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Healing is the final stage of the response of tissue to injury.

The capacity of a tissue for regeneration depends on its proliferative ability and on the type and severity of the damage.

Three broad groups of cells are considered in the context of the cell cycle (p.3).

**REGENERATION** involves two processes

1. **Proliferation** of surviving cells to replace lost tissue.
2. **Migration** of surviving cells into the vacant space.

The factors which control healing and repair are complex: they include the production of a variety of **growth factors**.
Healing of a wound demonstrates both epithelial regeneration (healing of the epidermis) and repair by scarring (healing of the dermis).

Two patterns are described depending on the amount of tissue damage. These are essentially the same process varying only in amount.

1. **Healing by first intention (primary union)**
   This occurs in clean, incised wounds with good apposition of the edges – particularly planned surgical incisions.

   - **Immediately:** Blood clot and debris fill the small cleft.
   - **2–3 hours:** Early inflammation close to edges. Mild hyperaemia and a few polymorphs.
   - **2–3 days:** Macrophage activity removing clot. Proliferation of blood vessels. Fibroblastic activity.
   - **10–14 days:** Scab loose and epithelial covering complete. Fibrous union of edges, but wound is still weak.
   - **Weeks:** Scar tissue still slightly hyperaemic. Good fibrous union, but not full strength.
   - **Months – years:** Devascularisation. Remodelling of collagen by enzyme action. Scar is now minimal and merges with surrounding tissues.
2. Healing by second intention (secondary union)
This occurs in open wounds, particularly when there has been significant loss of tissue, necrosis or infection.

**Early**

![Diagram showing early stages of wound healing](image)

- Cavity fills with blood and fibrin clot
- Acute inflammation commences at junction of living tissue

**A few days**

![Diagram showing a few days after injury](image)

- Scab dries out
- Mitotic activity in epithelium
- A single sheet of epithelial cells is being pushed between the surface debris and the underlying living tissue
- New capillary loops bring macrophages, neutrophils and fibroblasts

**1 week approximately**

![Diagram showing 1 week healing](image)

- Epithelium continues to grow across
- Surface debris has been shed
- Loose connective tissue formed by fibroblasts
- Capillary loops form small ‘granulations’ in the base of the wound. These can be seen by the naked eye and, historically, are the origin of the term ‘granulation tissue’. This term is now used in a wider context to describe tissue consisting of newly formed capillaries with fibroblasts and macrophages and occurring in many circumstances in addition to wounds.

**2 weeks onwards**

![Diagram showing 2 weeks healing](image)

- Epithelial covering complete
- Collagen arranged transversely
- Fewer cells
- Capillaries less prominent
Healing by second intention (continued)

Months

Note that the differences in the two types of wound healing are quantitative: the essential pathological processes are the same.

Wound contraction

Wound contraction, which is beneficial and begins early, is due mainly to the young, specialised ‘myofibroblasts’ in the granulation tissue exerting a traction effect at the wound edges. The exposed surface is reduced by gradual regeneration of the surface epithelium. The remodelling of the collagen continues for many months.

COMPLICATIONS

Contracture

Later, CONTRACTURE with distortion due to thickening and shortening of collagen bundles may cause serious cosmetic and functional disability, particularly in deep and extensive skin burns and around joints if muscles are seriously damaged.

Occasional complications

1. At the edges and base of a wound granulation tissue may form in excess and prevent proper healing (‘exuberant granulations’: ‘proud flesh’).

2. The formation of excess collagen in the form of thick interlacing bundles which causes marked swelling at the site of the wound is known as a KELOID. The essential cause is unknown. It is particularly common in black people.
FIBROSIS is the end result of WOUND HEALING, CHRONIC INFLAMMATION and ORGANISATION.

**Formation of fibrous tissue**

FIBROCYTES (and primitive stem cells) situated around capillaries and loose connective tissues

Enlarge to become active FIBROBLASTS and active PROTEIN SYNTHESIS begins

(2) adhesive glyco-proteins – FIBRONECTINS which provide a scaffolding and contribute to the progress of the repair process

STIMULUS – growth factor e.g. TGFβ (see p.48) derived from damaged cells and macrophages.

(1) INTRACELLULAR PRODUCTION of COLLAGEN precursors.
(a) Hydroxylation of proline and lysine (vit C required)
(b) Triple helix formation.

Secretion to EXTRACELLULAR SITE
(c) cleavage of terminal peptides

(d) Cross-linking + polymerisation

COLLAGEN FIBRE

REMODELLING follows: Action of COLLAGENASE → SCAR TISSUE + secretion of COLLAGEN

**Factors delaying healing**

1. Local
   INFECTION, a POOR BLOOD SUPPLY, excessive movement and presence of foreign material DELAY HEALING.

2. General
   DEFICIENCY of VITAMIN C
   DEFICIENCY of AMINO ACIDS (in malnutrition)
   DEFICIENCY of ZINC
   EXCESS of ADRENAL GLUCOCORTICOIDs
   DEBILITATING CHRONIC DISEASE

   Failure of proper collagen synthesis with delayed healing and weak scars.
INTERNAL SURFACES
The regeneration of the covering epithelium is very similar to that of the skin, as seen for example in the alimentary tract.
SOLID EPITHELIAL ORGANS

1. Following gross tissue damage – including supporting tissue (post-necrotic scarring).

   e.g. Kidney
   ![Kidney Diagram]

   Liver
   ![Liver Diagram]

   Progressive removal of dead tissue with organisation and COARSE SCAR formation

2. Following cell damage with survival of the supporting (reticular) tissues

   e.g. Tubular necrosis in kidney
   ![Kidney Tubular Necrosis]

   Perivenular hepatic cell necrosis
   ![Liver Perivenular Necrosis]

   Necrotic cells and debris
   Surviving supporting tissues
   Surviving cells

   Progressive removal of debris

   REGENERATION of epithelial cells at first undifferentiated

   RESTORATION to NORMAL

   Surviving cells proliferate and move along reticulin framework to the hepatic venule
**MUSCLE**
Muscle fibres of all 3 types – skeletal, cardiac and visceral – have only limited capacity to regenerate.

When a mass of muscle tissue is damaged, repair by SCARRING occurs. This is particularly important in the HEART after infarction.

If the damage affects individual muscle fibres diffusely and with varying severity, then regeneration of the specialised fibres is possible (e.g. the myocardium may recover completely from the effects of diphtheria toxin and virus infection).

**NERVOUS TISSUE**
**Central nervous system**
Regeneration does not occur when a neurone is lost.

In cases of acute damage, the initial functional loss often exceeds the loss of actual nerve tissue because of the reactive changes in the surrounding tissue. As these changes diminish, functional restoration commences.

Scarring within the CNS is by proliferation of ASTROCYTES and the production of fibrillar glial acidic protein – a process known as GLIOSIS.
NERVOUS TISSUE (continued)

Peripheral Nerves

When a peripheral nerve is damaged, the axon and its myelin sheath rapidly degenerate distally. The supporting tissues of the nerve (neurilemma) degenerate slowly.

Regeneration can occur because the central neurone of which the axon is a peripheral extension is remote from the site of damage.

A spinal motor nerve is taken as an example.

Normal spinal cord

Results of damage

WALLERIAN DEGENERATION of distal nerve

Axon disintegrates
Myelin disintegrates
Schwann cells survive
Fatty droplets

Cutting or crushing

Atrophy of muscle fibres

Mild degenerative changes in neurones

Loss of Nissl substance (RNA)
(chromatolysis)

Prominent Nissl substance (RNA)
Peripheral Nerves (continued)

Regeneration takes the form of a sprouting of the cut ends of the axons.

The results depend on the apposition of the distal remnant with the sprouting axons.

The best results are seen in crushing injuries where the sheaths remain in continuity.
BONE
A fracture is usually accompanied by damage to or haemorrhage into adjacent soft tissues which are repaired by the process of organisation (p.40), while the bone is repaired by regeneration.

Events following a fracture
(1) Immediate effects

Periosteum

Necrosis of ends of bone

Medulla

Damage to soft tissues with haemorrhage (haematoma) and fibrin deposition

Cortex

(2) Early reaction-inflamatory

First 4–5 days

Phagocytosis of debris and necrotic tissues

Early organisation: capillaries and fibroblasts

(3) Formation of callus
(early bone regeneration) – after 1 week.

Osteoblastic activity

Periosteal

Medullary

Resorption in healthy bone (seen on X-ray as rarefaction)

Provisional callus bridges the gap – first, osteoid tissue (may include cartilage) then woven bone

(4) Mature callus
– from 3 weeks onwards

Cortical gap healed by ossification

Osteoblastic and osteoclastic activity proceeding

(5) Remodelling of callus

Definitive – weeks into months

Osteoblasts and osteoclasts active

Lamellar bone

(6) Final reconstruction
Months later

Fracture site may be almost invisible
**Events following a fracture** *(continued)*

**Complications**

1. *Fat embolism* may occur in fracture of long bones due to entry of fat from the marrow cavity into the torn ends of veins.

2. *Infection*
   - If the overlying skin is breached in any way, i.e. the fracture is ‘compound’, the risk of infection is greatly increased; this is an important adverse factor in the healing process. E.g.

**PATHOLOGICAL FRACURE**

When the break occurs at the site of pre-existing disease of the bone, the term ‘pathological fracture’ is applied.

- **A common condition is a secondary tumour growing in and destroying the bone**
- **Mixture of tumour and haematoma – healing inhibited**
- **Very easily fractured**
# FACTORS INFLUENCING HEALING OF FRACTURES

## 1. Local factors

<table>
<thead>
<tr>
<th>ADVERSE</th>
<th>FAVOURABLE</th>
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<tbody>
<tr>
<td>(a) Infection</td>
<td>Good apposition</td>
</tr>
<tr>
<td>(b) Pathological fracture</td>
<td></td>
</tr>
<tr>
<td>(c) Poor apposition and alignment</td>
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- There may be interposition of soft tissue, e.g. muscle
- Large irregular callus: slow repair, permanent deformity of bone

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<th>(d) Continuing movement of bone ends</th>
<th>Good immobilisation</th>
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- Callus formation inhibited
- Fibrous union

- In extreme cases, a rudimentary joint (pseudoarthrosis) may form

<table>
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<tr>
<th>(e) Poor blood supply</th>
<th>Good blood supply</th>
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This is largely influenced by the anatomical site of the fracture, for example:

- Nutrient artery entering remote from the fracture or damaged by fracture (e.g. scaphoid, femoral head)
- Fracture through area devoid of periosteum (e.g. neck of femur)
- Minimal adjacent soft tissue (e.g. tibia).

## 2. General factors

<table>
<thead>
<tr>
<th>ADVERSE</th>
<th>FAVOURABLE</th>
</tr>
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<tbody>
<tr>
<td>(a) Old age</td>
<td>Youth</td>
</tr>
<tr>
<td>(b) Poor nutrition – e.g. famine conditions, malabsorption lead to lack of protein, calcium, vit D and vit C.</td>
<td>Good nutrition – especially protein, calcium, vit D and vit C.</td>
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