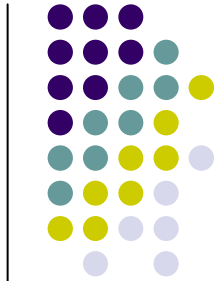


Week four lecture notes

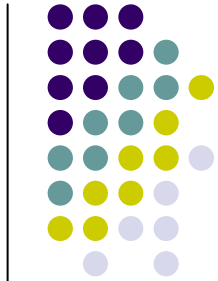
Why Study Wound Healing?

- 50 million surgical procedures performed each year in the US alone;
- Recovery from these procedures conservatively requires 250 million patient days -lost productivity and billions of dollars in lost or supplemental earnings;
- Despite the technical advances, complications resulting from surgery have not declined over the past 50 years;

Why Study Wound Healing?

- The wound healing response affects implant performance:
  - Blocks flow in catheters, cannulas and infusion pumps;
  - Forms impedance barriers around electrodes, drug delivery systems
  - Degrades polymeric materials; and,
  - Thrombus formation blocks dialysis membranes and vascular grafts,etc.

Wound Healing



- The process of tissue repair;
- A cascade of events that involves the interaction of various cellular and molecular components that acts in synchrony to effect wound closure by forming new tissue;
- The process can be understood as progressing through multiple stages, but realistically takes place as a continuum.

Different Tissues have Different Capacities to Heal

Regenerative capacity varies:

High capacity

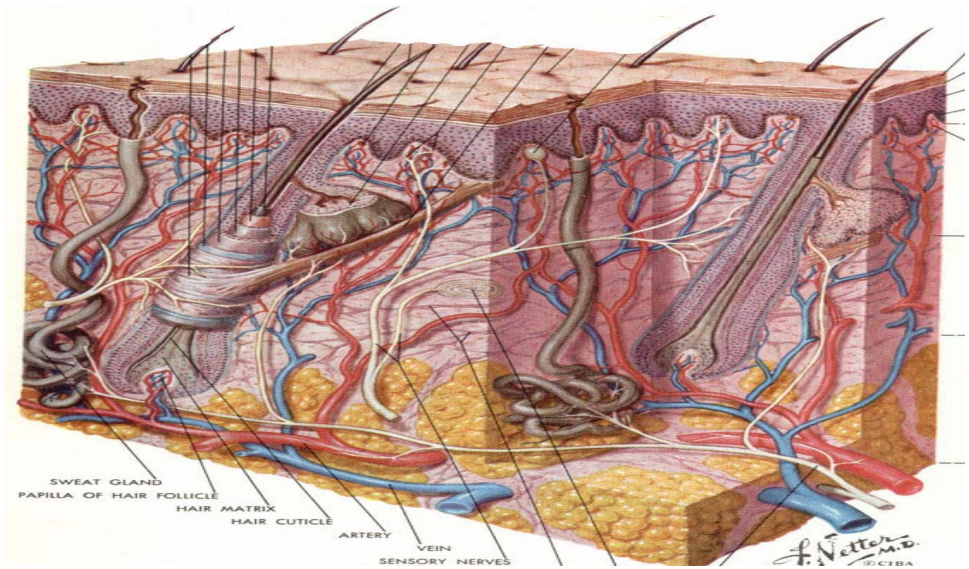
- epithelial, lymphoid, hematopoietic, mesenchymal tissues (cell types include fibroblasts, smooth muscle cells, osteoblasts, chrondrocytes, and endonthelial cells)
- Highly vascularized

Low capacity

- Nerve, muscle (skeletal and cardiac), cartilage

The Biology of Wound Healing - Vascularized Tissue

- Most of what we know has come from studies in skin of adult mammalian species;
- In general, wound healing proceeds slower and with more scarring as a function of increasing age



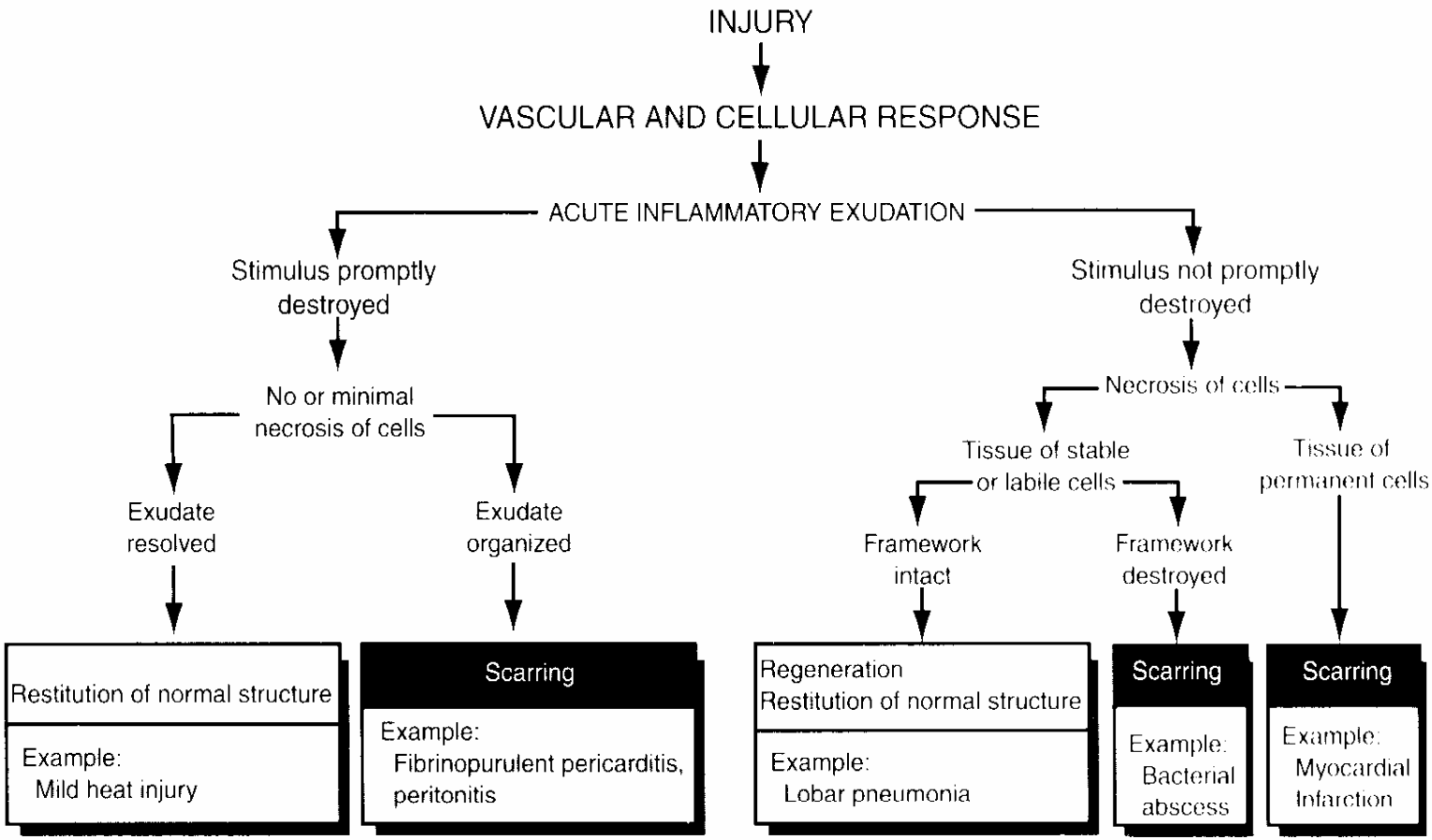
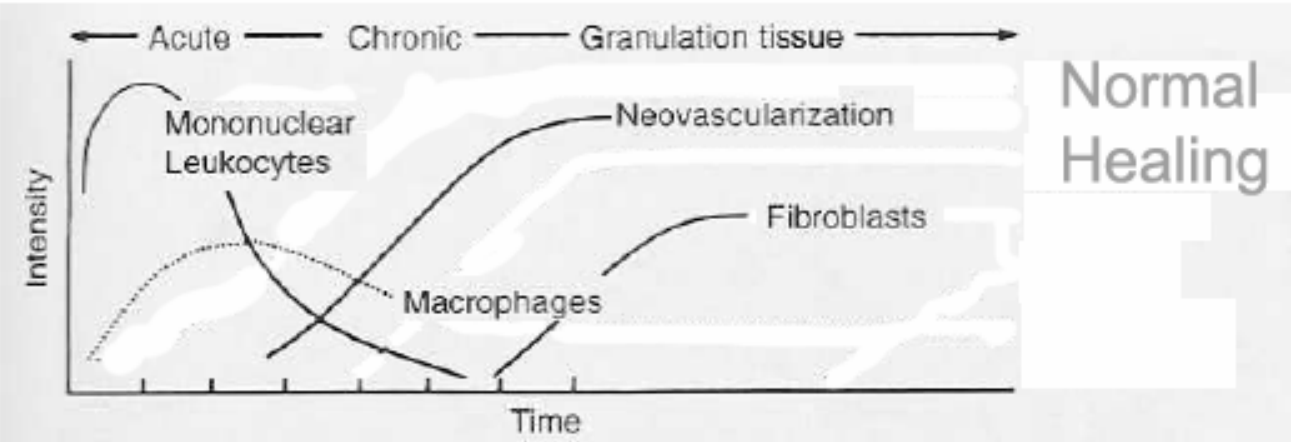


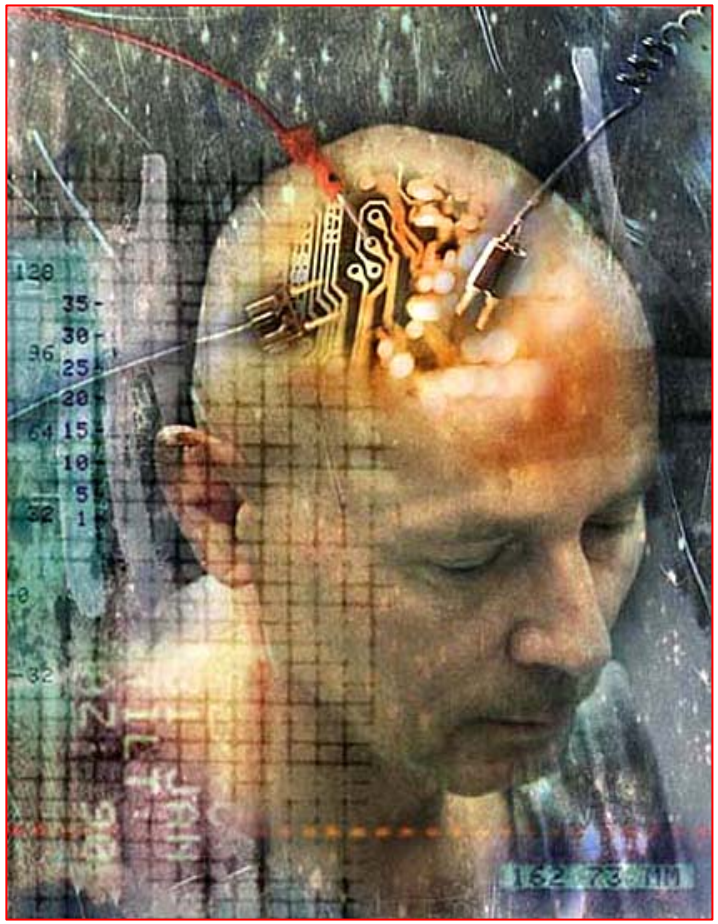
FIG. 11. Pathways of reparative responses after acute inflammatory injury. (Reproduced by permission from Cotran, R. S., Kumar, V., and Collins, T., 1999. *Robbins Pathologic Basis of Disease*, 6th ed. Saunders, Philadelphia.)

Sequence of Events Following Device Trauma :

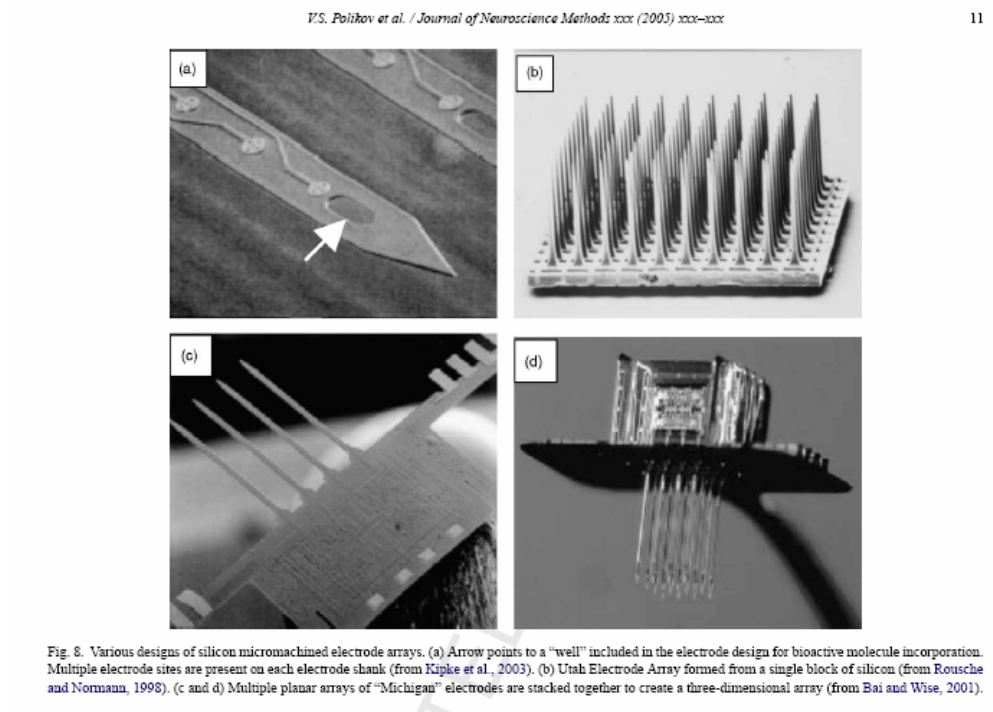
- Injury
- Acute inflammation
- Granulation tissue
- Mature extracellular matrix
- Wound contraction (Scar formation)



Neural Prosthetics



Neurotechnology/ brain machine interface market projection worldwide: > $7.2 billion (by 2008)



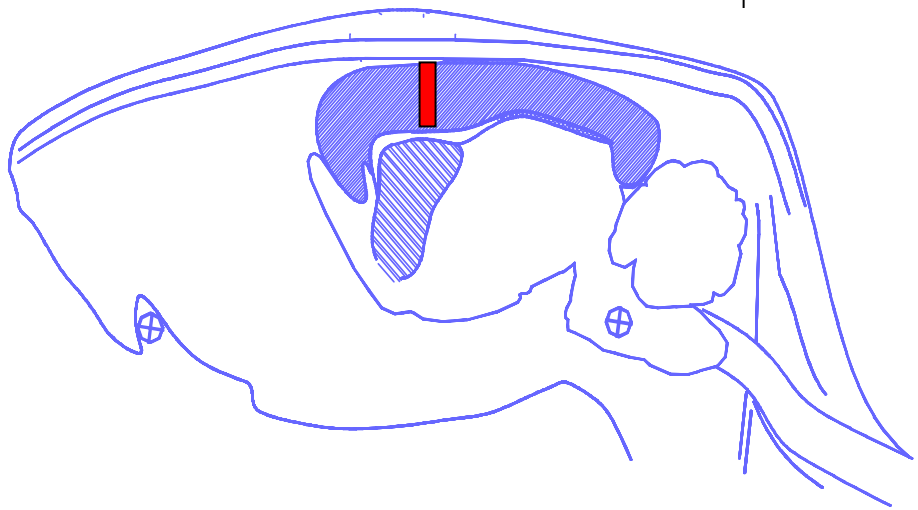
V.S. Polikov et al. / Journal of Neuroscience Methods xxx (2005) xxx–xxx 11

Fig. 8. Various designs of silicon micromachined electrode arrays. (a) Arrow points to a "well" included in the electrode design for bioactive molecule incorporation. Multiple electrode sites are present on each electrode shank (from Kipke et al., 2003). (b) Utah Electrode Array formed from a single block of silicon (from Rousche and Normann, 1998). (c and d) Multiple planar arrays of "Michigan" electrodes are stacked together to create a three-dimensional array (from Bai and Wise, 2001).

Methods (Electrode Implantation)

Sterilize and prepare electrode

Cerebral cortex
Adult rats (n=9)



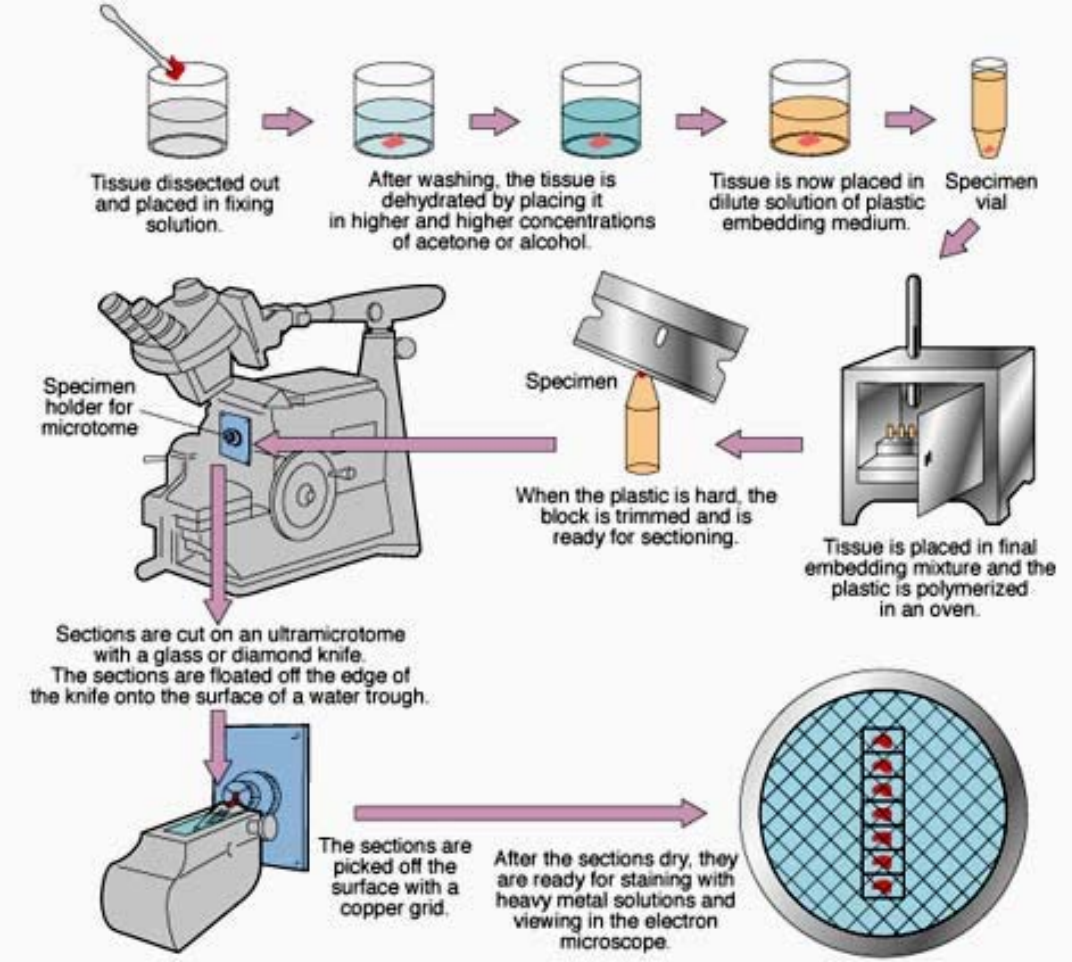
Sacrifice time points (weeks)

1 2 4 12

- **Retrieve electrodes**
- **Identify and quantify attached cells**

1. **Serial section**
2. **Immunostain**
3. **Microscopy**
4. **Digital images**
5. **Quantify reactivity**

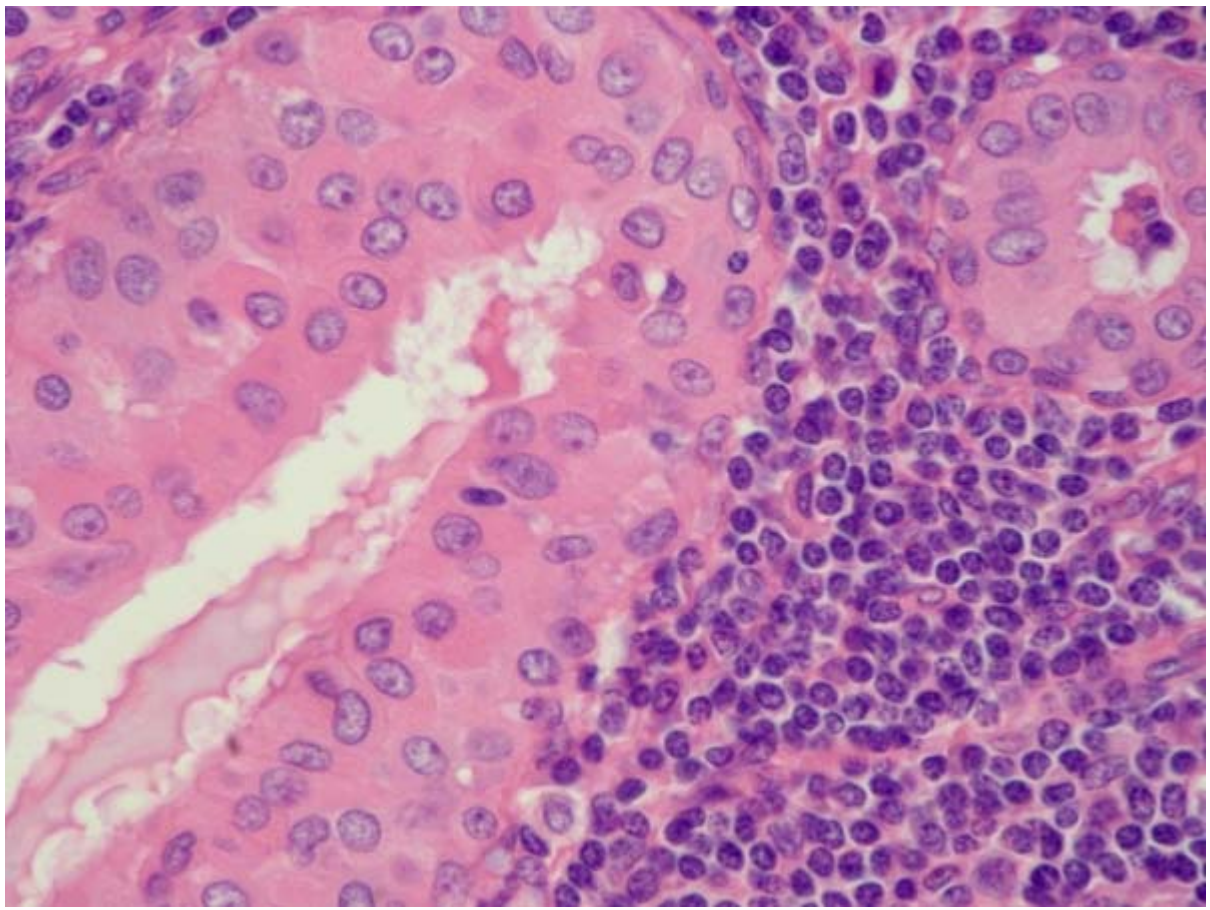
Making Tissue Sections



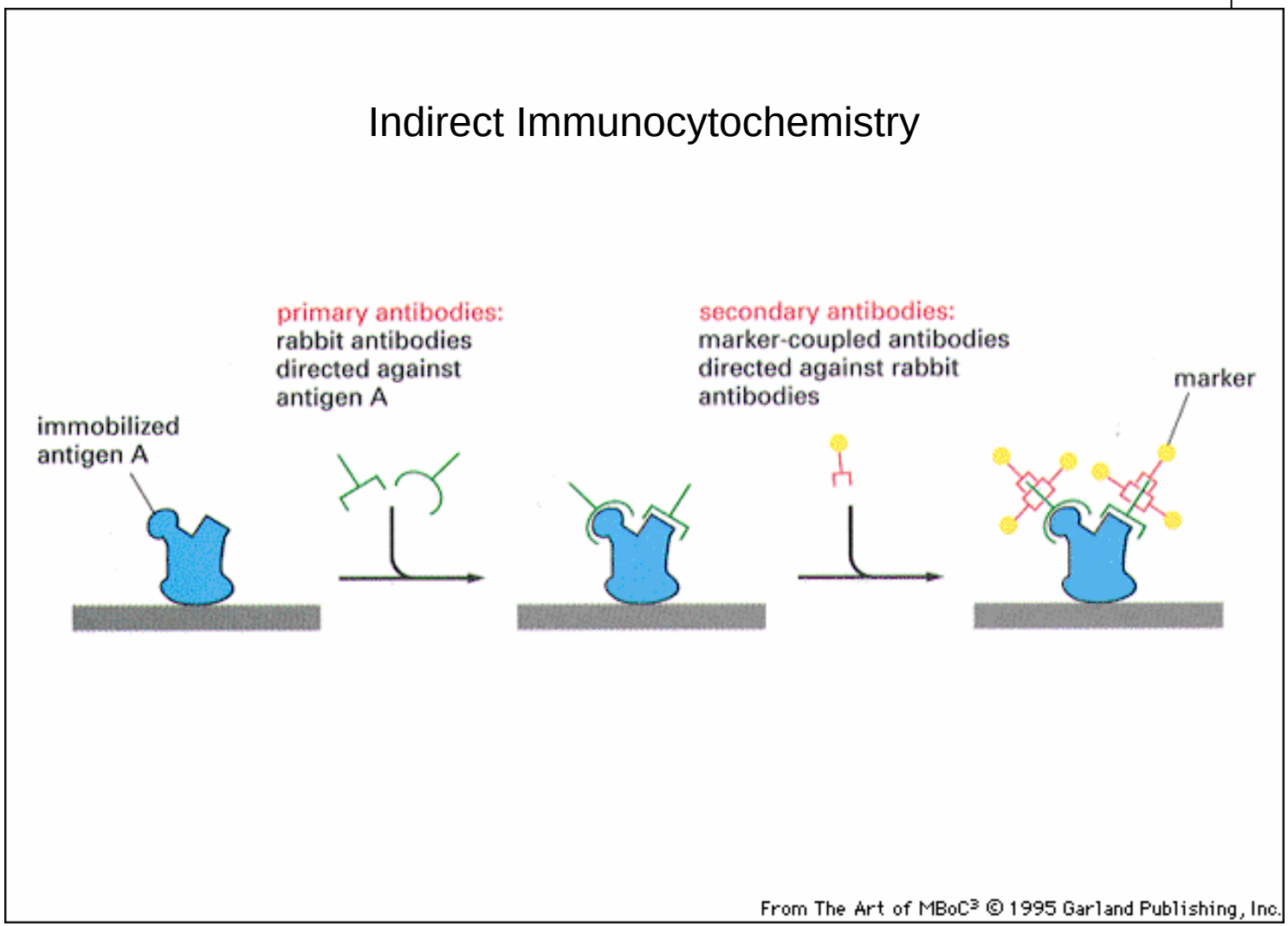
Microtomes

Hematoxylin and Eosin

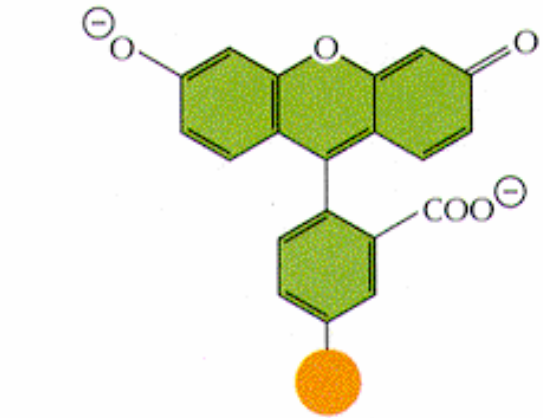
Background: hematoxylin-and-eosin, or H&E, is used for routine staining of tissue sections



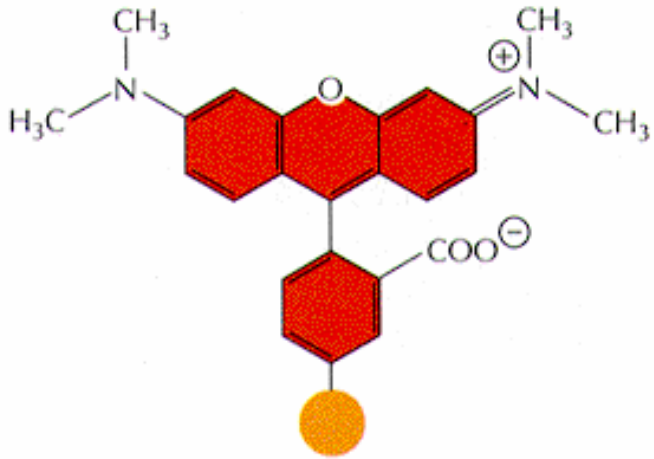
Antibodies are Used to Detect Specific Molecules



Flourescent Dyes

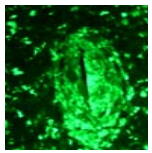


fluorescein (green)

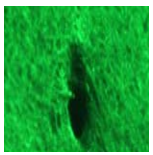


tetramethylrhodamine (red)

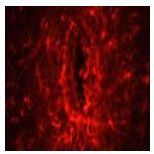
Primary antibodies used



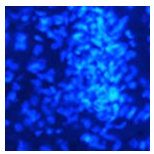
ED1: lysosomal glycoprotein, labels macrophages. Mouse IgG1



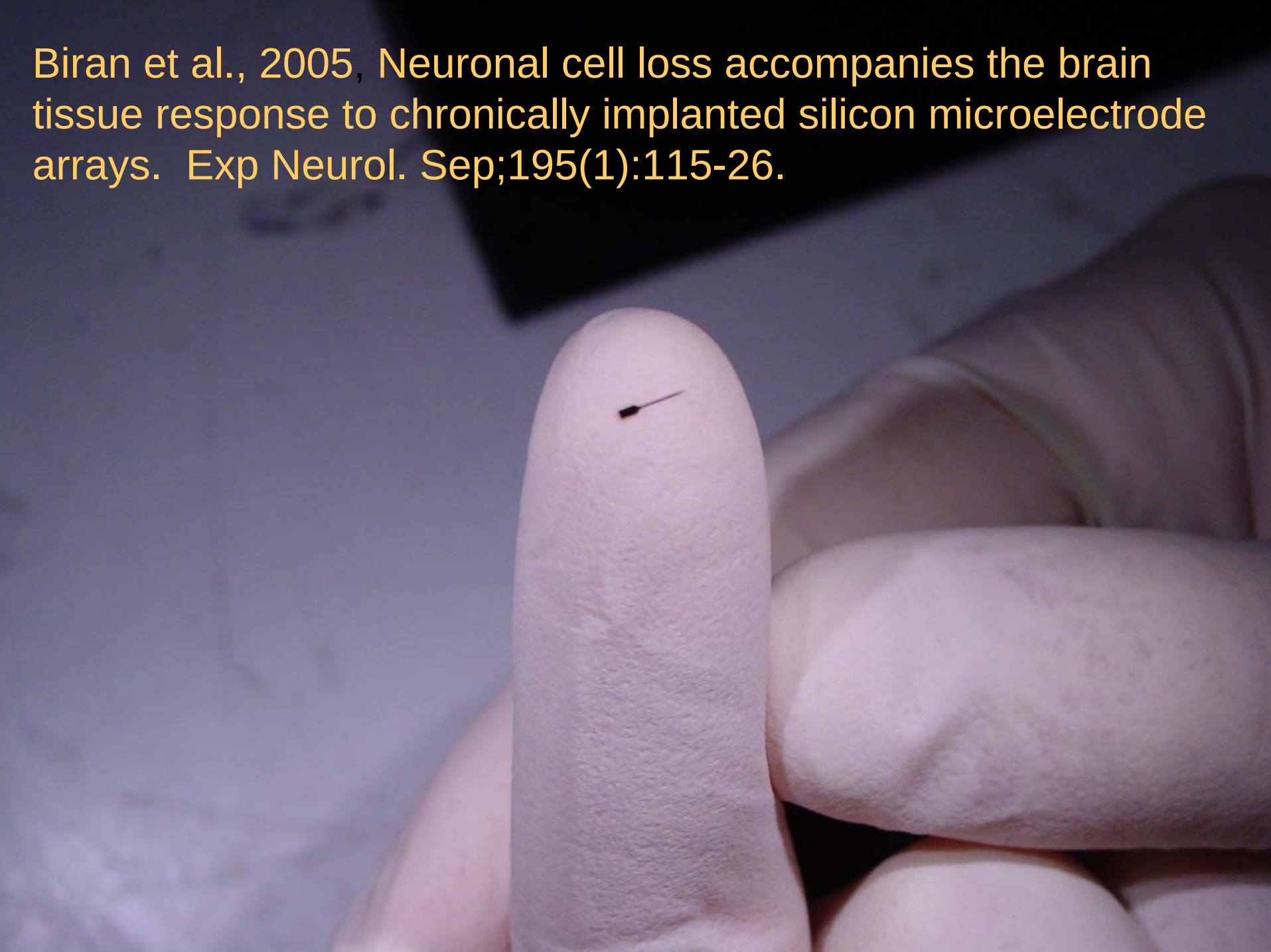
Neurofilament 160: medium neurofilament (type of intermediate filament), labels all neuronal processes. Mouse IgG1



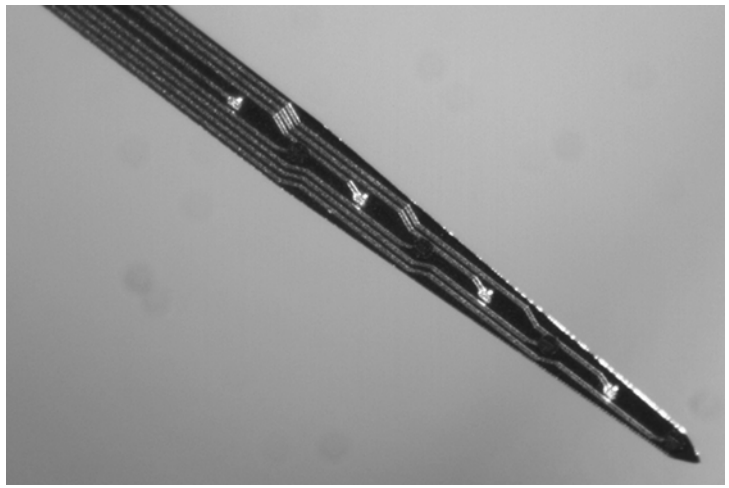
GFAP: glial fibrillary acidic protein, labels astrocytes or matrix producing cells. Rabbit IgG, polyclonal

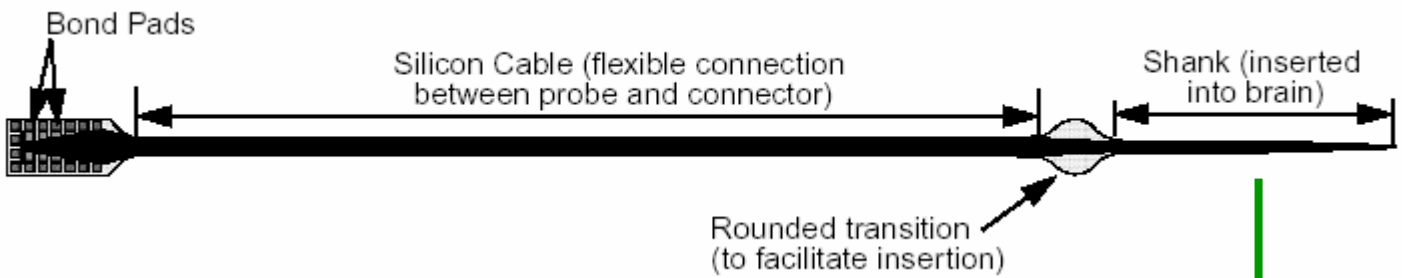


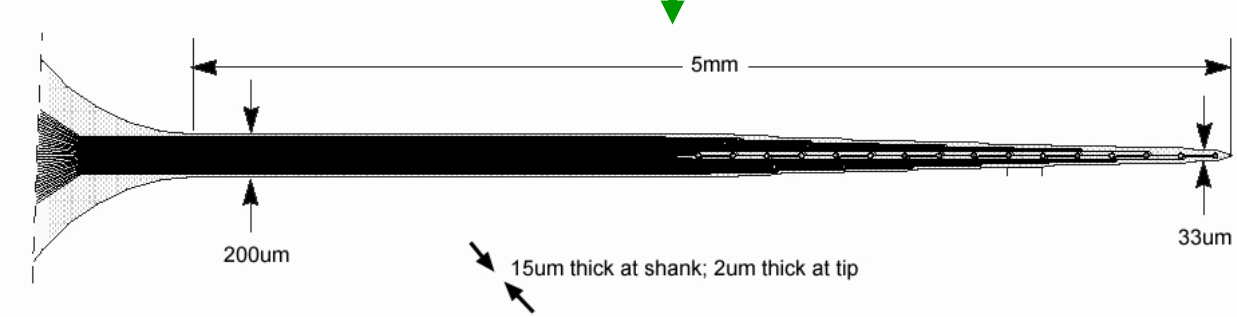
DAPI: intercalates in DNA, labels cell nuclei

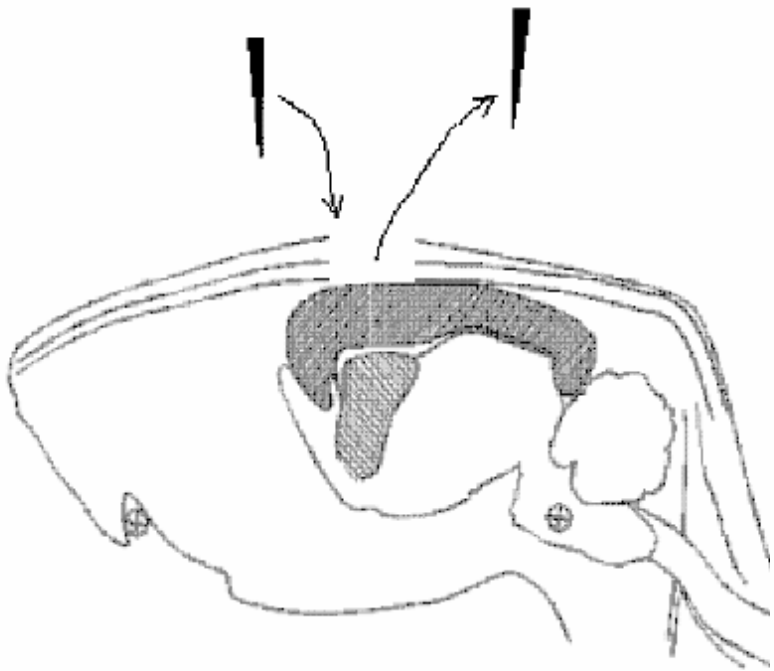

Biran et al., 2005, Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. Exp Neurol. Sep;195(1):115-26.

The Michigan Array

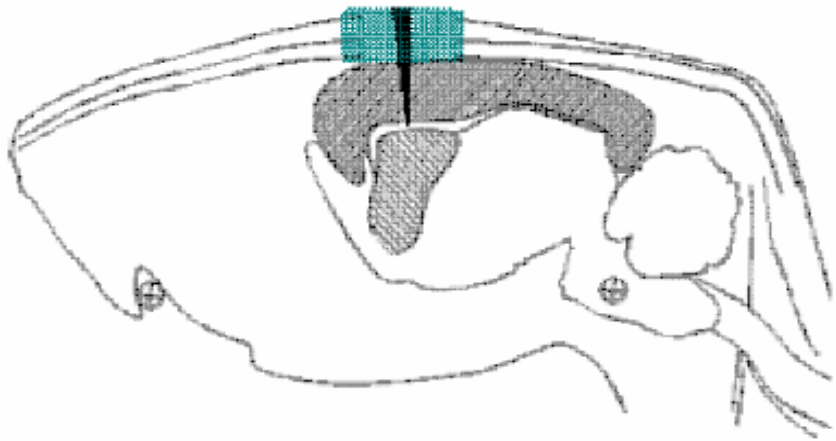






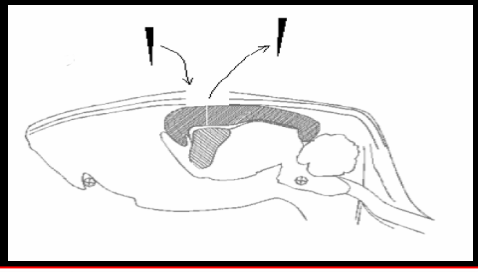


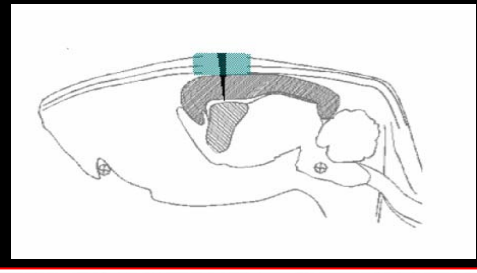
Microelectrode
Stab Wound



Indwelling
Implant

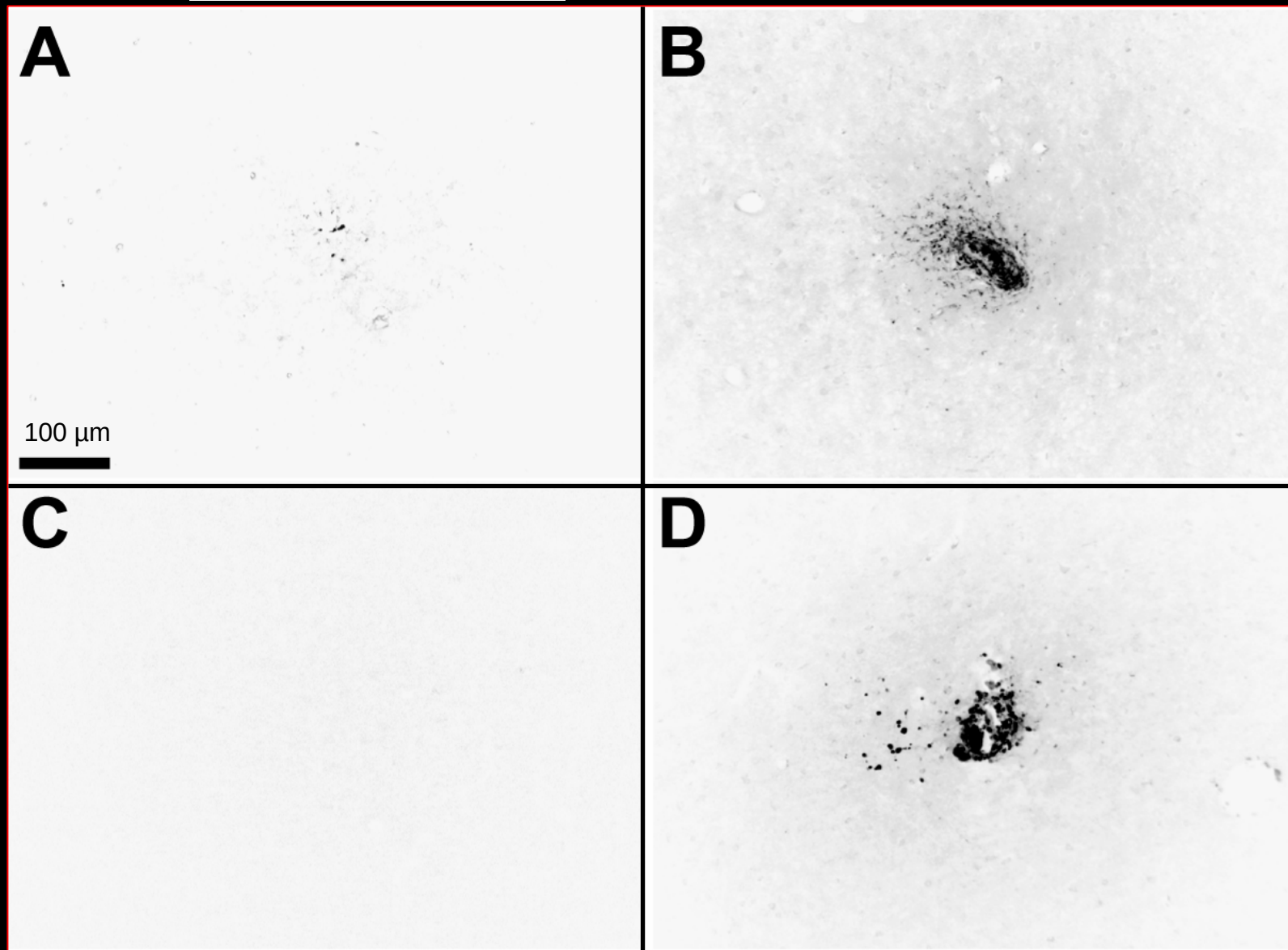
ED1



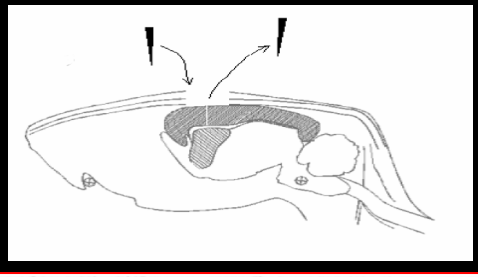


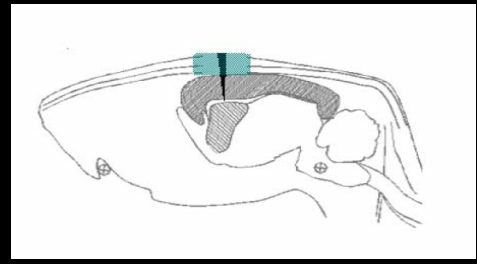
2 Wks.

4 Wks.



GFAP





2 Wks.

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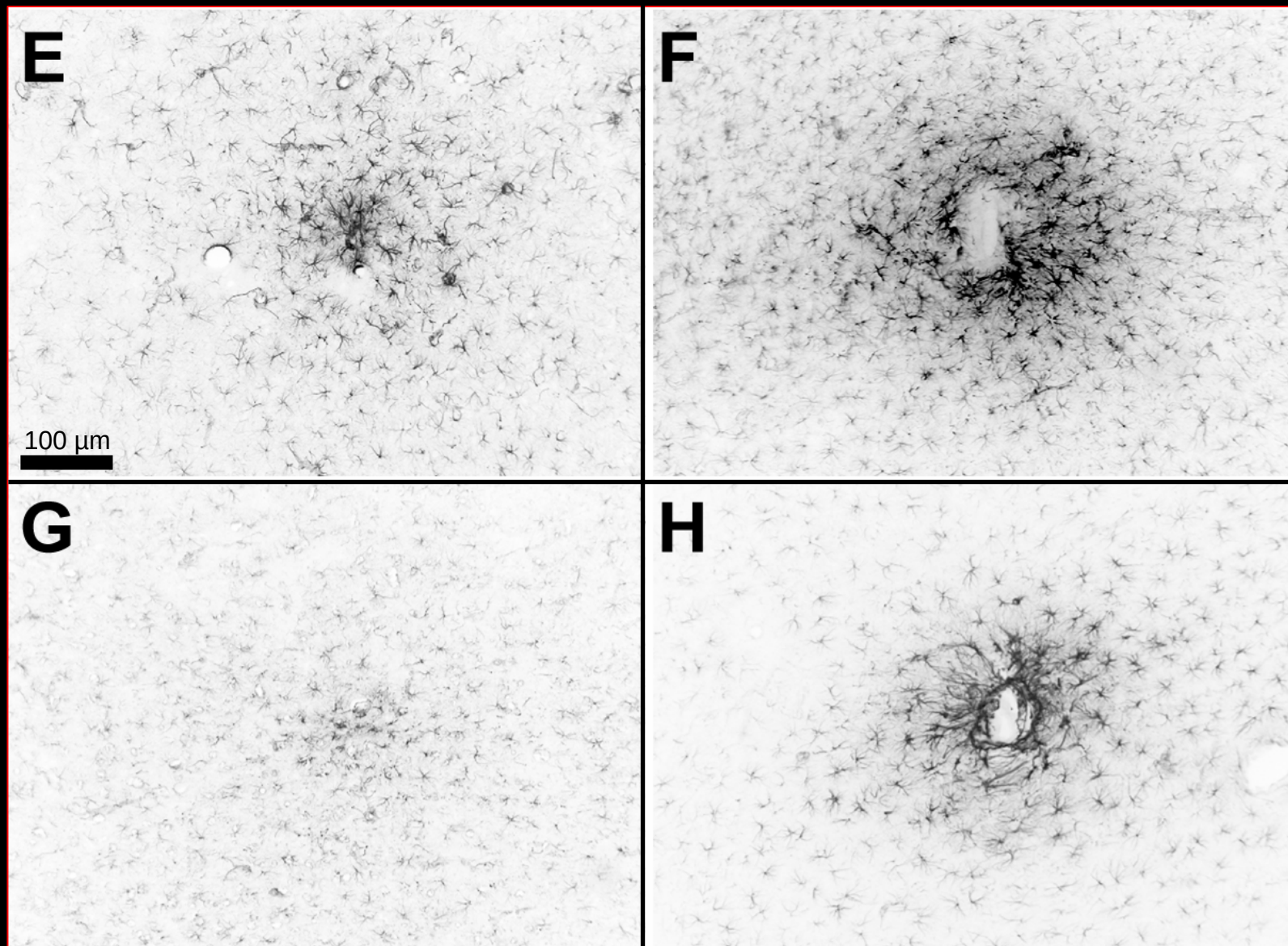
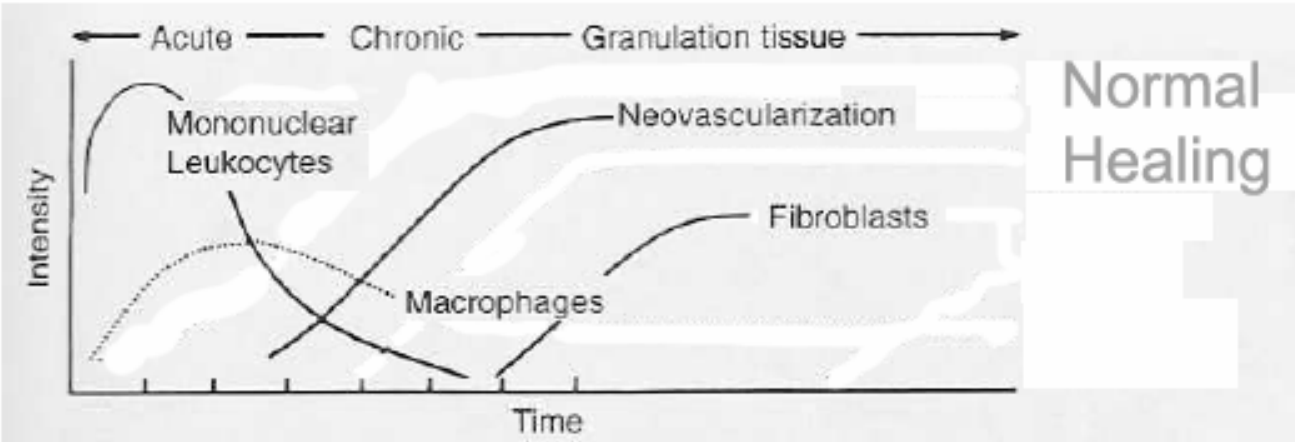
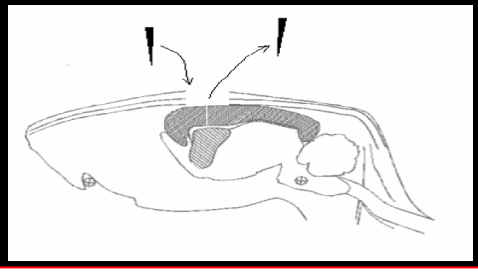


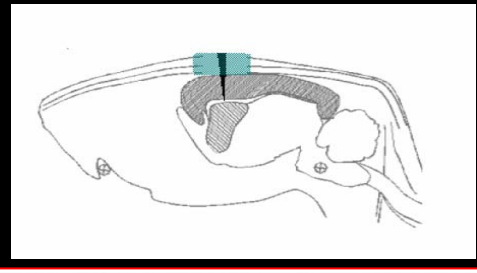
Sequence of Events Following Device Trauma :

- Injury
- Acute inflammation
- Granulation tissue
- Mature extracellular matrix
- Wound contraction (Scar formation)



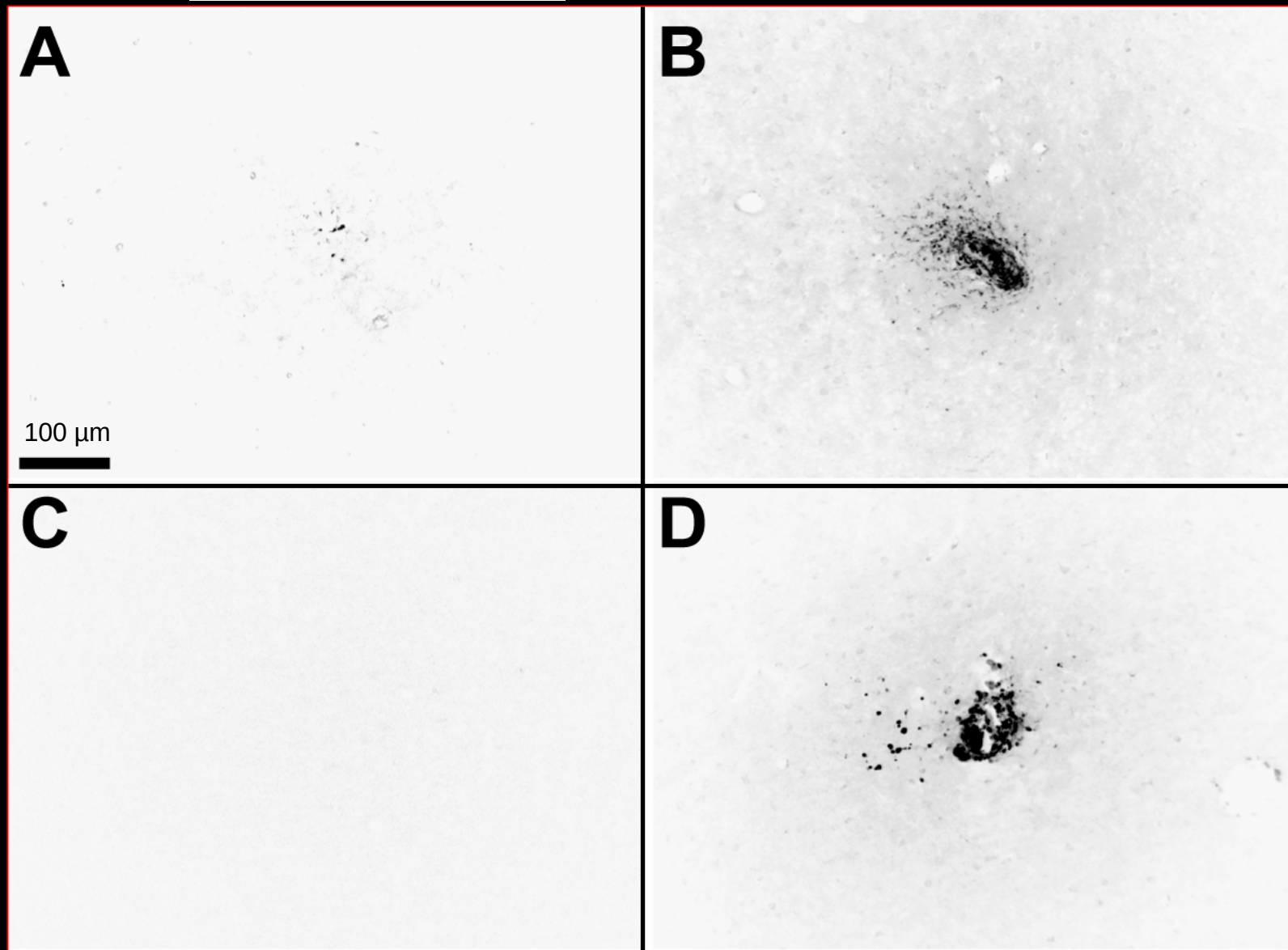
ED1



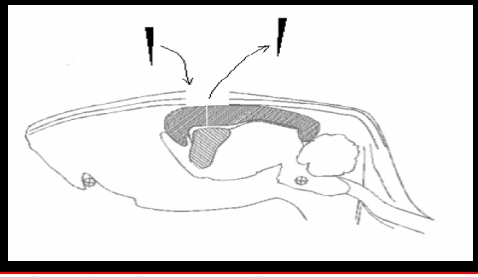


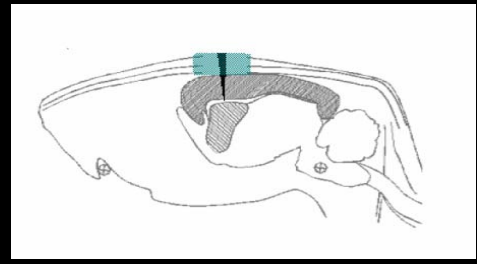
2 Wks.

4 Wks.



GFAP





2 Wks.

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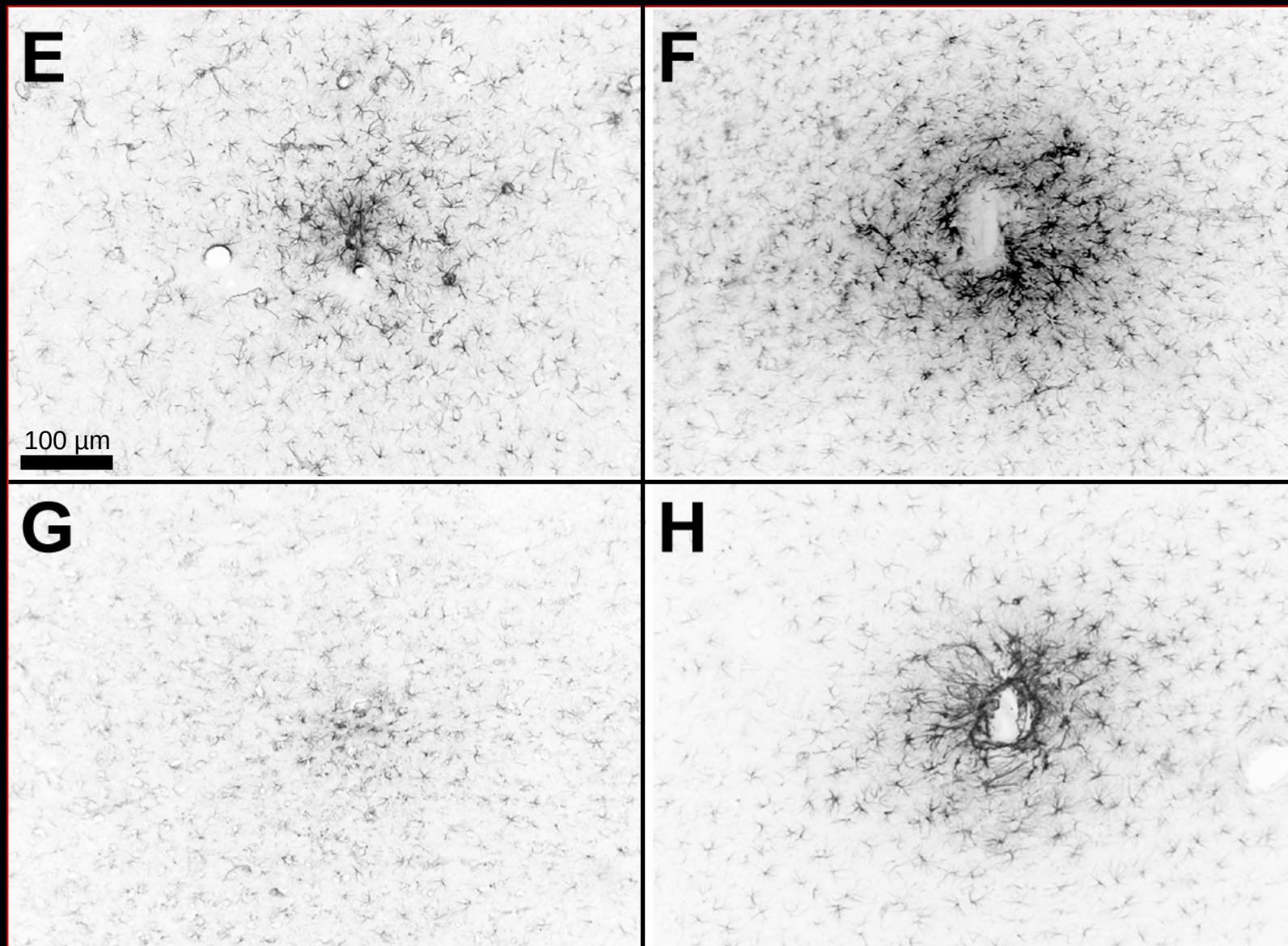
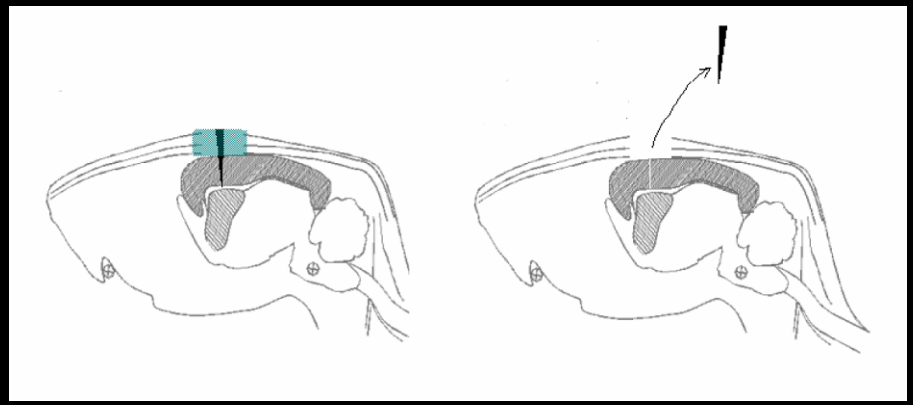
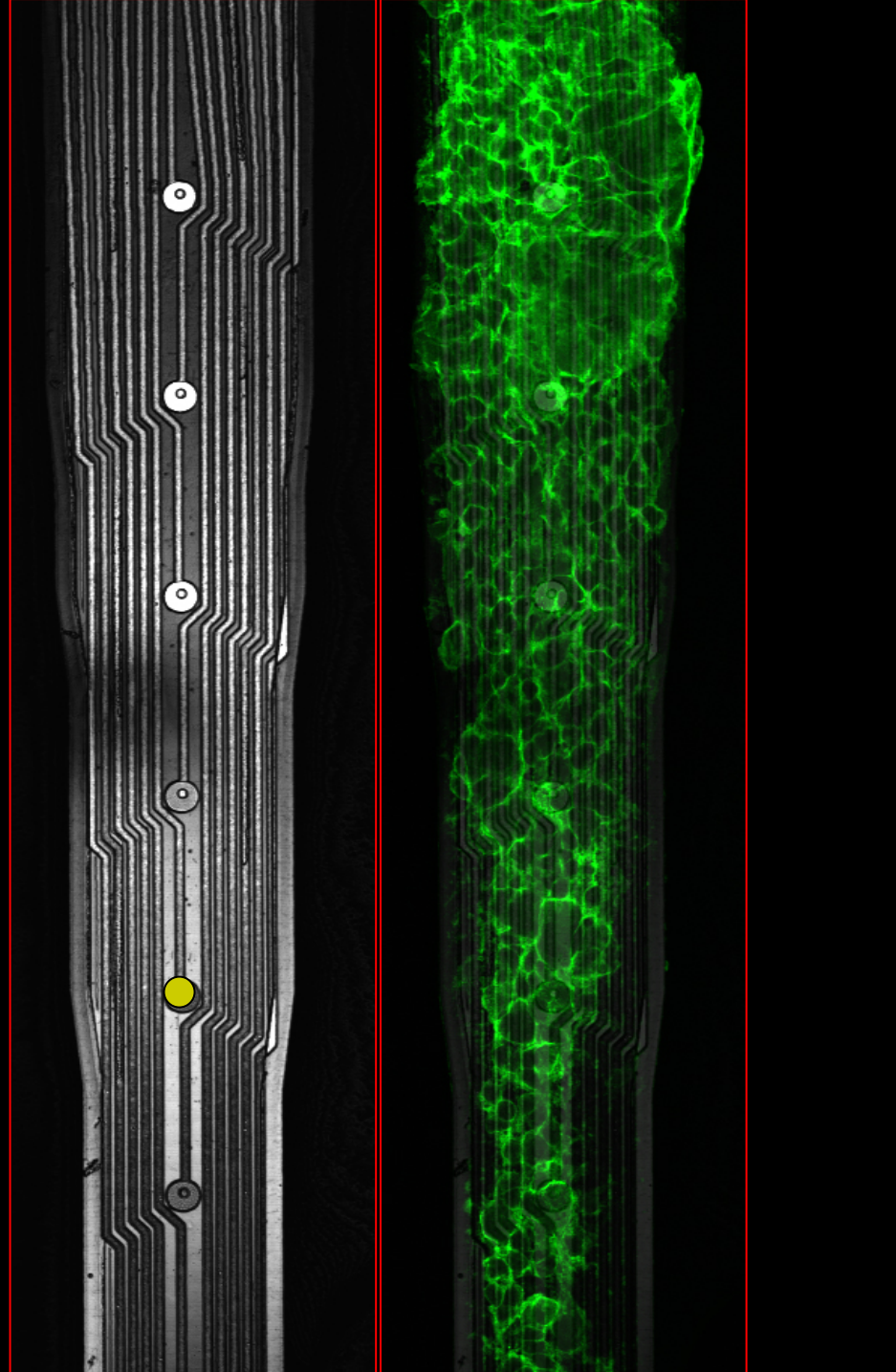


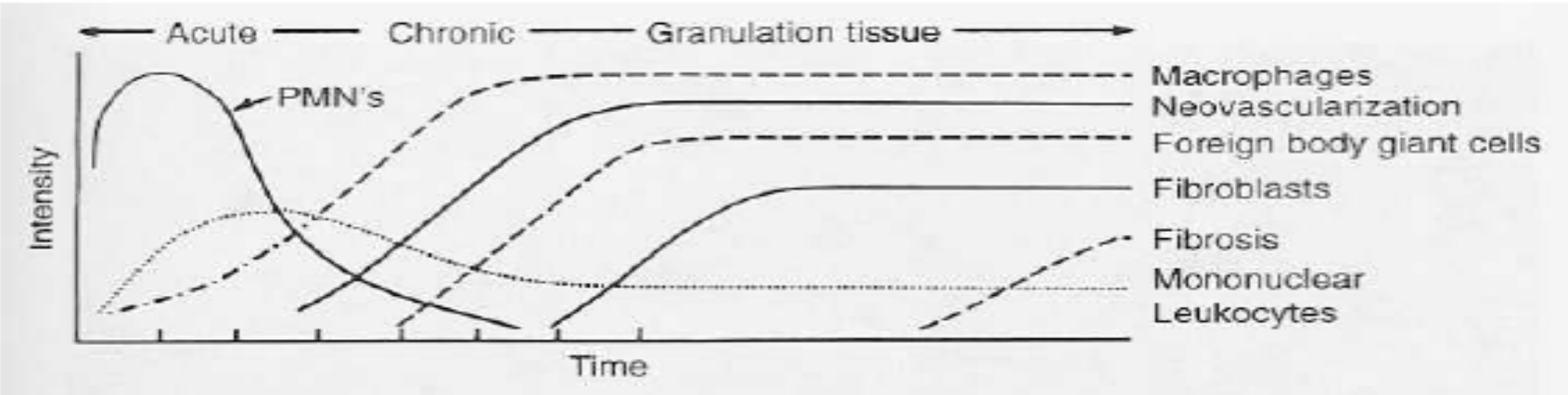
Retrieved Microelectrodes (3x-12)

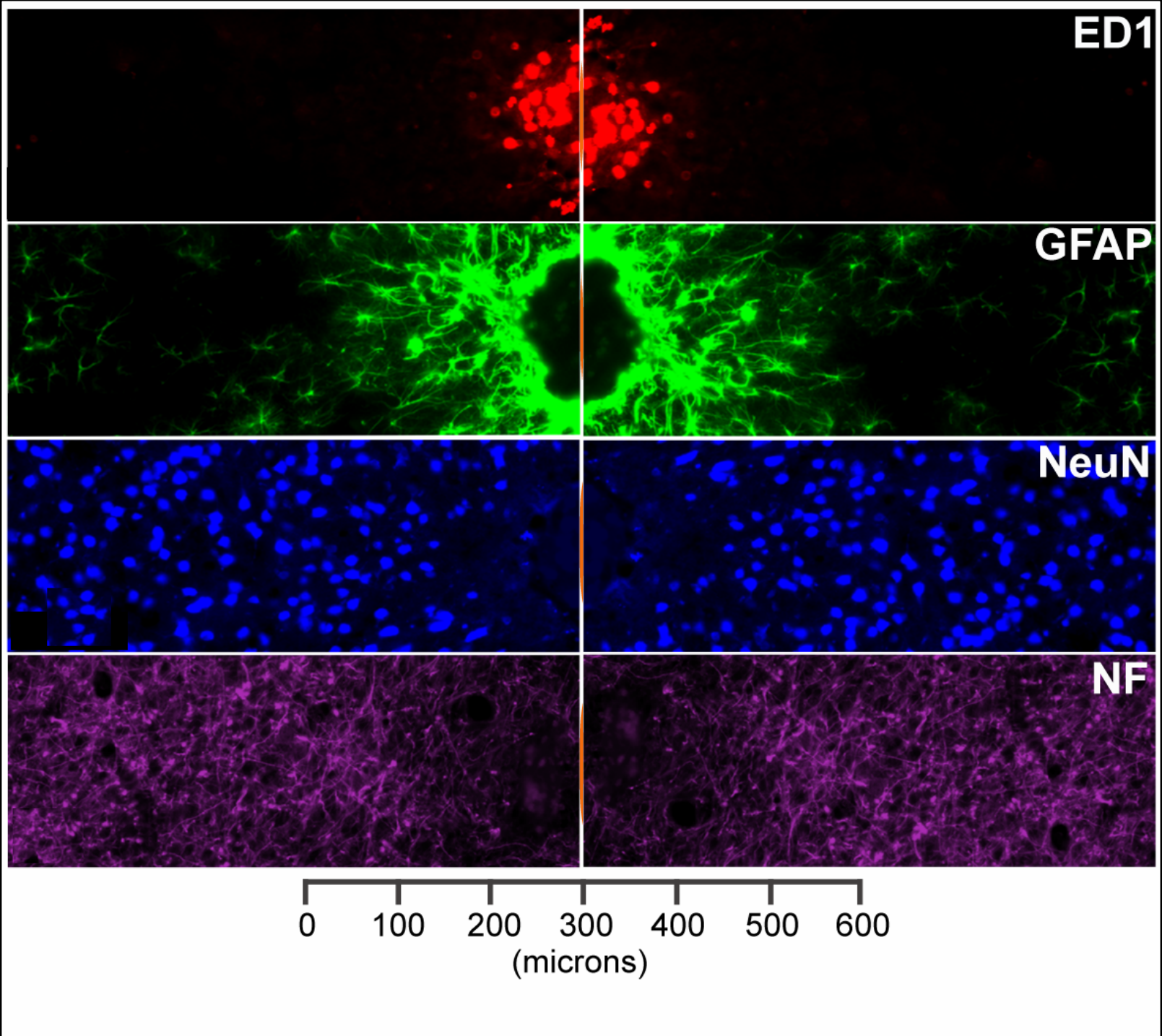




Sequence of Events Following Device Implantation:

- Injury
- acute inflammation
- chronic inflammation
- granulation tissue
- foreign body reaction
- fibrous encapsulation



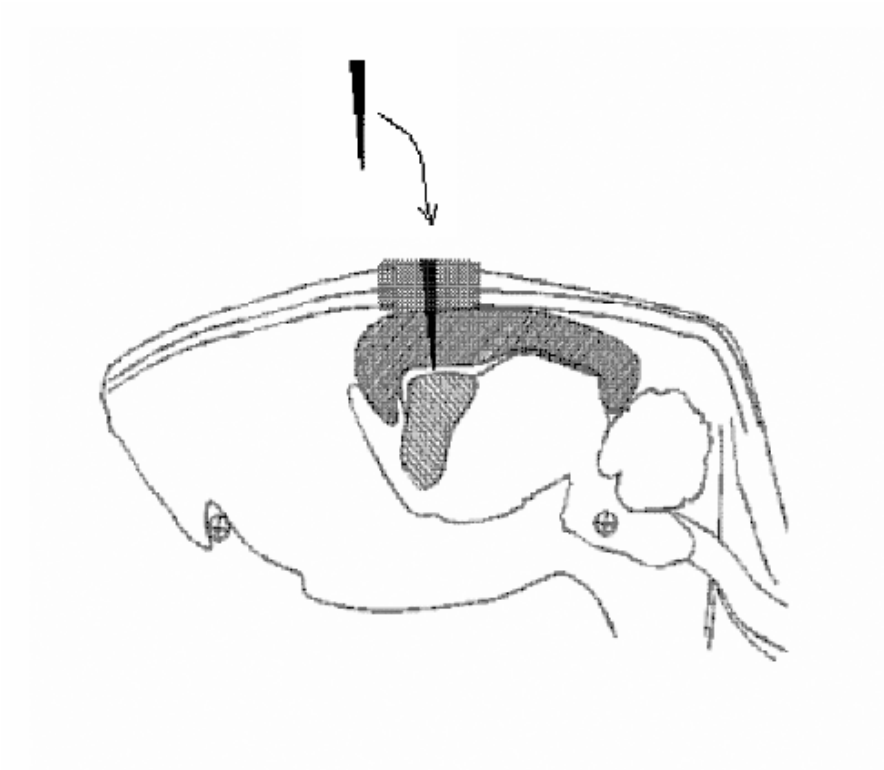

ED1
GFAP
NeuN
NF
0
100
200
300
400
500
600
(microns)

The Initial Events

- Initiation by mechanical injury - damage to vasculature
- Infiltration of Blood into Extracellular Space
- Coagulation-clot formation
- Complement activation-essential for clean up
- Platelet activation and degranulation
- Inflammation-edema
- Removal of damaged matrix and necrotic cell components
- Cell proliferation and recruitment including endothelial, epithelial, stromal and inflammatory cells

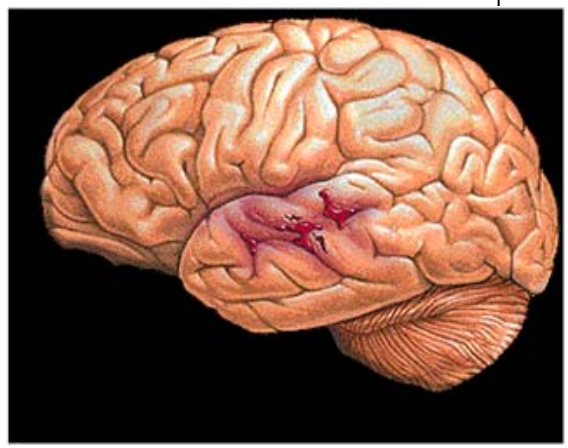
Coagulation and hemolysis

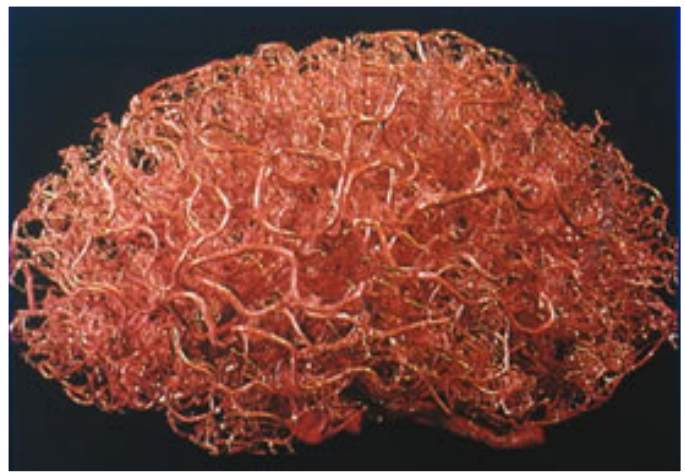
1. Damage to blood carrying vessels and/or contact with foreign materials can lead to coagulation.
2. Damage to the tissue of blood can lead to cellular destruction or hemolysis.



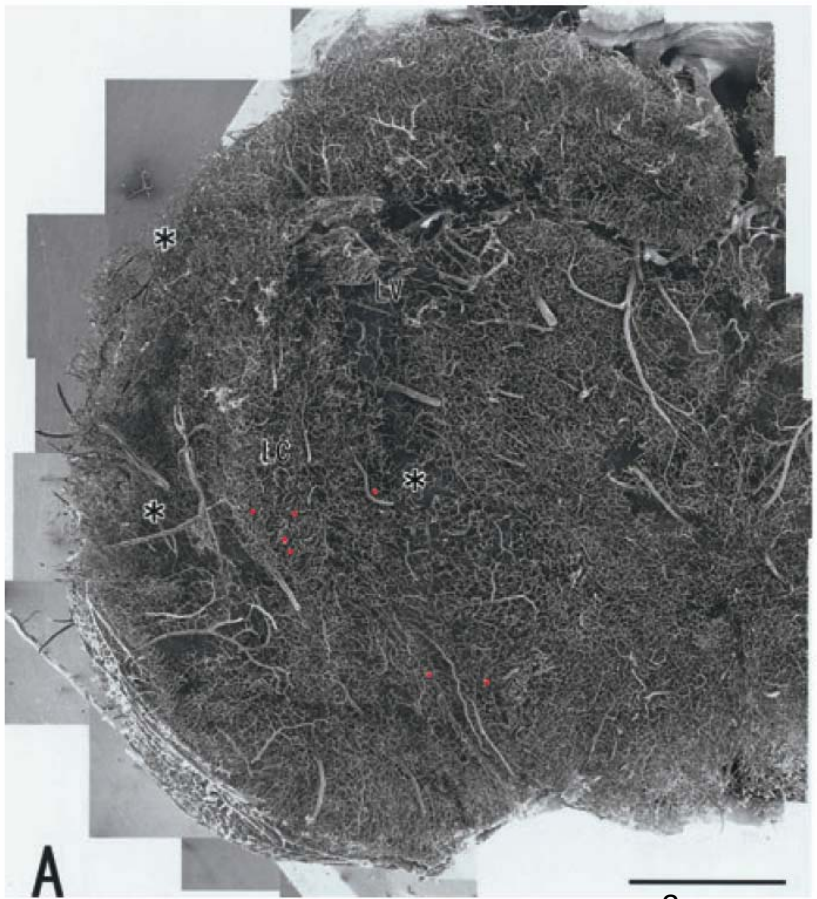
Vascularized Tissue

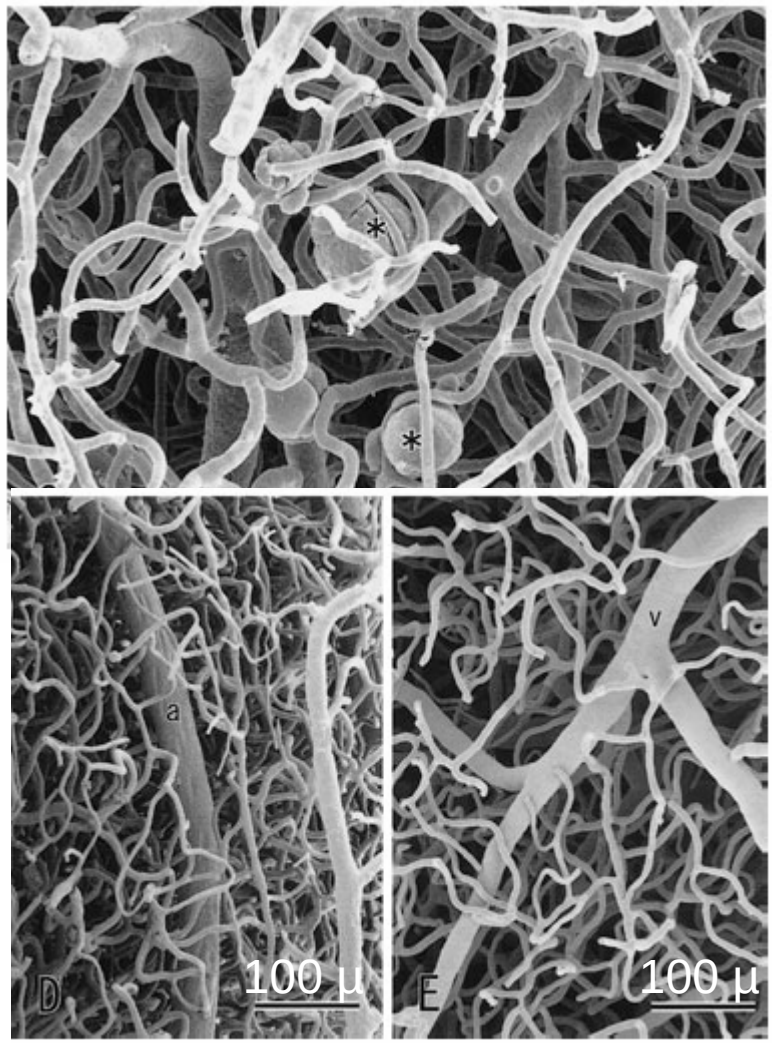
- Each cell is no more than 150 microns from its nearest blood blood vessel



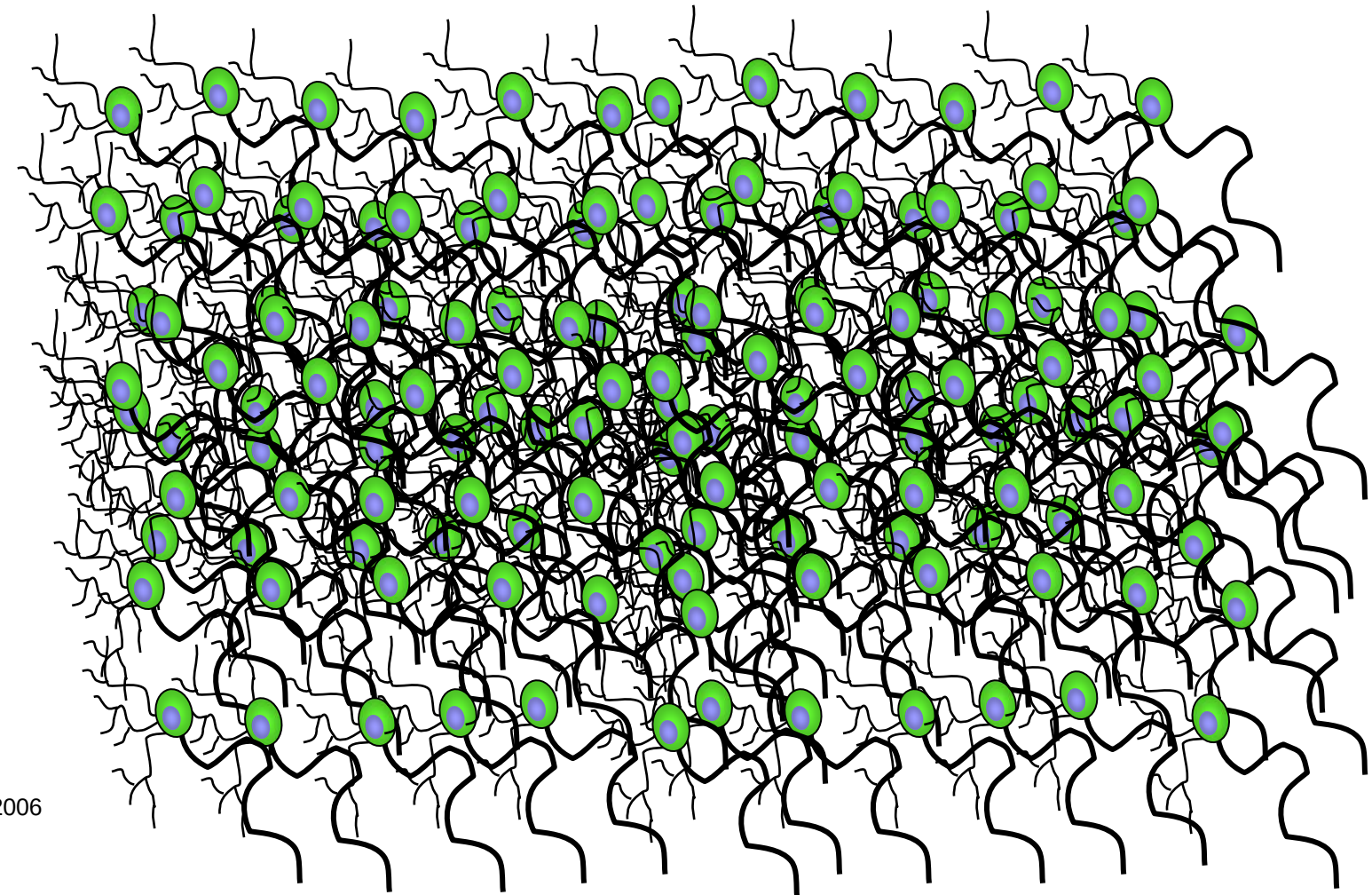


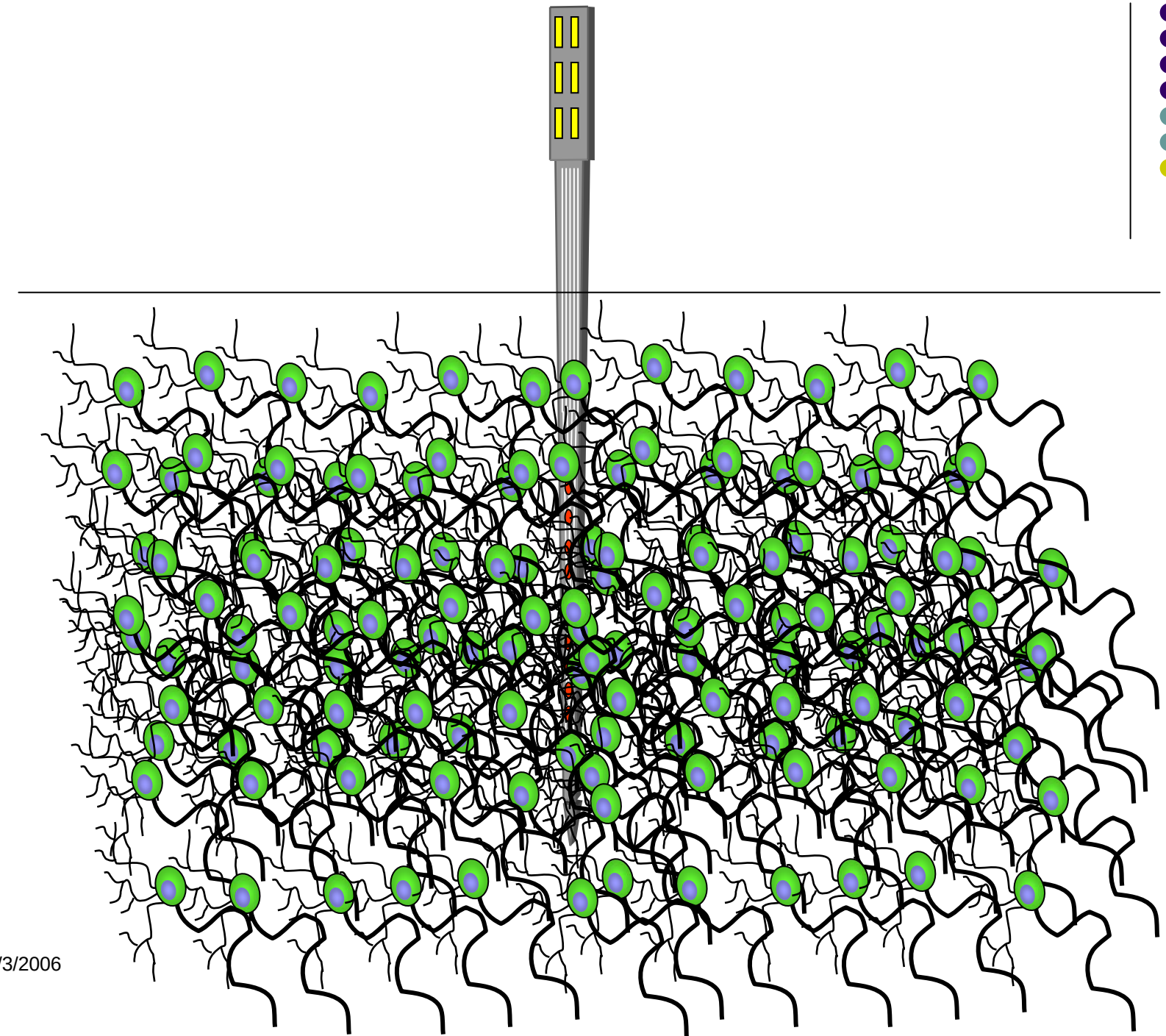
Vascular Casts of the Cerebral Blood Vessels in Rat Brain

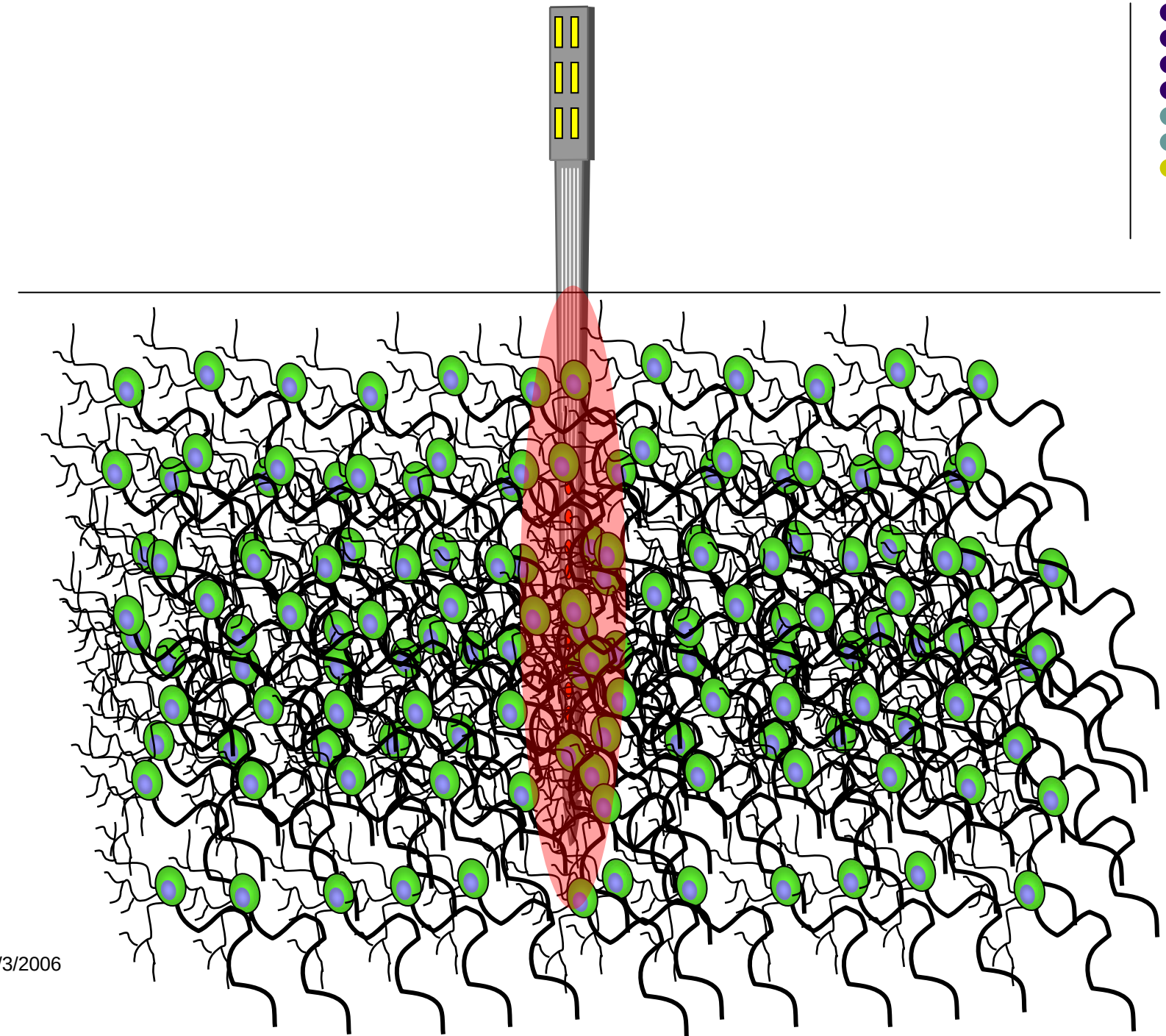


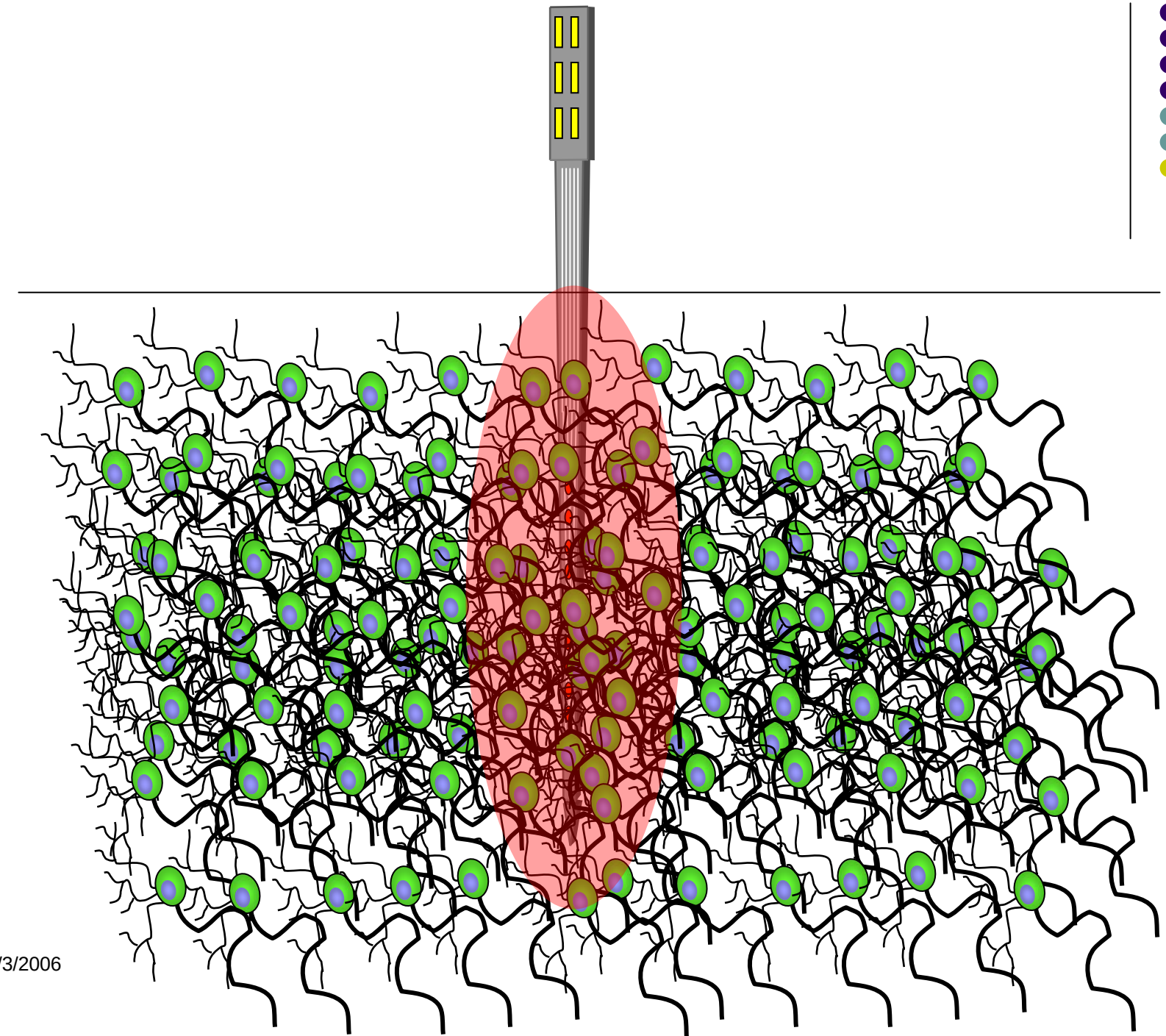


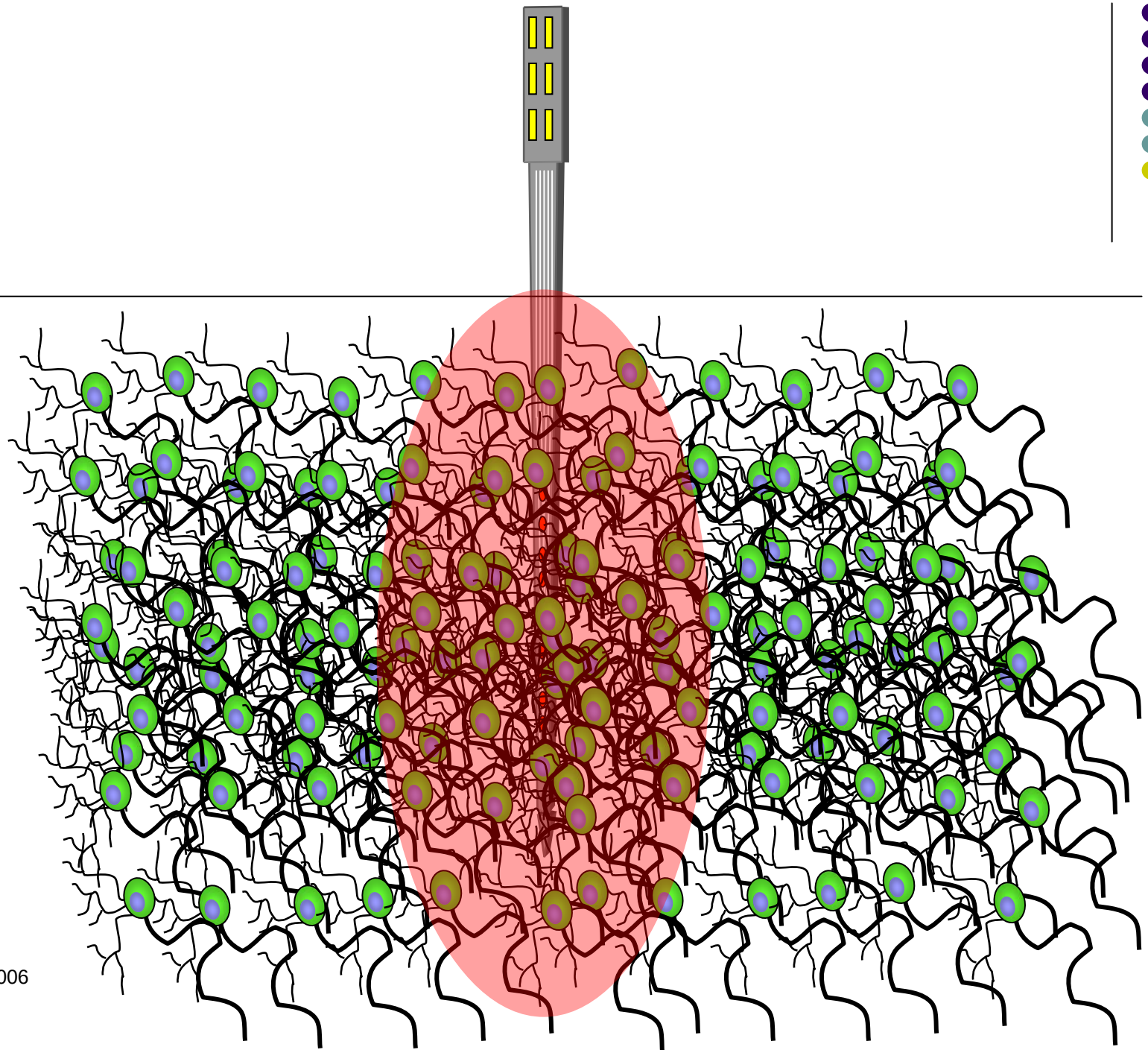
Ohtake et al., *Neuropathology* 2004; **24**, 219–227

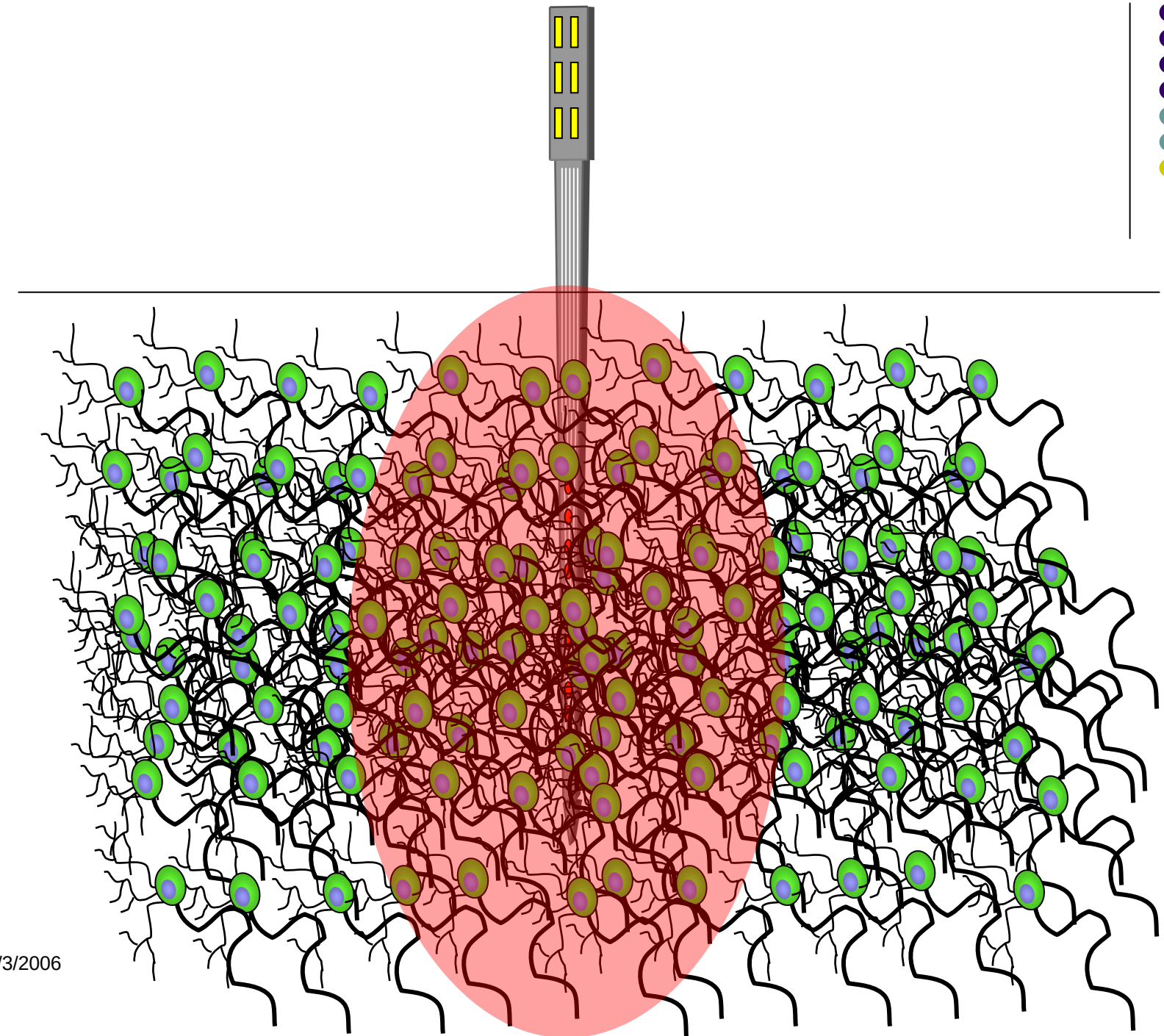




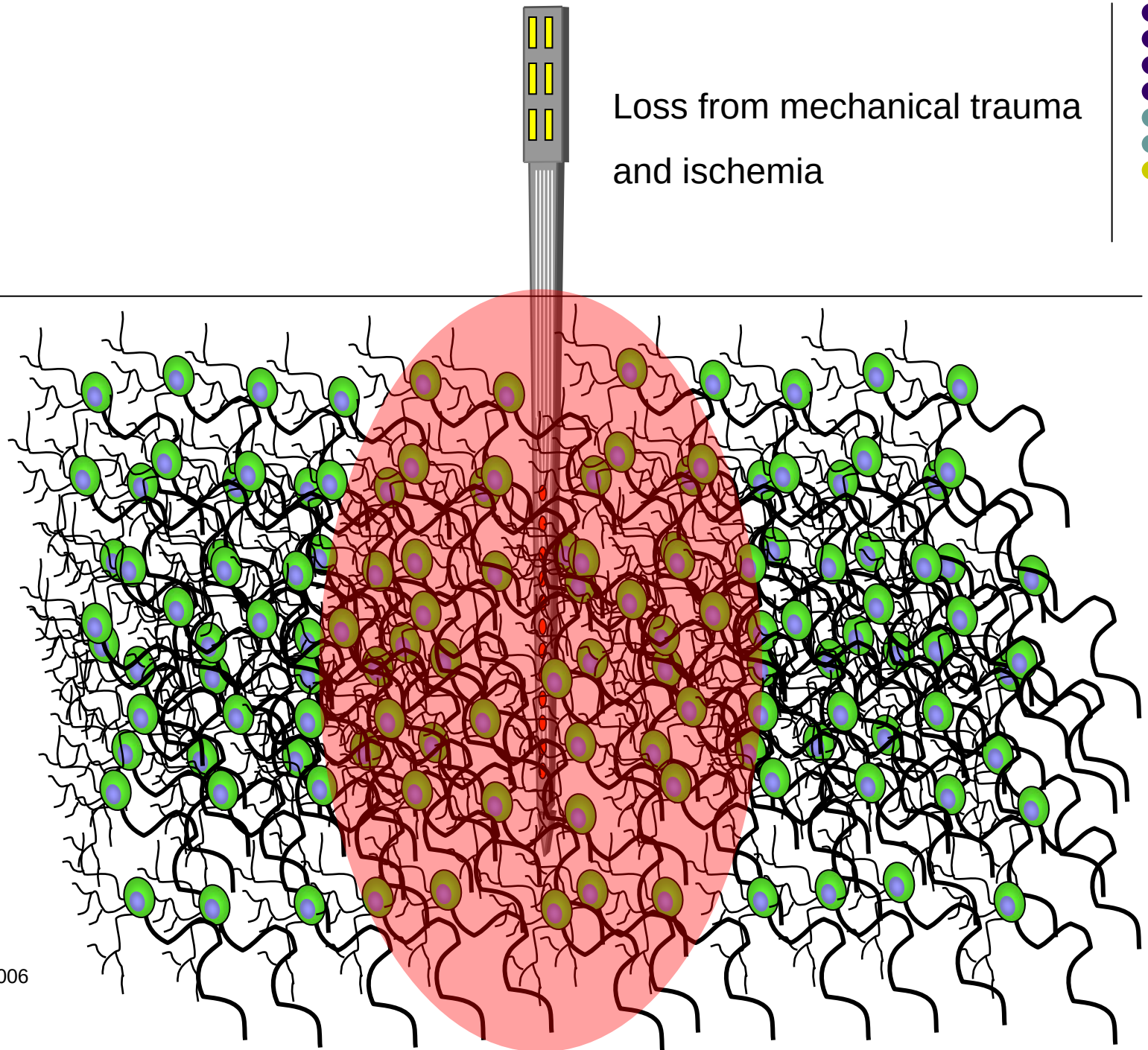








Loss from mechanical trauma and ischemia



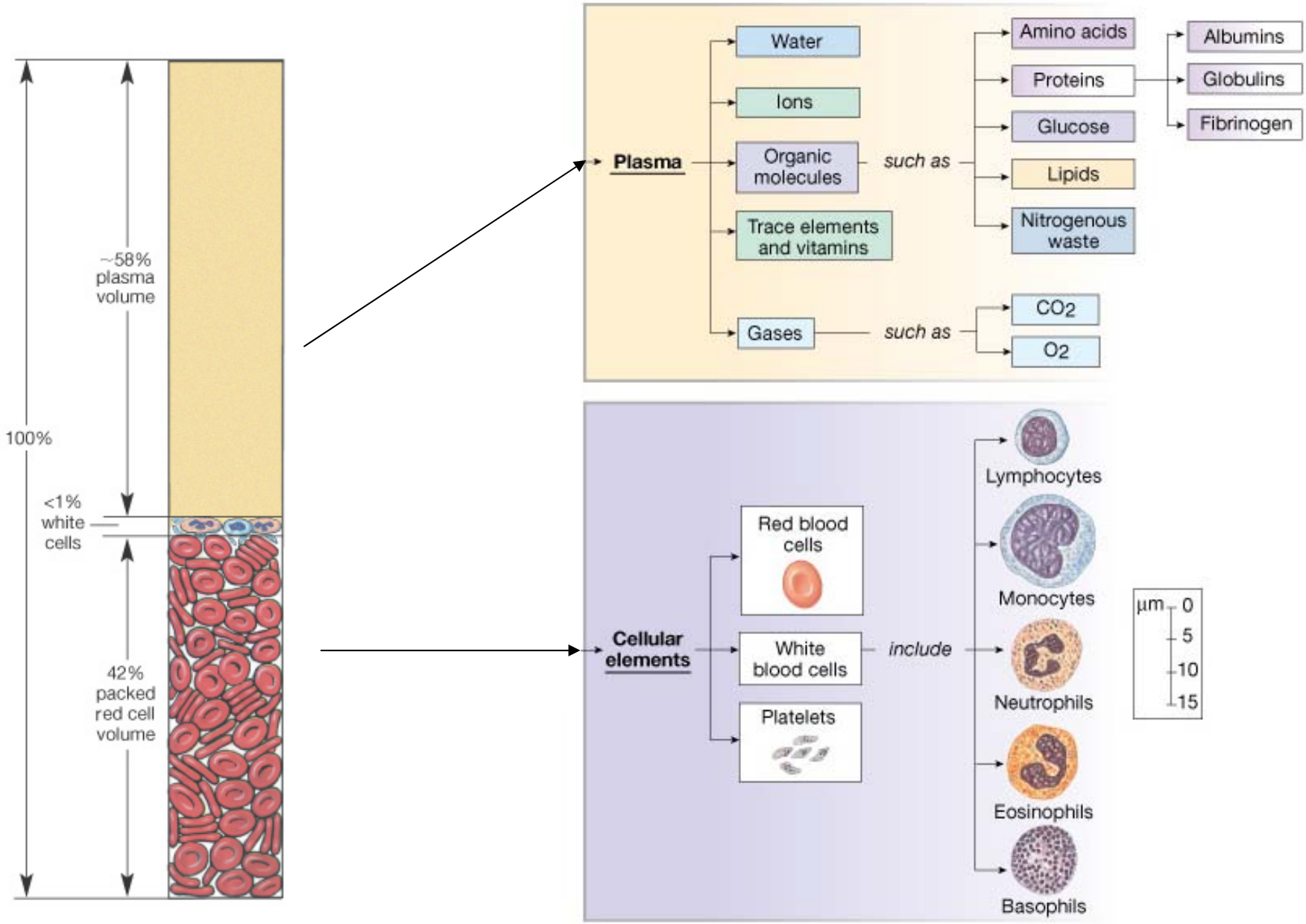
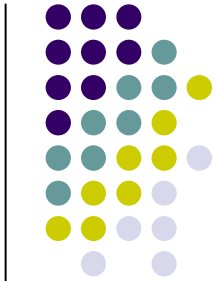


Figure 16-2: The blood count

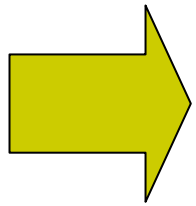
Soluble Components of Plasma



- Clotting factors
- Complement proteins
- Imunoglobulins
- Albumin
- Carrier proteins

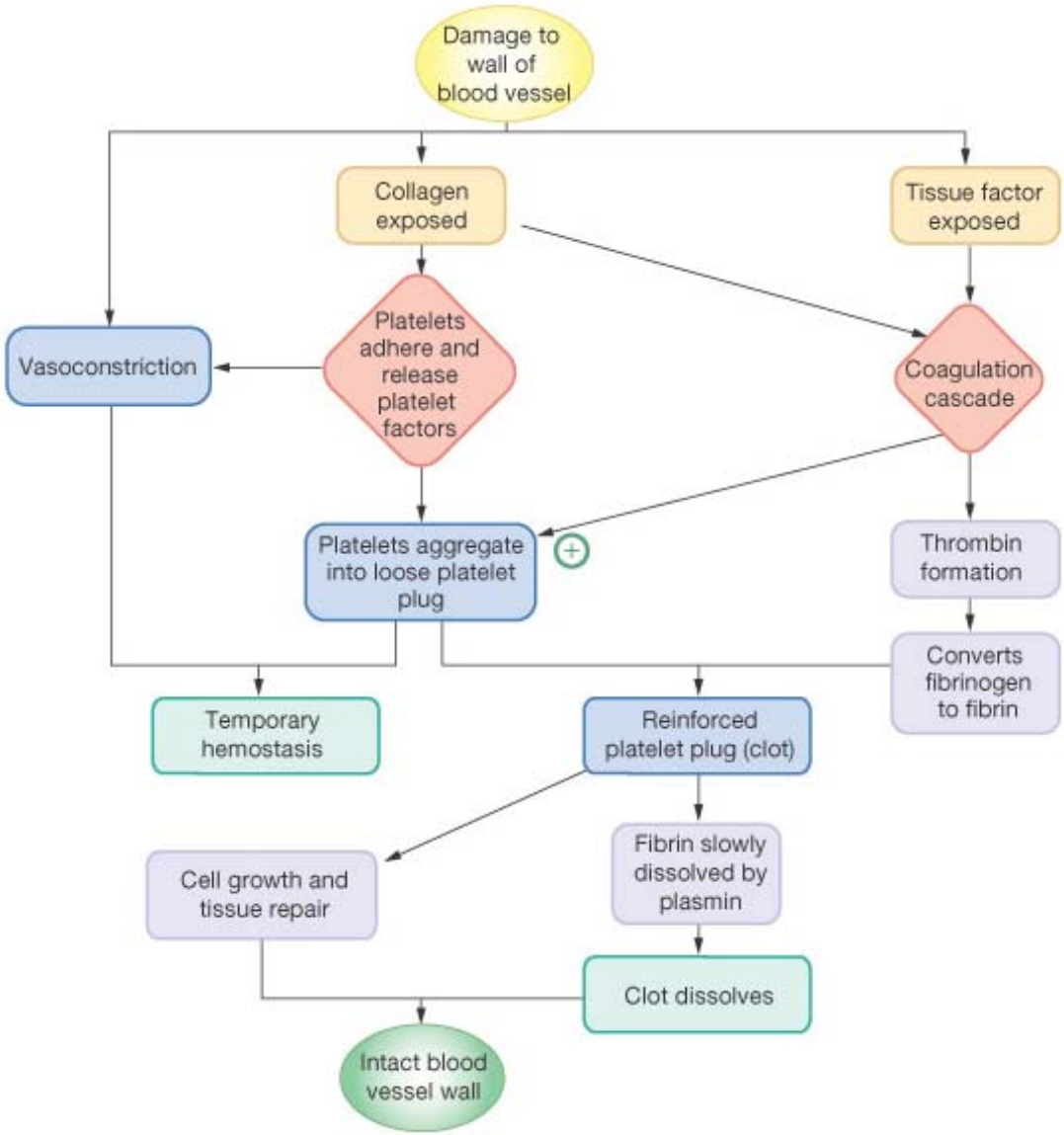
Soluble Components of Plasma

- Clotting factors
- Complement proteins
- Imunoglobulins
- Albumin
- Carrier proteins



Serine Proteases

Overview of blood coagulation

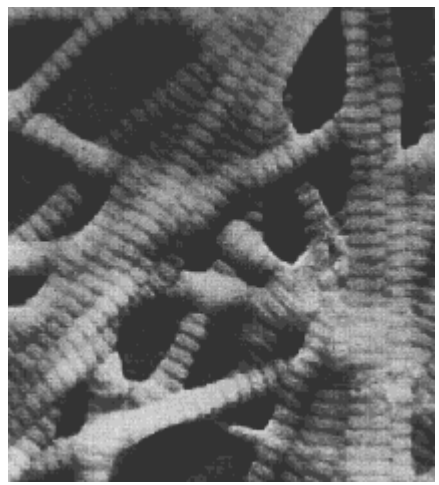


Collagens

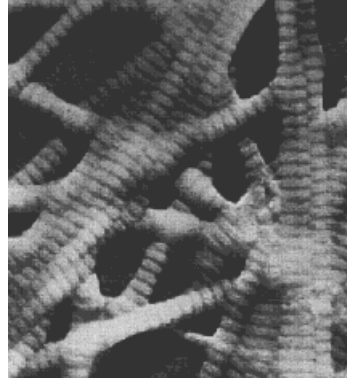
- insoluble, extracellular glycoproteins
- found in all animals
- the most abundant proteins in the human body

They are essential structural components of all **connective tissues**, such as

- cartilage
- bone
- tendons
- ligaments
- fascia
- skin



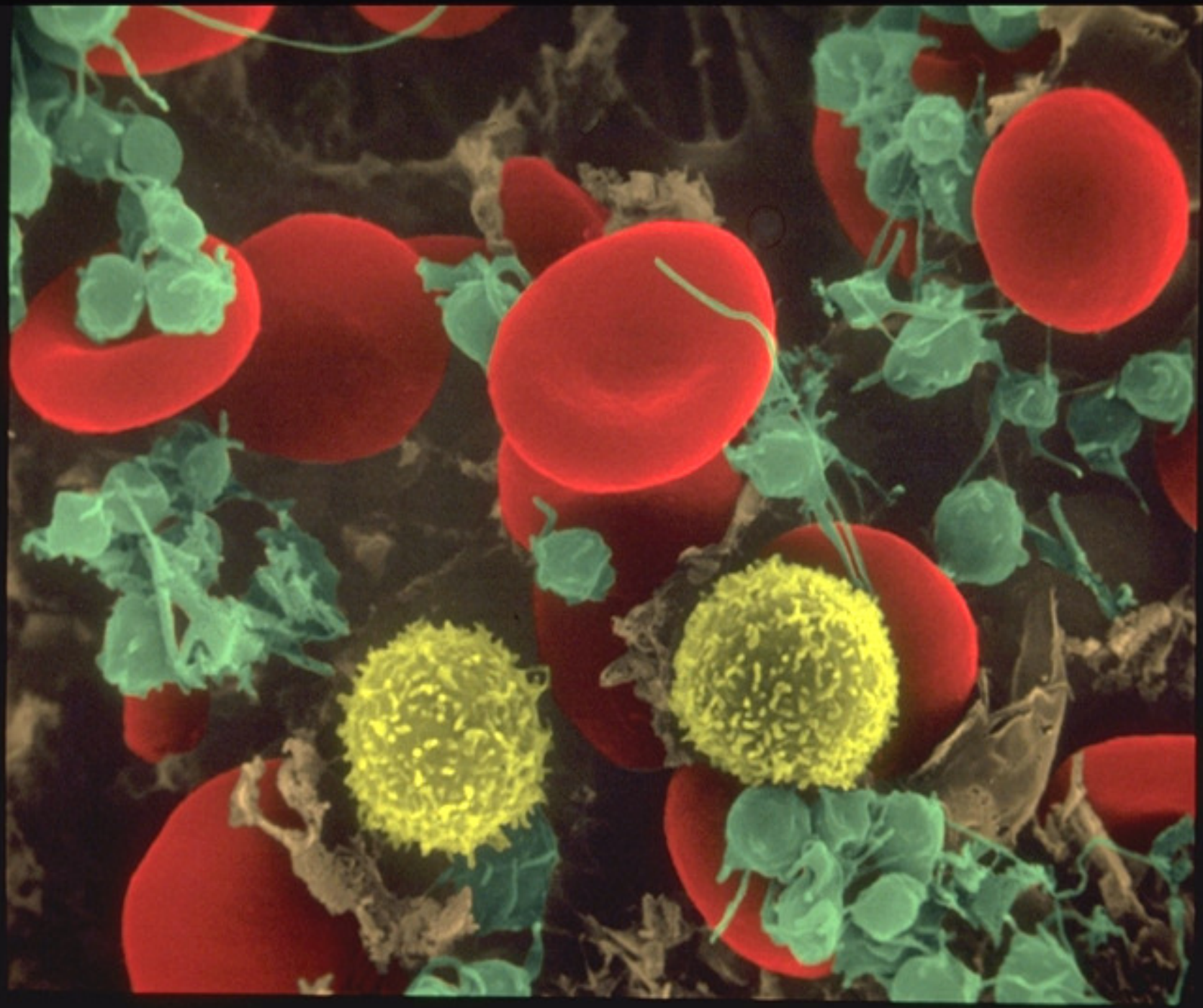
Collagens

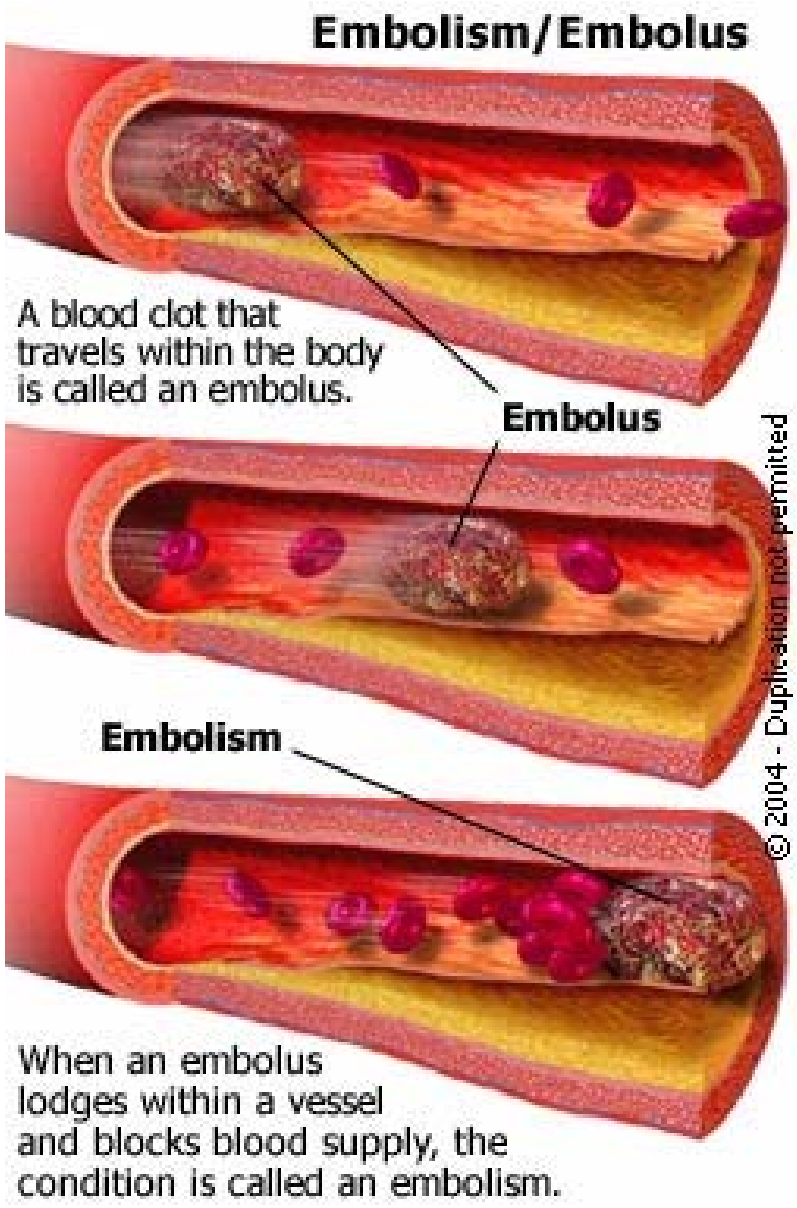


19 types of collagens have been found (so far) in humans.

The major ones are:

- **Type I**. The chief component of tendons, ligaments, and bones.
- **Type II**. Represents more than 50% of the protein in **cartilage**. It is also used to build the notochord of vertebrate embryos.
- **Type III**. Strengthens the walls of hollow structures like arteries, the intestine, and the uterus.
- **Type IV**. Forms the **basal lamina** of epithelia. (The basal lamina is often called the basement membrane, but is not related to lipid bilayer membranes.) A meshwork of Type IV collagens provides the filter for the blood **capillaries** and the glomeruli of the kidneys.




Embolism/Embolus
A blood clot that travels within the body is called an embolus.
Embolus
Embolism
When an embolus lodges within a vessel and blocks blood supply, the condition is called an embolism.
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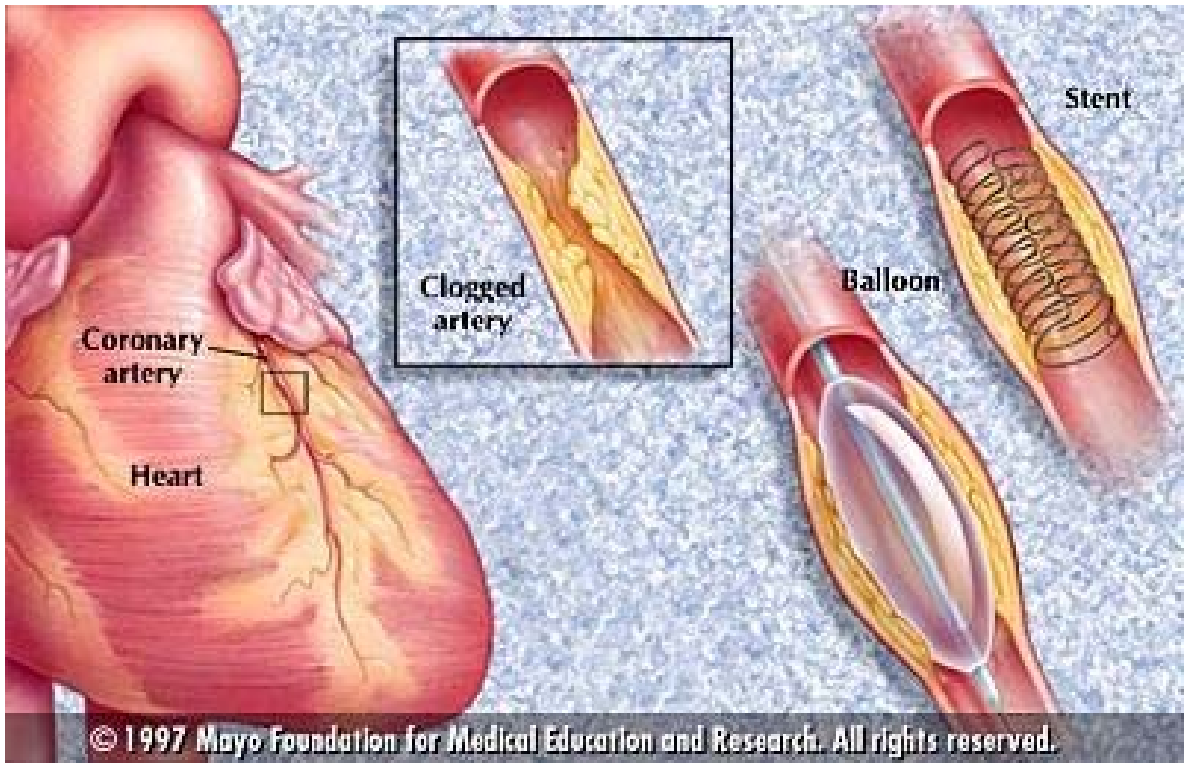
Clogged artery
Stent
Balloon
Coronary artery
Heart
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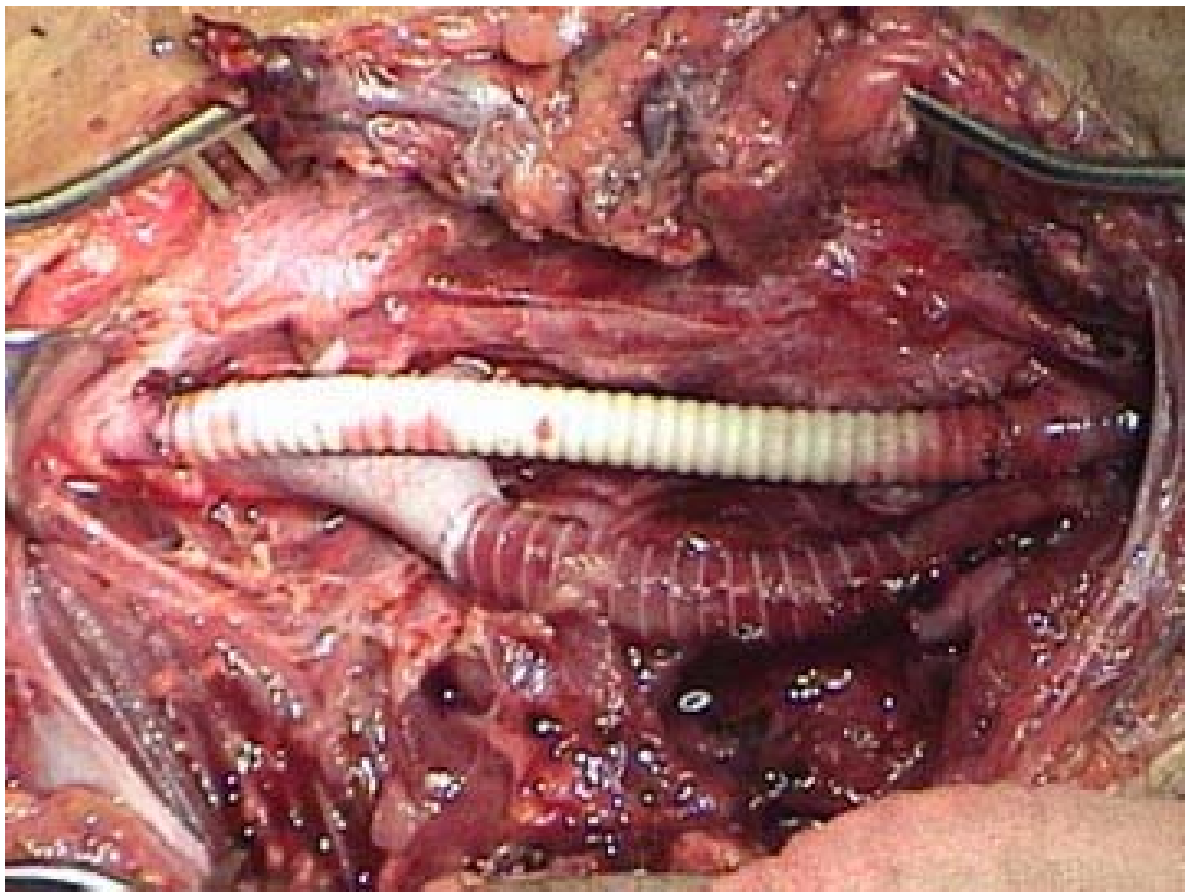
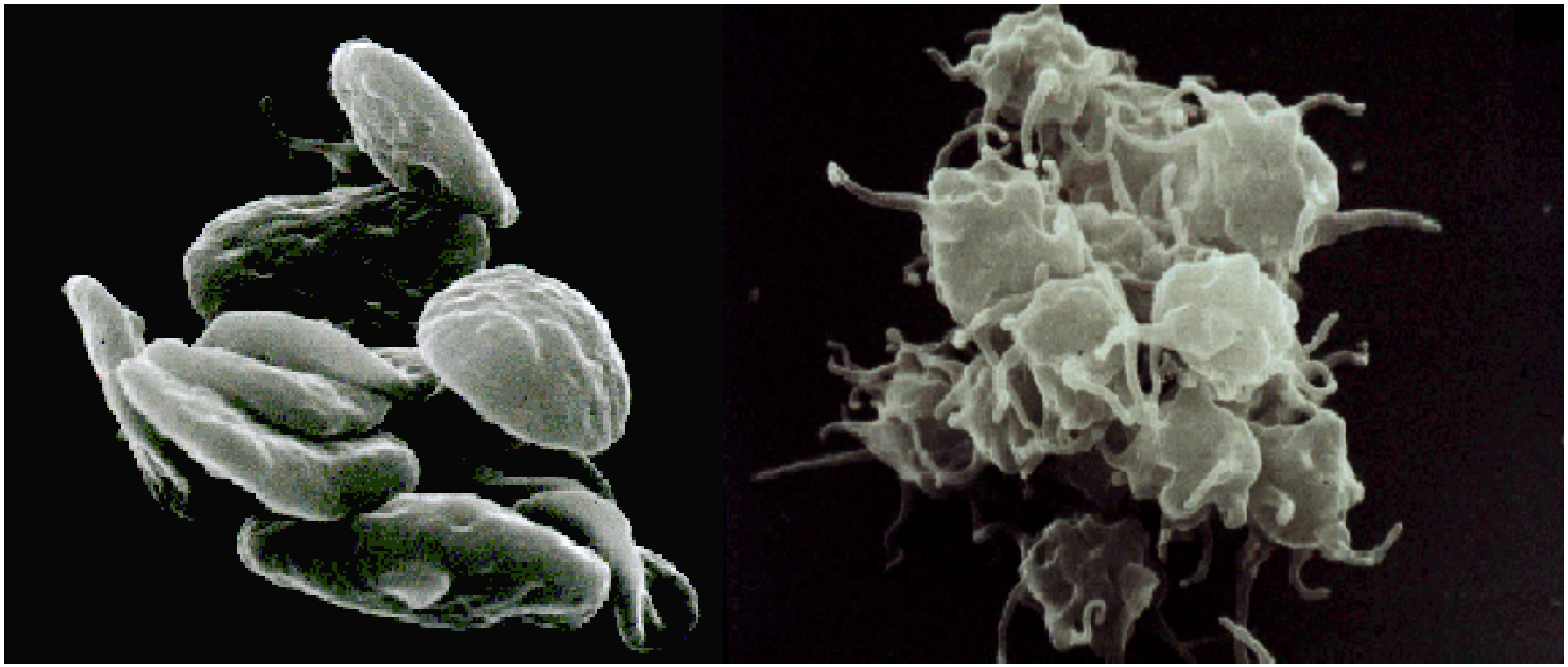
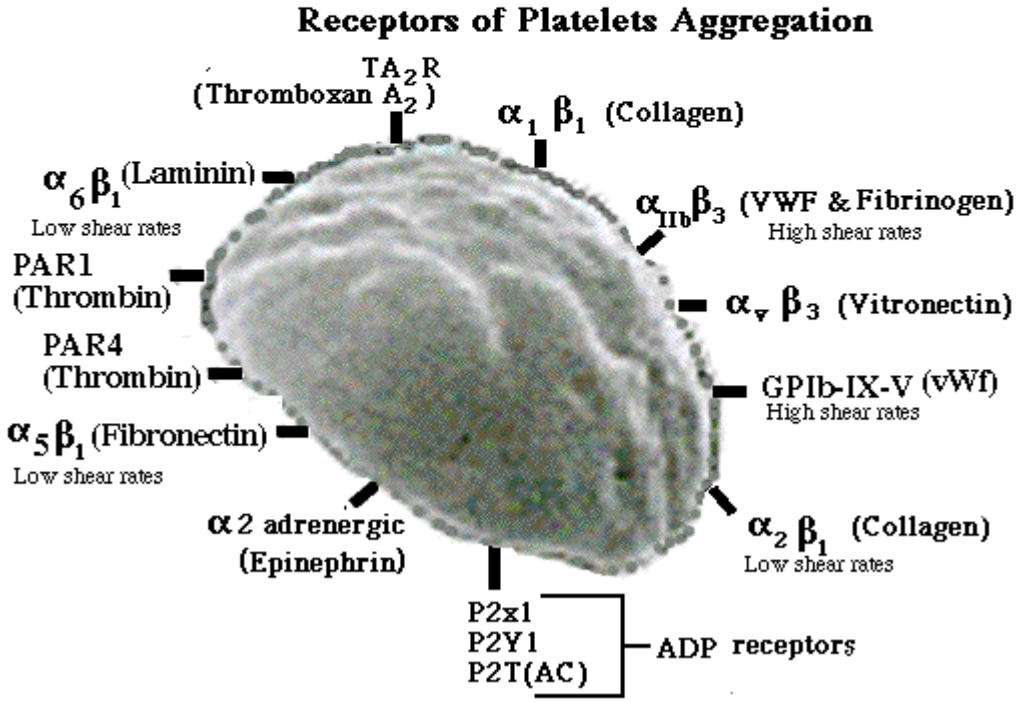


SEM of Platelets



150-350K per µL <50K/ µL uncontrolled bleeding


Receptors of Platelets Aggregation
TA2R
(Thromboxan A2)
α1 β1 (Collagen)
α6 β1 (Laminin)
Low shear rates
αIIb β3 (VWF & Fibrinogen)
High shear rates
PAR1
(Thrombin)
αv β3 (Vitronectin)
PAR4
(Thrombin)
GPIb-IX-V (vWf)
High shear rates
α5 β1 (Fibronectin)
Low shear rates
α2 adrenergic
(Epinephrin)
α2 β1 (Collagen)
Low shear rates
P2x1
P2Y1
P2T(AC)
ADP receptors

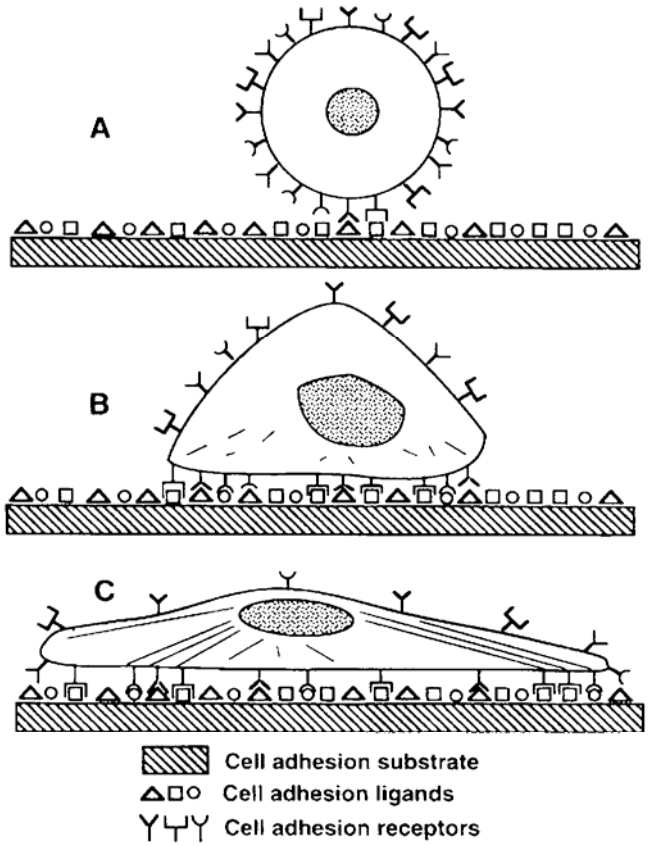
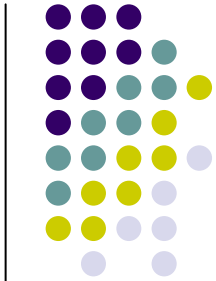


FIG. 12. Progression of anchorage-dependent mammalian cell adhesion. (A) Initial contact of cell with solid substrate. (B) Formation of bonds between cell surface receptors and cell adhesion ligands. (C) Cytoskeletal reorganization with progressive spreading of the cell on the substrate for increased attachment strength. (Reproduced by permission from Massia, S. P., 1999. Cell–extracellular matrix interactions relevant to vascular tissue engineering, in *Tissue Engineering of Prosthetic Vascular Grafts*, P. Zilla and H. P. Greisler, eds., RG Landes Co.)

Platelet Activation



- Bind to matrix and spread to cover the damaged surface;
- Temporary plug;
- Alpha granules
  - ADP, and epinephrine cause vasocontriction
  - growth factors (Platelet derived growth factor (PDGF), Fibronectin, von Willebron Factor)
  - cytokines (Transforming Growth Factor-beta (TGF-b);
- These substances bind to matrix, (chemotactic and /or mitogenic agents for leukocytes, endothelial cells and fibroblasts);

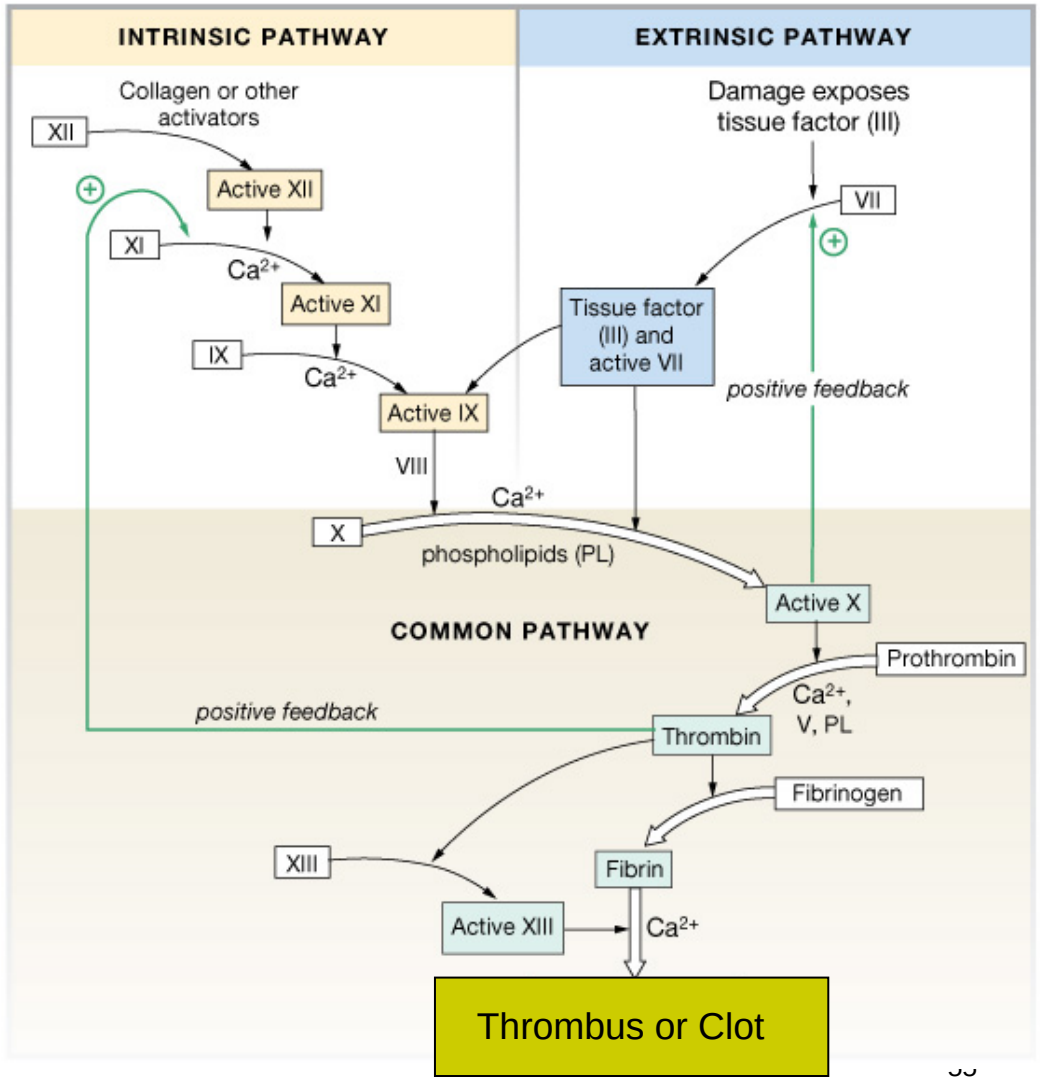
TGF-b

Chemoattractant for monocytes and fibroblasts

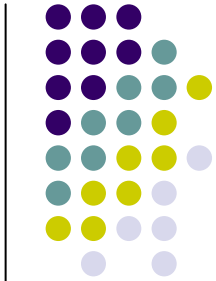
- Pro-fibrogenic
  - stimulates fibroblast proliferation
  - Stimulates fibroblasts to secrete matrix (collagen, fibronectin, and glycosaminoglycans) and therefore aids in the development of wound strength
  - Stimulates angiogenesis (new blood vessel development)

The Coagulation Cascade

- Initiated by damage to the wall of the endothelium
- Enzyme mediated
- Ca++
- Amplification
- Positive Feedback



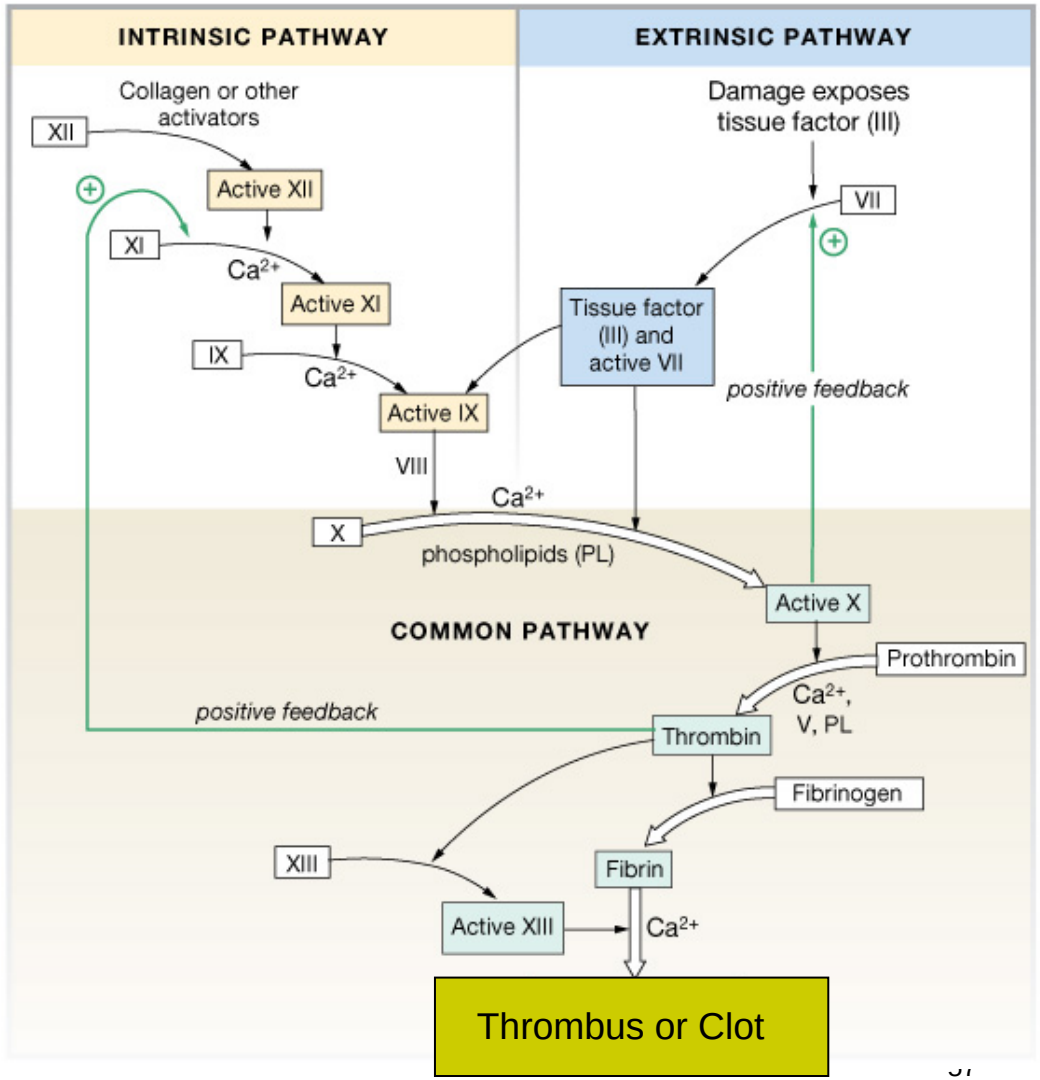
Serine Proteases



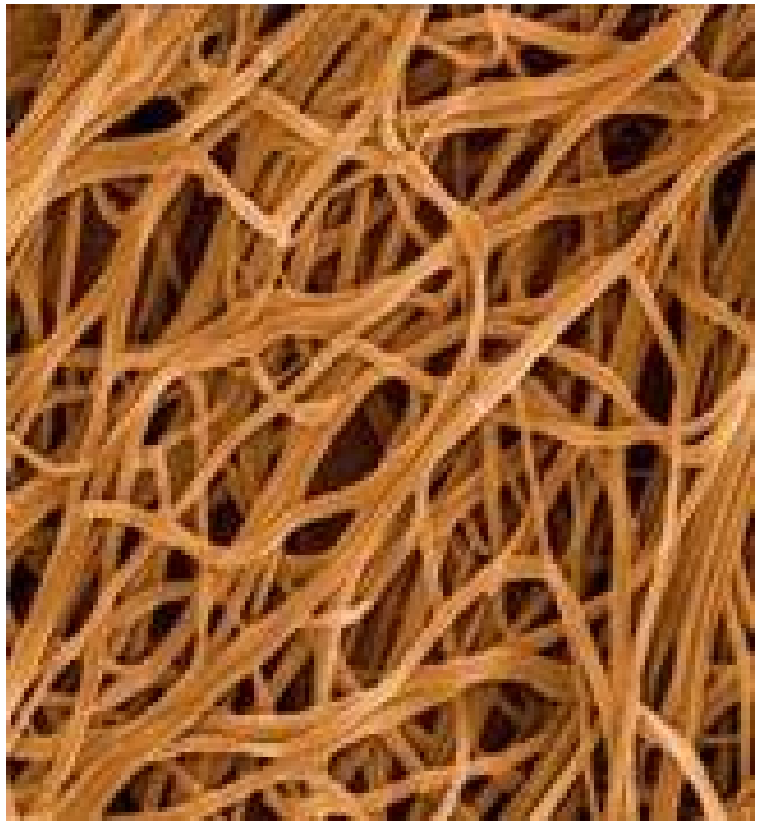
- Digestive Enzymes
- Clotting Factors
  - Factor X
  - Factor XI
  - Thrombin
  - Plasmin
- Complement Factors

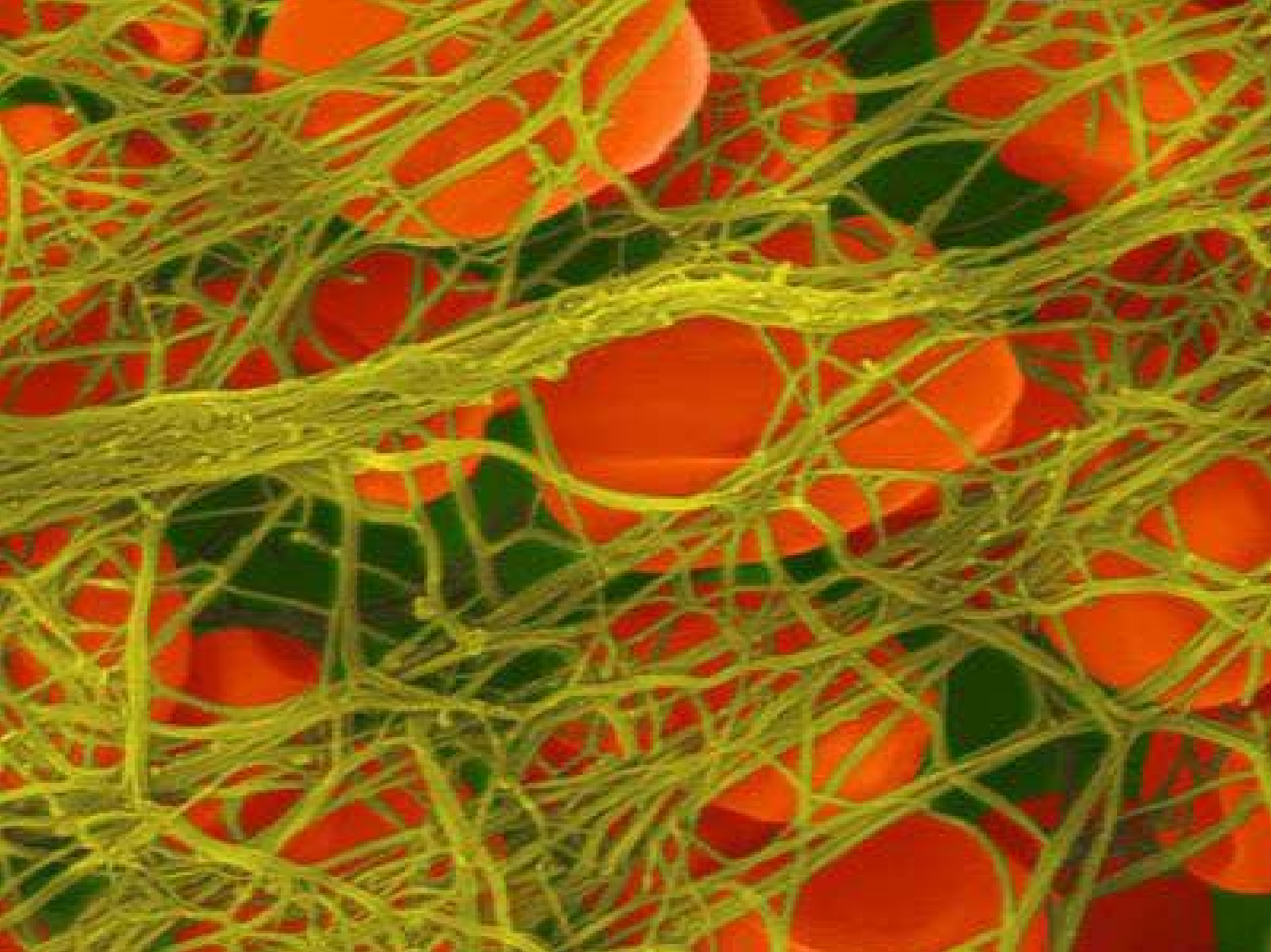
The Coagulation Cascade

- Initiated by damage to the wall of the endothelium
- Enzyme mediated
- Ca++
- Amplification
- Positive Feedback

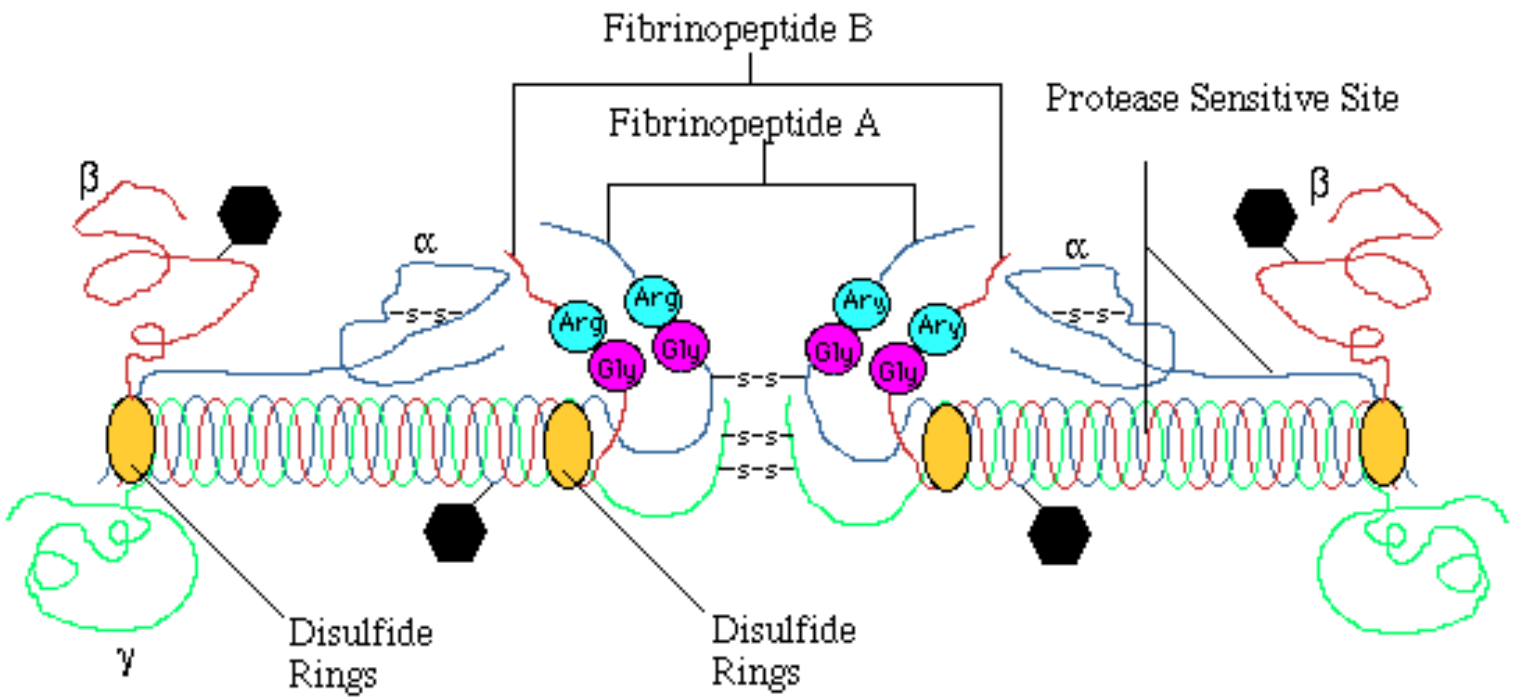


Fibrin Clot Formation

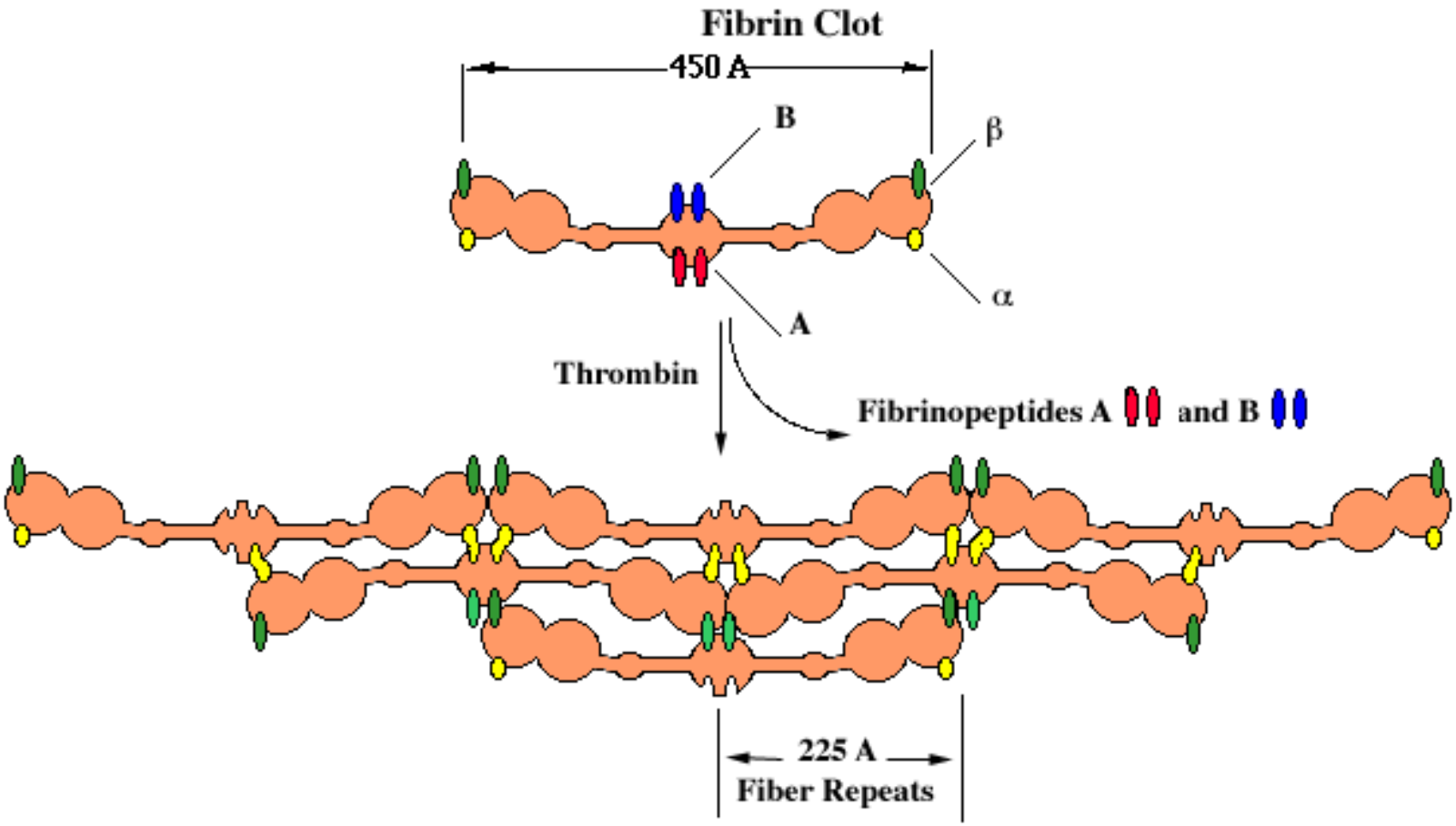




Fibrinogen Structure



The disulfide rings are regions containing three disulfide bonds cyclically linking homologous segments of the α, β, and, γ chains. N-linked polysaccharide are represented by filled hexagons. The Arg-Gly bonds that are cleaved by thrombin in fibrin activation are indicated.


Fibrin Clot
450 A
B
β
α
A
Thrombin
Fibrinopeptides A and B
225 A
Fiber Repeats

Dissolving the Clot and Anticoagulants

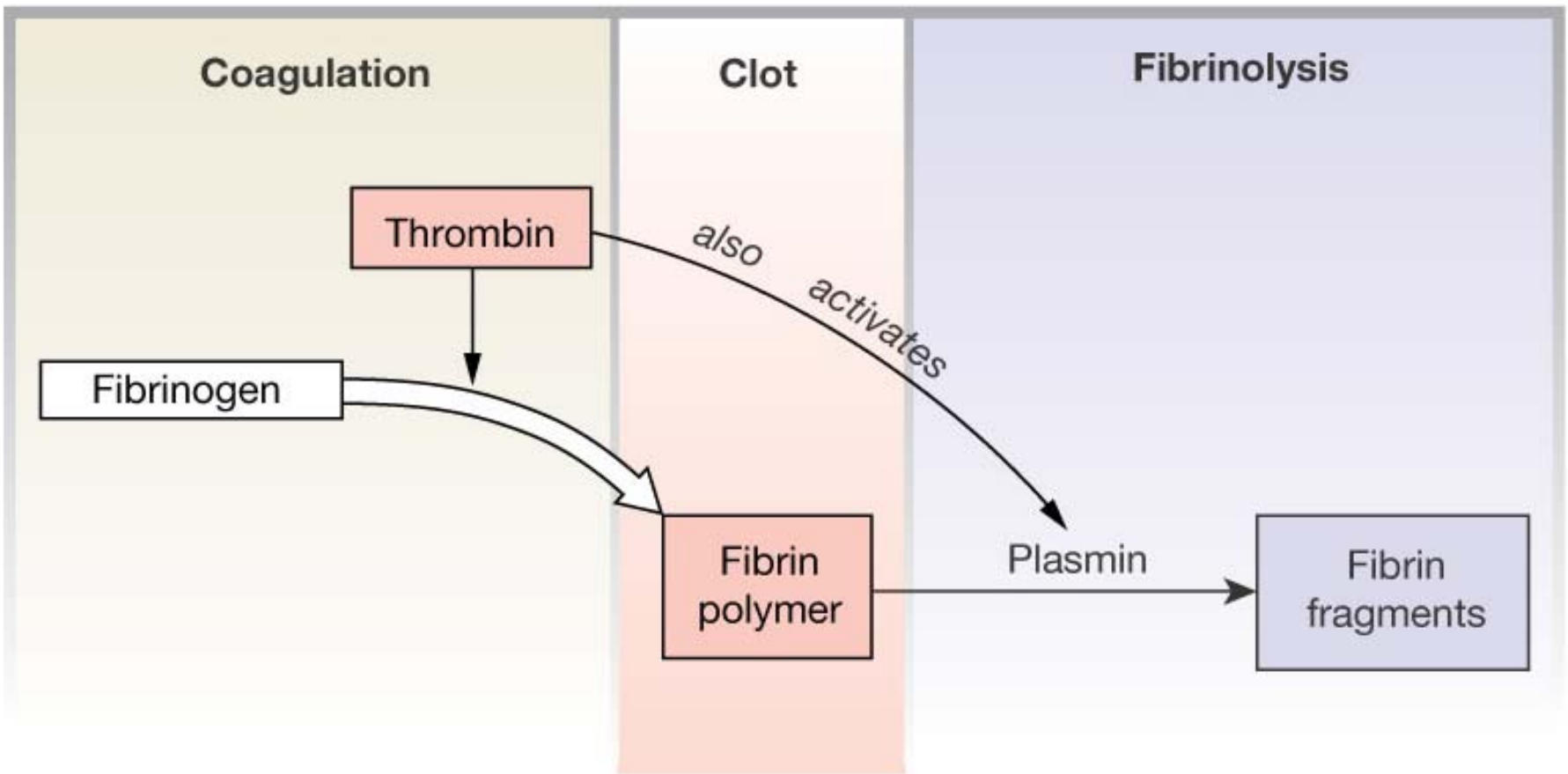


Figure 16-14: Coagulation and fibrinolysis

Serpins (Serine Protease Inhibitors)

Here is a list of a few important serine proteases and the serpins that control them.

Serine Protease	Serpin
Chymotrypsin	alpha-1-antichymotrypsin
Complement factor C1s	C1 Inhibitor (C1INH)
Elastase (secreted by neutrophils)	alpha-1-antitrypsin
Clotting factor 10 (X)	antithrombin III
Thrombin	antithrombin III
Plasmin	alpha-2-antiplasmin
Trypsin	pancreatic trypsin inhibitor

How Serpins Work

Inhibits the action of their respective serine protease by mimicking the three-dimensional structure of the normal substrate of the protease.

The serine protease binds the serpin instead of its normal substrate.

The protease makes a cut in the serpin leading to

- the formation of a covalent bond linking the two molecules;
- a massive allosteric change in the tertiary structure of the serpin;
- which moves the attached protease to a site where it can be
- destroyed.

Importance of Serpins

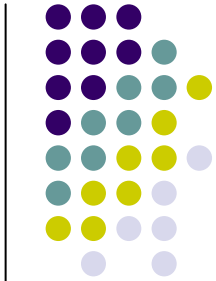
Almost 20% of the proteins found in blood plasma are serpins.

Their abundance reflects their importance: putting a stop to proteolytic activity when the need for it is over.

This is especially important for the

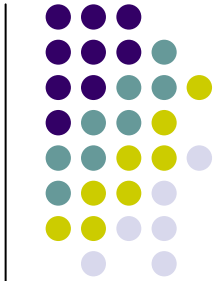
- clotting and
- complement
- systems where a tiny initial activating event leads to a rapidly amplifying cascade of activity.

Complement Activation



- Blood-materials interactions-protein adsorption;
- The Complement system is a complex cascade involving approximately 30 glycoproteins present in serum as well as cell surface receptors;
- Activation of the inflammation and immune related function.

Acute Inflammation



Lasts from minutes to days depending on the injury

Initial stages:

- rapid dilation of local capillaries
- increase in the permeability of their endothelial cell linings

Dilation leads to an increase in blood entry into the capillary beds

- loss of plasma through the capillary walls
- platelets and erythrocytes become sticky
- blood flow slower and sludgy

Causes of Acute Inflammation

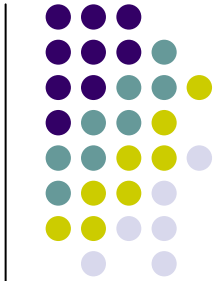
Tissue damage-physical agents

Irritant or corrosive chemicals

Tissue necrosis

Hypersensitivity reaction

Microbial infections



Clinical Signs of Inflammation:

Redness

Swelling

Heat

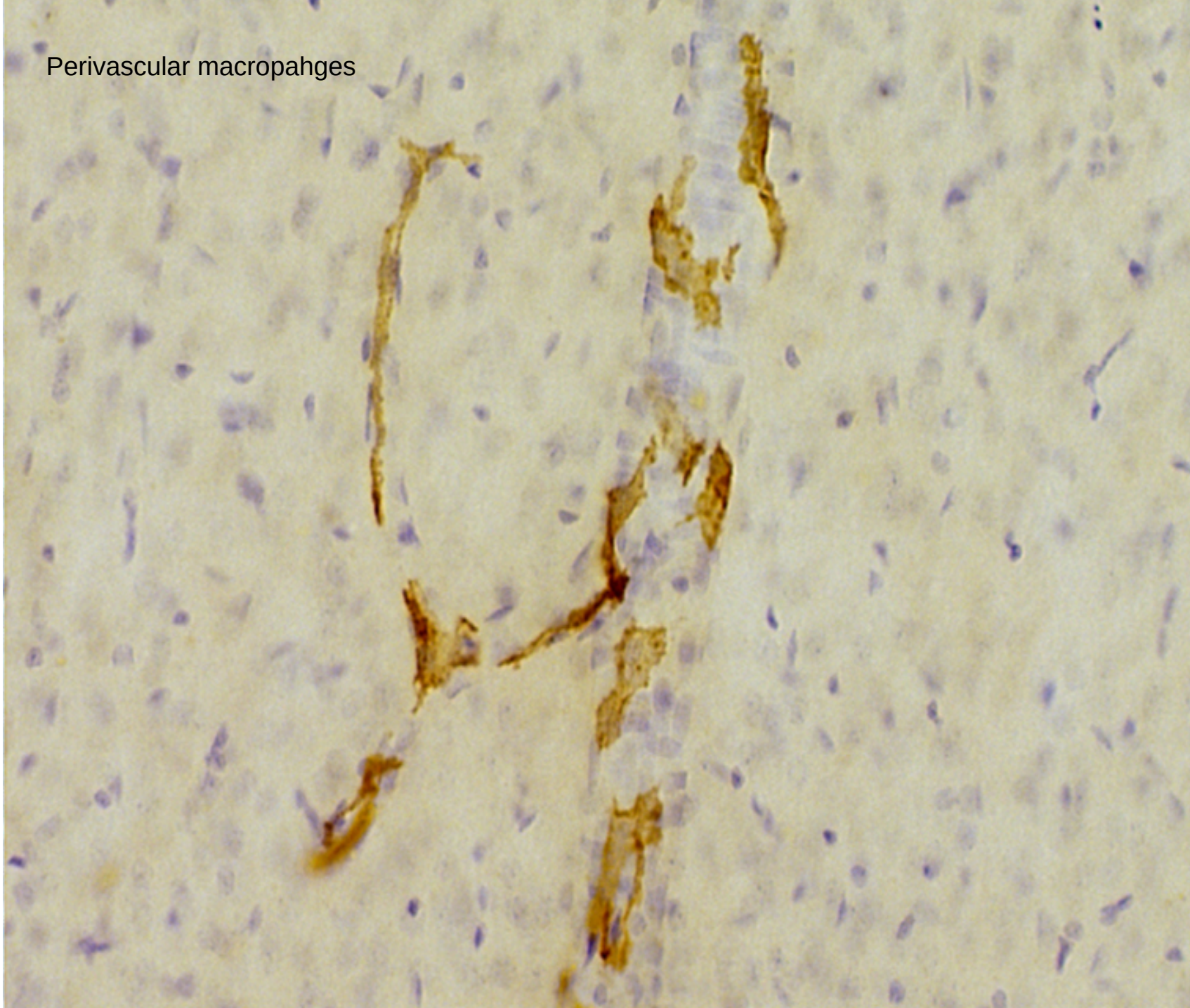
Pain

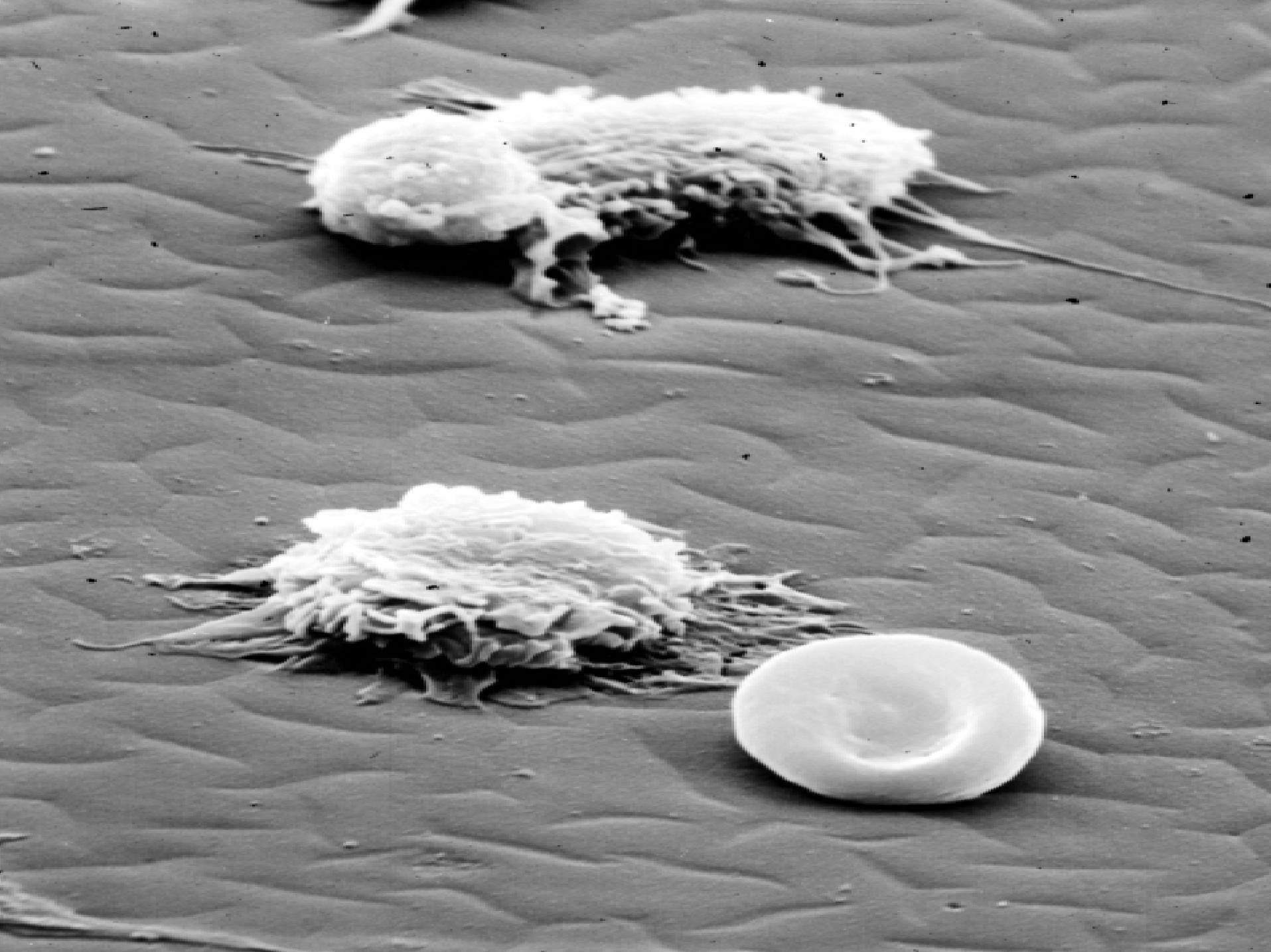
Loss of function

Neutrophil (a granulocyte) First Cells to Appear at Injury Site

- stick to capillary endothelium, penetrate between the endothelial cells and move into the surrounding damaged tissue;
- neutrophil emigration (diapedisis) begins minutes to hours after insult and may continue for as long as 24h;
- neutrophil activates when engages foreign particle such as a damaged cell, pathogen, damaged matrix, or a biomaterial; and, they
- release interleukin-1 (IL-1), Monocyte chemoattractant protein (MCP-1) tumor necrosis factor (TNF-alpha) called proinflammatory cytokines because they recruit monocytes to the injury site.

Perivascular macropahges





Monocytes -> Macrophages

Phagocytosis: Engulfing and degradation or digestion of fragments of tissue or material

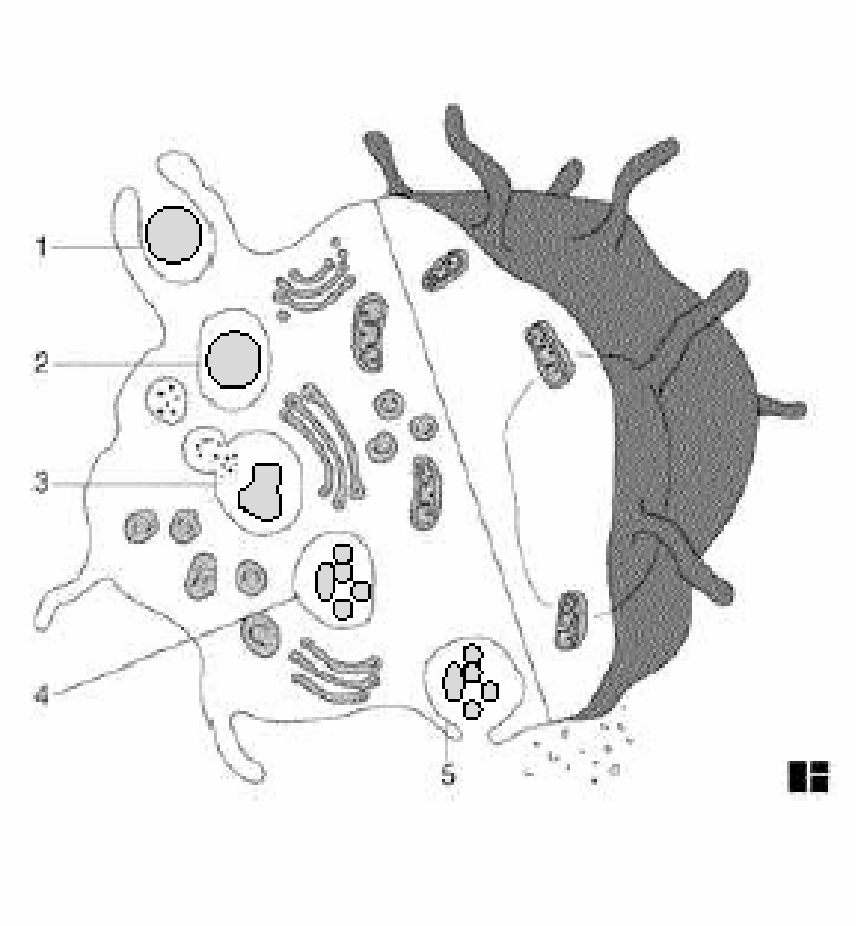
1. Attachment of the foreign particle to the long membrane evaginations, called pseudopodia.

2. Ingestion of the particle forming a "phagosome," which moves toward the lysosome.

3. Fusion of the lysosome and phagosome (phagolysosome), releasing lysosomal enzymes into the phagosome.

4. Digestion of the ingested material.

5. Release of digestion products from the cell.



Chronic Inflammation

Macrophages produce great number of biologically active products

- proteases
- chemotactic factors
- coagulation factors
- growth promoting factors
- cytokines
- Growth factors (e.g. PDGF, FGF, TGF-b, IL-1, TNF, VEGF) are essential for: the growth of fibroblasts and blood vessels and the regeneration of epithelial cells
  - stimulate the production of a wide variety of cells
  - initiate cell migration and differentiation
  - tissue remodeling and wound healing

TABLE 4 Tissues and Cells of MPS and RES

Tissues	Cells
Implant sites	Inflammatory macrophages
Liver	Kupffer cells
Lung	Alveolar macrophages
Connective tissue	Histiocytes
Bone marrow	Macrophages
Spleen and lymph nodes	Fixed and free macrophages
Serous cavities	Pleural and peritoneal macrophages
Nervous system	Microglial cells
Bone	Osteoclasts
Skin	Langerhans' cells
Lymphoid tissue	Dendritic cells

Angiogenesis-
growth of new blood vessels

- Under normal conditons, angiogeneis is quiescent in the adult human and stimulation of new blood vessels is thought to result from an alteration in the local balance of pro-angiogneic and anti-angiogenic growth factors.

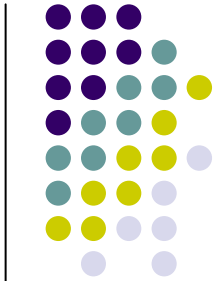
Angiogenesis-
growth of new blood vessels

- Induced by low oxygen levels
- Induced by low pH
- Induced by elevation of cytokines
- New blood vessels deliver oxygen, nutrients and inflammatory cells to the wound site that facilitates removal of debris.
- Increase in oxygen enhances collagen synthesis so it is thought that angiogensis must precede extracellular matrix maturation and remodelling.

Angiogenic Factors

- VEGF-vascular endothelial growth factor
  - Secreted by macrophages and fibroblasts
- bFGF-basic fibroblastic growth factor
- bFGF-elevated initially and after 48 hours decreases to baseline, whereas VEGF levels peak several days after injury

Fibroblast Play a Major Role in Wound Repair

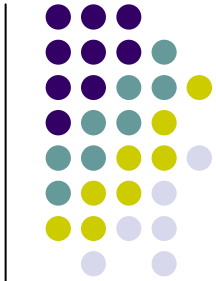


- Migration into the wound site
  - Integrin mediated cell-matrix attachment
- Proliferation in response to PDGF, FGF and TGF-beta
- Produce extracellular matrix
- Produce VEGF-stimulate angiogenesis

The combination of ECM, fibroblasts and new blood vessels is often referred to as granulation tissue.

- Differentiation into Myofibroblasts-smooth muscle like phenotype-alpha-smooth muscle actin and myosin-like motor proteins that augment contractile force.
- Contraction of Wound-Fibrous encapsulation
- Disappear by apoptosis after wound closure

Granulation Tissue



- hallmark of healing inflammation
- derives its name from the pink, soft granular appearance on the surface of healing wounds
- may be seen as early as 3-5 days following implantation of a biomaterial
- New small blood vessels are formed by budding or sprouting of preexisting vessels in a process known as “neovascularization” or “angiogenesis”
  - Angiogenesis involves proliferation, maturation, and organization of endothelial cells into capillary tubes

Myofibroblasts

- Main cellular type in granulation tissue
- Contain abundant stress filaments and smooth muscle like contractile machinery
- Are interconnected by gap junctions
- Main cellular type involved in extracellular matrix deposition;

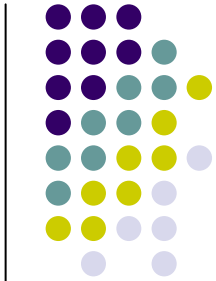
Wound Contraction & Scarring

- Late stage process
- Cells at the wound site generate tractional and contractional forces on secreted matrix molecules to assist in wound closure.
- The number of cells, the amount of matrix deposited and the force exerted determines whether the wound will close appropriately, as well as the amount of scar tissue produced-encapsulation tissue.

Mechanical Attachment of Cells

- Key event in the process
- May regulate whether the process occurs normally or in a pathologic manner.
- Involves a variety of matrix components and may be thought of as consisting of a series of linked stages including:
  - Initial cell matrix contact
  - Recruitment of attachment sites to focal contact formation;
  - Cytoskeletal organization and spreading;
  - Cell-matrix tractional force generation and eventual cell contraction;
  - Matrix deformation (shortening)

Outcomes of Acute Inflammation

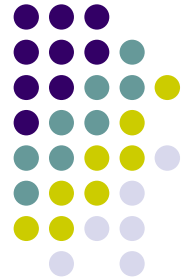


- **Complete resolution**
  - Limited tissue injury or short lived inflammation
  - In tissue capable of regeneration
    - Removal of chemical mediators
    - Normalization of vascular permeability
    - Cessation of leukocyte emigration
    - MF and lymph drainage clear edema, cells and debris
- **Scarring or fibrosis**
- **Abscess formation**
- **Progression to chronic inflammation**

Chronic Inflammation

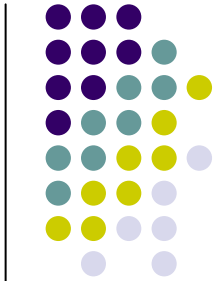
- Occurs when acute cannot be resolved
- Persistent infections
  - Select bacteria and fungi
    - Causal agents of tuberculosis and syphilis
  - Culminate in **granulomatous reaction**
- Prolonged exposure to toxic agents
  - Nondegradable exogenous material
    - Biomaterial
    - Inhaled particulate silica
- Autoimmune diseases
  - SLE, rheumatoid arthritis

Characteristics of Chronic Inflammation



- **Infiltration with mononuclear cells**
- **Tissue destruction**
- **Repair involving angiogenesis and fibrosis**
- Can go on for weeks, months or years where inflammation, tissue injury and healing proceed simultaneously

Infiltration with mononuclear cells



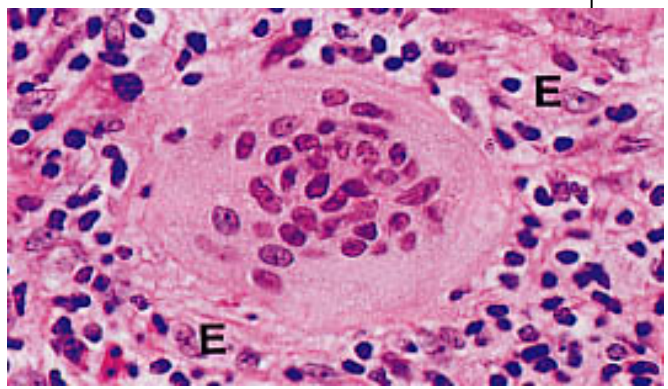
- **Blood monocytes, tissue macrophages**
  - Secrete many chemical mediators
    - proteases, complement components and coagulation factors, reactive oxygen species and NO, eicosanoids, cytokines (IL-1, TNF) and growth factors
  - Mediate tissue destruction
  - Mediate angiogenesis
    - formation of new blood vessels
  - Mediate fibrosis
- **Lymphocytes, plasma cells, eosinophils**

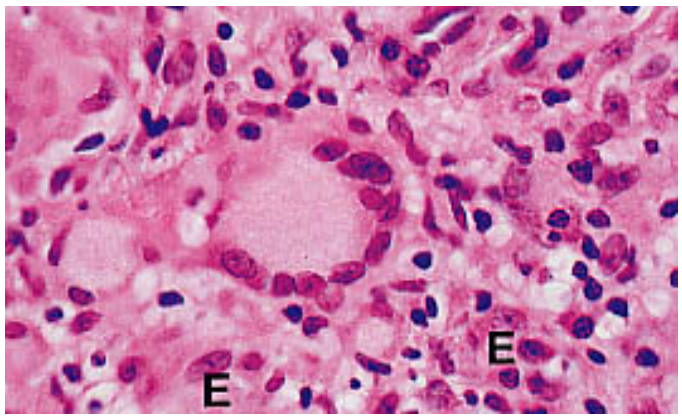
Granulomatous Inflammation

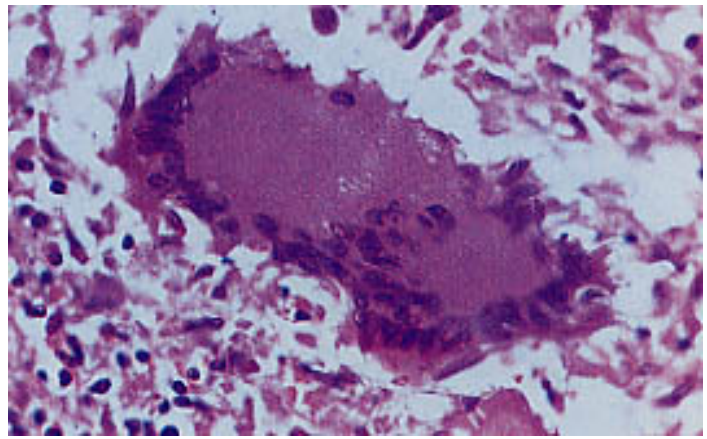
- A distinctive pattern of chronic inflammation
  - aggregations of **activated macrophages**
    - enlarged squamous cell-like appearance.
  - **foreign body giant cells**
  - **lymphocytes**
- Encountered in relatively few pathological states
  - TB, leprosy, syphilis,schistosomiasis, silicosis
  - Foreign bodies
    - Suture, vascular graft, breast implant

Foreign Body Giant cells

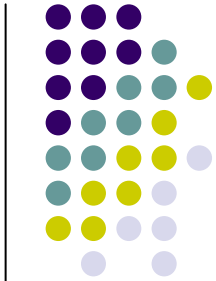
- Fusion of 100s of macrophages and monocytes







Chronic Inflammation



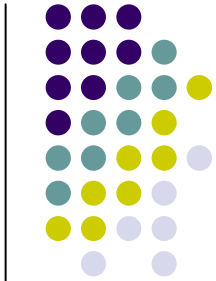
Persistent inflammatory stimuli such as a foreign body or biomaterial lead to chronic inflammation:

- chemical and physical properties of biomaterial
- motion in the implant site
- Confined to the implant site

Characterized by:

- the presence of macrophages, monocytes, and lymphocytes
- proliferation of blood vessels and connective tissue
- no exudates

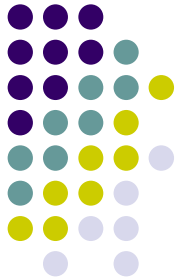
Foreign Body Reaction



consists of:

- multinucleated foreign body giant cells
- macrophages
- fibroblasts
- capillaries
- Multinucleated foreign body giant cells form upon coalescence of macrophages

Surfaces of Biomaterials



Three lectures:

2.02.04 – Surface Properties of Biomaterials

2.04.04 – Surface Characterization

2.06.04 – Surface and Protein Interactions

Three points:

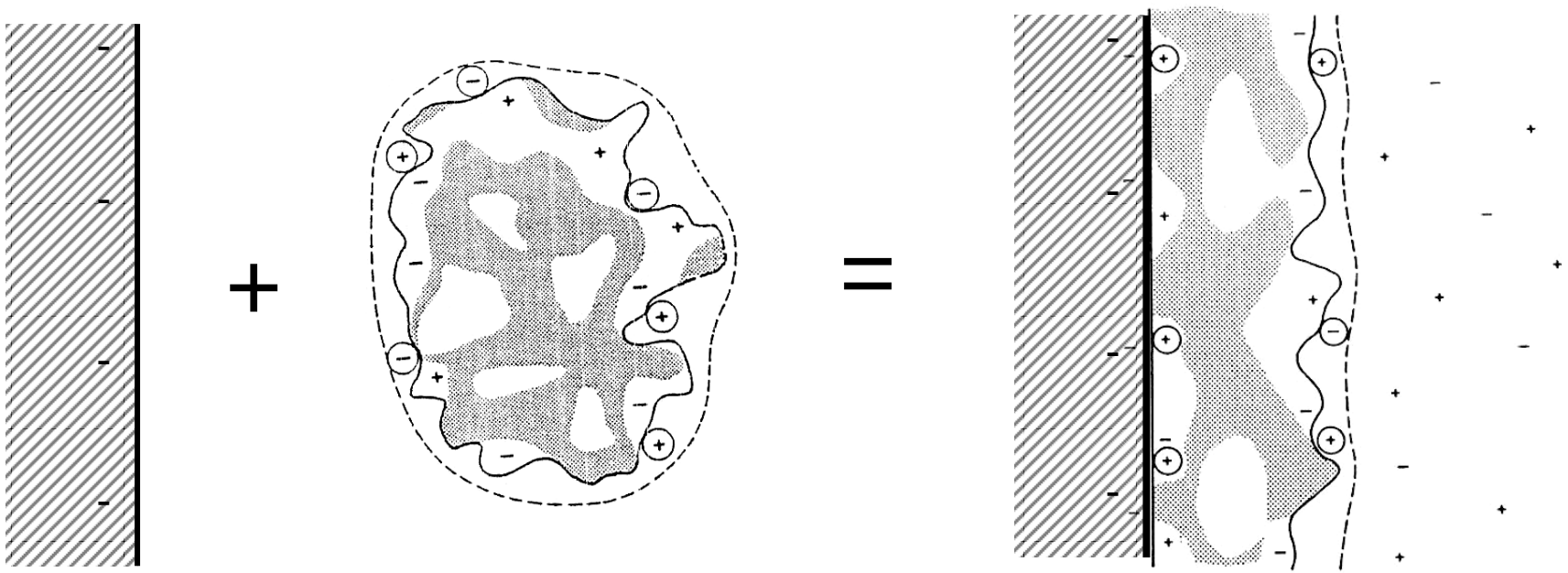
1 – Surfaces have unique properties

2 – We can (and do) measure these properties

3 – Because they affect biocompatibility

Protein Coating

Adsorption of proteins to a surface creates a new surface



Surface Protein Solution New Surface

Bioreaction – Short and Long Term

Implant into soft tissue:

9 Different Materials:

- Polyethylene
- Hydroxyapatite
- Polyurethane
- Silicone
- pHEMA
- PTFE (Gore-tex)
- Pyrolytic carbon
- Gold
- Titanium

Short Term Reaction:

- Differential Protein Adsorption
- Varied Activation of Host Response

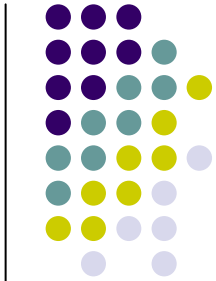
Long Term Reaction:

- Fibrous Encapsulation

Hydrophilic
Hydrophobic
Metal
Polymer
Hard/Soft

→ The SAME RESULT!

FBR Depends on the Geometry and the Form of the Implant



flat and smooth surfaces such as those found on breast prostheses; FBR is composed of a layer of macrophages one to two cells in thickness

relatively rough surfaces such as those found on the outer surfaces of vascular prosthesis; FBR composed of multiple layers of macrophages and foreign body giant cells at the surface

rough surfaces such as fabric-type materials; composed of macrophages and foreign body giant cells with varying degrees of granulation tissue

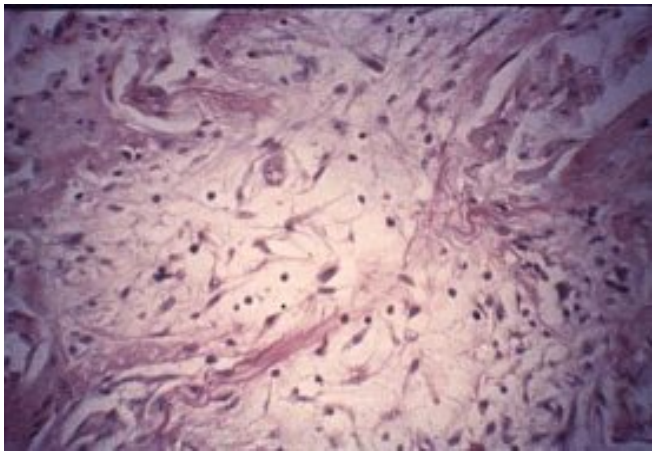
Foreign Body Reaction

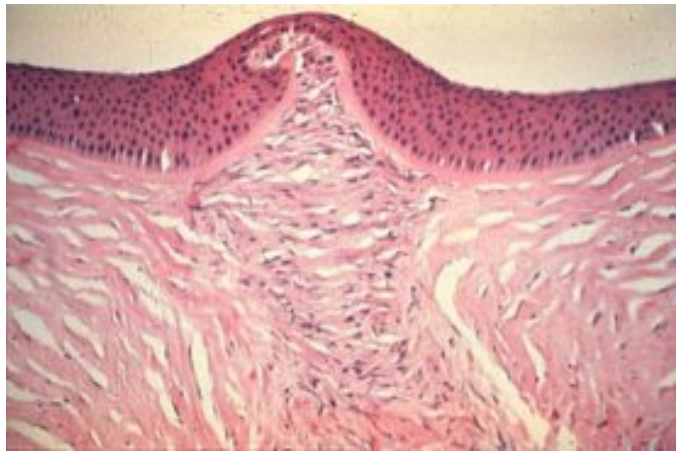
- FBR consisting mainly of macrophages and foreign body giant cells may persist at the tissue implant interface for the lifetime of the implant
- FBR is surrounded by a fibrous tissue that isolates the implant and the FBR from the local tissue environment
- Multinucleated foreign body giant cells may persist for the lifetime of the implant, it is not known whether they remain activated releasing their lysosomal contents, or become quiescent.

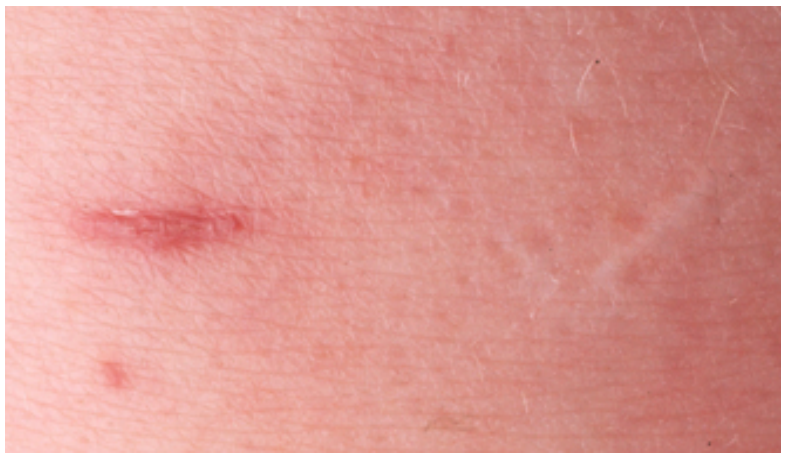
Fibrous Encapsulation

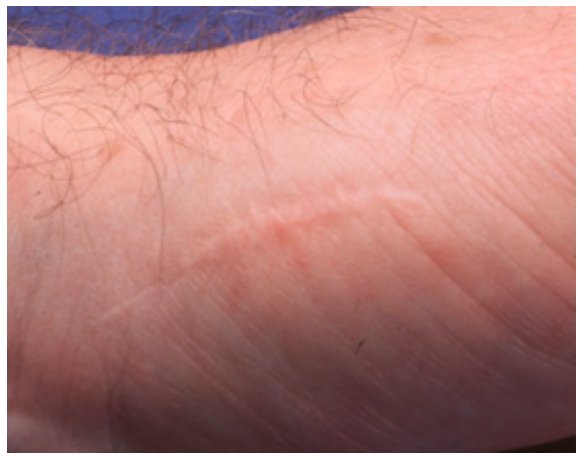
- End stage of healing response
- Usually four or more weeks after implantation
- A relatively acellular fibrous capsule
  - spindle shaped fibroblasts
  - small number of macrophages
- Presence of neutrophils suggests persisting inflammatory challenge
- Presence of macrophages suggests production of small particles by corrosion, depolymerization, dissolution or wear

Scars

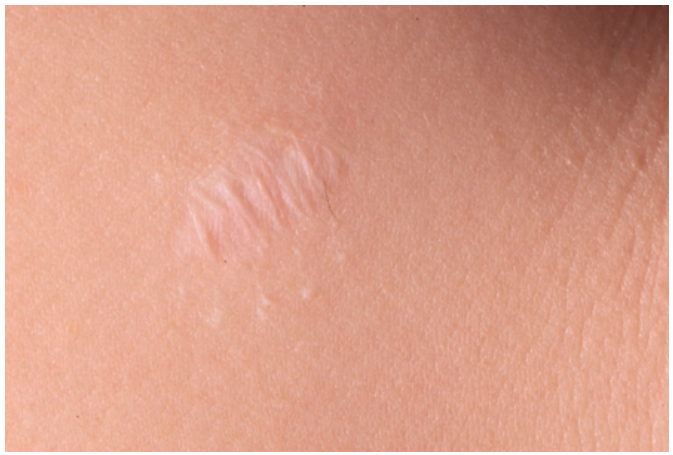


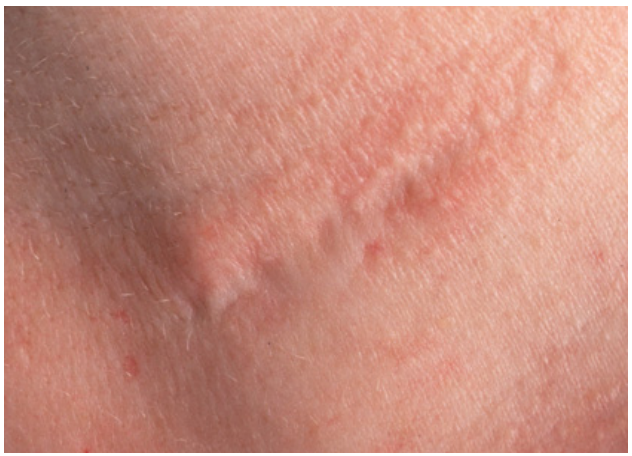






Mechanical Interference with Healing





- **Mechanical stress on the wound creates a larger scar, may cause dehiscence**
  - hypertrophic scarring where skin is repetitively stretched: neck, back, joints
  - inject steroids into scar to reduce size
  - cut skin along Langer's lines, with bundles, causes less wound gapping
  - evert edges

Fibrous Encapsulation

- Presence of lymphocytes suggests specific immune response
- Thickness of the capsule depends on the chemical activity (rate of release) of the material:
  - metals which corrode freely
  - polymers with leachable constituents
- Capsule thickness will increase with relative motion between the implant and the tissue
- Shape of the implant: capsule will be thicker over sharp edges

Possible outcomes for the implant:

- resorption: if the implant is resorbable then the implant site eventually resolves to a collapsed scar or, in the case of bone, may completely disappear
- integration: very limited occurrence in practice; close approximation of normal host tissue to the implant without an intervening capsule (e.g. implantation of pure titanium in bone)
- encapsulation: the most usual response

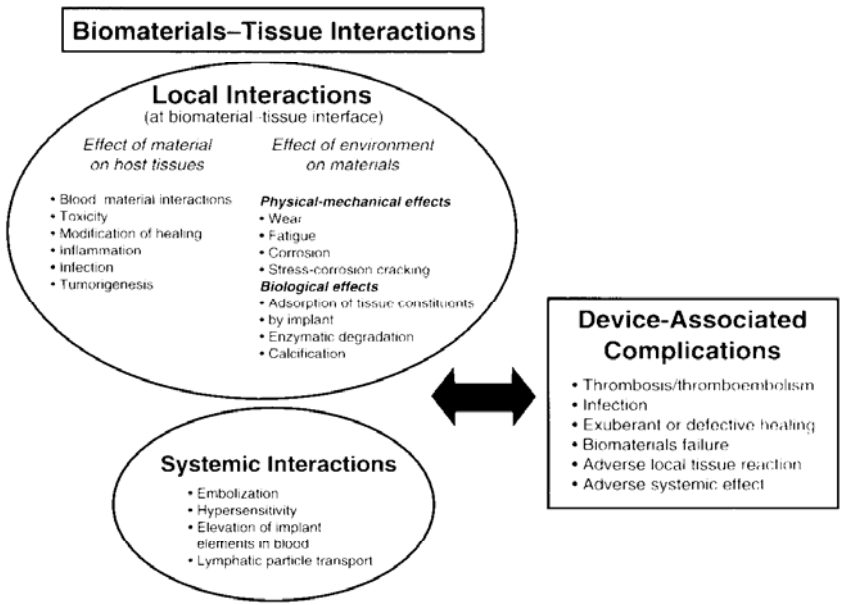
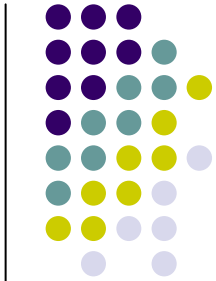


FIG. 1. Biomaterials–tissue interactions (reproduced from Schoen FJ). In: *Advances in Cardiovascular Medicine* (Harvey 1602–2002 Symposium, on the 4th Centenary of William Harvey's Graduation at the University of Pauda), Thiene G, Pessina AC (eds.), Universita degli Studi di Padova, 2002; 289–307.

Tissue Injury



- Necrosis (death by extrinsic means)
- Apoptosis (death by suicide)
- Atrophy (decrease in cell size and/ or function)
- Hypertrophy (increase in cell size)
- Hyperplasia (increase in cell numbers)
- Metaplasia (change in cell type)
- Change in phenotype (change in the type and/or amount of protein characteristic of a particular cell type)

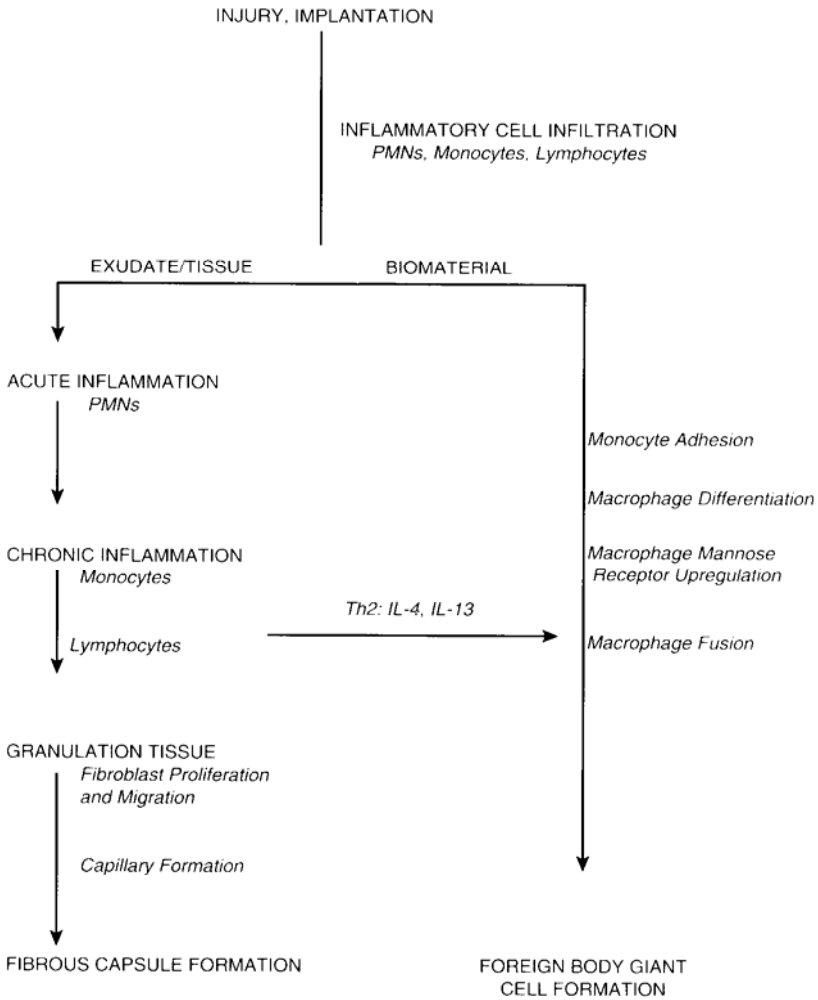


FIG. 8. Sequence of events involved in inflammatory and wound-healing responses leading to foreign-body giant cell formation. This shows the important of Th2 lymphocytes in the transient chronic inflammatory phase with the production of IL-4 and IL-13, which can induce monocyte/macrophage fusion to form foreign-body giant cells.

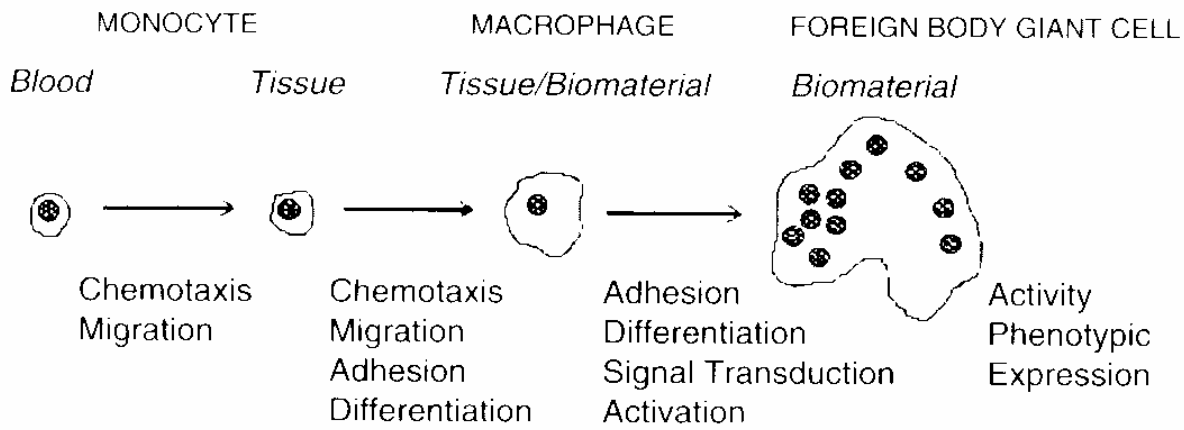
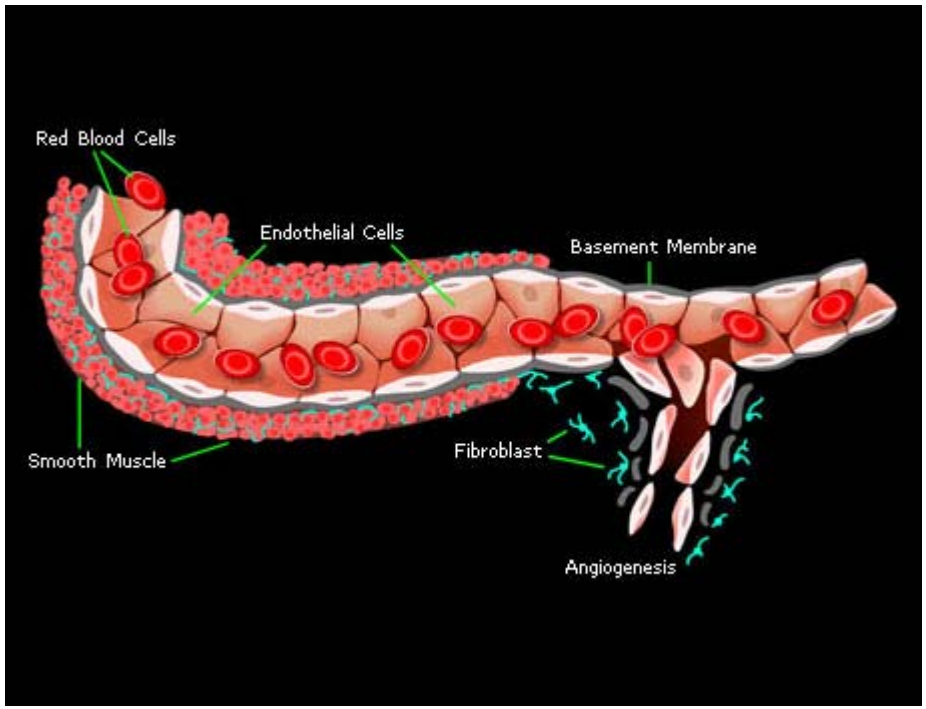


FIG. 5. *In vivo* transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign-body giant cell at the tissue–biomaterial interface. Little is known regarding the indicated biological responses, which are considered to play important roles in the transition to FBGC development.

Angiogenesis-
growth of new blood vessels

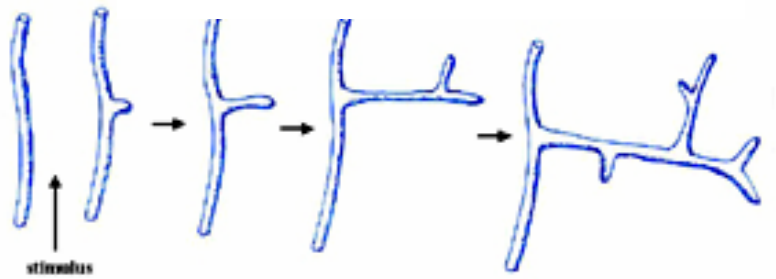
- A balance of pro-angiogenic and anti-angiogenic growth factors.



Angiogenesis-
growth of new blood vessels

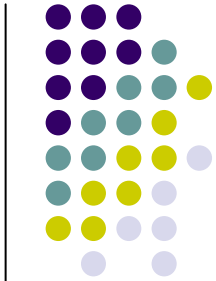
- low oxygen levels
- low pH
- cytokines
- New blood vessels deliver oxygen, nutrients and inflammatory cells to the wound site that facilitates removal of debris.
- Increase in oxygen enhances collagen synthesis so it is thought that angiogensis must precede extracellular matrix maturation and remodelling.

Angiogenic Factors



- VEGF-vascular endothelial growth factor
  - Secreted by macrophages and fibroblasts
- bFGF-basic fibroblastic growth factor
  - Secreted by fibroblasts
- bFGF-elevated initially and after 48 hours decreases to baseline, whereas VEGF levels peak several days after injury

Fibroblast Play a Major Role in Wound Repair

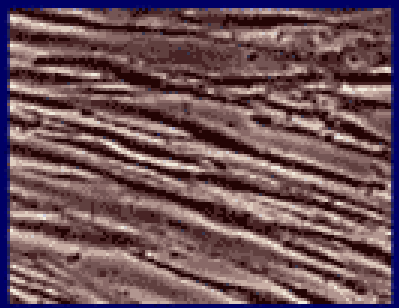


- Migration into the wound site
- Proliferation in response to PDGF, FGF and TGF-beta
- Produce extracellular matrix
- Produce VEGF-stimulate angiogenesis
  - granulation tissue.
- Differentiation into Myofibroblasts
- Contraction of Wound-Fibrous encapsulation
- Disappear by apoptosis after wound closure

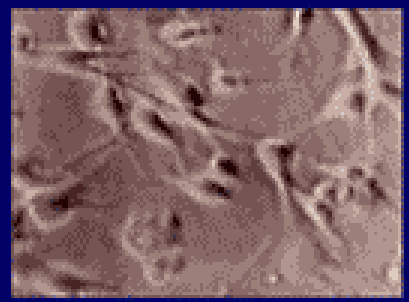
Myofibroblasts

- Main cellular type in granulation tissue
- Contain abundant stress filaments and smooth muscle like contractile machinery
- Are interconnected by gap junctions
- Main cellular type involved in extracellular matrix deposition;

Fibroblast populated collagen lattice - model of connective tissue remodelling and cell-matrix interaction



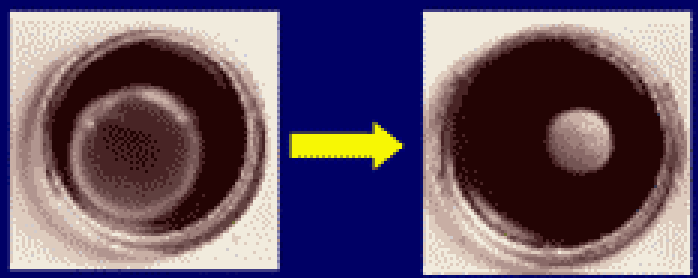
Monolayer culture



3-D lattice culture

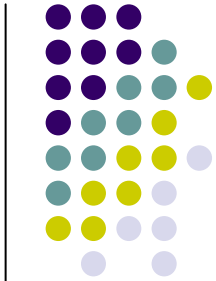
Gel contraction - quantified by diameter, area or wet weight

1 h



24 h

Outcomes of Acute Inflammation



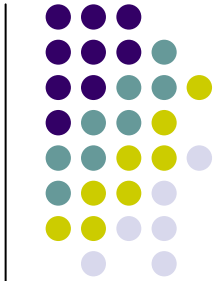
- Complete resolution
- Scarring or fibrosis
- Progression to chronic inflammation

Chronic Inflammation

Occurs when acute reaction cannot be resolved

- Persistent or severe infections
- Prolonged exposure to toxic agents
- Persistant injury

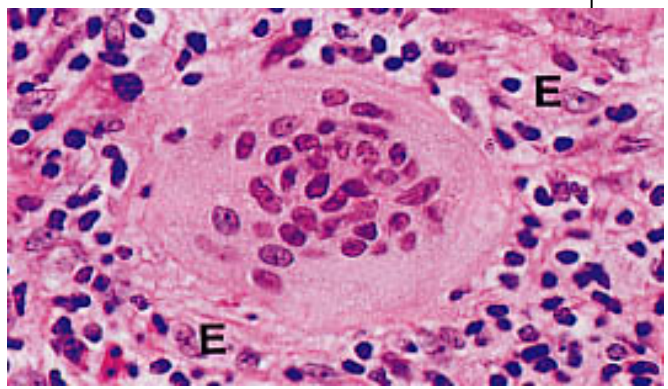
Characteristics of Chronic Inflammation

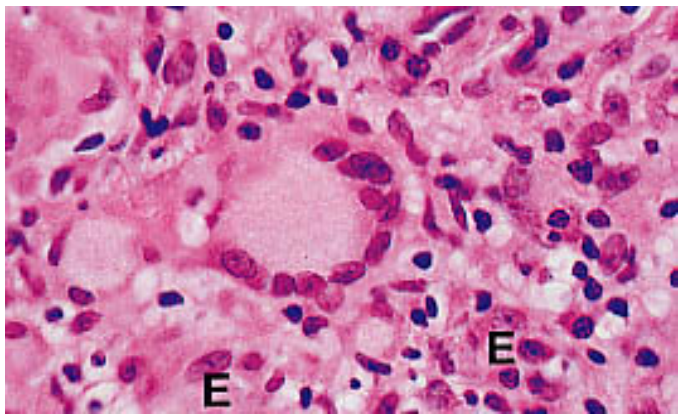


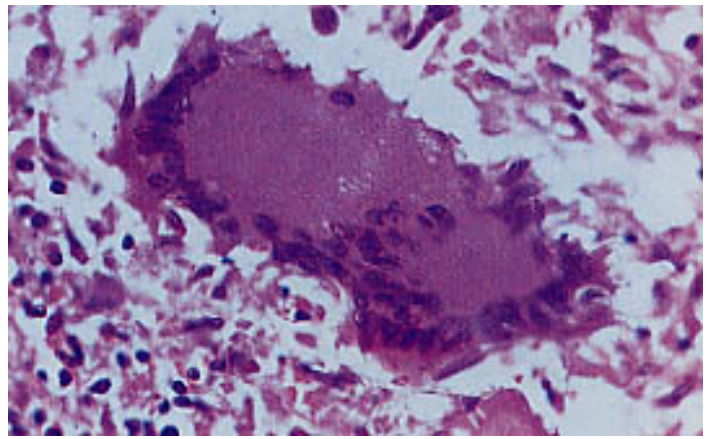
- Infiltration with macrophages
- Foreign body giant cells
- Tissue destruction
- Can go on for weeks, months or years where inflammation, tissue injury and healing proceed simultaneously

Foreign Body Giant Cells

- Fusion of 100s of macrophages and monocytes







Bioreaction – Short and Long Term

Implant into soft tissue:

9 Different Materials:

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- Silicone
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- PTFE (Gore-tex)
- Pyrolytic carbon
- Gold
- Titanium

Short Term Reaction:

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- Varied Activation of Host Response

Long Term Reaction:

- Fibrous Encapsulation

Hydrophilic
Hydrophobic
Metal
Polymer
Hard/Soft

→ The SAME RESULT!

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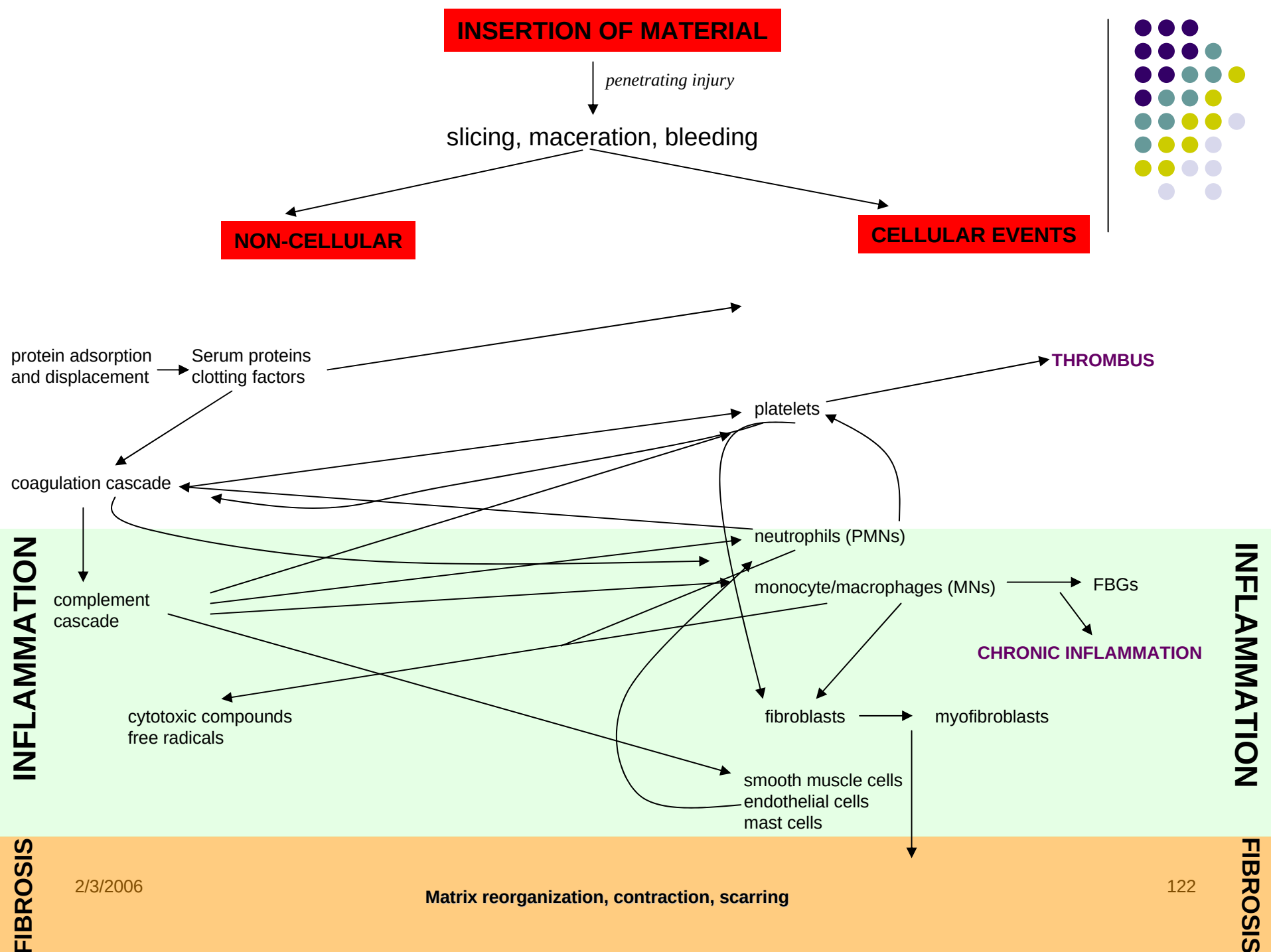
INSERTION OF MATERIAL
penetrating injury
slicing, maceration, bleeding
NON-CELLULAR
CELLULAR EVENTS
protein adsorption and displacement
Serum proteins clotting factors
THROMBUS
platelets
coagulation cascade
neutrophils (PMNs)
INFLAMMATION
complement cascade
monocyte/macrophages (MNs)
FBGs
CHRONIC INFLAMMATION
cytotoxic compounds free radicals
fibroblasts
myofibroblasts
smooth muscle cells
endothelial cells
mast cells
INFLAMMATION
FIBROSIS
Matrix reorganization, contraction, scarring
FIBROSIS