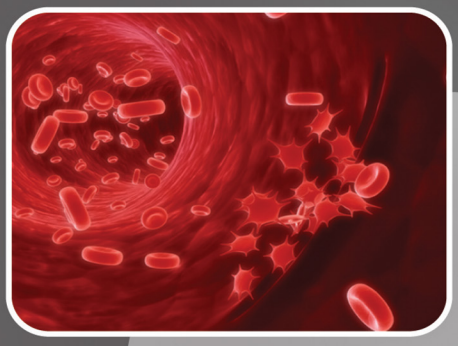
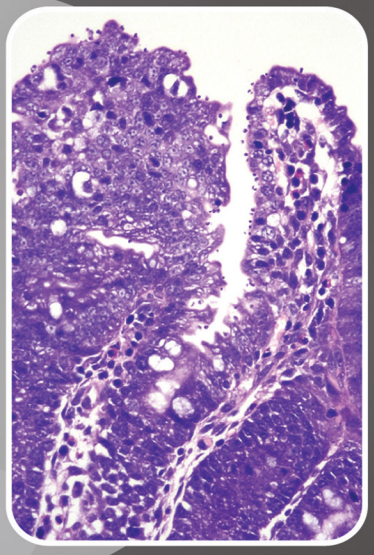
SYNOPSIS OF PATHOLOGY







Anoop N

JAYPEE

PATHOLOGY

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3 Chapter

Tissue Repair, Regeneration, Healing and Fibrosis

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CELL CYCLE

Phases of cell cycle are shown in the Figure 3.1.

SIGNALING MECHANISMS OF GROWTH FACTOR RECEPTORS

Autocrine Signaling

A substance acts predominantly on the tissue that secretes it. For example, T-cell proliferation increased by cytokines.

Compensatory epithelial hyperplasia (liver regeneration).

Paracrine Signaling

A substance acts on the cells, which are in the vicinity of the secreting cell. For example, recruiting cells for inflammation wound healing.

Endocrine Signaling

A regulatory substance like hormone is released into blood and acts on distant target cells. For example, insulin secretion as a response to hyperglycemia.

Receptors

1. With intrinsic enzyme activity (VEGF, FGF, HGF, EGF).

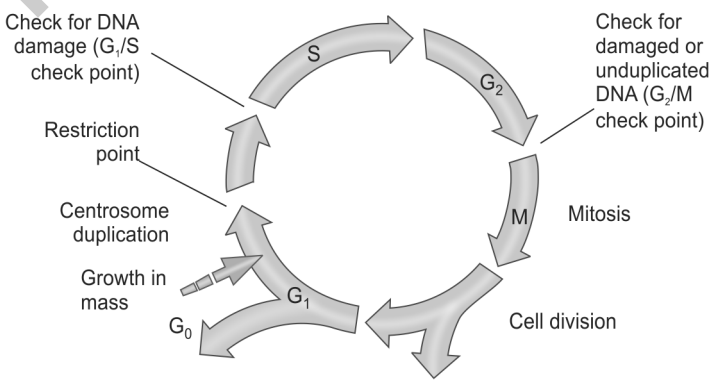


Fig. 3.1: Cell cycle

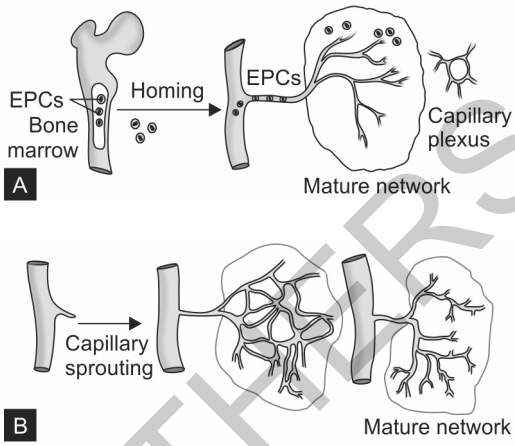
2. Without intrinsic enzyme activity (IFN, GH, erythropoetin).
3. G-protein coupled (epinephrine, ADH, serotonin, histamine, glucagon).

ANGIOGENESIS

1. Angiogenesis is the first process in the sequence of repair by connective tissue.
2. This repair occurs when the injury is severe or chronic and results in parenchymal damage, epithelia or stroma, etc.
3. Occur in four processes:
   a. Angiogenesis.
   b. Fibroblast proliferation.
   c. Scar formation by ECM.
   d. Remodeling (reorganization of fibrous tissue).
4. Angiogenesis starts within 24 hours of injury.
5. Occur by two processes:
   a. Vasculogenesis: Primitive vascular network is assembled from angioblasts.
   b. Angiogenesis: Capillary sprouts from pre-existing vessels and formation of new vessels.
6. The angioblasts are migrating from BM to the site (Fig. 3.2A).
7. Important process in healing and tumor growth.

Steps

1. Vasodilatation by NO.
2. Increased permeability of pre-existing vessels by VEGF (Fig. 3.2B).



Figs 3.2A and B: Angiogenesis. **A.** By mobilization of EPCs from BM; **B.** From pre-existing vessels.

3. Migration of angioblasts, EPCs to the injury site or migration of ECs and their proliferation.
4. Increased proliferation and remodeling into capillary tubes.
5. Recruitment of periendothelial cells.
   a. Pericytes for capillaries (small).
   b. SMCs for larger vessels.
6. New vessels will be leaky due to incompletely formed endothelial junctions and accounts for edematous granulation tissue.
7. The leakage is also due to ↑ permeability by VEGF.
8. Structural ECM participate through integrin receptors.
9. Non-structural ECM participate by ↑ cell migration, remodeling and ingrowth of vessels.

Involvement of Growth Factors

Most importent growth factors are VEGF and FGF-2.

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Vascular Endothelial Growth Factors

1. VEGF—A, B, C and D.
2. VEGF receptors—VEGFR 1, 2 and 3.
3. Most important in angiogenesis is VEGFR-2 (in ECs only).
4. The inducers for VEGFs are hypoxia, PDGF, TGF-α, TGF-β.
5. VEGF induces proliferation and motility of ECs and thus ↑ permeability.
6. VEGFR-2—migration of angioblasts from BM.

Fibroblast Growth Factor

1. FGF-2—increased proliferation of ECM.
   a. ↑ migration of macrophages and fibroblasts.
   b. ↑ migration of epithelial cells.
2. FGF-7—keratinocyte GF.
   a. Cutaneous wound healing.
   b. Also in oral cavity and gastrointestinal tract (GIT) lesions.

Others

1. Angioprotein 1 and 2—recruit periendothelial cells.
2. PDGF—recruit smooth-muscle cells (SMCs).
3. TGF-β—increase in production of ECM.

CUTANEOUS WOUND HEALING

Phases of wound healing is shown in the Figure 3.3.

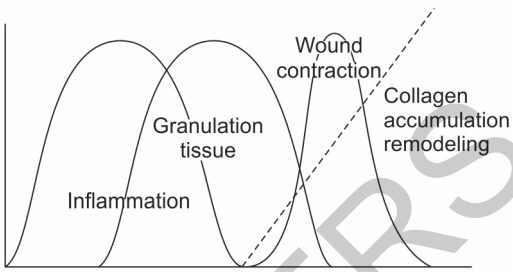

Fig. 3.3: Phases of wound healing

Steps

1. Epithelial proliferation—EGF, HGF.
2. Monocyte chemotaxis—PDGF, TGF-β, FGF.
3. Fibroblast migration—PDGF, TGF-β, FGF.
4. Fibroblast proliferation—PDGF, FGF.
5. Angiogenesis—VEGF, FGF.
6. Collagen synthesis—PDGF, TGF-β.
7. Collagenase secretion ↓ —PDGF, TGF-β, FGF.

Phases of Cutaneous Wound Healing

It has mainly three phases, they are:

1. Inflammation.
2. Granulation tissue formation.
3. Collagen (ECM) deposition and remodeling.

Healing by First Intention (Healing by 1° Union)

1. Healing of a clean (Fig. 3.4A) uninfected, incised wound approximated by sutures (surgically).
2. In incised wound, only less amount of cell death. So, epithelial regeneration predominates over fibrosis.

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3. Small scar and minimum wound contraction.
4. Within 24 hours—fibrin clot formation and invaded by (N).
   a. Basal cells proliferate and a thin epithelium below scab (24–48 hour).
5. Within/by 3 days—(N) replaced by macrophages.
   a. Granulation tissue invades into incision space.
   b. Vertical collagen fibers along margins.
6. By 5th day:
   a. Increased proliferation and thick epithelial layer.
   b. Neovascularization and more granulation tissue.
   c. Bridging of space by collagen fibers.
   d. Epidermis attains normal thickness and keratinization.
7. By 2nd week:
   a. More collagen and fibroblasts proliferation.
   b. Blanching with regression of ↑ vascular channels.
8. By 1 month:
   a. Scar comprised of more collagen and falls off.
   b. Normal epithelium and strength ↑ progressively.

Healing by Second Intention (Healing by 2° Union)

1. Occurs when cell (Fig. 3.4B) or tissue loss is more extensive such as in large wounds, abscess formation, ulceration, etc. Here:
   a. Inflammatory reaction is much more intense.
   b. Granulation tissue is abundant.
   c. Wound contracts by the action of myofibroblasts.
   d. Accumulation of ECM and formation of large scar.
2. Wound contraction occurs by 6 weeks is the main additional feature from first intention healing.

Factors Affecting Wound Healing Process

1. Infection, nutrition, steroids, diabetes, poor perfusion, foreign bodies, etc.
2. The type of tissue injured—efficient healing with labile cells.
3. The location of injury—healing becomes prolonged in tissue spaces.

Fracture Healing

1. Depends on whether the fracture is:
   a. Traumatic or pathological.
   b. Complete or incomplete.
   c. Simple, comminuted or compound.
2. Primary union.
   a. Occurs when the ends of fracture are approximated.
   b. Union takes place by medullary callus formation.
   c. Patient can be made ambulatory early.
   d. Extensive bone necrosis and slow healing.
3. Secondary union.
   i. More common.

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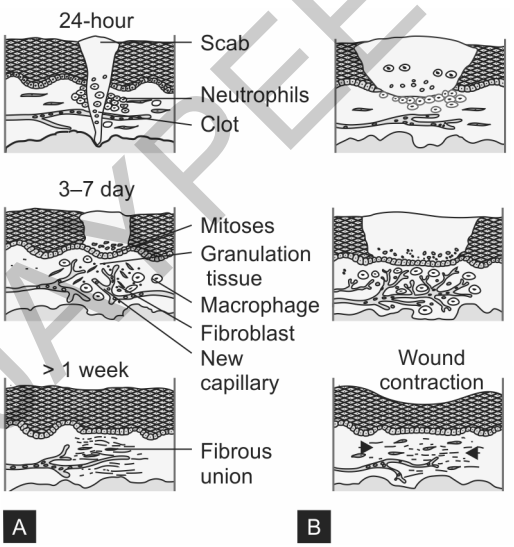
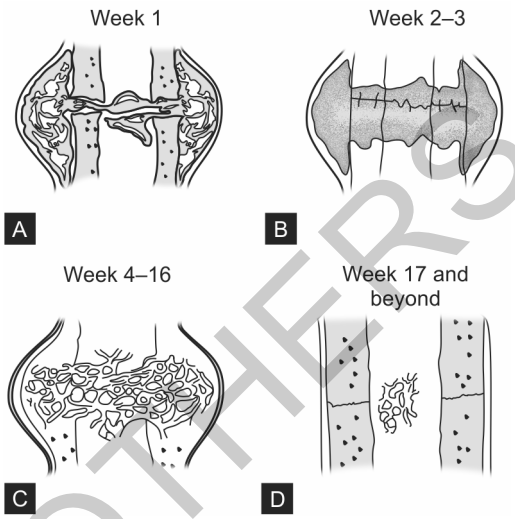
ii. Takes place by procallus formation, osseous callus formation, remodeling.
   a. *Procallus formation.*
      - Hematoma formation (Fig. 3.5A).
        - Due to bleeding from the torn blood vessels
        - Loose meshwork is formed by blood and fibrin clot, which acts as a framework for subsequent granulation tissue formation.
      - Local inflammation.
        - By PMNs and macrophages
        - Macrophages clear away the fibrin, red blood cells (RBCs), inflammatory exudate and debris
        - Necrosed bone is lysed by macrophages and osteoclasts.



Figs 3.4A and B: Wound healing. **A.** Healing by first intension; **B.** Healing by second intension



Figs 3.5A to D: Steps of fracture healing. **A.** Hematoma (inflammation); **B.** Soft callus; **C.** Hard callus; **D.** Remodeling.

- Ingrowth of granulation tissue.
  - Begins with neovascularization and mesenchymal cell proliferation from periosteum and endosteum
  - A soft tissue callus (Fig. 3.5B) is thus formed.
- Procallus formation.
  - This is the callus composed of woven bone and cartilage
  - The cells of inner layer of the periosteum have osteogenic potential and lay down collagen as well as osteoid matrix in the granulation tissue
  - This osteoid undergoes calcification to form woven bone callus (Fig. 3.5C)
  - The woven bone callus bridges the gap and gives rise to a spindle-

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shaped or fusiform appearance
  - In poorly immobilized fracture, the osteoblasts form cartilage at the site.

b. *Osseous callus formation.*
   - The woven bone and cartilage get cleared off
   - Newly formed blood vessels and osteoblasts invade and lay down osteoid, which calcified to form lamellar bone.

Remodeling

1. By osteoblastic and osteoclastic activity.
2. External callus cleared away, cortex is formed in place of intermediate callus and BM develops in internal callus (Fig. 3.5D).

Complications

1. Fibrous union.
2. Delayed union.
3. Malunion.
4. Non-union.

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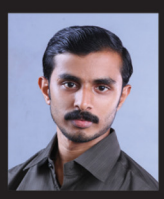
SYNOPSIS OF
PATHOLOGY

Salient Features

- Includes various selected, standard exam-oriented questions and answers
- Mainly emphasizes on the new pattern of examination
- Contains 50 clinical essay questions and their diagnosis
- Most of the topics have been simplified into flow charts
- Essential pictures are also included
- Also includes 'clinical pathology' notes, which have been prepared from various laboratory textbooks and that will be a great help to the readers for the examination
- Gives a basic knowledge about the subject and equips one for the examination.



Anoop N is an MBBS graduate from Government Medical College, Thrissur, Kerala, India. He is a well-known personality among the faculties and patients of Thrissur Medical College. He was an active member in the charity wing—*Pratheeksha* and has also been its President and General Secretary for two consecutive years during his MBBS period. He is an emerging young doctor who is constantly engaged in teaching others. *Synopsis of Pathology* is an attempt for the same.

Shelving
Recommendation
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