Pathology C601
Inflammation and Repair

Assignment page

Reading:

Robbins: Chapter 2 and 3

Wheater: Part 1:, pps 10-34

Clinical Lab Source:
- C-reactive Protein
- Erythrocyte Sedimentation Rate (sedimentation rate)
- WBC differential
- HIV testing
- Antistreptolysin antibodies (ASO)

Laboratory assignment: C601/C602 Histopathology manual, Inflammation and Repair chapter, pages 1-11. Know especially the following slides: 1, 7, 9, 43, 59, 65, 66, 76, 77

Be sure you understand these terms:
- inflammatory reaction
- exudate vs transudate
- chronic and acute inflammatory responses, how they differ
- hypersensitivity reaction
- humoral vs cellular components of inflammatory response
- granuloma vs granulation tissue
- labile, stable and permanent cell populations
- wound healing by primary and secondary intention
- scar tissue vs keloid
- elements retarding wound healing
- edema, anasarca and ascites

Online exercise: **How to interpret a CBC**. You will have until September 15 to log onto Quizsite and take the CBC quiz for credit.

Inflammation and Repair
Cell Growth and Differentiation:
Regulation and Adaptation

I. Complex reaction to injury of **vascularized tissue**. Events revolve around changing the permeability of the blood vessel. Process is intertwined with repair. There is no time to form a committee!

A. The fundamental aspect of repair

- get your warriors to the site of the battle

- support them while they're out there

B. May become the problem if not checked

- arthritis

- anaphylaxis

C. Basic elements: make it go like hell where the damage is, but not affect other areas of the organism (that's you)

- **increased blood flow locally**

- **increased permeability locally**

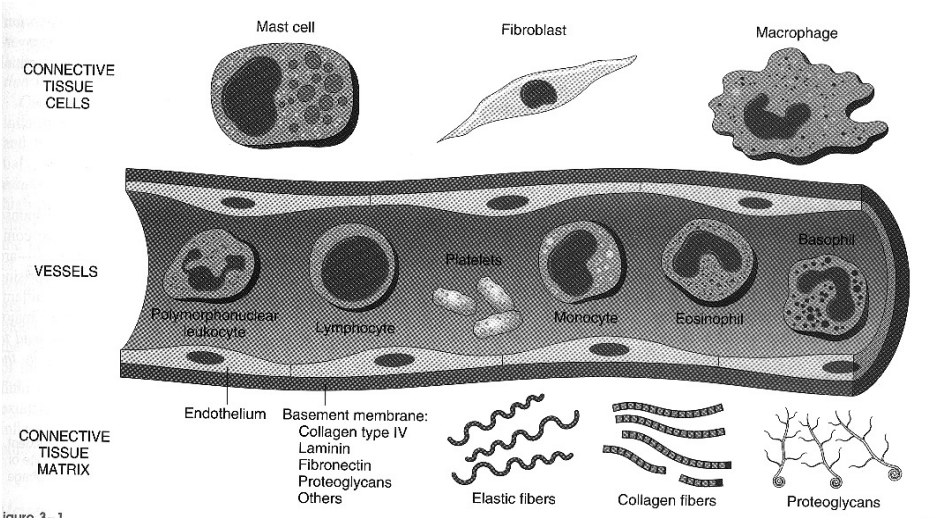
- **emigration of WBC's to area of damage**

D. Grand old terms

- **tumor**
- **rubor**
- **calor**
- **dolor**
- **functio laesa**

E. Terms you must know !!!!

- **EXUDATE**
    - **cell count?**
    - **protein**
    - **specific gravity**
- **TRANSUDATE**
    - **cell count?**
    - **protein**
    - **specific gravity**
- **EDEMA vs EFFUSION**



igure 3–1

ntravascular cells and connective tissue matrix and cells involved in the inflammatory response.

II. Vascular changes

A. Vasodilatation (actually, there is transient and evidently inconsequential initial constriction, forget about it.)

- increases blood flow

B. slowed transit time - **increased permeability**

1. Venuoles and to a lesser extent capillaries, not arterioles

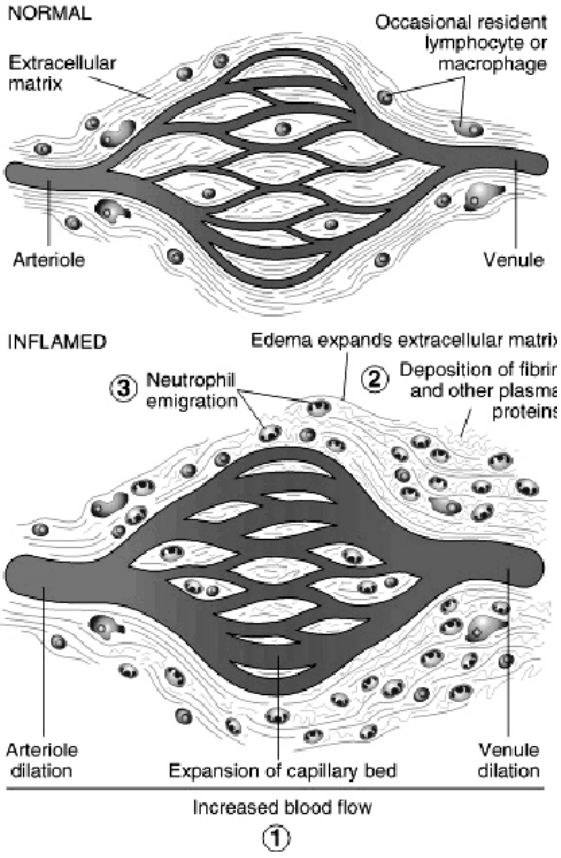
- endothelial cell contraction - physiological
- endothelial damage - pathological - vessels themselves are hurt

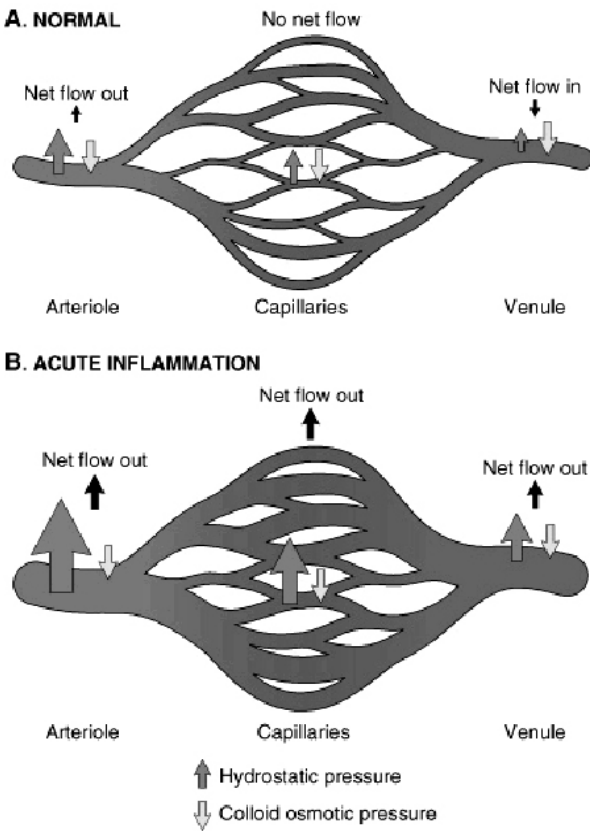
2. Stasis

3. outpouring of proteins and fluid

- edema

- "tumor" -swelling





C. Leukocyte margination and emigration. Endothelial cells are cloaking devices.

1. Adhesion

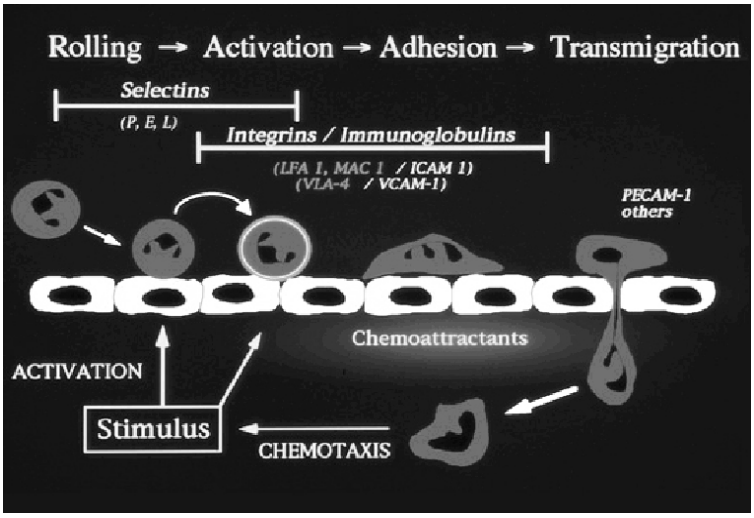
- selectins

- immunoglobulins

- integrins

2. leukocyte diapedesis - venuoles

3. chemotaxis
    - "bacterial products"
    - C'5 and C'3 products
    - cytokines
    - others from activated killing pathways in leukocytes



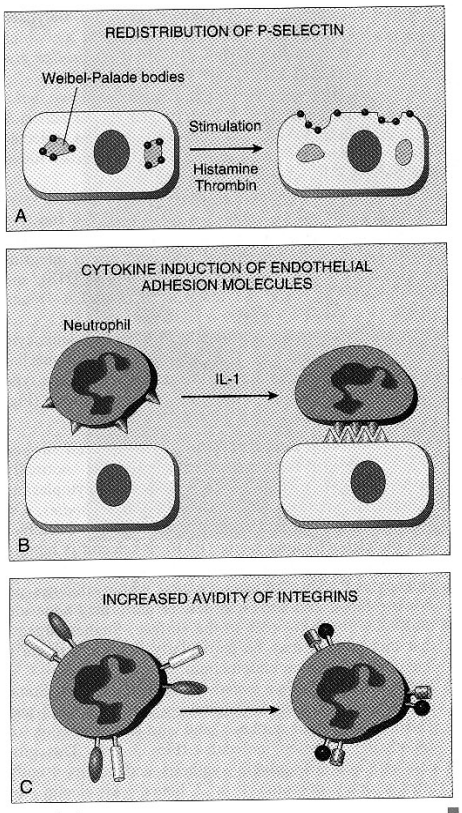


Figure 3–8 ■

Three mechanisms of mediating leukocyte endothelial adhesion. *A*, Redistribution of P-selectin. *B*, Cytokine activation of endothelium. *C*, Increased binding avidity of integrins (see text).

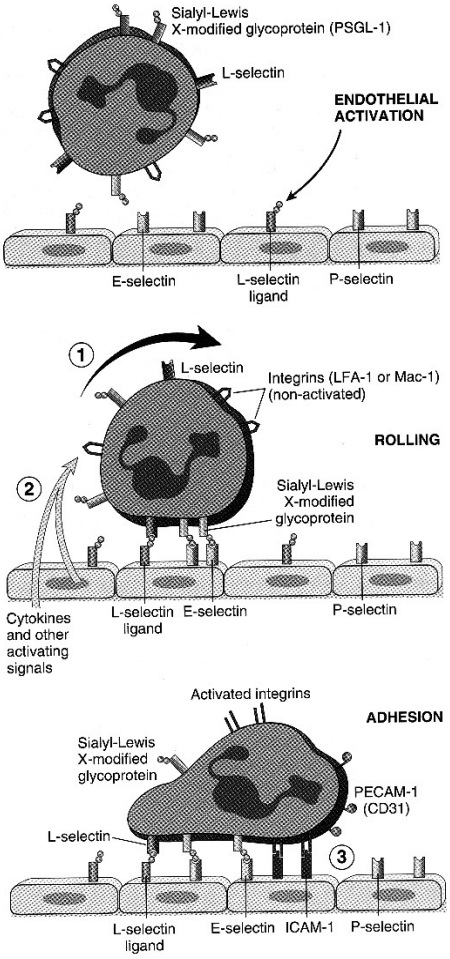
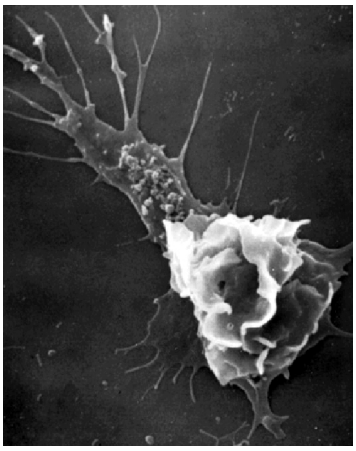


Figure 3–9 ■

Molecules mediating various steps of neutrophil extravasation in endothelial-neutrophil interaction. *Top, Endothelial activation:* Inflammatory mediators have upregulated the expression of E- and P-selectins on the endothelial cells. *Rolling*—E- and P-selectins bind sialyl-Lewis X on specific ligands, such as PSGL-1 and ESL-1, while L-selectin on the leukocytes binds carbohydrate moieties on ligand expressed on the endothelial cell. *Firm adhesion*—The leukocytes become activated by chemokines and increase the avidity of their β2 integrins for ICAM-1 expressed by endothelial cells. *Bottom, Transmigration*—leukocytes pass between adjacent endothelial cells, using PECAM-1 and other molecules. The colored balls represent sugar moieties and the various receptors are consistently color coded.

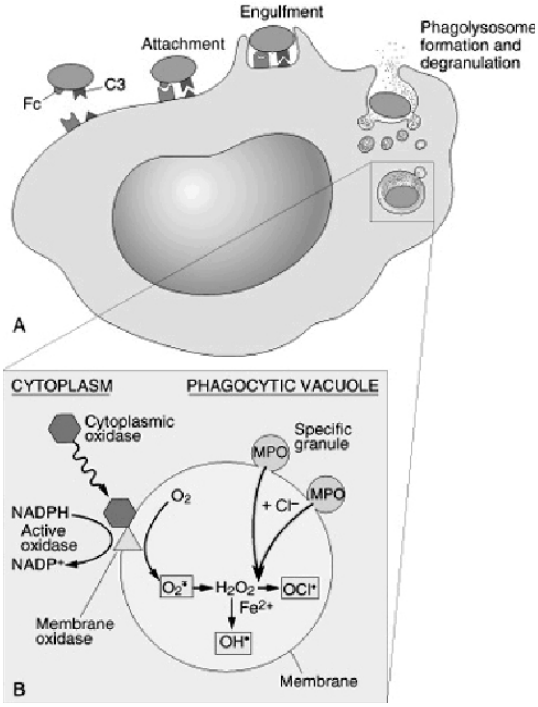
4. Phagocytosis



- recognition - ingestion

- killing

  - myeloperoxidase system
  - cationic rich protein
  - peroxides and superoxide ion
  - halide system



Ref: Robbins; Pathological Basis of Disease

5. Release of leukocyte products

- increases response intensity
- lysozyme
- oxygen derived materials
- can cause tissue damage on its own - "friendly fire" whatever the hell that can be.

6. Problems of response - practically everything you can think of

- absence of adhesive proteins

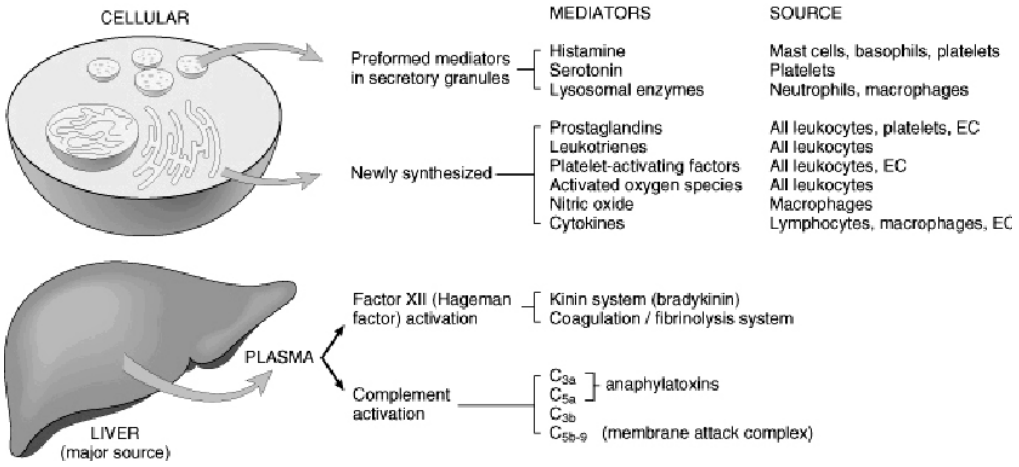
- can't phagocytize

- can't kill the bug
    - *Chronic Granulomatous Disease* - auto and X-linked types

III. Chemical mediators

- vasoactive amines
- proteases
- arachidonic acid, prostaglandins and things I can't spell
- platelet substances
- cytokines
- nitric oxide
- leukocyte constituents

A. Orchestrate and contain the response



B. Vasoactive amines

1. Histamine - know a little about this one

- mast cells and basophils - IGE
- dilates arterioles and increases vascular permeability
    - causes constriction of larger arteries
- all manner of things cause its release

2. Serotonin - IGE

- platelet
- increased permeability

C. Proteases

1. Bradykinin

- vasodilator and increased permeability

- Hagaman

  - negatively charged surfaces
  - prekallikrein etc...

2. Complement system products

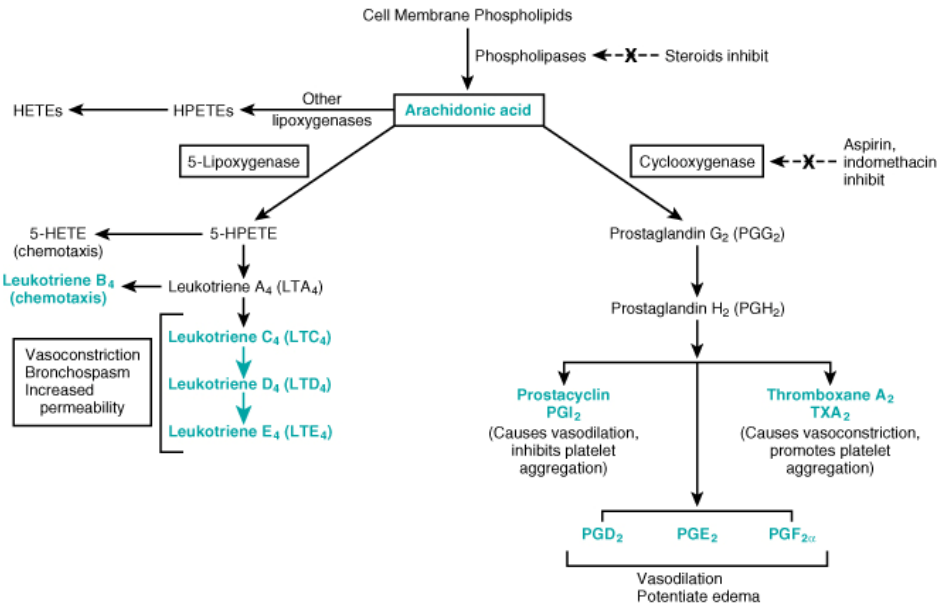
- C'3 and C'5 products

D. Arachidonic acid derivatives

1. autocrines - locally active, short lived hormones

2. vasodilation, pain, fever

3. know general properties



E. Platelet activating factor

1. phospholipid

2. more than just platelet activation

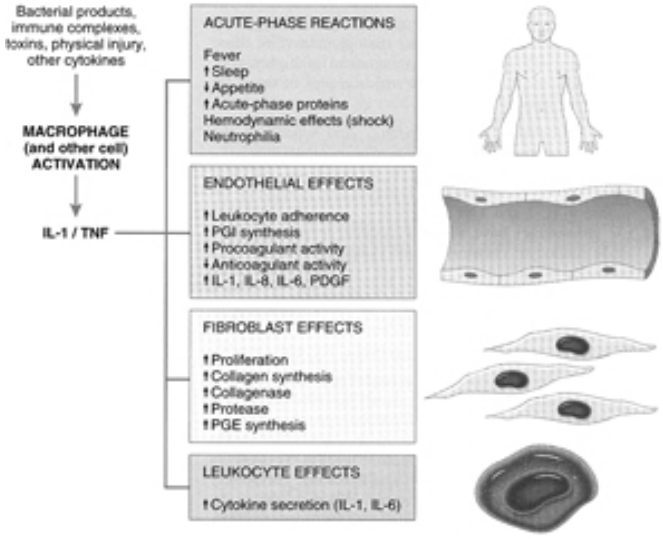
3. enhances production of mediators

F. cytokines - these will come up in greater detail when we do repair

- autocrines

- paracrines

- stimulates the endothelial cells in preparation for repair and production of new vessels

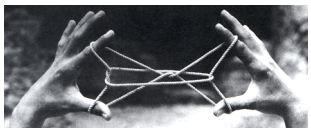


G. Nitric oxide

- smooth muscle relaxer

- platelet aggregation

- macrophage NO is important as a bug killer



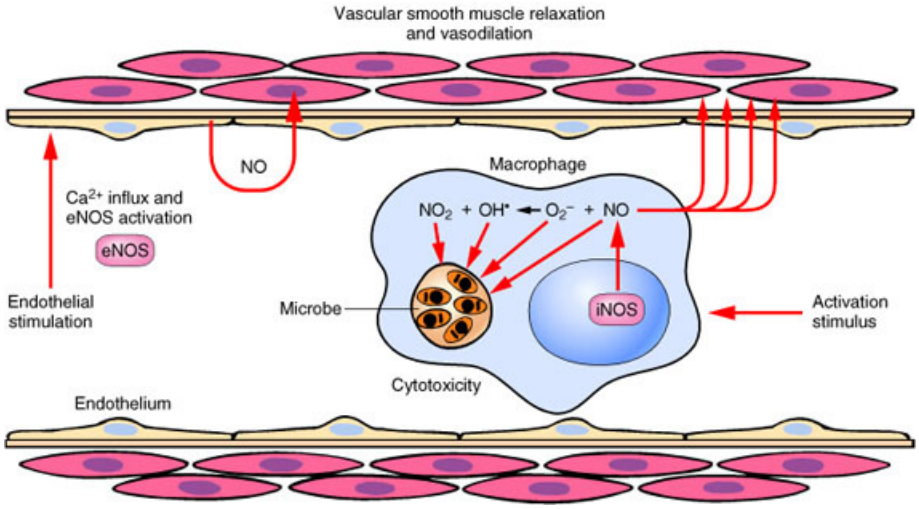
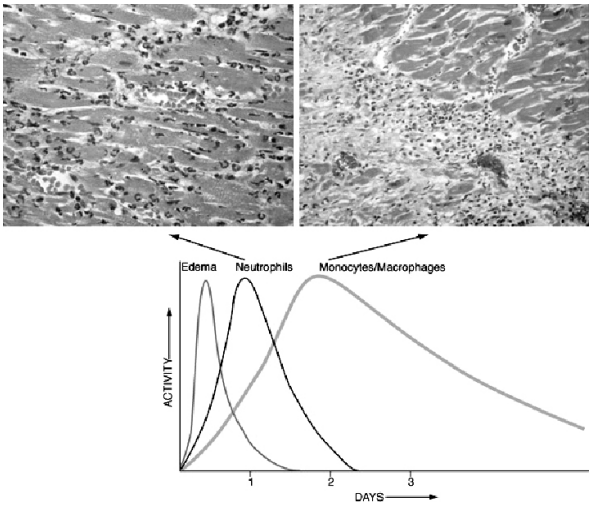


TABLE 2–5 Summary of Mediators of Acute Inflammation

Mediator	Source	Action		
		Vascular Leakage	*Chemotaxis*	*Other*
Histamine and serotonin	Mast cells, platelets	+	–	
Bradykinin	Plasma substrate	+	–	Pain
C3a	Plasma protein via liver	+	–	Opsonic fragment (C3b)
C5a	Macrophages	+	+	Leukocyte adhesion, activation
Prostaglandins	Mast cells, from membrane phospholipids	Potentiate other mediators	–	Vasodilation, pain, fever
Leukotriene B_4	Leukocytes	–	+	Leukocyte adhesion, activation
Leukotriene C_4, D_4, E_4	Leukocytes, mast cells	+	–	Bronchoconstriction, vasoconstriction
Oxygen metabolites	Leukocytes	+	–	Endothelial damage, tissue damage
PAF	Leukocytes, mast cells	+	+	Bronchoconstriction, leukocyte priming
IL-1 and TNF	Macrophages, other	–	+	Acute-phase reactions, endothelial activation
Chemokines	Leukocytes, others	–	+	Leukocyte activation
Nitric oxide	Macrophages, endothelium	+	+	Vasodilation, cytotoxicity

IV. OK so there's an acute inflammatory response, what happens now?

A. This is just the begining and the healing process is starting at almost the same time.



B. Outcomes of just acute inflammation (remember the exudates?)

1. Complete resolution, restoration of function

2. Connective tissue replacement, in other words scar formation
   - binds the broken members back together

3. **Abscess**
   - appearance

   - circumstances; which type of bug? Etc..

4. Progression to **chronic inflammation**

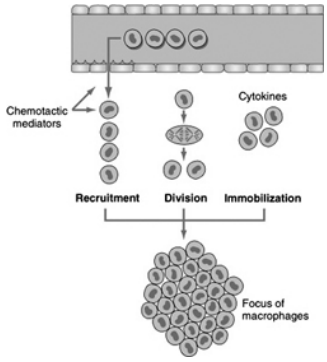
V. **Chronic inflammation**

A. Prolonged inflammation (weeks or months) in which active inflammation, **tissue destruction**, and healing all proceed simultaneously. "Low grade" and "smoldering"

B. Inflammatory cell type?

- differs from acute Can build the army on site! Big advantage.

- lymphocyte
- plasma cell
- macrophage
- more fibrosis and angiogenesis than acute



C. Circumstances

1. Persistent infection or exposure to toxin

2. Specific types of organisms (for some bugs, this is the only thing that works)

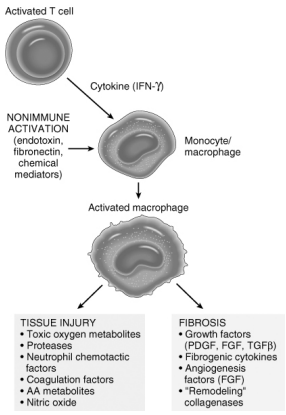
- **Granuloma**; simply wall it off, but always keep a watch on it!
  - this bugger often gets confused with an abscess, be sure you know the difference! (Hint: good test question here.)

- **caseous and non-caseous**

3. Autoimmune diseases (self perpetuating immune injury)

D. Mononuclear response (Why do we call it mononuclear? Can multinucleated cells be a part of this response?)

1. Macrophages; these guys are the big enchiledas for chronic inflammation



- fixed (no, not like you have your dog fixed)

- circulating

- recruitment

- local proliferation

- they stay at the site and produce lots of active substances

    - inflammatory and tissue injury substances

    - repair agents such as growth and angiogenesis factors

VI. Overview - cell growth - regulation - adaptation

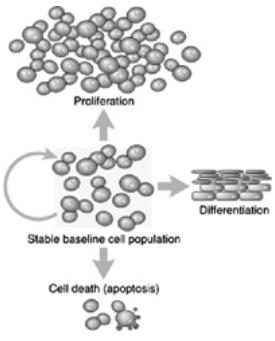
A. Integral part of repair and restoration of function, as well as adaptation to meet new demands on the system.

1. Regeneration - replacement - epithelium and RBC

    - preservation of underlying "framework" important for others

2. Replacement by connective tissue (scar), known as **fibroplasia**

3. Combination of the 1 and 2 in some percentage.



B. Differentiation, it's a balancing act that goes on all the time

1. Environment

2. Stimulus

    - growth

- death

3. Adaptation or alteration
   - **hyperplasia**
   - **hypertrophy**
   - **atrophy**
   - **metaplasia**

VII. Cell growth and categories

A. A great deal has recently been learned about cell growth and regulation. We need to know the basics.

1. Growth cycle: G_1 - S - G_2 - Mitosis - permanent vs quiescent or stable

2. Promoters and so-called competence factors
   - EGF
   - PDGF
   - TGF-alpha
   - VEGF
   - FGF

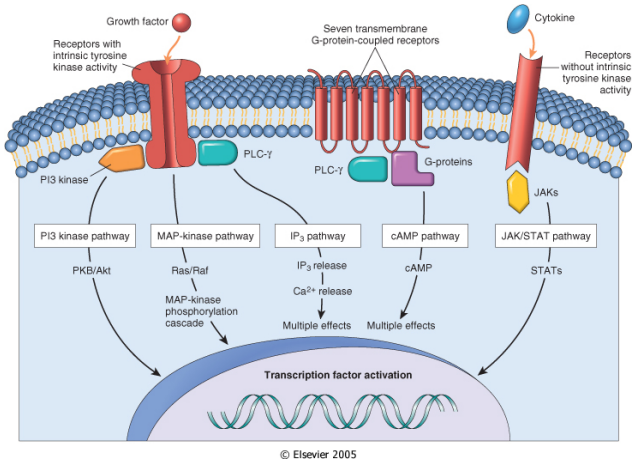
3. Transduction and second messengers
   - transmission of signal into the appropriate cell and initiation of growth or differentiation.
     - G-proteins
     - *ras family proteins*

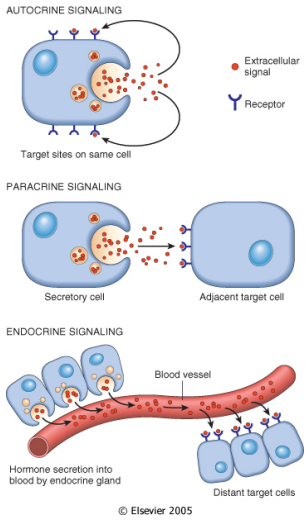
4. Gene expression resulting in cell division
   - *c- myc*

- *c-jun*

5. *Cyclins*

- complex with *cdc kinases* to phosphorylate the proteins involved in mitosis.





B. Inhibitory factors

1. "Contact inhibition"

2. Decrease levels of growth promoters

3. Decreased levels of inflammatory mediators

C. Categories of cells and tissues

1. Labile or continuously dividing
   - gut epithelium
   - RBC

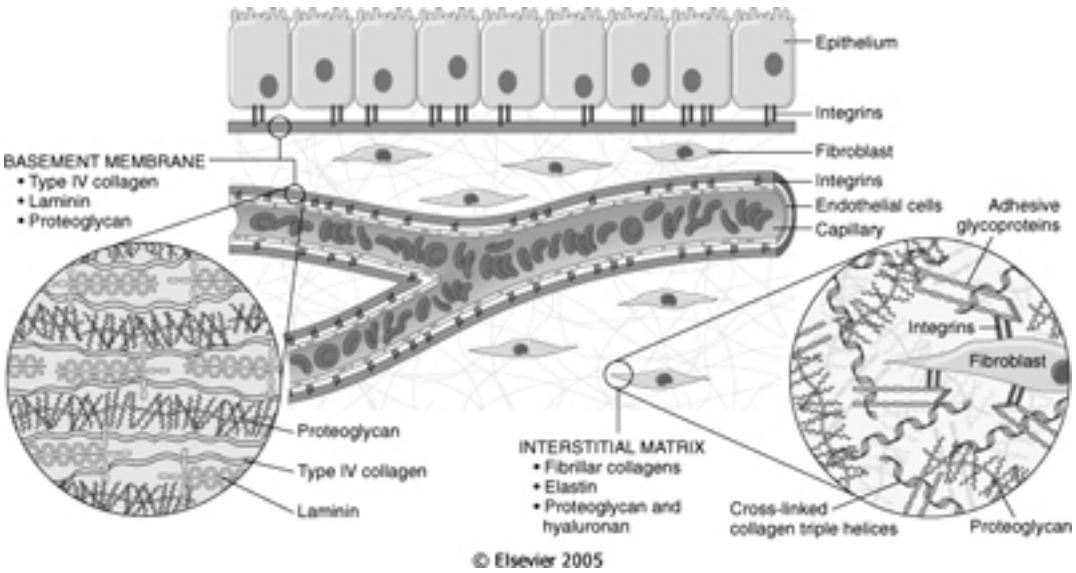
2. Stable or "quiescent" cells
   - hepatocyes

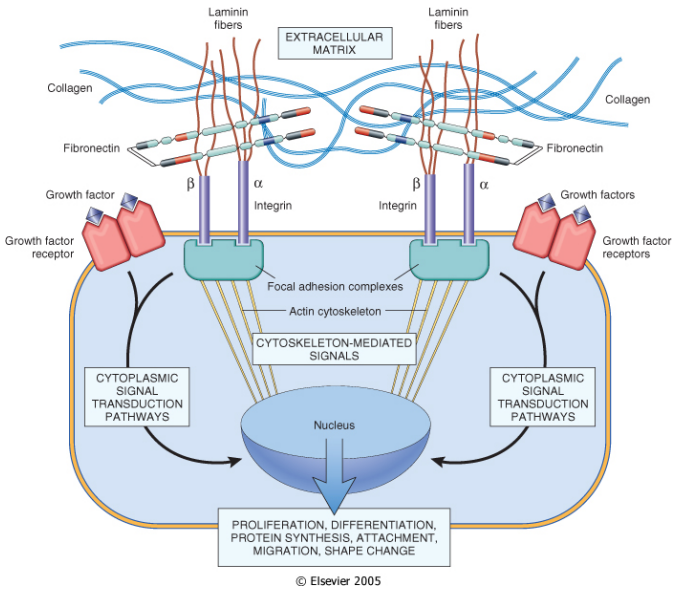
- renal tubular epithelium
    - preservation of stroma very important - framework - scaffold
    - basement membrane

3. Permanent or nondividing cells
    - neurons
    - cardiac muscle
    - skeletal muscle (?) Special situation
    - adult stem cells

C. Contribution of extracellular goop - probably much more than we realize now.

1. General composition - you know collagen, laminin and so on
2. Specialized proteins
    - fibronectin - I think this is pretty important
        - have some understanding of the various domains





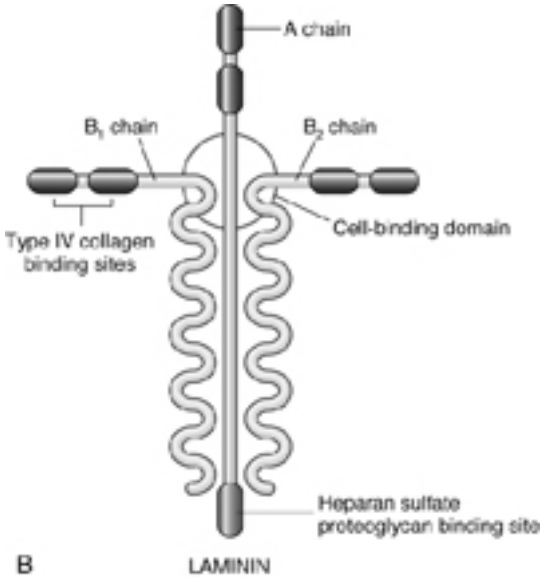


TABLE 3–1 Growth Factors and Cytokines Involved in Regeneration and Wound Healing

Cytokine	Symbol	Source	Functions
Epidermal growth factor	EGF	Platelets, macrophages, saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor alpha	TGF-α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and certain epithelial cells
Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of epithelial and endothelial cells, and of hepatocytes; increases cell motility
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells (see Table 3–3)
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, marcrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction; remodeling; inhibits platelet aggregation; regulates integrin expression
Fibroblast growth factor-1 (acidic), -2 (basic) and family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts, and many tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, fam wound contraction and matrix deposition
Transforming growth factor beta (isoforms 1, 2, 3); other members of the family are BMP and activin	TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; regulates integrin expression and other cytokines; induces TGF-β production
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Insulin-like growth factor-1	IGF-1	Macrophages, fibroblasts and other cells	Stimulates synthesis of sulfated proteoglycans, collagen, keratinocyte migration, and fibroblast proliferation; endocrine effects similar to growth hormone
Tumor necrosis factor	TNF	Macrophages, mast cells, T lymphocytes	Activates macrophages; regulates other cytokines; multiple functions
Interleukins	IL-1, etc.	Macrophages, mast cells, keratinocytes, lymphocytes, and many tissues	Many functions. Some examples: chemotactic for PMNs (IL-1) and fibroblasts (IL-4), stimulation of MMP-1 synthesis (IL-1), angiogenesis (IL-8), TIMP synthesis (IL-6); regulation of other cytokines
Interferons	IFN-α, etc.	Lymphocytes and fibroblasts	Activates macrophages; inhibits fibroblast proliferation and synthesis of MMPs; regulates other cytokines

BMP, bone morphogenetic proteins; PMNs, polymorphonuclear leukocytes; MMPs, matrix metalloproteinases; HA, hyaluronic acid; TIMP, tissue inhibitor of matrix metalloproteinase.
Modified from Schwartz SI: *Principles of Surgery*, McGraw Hill, New York, 1999.

VIII. Adaptations and modifications

A. General stuff

- response to something
- physiological
- pathological
- up and down-regulation
- induction of new proteins
- major modifications to altered environment

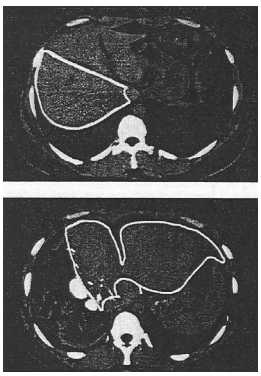
B. Hyperplasia - increase in **numbers** of cells, therefore stimulation of cell division

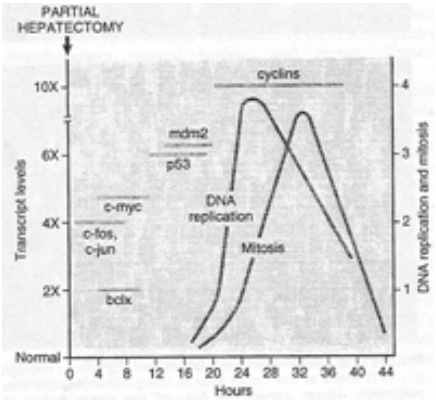
1. Physiological

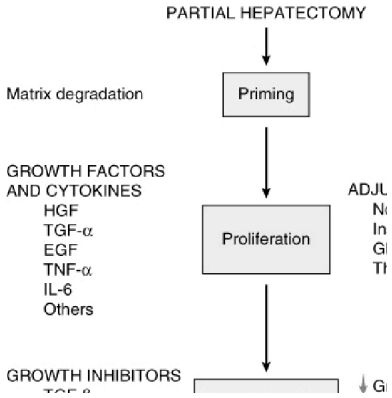
- hormonal mediated - pregnancy and breast growth

- compensatory - restoration of cells after injury or disease

- stable, labile and permanent cell populations
- liver after hepatitis







2. Pathological

- excessive or unbalanced
- exogenous estrogens

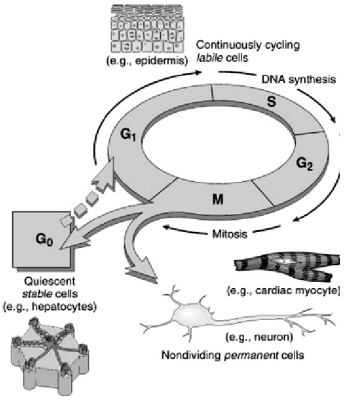
IX. Repair

A. What's the best you can hope for?

- labile

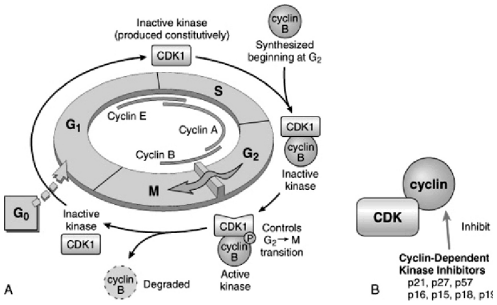
- stable

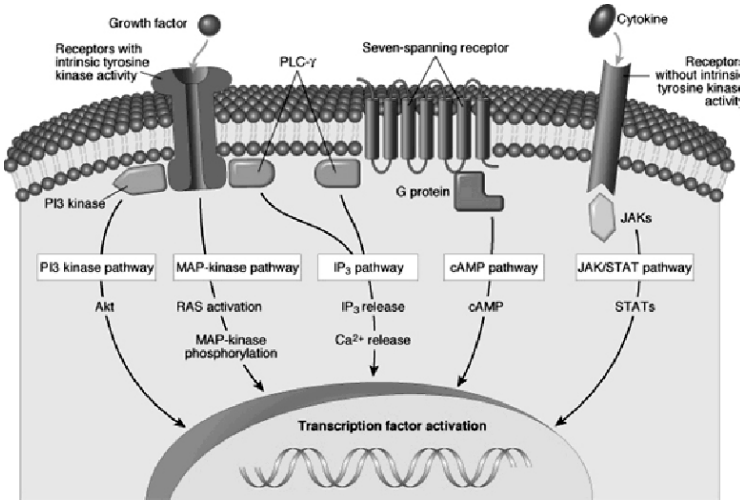
- permenant



B. Complete restoration of function and no evidence that anything ever happened

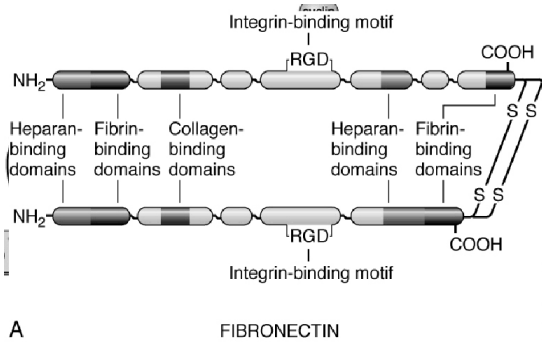
C. Signaling Mechanisms:



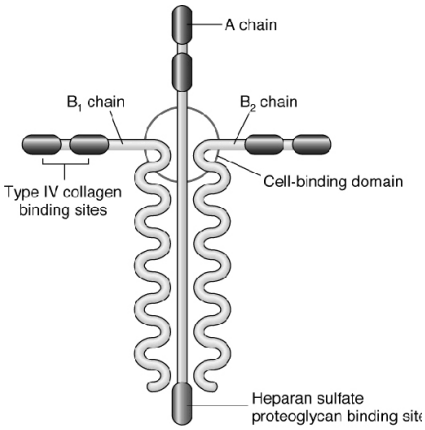


1. Stimulation of cell growth for tissue replacement:

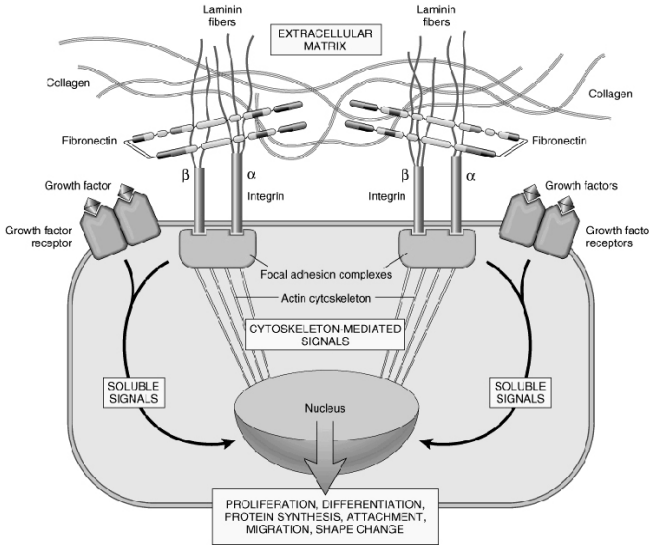
Underlying framework must be there!



A FIBRONECTIN



B LAMININ



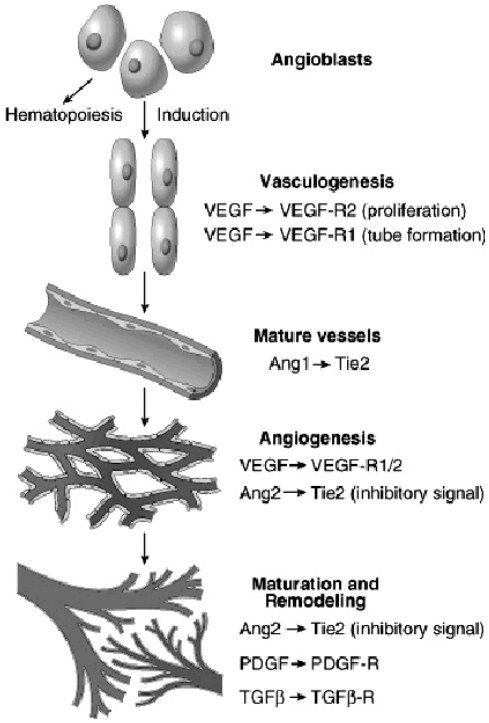
D. Repair by connective tissue, simply bind the broken members back together

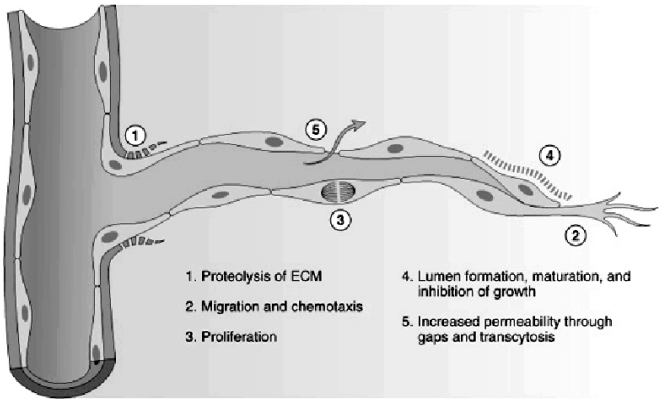
- **GRANULATION TISSUE;** OK this is not granuloma, be sure you know the difference!!

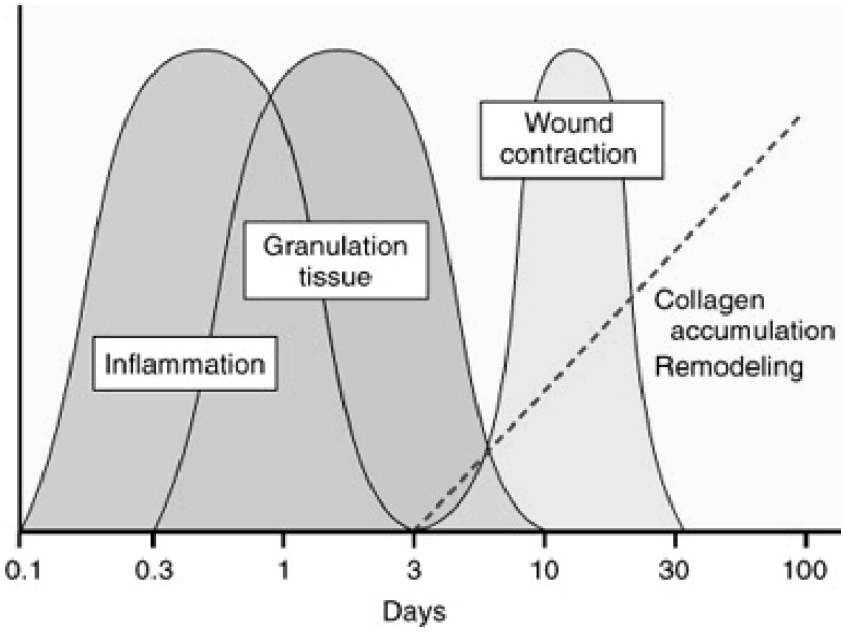
- fibroblasts

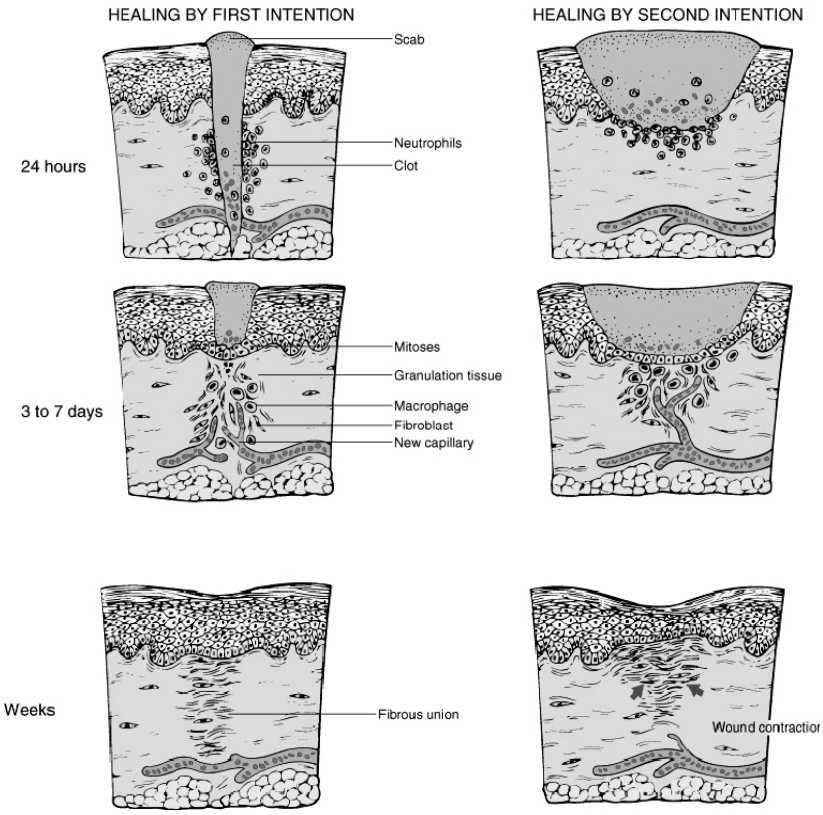
- angioblasts

- “guiding proteins”



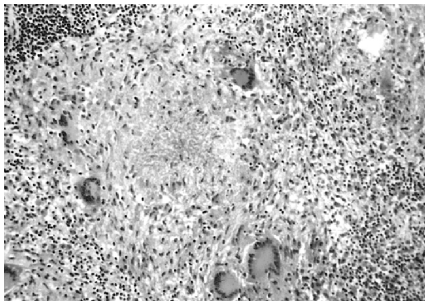






E. **Granulomatous inflammation**; OK, this is not granulation tissue, although there will be some element of fibrosis and angiogenesis.

- specialized response to an agent that cannot be eliminated or removed from the body.
- cellular constituents
  - giant cells
  - **EPITHELOID APPEARING MACROPHAGES**
  - lymphocytes



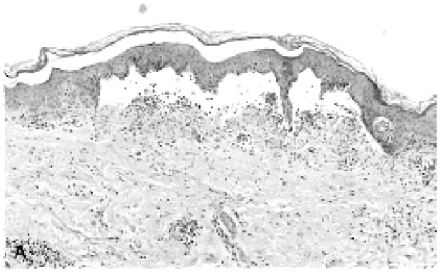
- fibroblasts

- circumstances
    - foreign matter
        - silica, coal dust, wooden splinter
        - berylium
    - certain bugs
        - *tuberculosis*
        - fungi
        - parasites

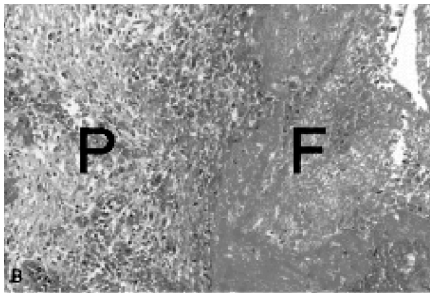
    - Who knows?
        - Sarcoidosis (non-caseating granuloma)

X. Commonly observed morphological patterns

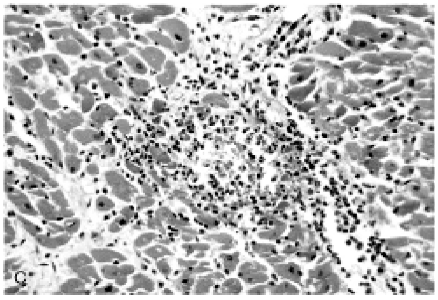
A. **Serous** (know what is meant by the term "effusion")



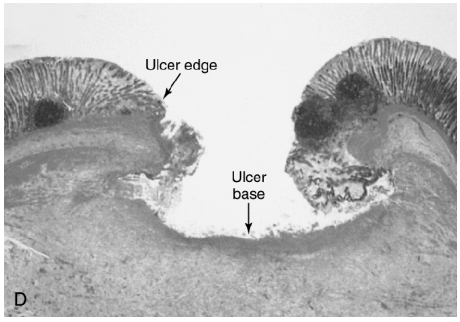
B. **Fibrinous**



C. **Suppurative or Purulent** (pus, what the heck is this?)



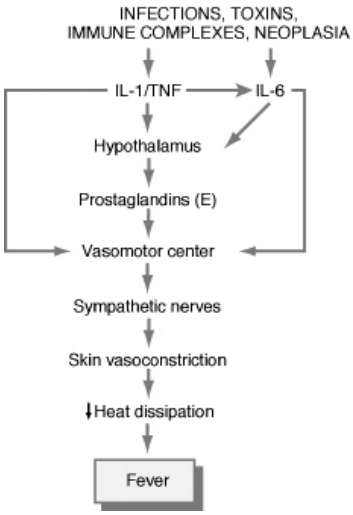
D. **Ulcer** (how is this thing ever going to heal?)



XI. OK, so you have a zit the size of marsh mellow on the end of your nose. What are the **systemic effects**?

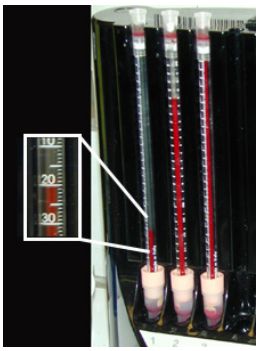
A. How do you feel?

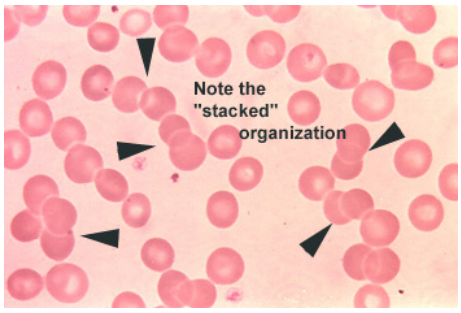
- local



- system wide

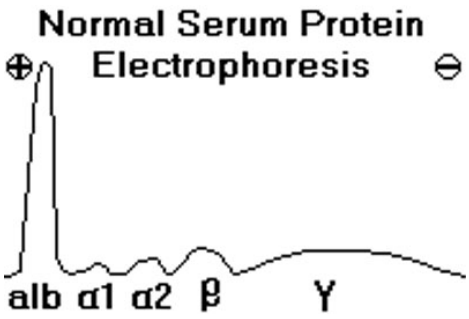
B. Serum proteins

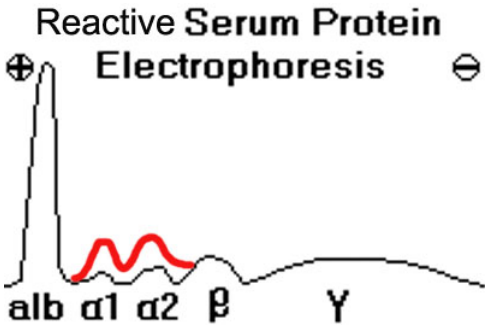




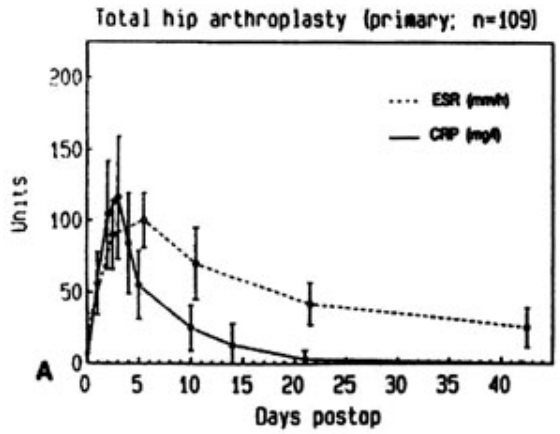
- "sedimentation rate"

- acute phase reaction proteins





- CRP

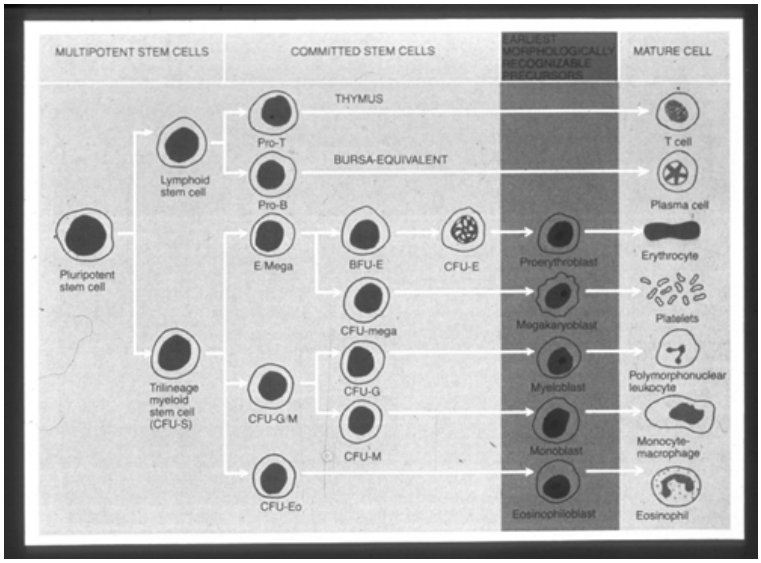


C. Inflammatory cell changes, blood and bone marrow?

- cell type

- maturity

- number



D. Iron levels (what do you think happens if the inflammatory process goes on

chronically?)

XII. Wound healing

- terms
- process
- outcome
- “too much”

A. Primary union or healing by first intention

B. Second intention

Note: The two above rely on the same participants, it’s just that the problems are of a different scale. No, you don’t have to memorize the types of collagen.

C. What can go wrong?

- re-injury

- foreign material in wound

- infection

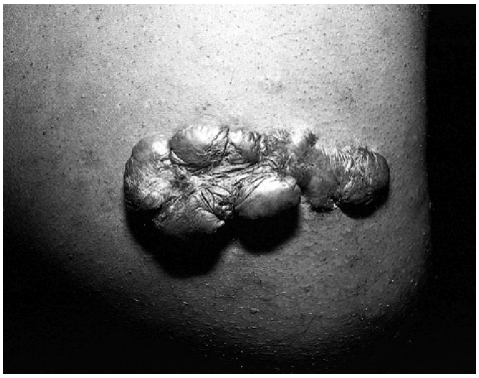
- poor nutrition

- genetic factors

    - bleeding and protein abnormalities
    - diabetes

- vascular supply

D. "Too much" response

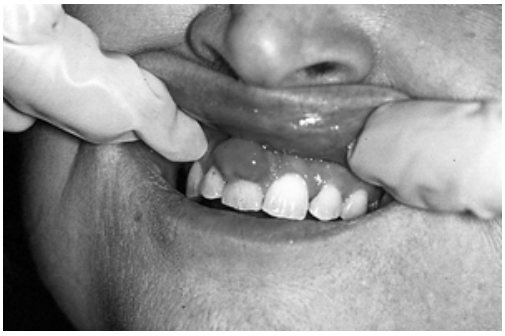


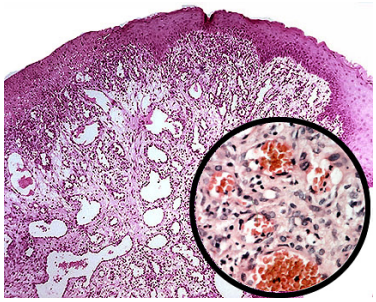
- keloid
    - who gets these?

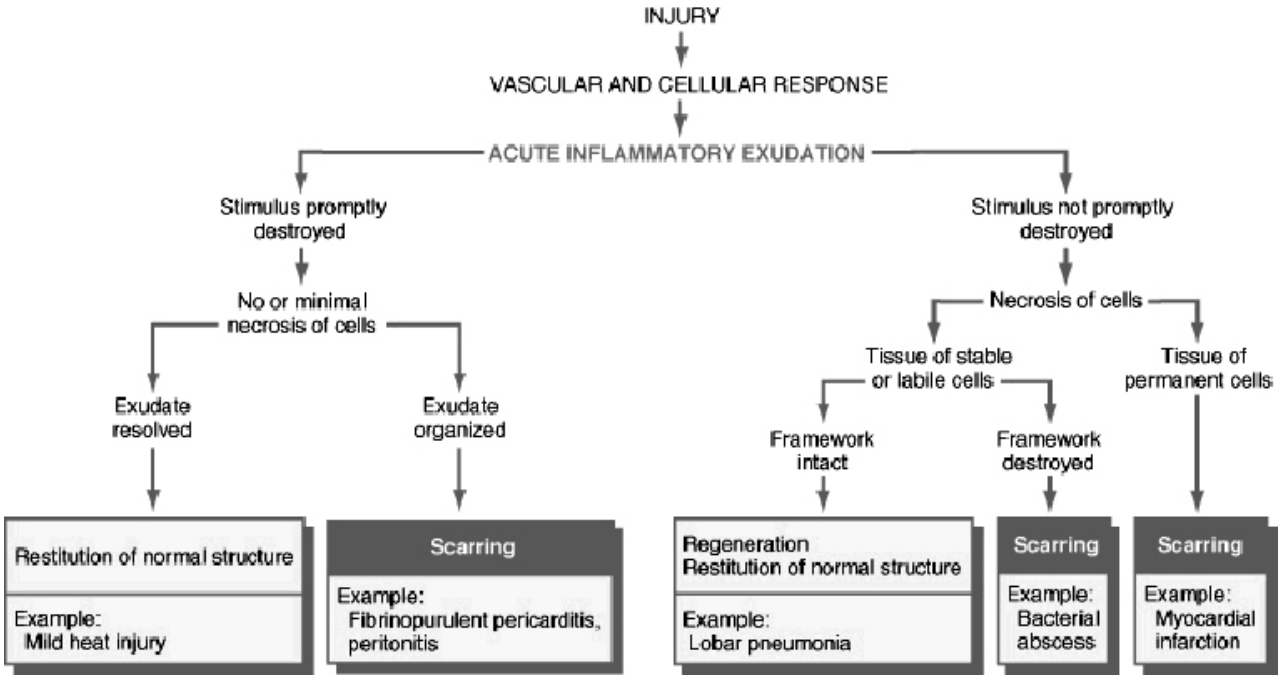
- desmoid (aggressive bugger!)

- "proud flesh"

- "pyogenic granuloma"
    - wrong on both counts, but that's what it's called!






INJURY
VASCULAR AND CELLULAR RESPONSE
ACUTE INFLAMMATORY EXUDATION
Stimulus promptly destroyed
Stimulus not promptly destroyed
No or minimal necrosis of cells
Necrosis of cells
Exudate resolved
Exudate organized
Tissue of stable or labile cells
Tissue of permanent cells
Framework intact
Framework destroyed
Restitution of normal structure
Example: Mild heat injury
Scarring
Example: Fibrinopurulent pericarditis, peritonitis
Regeneration Restitution of normal structure
Example: Lobar pneumonia
Scarring
Example: Bacterial abscess
Scarring
Example: Myocardial infarction