CHS 2413
Pathology and Physiopathology

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Summary

This talk has covered….

- Wound
- Wound Healing
- Phases of healing
- Factors Impaired Wound Healing
- Wound Healing and the Presence of Biomaterials
- Mechanisms of Disease: Regeneration and Fibrous Repair
- Special features of healing in specific organs
- Cellular response in Regeneration or Healing (repair)

WOUND HEALING

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Factors improved wound healing

Electro-stimulation

- Electrical current applied to wounds
  - Increases migration of cells
  - 109% increase in collagen
  - 40% increase in tensile strength
  - 1 to 50 mA direct or pulsed based on wound

Hyperbaric Oxygen

  - Developed 1662 by Henshaw: Domicillium
  - Atmospheric pressure at sea level = 1 ATA = 1.5ml O2/dL
  - Normal SubQ O2 tension is 30-50 mmHg.
  - SubQ O2 tension < 30 mmHg = chronic wound

Factors that impede healing

- Extent of injury
  - Microtears vs. macrotears
- Edema
  - Increased pressure causes separation of tissue, inhibits neuro-muscular control, impedes nutrition, neurological changes
- Separation of tissue
  - How tissue is torn will effect healing
    - Smooth vs. jagged
- Traction on torn tissue, separating 2 ends
  - Ischemia from spasm spasm
- Atrophy
- Hemorrhage
  - Bleeding causes same neg. effect as edema
- Poor vascular supply
  - Tissues with poor vascular supply heal at a slower rate
  - Failure to deliver phagocytic cells and fibroblasts for scar formation
- Corticosteroids
  - In early stages shown to inhibit healing
- Keloids or hypertrophic scars
- Infection
- Health, Age and nutrition

Wound Healing and the Presence of Biomaterials

Topics:

- Formation of Granulation Tissue
- Foreign Body Reaction
- Fibrous Encapsulation
- Chronic Inflammation
- Types of Implant Resolution
- Repair vs. Regeneration

Complications of Repair

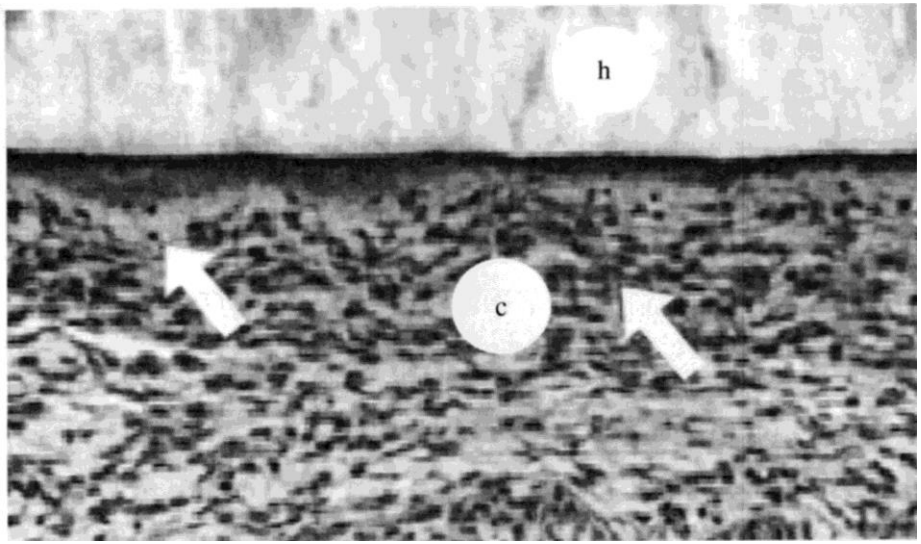
- Insufficient fibrosis:
  - Wound dehiscence; hernia; ulceration
- Excessive fibrosis:
  - Cosmetic scarring; hypertrophic scars; keloid
- Excessive contraction:
  - Limitation of joint movement (Contractures); obstruction of tubes & channels (Strictures)

Chronic Wound Healing (Non Healing Ulcer)

Delayed or obstructed Healing Phase

Characterized by the presence of mononuclear cells, including lymphocytes and plasma cells

Can include presence of ***granulomas –*** a layered structure comprised of a nonphagocytosable particle surrounded by a layer of FBGCs, a layer of modified macrophages called *Epithelioid cells*, and surrounded by a layer of lymphocytes



Subcutaneous model showing:

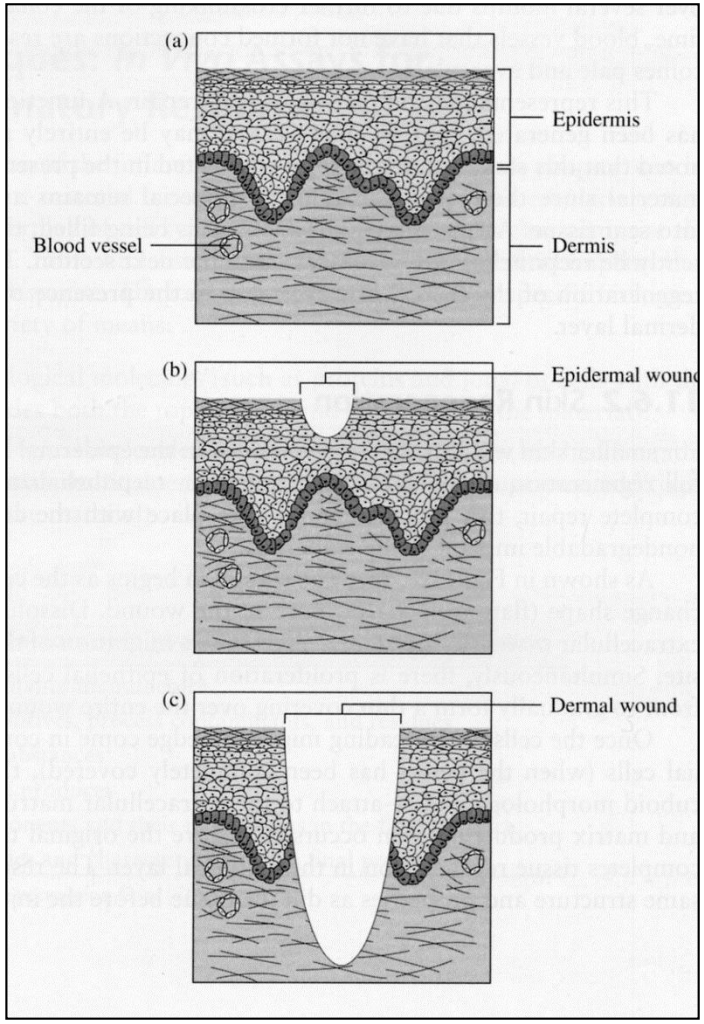
- Polymer hydrogel implant (h)
- Macrophages (right arrow)
- Lymphocytes (left arrow)
- C: beginning of fibrous capsule

Wound healing in Skin

Repair vs. Regeneration

Regeneration is regrowth of thin outer *epidermal* layer

Repair involves healing of the internal *dermal* layer, often ends with a scar.



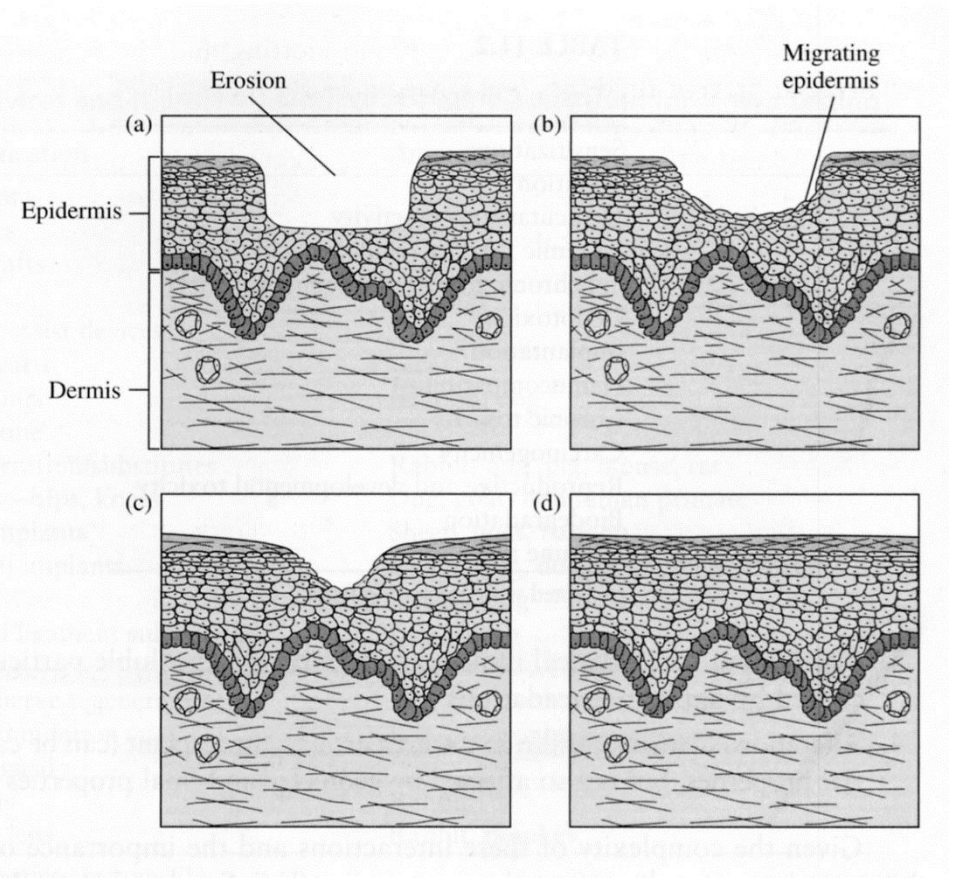
Skin Regeneration

In the epidermis, this process is called *reepithelilization.*

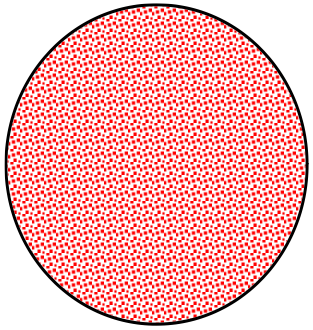
Cells at edge of wound flatten to cover more of the wound, releasing attachment to ECM to migrate across wound

Epithelial cells gradually cover the entire wound site

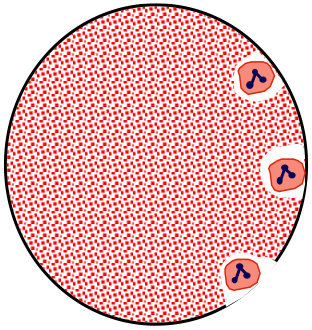
ECM attachments are reestablished, and cells recover original shape



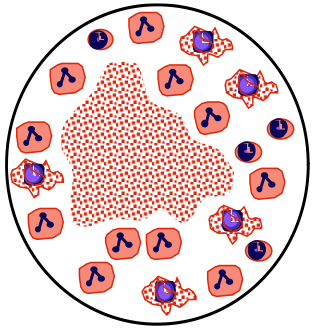
SKIN FIBROUS REPAIR:
The development of a fibrous scar..



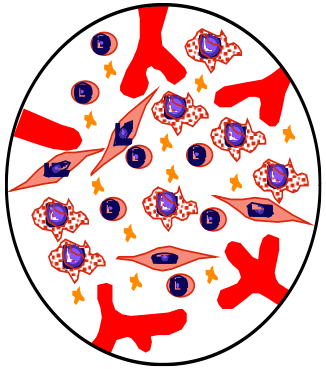
1) Exudate clots.



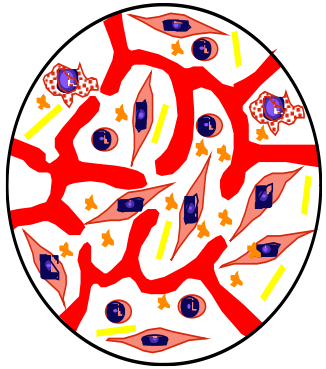
2) Neutrophils infiltrate and digest clot



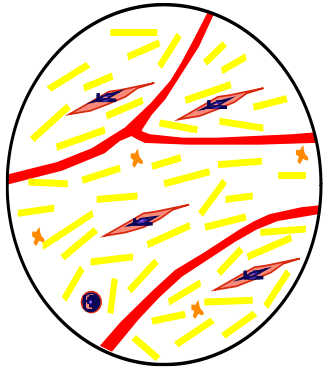
3) Macrophages and lymphocytes are recruited



4) Vessels sprout, myofibroblasts make glycoproteins



5) Vascular network; glycol protein collagen synthesised; macrophages reduced



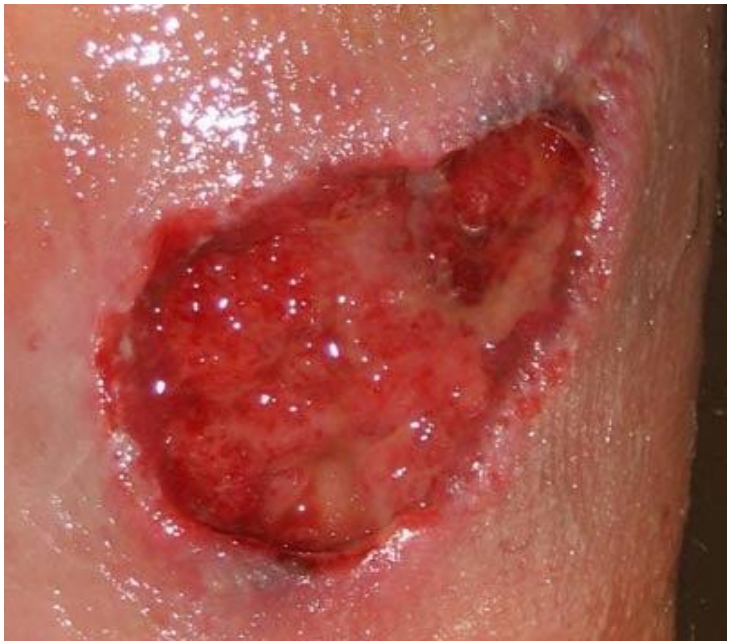
6) Maturity. Cells much reduced; collagen matures, contracts, remodels

Replacement of necrotic tissue

- resorption by macrophages
- dissolution by enzymes
- replacement by granulation tissue
  - uniform mechanism irrespective of inicial trigger
  - the same microscopic appearance
  - angiogenesis
  - migration and proliferation of fibroblasts
  - deposition of ECM
  - maturation and reorganization

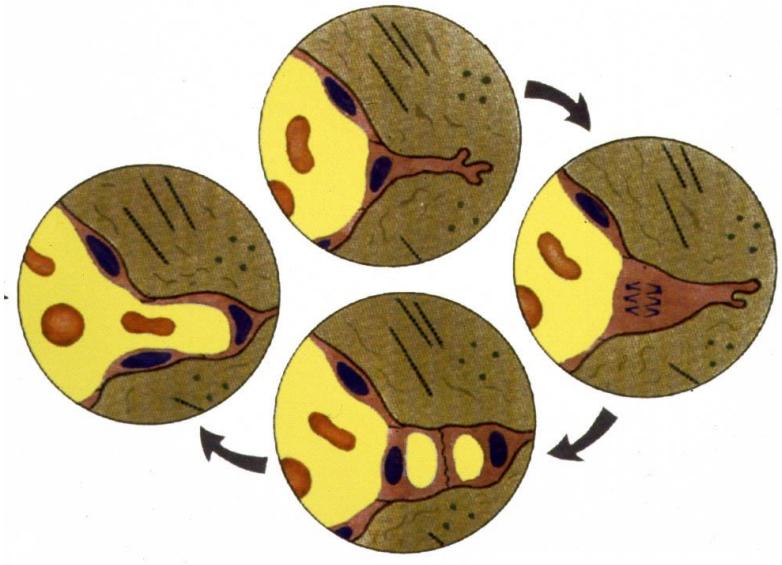
Granulation tissue

- new-formed connective tissue, apparent from 3rd day
- thin-walled capillary vessels
- fibroblasts
- loose extracellular matrix
- stimulation
  - PDGF, VEGF, FGF, TGF, TNF, EGF
- inhibition
  - INFalfa, prostaglandins, angiostatins
- control
  - cyclins, cyclin dependent kinases



Angiogenesis

- neovascularization
- x vasculogenesis (embryonic process only)
- highly complex phenomenon
- angiogenic factors (FGF, VEGF)
- antiangiogenic factors
- healing, collateral circulation, tumors



Fibrosis and Remodeling

- scar formation
- fibroblasts
- myofibroblasts
  - spindle cells of both fibroblastic and smooth muscle phenotype
  - production of collagen fibres
  - wound contraction
- abundant collagen fibres bridging the defect
- devoid of inflammatory cells
- reepithelization of surface defect
  - from skin appendages and/or from periphery
- secondary changes
  - calcification (dystrophic)
  - ossification (metaplastic)
- remodeling
  - synthesis and degradation of ECM
  - metalloproteinases (MPs), tissue inhibitors of MPs

Pathological aspects of healing

- Scar and contracture
- keloid
  - excessive amount of collagen
- Malignancy

Keloids

Keloids

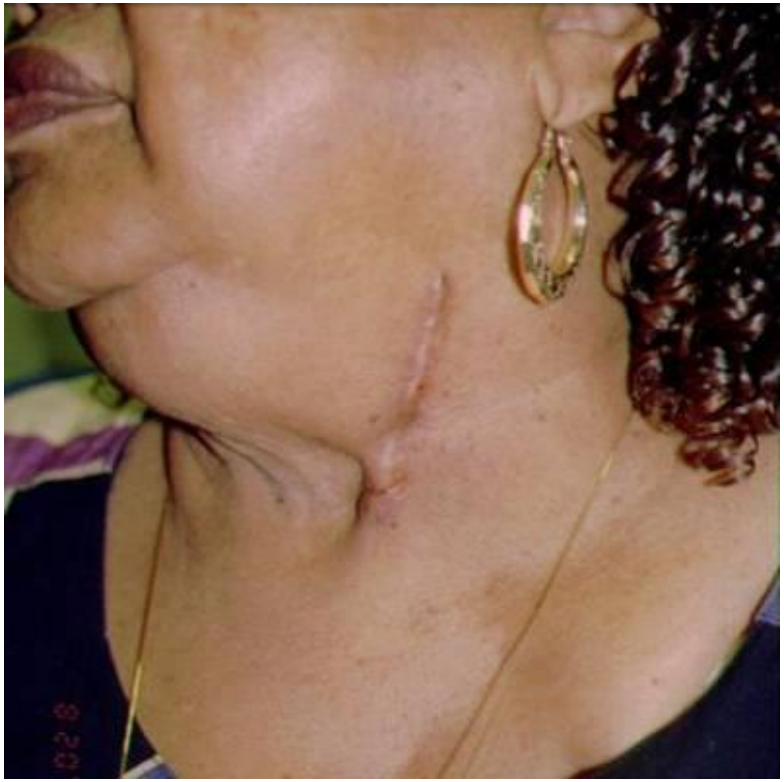
- Extends beyond original bounds
- Raised and firm
- Rarely occur distal to wrist or knee
- Predilection for sternum, mandible and deltoid
- Rate of collagen synthesis increased
- Water content higher
- Increased glycosaminoglycans

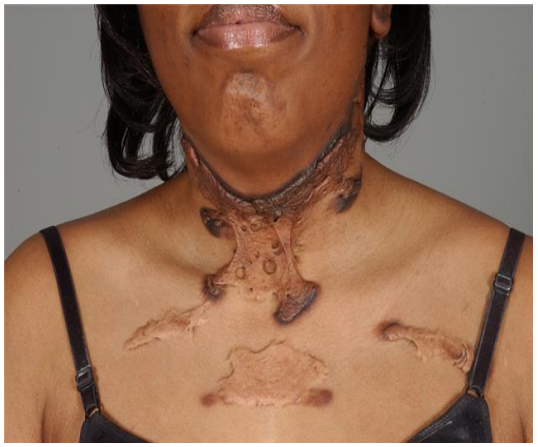
Treatment

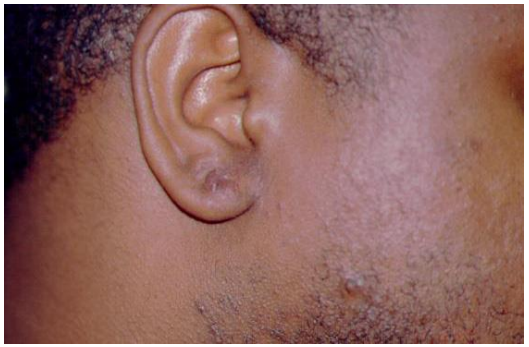
- Triamcinolone injections
- 3-4 weeks
- Cross linking modulated
- Injections continued until no excess abnormal collagen
- Excise
- Prevention during healing – pressure and injection

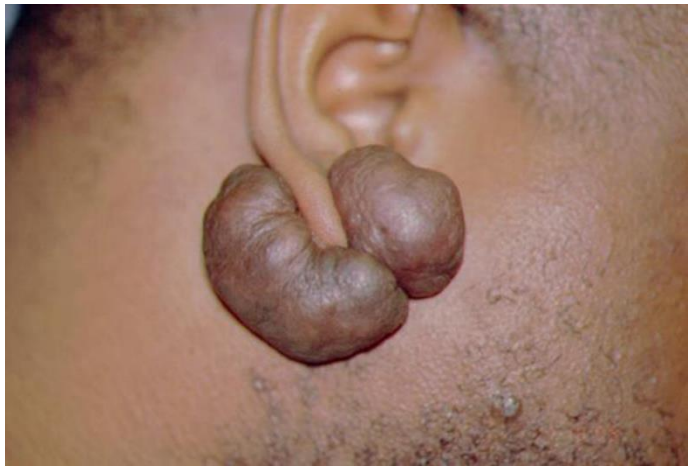
Hypertrophic Scar

Keloid

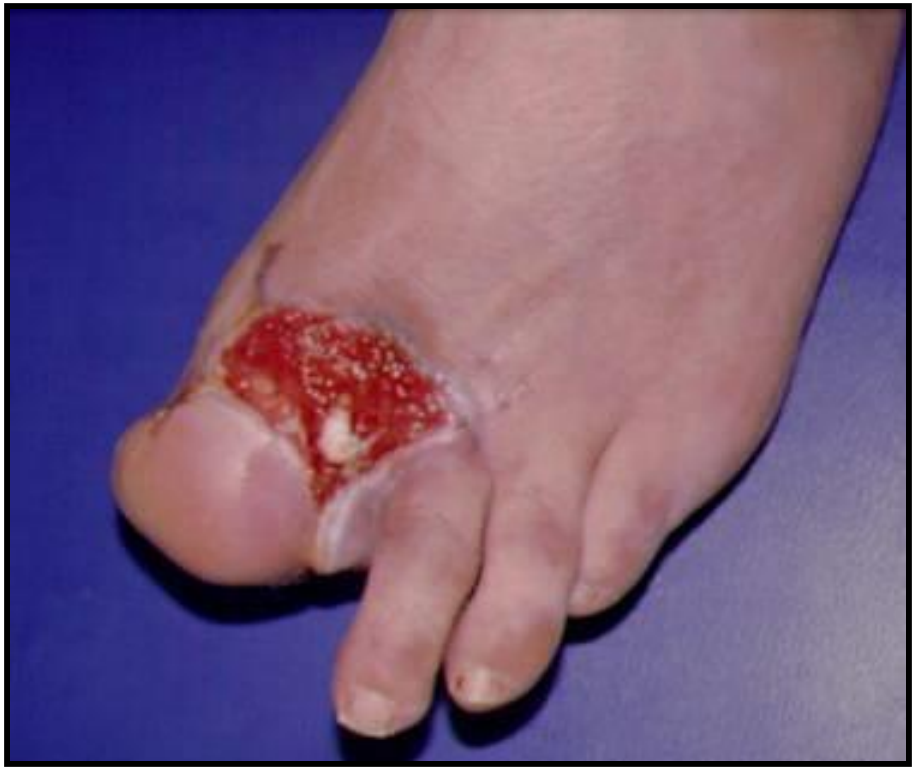


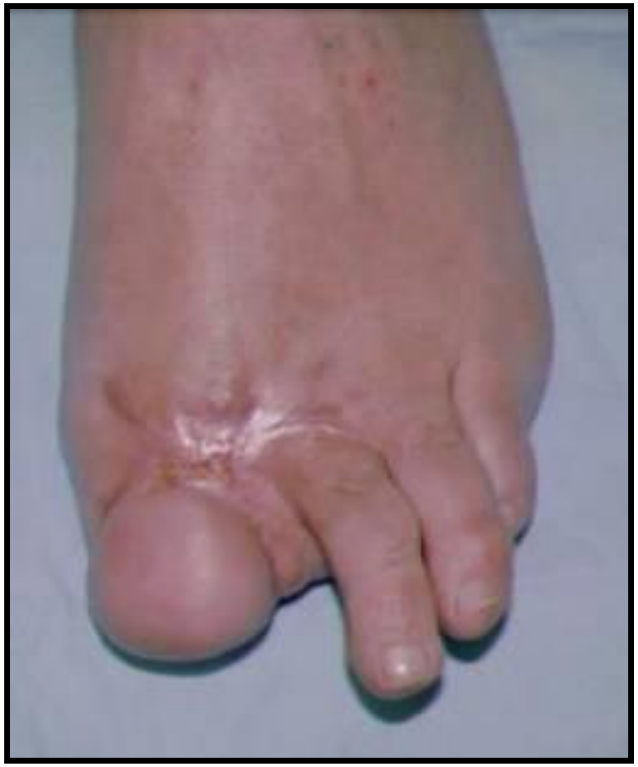




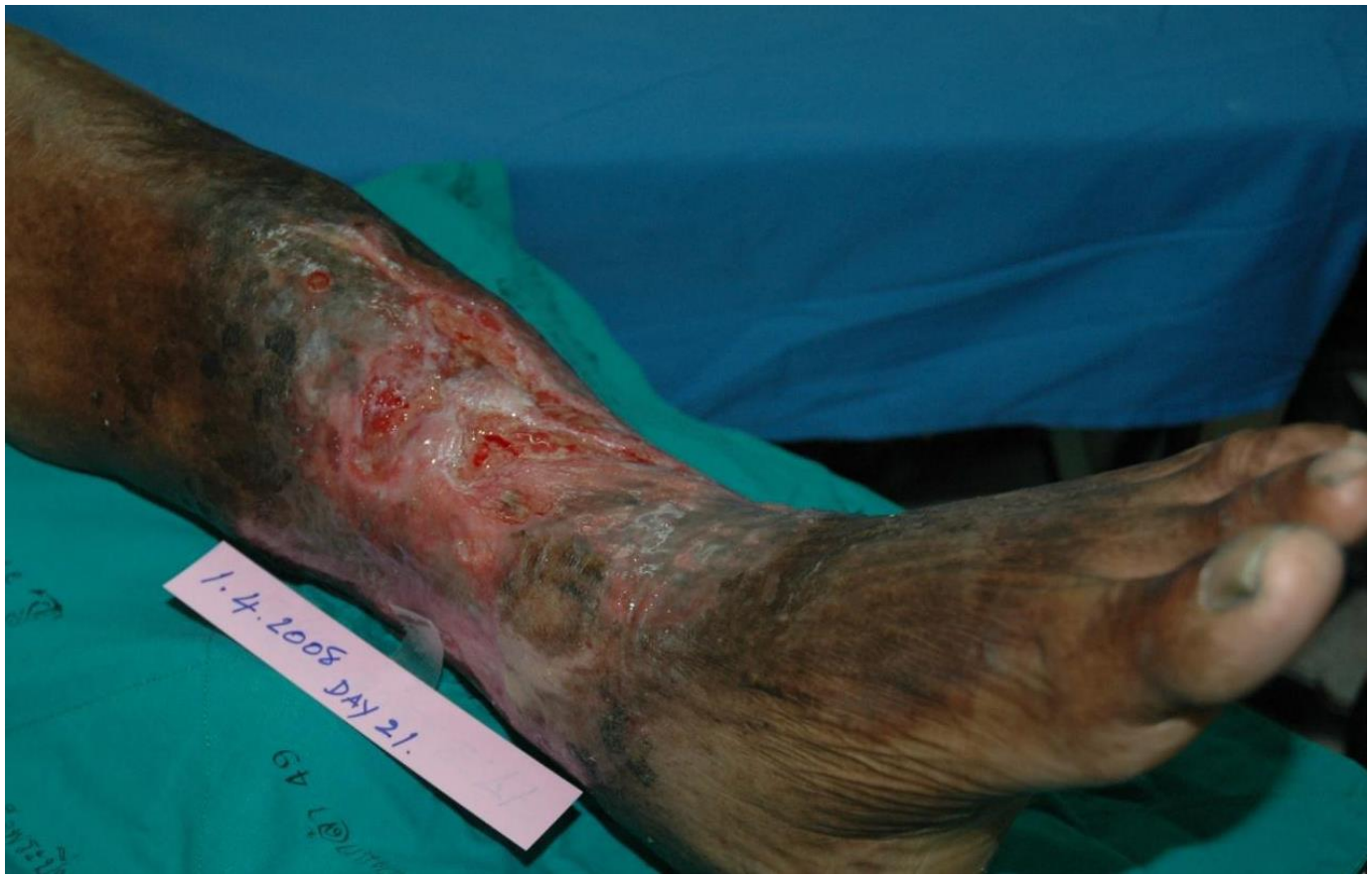


Secondary Wound Healing



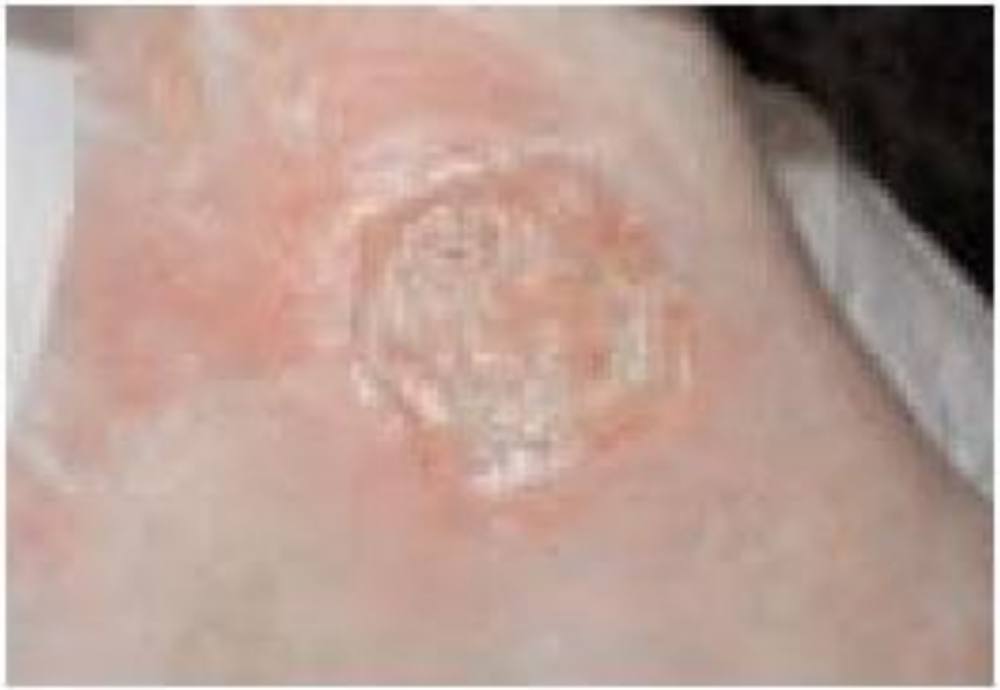


Clinical pictures of different wound types



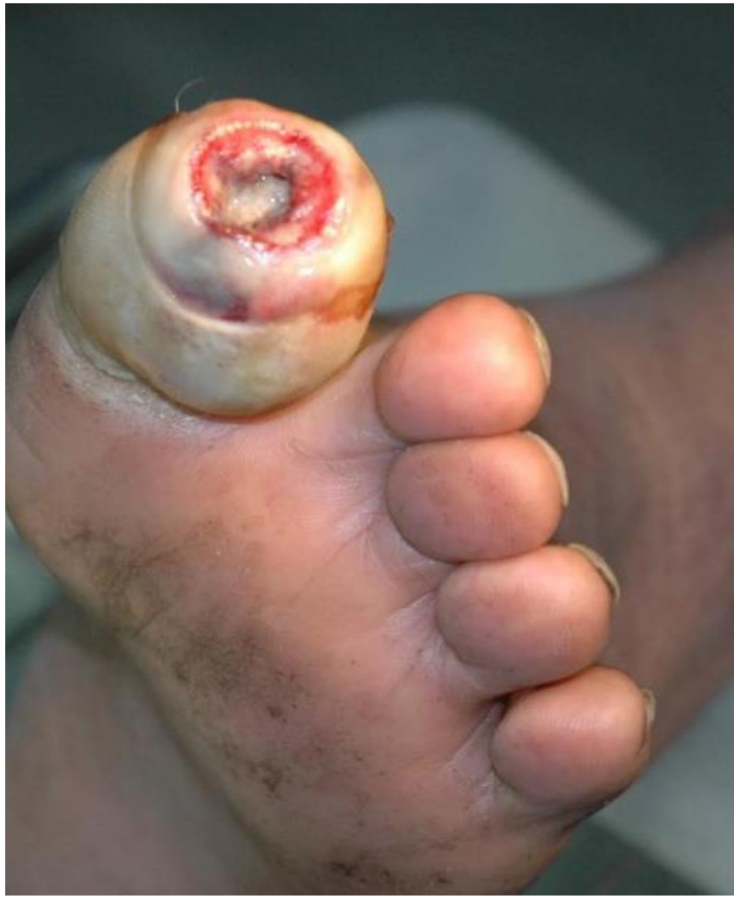
Venous leg ulcer

Clinical pictures of different wound types



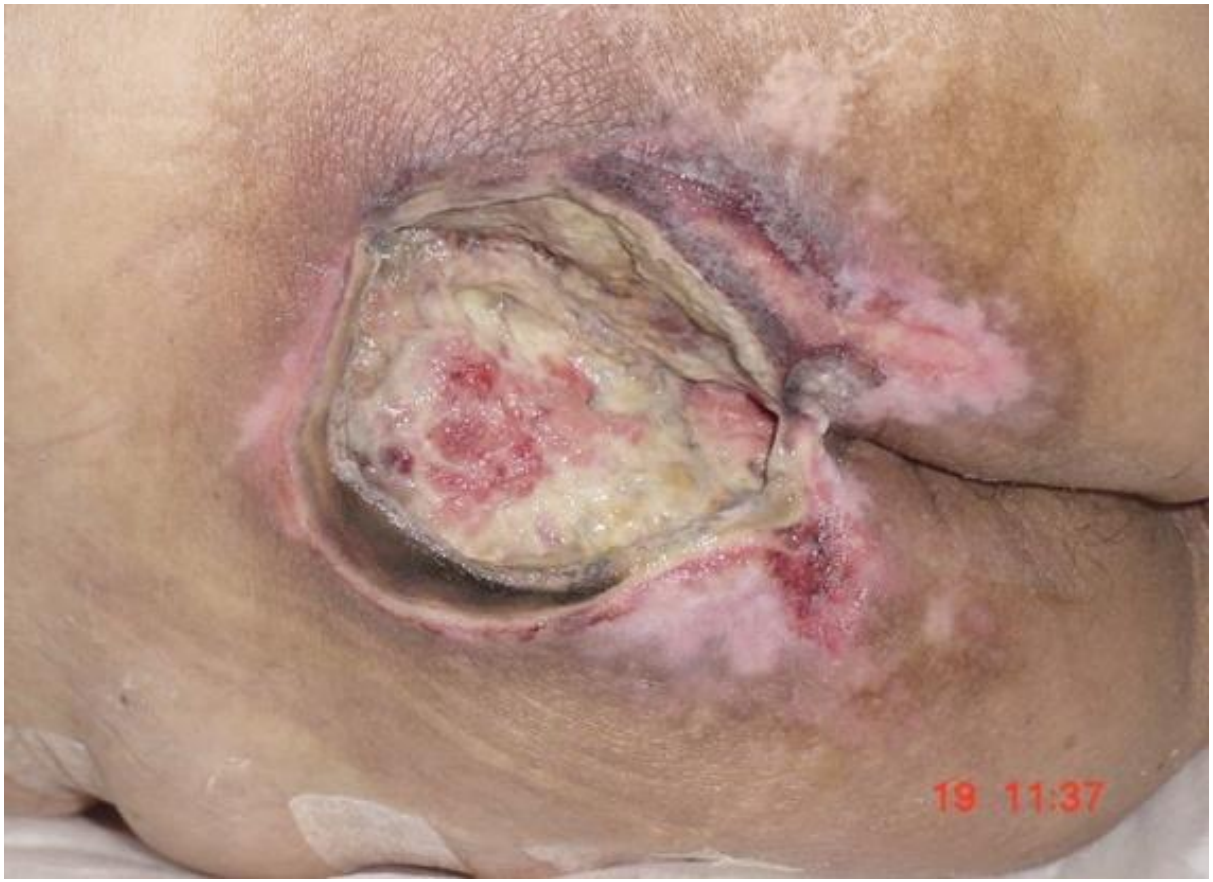
Arterial leg ulcer

Clinical pictures of different wound types



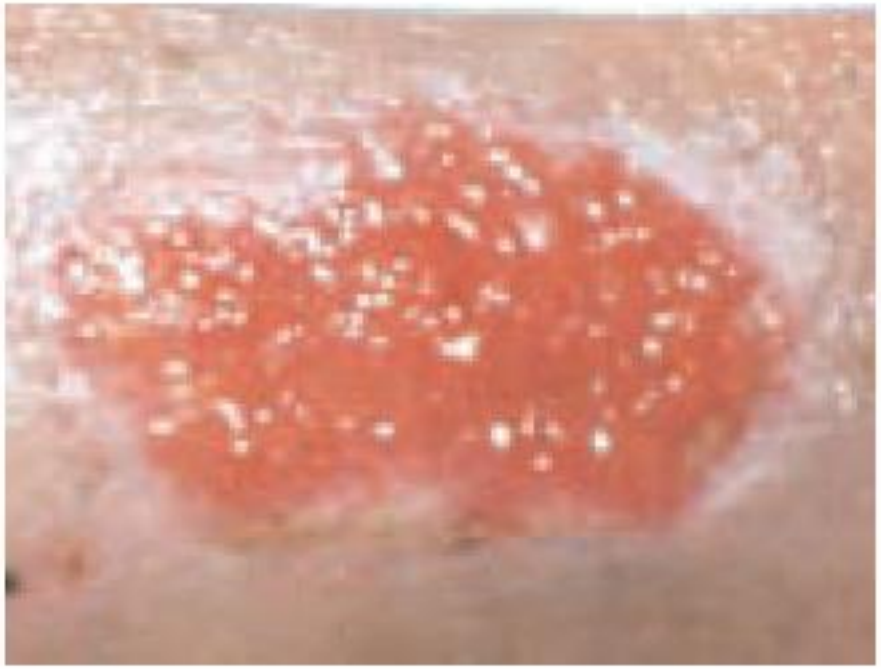
Diabetic foot ulcer

Clinical pictures of different wound types



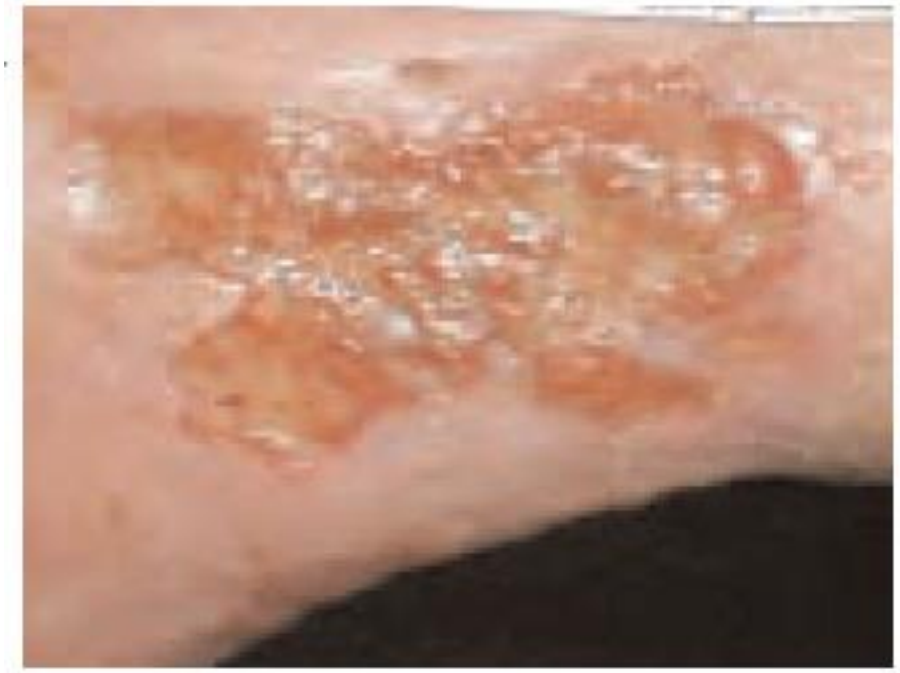
Pressure ulcer

Clinic signs



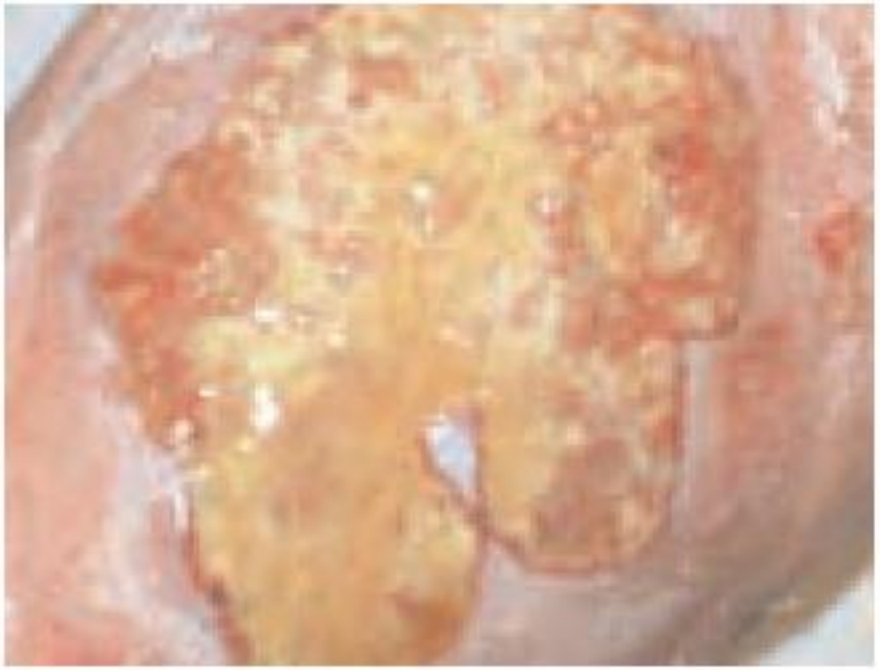
Contamination/colonisation

Clinic signs



Critical colonisation/local infection

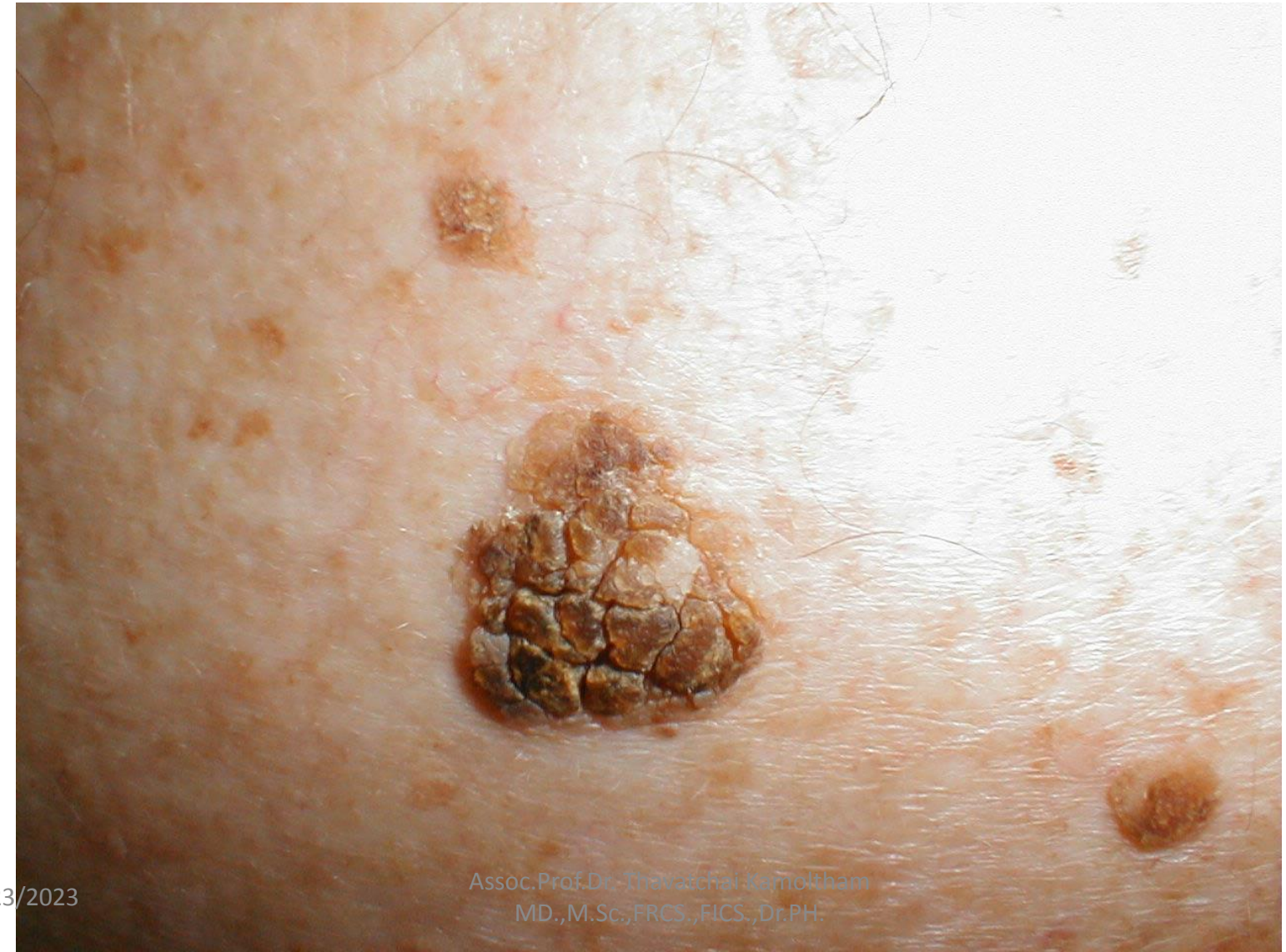
Clinic signs



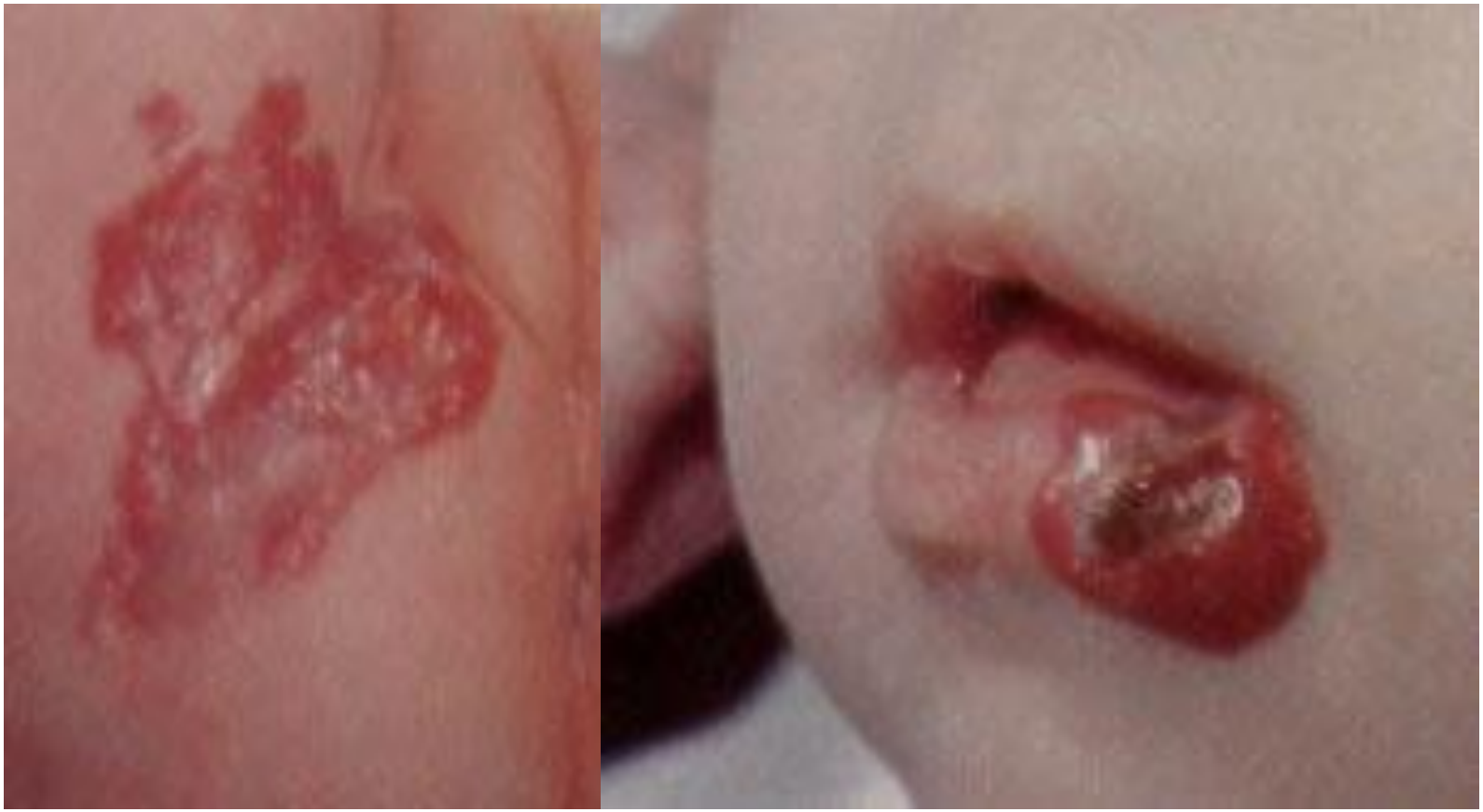
Infection

Diabetic foot ulcers

Seborrheic Keratoses

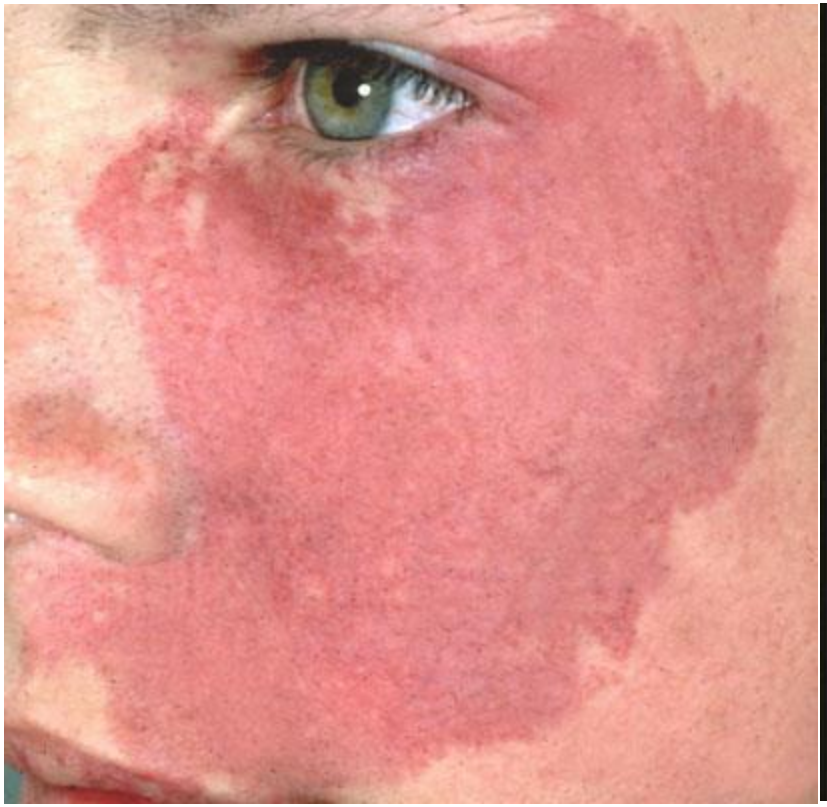


Involuting Hemangiomas

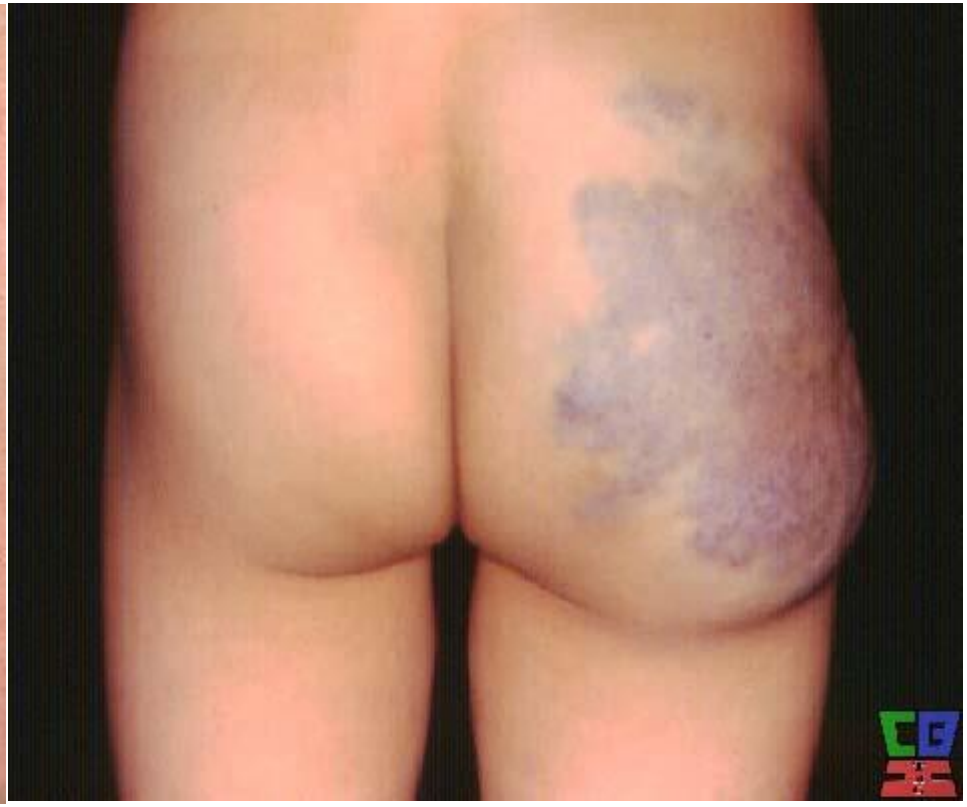


Non-involuting Hemangiomas

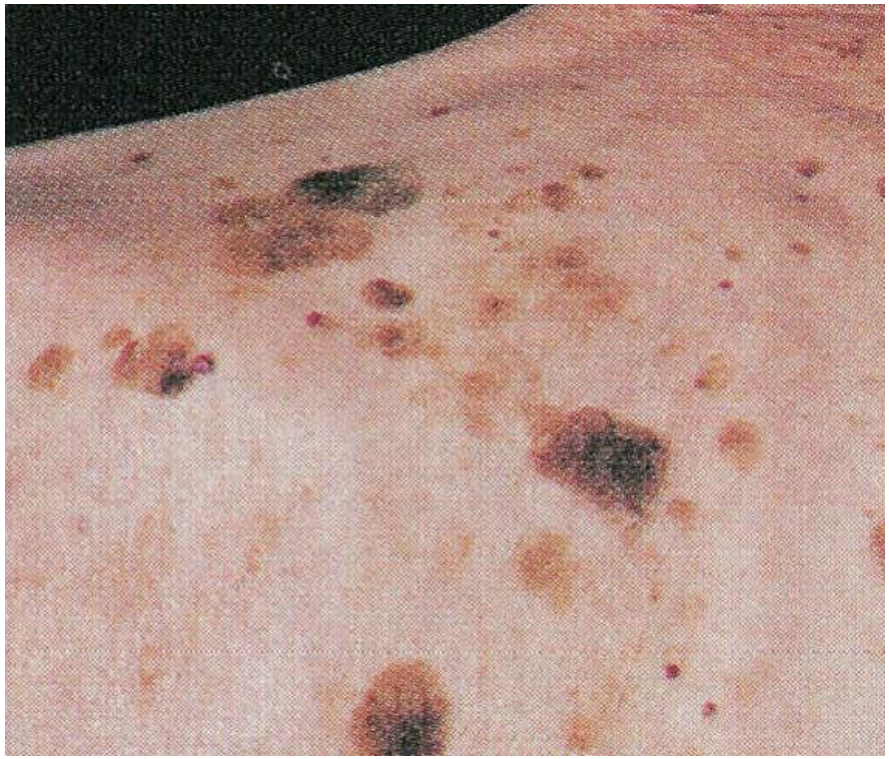
Port Wine Stain

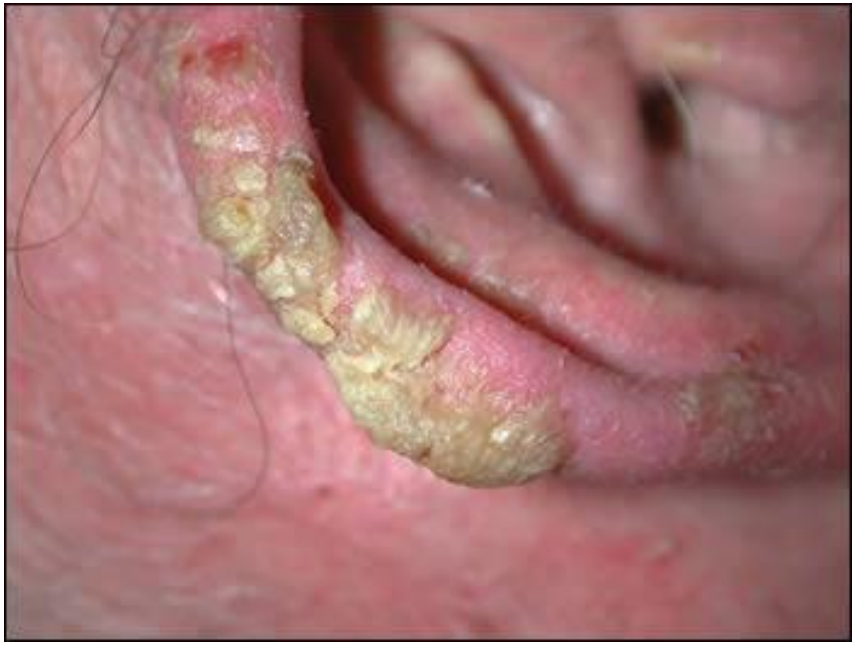


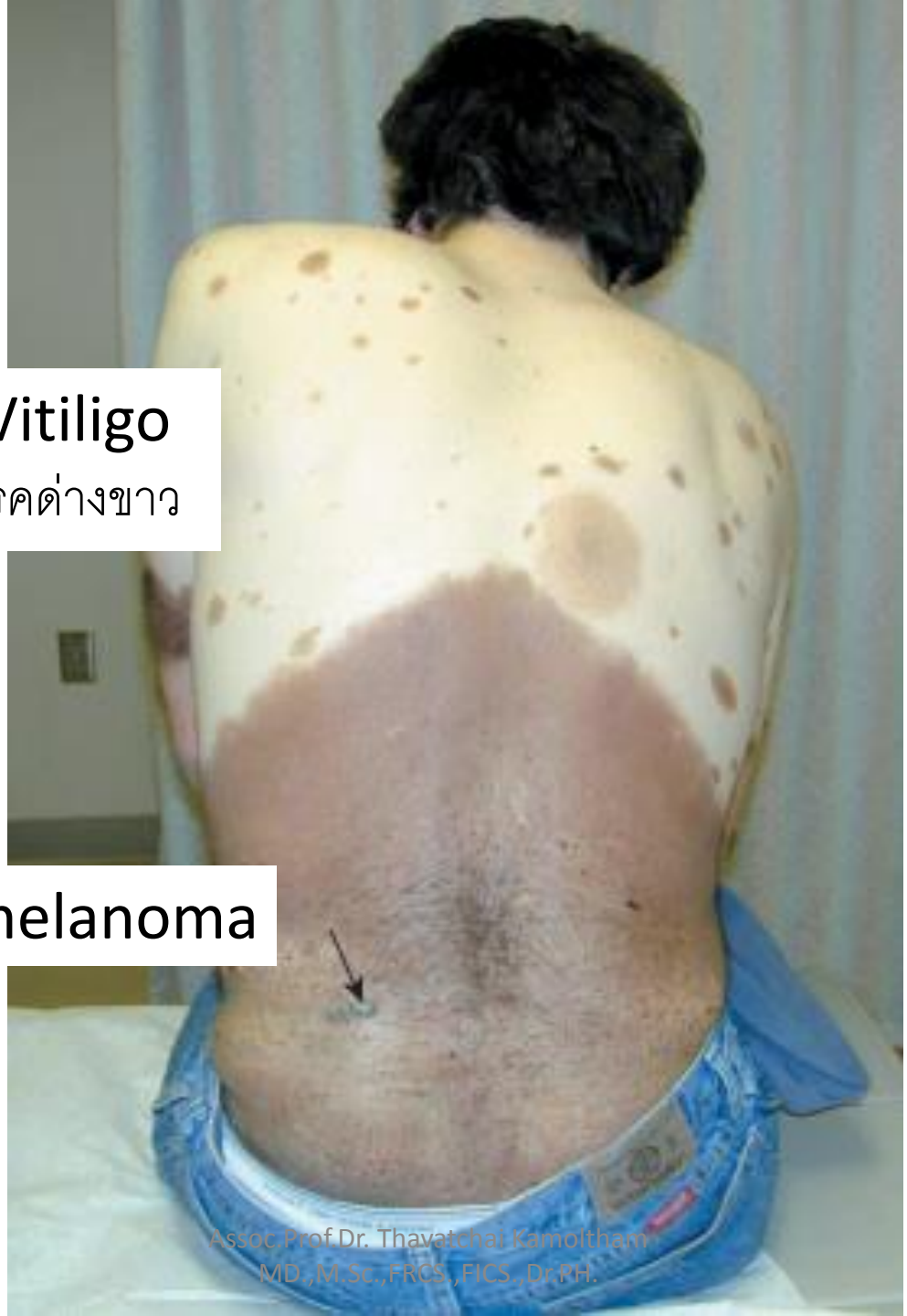
Cavernous Hemangioma



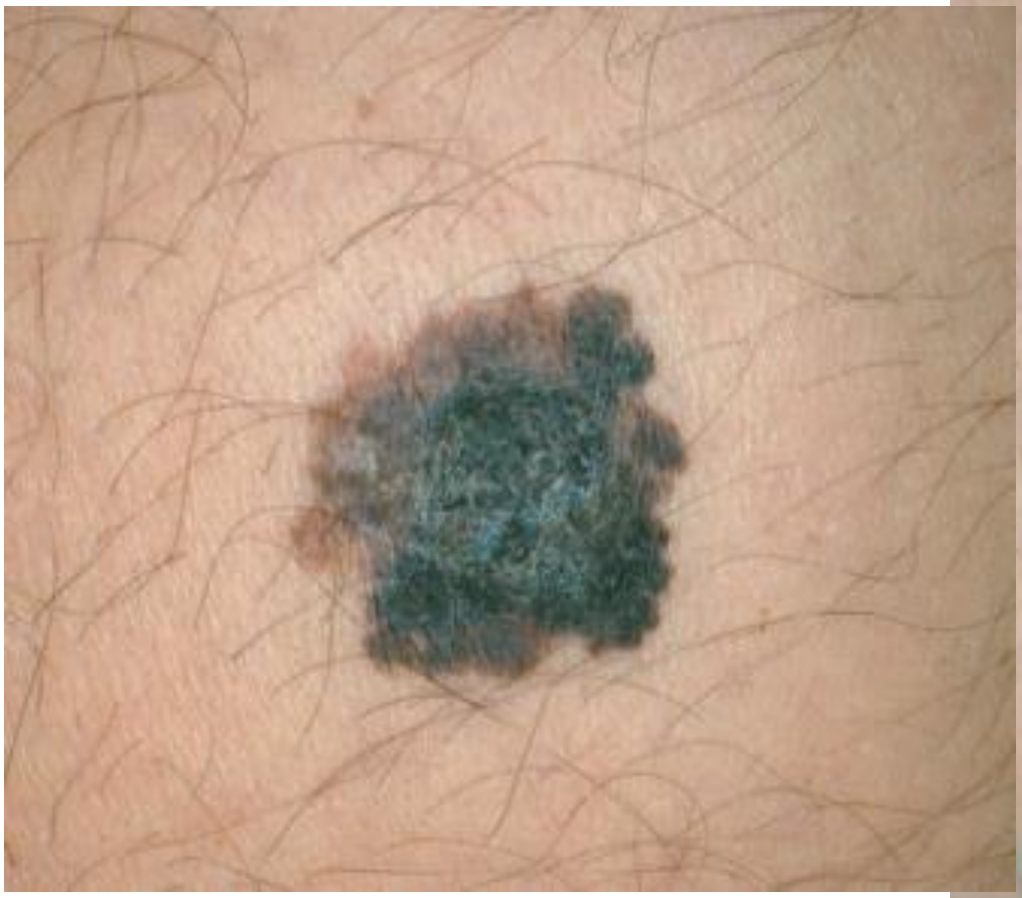
Actinic Keratoses



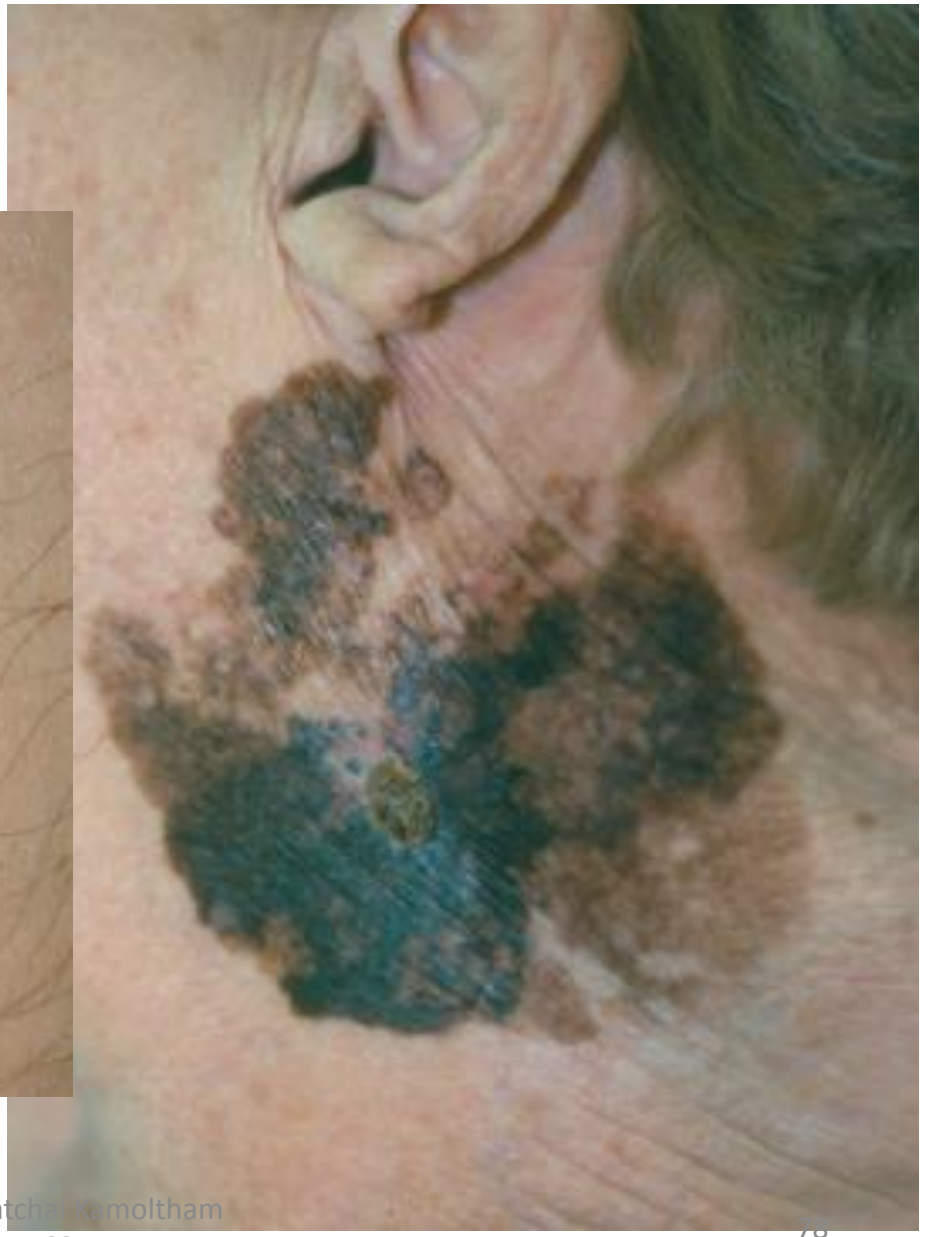




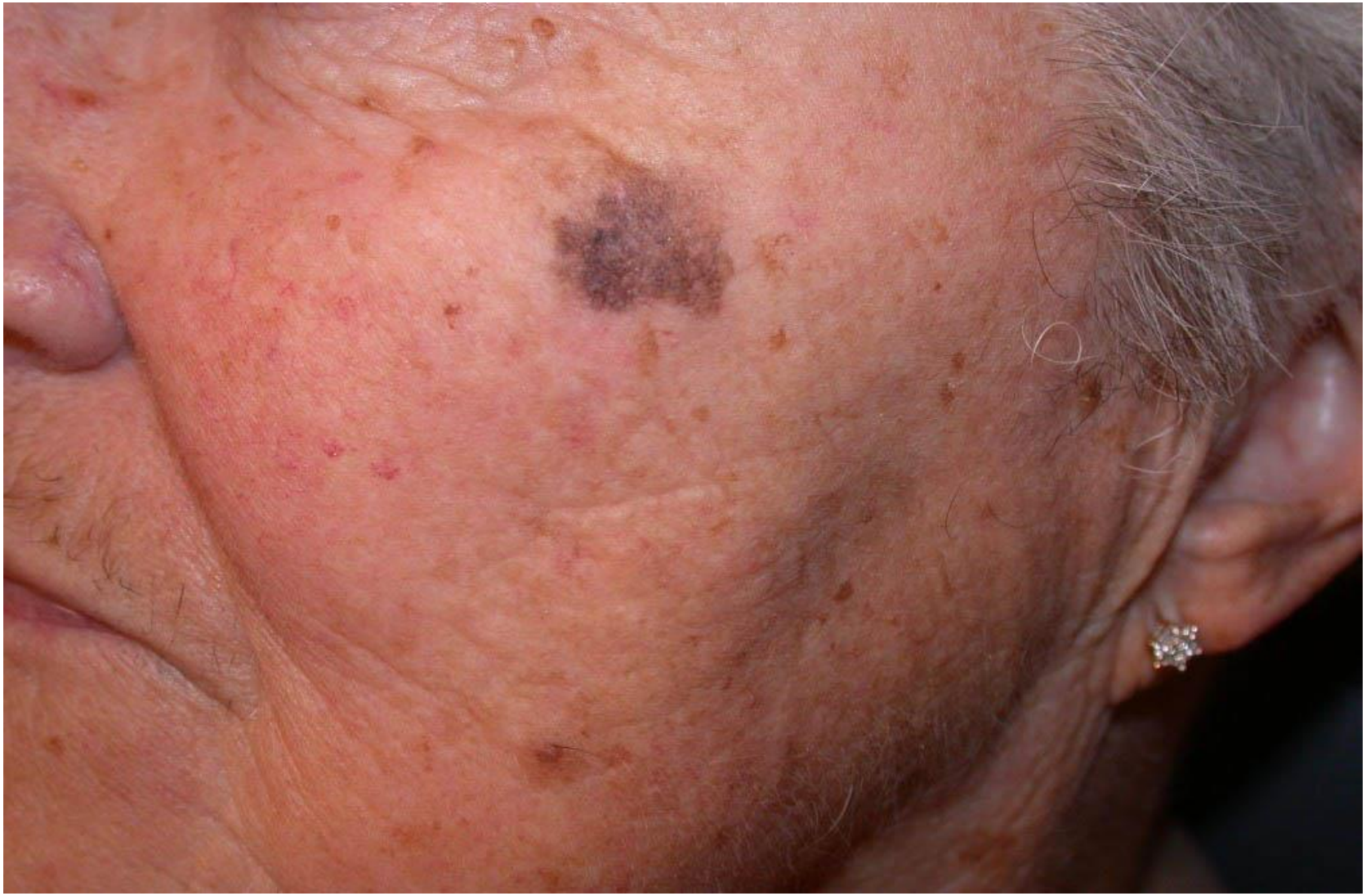
Superficial spreading melanoma



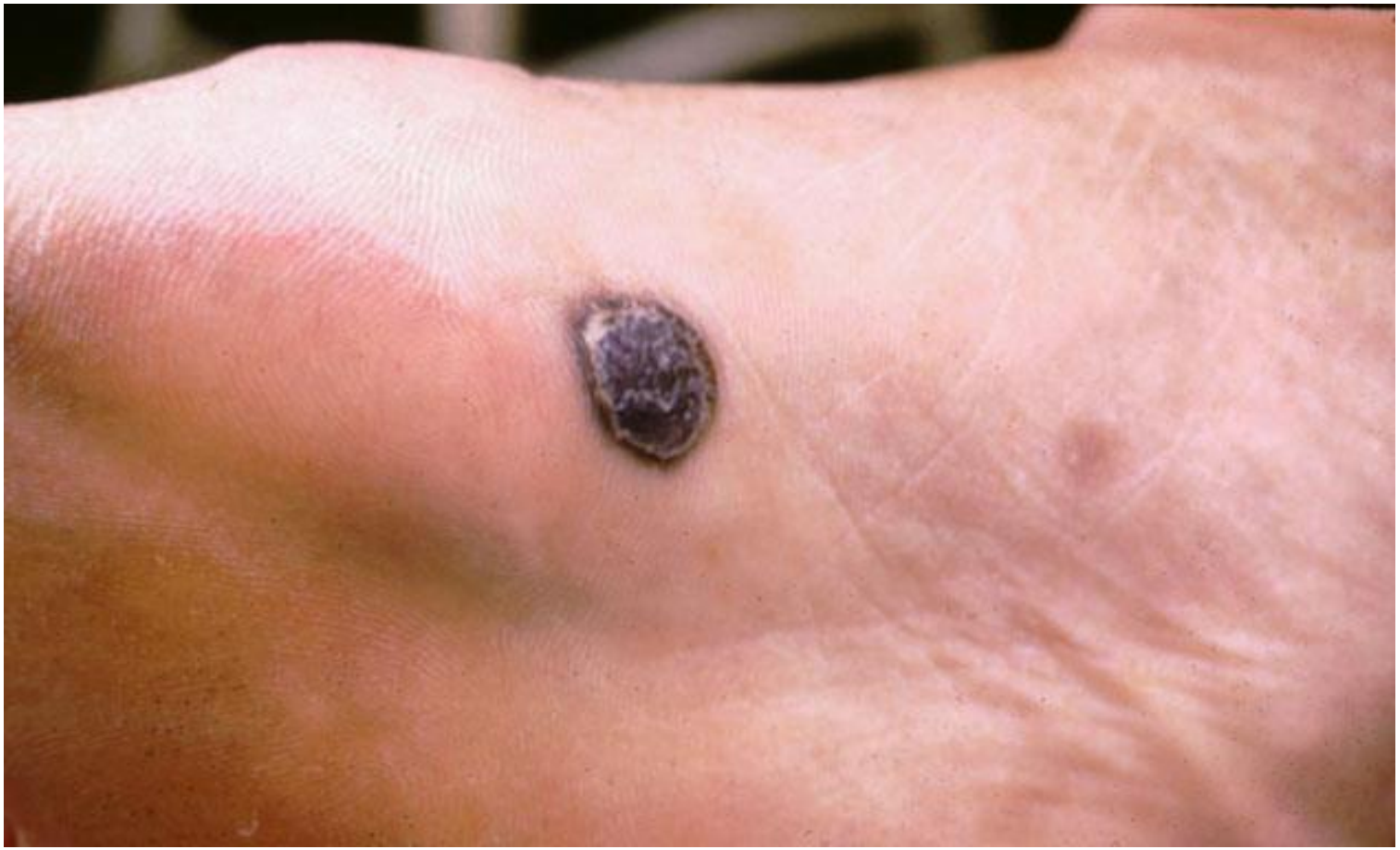
Lentigo maligna melanoma



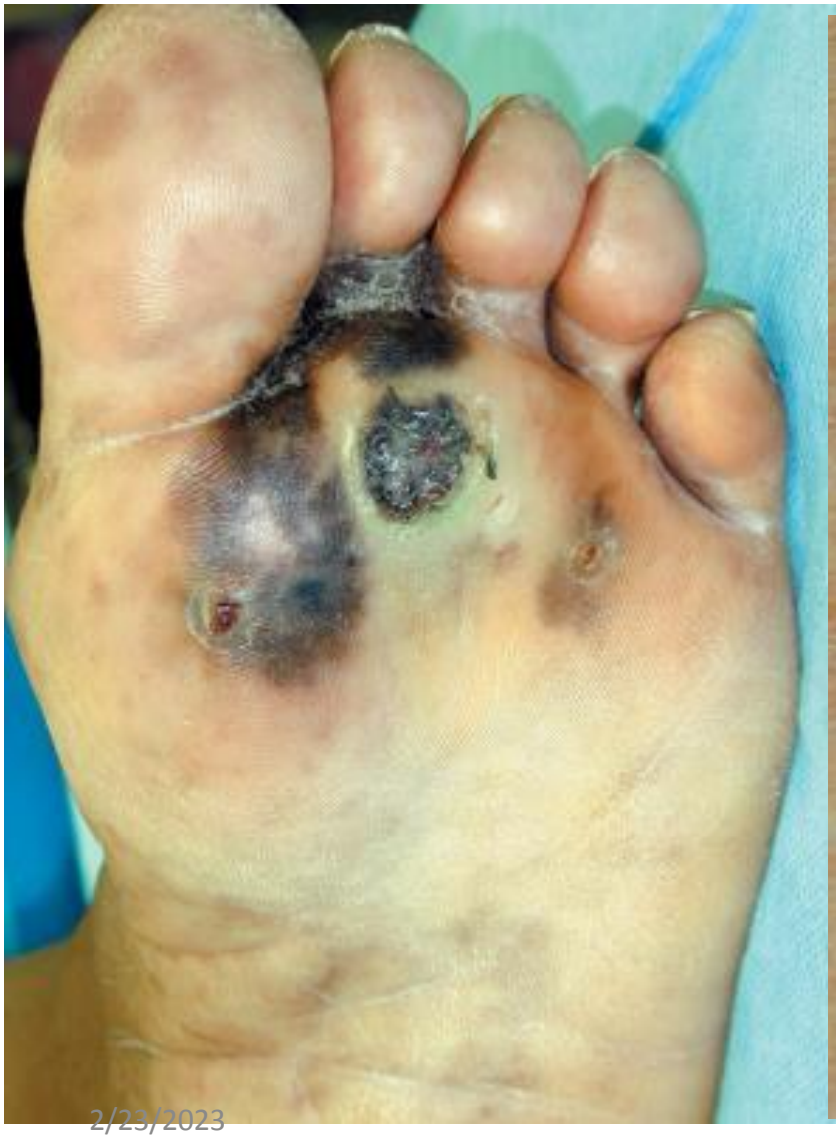
Lentigo Maligna



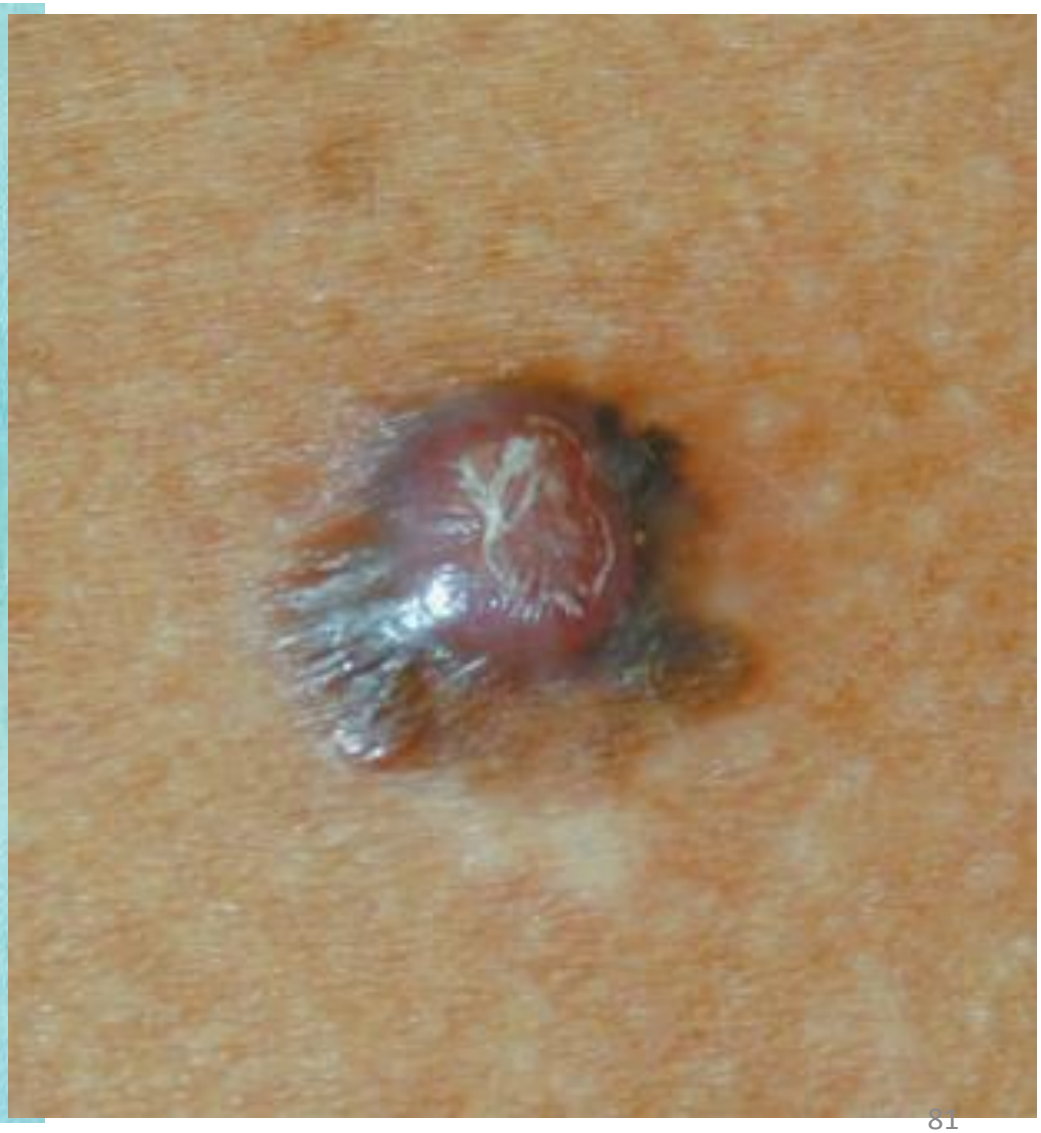
Acral Lentiginous



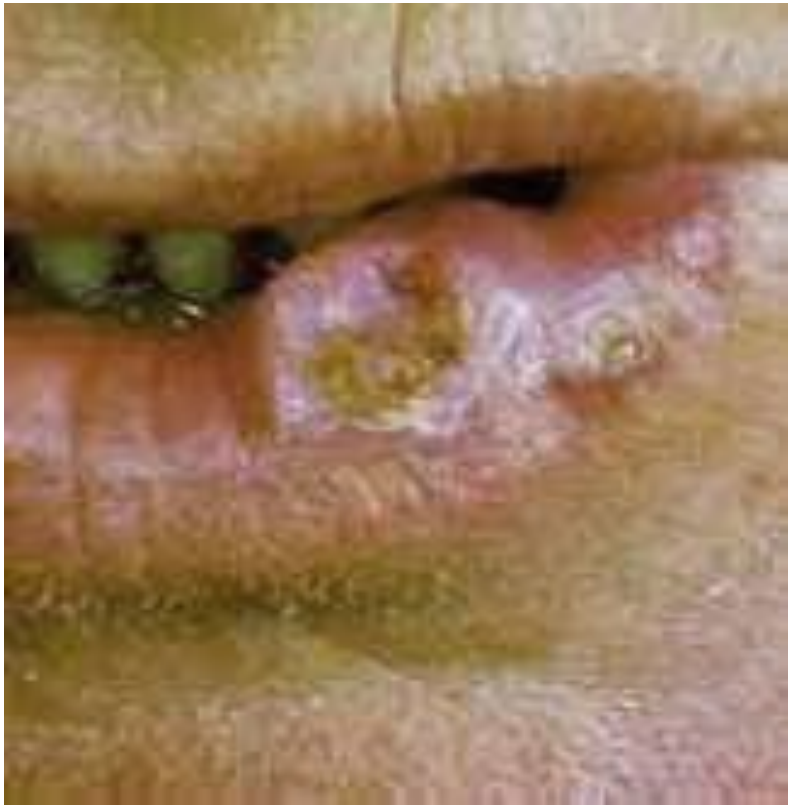
Acral lentiginous melanoma

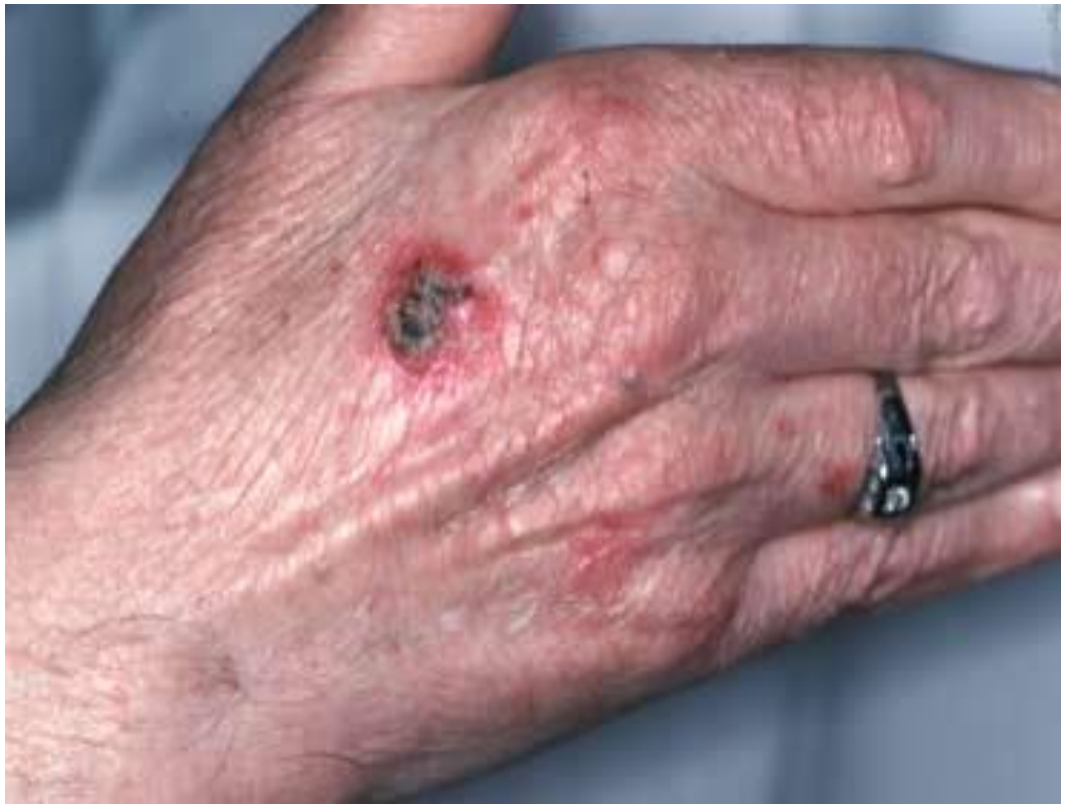


Nodular melanoma

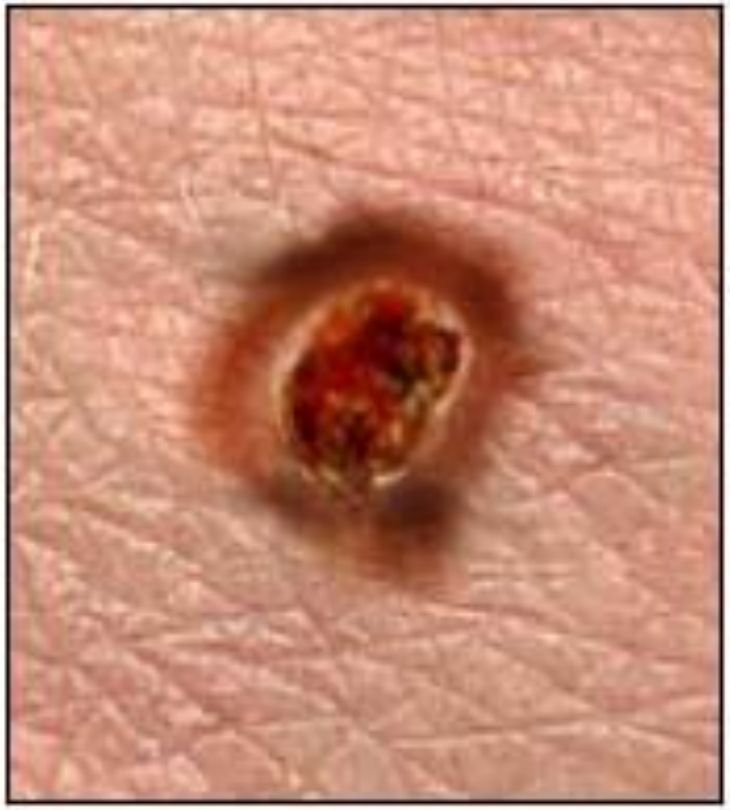


Squamous Cell Carcinoma

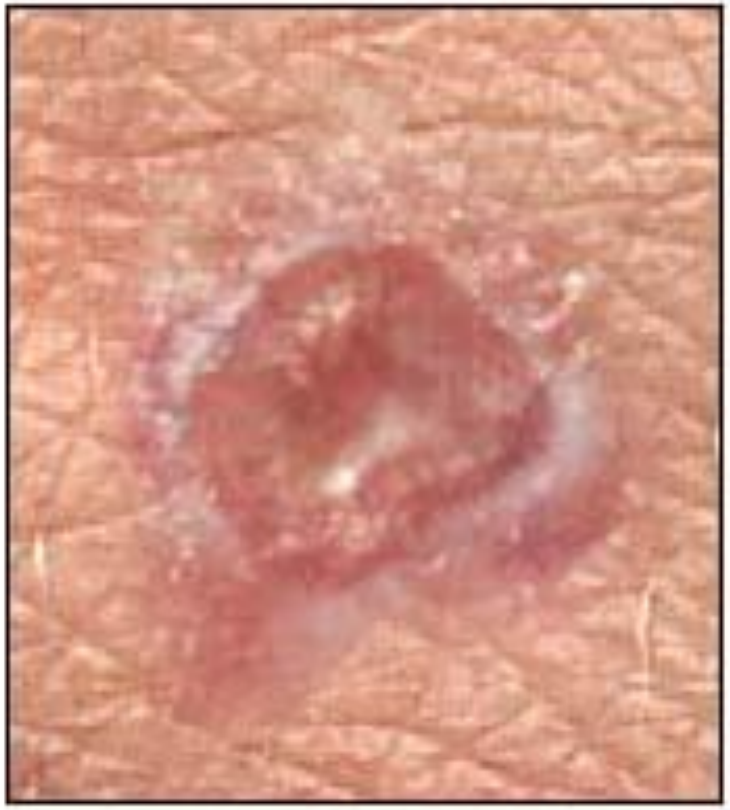




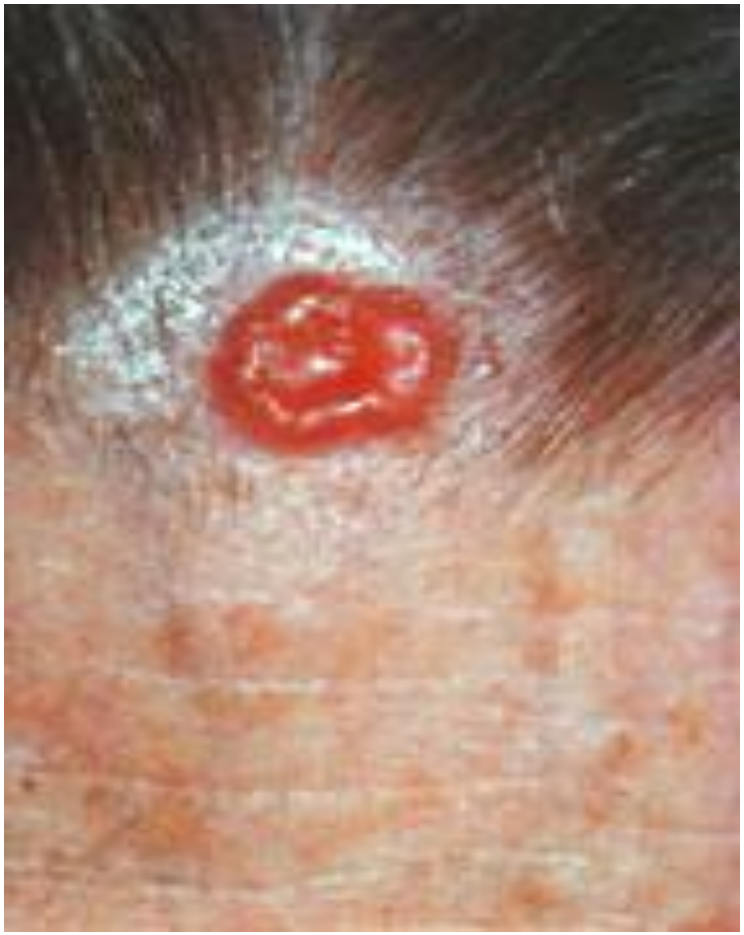
Squamous cell carcinoma

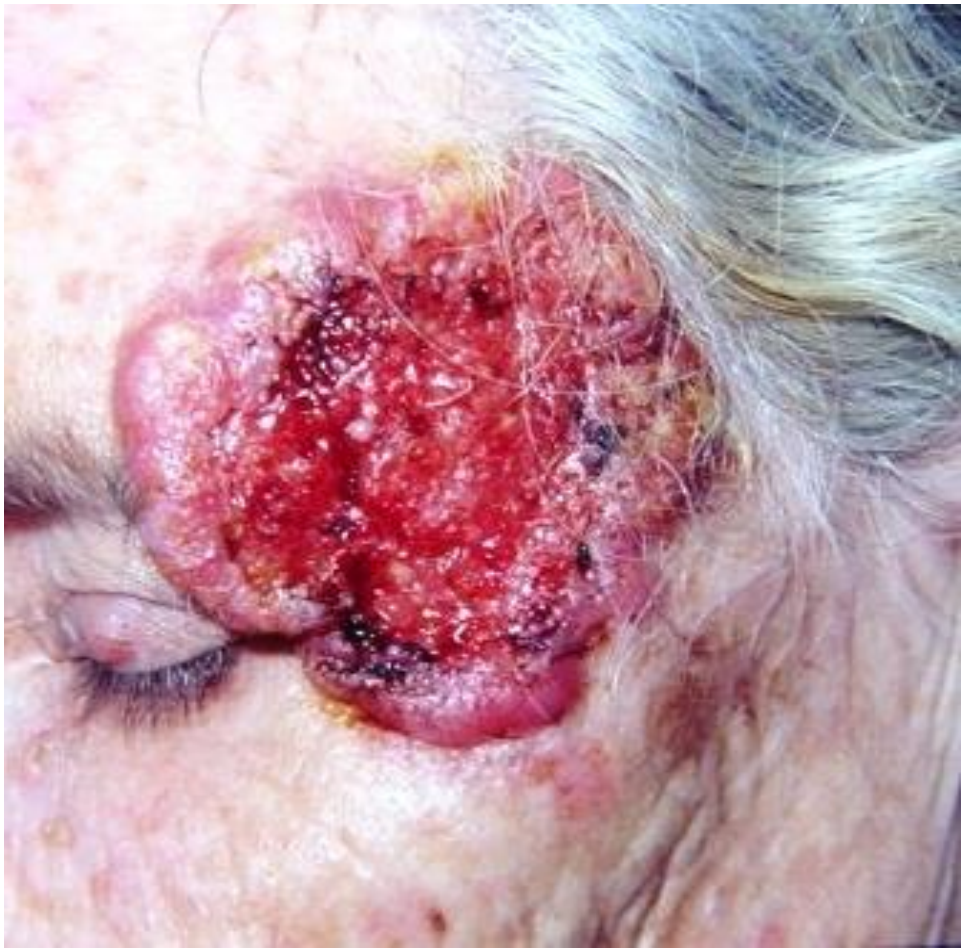


Basal cell carcinoma



Basal Cell Carcinoma

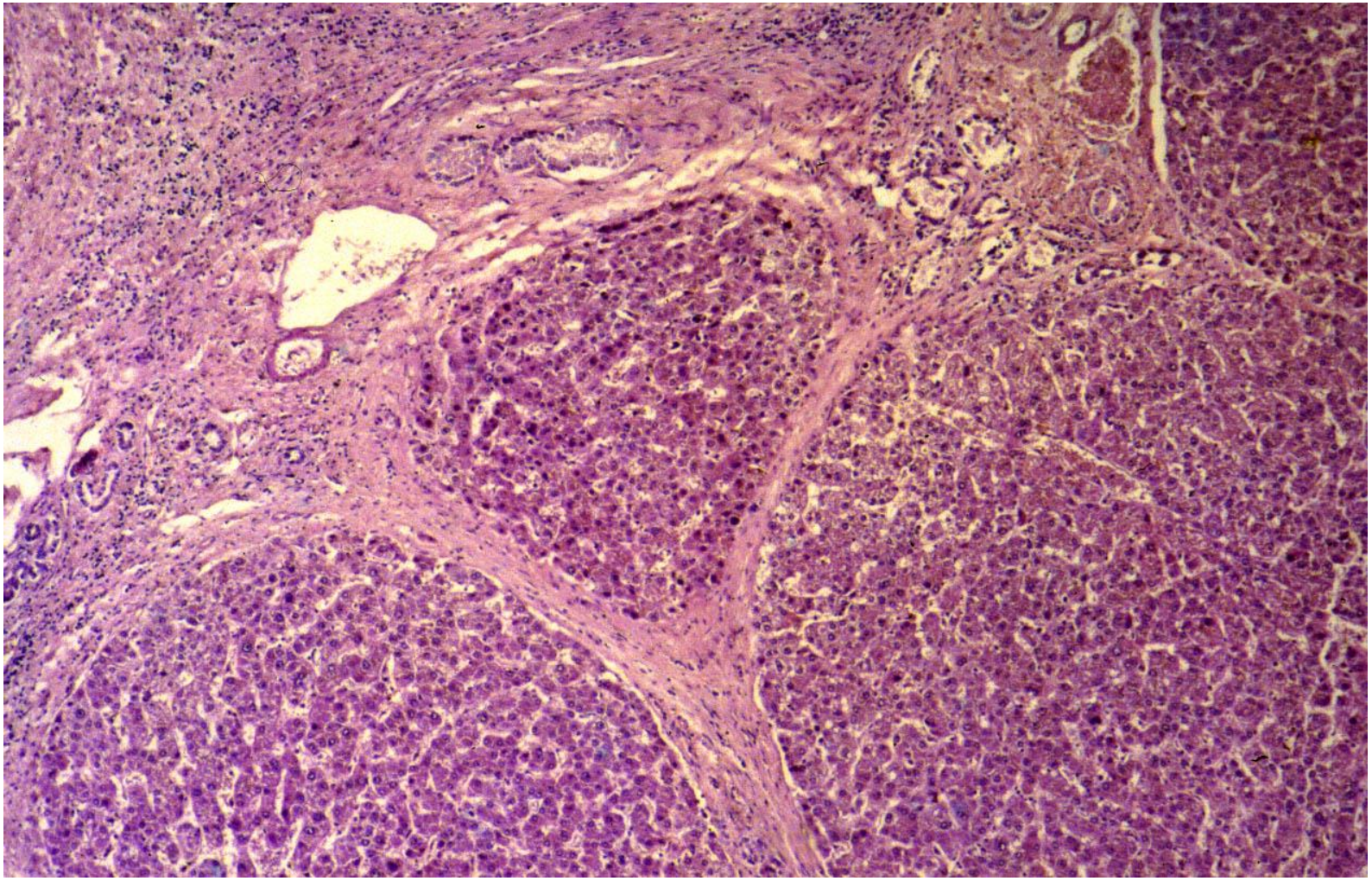




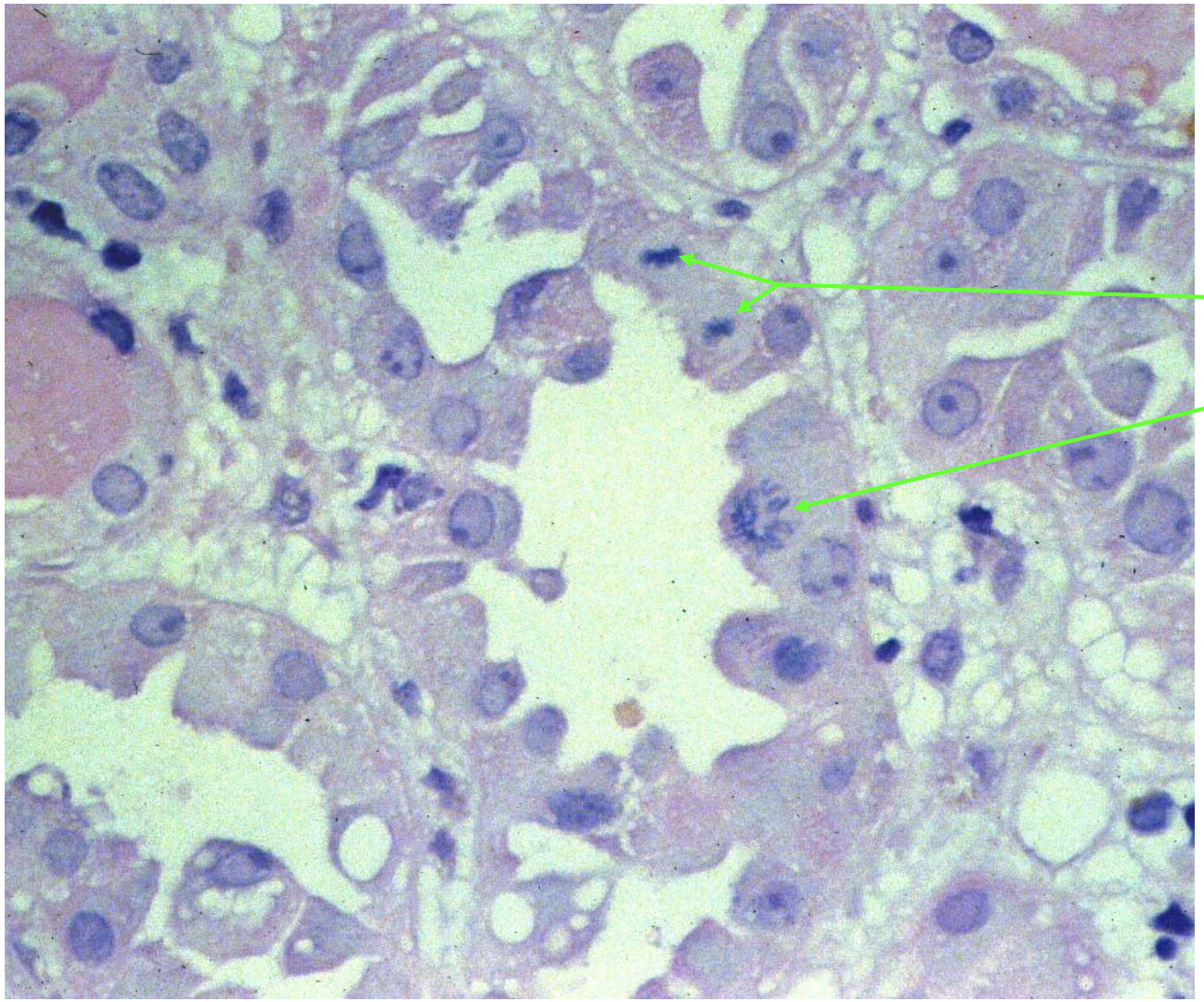
Special features of healing in specific organs

- Liver (n.b. regeneration in acute versus chronic damage)
- Kidney (n.b. 'acute tubular necrosis')
- Heart (see 'myocardial infarction')
- Bone (n.b. 'Callus')
- Cartilage (Can it???)
- Peripheral nerve (n.b. 'Wallerian degeneration'; axon sprouting)
- Central nervous system (n.b. gliosis)

Alcoholic cirrhosis in the liver



Acute damage to kidney - regeneration



Healing Process-Ligament Sprains

- Physiology
  - Inflammatory phase-loss of blood from damaged vessels and attraction of inflammatory cells
  - During next 6 weeks-vascular proliferation with new capillary growth and fibroblastic activity
    - Immediately to 72 hours
      - If extraarticular bleeding in subcutaneous space
      - If intraarticular bleeping occurs in inside joint capsule
- Essential that 2 ends of ligament be reconnected by bridging of clot
  - Collagen fibers initially random woven pattern with little organization
  - Failure to produce enough scar and of ligament to reconnect 2 reasons ligaments fail
- Maturation
  - May take 12 months to complete
  - Realignment/remodeling in response to stress and strains placed on it

Healing Process-Ligament Sprains

- Factors that effect healing
  - Surgery or non surgical approach
    - Surgery of extraarticular ligaments stronger at first but may not last over time
    - Non surgical will heal through fibrous scarring , but may also have some instability
  - Immobilization
    - Long periods of immobilization may decrease tensile strength weakening of insertion at bone
    - Minimize immobilization time
    - Surrounding muscle and tendon will provide stability through strengthening and increased muscle tension

Healing Process-Cartilage

- Cartilage
  - Rigid connective tissue that provides support
    - Hyaline cartilage: articulating surface of bone
    - Fibro cartilage: interverterbral disk and menisci. Withstands a great deal of pressure
    - Elastic cartilage: more flexible than other types-auricle of ear and larynx
- Physiology of healing
  - Relatively limited healing capacity
    - Dependant on damage to cartilage alone or subchondral bone.
    - Articular cartilage fails to elicit clot formation or cellular response
    - Subchondral bone can formulate granulation tissue and normal collagen can form

Healing Process-Bone

- Similar to soft tissue healing, however regeneration capabilities somewhat limited
  - Bone has additional forces such as torsion, bending and compression not just tensile force
  - After 1 week fibroblast lay down fibrous collagen
  - Chondroblast cells lay down fibrocartilage creating callus
  - At first soft and firm, but becomes more firm and rubbery
  - Osteoblast proliferate and enter the callus
- Form cancellous bone and callus crystallizes into bone
- Osteoclasts reabsorb bone fragments and clean up debris
  - Process continues as osteoblast lay down new bone and osteoclasts remove and break down new bone
    - Follow Wolfs law-forces placed on callus-changes size, shape and structure
    - Immobilization longer 3 to 8 weeks depending on the bone

Healing Process-Muscle

- Similar to other soft tissue discussed
  - Hemorrhage and edema followed by phagocytosis to clean up debris
  - Myoblastic cells from in the area and regenerate new myofibrils
  - Active contraction critical to regaining normal tensile strength according to Wolff's Law
  - Healing time lengthy-Longer than ligament healing
    - Return to soon will lead to re-injury and become very problematic
    - 6-8 weeks?

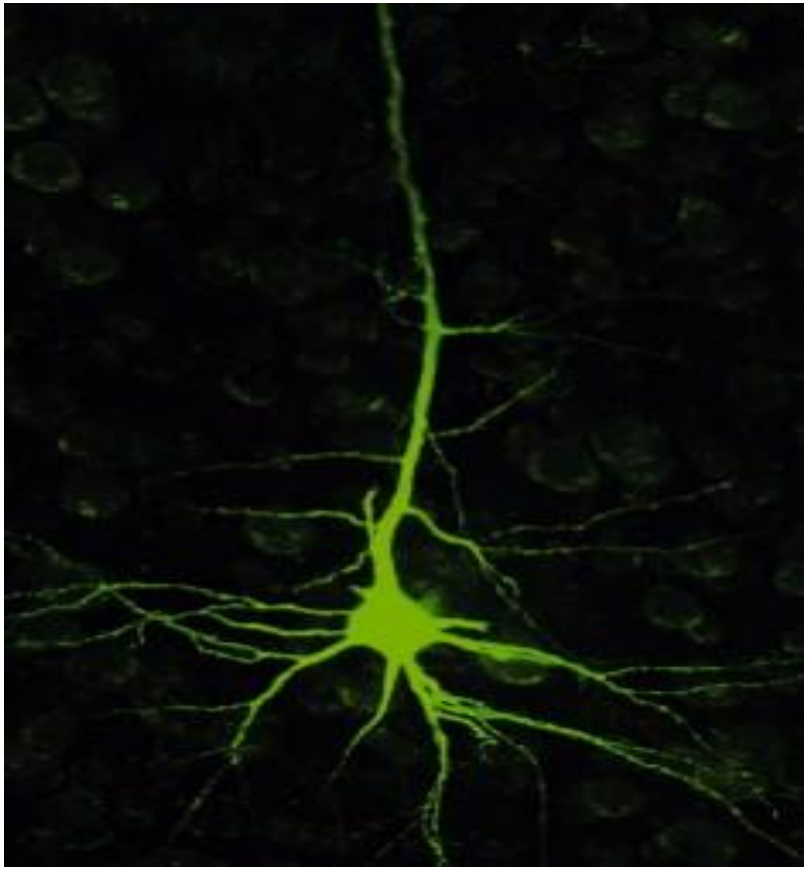
Healing Process-Tendon

- Not as vascular as muscle
  - Can cause problems in healing
  - Fibrous union required to provide extensibility and flexibility
    - Abundance of collagen needed to achieve good tensile strength
    - Collagen synthesis can become excessive can result in fibrosis: adhesions from in surrounding structures
      - Interfere with gliding and smooth movement
      - Tensile strength not sufficient to permit strong pull for 4 to 5 weeks
        - » At risk of strong contraction pulling tendons ends apart

Healing Process-Nerve

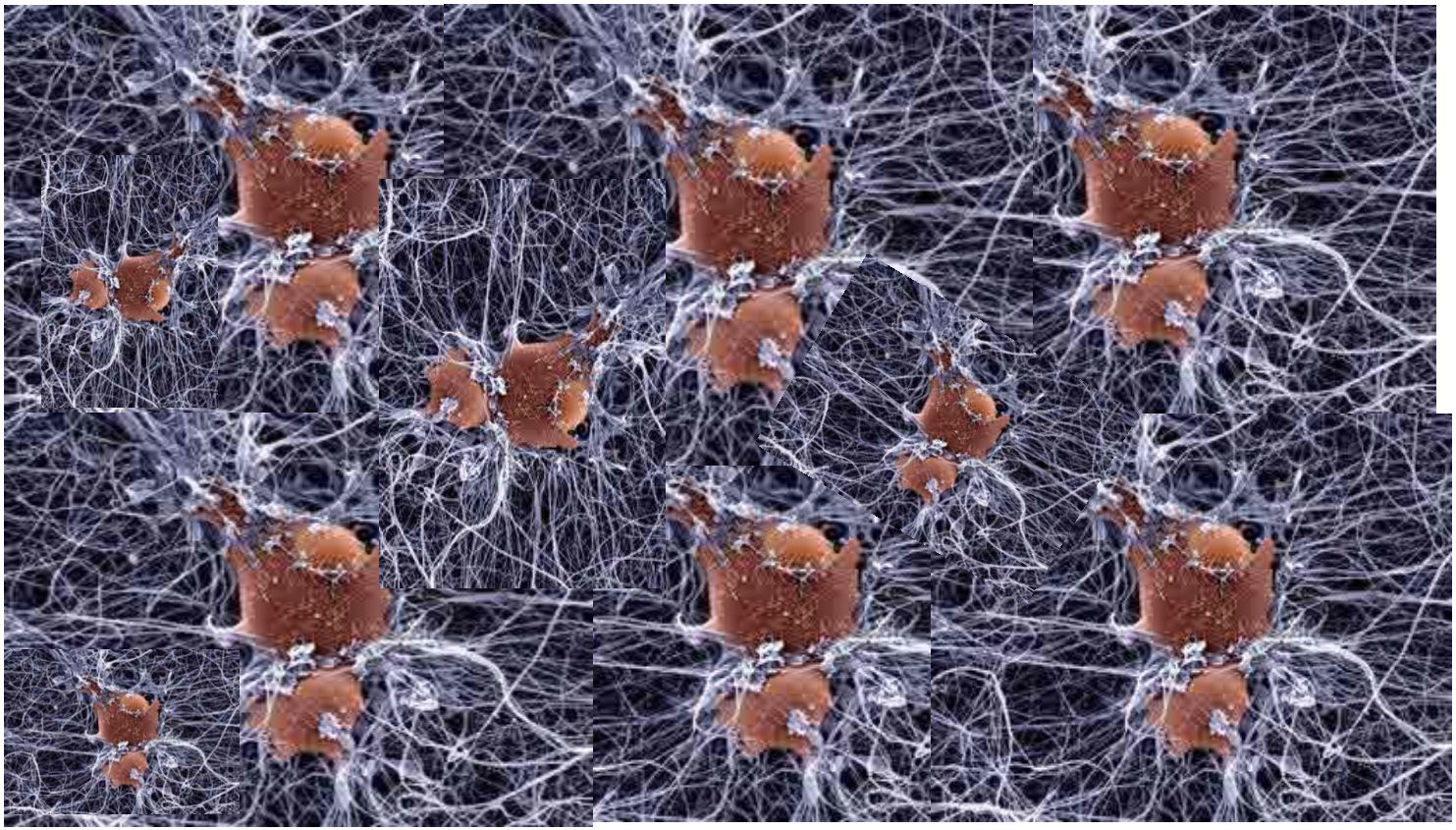
- Nerve cell is specialized and cannot regenerate once nerve cell dies
  - Injured peripheral nerve- nerve fiber can regenerate if injury does not affect cell body
  - Regeneration is very slow 3-4 mm /day
    - Axon regeneration obstructed by scar formation
    - Damaged nerve within CNS regenerate poorly compared to peripheral nervous system
      - Lack connective tissue sheath and nerve cells fail to proliferate

Nerve Cell



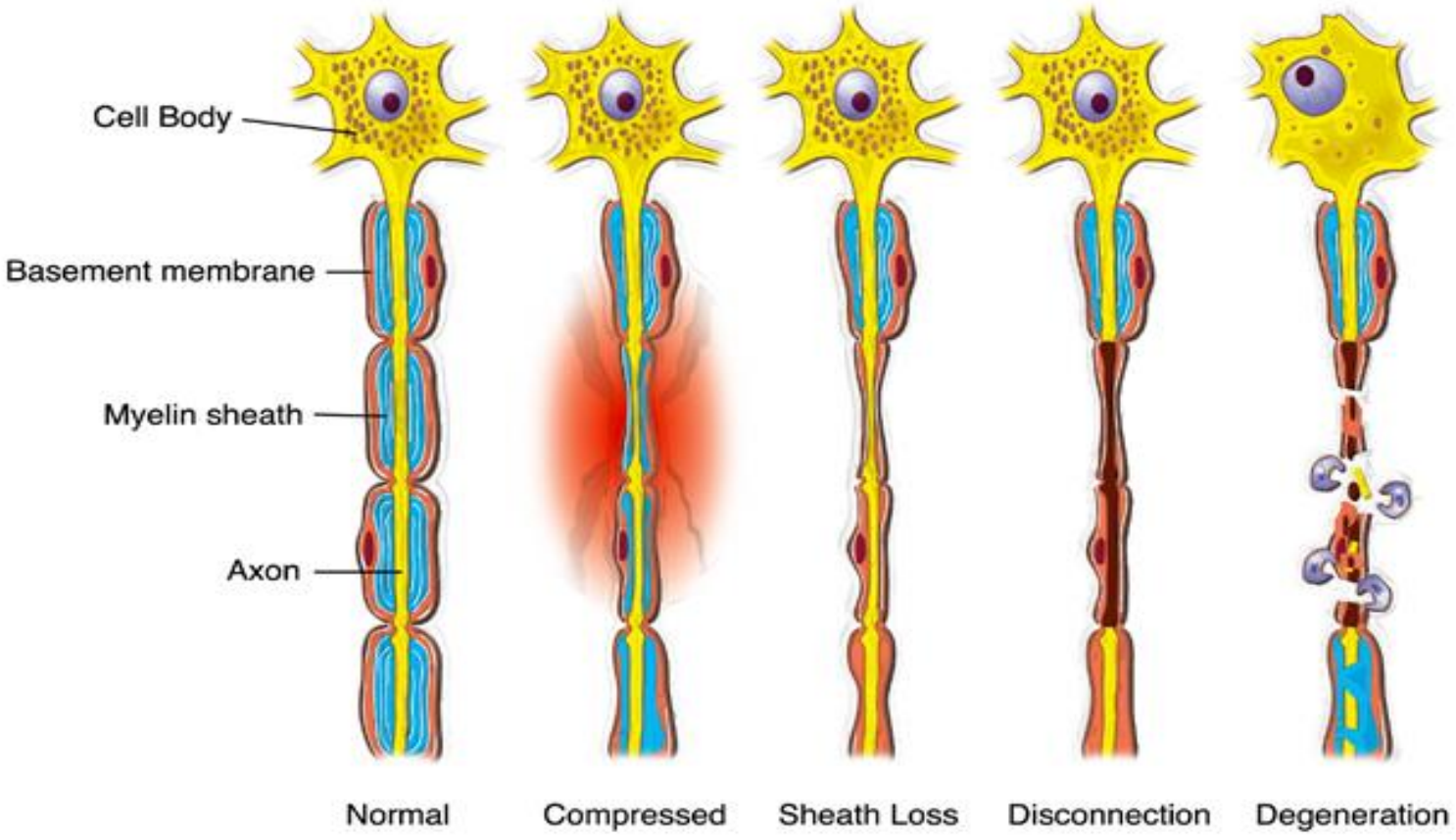
- The function of a neuron is to communicate information, which it does by two methods. Electric signals process and conduct information within a cell, while chemical signals transmit information between cells.
- Nerve cells control sensations in the body and other functions such as help to store memory in the brain.

Nerve Cells In The Brain



Types of Nerve Damage

Nerve injuries types		
Neurapraxia	Axonotmesis	Neurotmesis



3 basic Stages of Nerve regeneration

1.Wallerian degeneration

- Distal axon degeneration, following section or severe injury, with degeneration of the myelin. The process occurs within 7-10 days of injury and this portion of the nerve is inexcitable electrically.

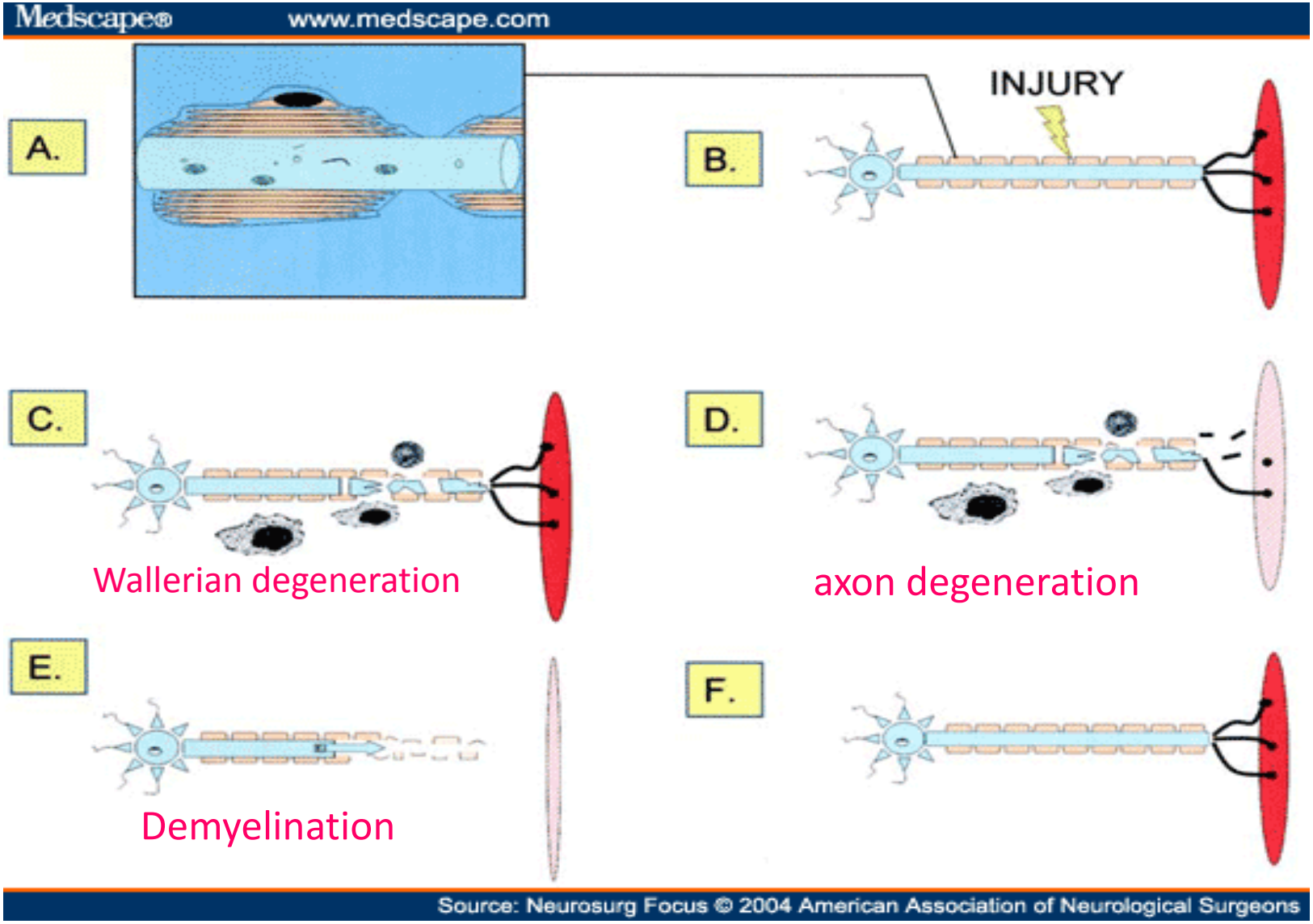
2. axon degeneration

- Distal degenerated nerve is inexcitable electrically.
- Regeneration can occur since the basement membrane of the Schwann cell survives and act as a skeleton along which tha axon regrows up to a rate of about 1mm per day.

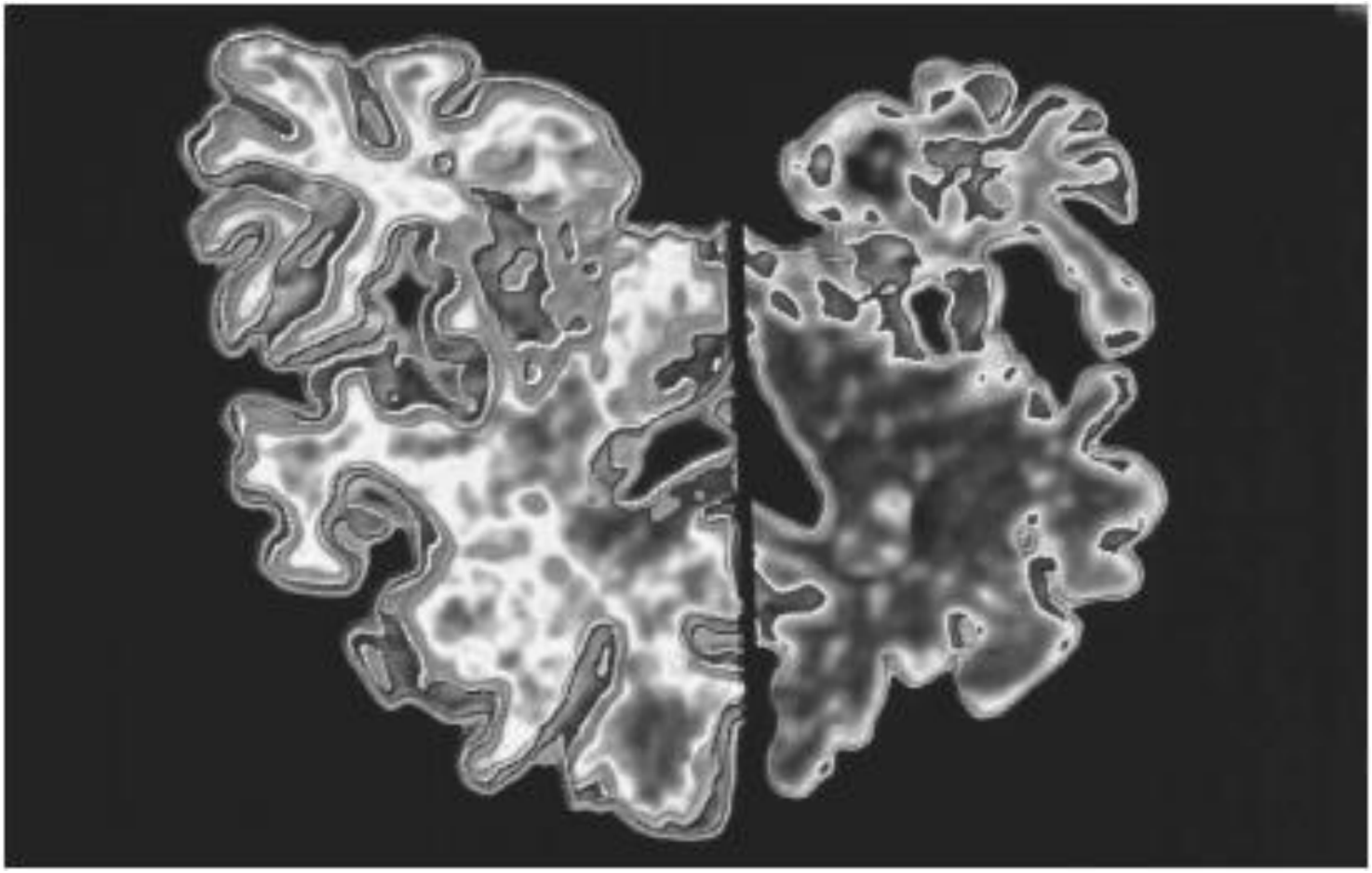
3. Demyelination

- Segmental destruction of the myelin sheath occurs without axonal damage. The primary lesion affects the Schwann cell and causes marked slowing of conduction or conduction block.
- Local demyelination is caused by inflammation, eg: Guillain-Barre syndrome.

Nerve injury and repair



Alzheimer's Disease
Brain Degeneration



Factors controlling regeneration:

Complex and poorly understood.

- 'Growth factors'
  - EGF, PDGF, FGF, IGF ...
  - Hormones e.g. ACTH, œstrogen, growth hormone...
- Contact with basement membranes & adjacent cells
  - Signalling through **integrins**

- NOTE: importance of growth control in CANCER.

Growth Factors (GFs)

What is GFs

- Polypeptides
- Cytokines

Function

- LOCOMOTION
- CONTRACTILITY
- DIFFERENTIATION
- ANGIOGENESIS

Growth Factors (GFs)

- Epidermal
- Transforming (alpha, beta)
- Hepatocyte
- Vascular Endothelial
- Platelet Derived
- Fibroblast
- Keratinocyte
- Cytokines (TNF(Tumor Necrosis Factor), IL-1 Interleukins, Interferons)

CELL PLAYERS (source AND targets)

- Lymphocytes, especially T-cells
- Macrophages
- Platelets
- Endothelial cells
- Fibroblasts
- Keratinocytes
- "Mesenchymal" cells
- Smooth muscle cells

E (Epidermal) GF

- Made in platelets, macrophages
- Present in saliva, milk, urine, plasma
- Acts on keratinocytes to migrate, divide
- Acts on fibroblasts to produce “granulation” tissue

T (Transforming) GF-alpha

- Made in macrophages, T-cells, keratinocytes
- Similar to EGF, also effect on hepatocytes

H (Hepatocyte) GF

- Made in “mesenchymal” cells
- Proliferation of epithelium, endothelium, hepatocytes
- Effect on cell “motility”

VE (Vascular Endothelial) GF

- Made in mesenchymal cells
- Triggered by HYPOXIA
- Increases vascular permeability
- Mitogenic for endothelial cells
- KEY substance in promoting “granulation” tissue

PD (Platelet Derived) GF

- Made in platelets, but also MANY other cell types
- Chemotactic for MANY cells
- Mitogen for fibroblasts
- Angiogenesis
- Another KEY player in granulation tissue

F (Fibroblast) GF

- Made in MANY cells
- Chemotactic and mitogenic, for fibroblasts and keratinocytes
- Re-epithelialization
- Angiogenesis, wound contraction
- Hematopoesis
- Cardiac/Skeletal (striated) muscle

T (Transforming) GF-beta

- Made in MANY CELLS
- Chemotactic for PMNs and MANY other types of cells
- Inhibits epithelial cells
- Fibrogenic
- Anti-Inflammatory

K (Keratinocyte) GF

- Made in fibroblasts
- Stimulates keratinocytes: Migration, Proliferation, Differentiation

I (Insulin-like) GF-1

- Made in macrophages, fibroblasts
- Stimulates: Sulfated proteoglycans, Collagen, Keratinocyte migration and Fibroblast proliferation
- Action similar to GH (Pituitary Growth Hormone)

TNF

- Made in macrophages, mast cells, T-cells
- Activates macrophages (cachexin)
- KEY influence on other cytokines
- The MAJOR TNF is TNF-alpha

Interleukins

- Made in macrophages, mast cells, T-cells, but also MANY other cells
- MANY functions: Chemotaxis, Angiogenesis, REGULATION of other cytokines

INTERFERONS

- Made by lymphocytes, fibroblasts
- Activates MACROPHAGES
- Inhibits FIBROBLASTS
- REGULATES other cytokines

Questions?