replaced by osteons oriented as it was before the fracture had occurred over a period of weeks. In contact healing bone, which occurs where the gap at the fracture site is less than 0.01mm and strain is less than 2%, osteons grow directly across the fracture site parallel to the long axis of the bone. There is formation of a cutting cone passing across the fracture site where osteoclasts ream out a tunnel in the dead bone down which a blood vessel grows. This brings in osteoblasts which lay down lamellar bone.

**Biological factors involved in fracture repair**

Following a fracture various genes are switched on and off during the different phases of fracture healing. During the inflammatory phase platelets involved in the clotting cascade along with polymorphonuclear leucocytes, lymphocytes, monocytes and macrophages release cytokines that stimulate angiogenesis. Tumour necrosis factor α (TNFα) expressed by macrophages and other inflammatory cells, increases in concentration within 24 hours and returns to baseline within 72 hours post trauma, induces secondary inflammatory signals and acts as a chemotactic agent to recruit other cells. They act on TNF1 and TNF2 receptors expressed by both osteoblasts and osteoclasts, the latter receptor thought to be having a specific role in fracture healing as it is expressed only following injury. Other factors involved at interleukin 1 (IL-1) produced by macrophages overlapping with TNFα in a biphasic manner which promotes angiogenesis and primary cartilage callus and induces IL-6 production by osteoblasts which has other roles of allowing differentiation of osteoblasts and osteoclasts. Mesenchymal stem cells are recruited by the stromal cell-derived factor1/CXCR4 signalling axis to the site of injury along with transformation growth factor -β (TGF-β) proteins including bone morphogenetic proteins (BMP), BMP-7 (osteogenic protein-1 (OP-1)), BMP-2 and BMP-4. The differentiation of granulation tissue to lamellar bone occurs with a progressive reduction in strain when the fracture haematoma is converted to cartilaginous tissue, mineralised and subsequently ossified.

**Theories and concepts in fracture healing**

Initially proposed by Pauwels and later studied and described by Perren mechanical stimuli govern how a callus is formed and a fracture heals. Perren’s interfragmentary strain theory proposed that a tissue couldn’t exist in an environment where the interfragmentary strain exceeds the strain tolerance of the extracellular matrix of the tissue. Lamellar bone ruptures at a strain of 2%, while for cartilage the strain needed to rupture is about 10% and granulation tissue can withstand strains up to 100%. The differentiation of granulation tissue to lamellar bone occurs with a progressive reduction in strain when the fracture haematoma is converted to cartilaginous tissue, mineralised and subsequently ossified.

During the process of fracture healing there is a lattice of extracellular matrix over which the osteogenic cells proliferate acted upon by the different growth factors. As the fracture healing progresses mechanical
factors as described by the Perren’s theory plays a crucial role in formation of bridging bony callus formation and completion of healing. The interaction of these four factors (Figure 3), cells, growth factors, matrix scaffold and mechanical stability has been described as the diamond concept15.

**Clinical application**

Knowledge of the biology of fracture healing has enabled management of non-unions and delayed unions by influencing factors involved. Genetically engineered stem cells have been shown in experimental studies the enhance fracture healing16. Bone morphogenic proteins have been used in clinical practice to stimulate fracture healing17,18. Bone grafts have been used in roles of osteoinduction, incorporation and along with bioactive glass, ceramics and hydroxyapatite as a scaffold for osteoconduction19. Improving local vascularity with tissue flaps help improve healing in open fractures or avascular fracture sites. Concepts of relative stability and absolute stability have been exploited to influence the type of healing. Primary bone healing with absolute stability enables restoration of anatomy in non comminuted and intraarticular fractures while secondary healing with relative stability fixation preserves tissue biology in comminuted fractures20.

**Conclusion**

Fracture healing is a biological process involving interaction of cells with growth factors. It is triggered following a disruption in the mechanical continuity of the bone where a cascade of events aims to restore the bone to its preinjury state.

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**References**

References can be found online at www.boa.ac.uk/publications/JTO or by scanning the QR Code.
References