Tissue Repair

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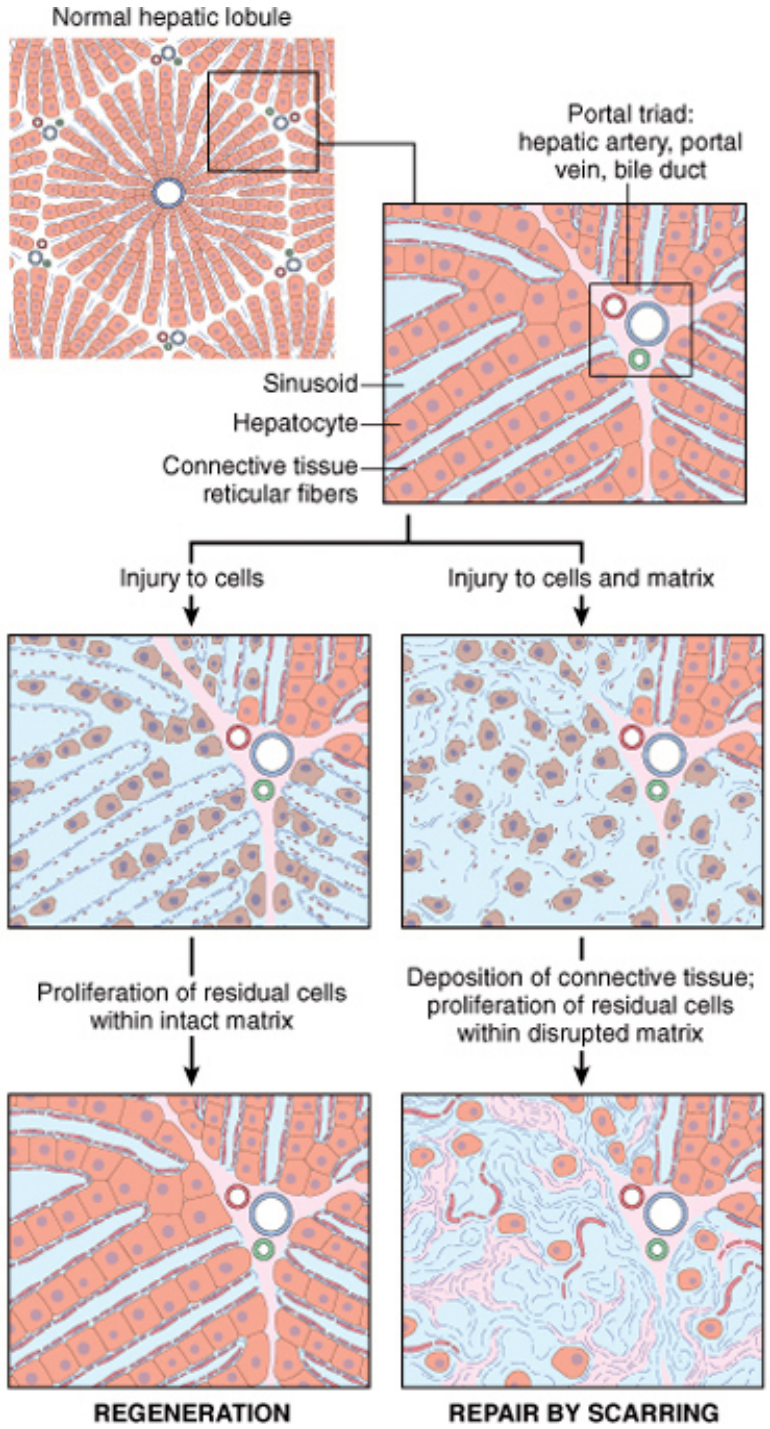
TISSUE REPAIR

- Tissue repair = restoration of tissue architecture and function after an injury
- Occurs in two ways:
  - Regeneration of injured tissue
  - Replacement by connective tissue (scarring)
- Usually, tissue repair involves both processes
- Involves cell proliferation, and interaction between cells and extracellular matrix


Normal hepatic lobule
Portal triad:
hepatic artery, portal
vein, bile duct
Sinusoid
Hepatocyte
Connective tissue
reticular fibers
Injury to cells
Injury to cells and matrix
Proliferation of residual cells
within intact matrix
Deposition of connective tissue;
proliferation of residual cells
within disrupted matrix
REGENERATION
REPAIR BY SCARRING

LECTURE OVERVIEW

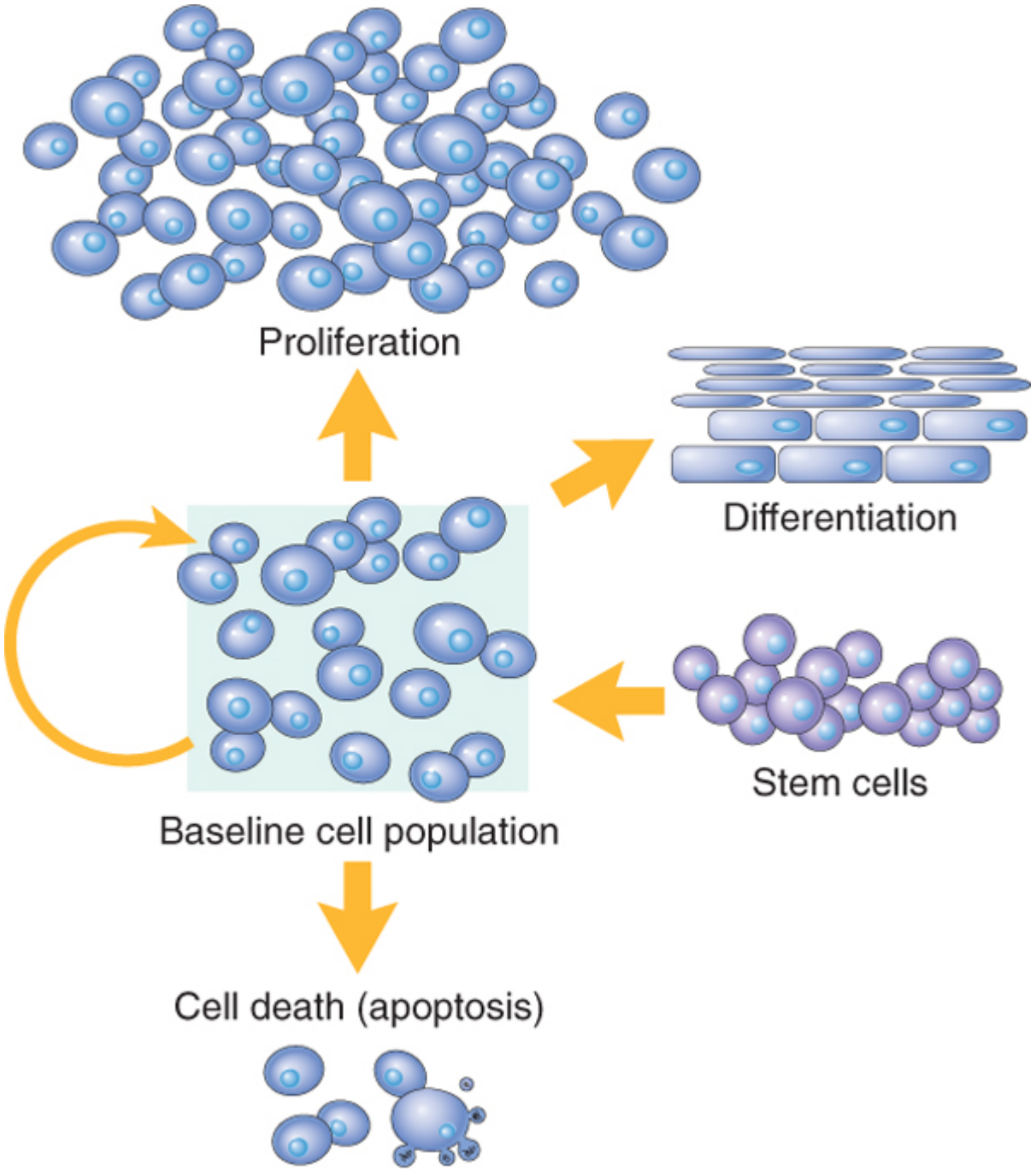
- Important background facts
  - cellular proliferation
  - growth factors
  - the extracellular matrix
- The process of tissue repair
  - regeneration
  - scarring
  - an illustration: skin wound healing
  - why do good wounds go bad?

LECTURE OVERVIEW

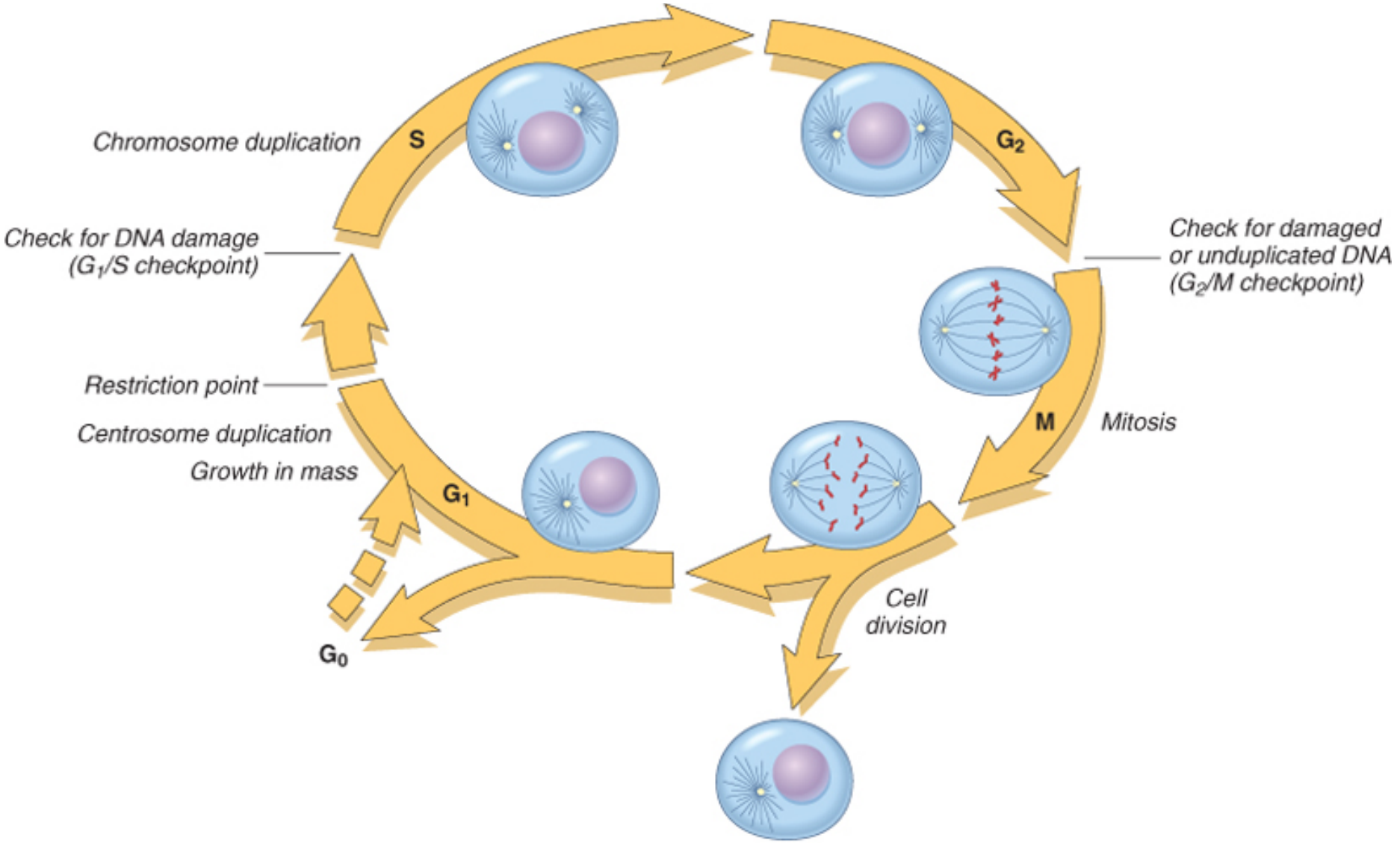
- Important background facts
  - cellular proliferation

CELLULAR PROLIFERATION

- Lots of cells proliferate during tissue repair:
  - injured tissue remnants
  - vascular endothelial cells
  - fibroblasts
- You need to know a few things about:
  - the cell cycle
  - the proliferative capacities of different tissues
  - stem cells
  - growth factors
  - the extracellular matrix


Proliferation
Differentiation
Stem cells
Baseline cell population
Cell death (apoptosis)

The Cell Cycle



CELLULAR PROLIFERATION

Tissues of the body are divided into three groups:

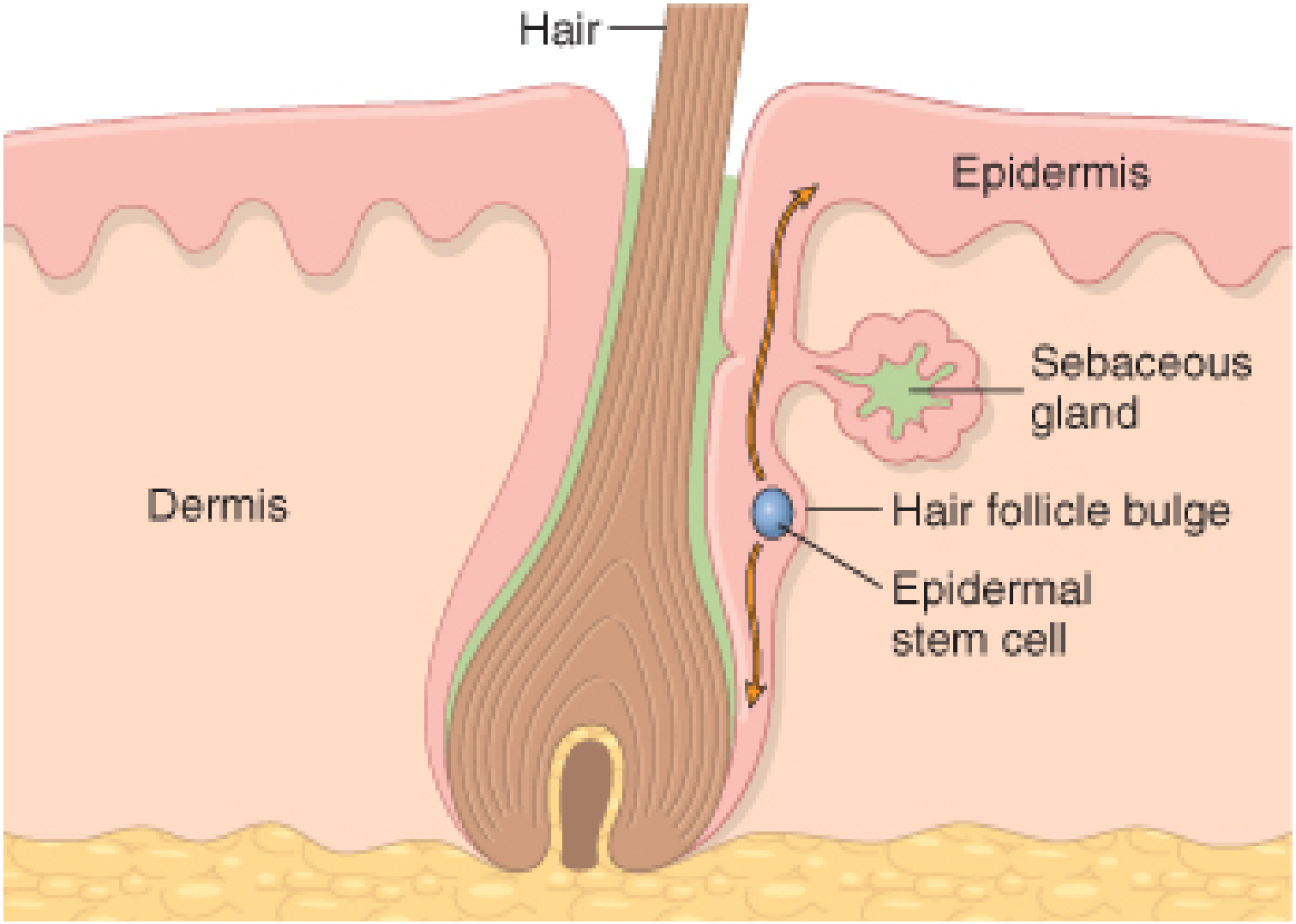
- Continuously dividing (labile) tissues
- Stable tissues
- Permanent tissues

CELLULAR PROLIFERATION

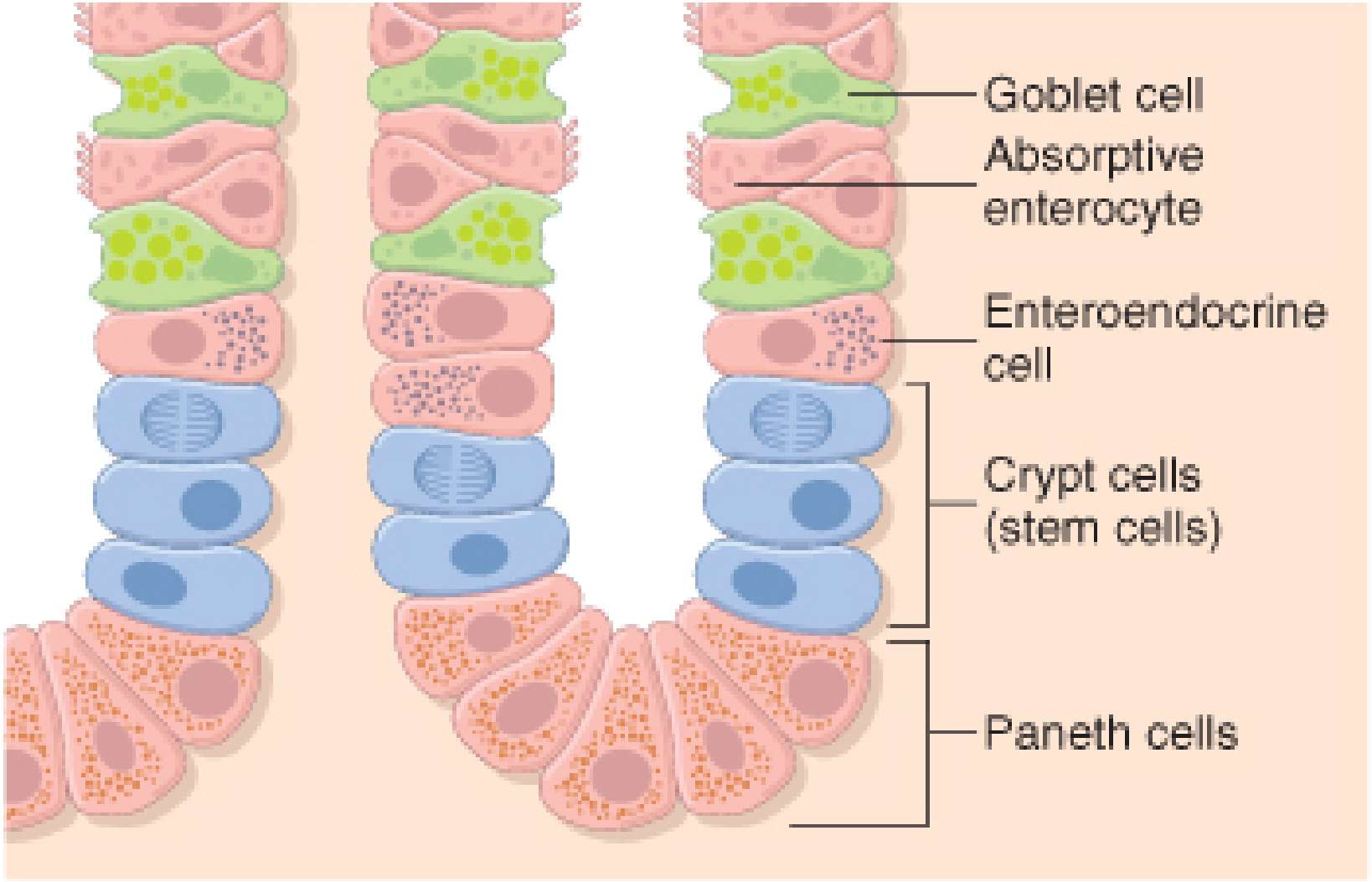
Tissues of the body are divided into three groups:

- Continuously dividing (labile) tissues
  - cells are continuously proliferating
  - can easily regenerate after injury
  - contain a pool of stem cells
  - examples: bone marrow, skin, GI epithelium

Stem cells in skin



Stem cells in GI epithelium



CELLULAR PROLIFERATION

Tissues of the body are divided into three groups:

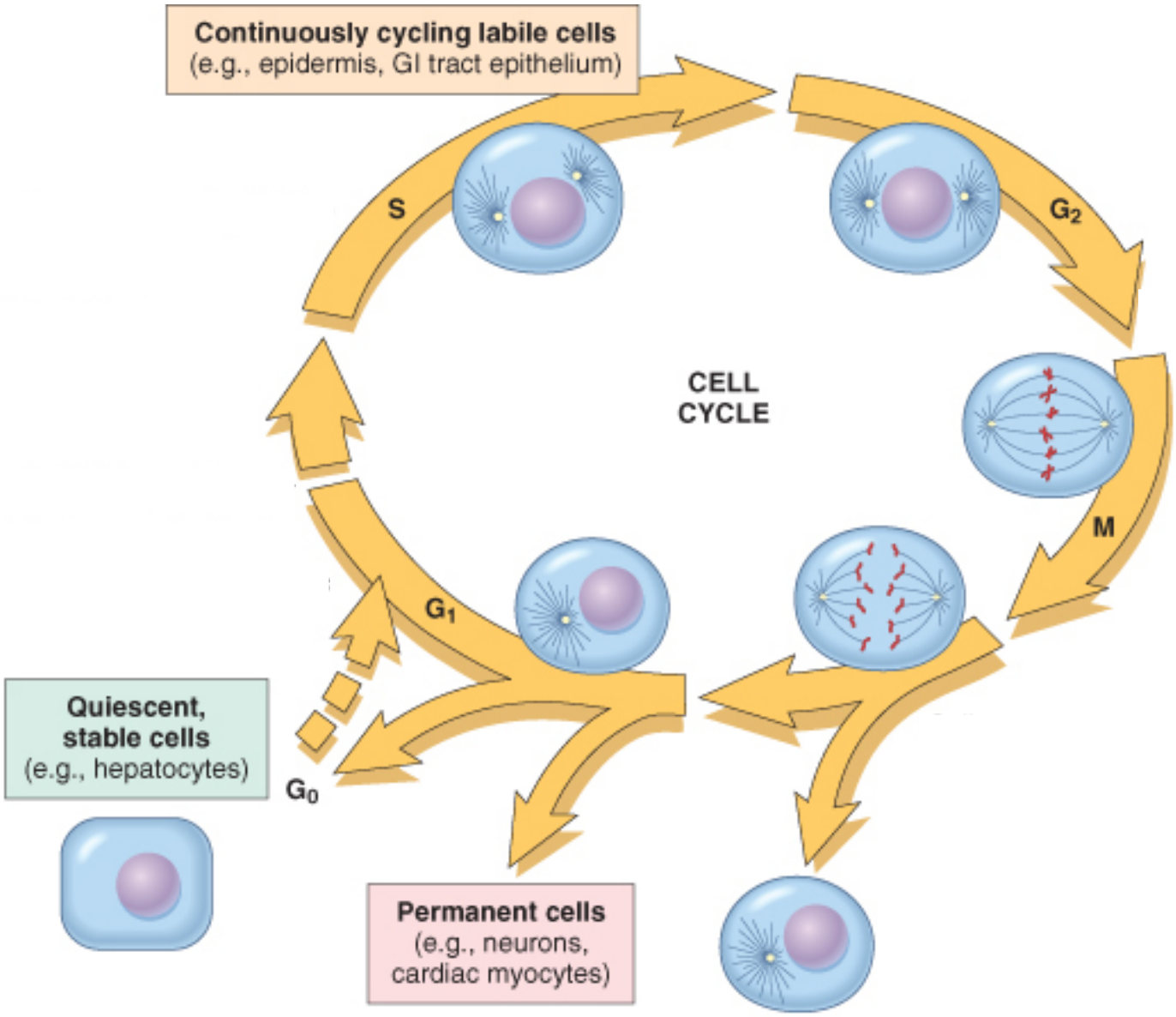
- Continuously dividing (labile) tissues
- Stable tissues
  - cells have limited ability to proliferate
  - limited ability to regenerate (except liver!)
  - normally in G_0, but can proliferate if injured
  - examples: liver, kidney, pancreas

CELLULAR PROLIFERATION

Tissues of the body are divided into three groups:

- Continuously dividing (labile) tissues
- Stable tissues
- Permanent tissues
  - cells can’t proliferate
  - can’t regenerate (so injury always leads to scar)
  - examples: neurons, cardiac muscle

The Cell Cycle and Different Cell Populations

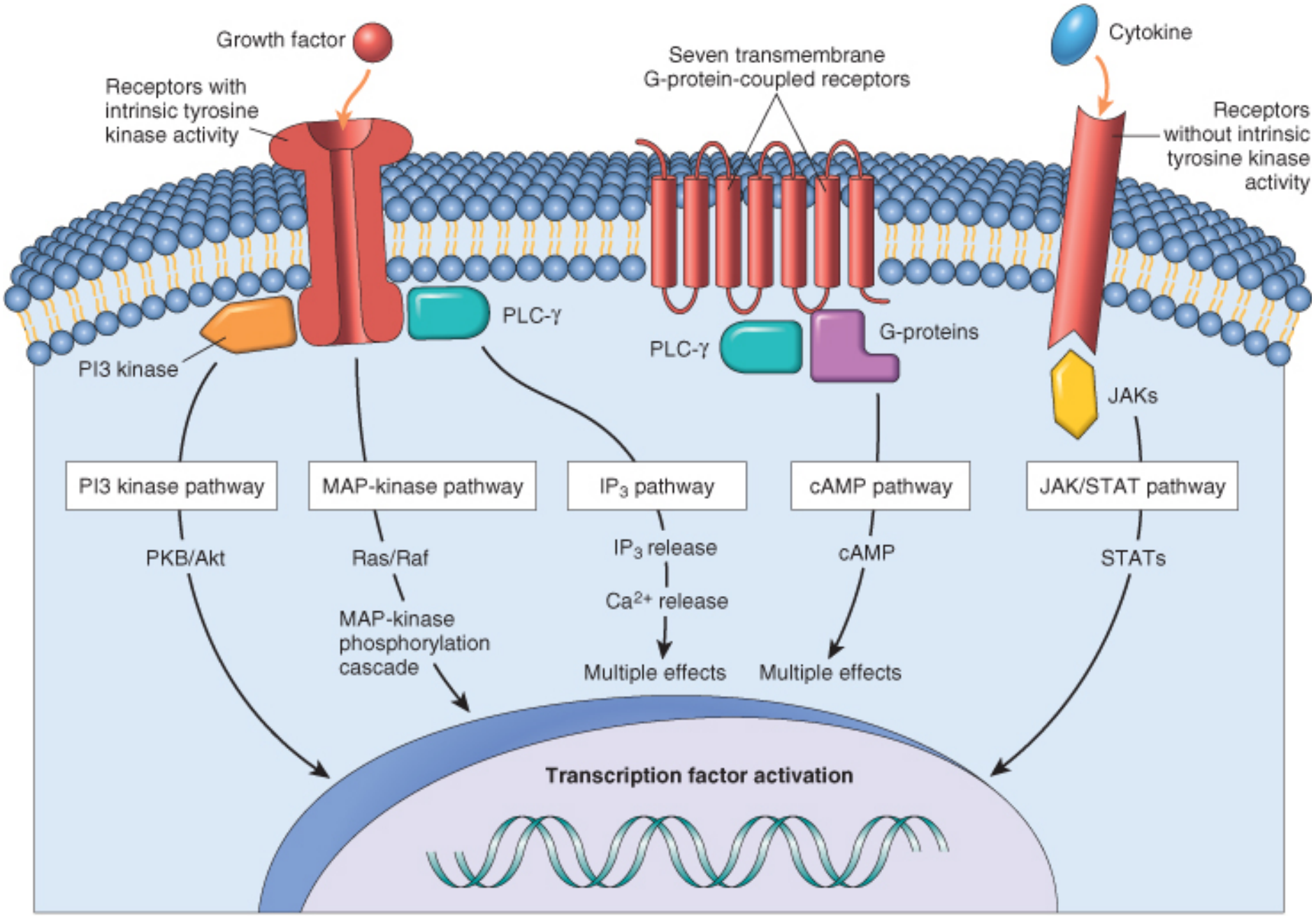


LECTURE OVERVIEW

- Important background facts
  - cellular proliferation
  - growth factors

GROWTH FACTORS

- Very important in tissue repair.
- Actions:
  - stimulate cell division and proliferation
  - promote cell survival
- Huge list! Usually have “GF” in name:
  - EGF
  - TGF
  - PDGF


Growth factor
Receptors with intrinsic tyrosine kinase activity
Seven transmembrane G-protein-coupled receptors
Cytokine
Receptors without intrinsic tyrosine kinase activity
PLC-γ
PI3 kinase
PLC-γ
G-proteins
JAKs
PI3 kinase pathway
MAP-kinase pathway
IP3 pathway
cAMP pathway
JAK/STAT pathway
PKB/Akt
Ras/Raf
IP3 release
Ca2+ release
cAMP
STATs
MAP-kinase phosphorylation cascade
Multiple effects
Multiple effects
Transcription factor activation

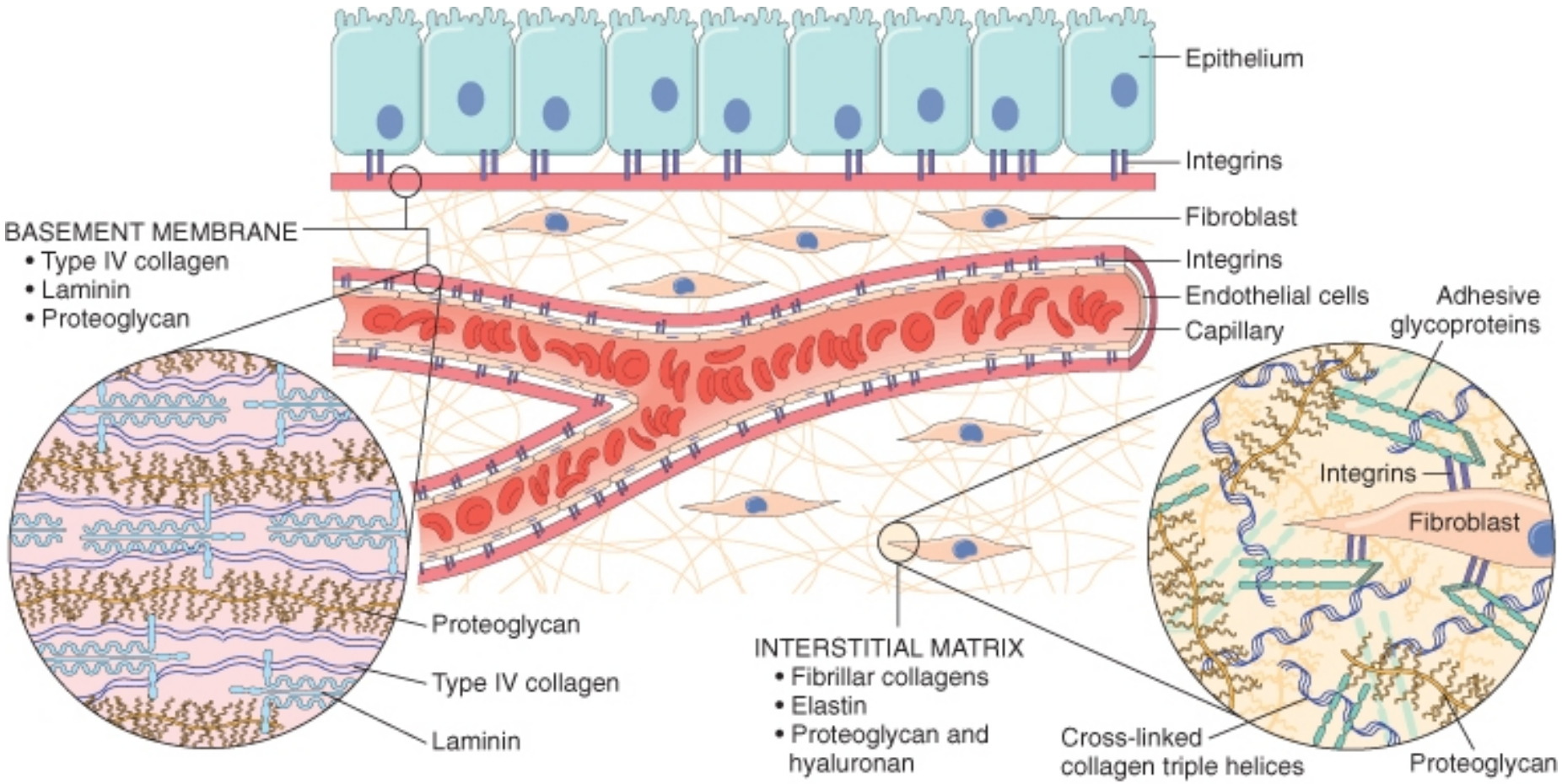
LECTURE OVERVIEW

- Important background facts
  - cellular proliferation
  - growth factors
  - the extracellular matrix

THE EXTRACELLULAR MATRIX

- ECM is the network that surrounds cells
- Two forms: interstitial matrix and basement membrane
- Does lots of things!
  - Sequesters water and minerals
  - Gives cells a scaffold to adhere to
  - Stores growth factors

The Extracellular Matrix



THE EXTRACELLULAR MATRIX

- Bottom line: ECM regulates proliferation, movement, and differentiation of the cells living in it.
- If you screw up your ECM, you can't regenerate! You'll form a scar instead.

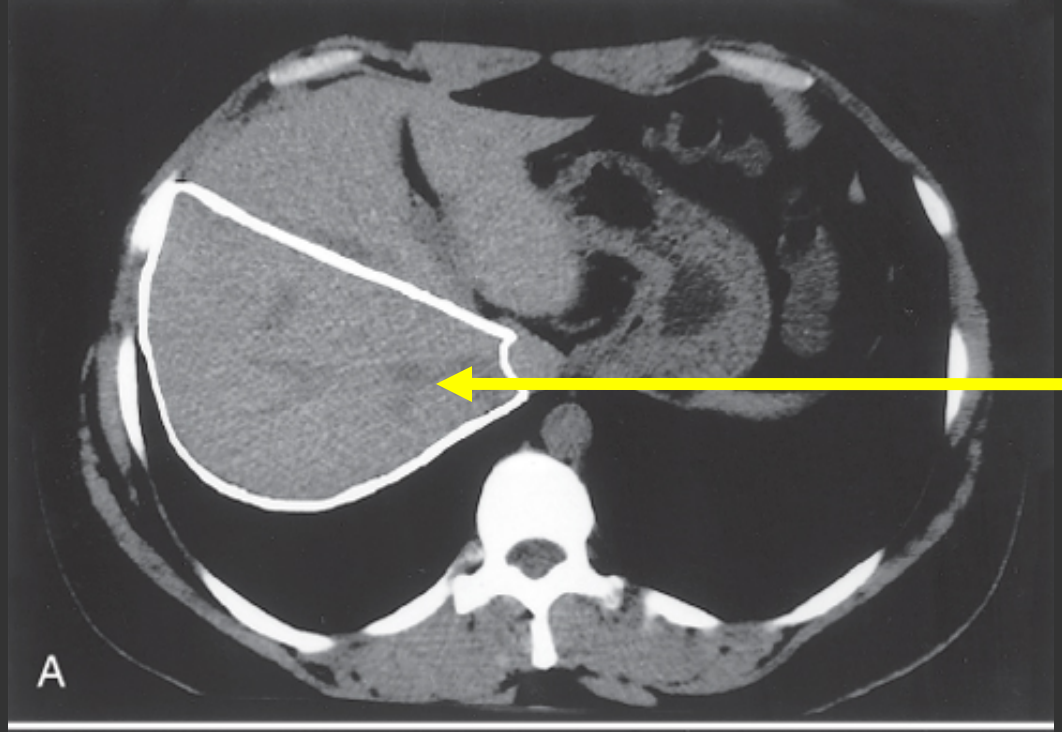
LECTURE OVERVIEW

- Important background facts
  - cellular proliferation
  - growth factors
  - the extracellular matrix
- The process of tissue repair
  - regeneration

REGENERATION

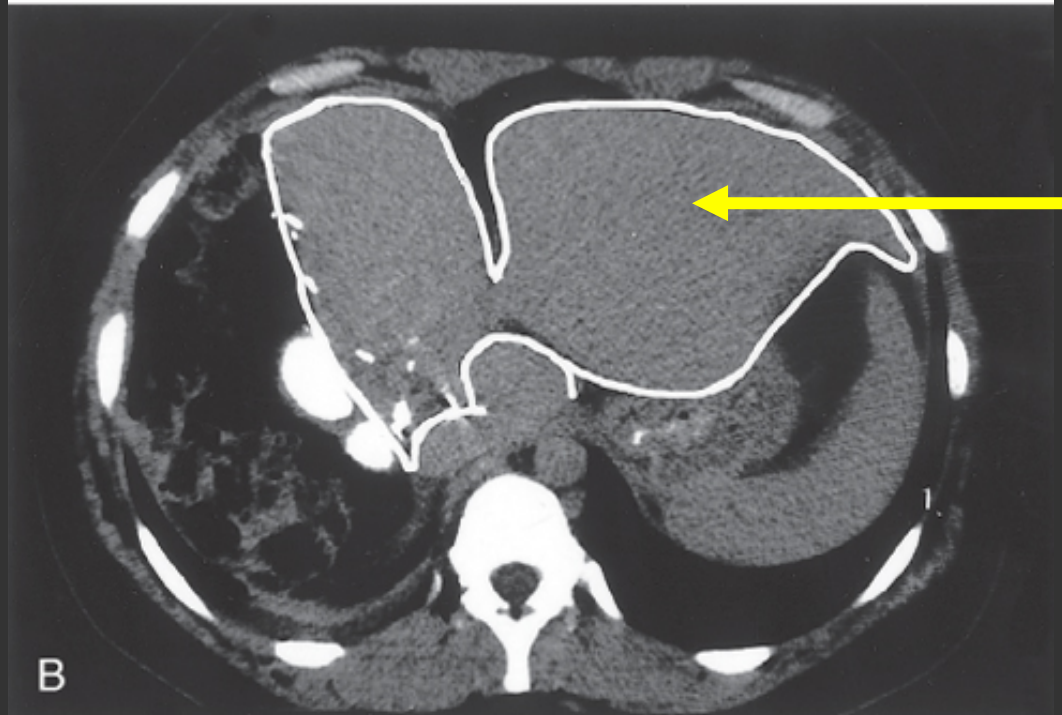
- Occurs all the time in labile tissues
  - Cells are constantly being lost and replaced
  - If demand increases, supply increases easily
- Occurs in limited form in stable tissues
  - Remove one kidney: the other one undergoes hypertrophy and hyperplasia
  - Remove half of the liver: it will grow back
- Only occurs if residual tissue is intact!

Liver before resection



right lobe to be resected

Liver 1 week after resection



left lobe now enlarged

LECTURE OVERVIEW

- Important background facts
  - cellular proliferation
  - growth factors
  - the extracellular matrix
- The process of tissue repair
  - regeneration
  - scarring

SCARRING

- If injury is severe, regeneration can't happen
- So, fibrosis (a scar) replaces the injured tissue
- Four components to this process:
  - new vessel formation (angiogenesis)
  - fibroblast proliferation
  - synthesis of collagen (scar formation)
  - remodeling of scar

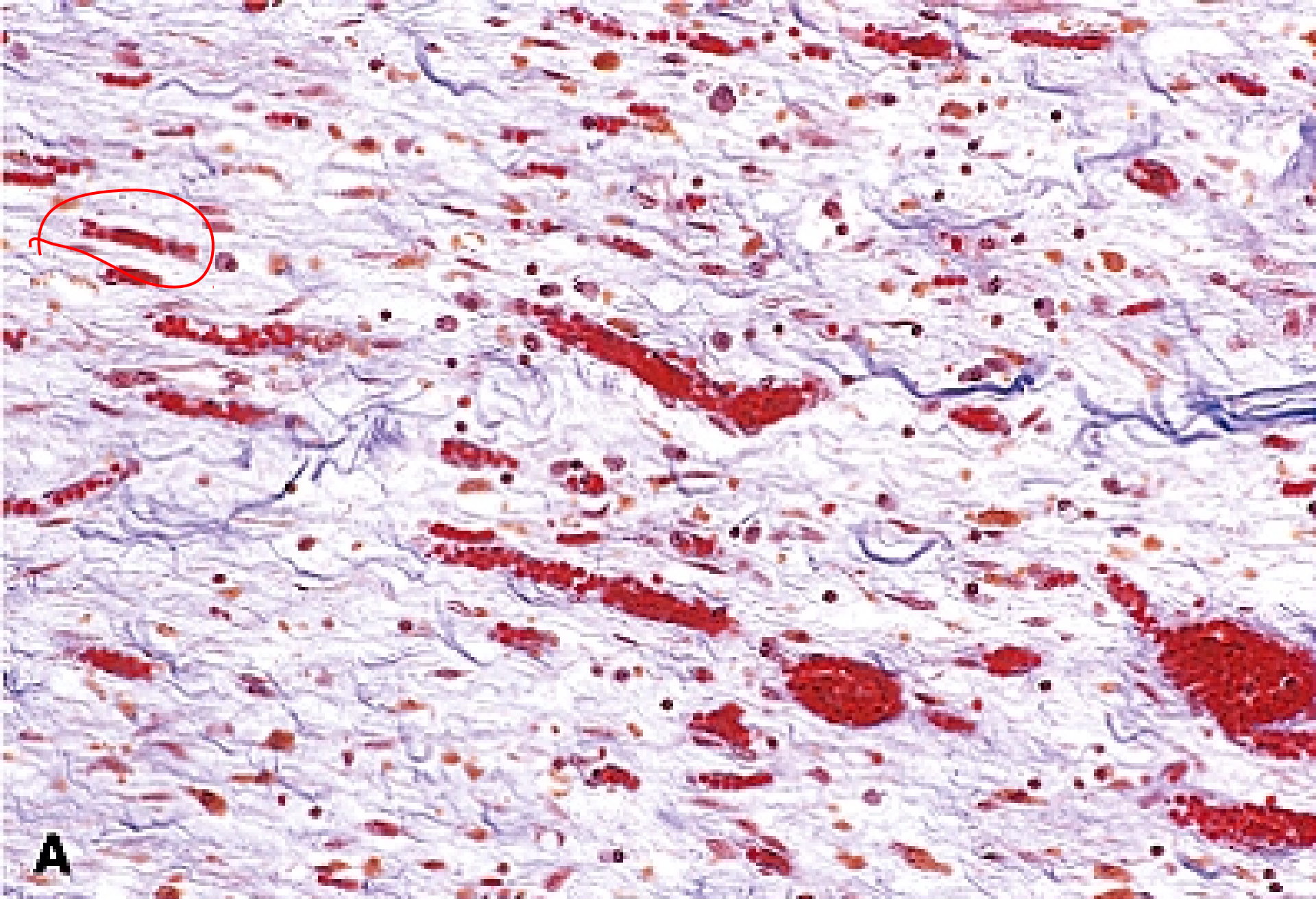
SCARRING

- By 24 hours:
  - Endothelial cells start proliferating
  - Fibroblasts emigrate
- By 3-5 days:
  - granulation tissue present
- Weeks later:
  - dense fibrosis (scar)
  - scar is remodeled over time

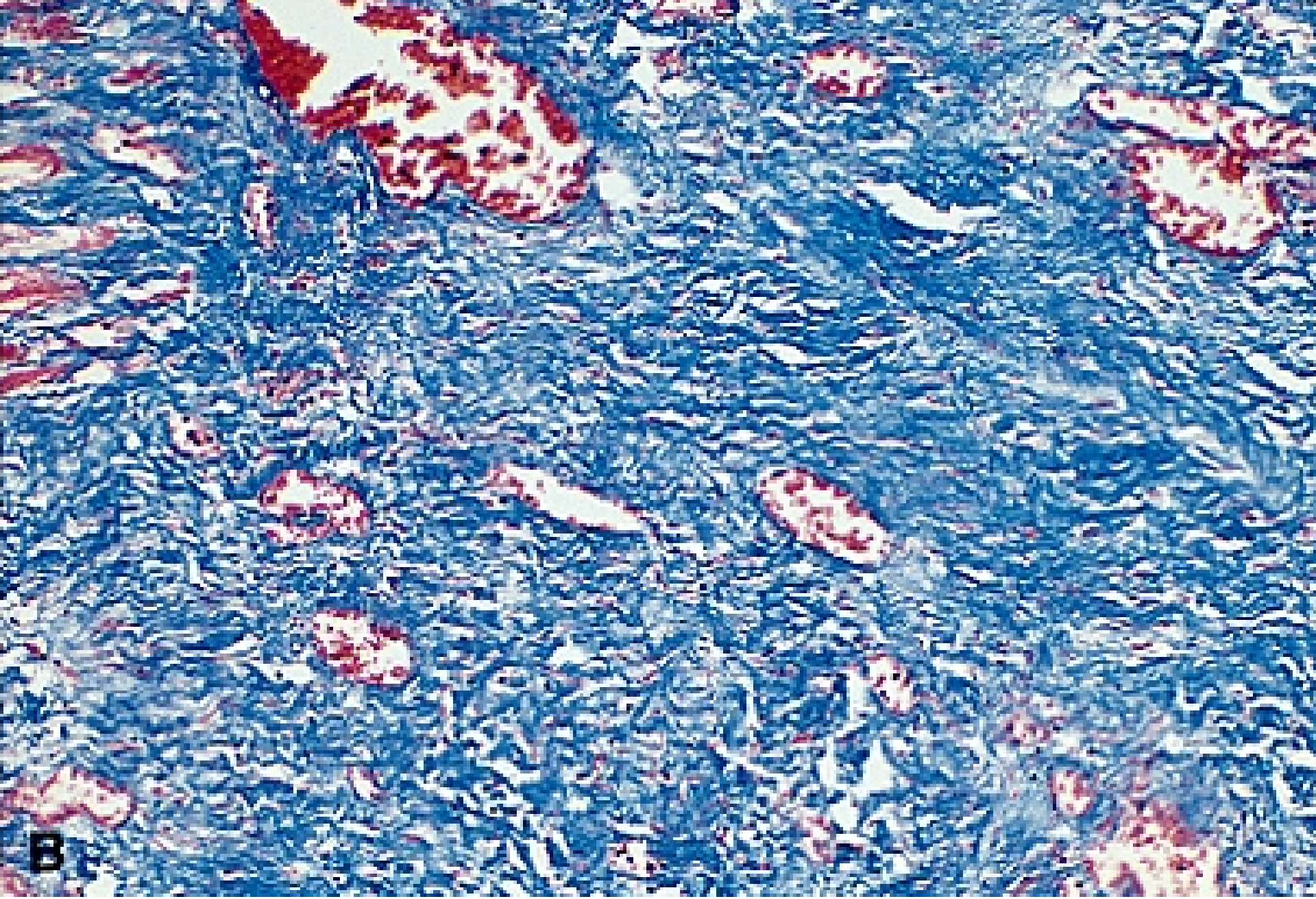
SCARRING

Summary:

1. make granulation tissue
2. turn it into a chunk of collagen



Granulation tissue



Scar

LECTURE OVERVIEW

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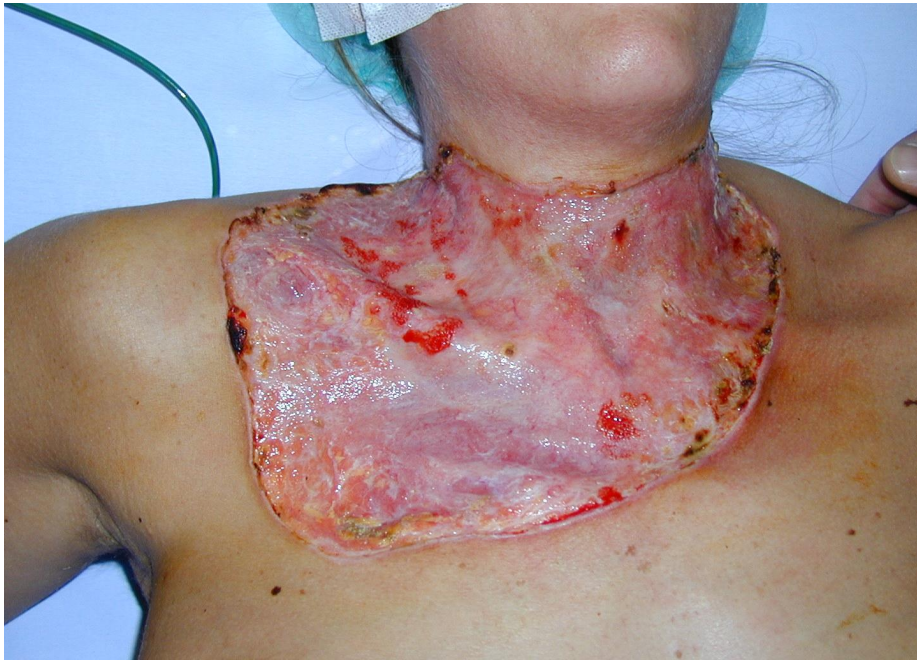
  - regeneration
  - scarring
  - an illustration: skin wound healing

SKIN WOUND HEALING

- First intention
- Second intention

first intention healing



second intention healing

SKIN WOUND HEALING

Healing by First Intention

- Occurs in small wounds that close easily
- Epithelial regeneration predominates over fibrosis
- Healing is fast, with minimal scarring/infection
- Examples:
  - Paper cuts
  - Well-approximated surgical incisions
  - Replaced periodontal flaps

SKIN WOUND HEALING

Healing by First Intention: Timeline

- By 24 hours
- By 3-7 days
- Weeks later

SKIN WOUND HEALING

Healing by First Intention: Timeline

- By 24 hours
  - clot forms
  - neutrophils come in
  - epithelium begins to regenerate

SKIN WOUND HEALING

Healing by First Intention: Timeline

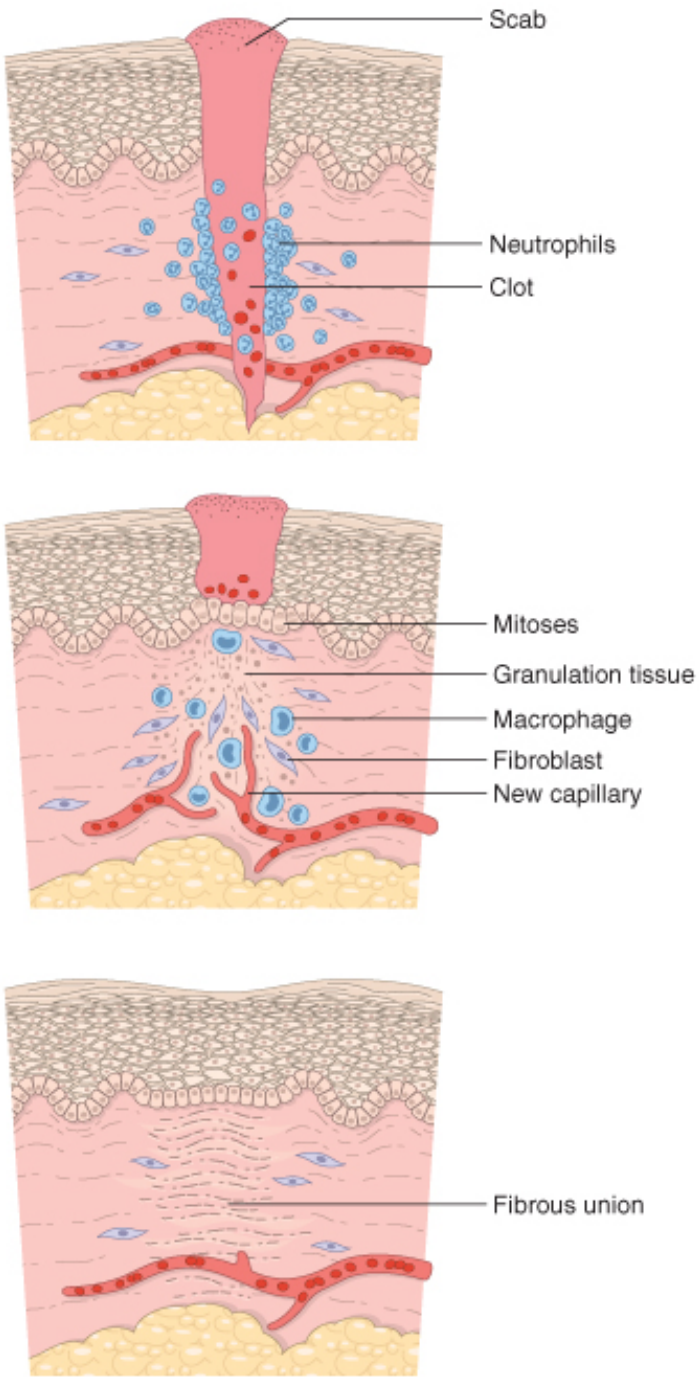
- By 24 hours
- By 3-7 days
  - macrophages come in
  - granulation tissue is formed
    - new blood vessels
    - fibroblasts
  - collagen begins to bridge incision
  - epithelium increases in thickness

SKIN WOUND HEALING

Healing by First Intention: Timeline

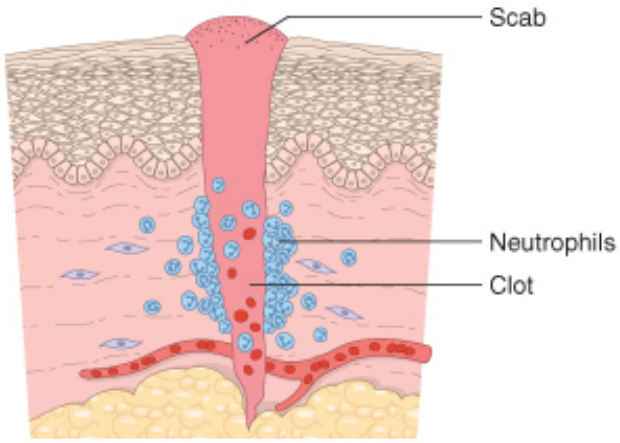
- By 24 hours
- By 3-7 days
- Weeks later
  - granulation tissue gone
  - collagen is remodeled
  - epidermis full, mature
    (but without dermal appendages!)
  - eventually, scar forms

HEALING BY FIRST INTENTION

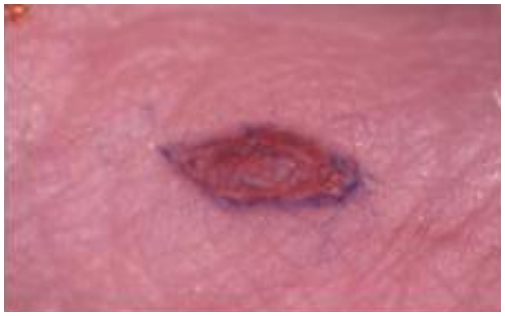


HEALING BY FIRST INTENTION

24 hours

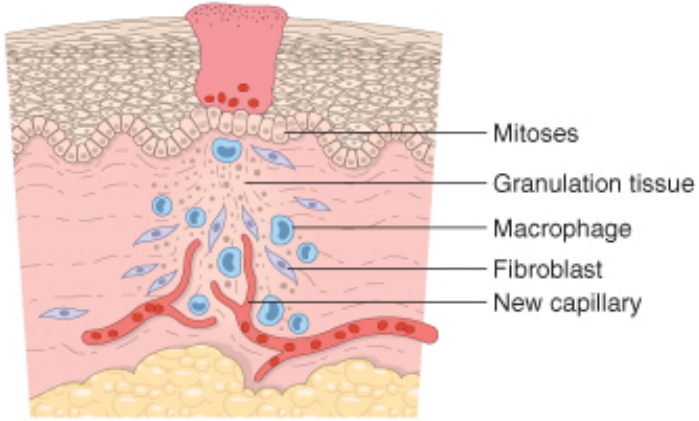


6 hours



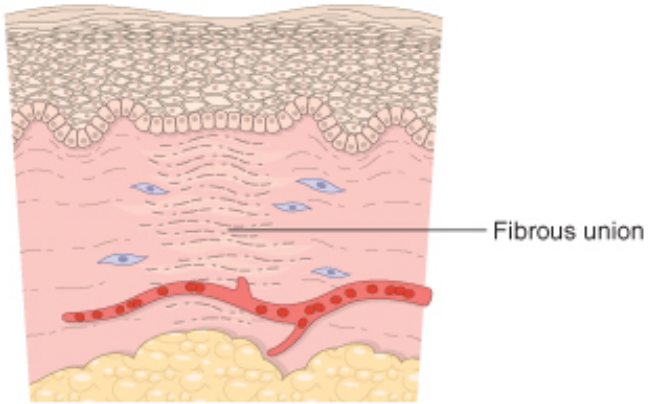
24 hours

3 to 7 days



2 days

Weeks



1 week

SKIN WOUND HEALING

Healing by Second Intention

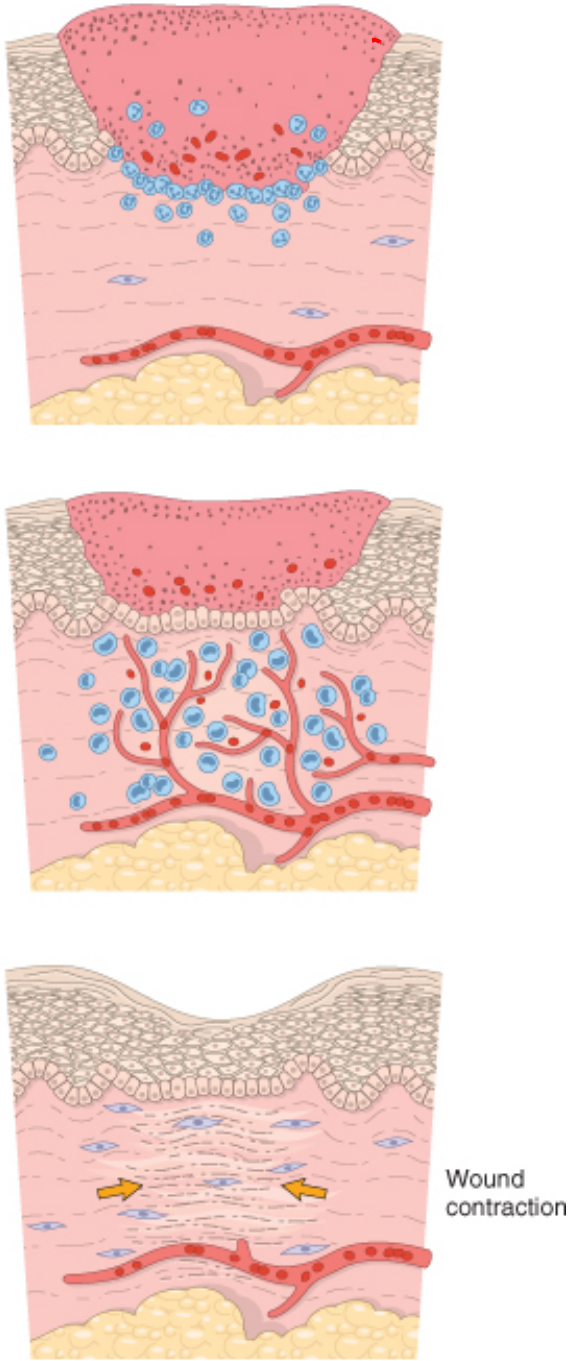
- Occurs in larger wounds that have gaps between wound margins
- Fibrosis predominates over epithelial regeneration
- Healing is slower, with more inflammation and granulation tissue formation, and more scarring
- Examples:
  - Infarction
  - Large burns and ulcers
  - Extraction sockets
  - External-bevel gingivectomies

SKIN WOUND HEALING

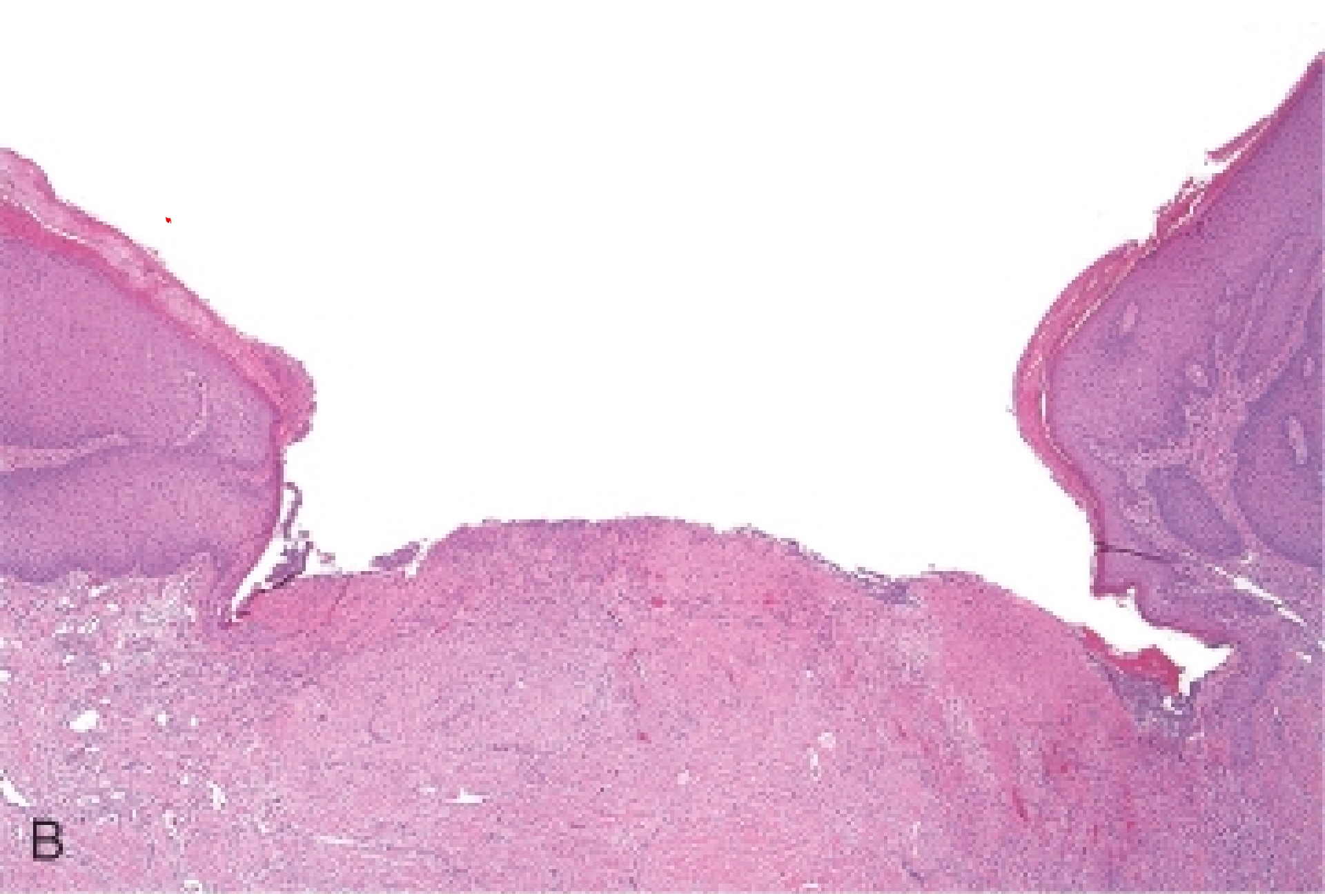
Second intention healing has:

- More inflammation
- More granulation tissue
- Wound contraction

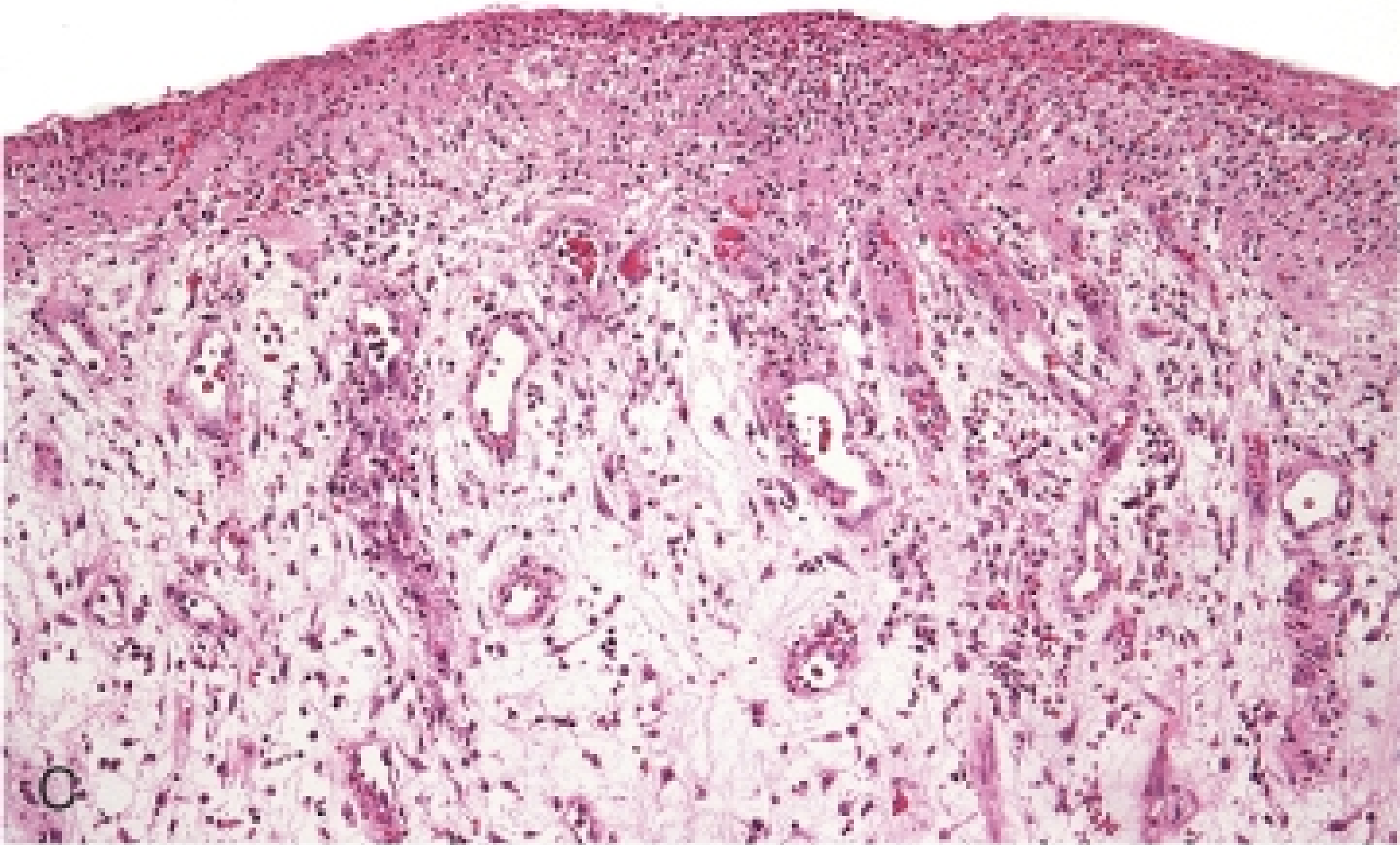
HEALING BY SECOND INTENTION



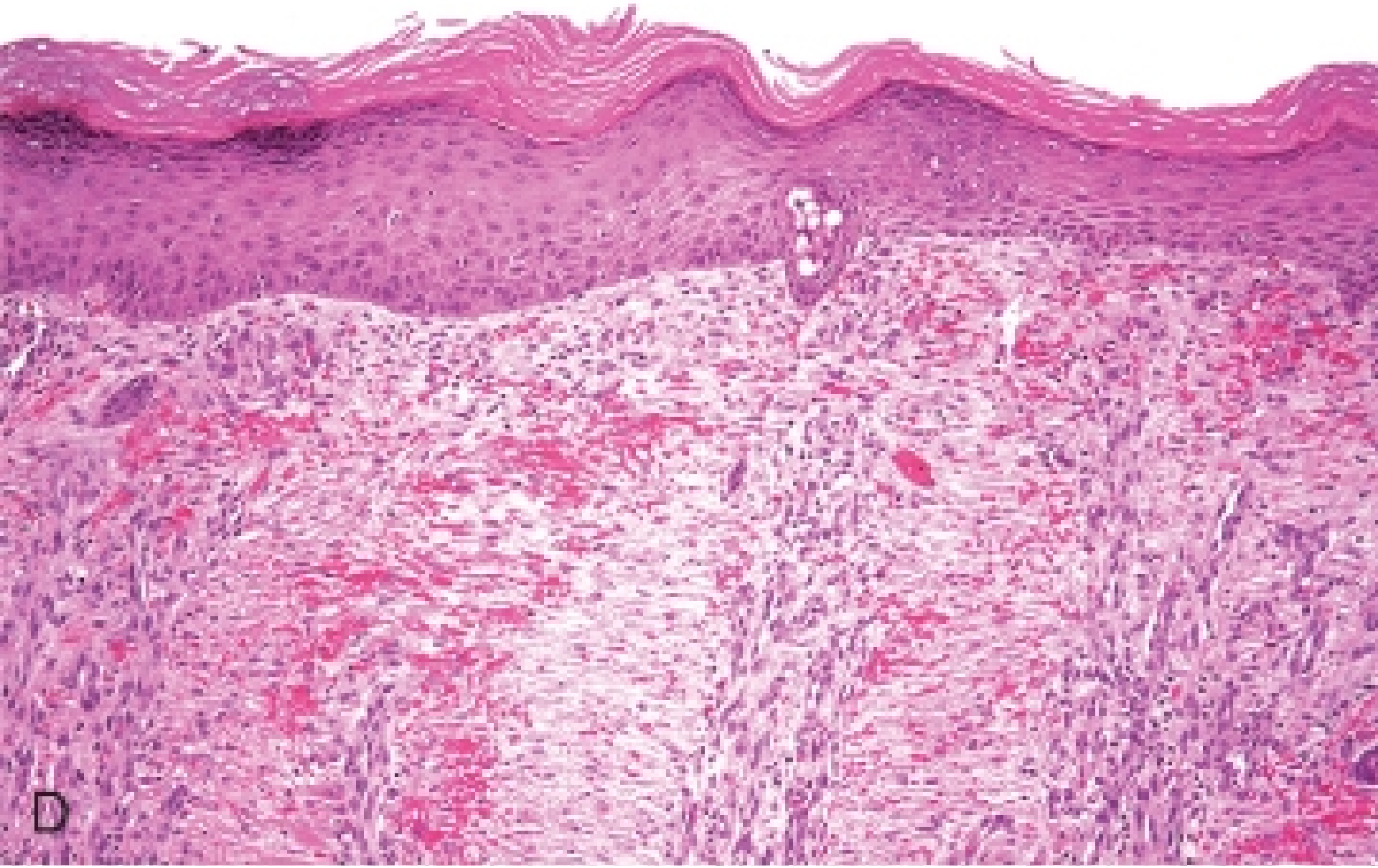
Pressure ulcer of skin



Skin ulcer: large gap between edges



Skin ulcer: granulation tissue



Skin ulcer: re-epithelialization

SKIN WOUND HEALING

Wound Strength

- At suture removal: 10%
- Rapid increase over next 4 weeks
- At third month: 70-80%

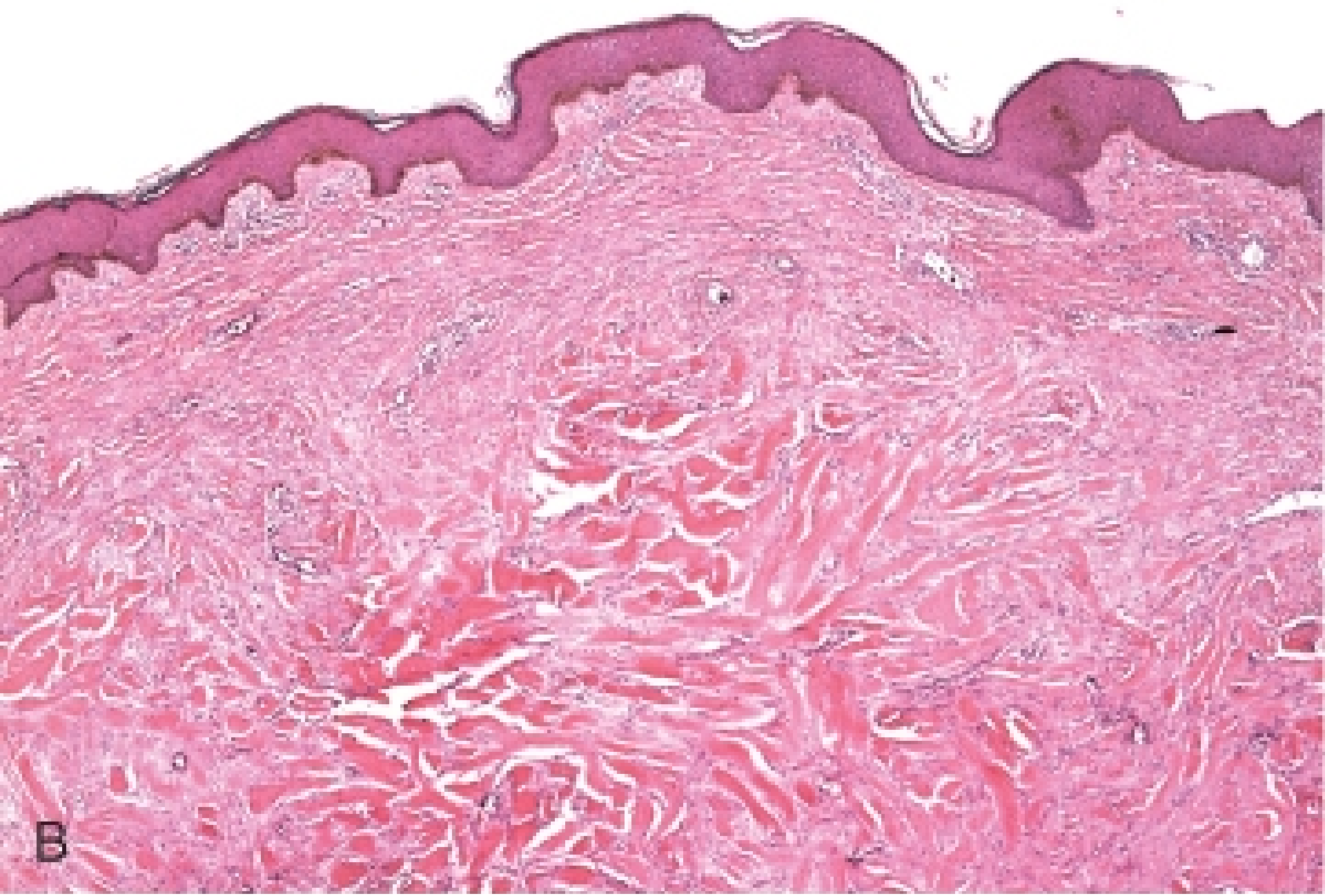
LECTURE OVERVIEW

- Important background facts
  - cellular proliferation
  - growth factors
  - the extracellular matrix
- The process of tissue repair
  - regeneration
  - scarring
  - an illustration: skin wound healing
  - why do good wounds go bad?

WHY DO GOOD WOUNDS GO BAD?

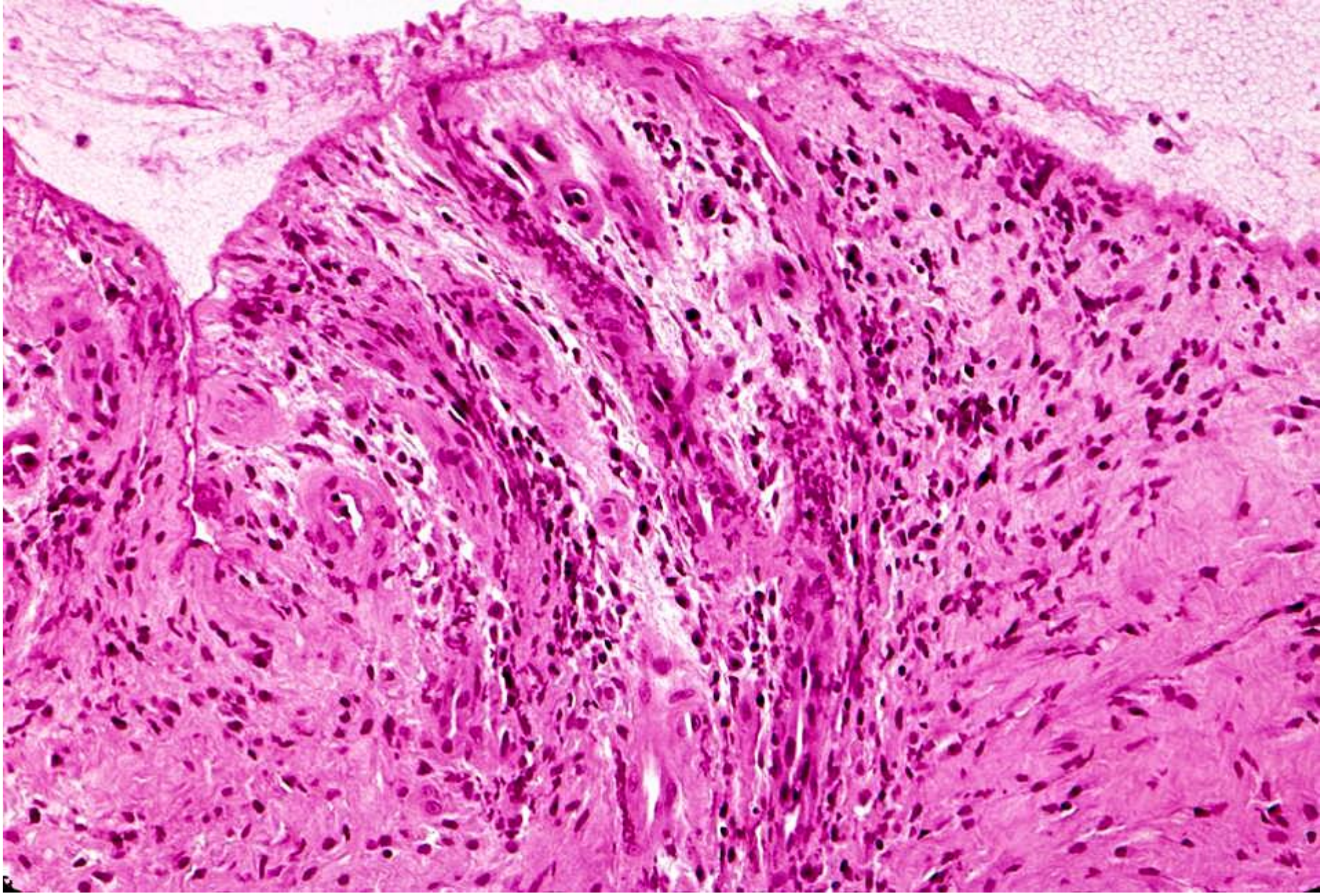
- Extrinsic factors
  - Infection
  - Diabetes
  - Steroids
- Type of tissue injured (labile vs. permanent)
- Aberrant cell growth or ECM production
  - Keloid scars
  - Proud flesh

Keloid scar

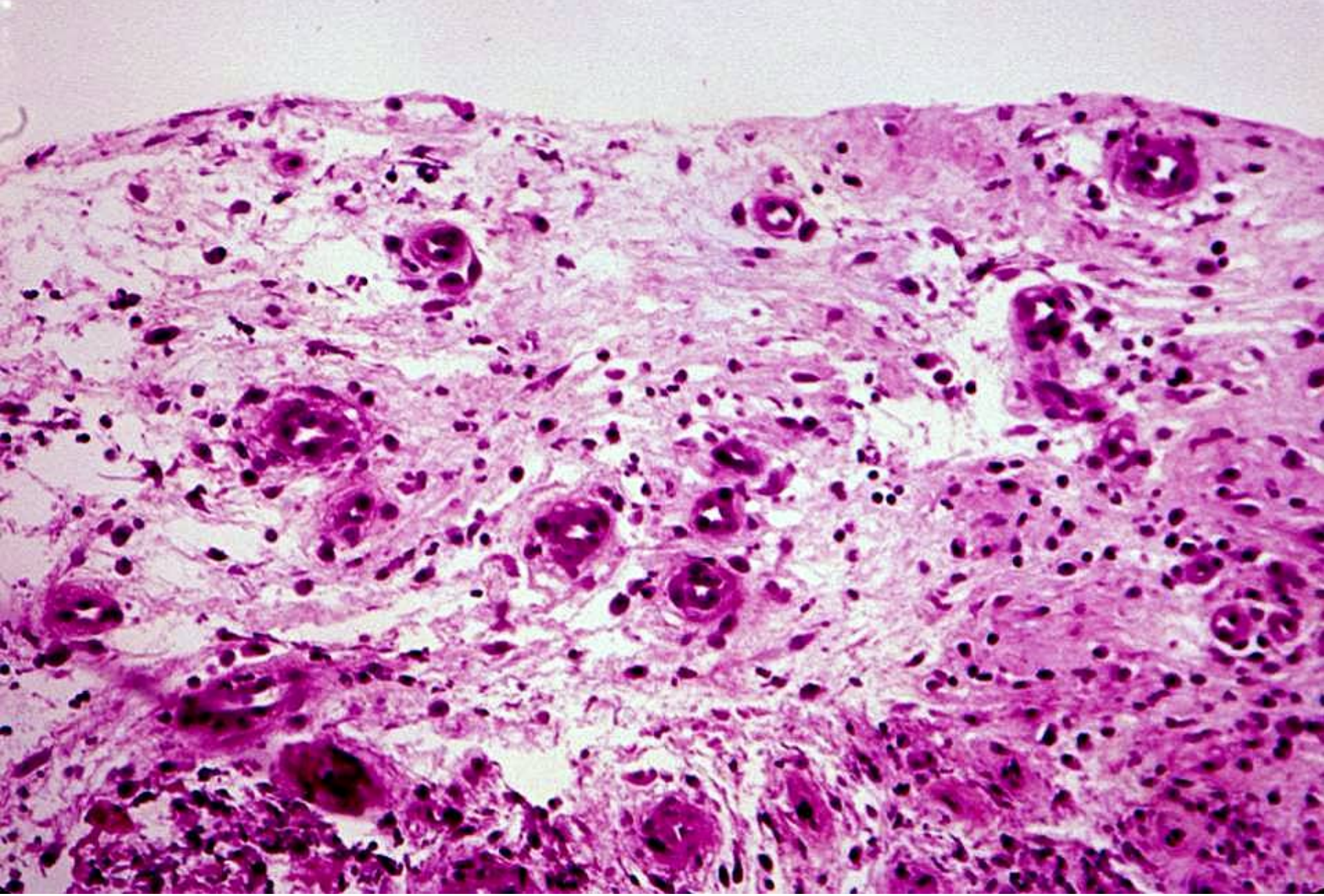


Keloid scar

Proud flesh



Proud flesh



Proud flesh

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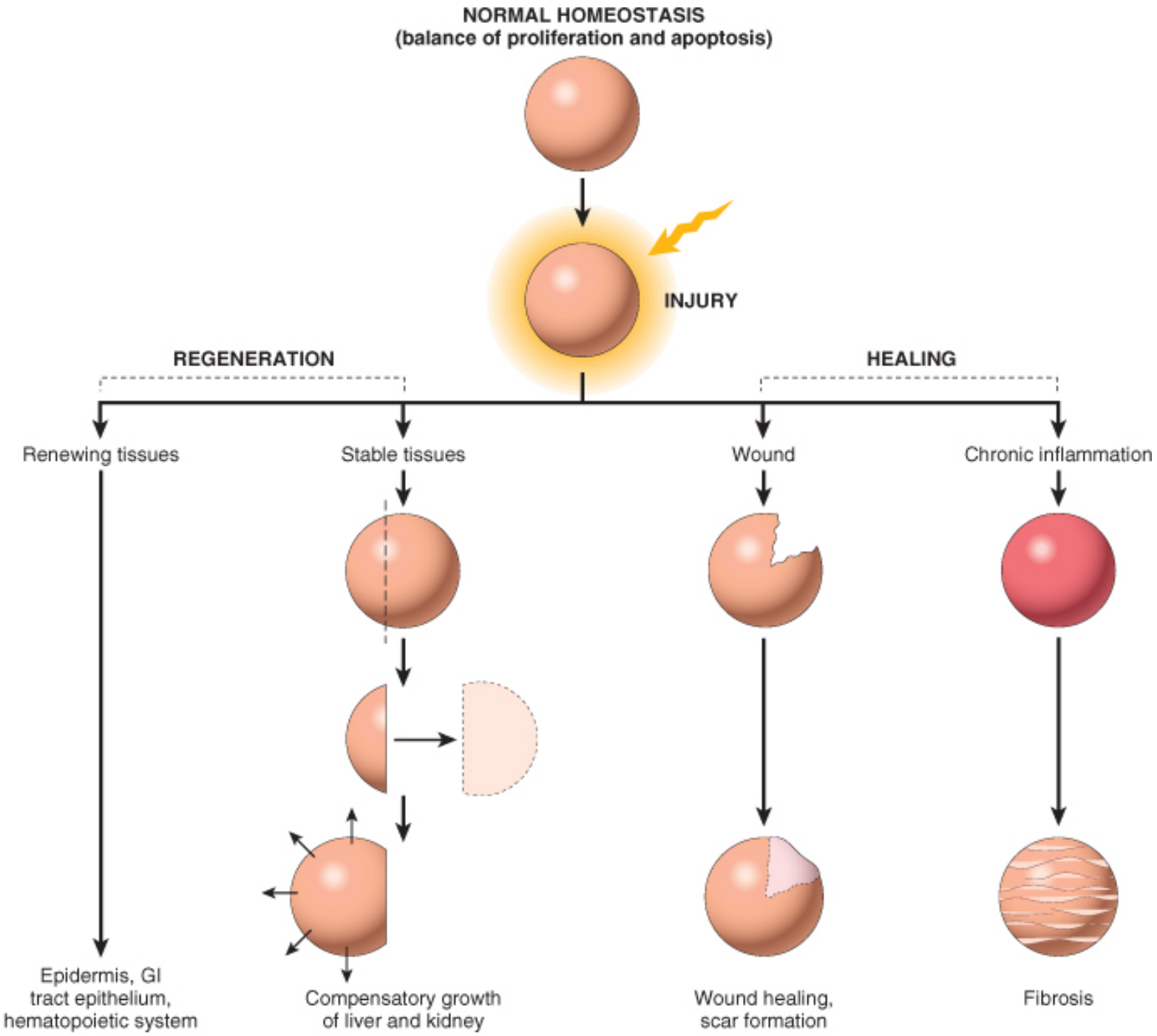
TISSUE REPAIR SUMMARY

- Not all injuries result in permanent damage; some are resolved almost completely
- More often, there is some degree of scarring
- Scar is usually good (provides a resilient patch) but occasionally bad (can cause permanent dysfunction)


NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)
INJURY
REGENERATION
HEALING
Renewing tissues
Stable tissues
Wound
Chronic inflammation
Epidermis, GI tract epithelium, hematopoietic system
Compensatory growth of liver and kidney
Wound healing, scar formation
Fibrosis