

Tissue Repair: Regeneration, Healing and Fibrosis Wound Healing

Patrice F. Spitalnik, MD
pfs2101@columbia.edu

Growth Factors

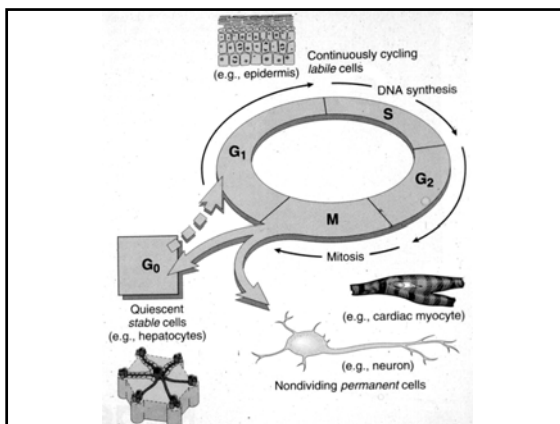
- Vascular Endothelial growth factor (**VEGF**)
– increased vascular permeability
- Transforming Growth Factor-Beta (**TGF-B**)
- Platelet Derived Growth Factor (**PDGF**)
- Epidermal Growth Factor (**EGF**)
- Fibroblast Growth Factor (**FGF**)

Learning Objectives

- Differentiate regeneration from repair by fibrosis
- Understand multiple factors and different cell types in the stages of wound healing.
- Know difference between healing by first and second intention
- Understand factors that influence outcome of wound healing and repair.

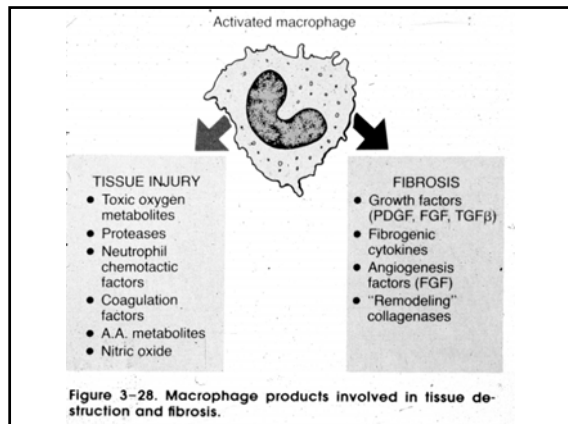
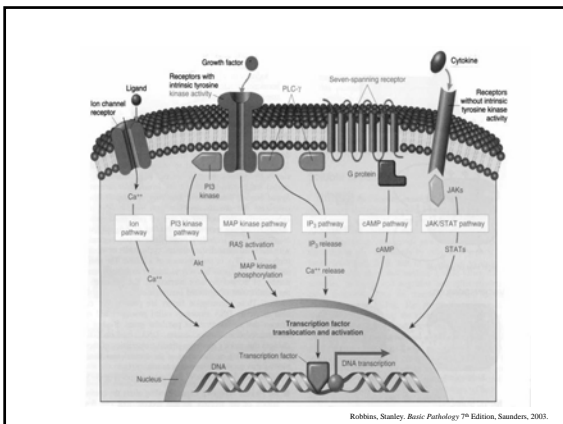
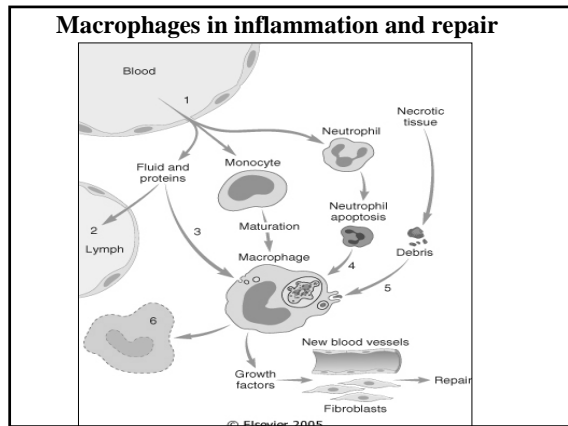
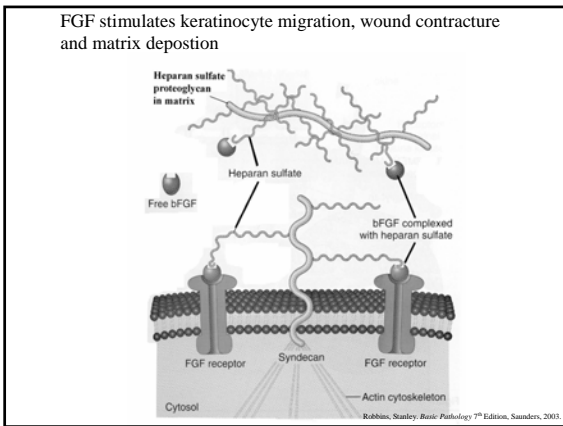
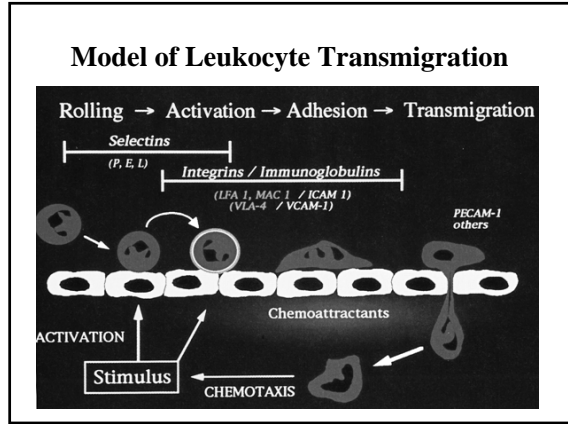
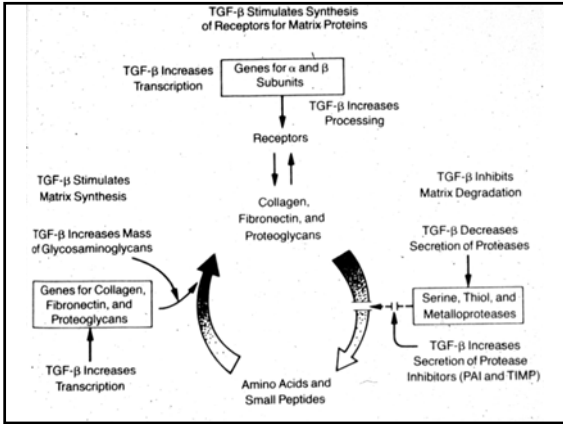
TGF- beta

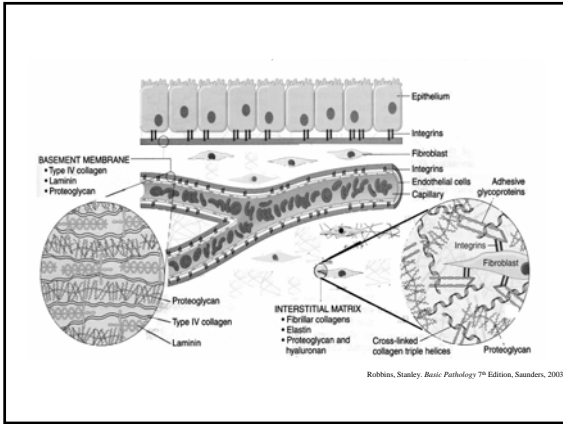
- Produced by:
 - Platelets and macrophages
- **MOST IMPORTANT FACTOR IN WOUND HEALING**
- Actions:
 - Monocyte chemotaxis
 - Fibroblast migration and proliferation
 - Angiogenesis and fibronectin synthesis
 - Collagen and ECM:
 - Increased synthesis
 - Decreased degradation by MMP's, increased TIMP's



Growth Factors and Wound Healing

- **VEGF** and **FGF** - produced by macrophages and increases angiogenesis
- **PDGF** – produced by platelets, is mitogenic for fibroblasts and increases collagen
- **EGF** – produced by macrophages, is mitogenic for keratinocytes and macrophages - **GRANULATION TISSUE**



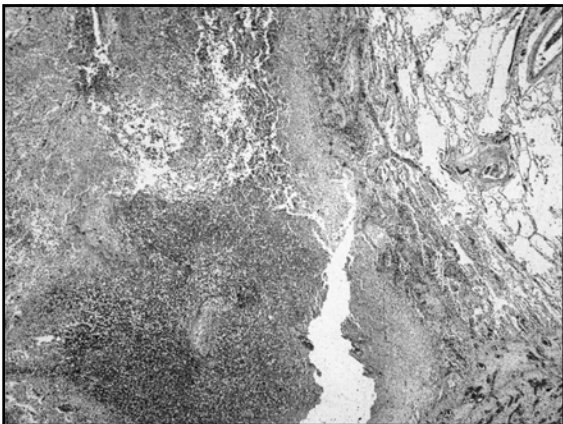
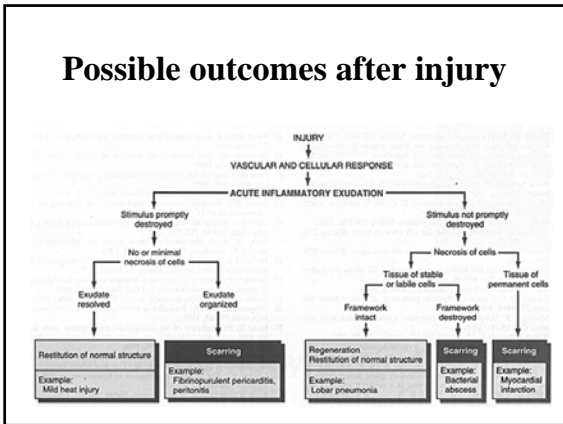
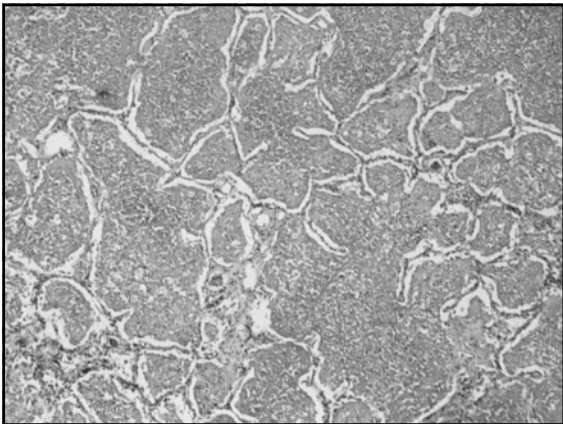


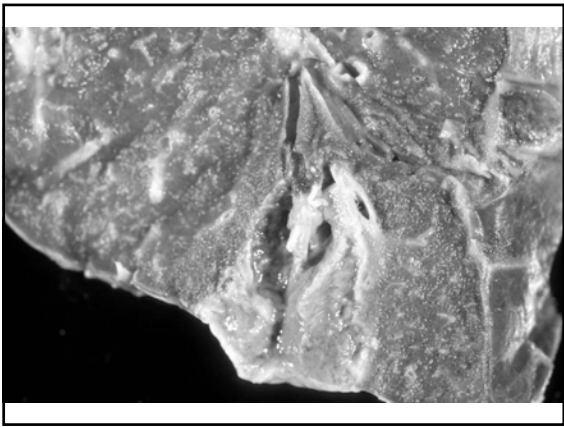
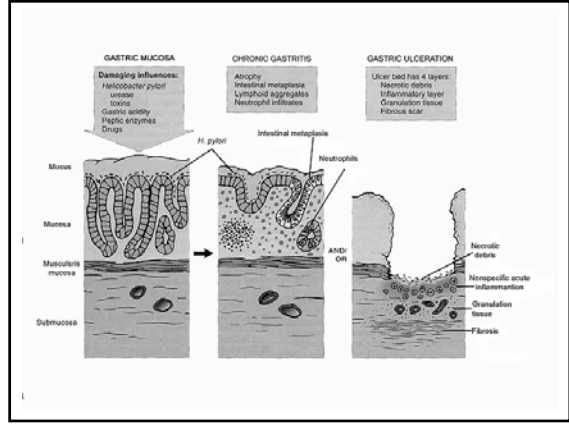
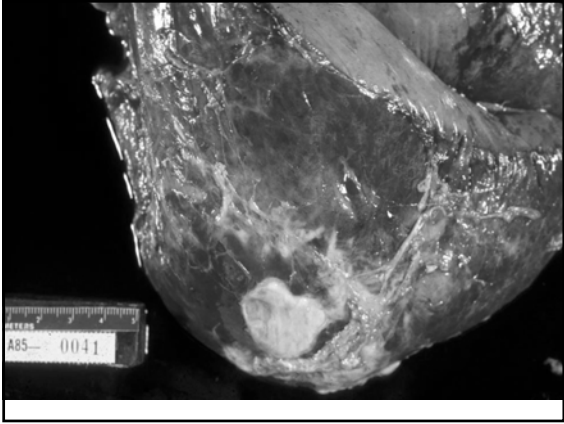
Regeneration

- If the connective tissue framework is intact
- If the cells are not post-mitotic
- THEN:
- Complete restoration of the structure and function of the tissue is possible

Healing is an Outcome for:

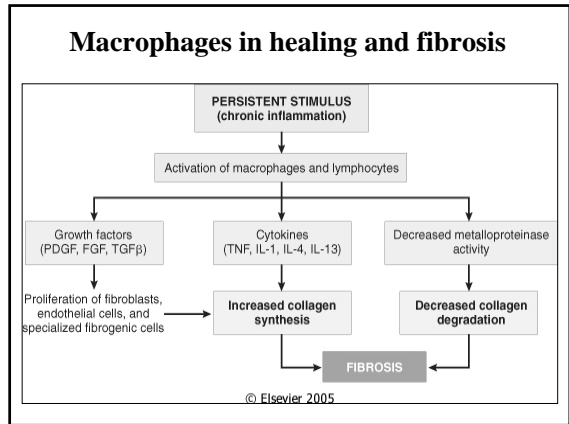
- Acute Inflammation
- Chronic Inflammation
- Ischemic Necrosis
- Skin Wounds
- Bone Fractures





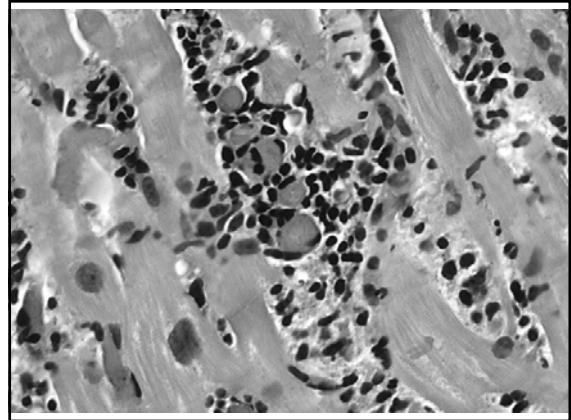
Chronic Peptic Ulcer

Fibrosis below the ulcer bed



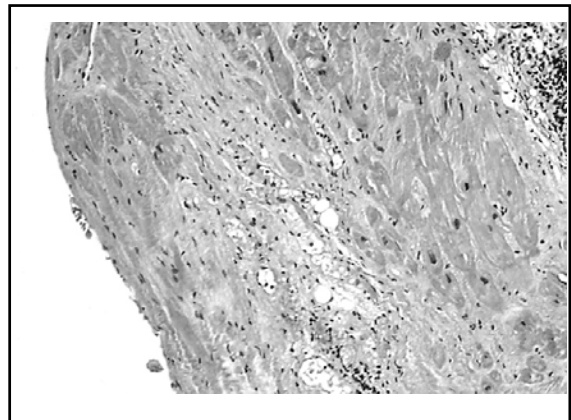
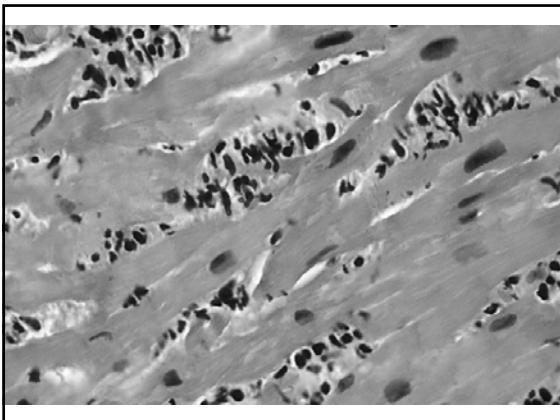
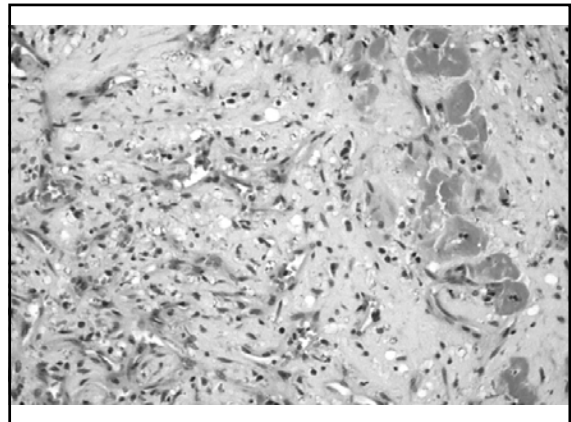
Scar Formation

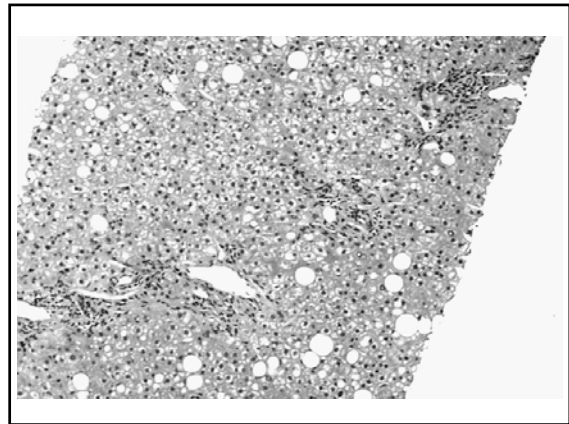
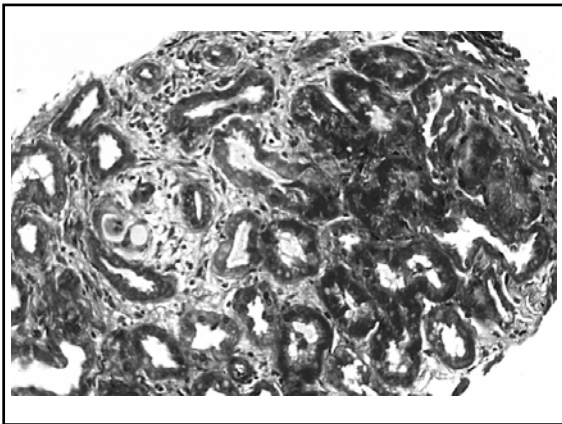
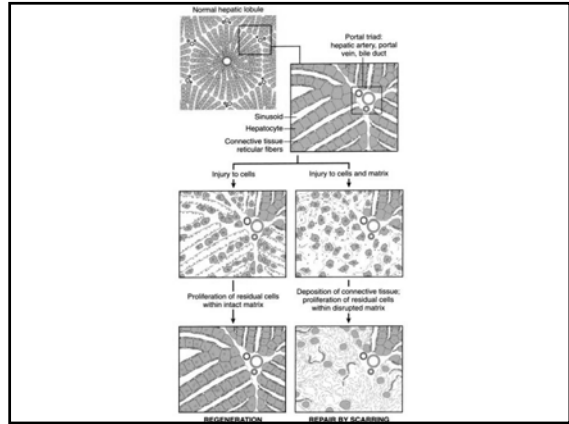
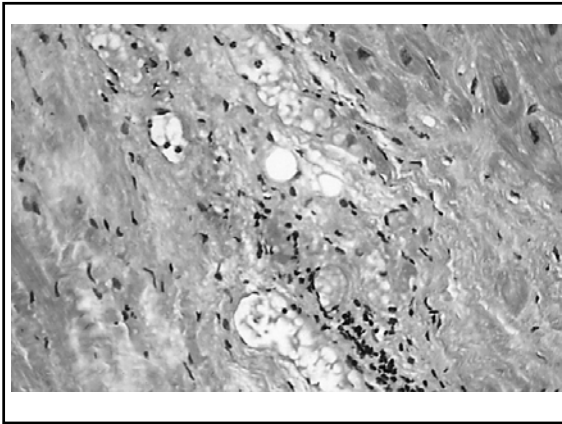
- If there is substantial damage with loss of the basement membrane or connective tissue framework then:
- Fibrosis or a scar results



Repair by Fibrosis

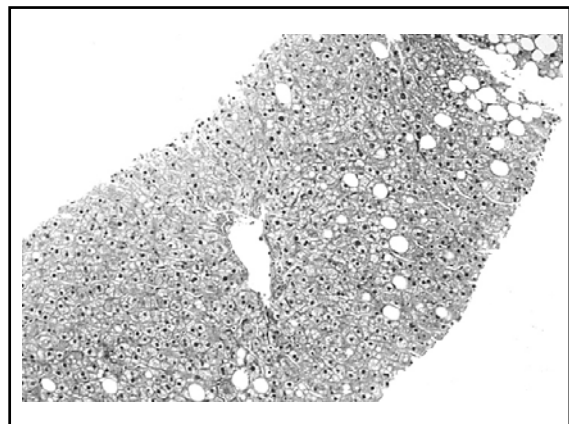
- Angiogenesis
- Migration and proliferation of fibroblasts
- Deposition of extracellular matrix
- Organization of collagen “remodeling”
- Fibrosis – scar formation

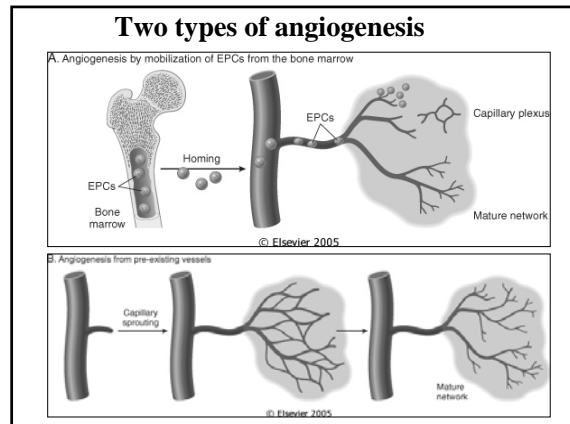
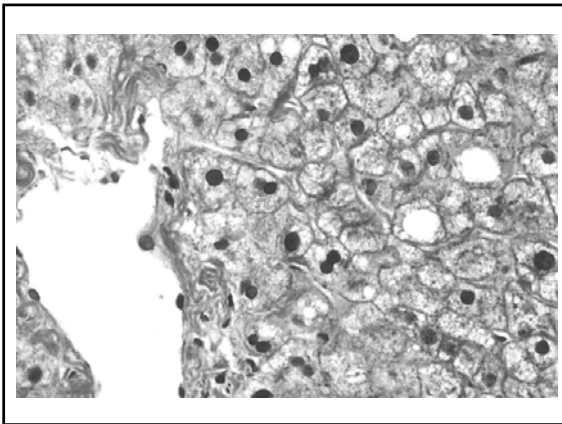
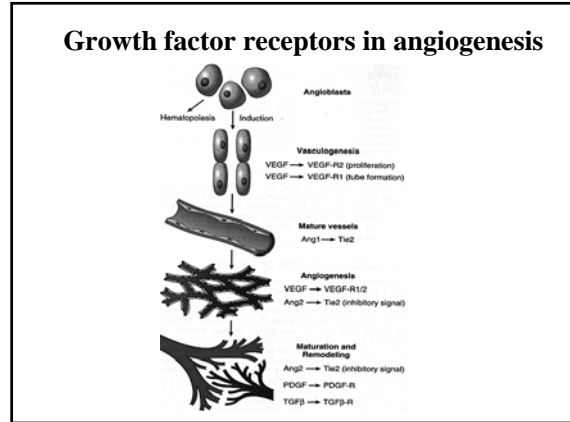
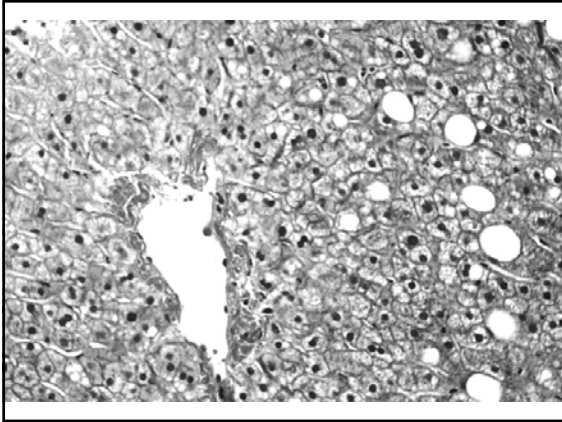




Scarring in the Liver

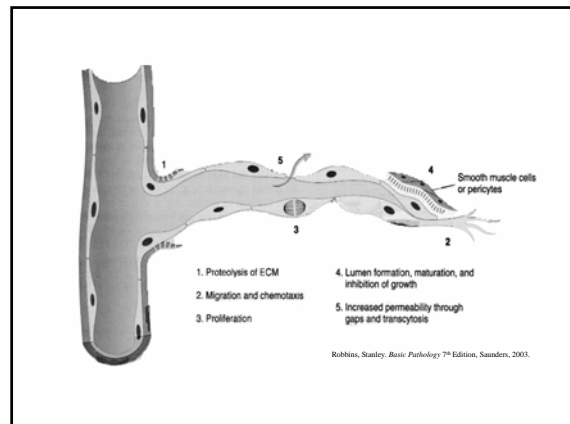
- Healing by fibrosis after inflammation
- TGF beta implicated in excessive collagen formation

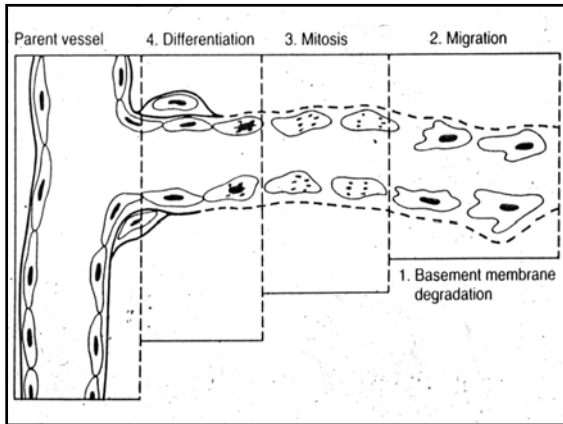




Angiogenesis

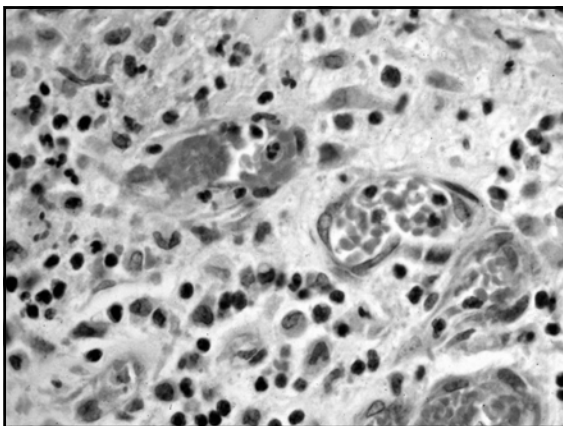
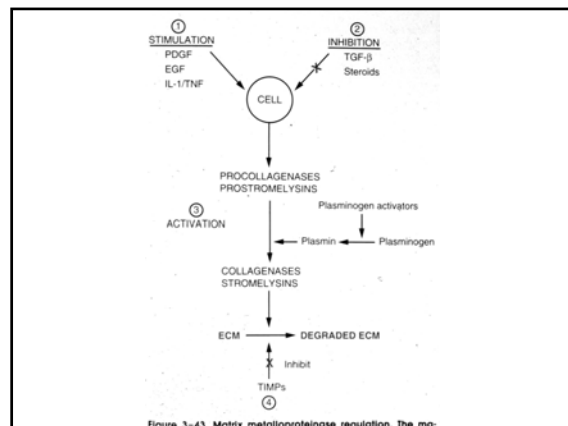
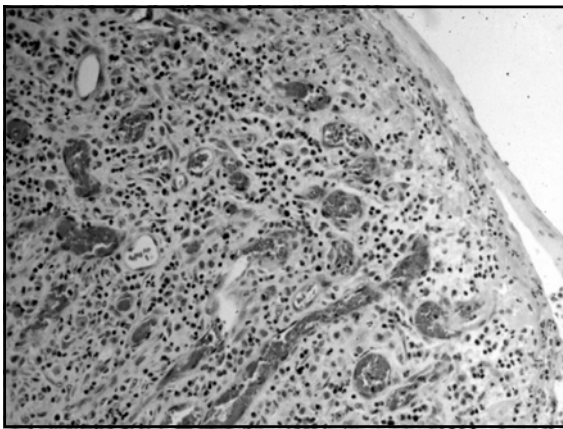
- Proteolysis of vessel basement membrane
- Endothelial cell migration and proliferation
- Pericyte recruitment





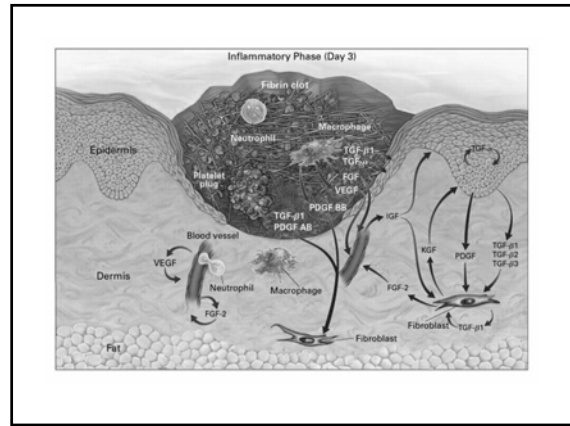
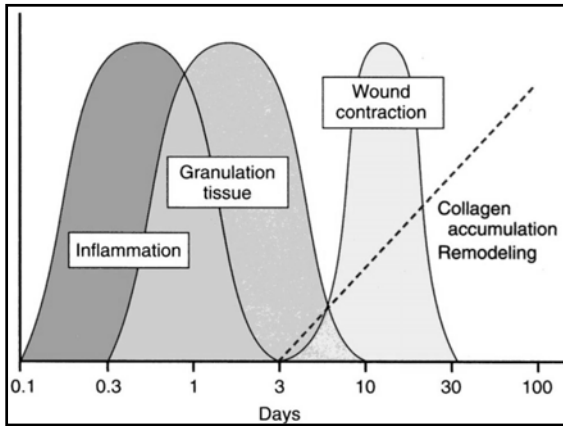
ECM and Tissue Remodeling

- Outcome of repair: balance between synthesis and degradation of matrix
- **MMP's** are synthesized by fibroblasts, macrophages, neutrophils, epithelial cells, etc destroy matrix (inactive form) activated by proteases and plasmin and inhibited by **TIMP's**-synthesized by mesenchymal cells



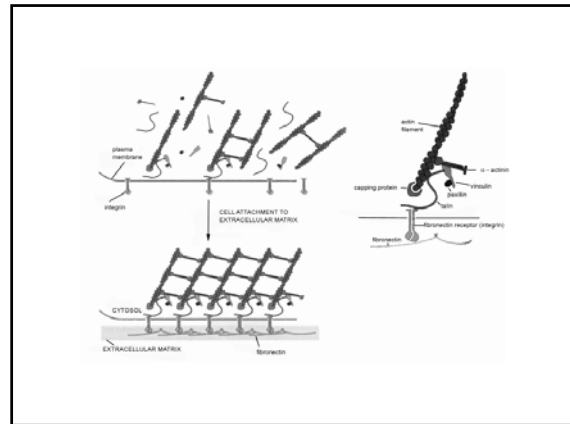
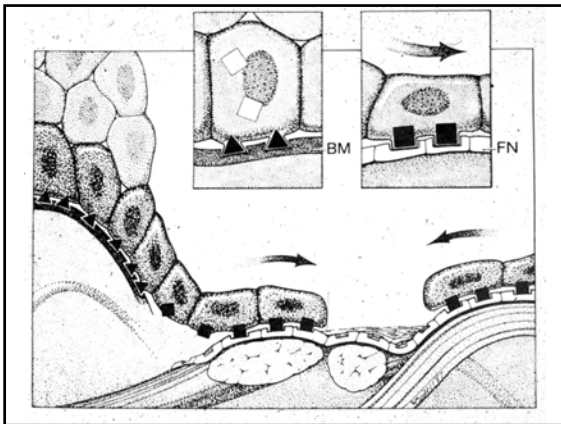
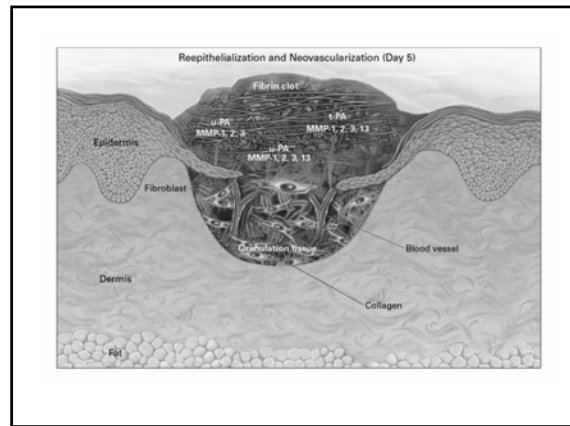
Overview of Cutaneous Wound Healing

- A defect in the skin occurs
- Fibrin fills in defect – scab forms
- Epithelial regeneration beneath scab
- Granulation tissue – angiogenesis
- Wound contraction
- Collagen remodeling



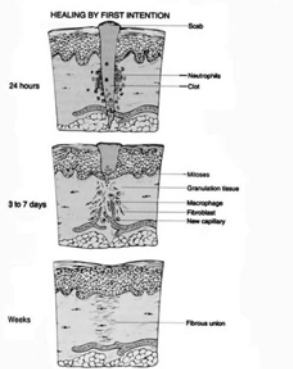
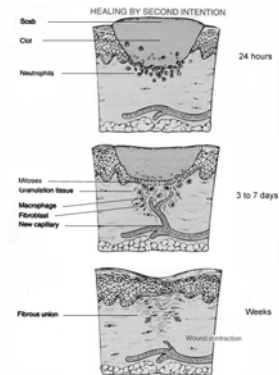
Cell Migrations in Wound Healing

- **Platelets** form a blood clot and secrete fibronectin (FN) and TGF-beta
- **Macrophages** move in as part of granulation tissue and secrete fibronectin
- **Keratinocytes** or other epithelial cells detach from the basement membrane at wound edge and migrate on fibronectin rich matrix across wound to fill in defect (cells switch receptors from those for BM to FN receptors)



Healing by Primary Intention

- Surgical incision
- Edges easily joined together
- Small amount of granulation tissue
- Little fibrosis
- Wound strength 70-80% of normal by 3 months



Inhibition of Repair

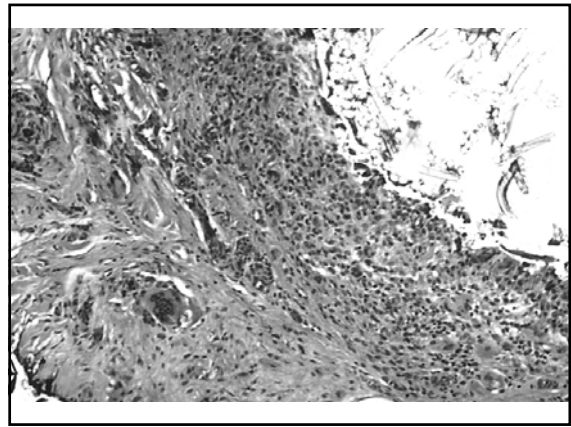
- Infection with inadequate nutrition (Vitamin C is essential for collagen)
- Glucocorticoids inhibit inflammation with decreased wound strength and less fibrosis.
- Poor perfusion due to diabetes or atherosclerosis.
- Foreign bodies left in the wound.
- Chronic inflammation leads to excess, disabling fibrosis as in rheumatoid arthritis, pulmonary fibrosis and cirrhosis.

Healing by Second Intention

- Large wound, may be infected
- Edges not brought close together
- Large amount of granulation tissue
- Scar formation and contracture

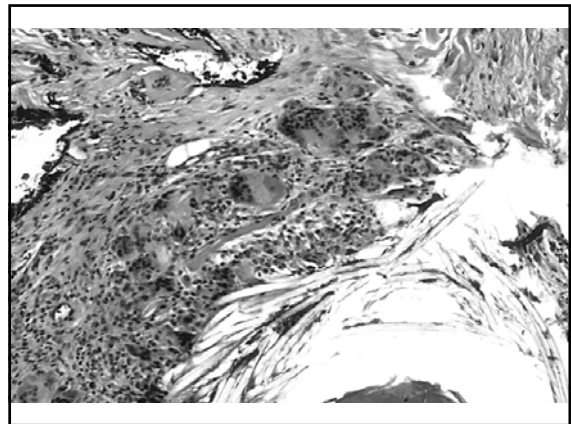
Diabetic Foot Ulcer Case #1

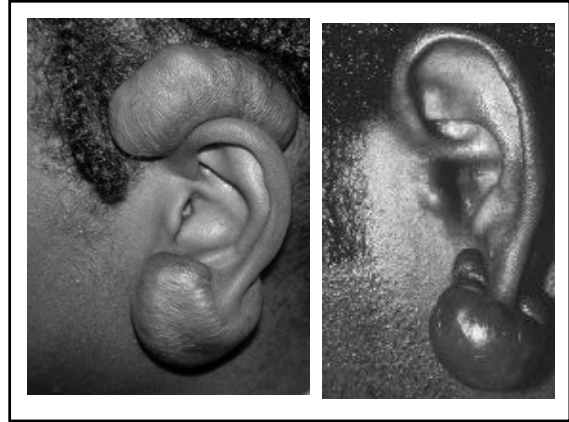
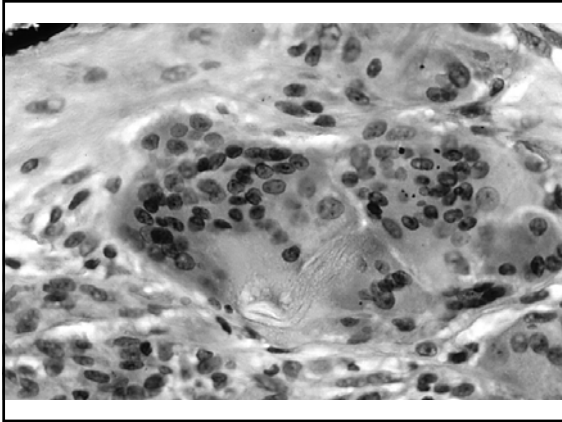
- A 52 year old woman has had fairly well controlled type 2 diabetes mellitus for the past 20 years.
- In the last three months, she has noticed a non-healing ulcer on her heel.
- She asks you what can be done to make it heal better.



Diabetic Foot Ulcer Case #2

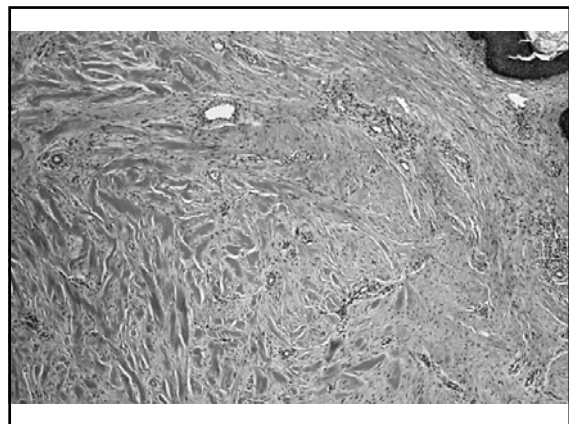
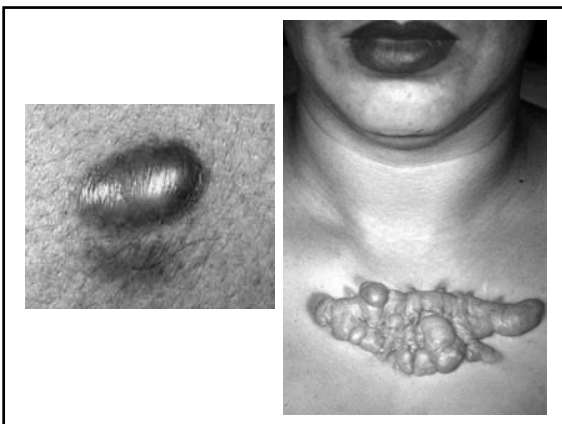
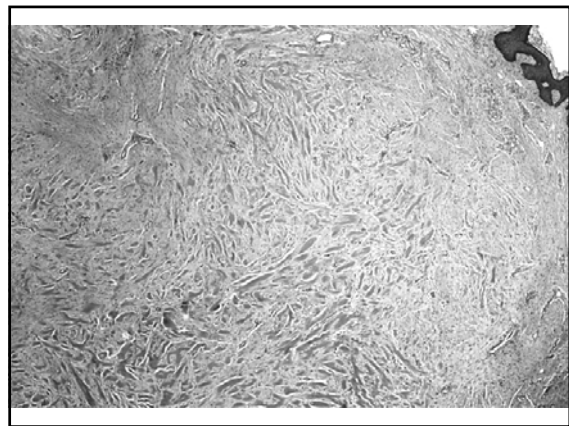
- This is a 63 year old male with Type 2 diabetes mellitus for the past 10 years.
- He requires insulin.
- He presents to you with the complaint of a painless sore on the sole of his foot directly beneath a metatarsal head.
- He asks why his foot has difficulty healing.





Abnormal Repair Processes

- Inadequate scar formation - dehiscence, ulceration
- Excessive scar formation – keloids
- Contracture – exaggeration of normal process (soles, palms, thorax) especially with serious burns





Concluding Points

Minor damage acute inflammation (neutrophils), granulation tissue (macrophages, ECM production, angiogenesis) and **healing** (tissue regeneration).

Extensive damage acute and chronic inflammation, large granulation tissue, fibrosis, and **scarring**.

DO NOT CONFUSE GRANULATION TISSUE WITH GRANULOMA

granulation tissue - normal healing

granuloma - chronic inflammation in some intracellular infections, **TB, foreign body reactions, sarcoid, or some fungal infections.**



Strategies for Modulating Wound Healing

Stimulators:

- Increase epithelial migration
- Increase wound strength, collagen synthesis, TGF-beta
- PDGF used to accelerate healing with chronic pressure sores and diabetic ulcers
- FGF used with success for chronic pressure sores

Modulators:

- Delay collagen synthesis (keloids)
- Prevent wound contracture (burns)