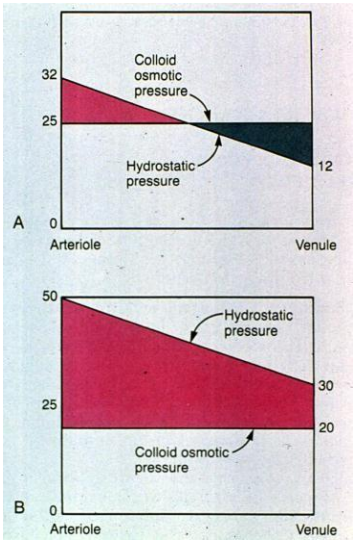
Inflammation

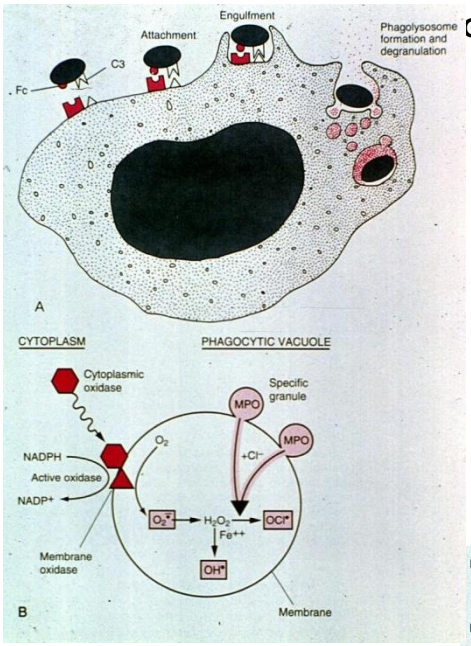
- Reaction of vascularized living tissue to local injury
- Reaction of tissues to injury, characterized by clinically by SHARP and loss of function
    - Pathologically by vasoconstriction followed by vasodilation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, deposition of fibrin, and according to some sources the processes of repair, the production of new capillaries, and fibroblasts, organization, and cicatrization
- -itis – appendicitis, cellulitis, meningitis, pneumonitis, nephritis, myocarditis
    - Microbial infection – pneumonia, skin infections, etc
    - Physical agents – burns, trauma, cuts, radiation
    - Chemicals – toxins, caustic substances
    - Others – immunological, rheumatoid arthritis
- Acute inflammation - <48h – PMNs
- Chronic inflammation - >48h – mononuclear cells (macrophages, lymphocytes, plasma cells)
    - Exception – abscess, even greater than 48h, always has PMNs
    - Acute inflammation
    - Usually involve PMNs are mediators, changes which occur within minutes to days after injury
        - Minor damage – 15-30 minutes
        - Major damage – a few minutes
    - Changes in vascular flow and caliber (hemodynamics)
        - Vasoconstriction – transient, inconstant
        - Vasodilation – first arterioles, then capillaries, then venules
        - Slowed circulation – albumin-rich fluid leaking into extravascular tissue RBC concentration in small vessels and increased blood viscosity
        - Leukocyte margination – PMNs become oriented at vessel periphery and start to stick
    - Vascular permeability (leakage)
        - Starling's hypothesis – for normal tissue, intravascular hydrostatic pressure ~ colloid osmotic pressure

    - Inflammation – increased intravascular hydrostatic pressure, decreased colloid osmotic pressure – results in edema
  - Leukocyte exudation
    - Margination, rolling, adhesion
    - Diapedesis (transmigration across endothelial border)
    - Migration towards chemostatic agent
    - Phagocytosis

- Lymphatic involvement – responsible for draining edema
  - Edema – excess fluid in interstitial tissue or serous cavities
  - either transudate or an exudate
    - Transudate – ultrafiltrate of blood plasma
    - Endothelium permeability usually normal
    - Low protein content (usually albumin)
    - Specific gravity < 1.012
    - Exudate – blood plasma filtrate mixed with inflammatory and cellular debris
    - Endothelial permeability usually altered
    - High protein content
    - Specific gravity > 1.020
    - Pus – purulent exudate – inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris

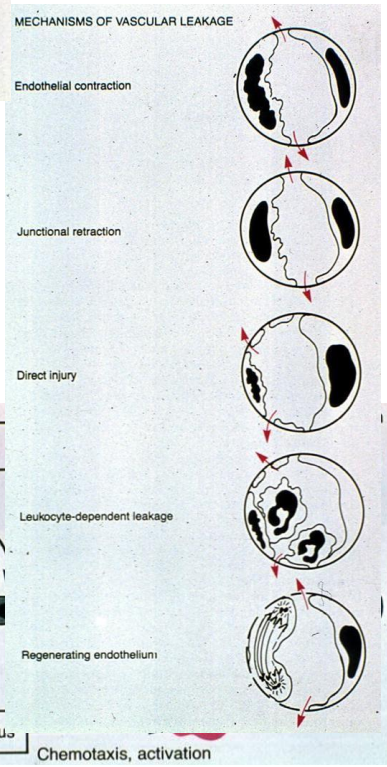
- Phagocytosis
  - Recognition and attachment
  - Engulfment
  - Killing/degradation
    - Oxygen dependent – myeloperoxidase dependent (MOST IMPORTANT), and myeloperoxidase independent
      - Oxygen independent
  - Defects in leukocytes function
    - Margination and adhesion – ^OH, steroids, AR leukocyte adhesion





deficiency

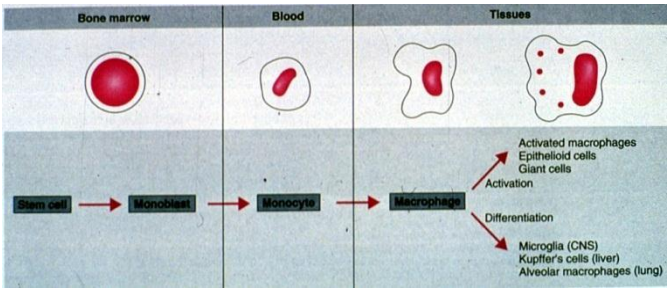
- Emigration towards chemotactic stimulus – drugs, chemotaxis inhibitors
- Phagocytosis – chronic granulomatous disease (CGD)



- These systems seem to be interrelated –
- seems to be a very good system
- of checks and balances
- Acute inflammation has 4 outcomes
  - Abscess formation
  - Progression to chronic inflammation
  - Resolution – tissue returns to normal
  - Healing – tissue scars or fibrosis

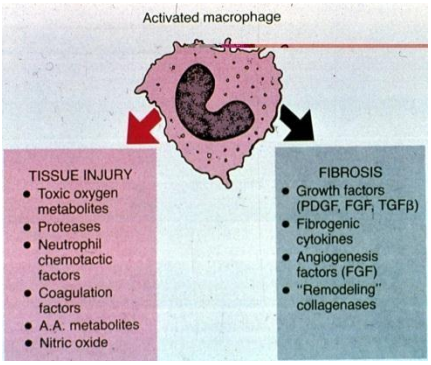
- Abscess – circumscribed collection of pus appearing in an acute or chronic localized infection, and associated with tissue destruction and, frequently, swelling
  - Usually the result of a pyogenic organism
  - A hole filled with goo (usually of dead neutrophils)
  - Abscess is always filled with PMNs, acute or chronic
- Chronic inflammation
    - Greater than 48h – mononuclear cells – primarily macrophages, lymphocytes, plasma cells
  - Arises if various organs in 1 of 3 ways
    - Follows acute inflammation

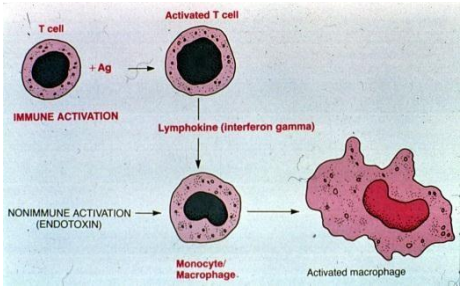
    - After repeated bouts of acute inflammation (pneumonia)
    - Without prior acute inflammation – exception is that a viral infection ALWAYS elicits lymphocytic response instead of PMNs, even in acute cases (bacteria elicits PMN acute response)
- Histologic chronic inflammation
    - Lymphocytes, plasma cells, macrophages (aka histiocytes, kuppfer cells, etc – are central to chronic inflammation like PMNs are to acute inflammation)



    - Fibroblast proliferation and small vessels
    - Increased connective tissue
    - Tissue destruction
- All macrophages come from the same cell line, but differ in their microenvironment
    - They belong to the mononuclear phagocyte system (RES) – consists of bone marrow, peripheral blood, and tissue
    - All MOs are slower than PMNs – primary reason different cells respond for acute vs chronic
        - Can both phago and pino cytosis
        - Can be activated – especially by lymphokines, T-cells, anything that disturbs cell membrane
            - Allows for more aggressive behavior in inflammation
        - Secrete large quantities of chemical mediators
- Macrophage functions
    - Produce toxic, biologically active substances (ex:// O_2 metabolites)
    - Cause influx of other cells (Ex:// other macrophages and lymphocytes)
    - Cause fibroblast proliferation and collagen deposition

  - Phagocytosis
  - Begin emigration during acute phase and are predominant cell type by 48h
- Macrophage accumulation
  - Continued recruitment from circulation – secondary chemotactic factors
  - Cell division
  - Prolonged survival once activated
- Other cells in chronic inflammation – Lymphocytes, Plasma cells, Eosinophils, PMNs

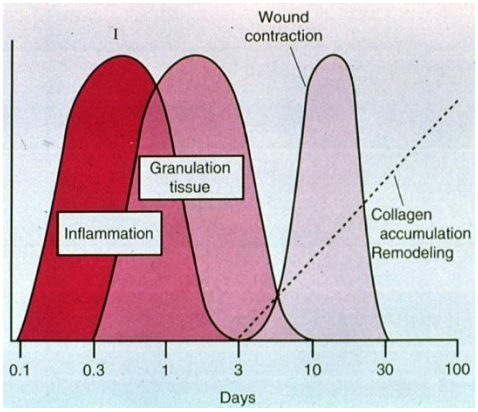




- Chronic granulomatous inflammation and giant cells
  - A type of chronic inflammation defined by *presence of granulomas*, small 0.5-2mm collections of modified "epithelioid" histiocytes/macrophages and (langhan's) giant cells (coalesced histiocytes), usually surrounded by a rim of lymphocytes

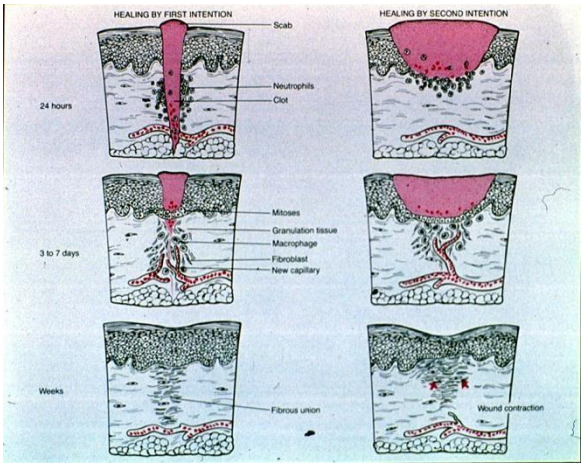
- Granumolas occur in response to various diseases – foreign body, TB, fungal, sarcoidosis, schitosomiasis, leprosy
  - 2 factors needed for granuloma formation
    - Presence of indigestible organisms or particles (TB, mineral oil, etc)
    - Cell mediated immunity (T-cells)
      - HIV decreases number of T4 cells (humoral response is B cells)

- Outcomes of Chronic Inflammation
  - Resolution/regeneration – tissue returns to normal state
  - Repair/healing – healing by CT /fibrosis/scarring
  - Can continue indefinitely (ex:// rheumatoid arthritis)
- Resolution
  - Removal of offending agent
  - Regenerative ability of cells have been destroyed
    - Labile cells – cells which continue to proliferate throughout life (gut, skin, marrow)
    - Stable cells – retain ability to proliferate, but usually don't unless stimulated (liver, kidney, pancreas, bone)
    - Permanent cells – cannot reproduce themselves after birth (neurons, cardiac, skeletal muscle)
  - Intact stromal framework – cells sit on a scaffolding, like the basement membrane



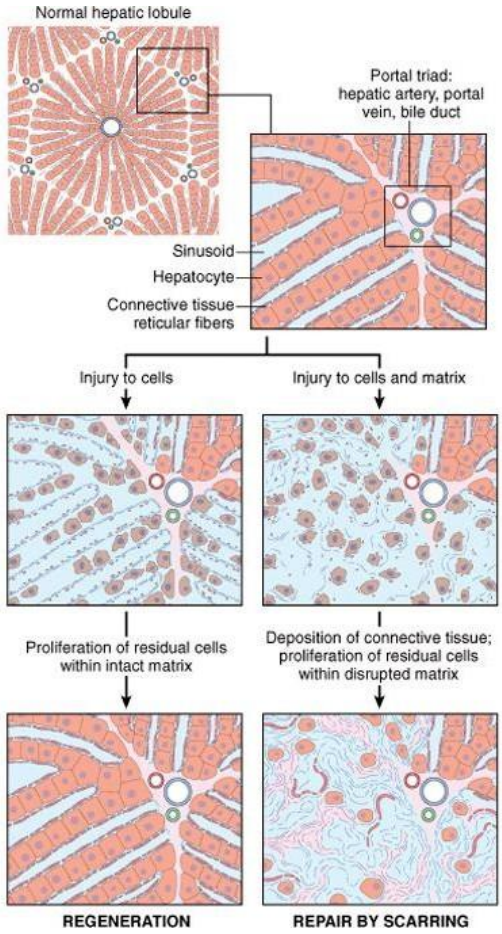
- Repair
  - Damage to parenchymal cells and stromal framework which results in replacement of non regenerated parenchymal cells by connective tissue which, over time, produces fibrosis and scarring
  - Granulation tissue – early specialized vascular and fibrosis tissue formed
    - Grossly it looks pink and granular, histologically can see vessels and fibroblasts
  - Granulation tissue is not same as granuloma (macrophage collection)
  - Components necessary for repair
    - Angiogenesis/neovascularization of new vessels
    - Migration and proliferation of fibroblasts
    - Deposition of ECM
    - Remodeling or maturation and organization of fibrous tissue
- Wound Healing
  - First intention – suture, closing the wound

- Second intention – leave scar open to heal
  - Hole is filled with abundant granulation tissue
  - With time, wound contacts more than a wound healed via first intention. This occurs with passage of time and secondary to myofibroblasts



- Wound Strength
  - 1 week – wound strength ~ 10% strength of unwounded skin
  - Increases rapidly over next 4 weeks
  - Peaks at 3rd month, achieves 70-80% tensile strength of unwounded skin
- Additional definitions
  - Serous inflammation – outpouring of thin fluid that, depending on injury site, is derived from either blood serum or secretions of mesothelial cells lining peritoneal, pleural, and pericardial cavities
  - Fibrinous inflammation – serous fluid and plasma proteins (like fibrinogen). Seen commonly in infections of pleural cavity and pericardial sac
  - Suppurative/purulent inflammation – serous and fibrinous and pus (purulent exudate). Especially common with Staph., one of several pus producing organisms. (acute appendicitis)
  - Ulcer – local defect, or excavation of the surface of an organ or tissue, which is produced by sloughing (shedding) of inflammatory necrotic tissue. Ulceration is defined by the presence of necrotic tissue on or near the surface.

Tissue Repair



- Regeneration
- Scarring
- Combination of both

- Lots of cells proliferate during tissue repair
  - Injured tissue remnants
  - Vascular endothelial cells
  - Fibroblasts
- G1 (G0) □ S □ G2 □ M □ G1
- 3 groups of tissues
  - Labile (continuously dividing)
    - Can easily regenerate after injury
    - Contains a pool of stem cells
      - Bone marrow, skin, GI epith
  - Stable
    - Limited proliferative ability
    - Limited regenerative ability (Except liver)
    - Normally in G0
      - Liver, kidneys, pancreas
  - Permanent tissues
    - Can't proliferate or regenerate
      - Always leaves a scar
      - Neurons, cardiac
- Growth Factors
  - Important in tissue repair
    - Stimulate cell division and proliferation
    - Promote cell survival
  - Very large list, usually has GF in it (growth factor)
- ECM is anything outside the cell
  - Interstitial matrix and basement membrane
    - Sequesters water, minerals, gives cells scaffolding, stores growth factors
  - Regulates proliferation, movement, and differentiation of cells living in it
  - If you screw up ECM, you cannot regenerate □ scarring only

Regeneration

- Only occurs if residual tissue is intact
- Occurs all the time in labial tissue
    - Cells constantly being lost and replaced
    - If demand increases, supply increases readily
- Occurs limited in stable tissues
    - More like compensatory hyperplasia than true regeneration

Scarring

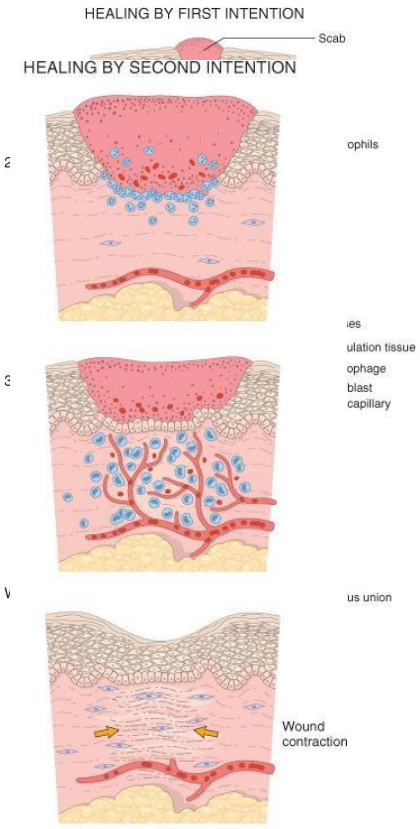
- Scar replaces injured tissue
    - New vessels form (angiogenesis)
    - Fibroblast proliferation
    - Synthesis of collagen (scar formation)
    - Remodeling of scar
- Timeline
    - 24h – endothelial cells start proliferation, fibroblasts emigrate
    - 3-5 days – granulation tissue present (pure granulation tissue does NOT have PMNs)
        - Fibroblasts, new vessels (endothelial cells), loose matrix)
    - Weeks later – dense fibrosis (scar), scar is remodeled over time
- Summary
    - Make granulation tissue
    - Turn it into a chunk of collagen

Epithelial Healing

- First intention – small wounds, close together
    - Epithelial regeneration > fibrosis
    - Healing is fast – minimal scarring and infection
    - Tissue must be close enough together that cells can “contact” instead of growing from the basement membrane up
- 24h
    - Clot forms, Neutrophils come in
    - Epithelium begins to regenerate
- 3-7 days
    - Macrophages come in, Granulation tissue is formed (angiogenesis, fibroblasts)

  - Collagen begins to bridge incision,
    Epithelium increases inthickness
- Weeks later
  - Granulation tissue disappears, Collagen is remodeled
  - Epidermis is full, mature and eventually a scar forms

- Second intention
  - Large wounds with gaps between margins
  - Fibrosis predominates over epithelial regeneration
  - Healing is slow, **more inflammation and more granulation**



tissue, more scarring
    - Infarction, burns, ulcers, extraction sockets, external-bevel gingivectomies
    - **Has wound contraction**
- Wound Healing
    - At suture removal – 10% strength
    - Rapidly increases over next 4 weeks
    - At 3rd month, 70-80%
- Wound Degeneration
    - Extrinsic factors
        - Infection
        - Diabetes – peripheral vascular condition
        - Steroids – anti-inflammatory
    - Type of tissue injured (labial vs permanent)
    - Aberrant cell growth or ECM production
        - Keloid scar – excess collagen bundles
        - Proud flesh – excess granulation tissue

Summary

- Not all injuries result in permanent damage – some are removed almost completely
    - Usually there is some scarring
- Scar is usually good (provides resilient patch) but can be bad (can cause permanent dysfunction)