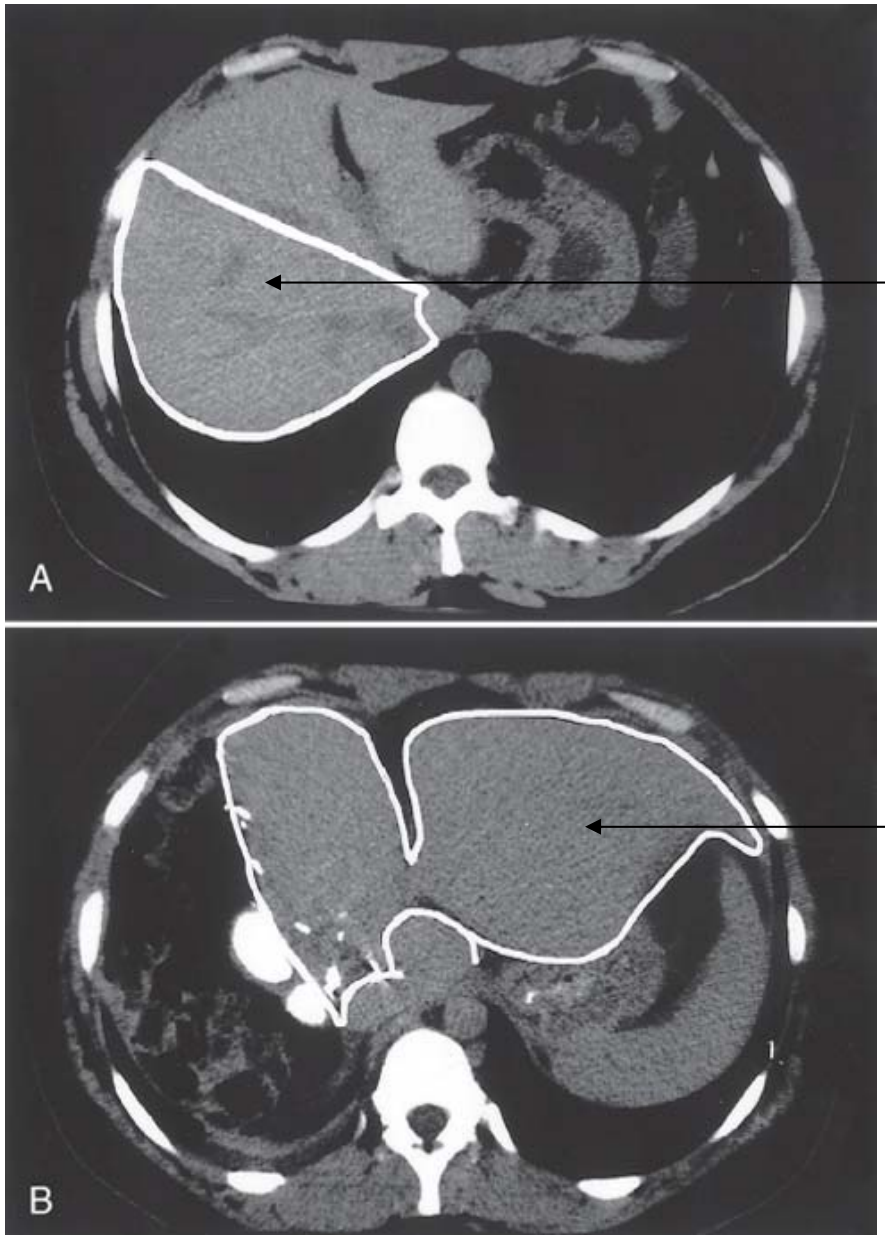
Healing

- Body response to injury in an attempt to restore normal structure and function.
- Involves 2 processes:
  - Regeneration: healing takes place by proliferation of parenchymal cells, results in complete restoration of the original tissues.
    requires intact C.T. scaffold
    e.g- hematopoietic system, epithelia of skin, GIT
  - Repair: healing takes place by proliferation of connective tissue elements, results in fibrosis and scarring.

    e.g- incisional skin wounds, MI, constrictive pericarditis, cirrhosis



right lobe to be resected

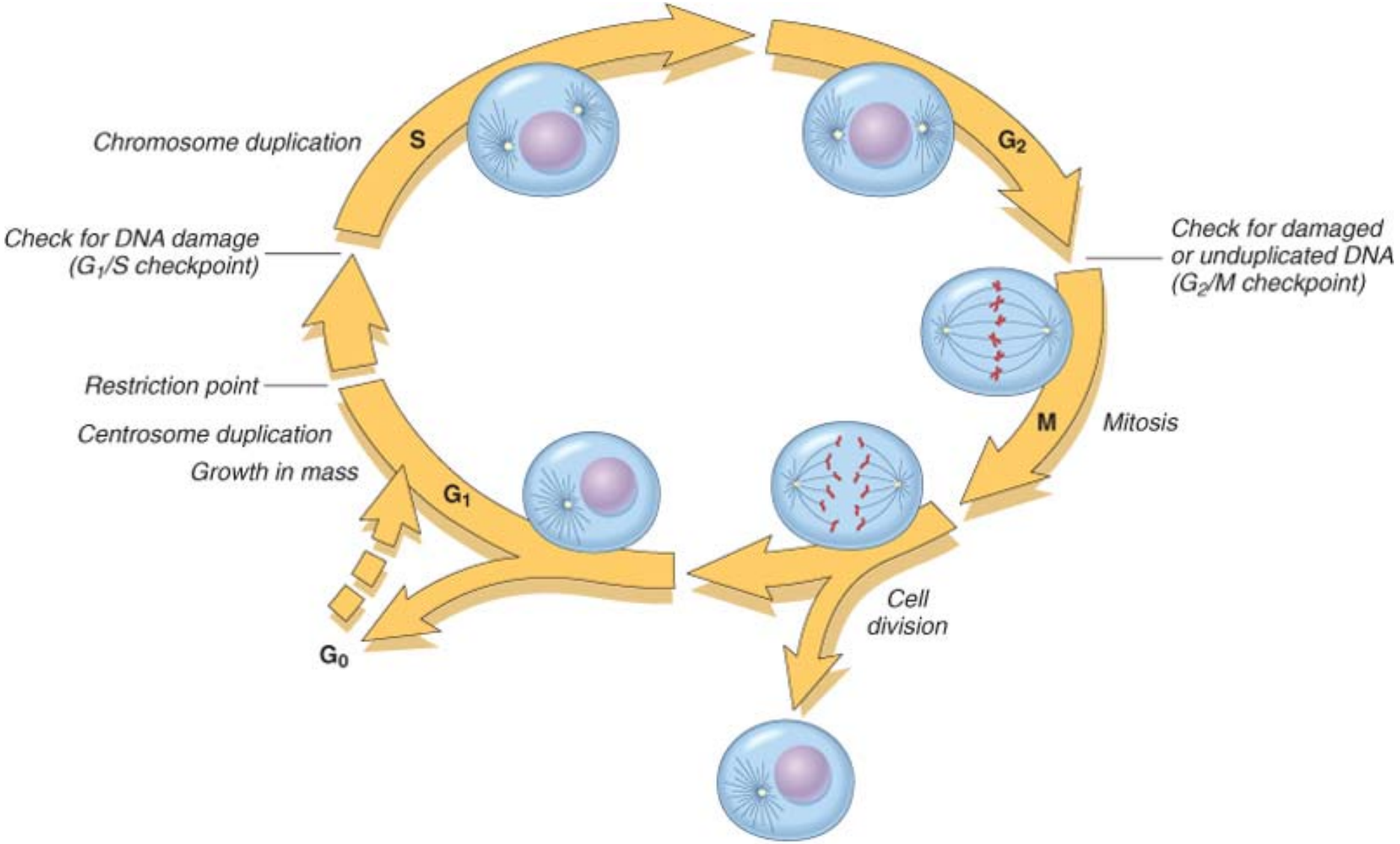
left lobe now enlarged

Tissue proliferative activity

Cell cycle

- G_1 (pre-synthetic)
- S (DNA synthesis)
- G_2 (pre- mitotic)
- M (mitotic)
- G_0

The Cell Cycle



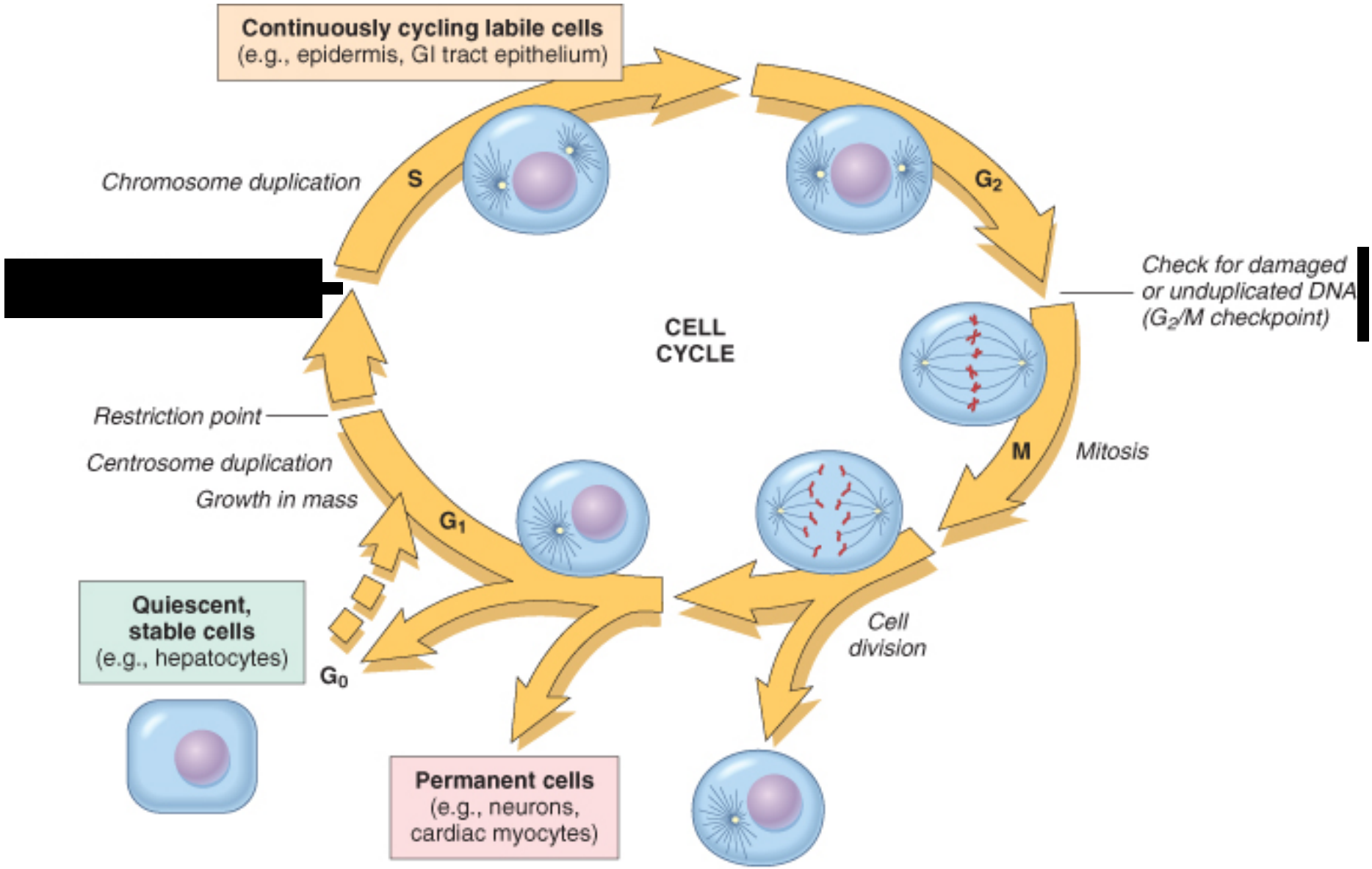
Types of cells

- Labile (always dividing) cells:
  - Replace dying cells
  - Epithelia: skin, oral cavity, exocrine ducts, GIT, FGT, hematopoietic cells
- Stable (quiescent) cells:
  - Usually G_0 and low rate of division
  - Driven into G_1 and rapid proliferation
  - Liver, kidney, pancreas, endothelium, fibroblasts

Types of cells

- Permanent (non-dividing) cells:
  - Permanently removed from cell cycle
  - Irreversible injury leads only to scar
  - Nerve cells, myocardium, skeletal muscle

The Cell Cycle and Different Cell Populations



Growth Factors

- Very important in tissue repair.
- Actions:
  - stimulate cell division and proliferation
  - promote cell survival
- Epidermal growth factor (EGF)- Keratinocytes,fibroblasts
- Vascular endothelial growth factor (VEGF)-Angiogenesis
- Transforming growth factor (TGF)-Fibrogenesis
- Platelet-derived growth factor (PDGF)
  - Migration and proliferation of fibroblasts, smooth muscle, and monocytes

Repair

- Repair is the replacement of injured tissue by fibrous tissue. Two processes are involved in repair:
  - Granulation tissue formation
  - Contraction of wounds

Granulation Tissue Formation

- Granular and pink appearance of the tissue.
- Each granule corresponds histologically to proliferation of new small blood vessels and young collagen.

Phases in the formation of granulation tissue

- Phase of inflammation- Following trauma, blood clots at site of injury. There is acute inflammatory response with exudation of plasma, neutrophils and some monocytes within 24 hours.
- Phase of clearance- proteolytic enzymes liberated from neutrophils, and phagocytic activity of macrophages clear off the necrotic tissue, debris and red blood cells.
- Phase of in growth of granulation tissue- consists of 2 main processes:

  - angiogenesis or neovascularisation

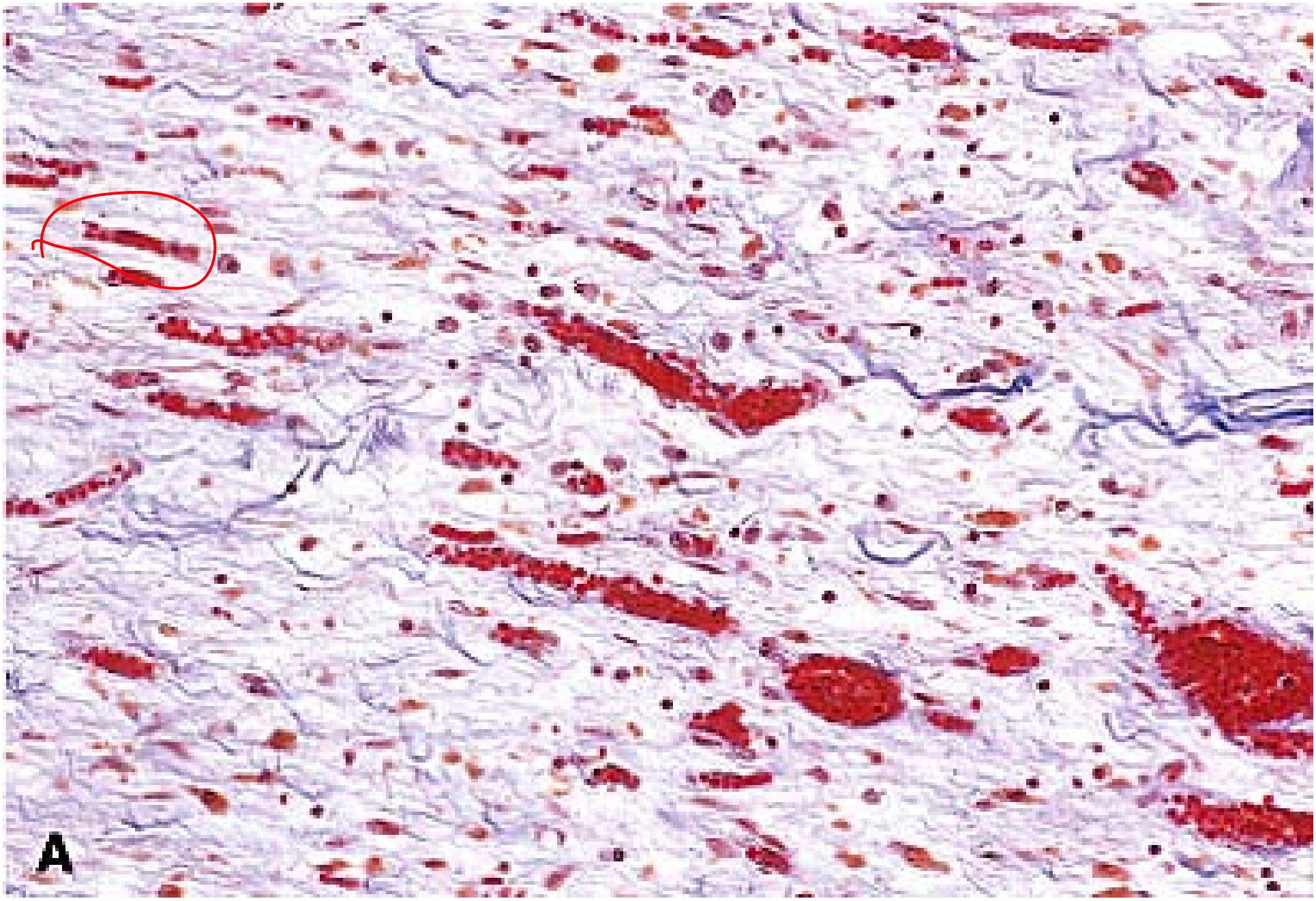
  - fibrogenesis

Angiogenesis (neovascularisation)

- Formation of new blood vessels takes place by proliferation of endothelial cells
- Initially, proliferated endothelial cells are solid buds but within few hours develop lumen.
- Newly formed blood vessels are more leaky, accounting for oedematous appearance of granulation tissue.
- Soon, blood vessels differentiate into arterioles, venules and capillaries.
- Factors: VEGF, PDGF, TGF-b, FGF and surface integrins

Fibrogenesis

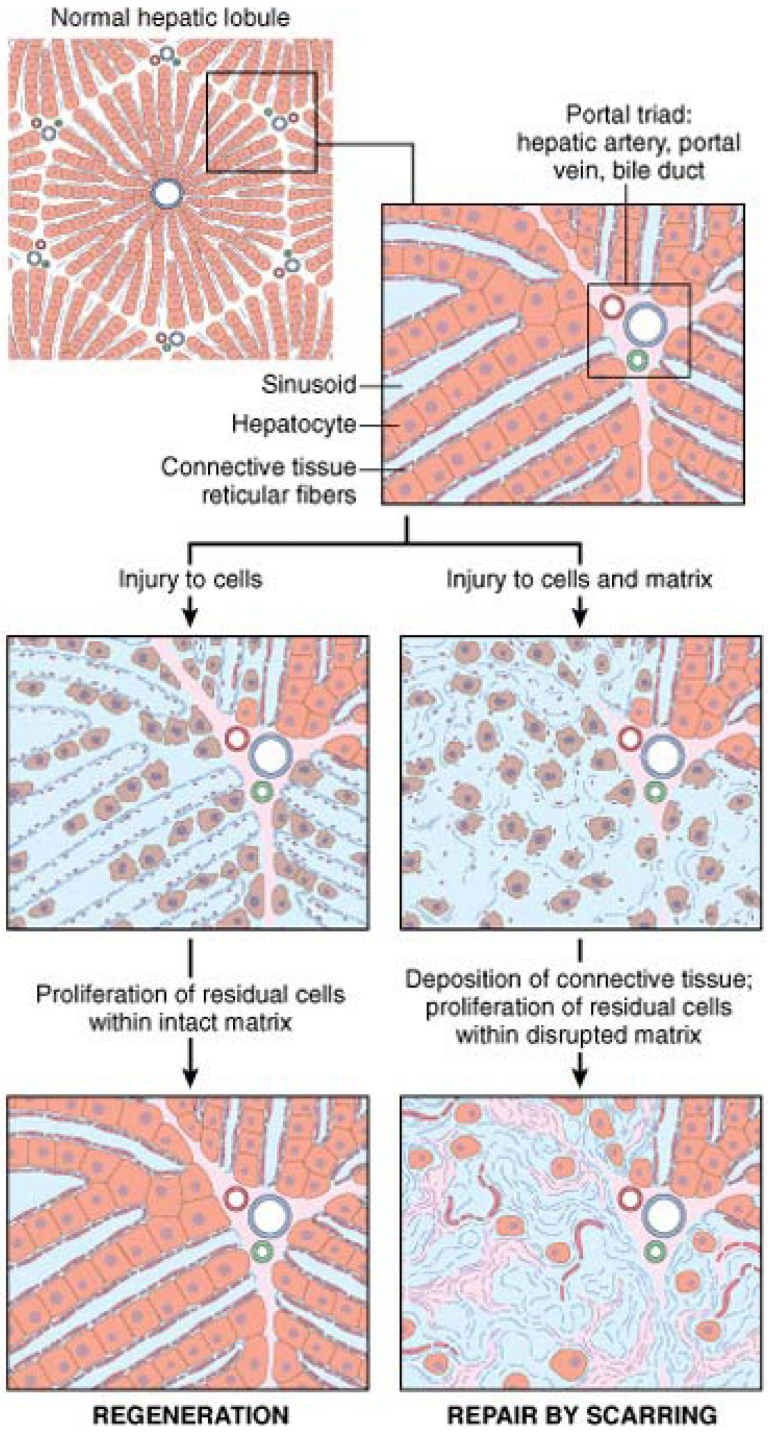
- Proliferation of fibroblasts.
- *Myofibroblasts - s*ome of the fibroblasts have morphologic and functional characteristics of smooth muscle cells.
- Collagen fibrils begin to appear by about 6th day.
- As maturation proceeds, more and more of collagen is formed while the number of active fibroblasts and new blood vessels decreases.
  - Growth factors (TGF-β, PDGF, EGF, FGF)
  - Cytokines (IL-1, TNF-α)



Granulation tissue

Contraction of Wounds

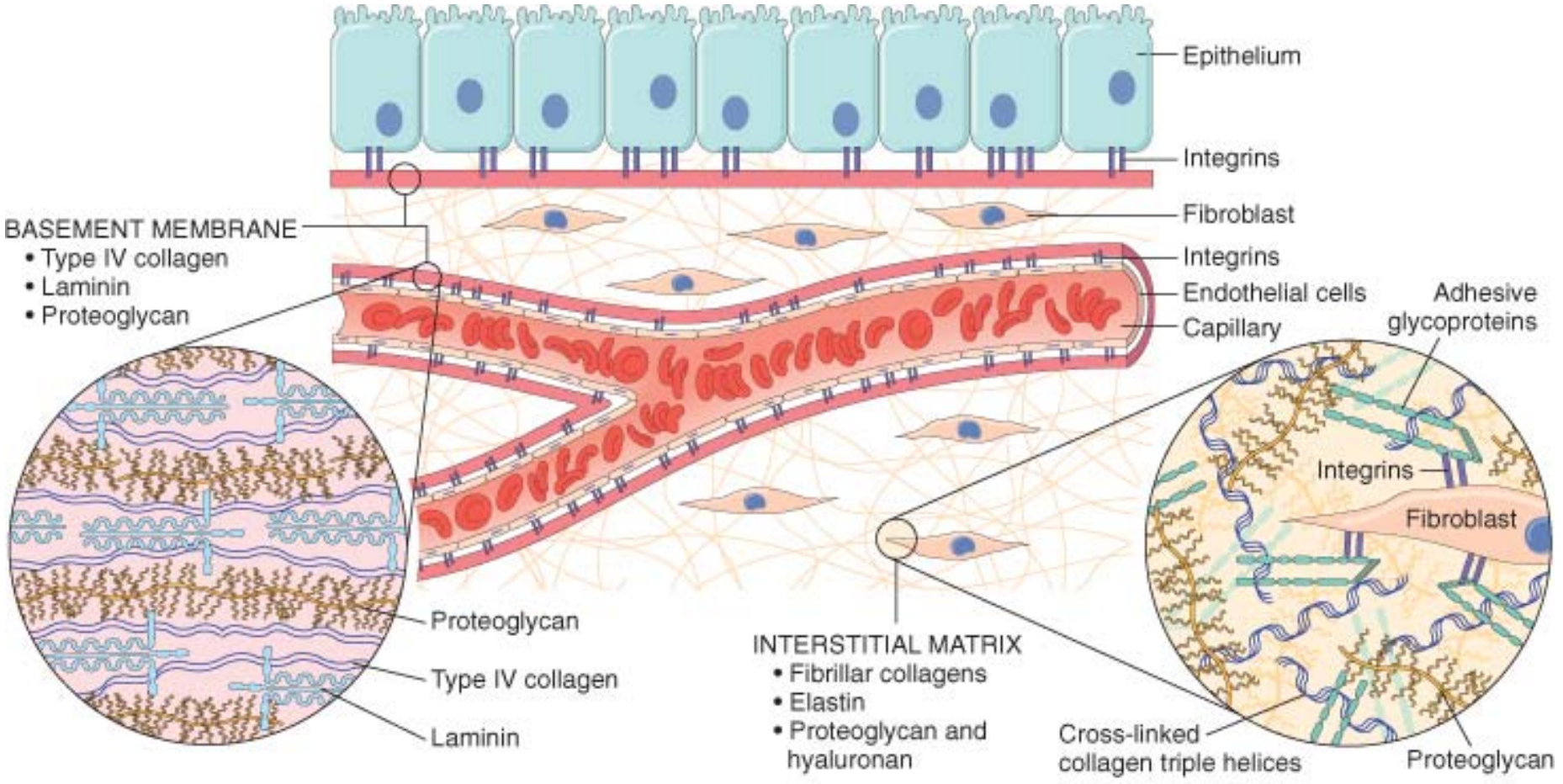
- The wound starts contracting after 2-3 days and process is completed by the 14th day.
- The wound is reduced by approximately 80% of its original size.
- Mechanism of wound contraction
  - Dehydration
  - Contraction of collagen
  - Myofibroblasts- have features intermediate between those of fibroblasts and smooth muscle cells. Their migration into the wound area and their active contraction decreases the size of the defect.

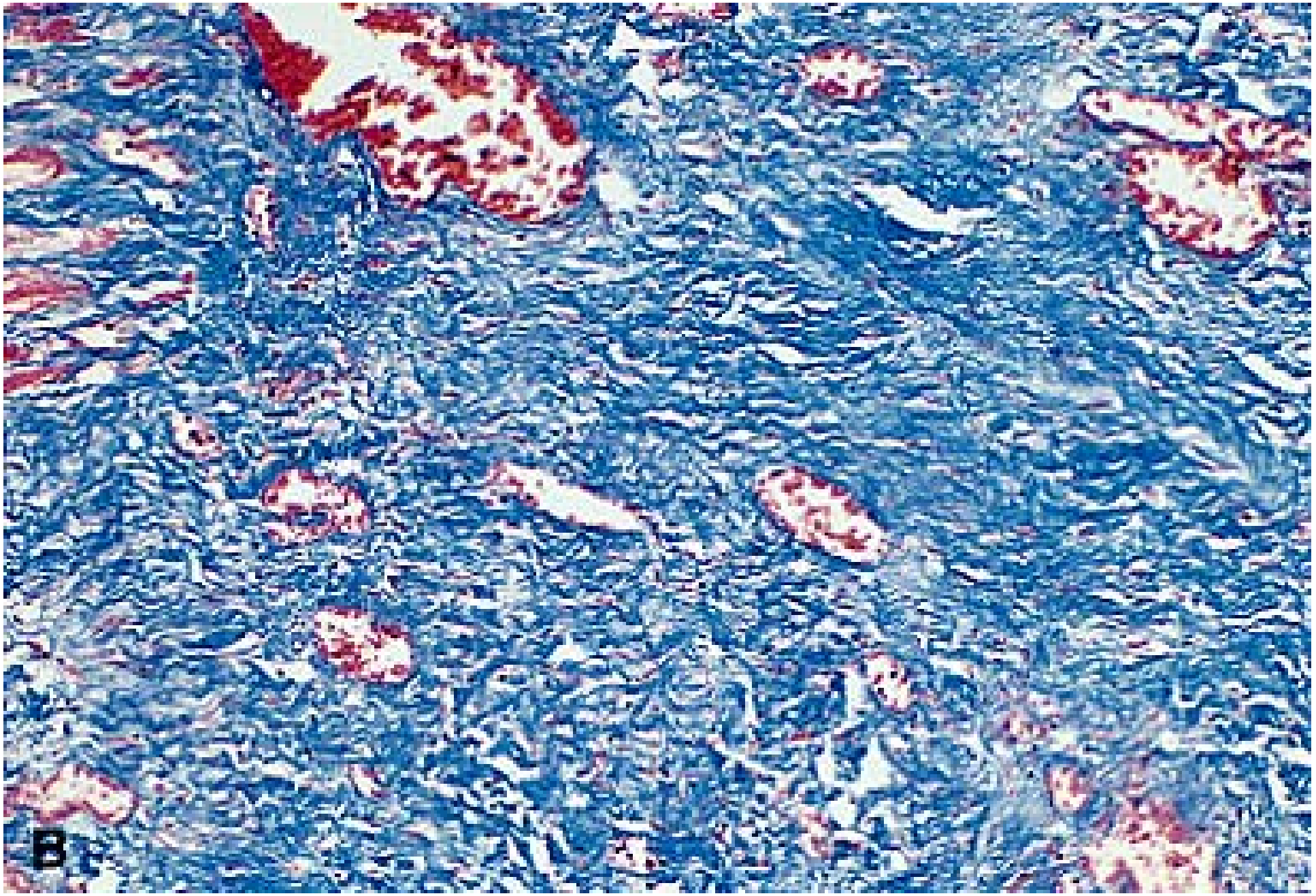

Normal hepatic lobule
Portal triad:
hepatic artery, portal
vein, bile duct
Sinusoid
Hepatocyte
Connective tissue
reticular fibers
Injury to cells
Injury to cells and matrix
Proliferation of residual cells
within intact matrix
Deposition of connective tissue;
proliferation of residual cells
within disrupted matrix
REGENERATION
REPAIR BY SCARRING

Extracellular Matrix (ECM)

- ECM is the network that surrounds cells
- Two forms: interstitial matrix and basement membrane
- ECM provides support, adhesion substrate, reservoir for factors; protein components
  - Collagens: most common, 14 types
    - I-III: interstitial/fibrillar, most abundant
    - IV-VI: non-fibrillar, basement membranes
  - Adhesive glycoproteins: *e.g.*, Laminin, fibronectin, integrins which bind ECM components to each other, and to other cells
  - Proteoglycans: sugars linked to proteins; influence ECM permeability and structure

The Extracellular Matrix





Scar