Tissue Renewal & Repair : Regeneration, Healing And Fibrosis

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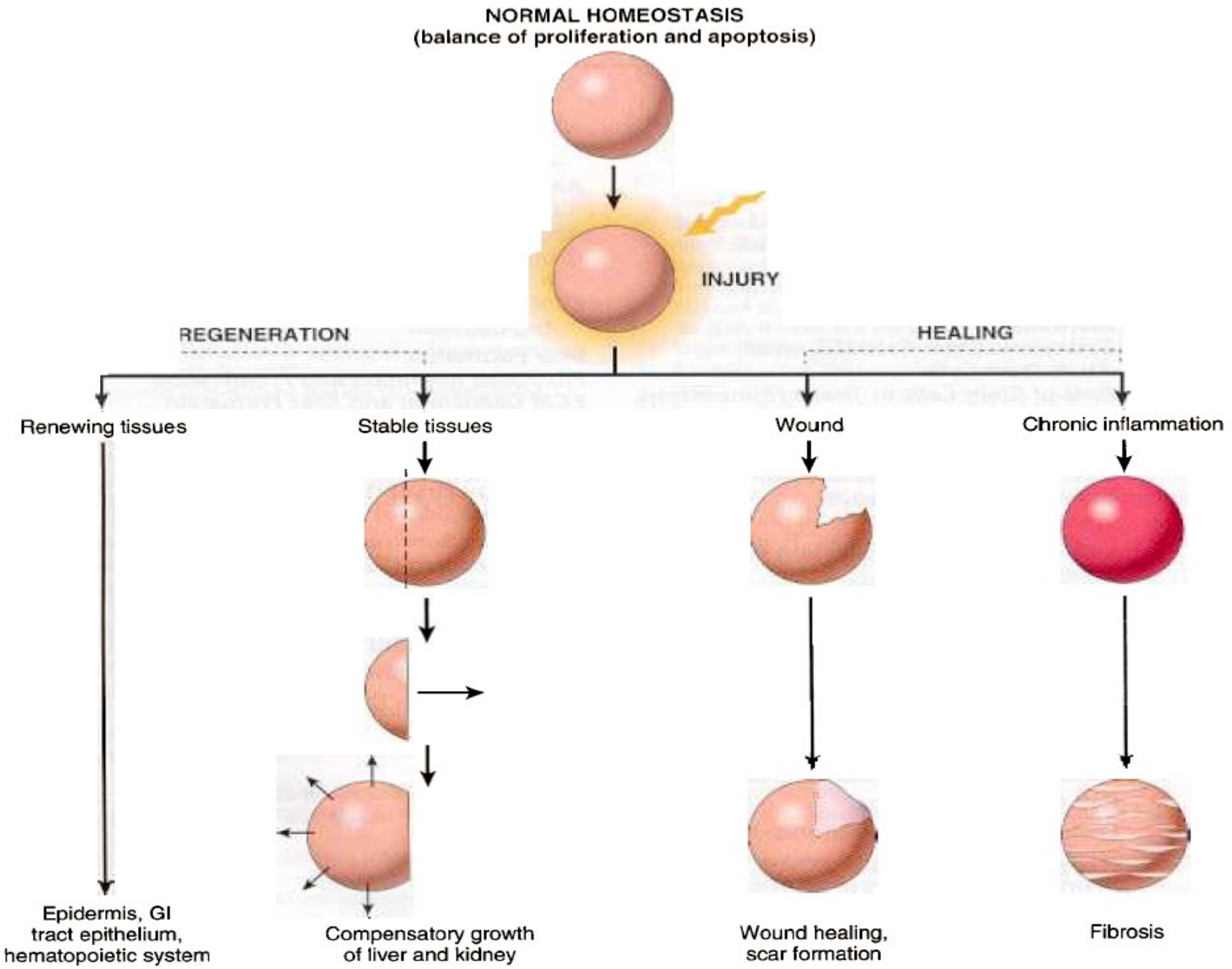
Definitions

- **Regeneration** :
- to growth of cells and tissues to replace lost structures
- Kidney, Liver
- hematopoietic system , epithelia of the skin and gastrointestinal tract

- **Healing** :

is a tissue response to
(1) a wound (commonly in the skin)
(2) to inflammatory processes in internal organs
(3) to cell necrosis in organs incapable of regeneration
Regeneration + Scar formation (stomach, heart, pericard,..)

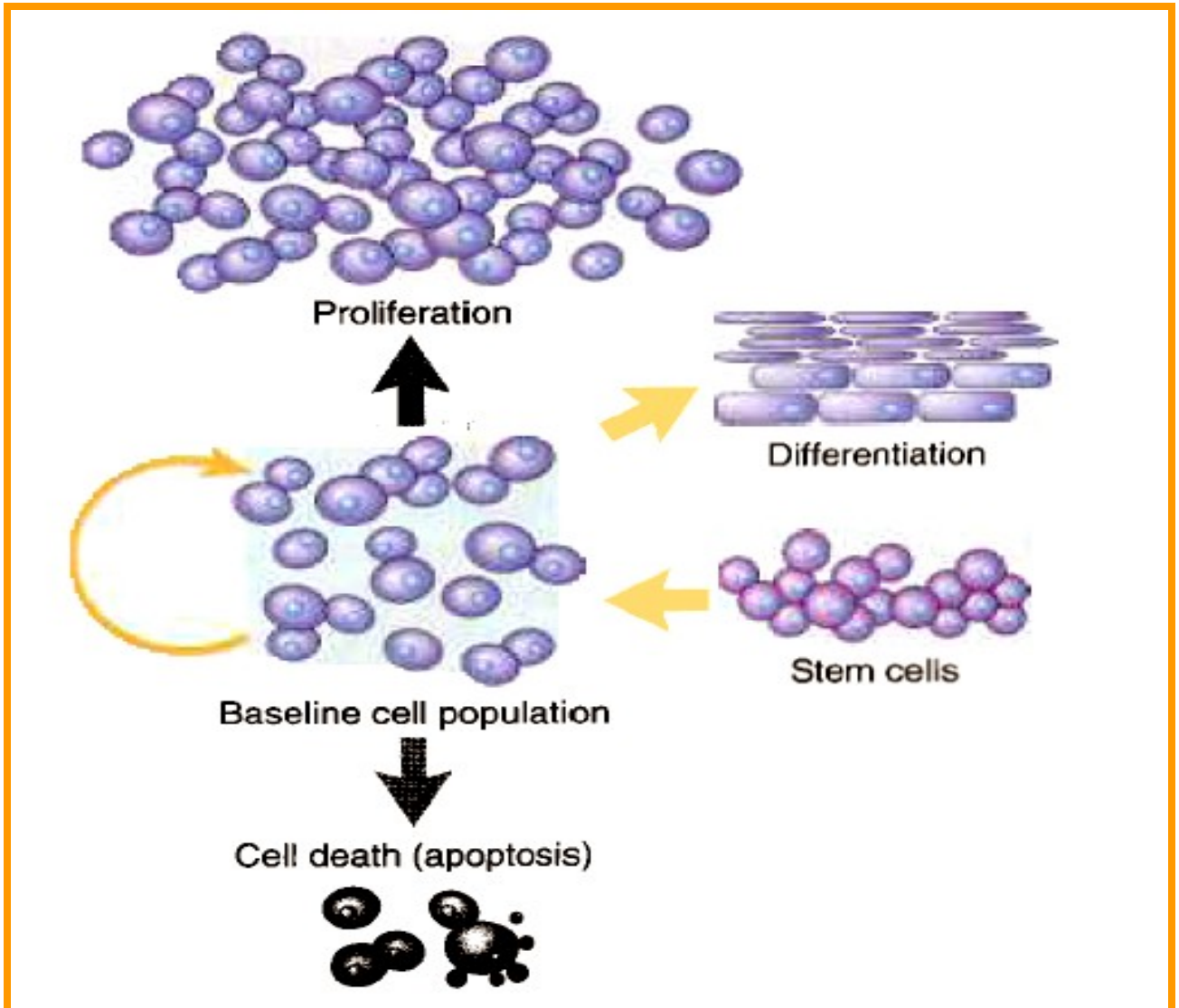

NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)
INJURY
REGENERATION
HEALING
Renewing tissues
Stable tissues
Wound
Chronic inflammation
Epidermis, GI tract epithelium, hematopoietic system
Compensatory growth of liver and kidney
Wound healing, scar formation
Fibrosis

Regeneration & Healing

Regeneration requires an intact connective tissue scaffold.

By contrast, healing with scar formation occurs if the extracellular matrix (ECM) framework is damaged, causing alterations of the tissue architecture

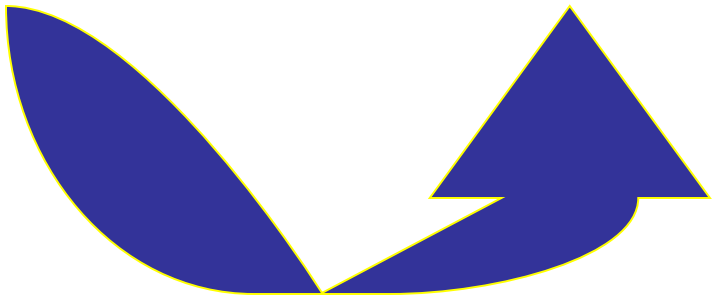
Control of Normal Cell Proliferation and Tissue Growth



Cell proliferation

Physiologic

Pathologic



Control of Normal Cell Proliferation and Tissue Growth

- Liver and kidney
- Myocytes and neurons: terminally differentiated cells
- bone marrow and the epithelia of the skin and gut

1. Continuously dividing tissues (labile tissues)

surface epithelia, stratified squamous surfaces of the skin, oral cavity, vagina, and cervix; the lining mucosa of all the excretory ducts of the glands of the body (salivary glands, pancreas, biliary tract); the columnar epithelium of the gastrointestinal tract and uterus; the transitional epithelium of the urinary tract, and cells of the bone marrow and hematopoietic tissues

2- Quiescent (stable) tissues

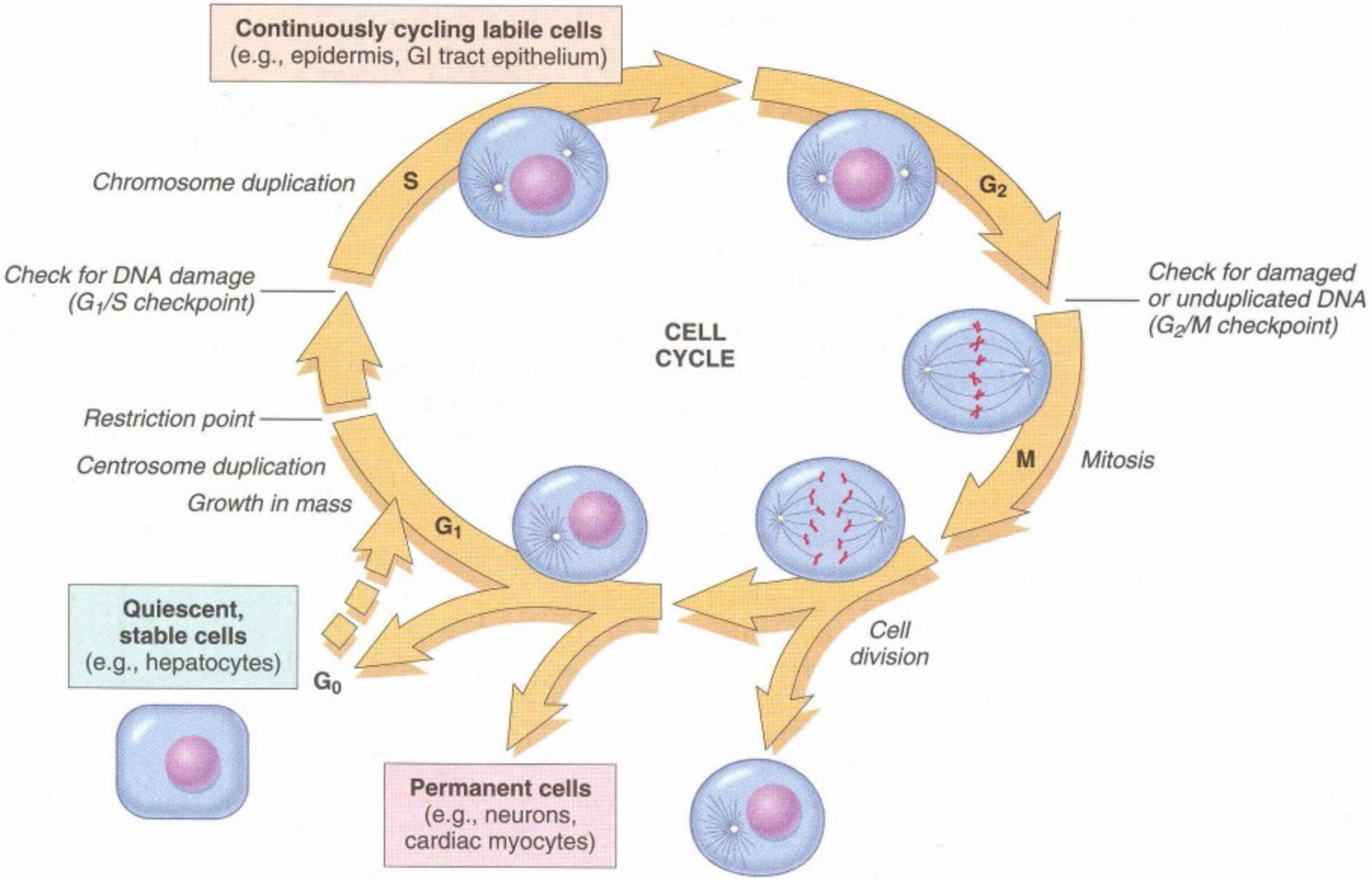
parenchymal cells of liver, kidneys, and pancreas; mesenchymal cells, such as fibroblasts and smooth muscle; vascular endothelial cells

resting lymphocytes and other leukocytes

3- Nondividing (permanent) tissues

neurons and skeletal and cardiac muscle cells

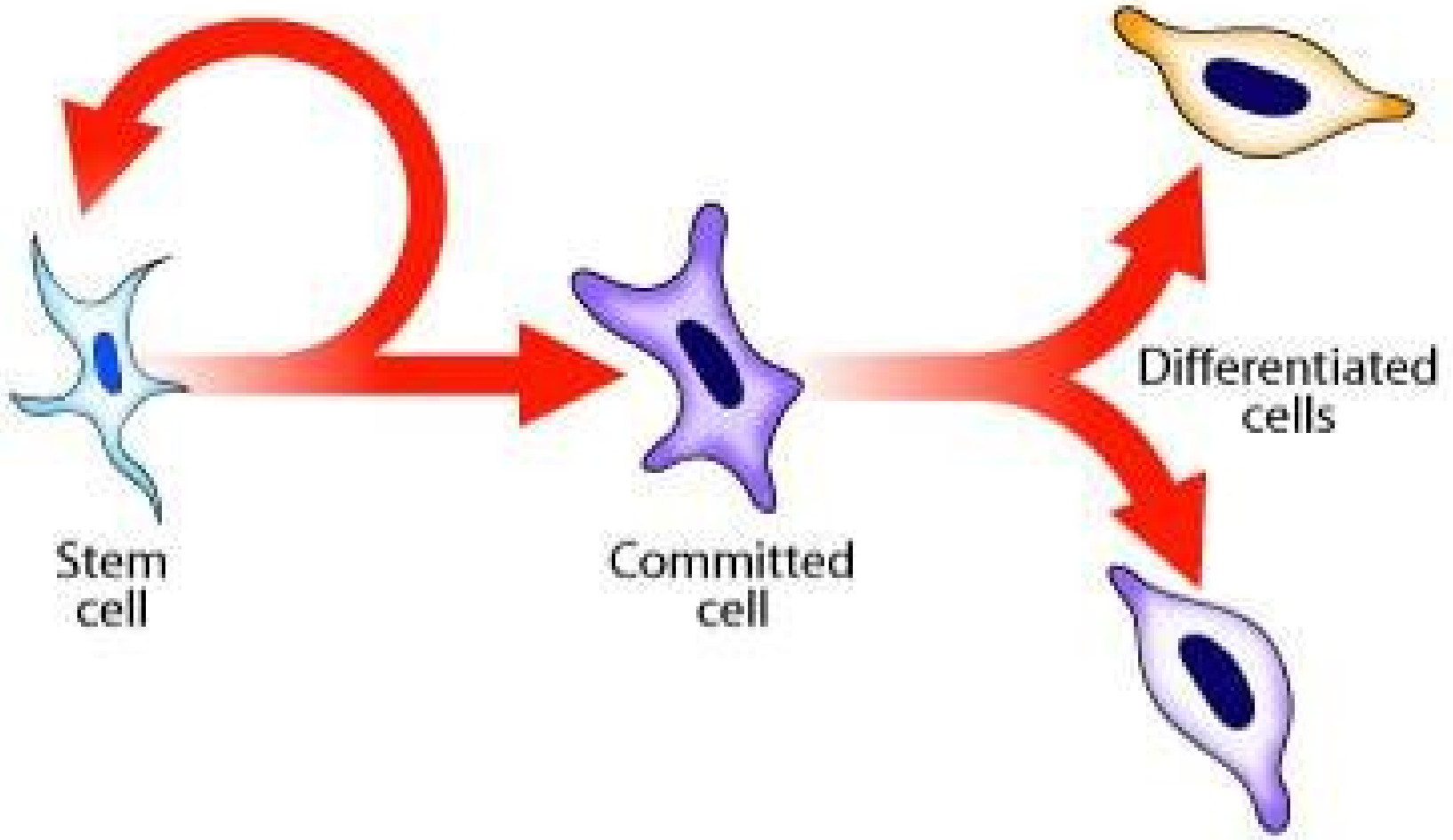
TISSUE-PROLIFERATIVE ACTIVITY

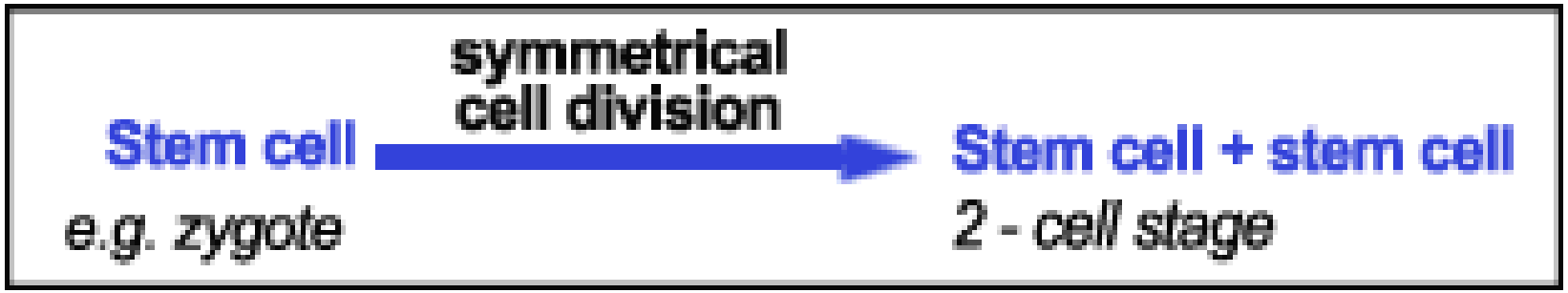


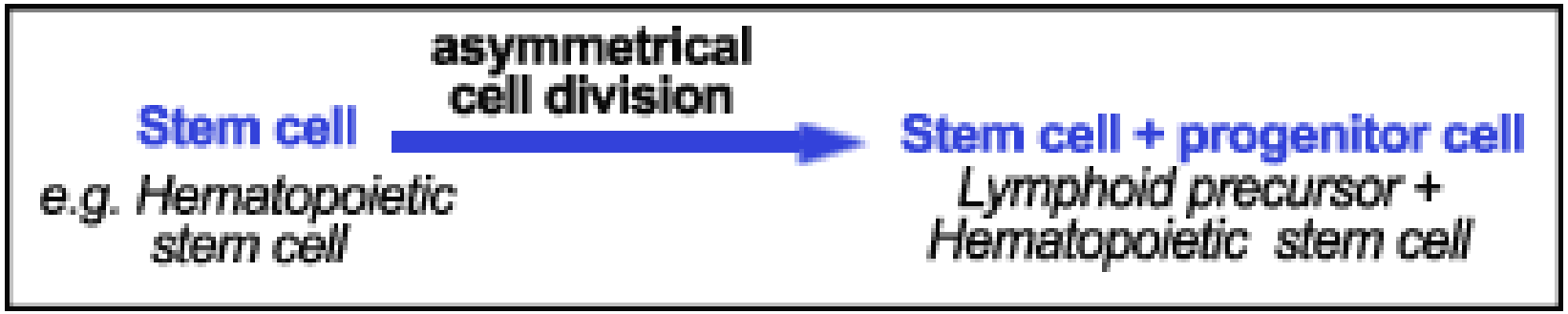
STEM CELLS

Regenerative Medicine

- Prolonged self-renewal capacity
- Asymmetric replication


Stem cell
Committed cell
Differentiated cells

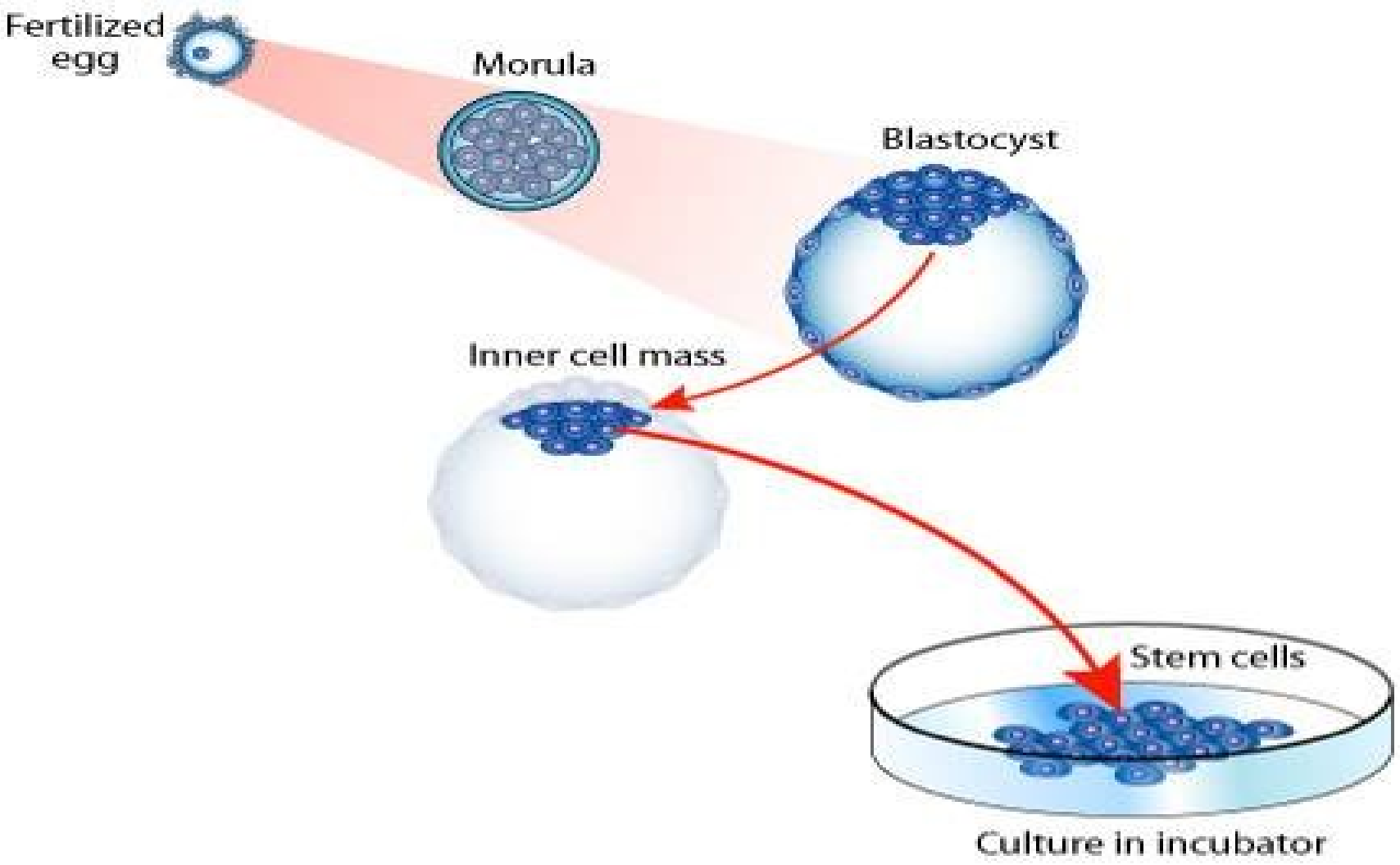

symmetrical
cell division
Stem cell
Stem cell + stem cell
e.g. zygote
2 - cell stage

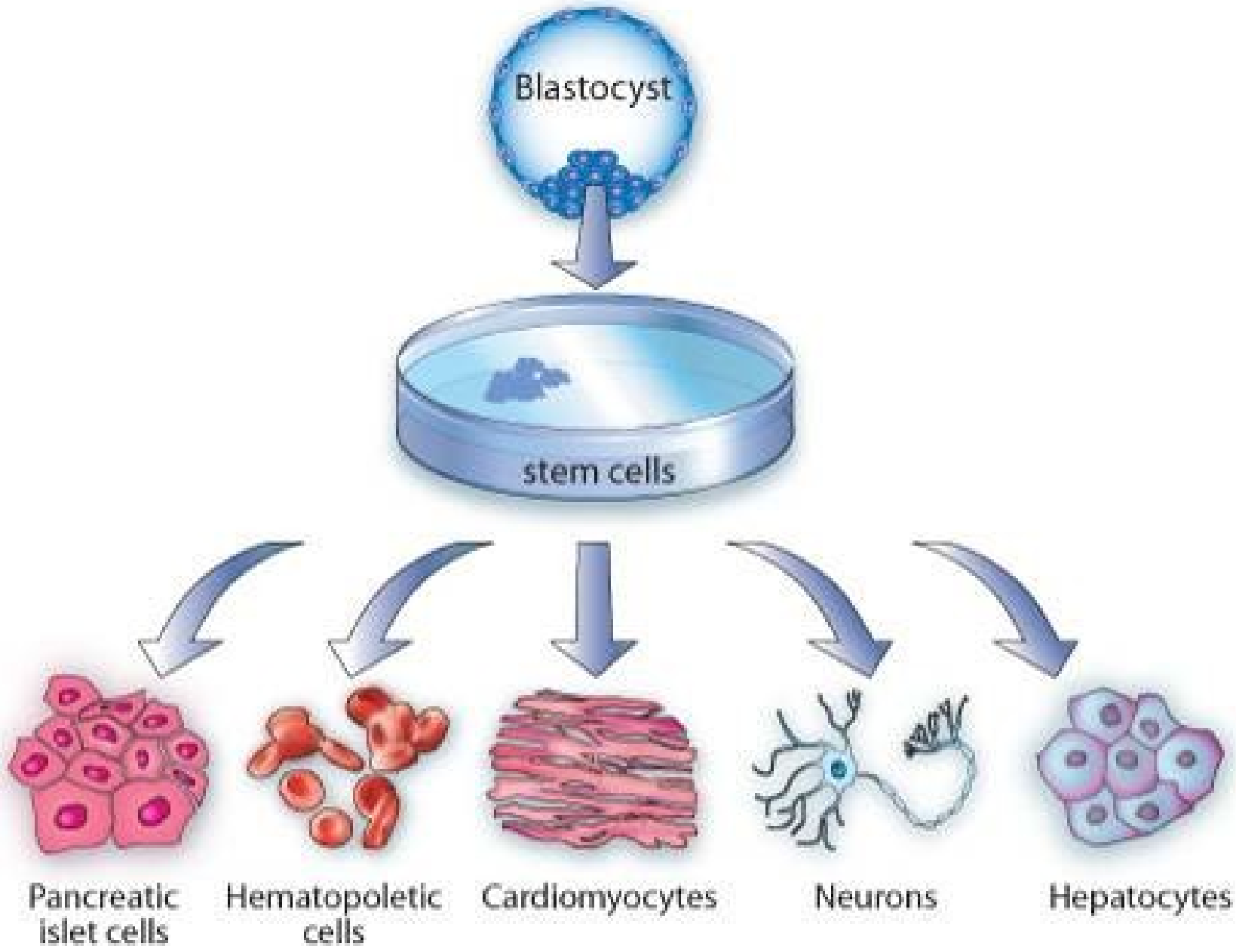

asymmetrical
cell division
Stem cell
Stem cell + progenitor cell
e.g. Hematopoietic
stem cell
Lymphoid precursor +
Hematopoietic stem cell

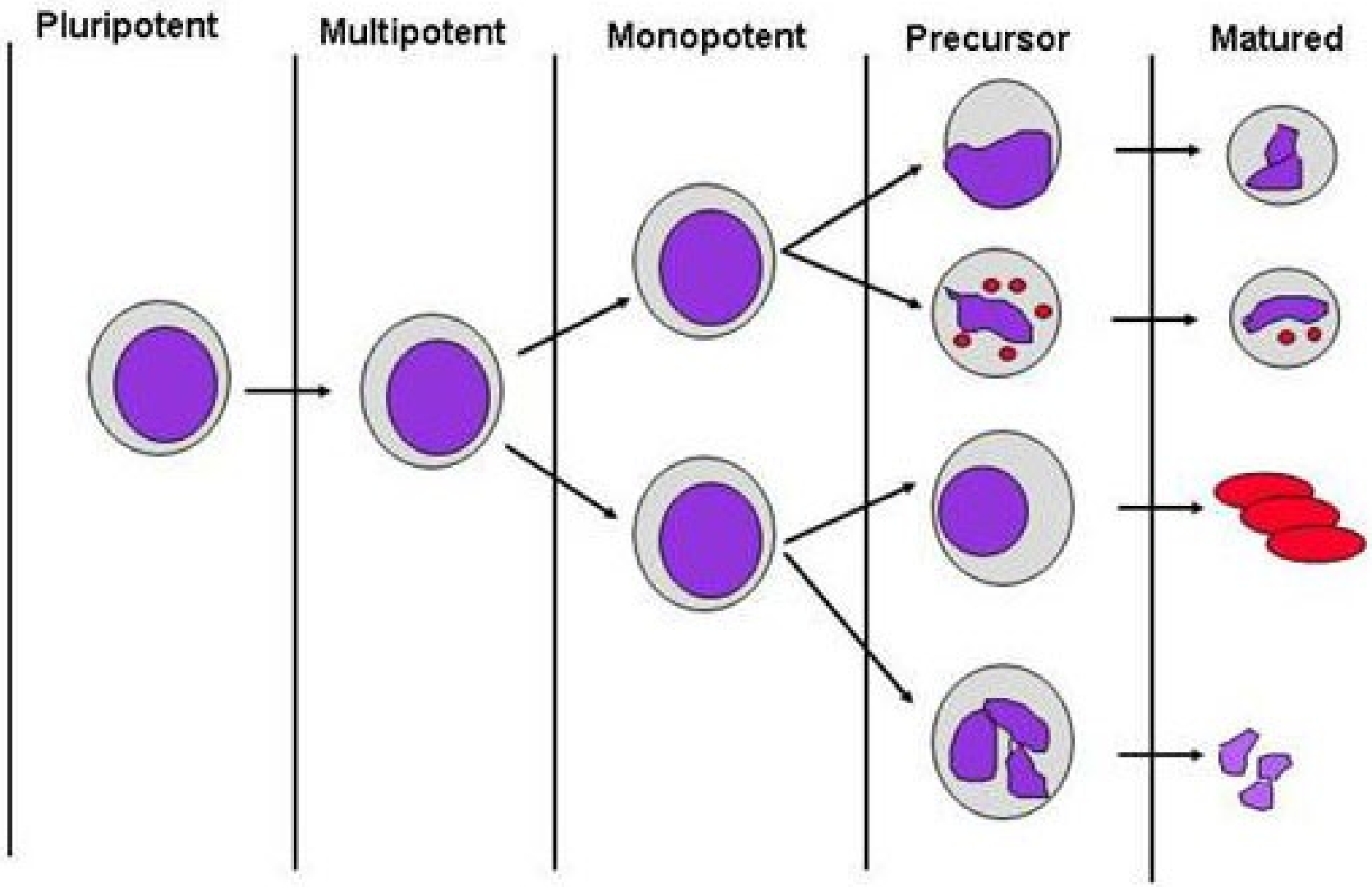
Regenerative Medicine

- The realization that some stem cells present in tissues of humans and mice may be similar to embryonic stem cells
- Identification of stem cells in various tissues, including the brain
- Recognition that stem cells from various tissues and particularly from the bone marrow may have broad developmental plasticity

Embryonic Stem Cells (ES)




Blastocyst
stem cells
Pancreatic islet cells
Hematopoletic cells
Cardiomyocytes
Neurons
Hepatocytes


Pluripotent
Multipotent
Monopotent
Precursor
Matured

Embryonic Stem Cells (ES)

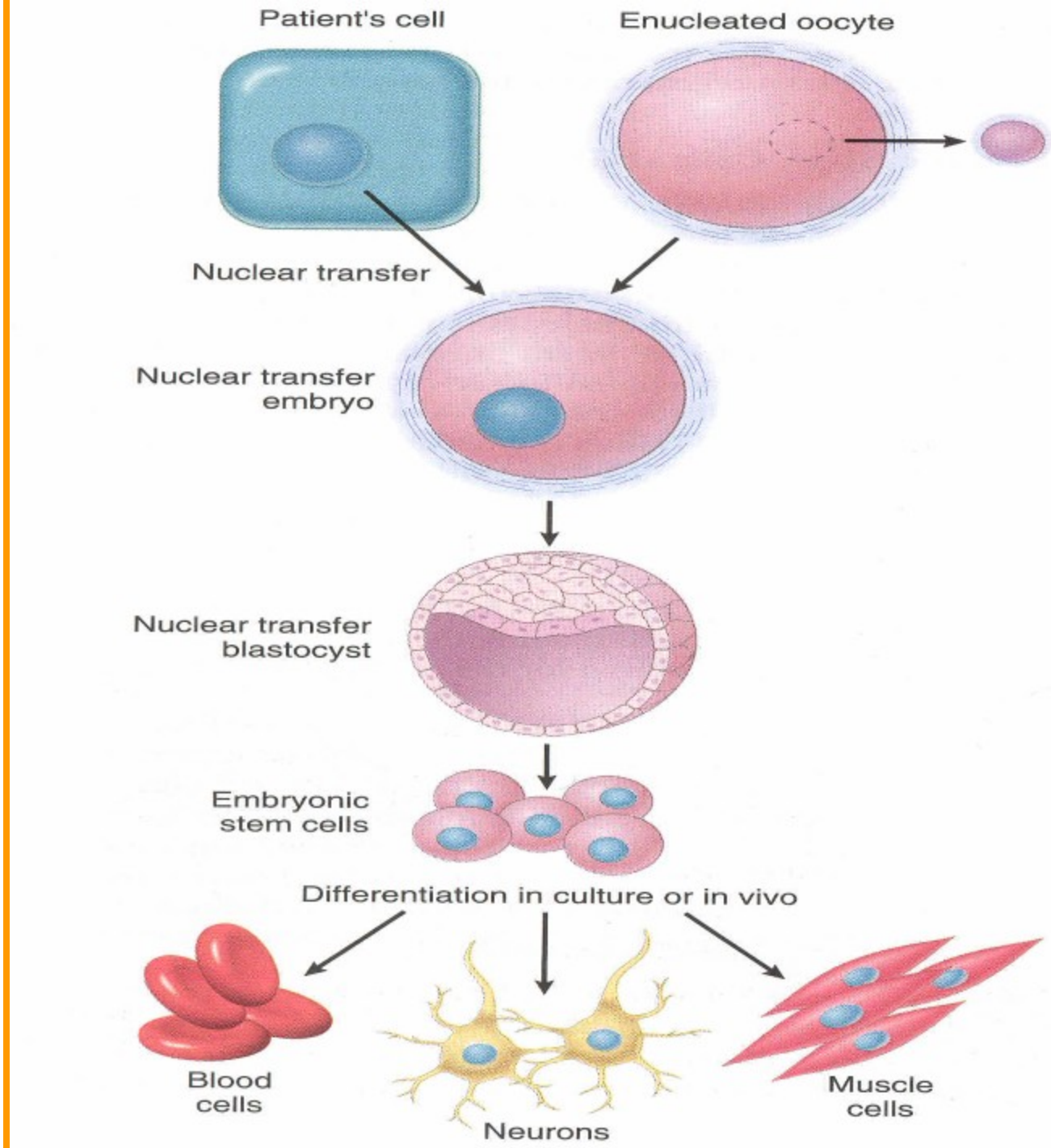
- Study the specific signals and differentiation steps required for the development of many tissues
- Knockout mice

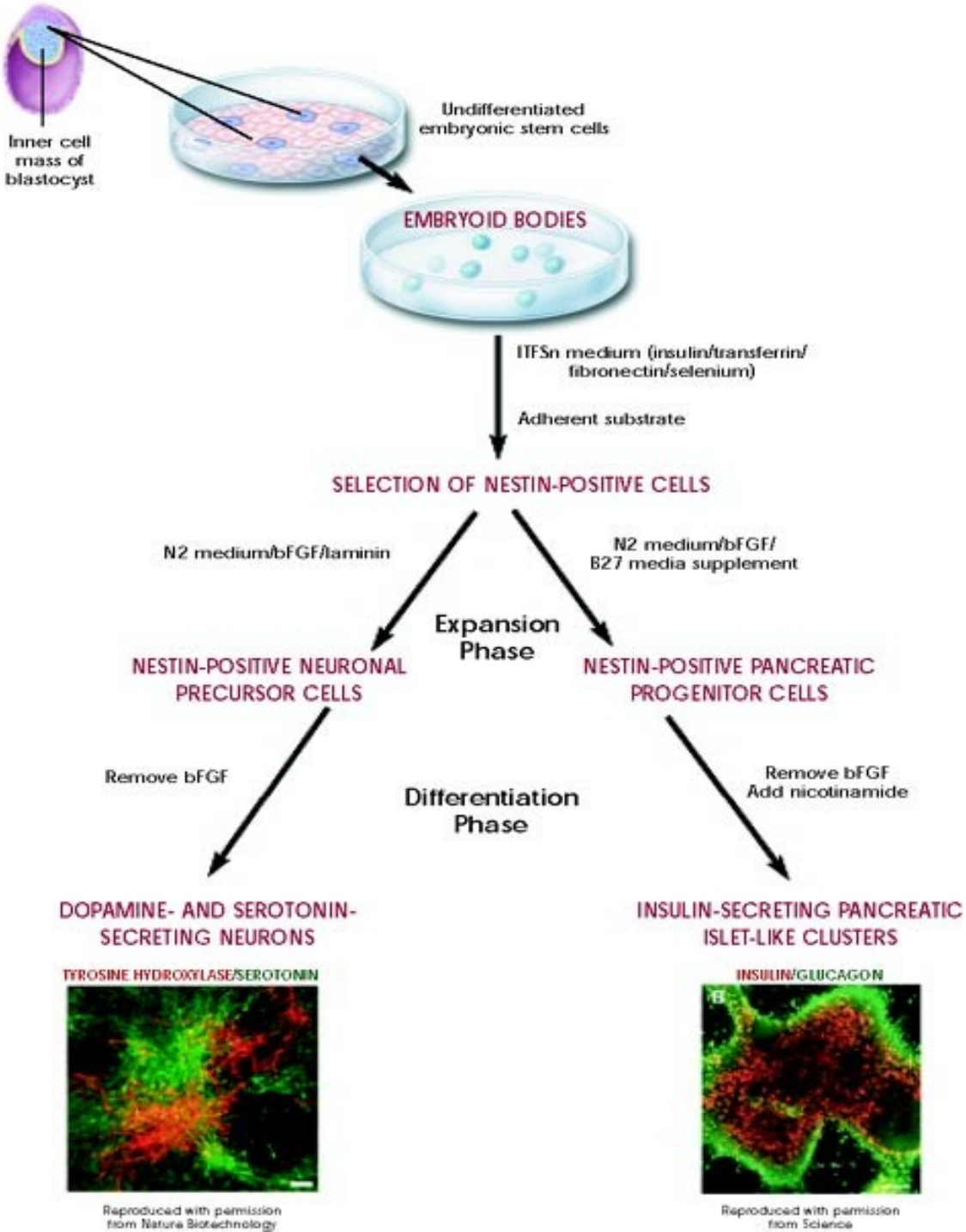
Embryonic Stem Cells (ES)

In the future, be used to repopulate damaged organs

(**Therapeutic cloning**)

Therapeutic cloning




Inner cell mass of blastocyst
Undifferentiated embryonic stem cells
EMBRYOID BODIES
ITFSn medium (insulin/transferrin/ fibronectin/selenium)
Adherent substrate
SELECTION OF NESTIN-POSITIVE CELLS
N2 medium/bFGF/laminin
N2 medium/bFGF/ B27 media supplement
Expansion Phase
NESTIN-POSITIVE NEURONAL PRECURSOR CELLS
NESTIN-POSITIVE PANCREATIC PROGENITOR CELLS
Remove bFGF
Differentiation Phase
Remove bFGF Add nicotinamide
DOPAMINE- AND SEROTONIN-SECRETING NEURONS
TYROSINE HYDROXYLASE/SEROTONIN
INSULIN-SECRETING PANCREATIC ISLET-LIKE CLUSTERS
INSULIN/GLUCAGON
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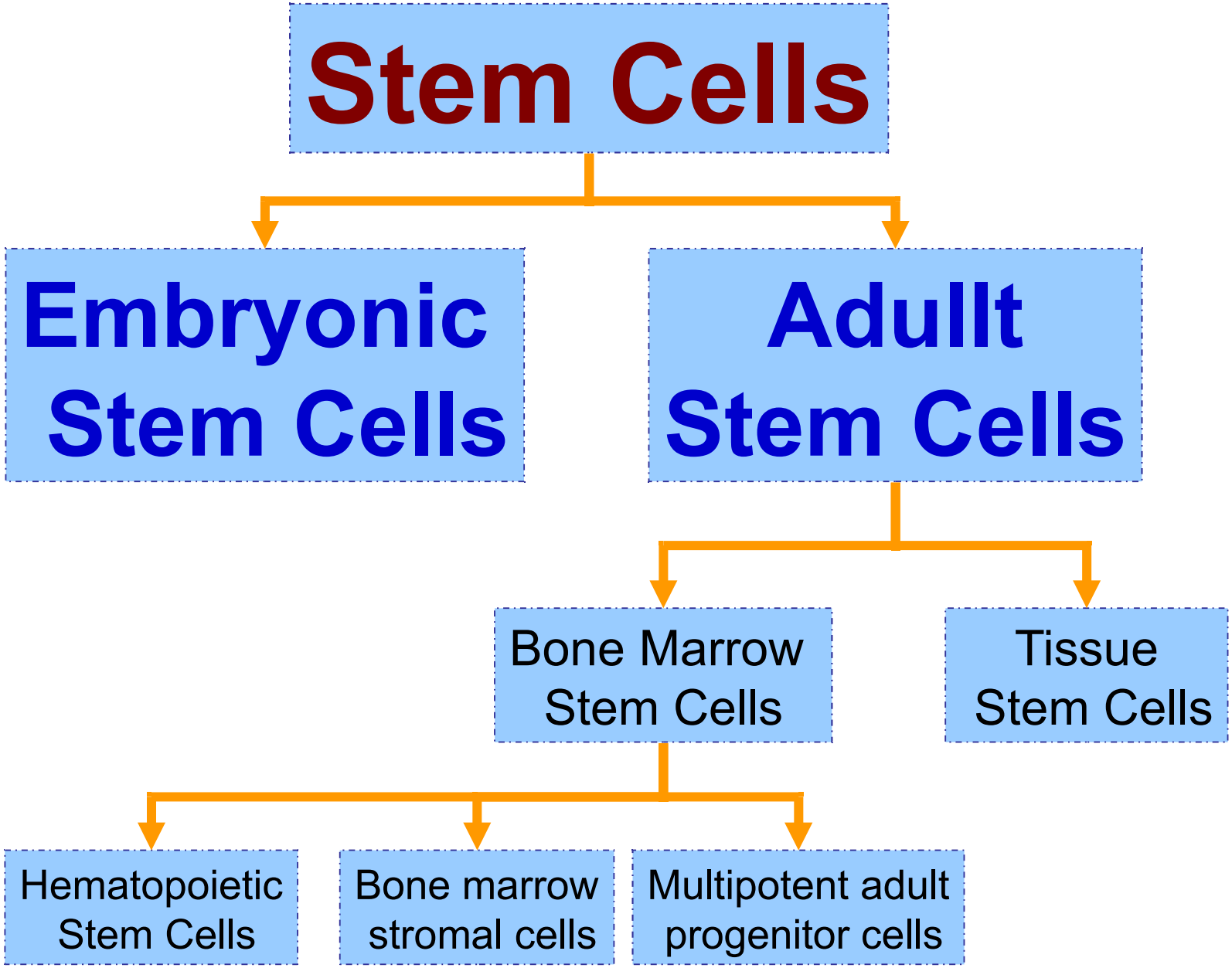
Adult Stem Cells

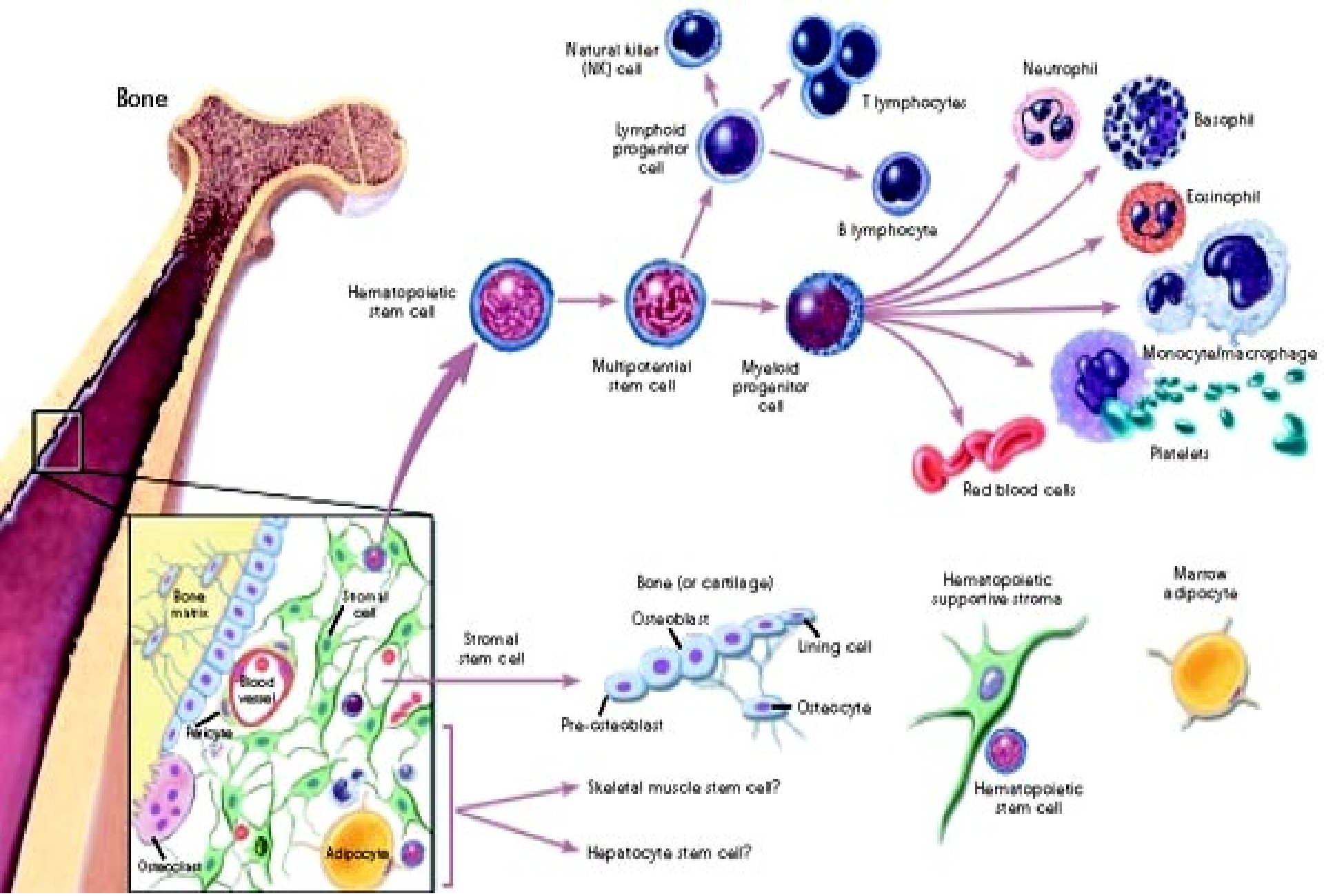
Pluripotent or a more Restricted differentiation ?

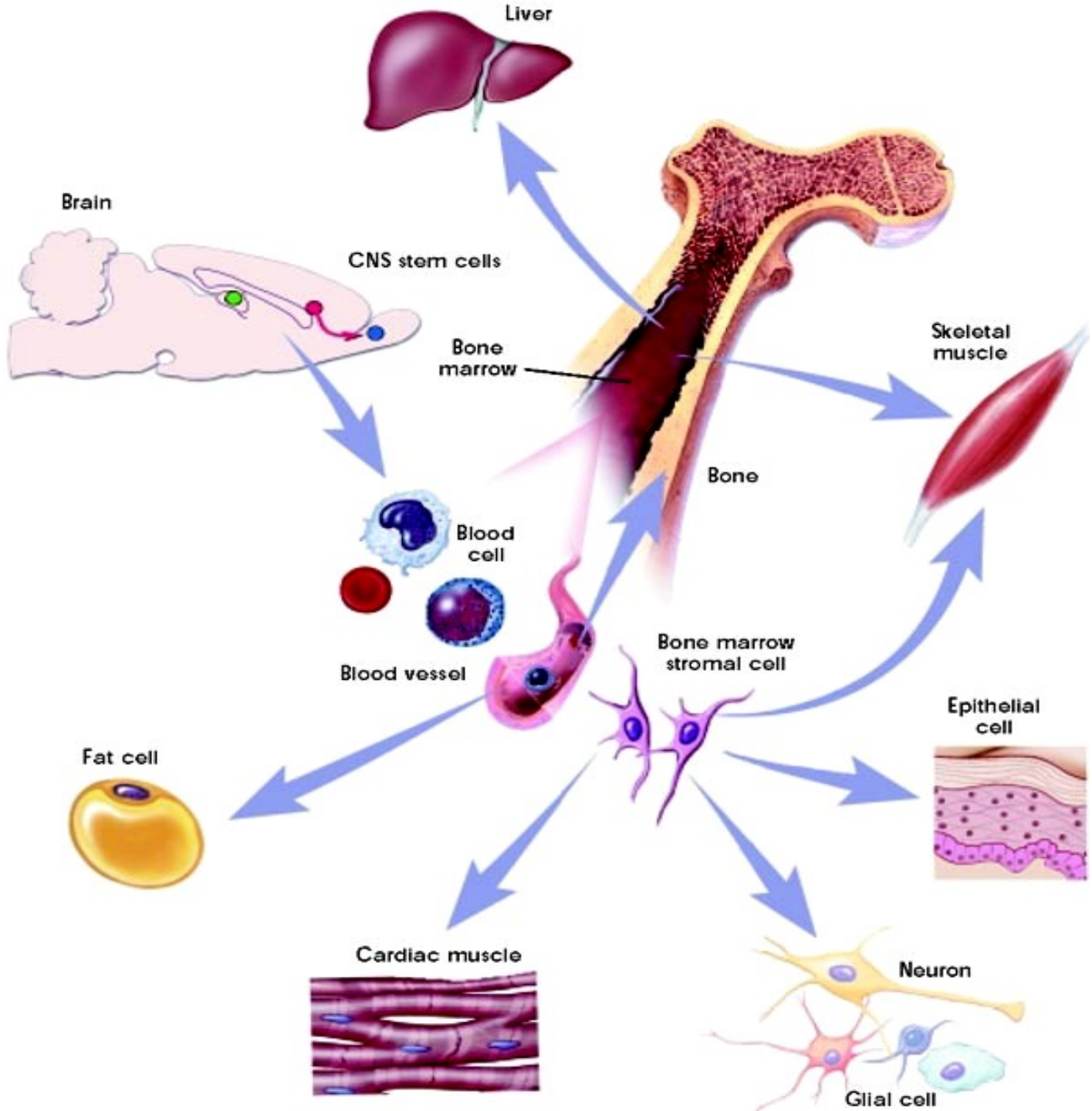

Stem Cells
Embryonic Stem Cells
Adullt Stem Cells
Bone Marrow Stem Cells
Tissue Stem Cells
Hematopoietic Stem Cells
Bone marrow stromal cells
Multipotent adult progenitor cells

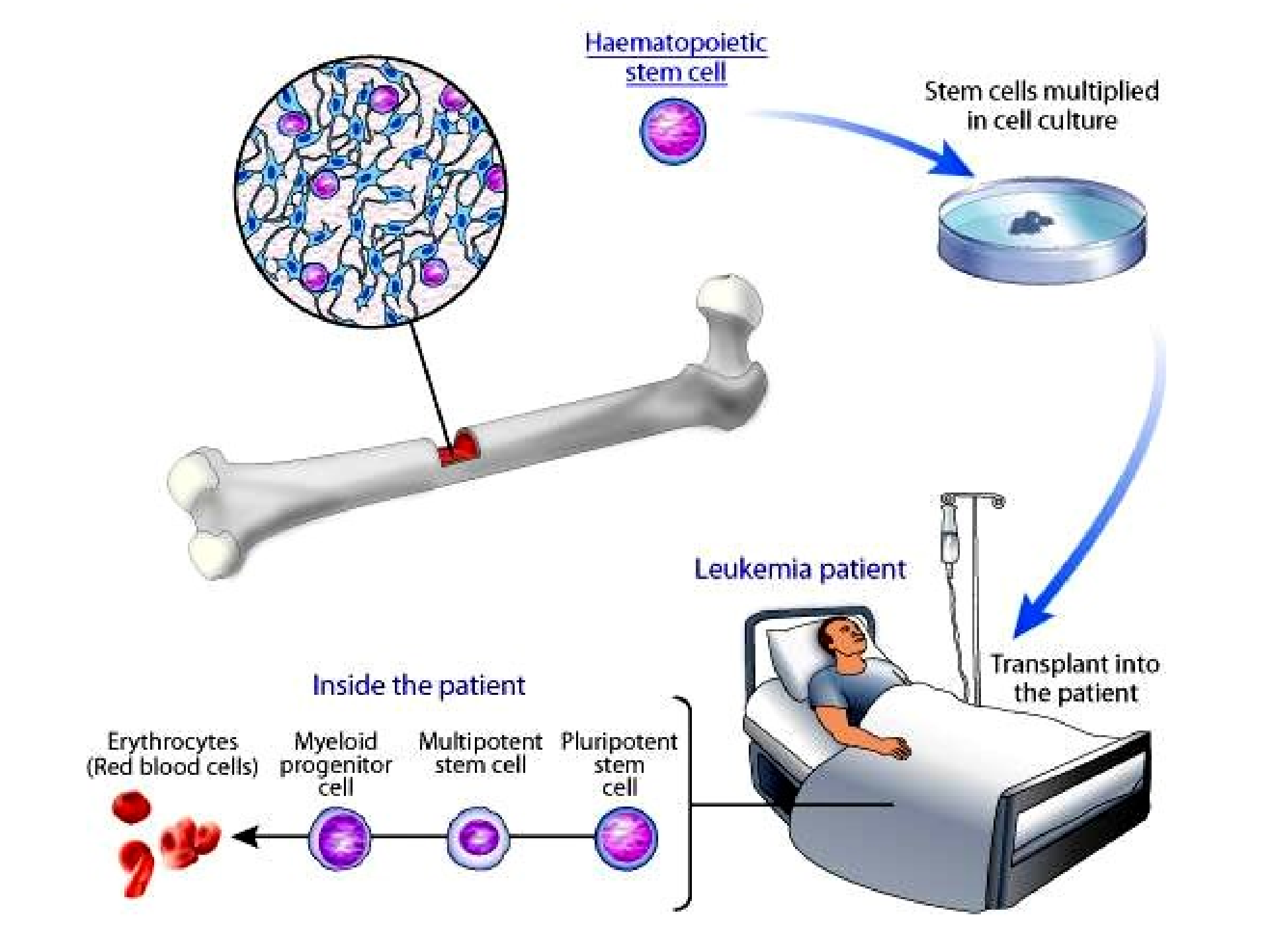
Bone Marrow Stem Cells

Hematopoietic Stem Cells (HSCs)

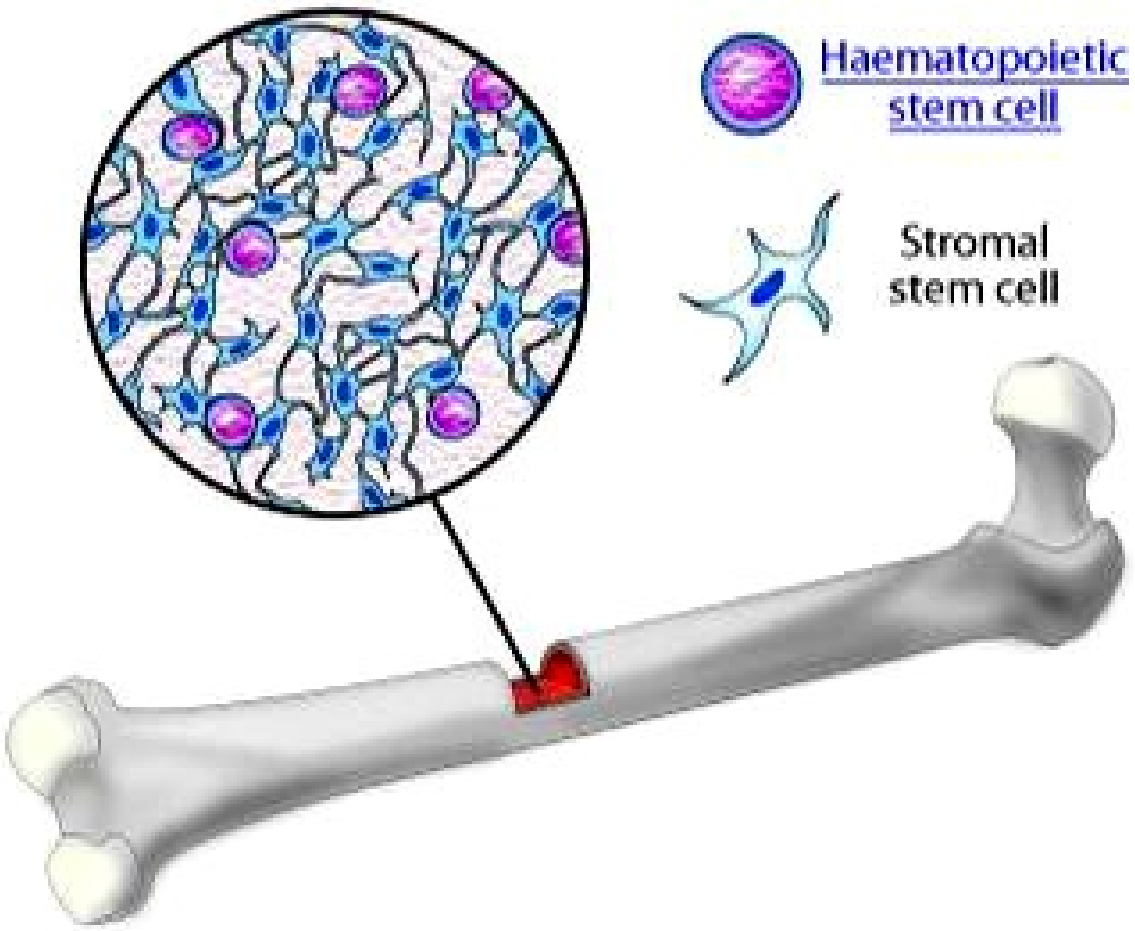
- collected directly from the bone marrow, umbilical cord blood, and from circulating blood of individuals receiving cytokines
- capable of giving rise to neurons, hepatocytes, and other cell types
- **Transdifferentiation:** A change in stem cell differentiation from one cell type to another
- **Developmental plastisity:** The multiplicity of stem cell differentiation options
- **Cell fusion:** transplanted HSCs fuse with host cells and transfer genetic material to them, thus giving the false appearance of having transdifferentiated with generation of new cells in the host


Bone
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelets
Red blood cells
Bone matrix
Stromal cell
Blood vessel
Fibrocyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte


Liver
Brain
CNS stem cells
Bone marrow
Skeletal muscle
Bone
Blood cell
Blood vessel
Bone marrow stromal cell
Epithelial cell
Fat cell
Cardiac muscle
Neuron
Glial cell


Haematopoietic stem cell
Stem cells multiplied in cell culture
Leukemia patient
Transplant into the patient
Inside the patient
Erythrocytes (Red blood cells)
Myeloid progenitor cell
Multipotent stem cell
Pluripotent stem cell

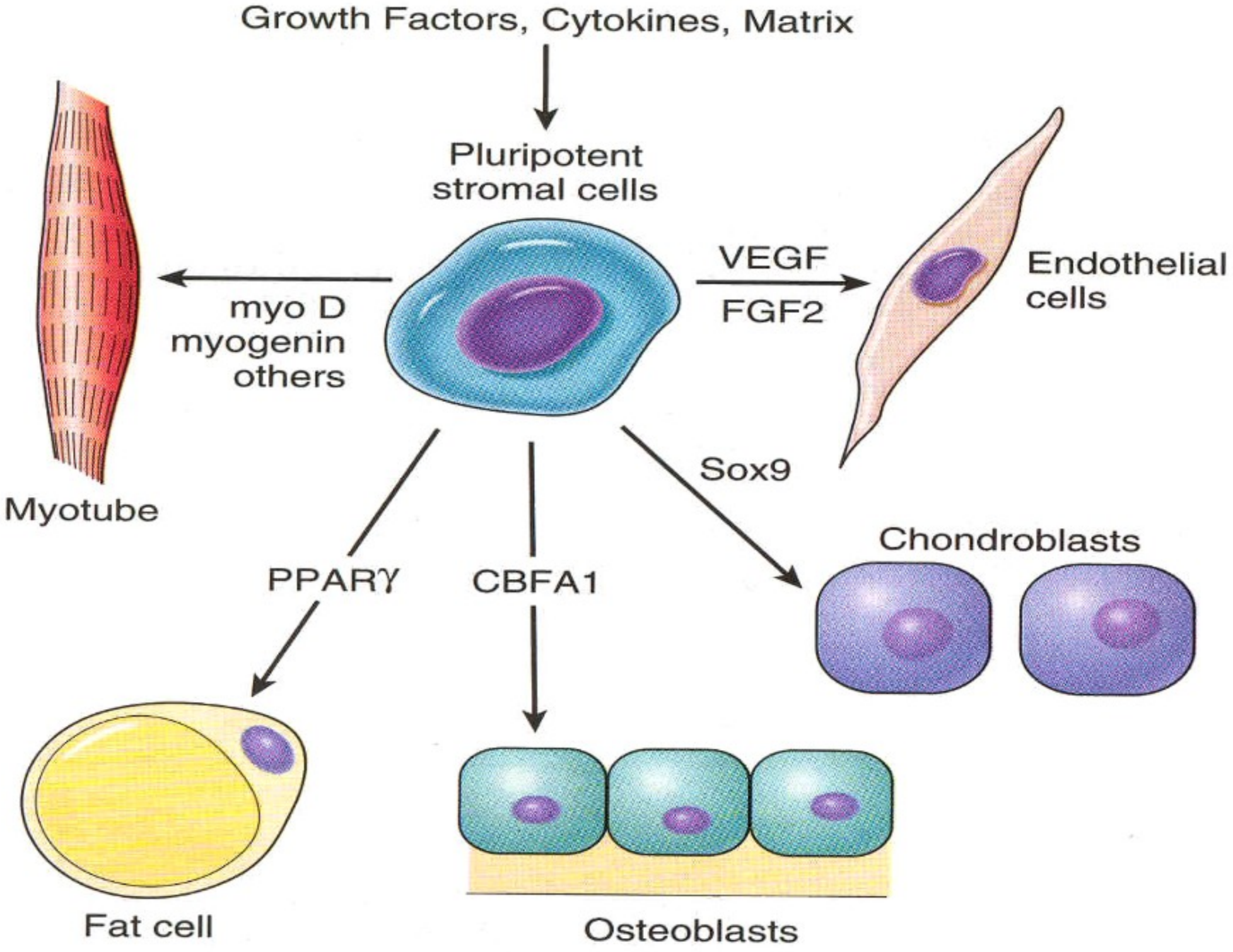
Bone Marrow Stem Cells
Stromal cells



Bone Marrow Stem Cells

Bone marrow stromal cells

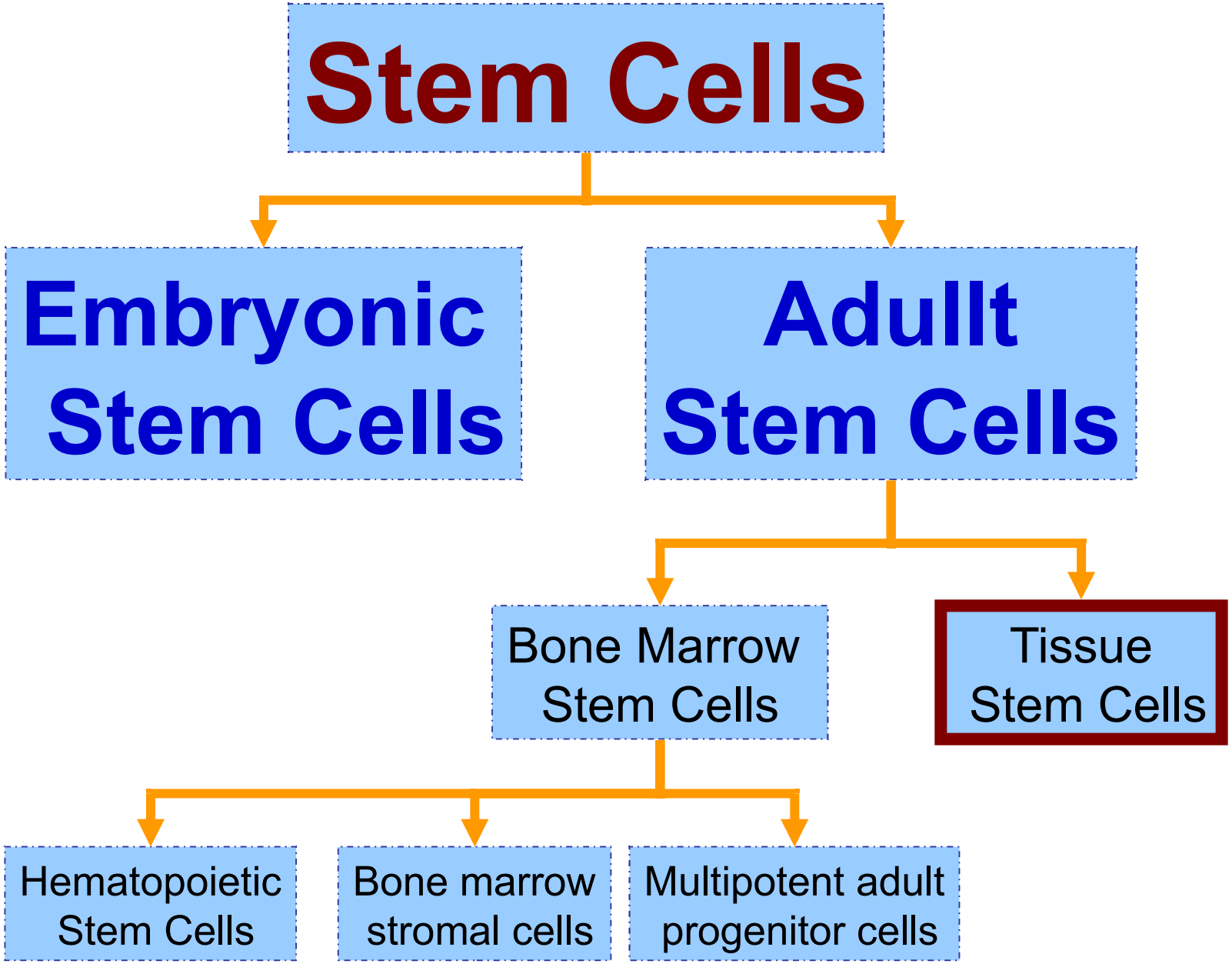
- Depending on the tissue environment, can generate chondrocytes, osteoblasts, adipocytes, myoblasts, and endothelial cell precursors


Growth Factors, Cytokines, Matrix
Pluripotent stromal cells
myo D
myogenin
others
Myotube
VEGF
FGF2
Endothelial cells
Sox9
Chondroblasts
PPARγ
CBFA1
Fat cell
Osteoblasts

Bone Marrow Stem Cells

Multipotent adult progenitor cells (MAPCs)

- mesodermal, endodermal, and euroectodermal cell types
- isolated from muscle, brain, and skin, and, similar to bone marrow MAPCs, can be made to differentiate into endothelium neurons, hevatocytes and other cell types
- MAPCs constitute a population of stem cells derived from, or closely related to, ES cells


Stem Cells
Embryonic Stem Cells
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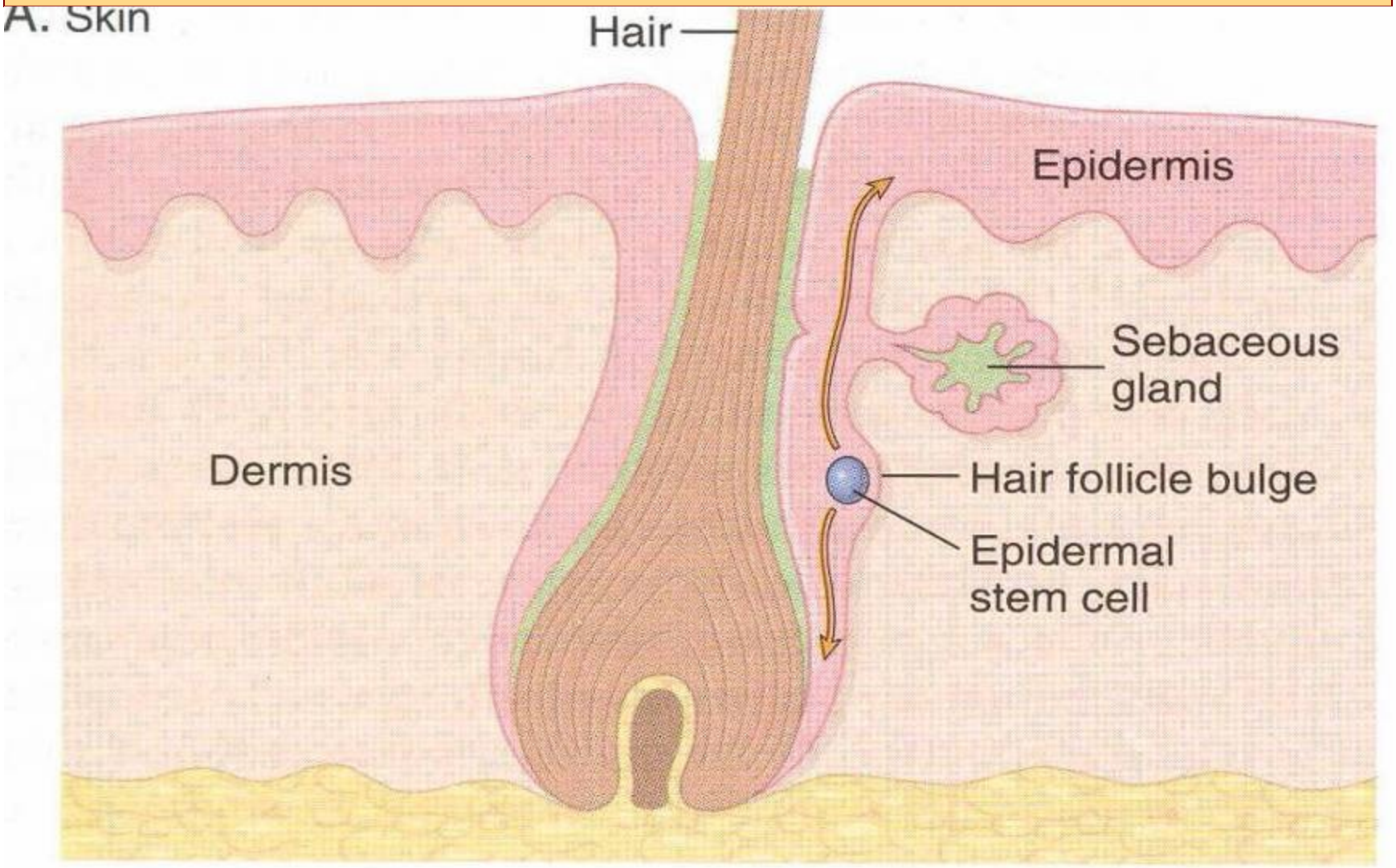
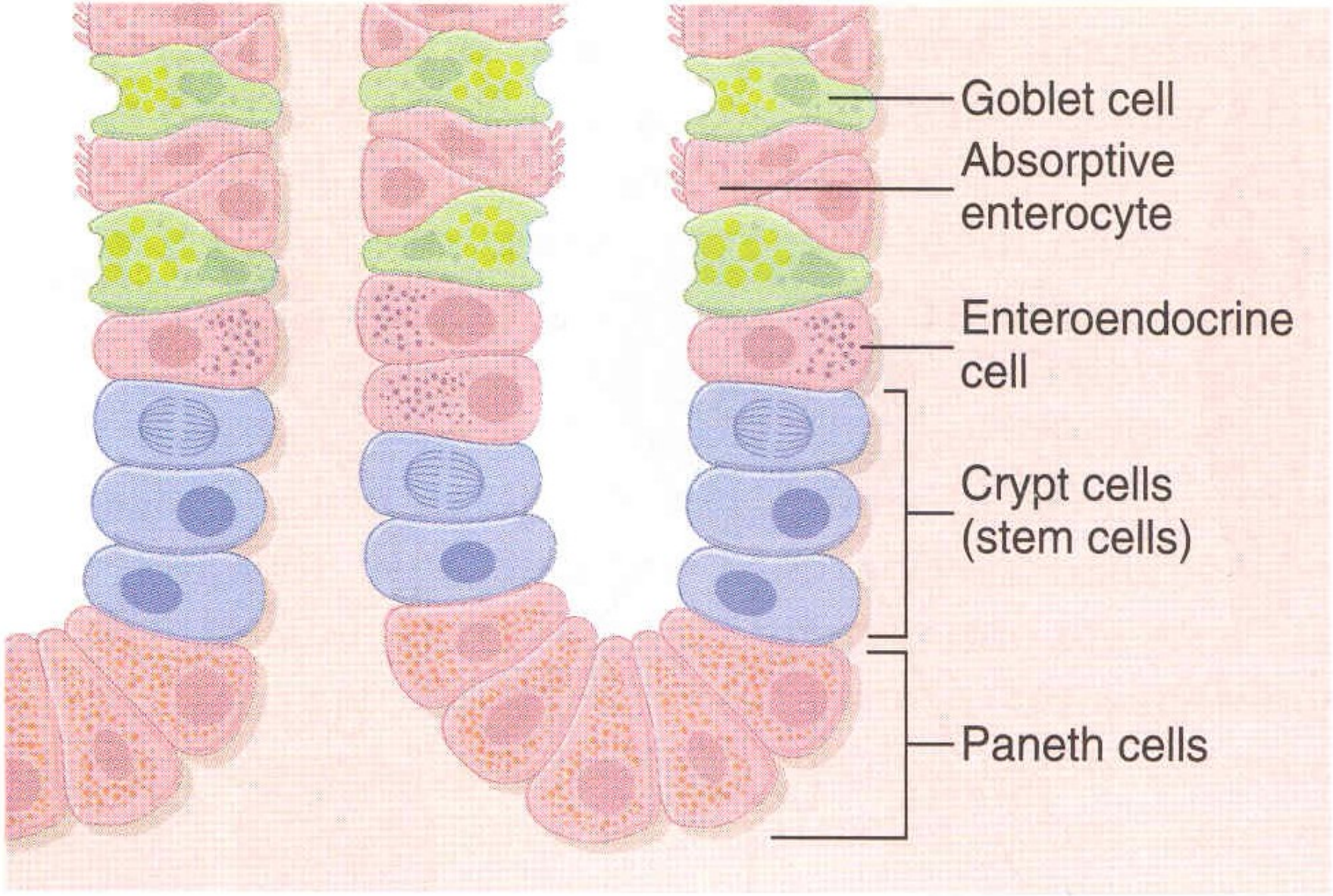
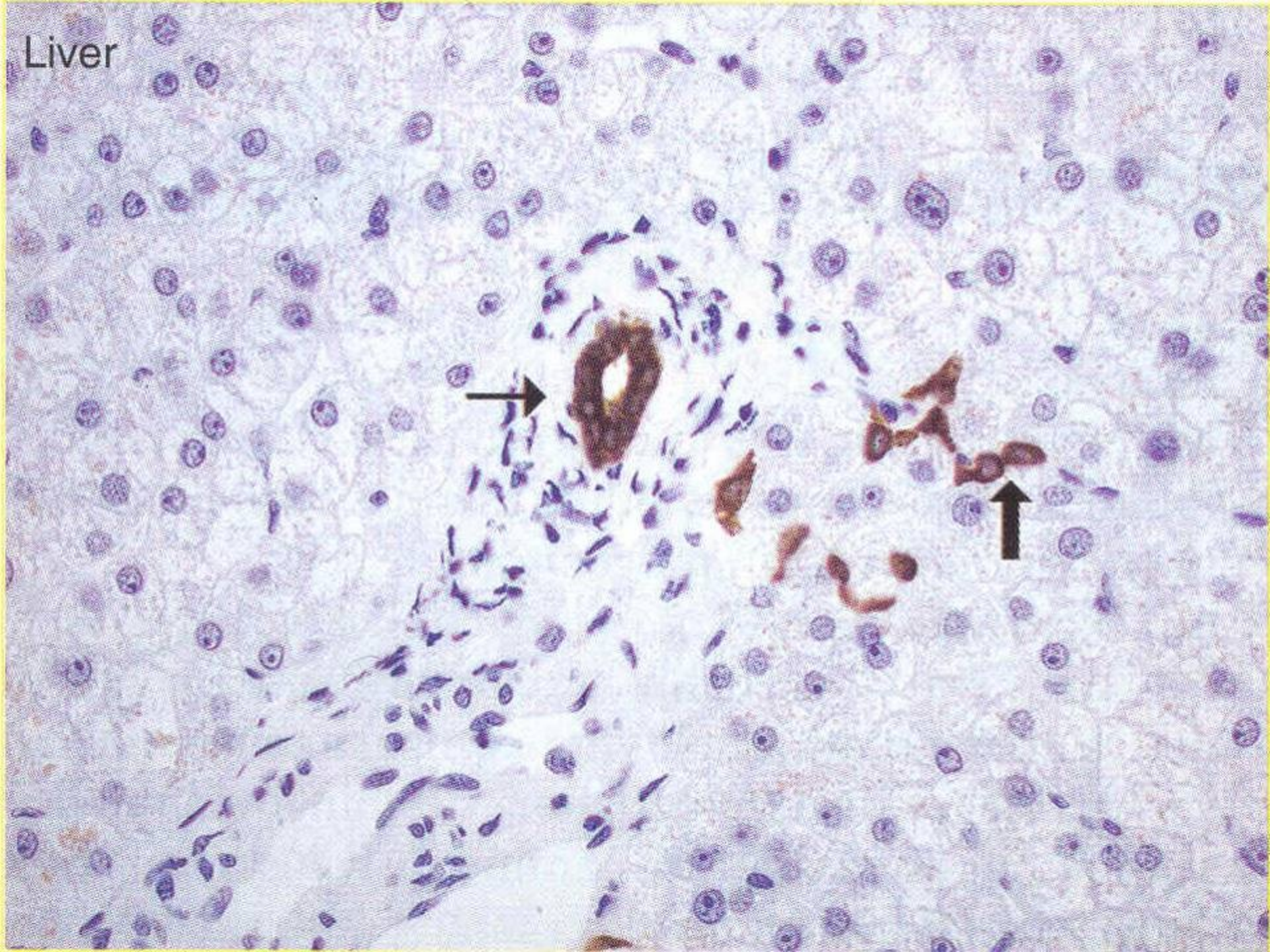
Bone marrow stromal cells
Multipotent adult progenitor cells

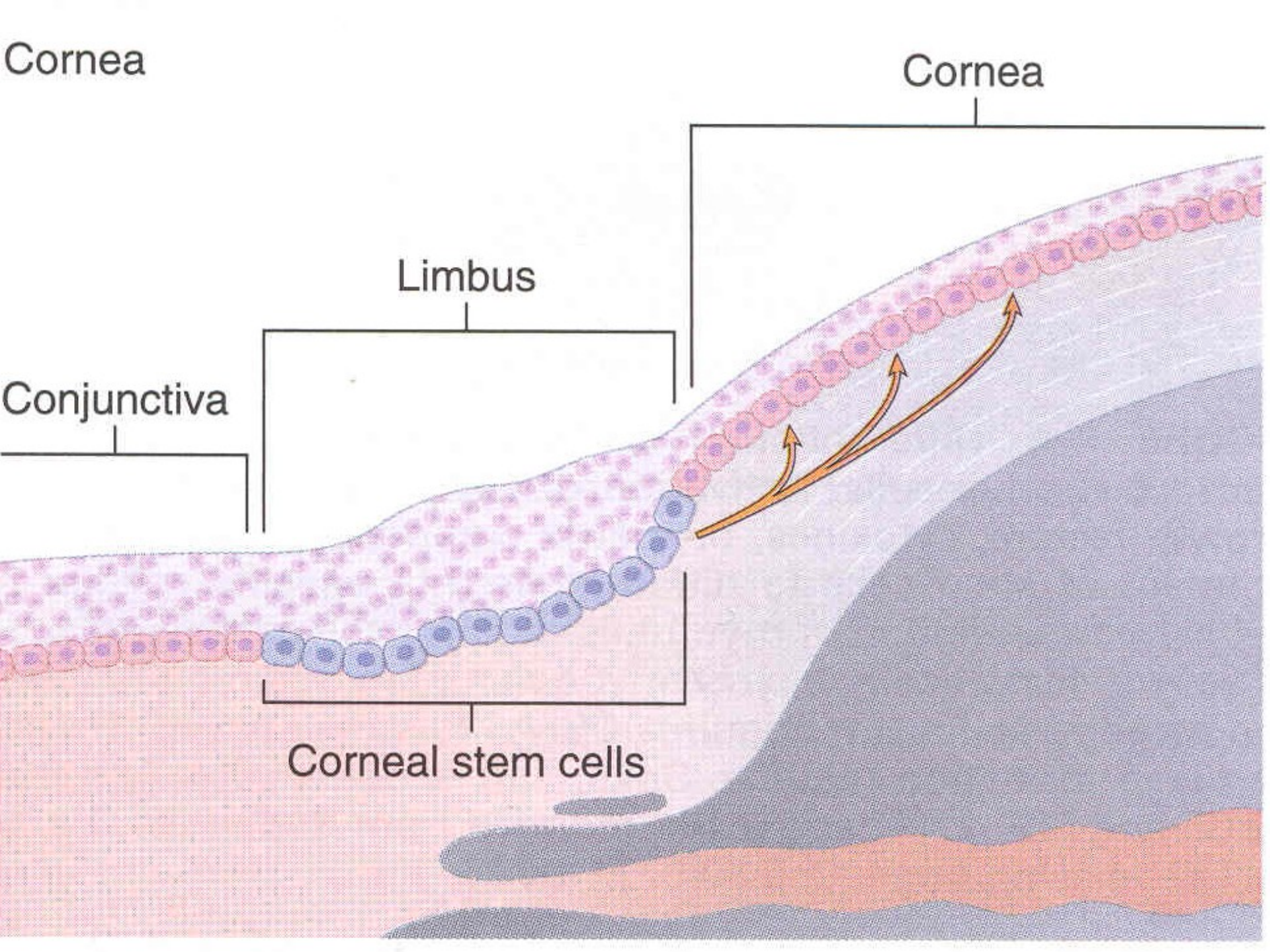
Tissue Stem cells



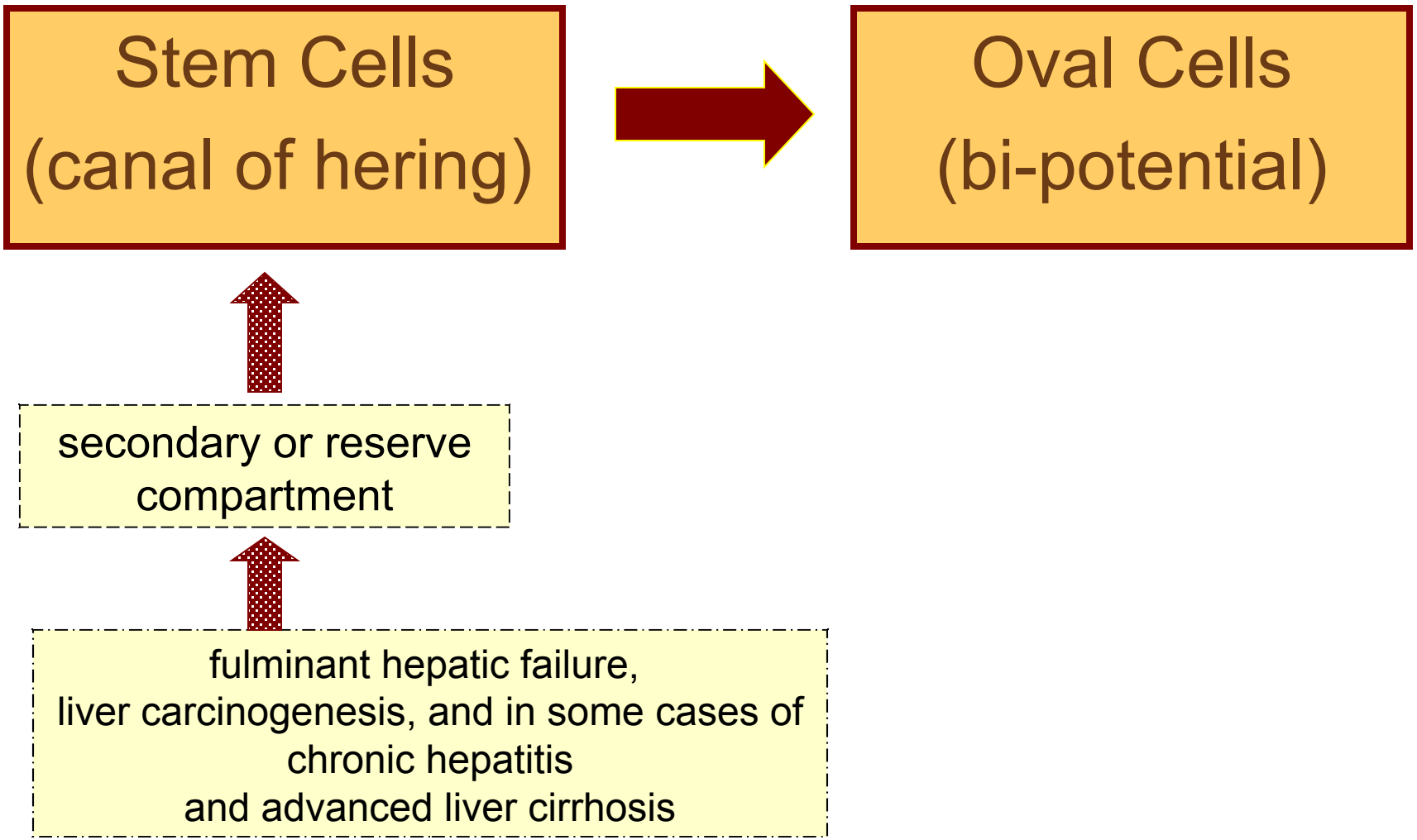
B. Intestine


Goblet cell
Absorptive enterocyte
Enteroendocrine cell
Crypt cells (stem cells)
Paneth cells


Liver


Cornea
Cornea
Limbus
Conjunctiva
Corneal stem cells

Liver stem cells



Neural stem cells

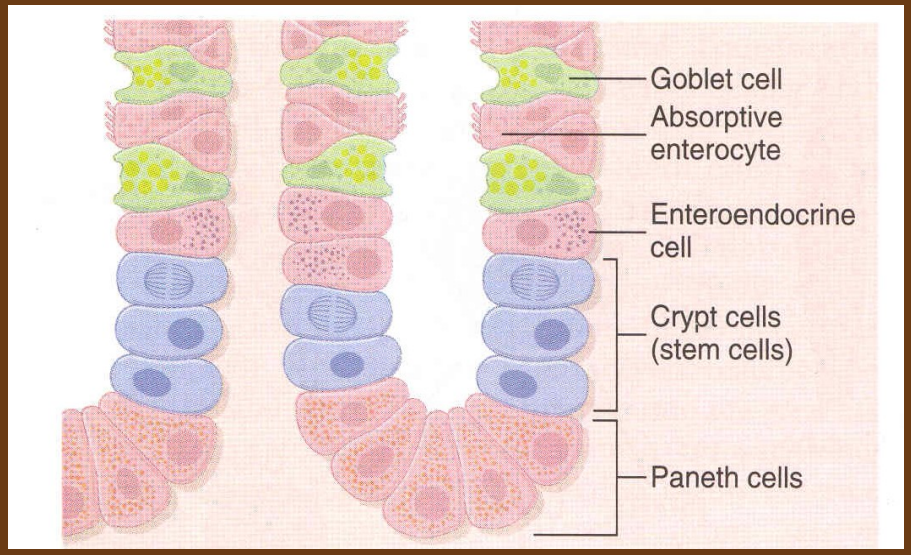
- rodent brains: olfactory bulb, and dentate gyrus of the hippocampus
- Canaries: vocal center neurogenesis
- mammalian hippocampus

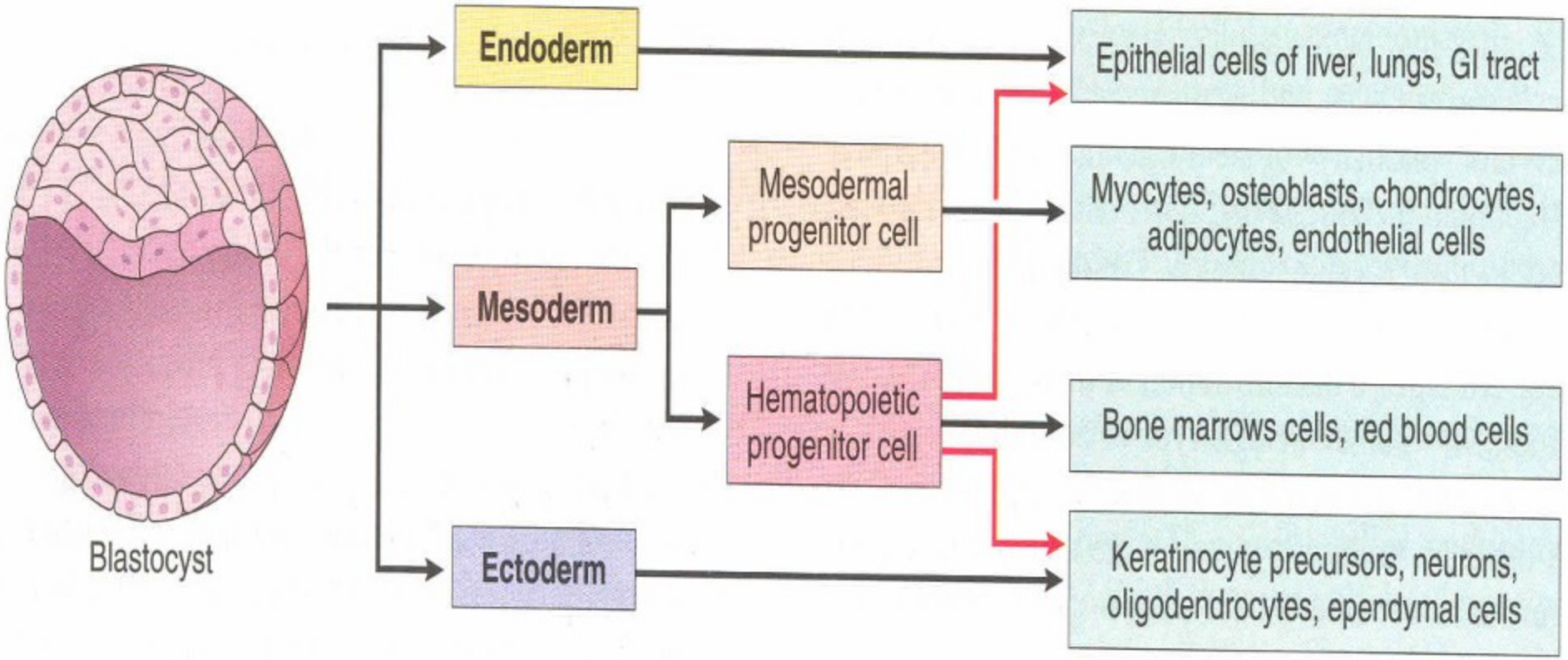
Skeletal and Cardiac muscle

- In contrast to hepatocytes, myocytes of skeletal muscle do not divide, even after injury.
- satellite cells (beneath the myocyte basal lamina)
- Stem cells have not been found in cardiac muscle

Epithelial Tissue

1. Stem cells
2. Highly proliferative intermediate cells that constitute an amplifying compartment




Endoderm
Mesoderm
Ectoderm
Mesodermal progenitor cell
Hematopoietic progenitor cell
Blastocyst
Epithelial cells of liver, lungs, GI tract
Myocytes, osteoblasts, chondrocytes, adipocytes, endothelial cells
Bone marrows cells, red blood cells
Keratinocyte precursors, neurons, oligodendrocytes, ependymal cells

Key events in stem cell research

- **1960s** - Joseph Altman and Gopal Das present evidence of adult neurogenesis, ongoing stem cell activity in the brain; their reports contradict Cajal's "no new neurons" dogma are largely ignored
- **1963** - McCulloch and Till illustrate the presence of self-renewing stem cells in mouse bone marrow
- **1968** - bone marrow transplant between two siblings successfully treats SCID
- **1978** - haematopoietic stem cells are discovered in human cord blood
- **1981** - mouse embryonic stem cells are derived from the inner cell mass
- **1992** - neural stem cells are cultured *in vitro* as neurospheres
- **1995** - President Bill Clinton signs into law the Dickey Amendment which makes it illegal for Federal money to be used for research where stem cells are derived from the destruction of the embryo.

Key events in stem cell research

- **1997** - leukemia is shown to originate from a haematopoietic stem cell, the first direct evidence for cancer stem cells
- **1998** - James Thomson and coworkers derive the first human embryonic stem cell line at the University of Wisconsin-Madison.
- **2000s** - several reports of adult stem cell plasticity are published
- **2003** - Dr. Songtao Shi of NIH discovers new source of adult stem cells in children's primary teeth
- **2004-2005** - Hwang Woo-Suk claims to have created several human embryonic stem cell lines from unfertilised human oocytes. The lines are later shown to be fabricated
- **July 19, 2006** - President George W. Bush vetoes a bill which would have allowed Federal money to be used for research where stem cells are derived from the destruction of the embryo

Stem Cell Information

The **National Institutes of Health** resource for stem cell research

Frequently Asked Questions
- What are stem cells?
- Can they cure diseases?
- Are there ethical issues?
- What is the U.S. policy?
- More FAQs
- Links to related resources

Stem Cell Research
- Stem Cell Registry
- Current Research
- Upcoming Events
- Funding for Research
- Training Programs
- Scientific Literature

Tools
- Site Map
- Glossary
- Downloads
- Text: smaller | BIGGER

The Promise of Stem Cells

Stem cells can develop into different cell types. They may offer a renewable source of replacement cells to treat diseases, conditions, and disabilities.

Learn more about stem cells

U.S. Policy on Stem Cell Research

In 2001, President George W. Bush announced that federal funds may be awarded for research using human embryonic stem cells that meet approved criteria.

Read the eligibility criteria

The NIH Stem Cell Registry

The Registry lists human embryonic stem cell (hESC) lines eligible for federal funding and provides contact information to help investigators acquire stem cells.

Find hESC lines on the Registry

hESC lines now available from the
National Stem Cell Bank

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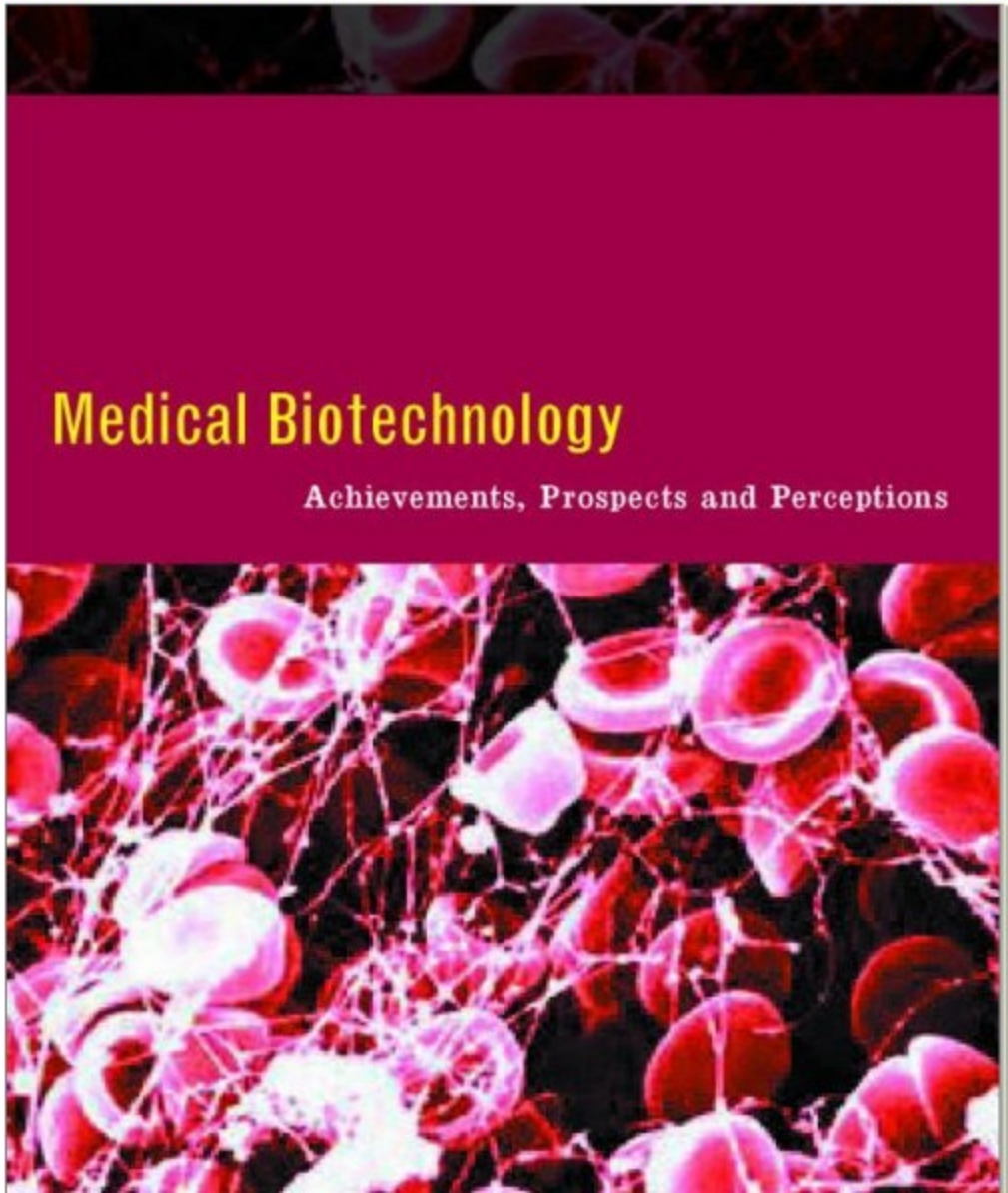

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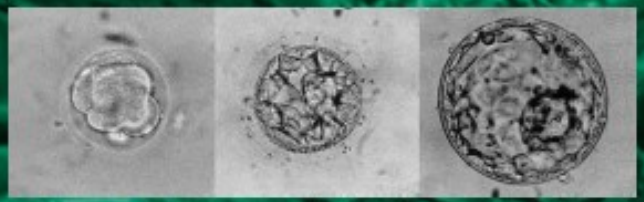
METHODS IN MOLECULAR BIOLOGY™ 331

Human Embryonic Stem Cell Protocols

Edited by

Kursad Turksen



Includes Companion CD

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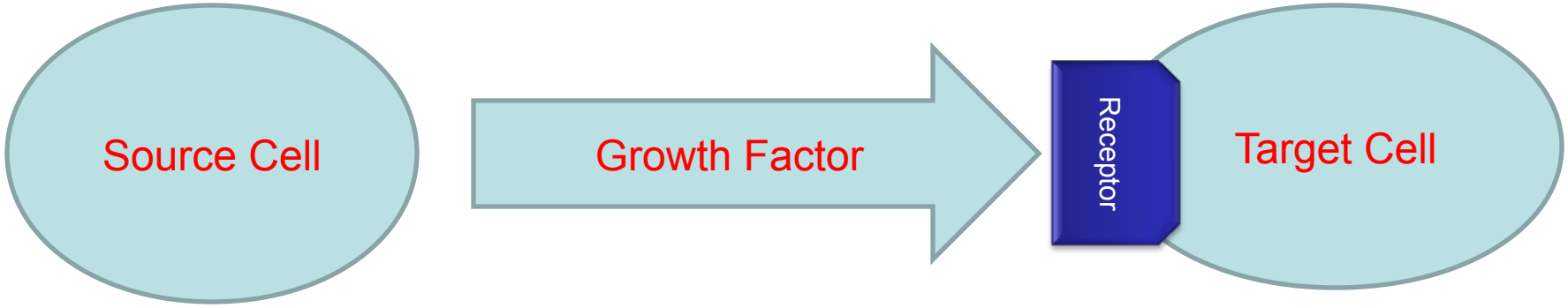
REGENERATIVE BIOLOGY AND MEDICINE

David L. Stocum

GROWTH FACTORS

- Polypeptide growth factors
- Restricted cellular targets ?

Cell proliferation, cell locomotion, contractility, differentiation, and angiogenesis



Epidermal Growth Factor (EGF) and Transforming Growth Factor-a (TGF-a)

- Common receptor : EGFR
- EGF: Precocious tooth eruption and eyelid opening in newborn mice

Symbol	Source	Functions
EGF	Platelets, macrophages, saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
TGF-α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and certain epithelial cells

HGF: scatter factor, hepatocyte and billary duct,

VEGF: Vasculogenesis, Angiogenesis
Mice that lack a single allele of the gene (heterozygous VEGF knockout mice) die during embryonic development with defective vasculogenesis

Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of epithelial and endothelial cells, and of hepatocytes; increases cell motility
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells (see Table 3–3)
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, marcrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction; remodeling; inhibits platelet aggregation; regulates integrin expression

FGF

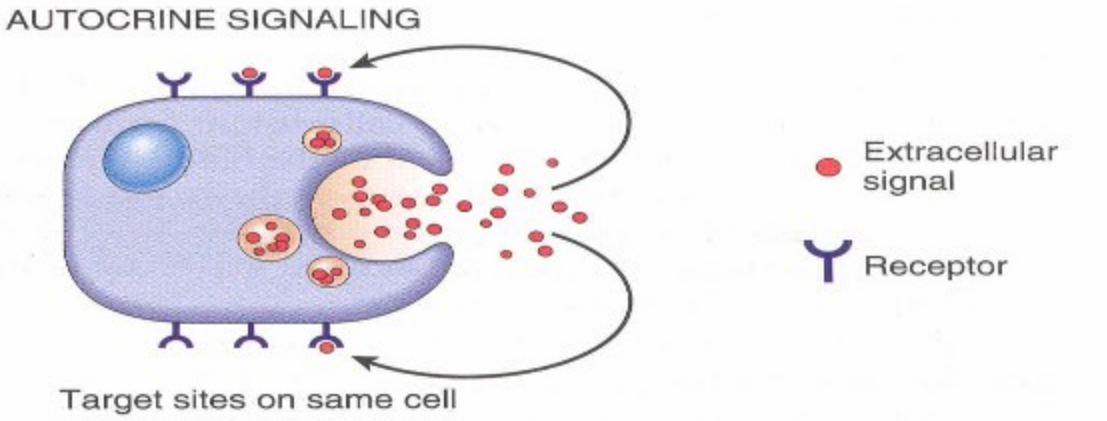
- New blood vessel formation (angiogenesis): FGF-2
- Wound repair
- Development
- Hematopoiesis

TGF-β and Related Growth Factors

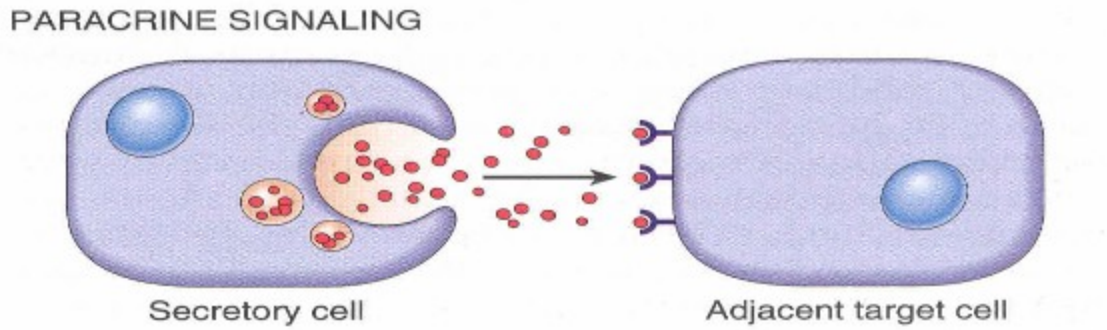
TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; regulates integrin expression and other cytokines; induces TGF-β production

1. TGF-β is a growth inhibitor for most epithelial cell types and for leukocyte
2. The effects of TGF-β on mesenchymal cells depend on concentration and culture conditions, it generally stimulates the proliferation of fibroblasts and smooth muscle cells
3. TGF-β is a potent fibrogenic agent
4. TGF- has a strong anti-inflammatory effect

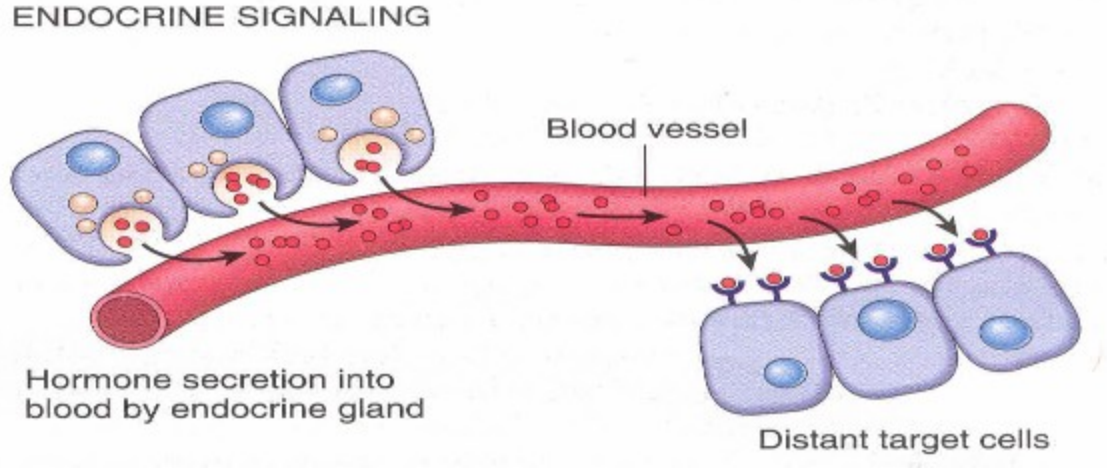
SIGNALING MECHANISMS IN CELL GROWTH



liver regeneration, proliferation of antigen stimulated lymphocytes, and the growth of some tumors

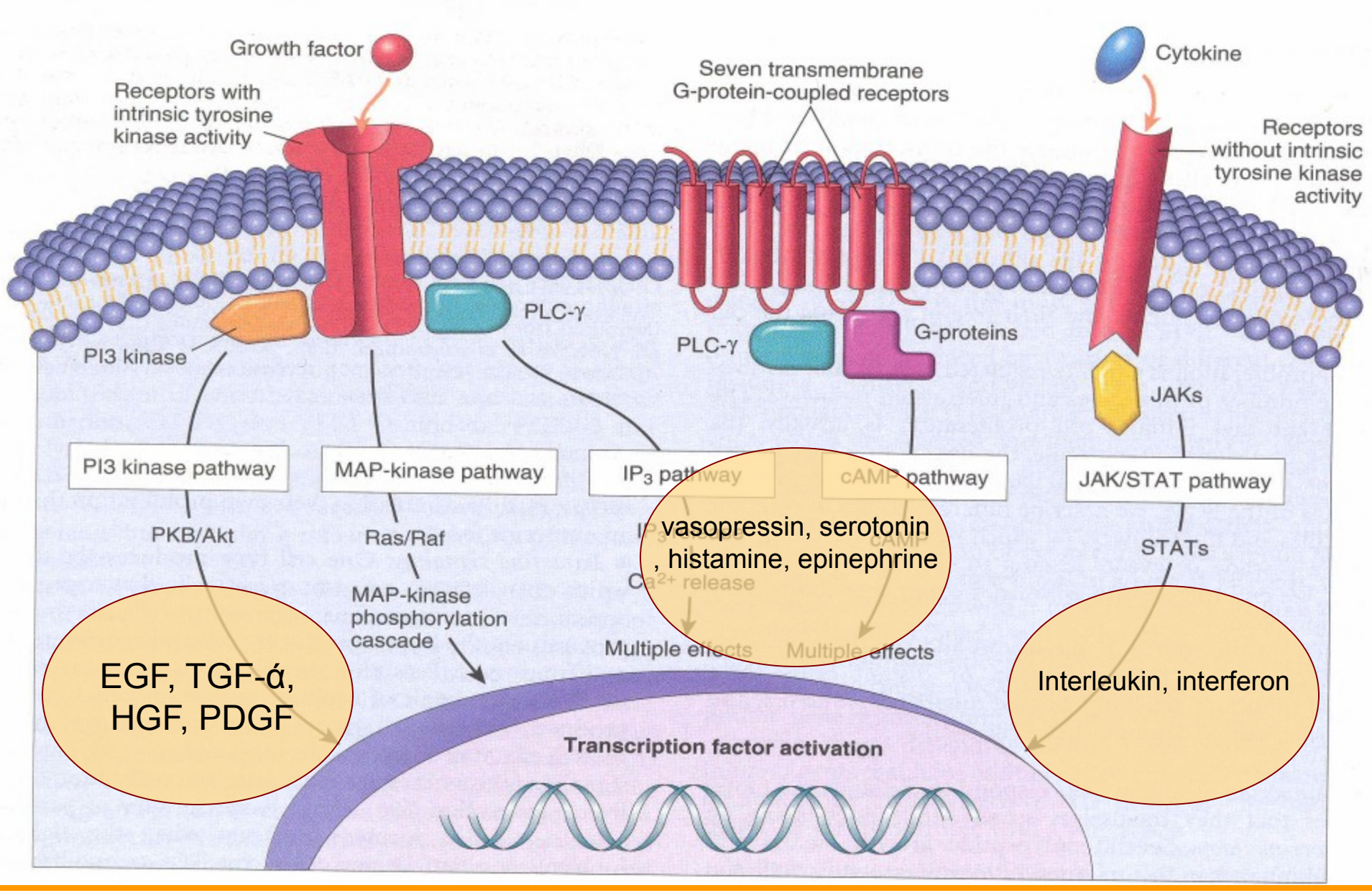


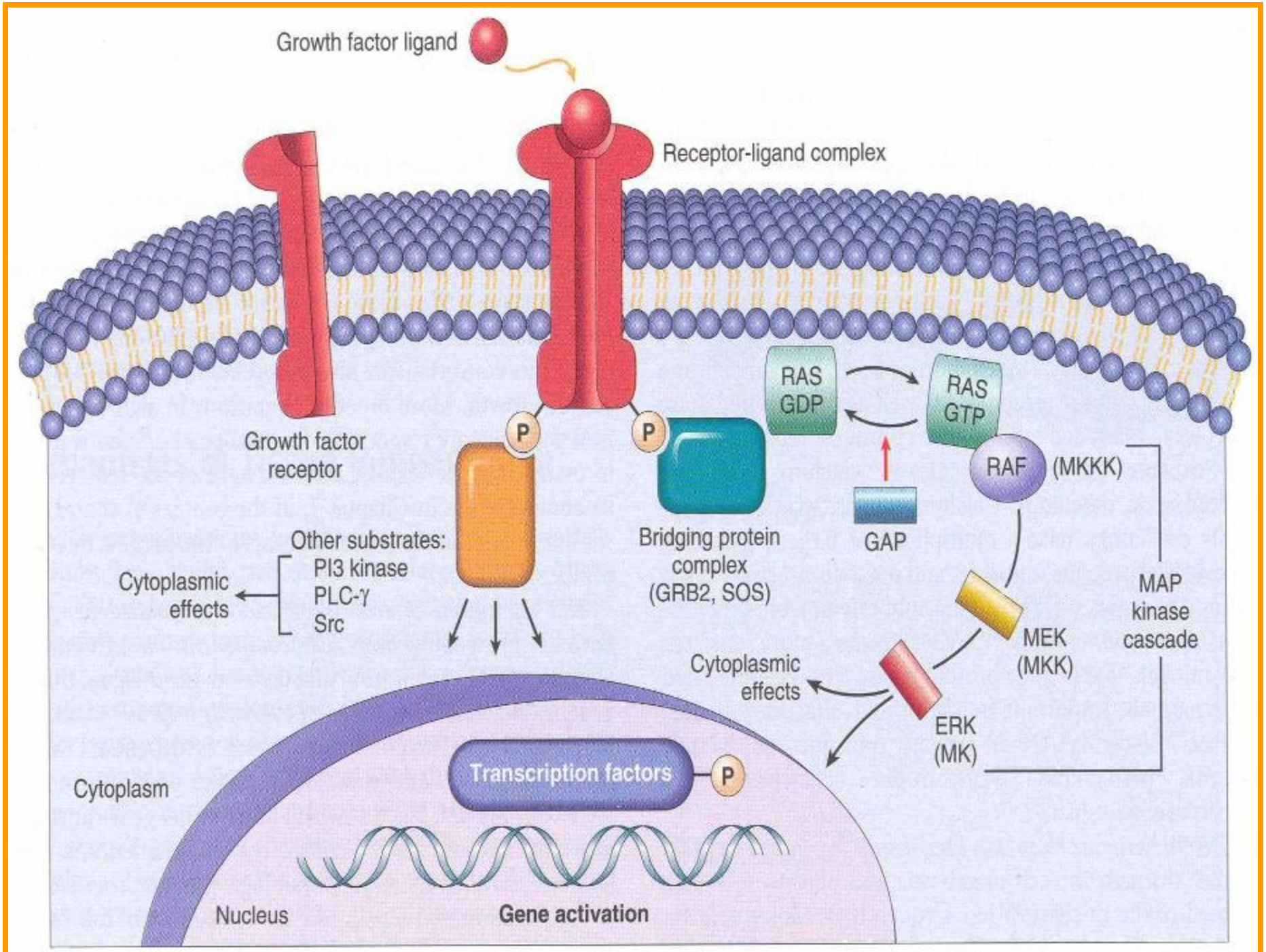
Healing of wounds, hepatocyte replication



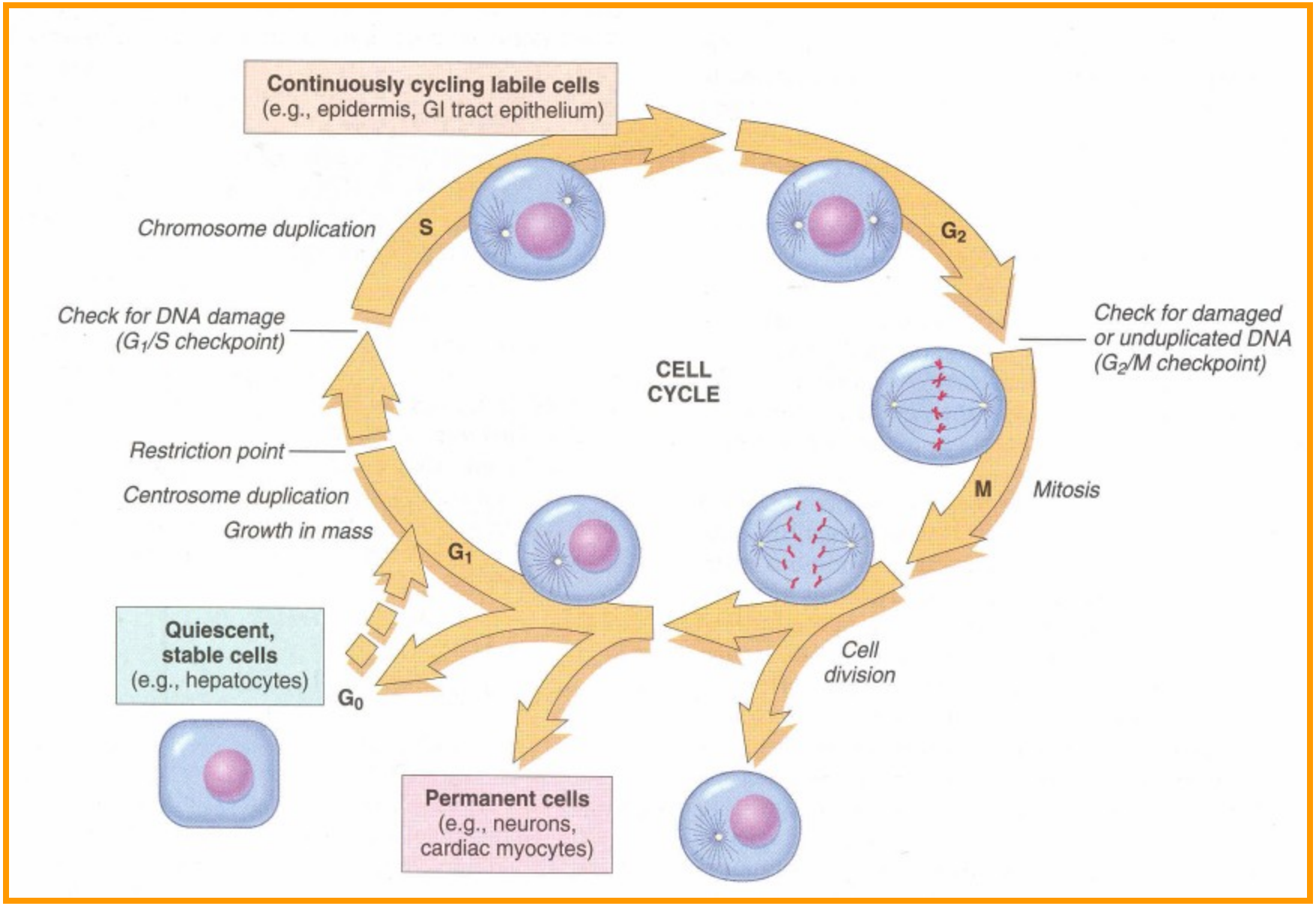
Hormones,
HGF,
Several cytokines

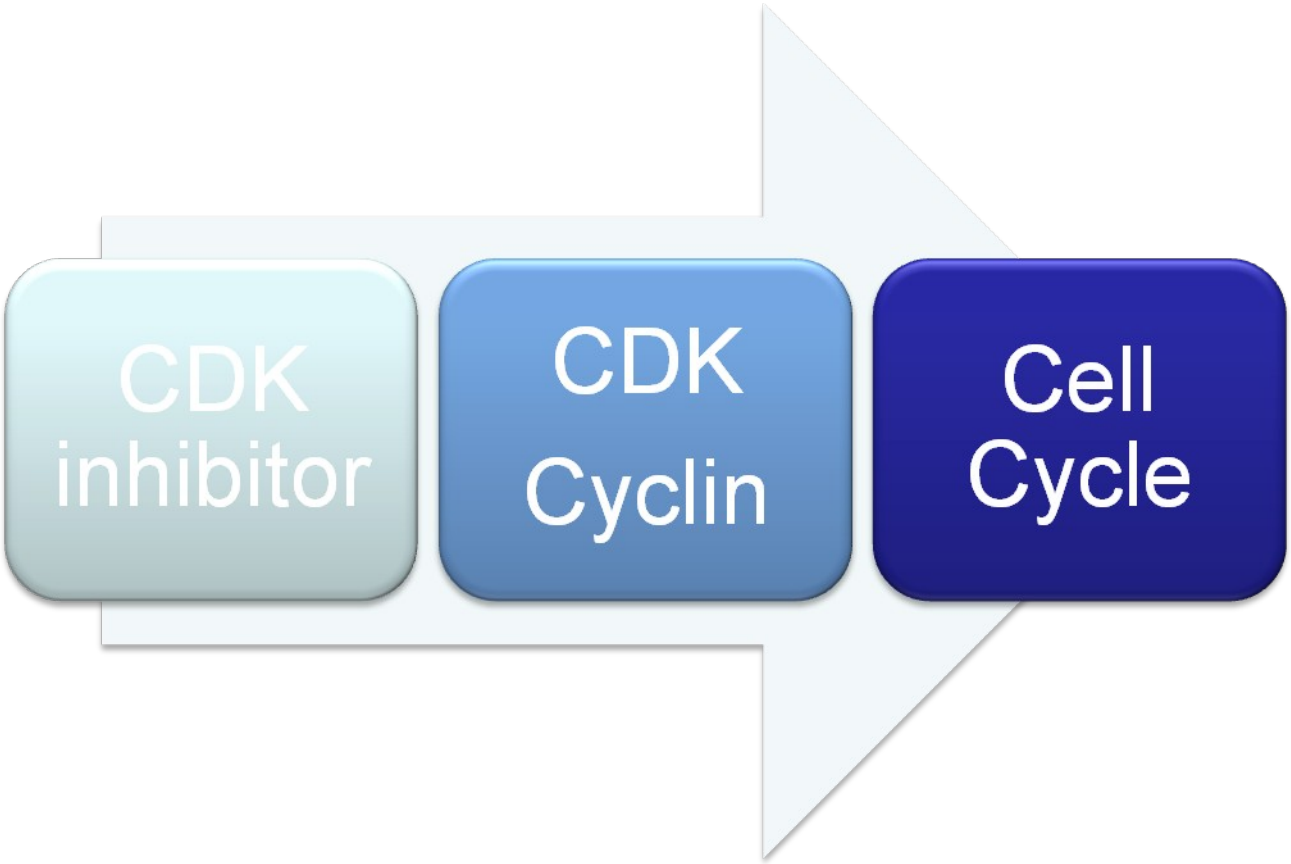
Receptors and Signal Transduction Pathways

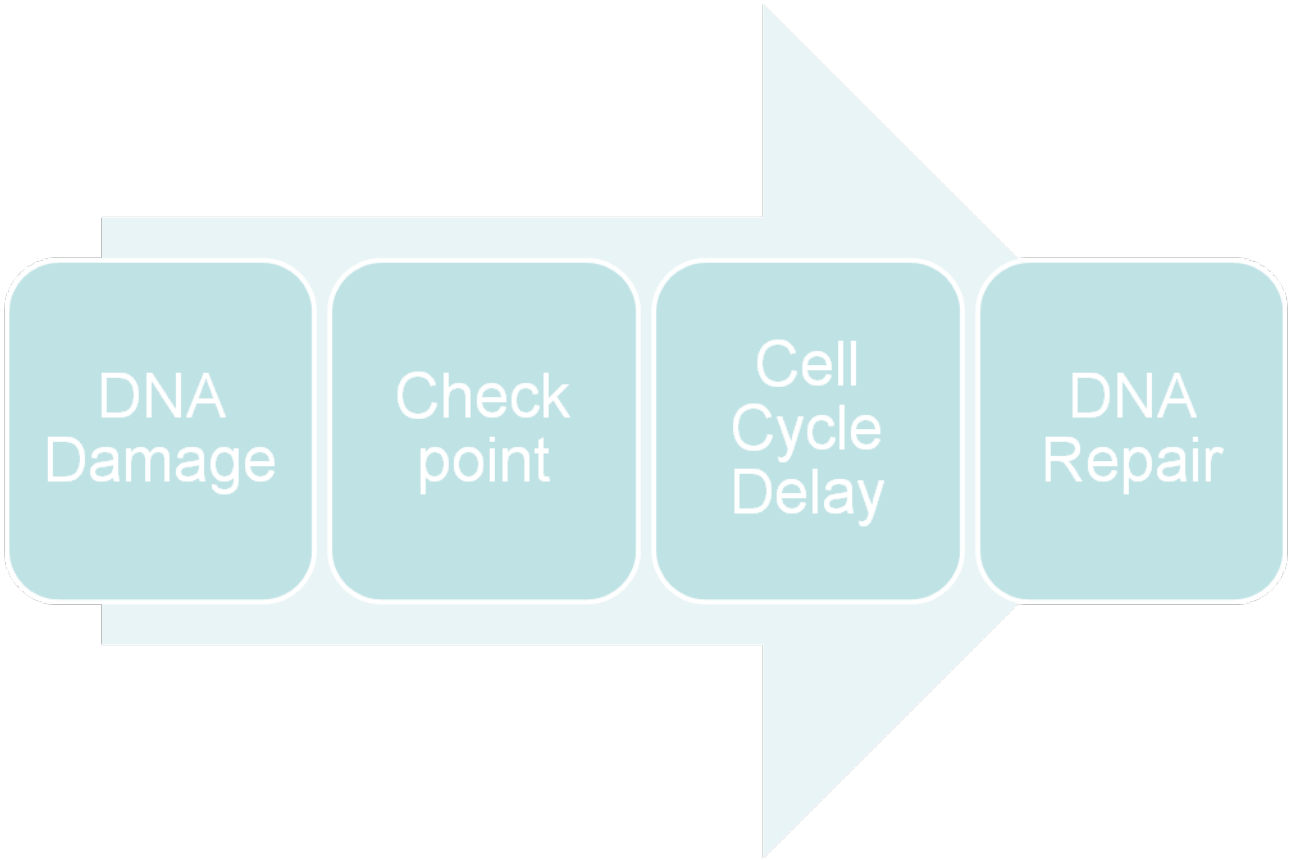


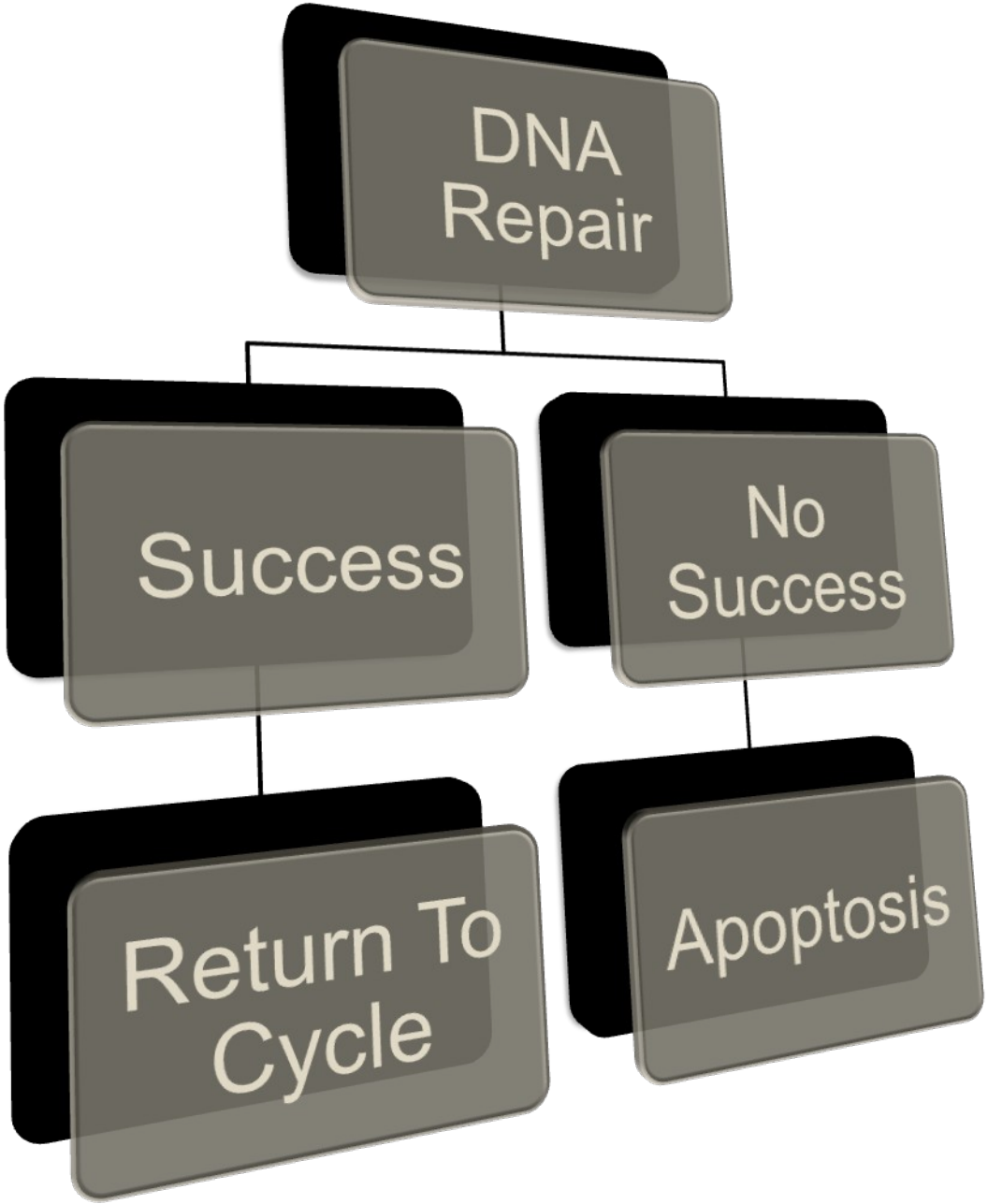

Growth factor ligand
Receptor-ligand complex
Growth factor receptor
P
P
RAS GDP
RAS GTP
RAF
(MKKK)
GAP
Bridging protein complex (GRB2, SOS)
Other substrates:
PI3 kinase
PLC-γ
Src
Cytoplasmic effects
MAP kinase cascade
MEK (MKK)
Cytoplasmic effects
ERK (MK)
Transcription factors
P
Cytoplasm
Nucleus
Gene activation

CELL CYCLE AND THE REGULATION OF CELL REPLICATION




CDK inhibitor
CDK Cyclin
Cell Cycle


DNA Damage
Check point
Cell Cycle Delay
DNA Repair


DNA Repair
Success
No Success
Return To Cycle
Apoptosis

CELL CYCLE AND THE REGULATION OF CELL REPLICATION

1. The replication of cells is generally stimulated by growth factors or by signaling from ECM components through integrins
2. the cell cycle has multiple controls and redundancies, particularly during the transition between the G and S phases
3. Progression through the cell cycle, and particularly the G,/S transition, is tightly regulated by proteins called cyclins and associated enzymes called cyclin-dependent kinases (CDKs)
4. The activity of cyclin-CDK complexes is tightly regulated by inhibitors, which are called CDK inhibitors
5. Checkpoint: ensure that cells with damaged DNA or chromosomes do not complete replication
6. The G1/S checkpoint checks the integrity of DNA before replication, whereas the G2/M checkpoint checks DNA after replication and monitors whether the cell can safely enter mitosis

CELL CYCLE AND THE REGULATION OF CELL REPLICATION

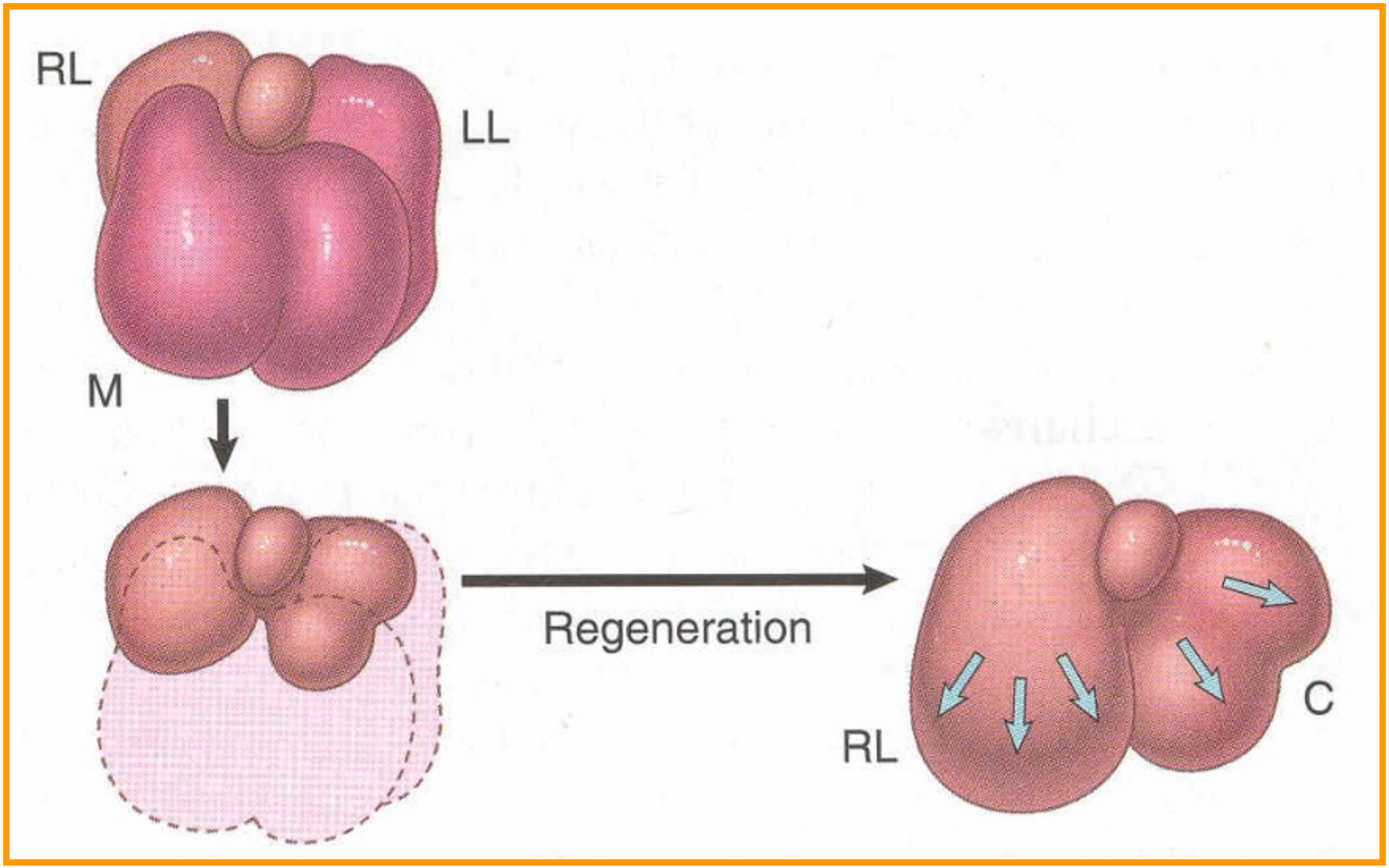
7- Checkpoint activation delays the cell cycle and triggers DNA repair mechanisms. If DNA damage is too severe to be repaired, the cells are eliminated by apoptosis

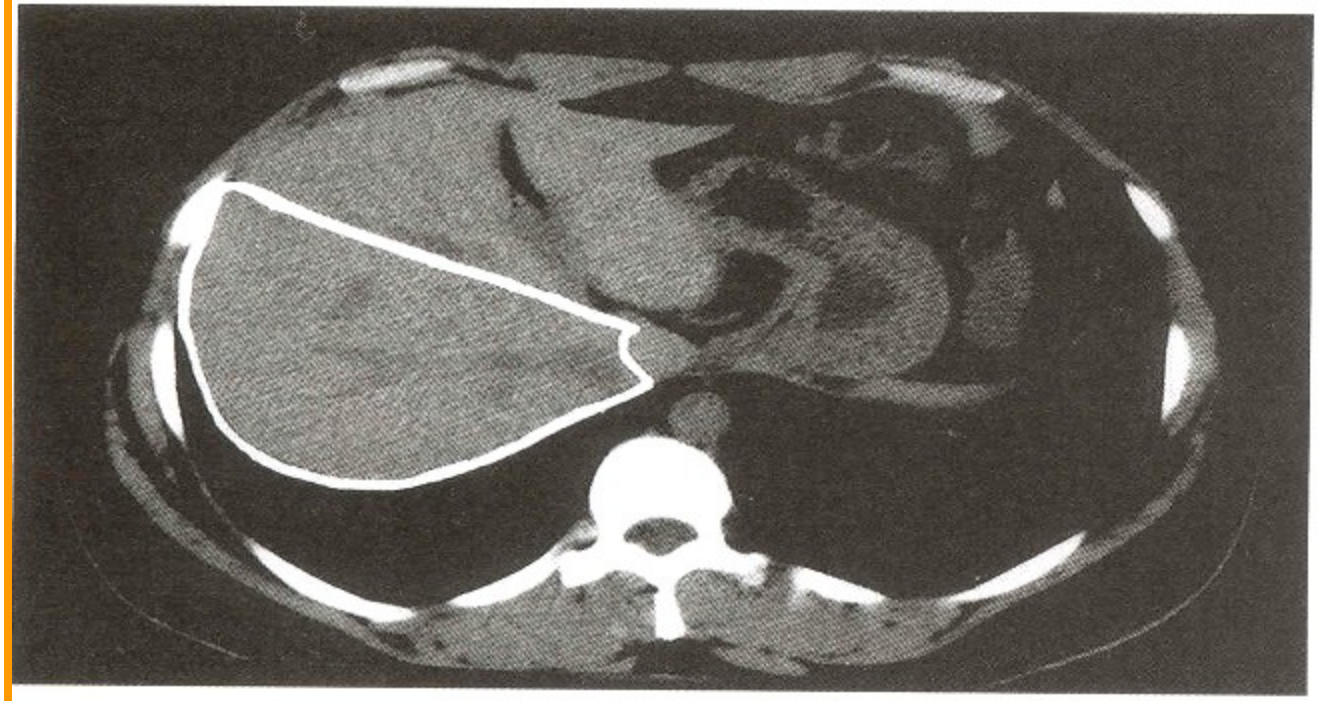
8- Checkpoint defects allow the replication of cells with DNA strand breaks and chromosome abnormalities that may cause tissue alterations and neoplasia

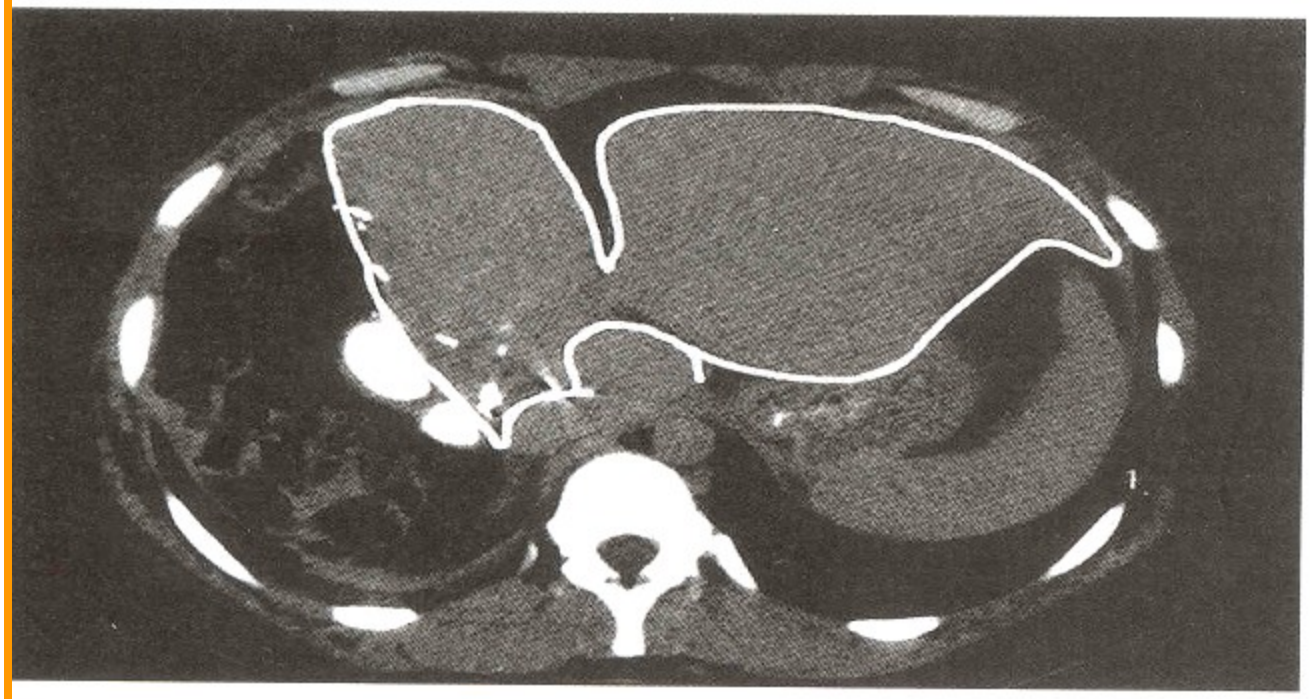
Mechanisms of Tissue Regeneration

- **Compensatory growth** processes that involve hypertrophy and hyperplasia. They restore the functional capacity of an organ without necessarily reconstituting its original anatomy
- liver regeneration
- regeneration of the liver after partial hepatectomy involves the replication of mature cells without stem cell participation
- kidney, pancreas, adrenal glands, thyroid, and the lungs of very young animals, are also capable of compensatory growth, although they display it in less dramatic form than the liver

Liver Regeneration



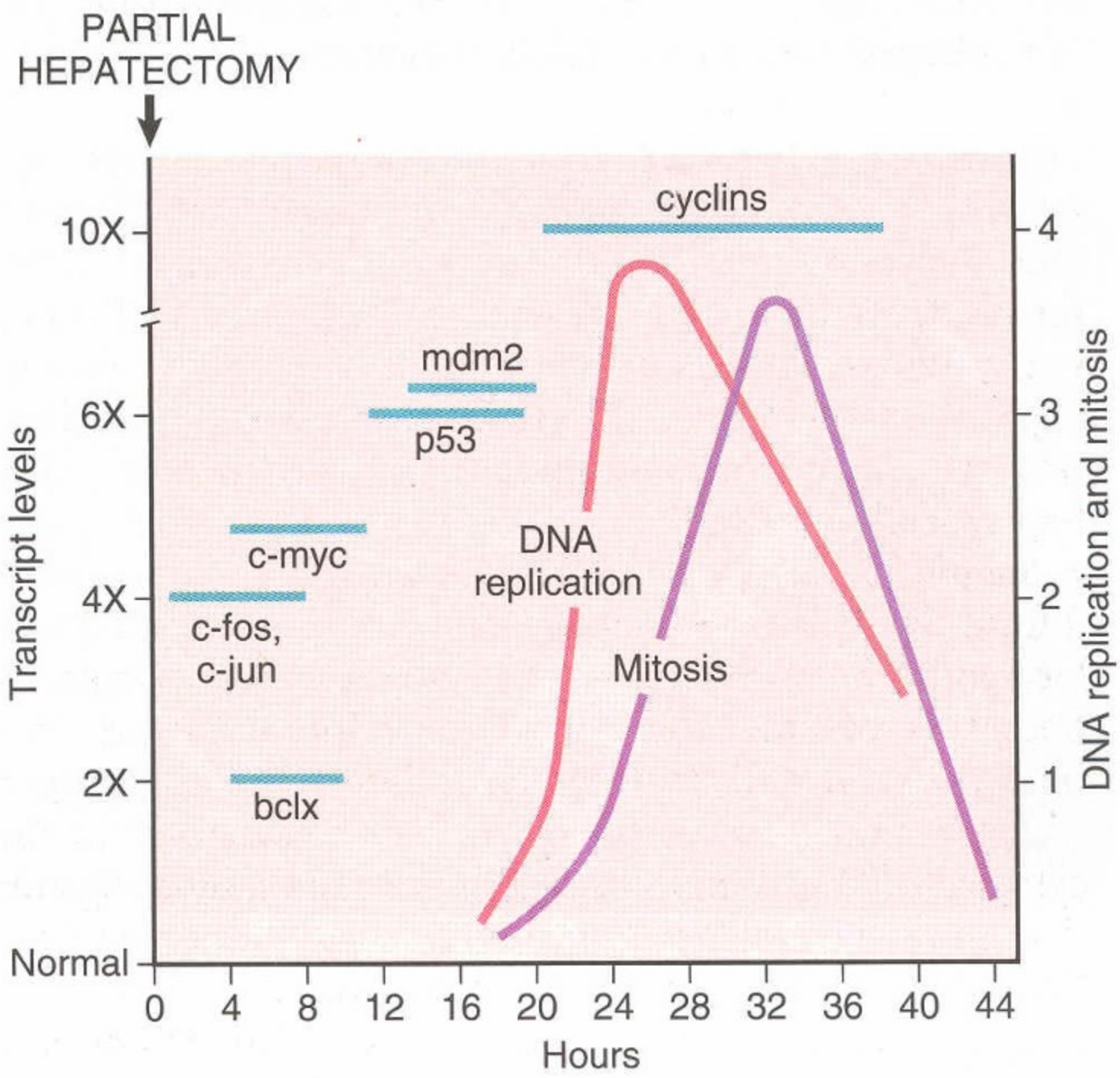


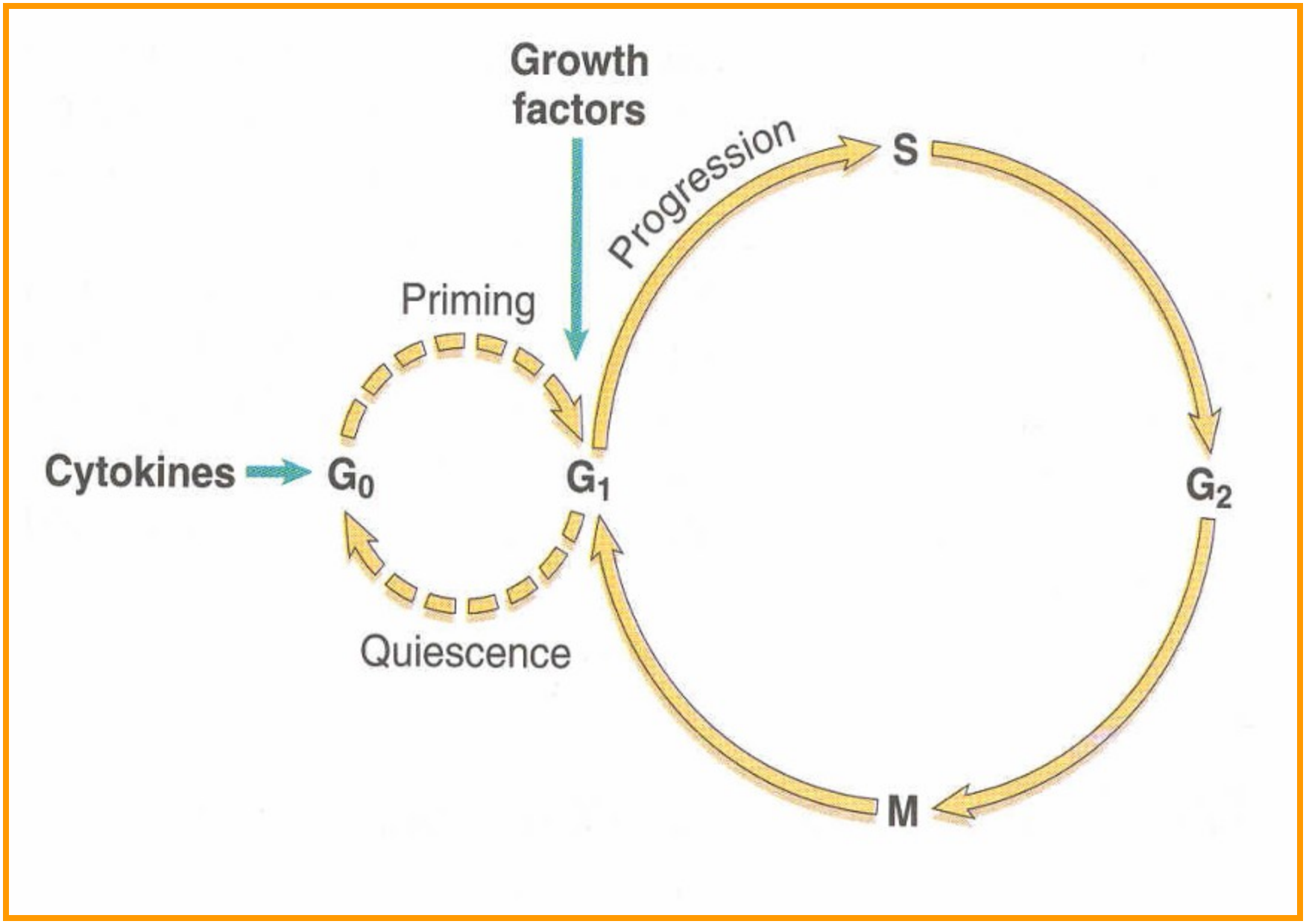


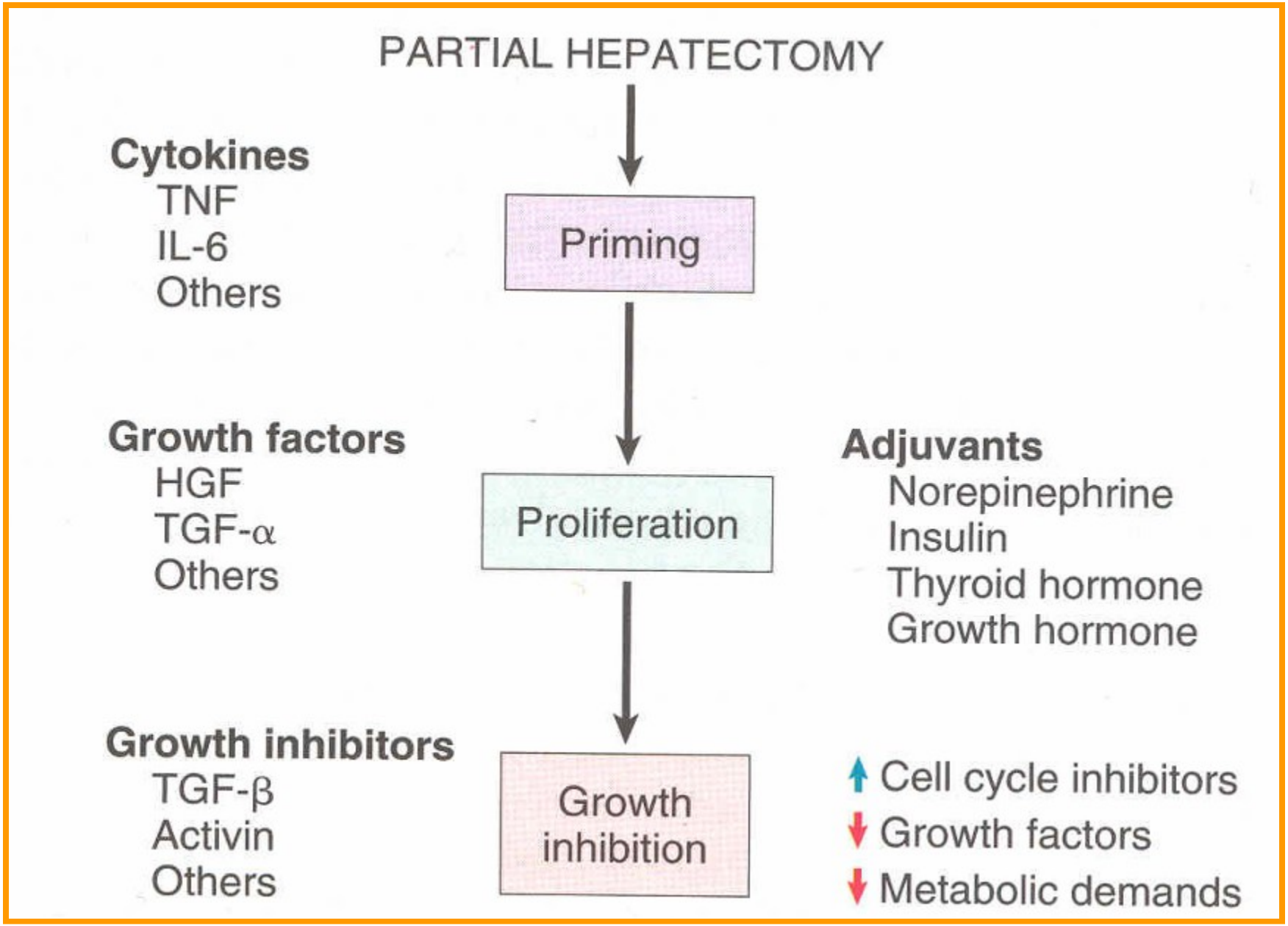
Important !

The end-point of liver regeneration after partial hepatectomy is:

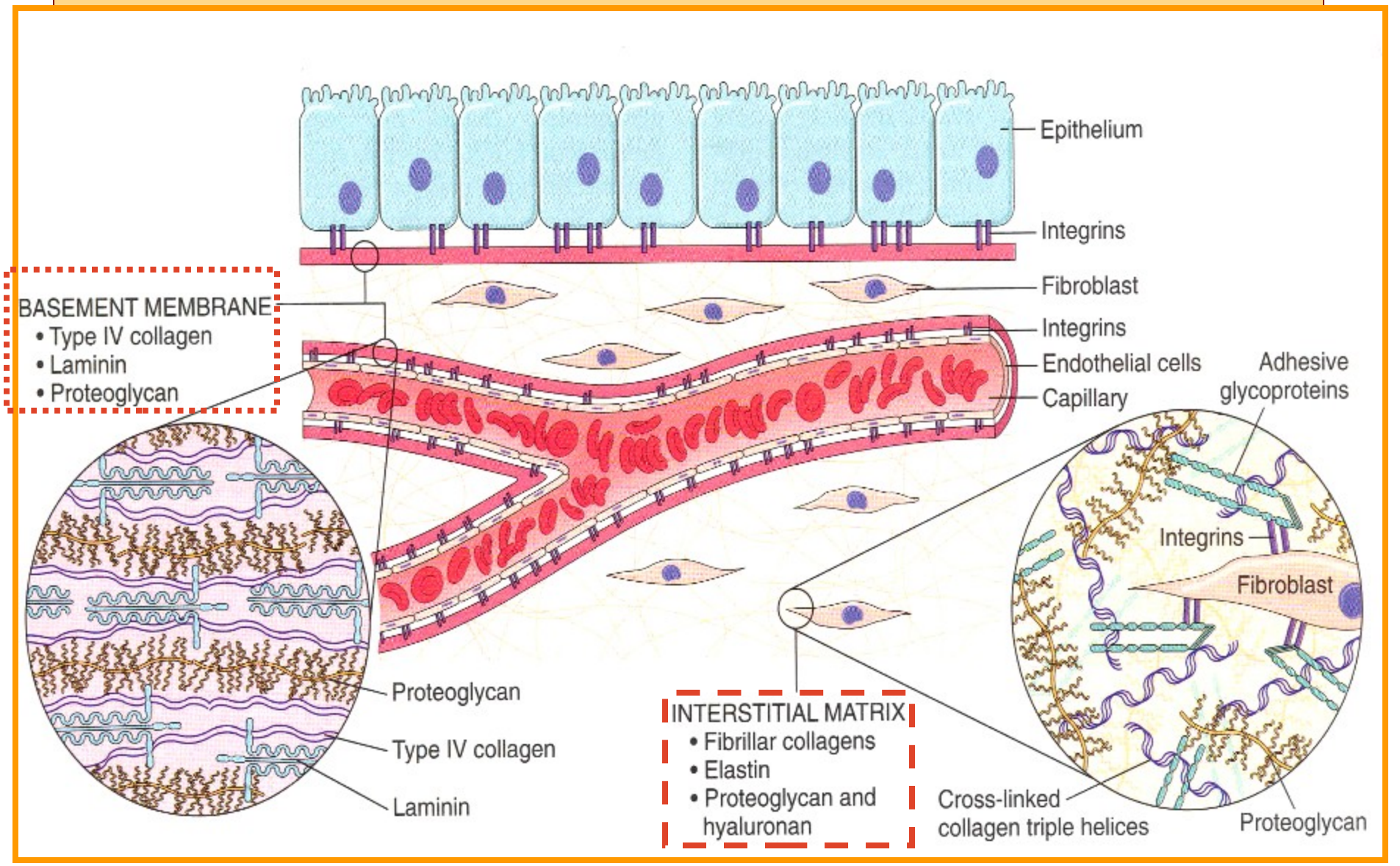
The restitution of functional mass rather than form


PARTIAL
HEPATECTOMY
cyclins
10X
mdm2
6X
p53
c-myc
DNA
replication
4X
c-fos,
c-jun
Mitosis
2X
bclx
Normal
Transcript levels
DNA replication and mitosis
4
3
2
1
0
4
8
12
16
20
24
28
32
36
40
44
Hours


Growth factors
Progression
S
Priming
Cytokines
G_0
G_1
G_2
Quiescence
M


PARTIAL HEPATECTOMY
Cytokines
TNF
IL-6
Others
Priming
Growth factors
HGF
TGF-α
Others
Proliferation
Adjuvants
Norepinephrine
Insulin
Thyroid hormone
Growth hormone
Growth inhibitors
TGF-β
Activin
Others
Growth inhibition
Cell cycle inhibitors
Growth factors
Metabolic demands

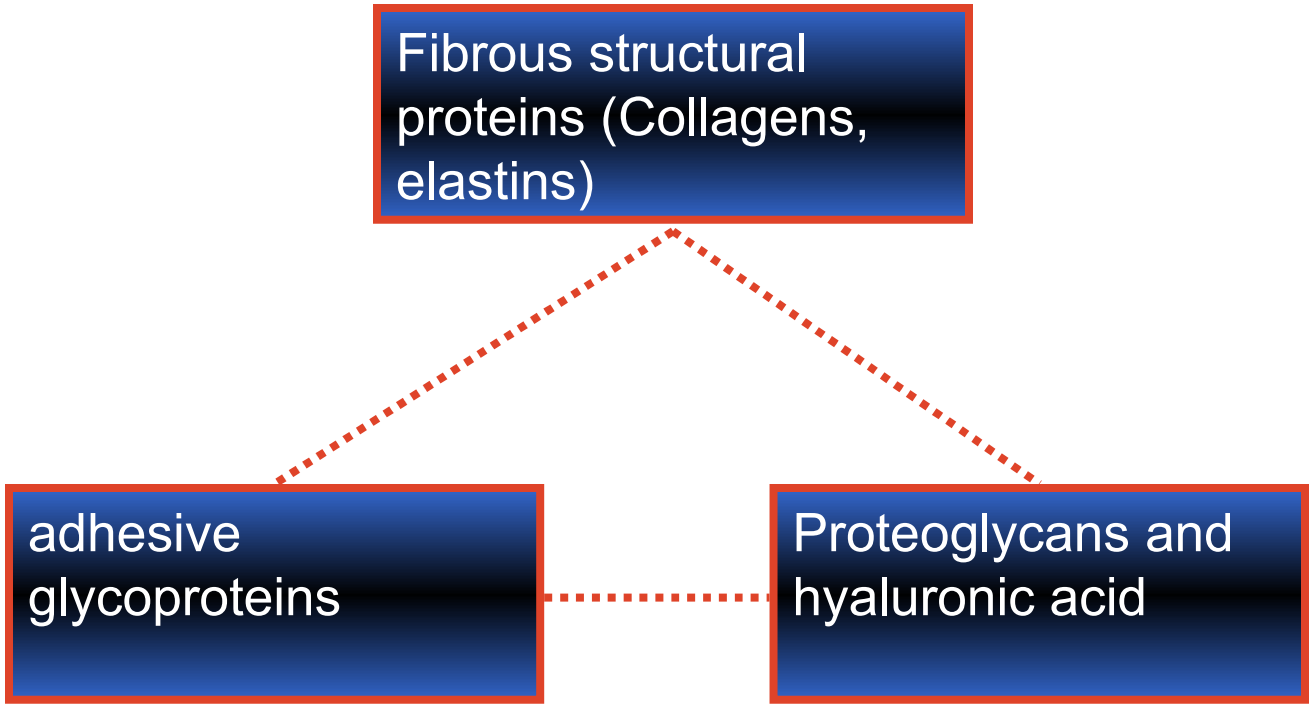
Extracellular Matrix (ECM) Cell-Matrix Interactions



Extracellular Matrix Functions

- Matrix proteins sequester water that provides turgor to soft tissues and minerals that give rigidity to skeletal tissues
- Reservoir for growth factors controlling cell proliferation
- important for cell-to-cell interactions and provides a substratum for cells to adhere, migrate, and proliferate, directly modulating cell form and function
- Synthesis and degradation of ECM accompanies morphogenesis, wound healing, and chronic fibrotic processes, as well as tumor invasion and metastasis

ECM Structure



1. Interstitial matrix
2. Basement membrane (BM)

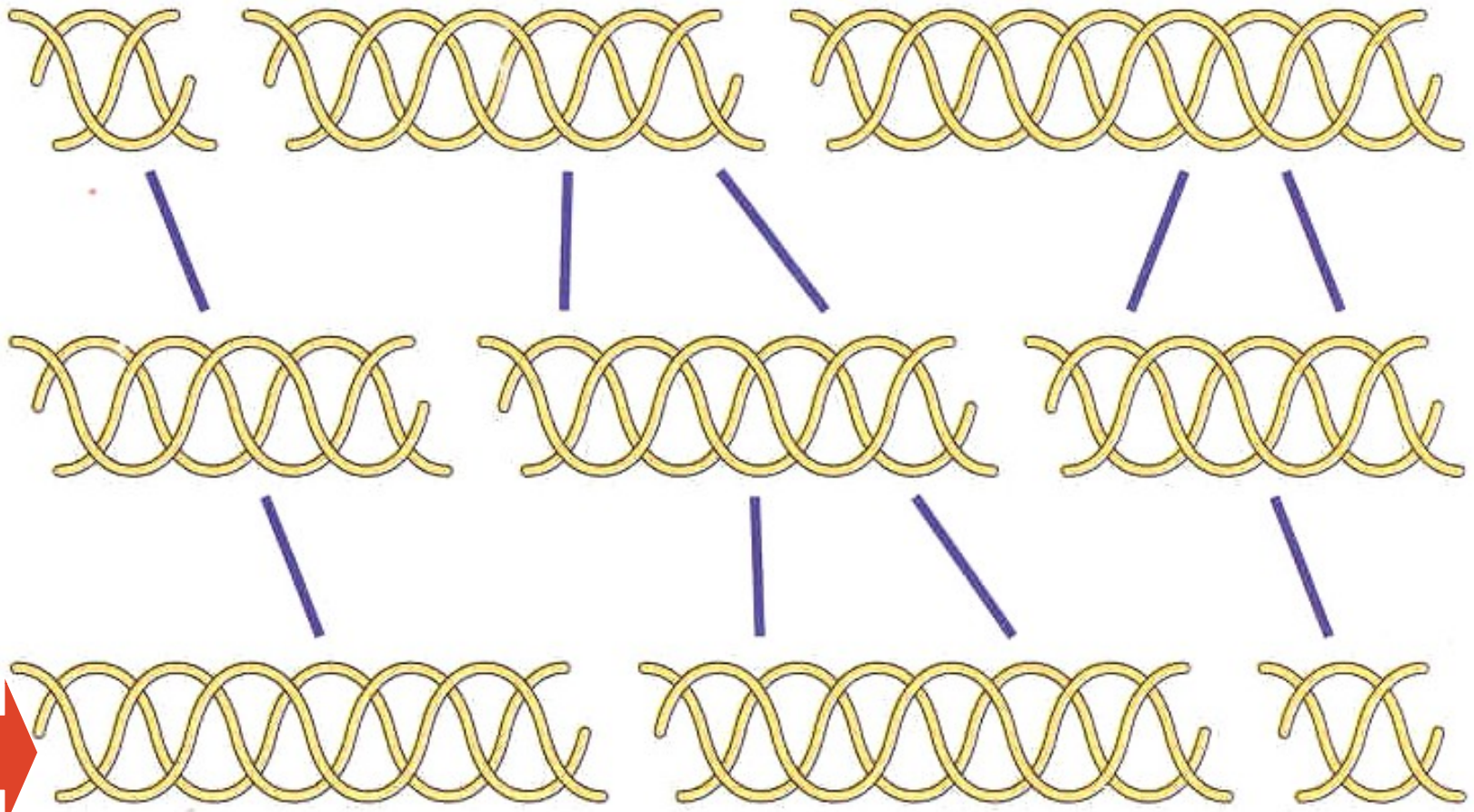
Basement membrane (BM)

- Produced by epithelial and mesenchymal cells
- A network of amorphous nonfibrillar collagen (mostly type IV), laminin, heparan sulfate, proteoglycan, and other glycoproteins

COLLAGEN

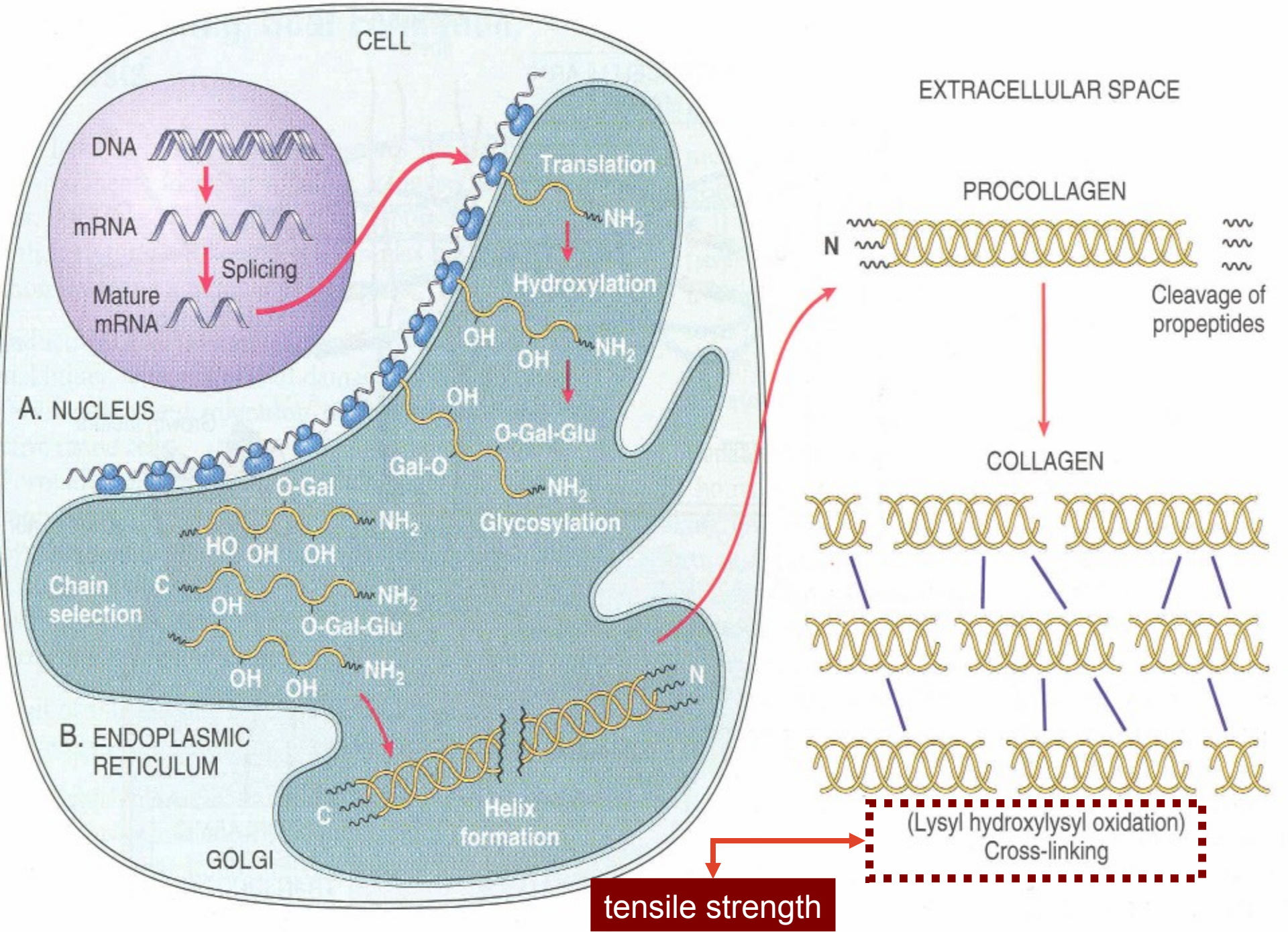
Collagen is the most common protein in the animal world

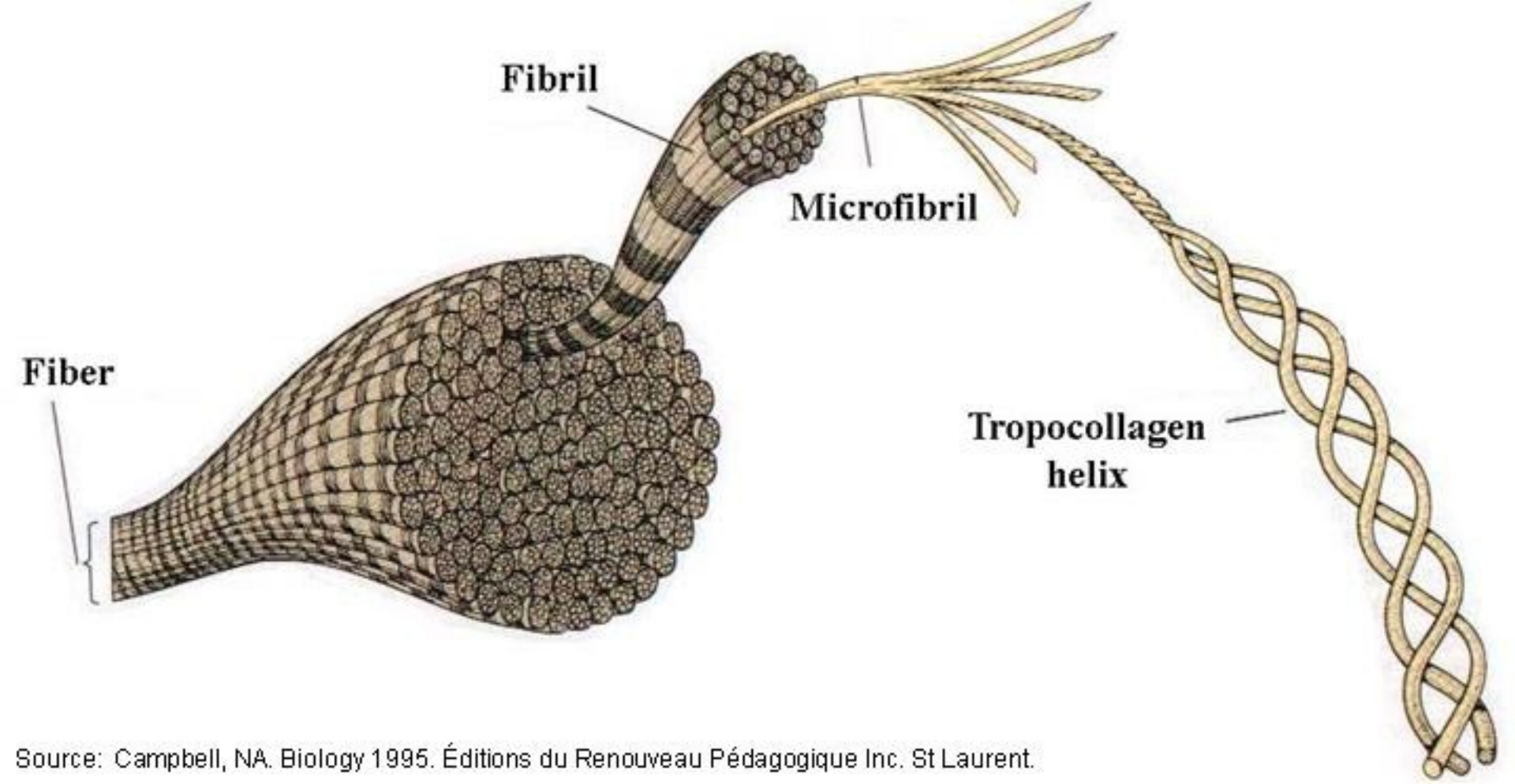
COLLAGEN



(Lysyl hydroxylysyl oxidation)
Cross-linking

Pro collagen

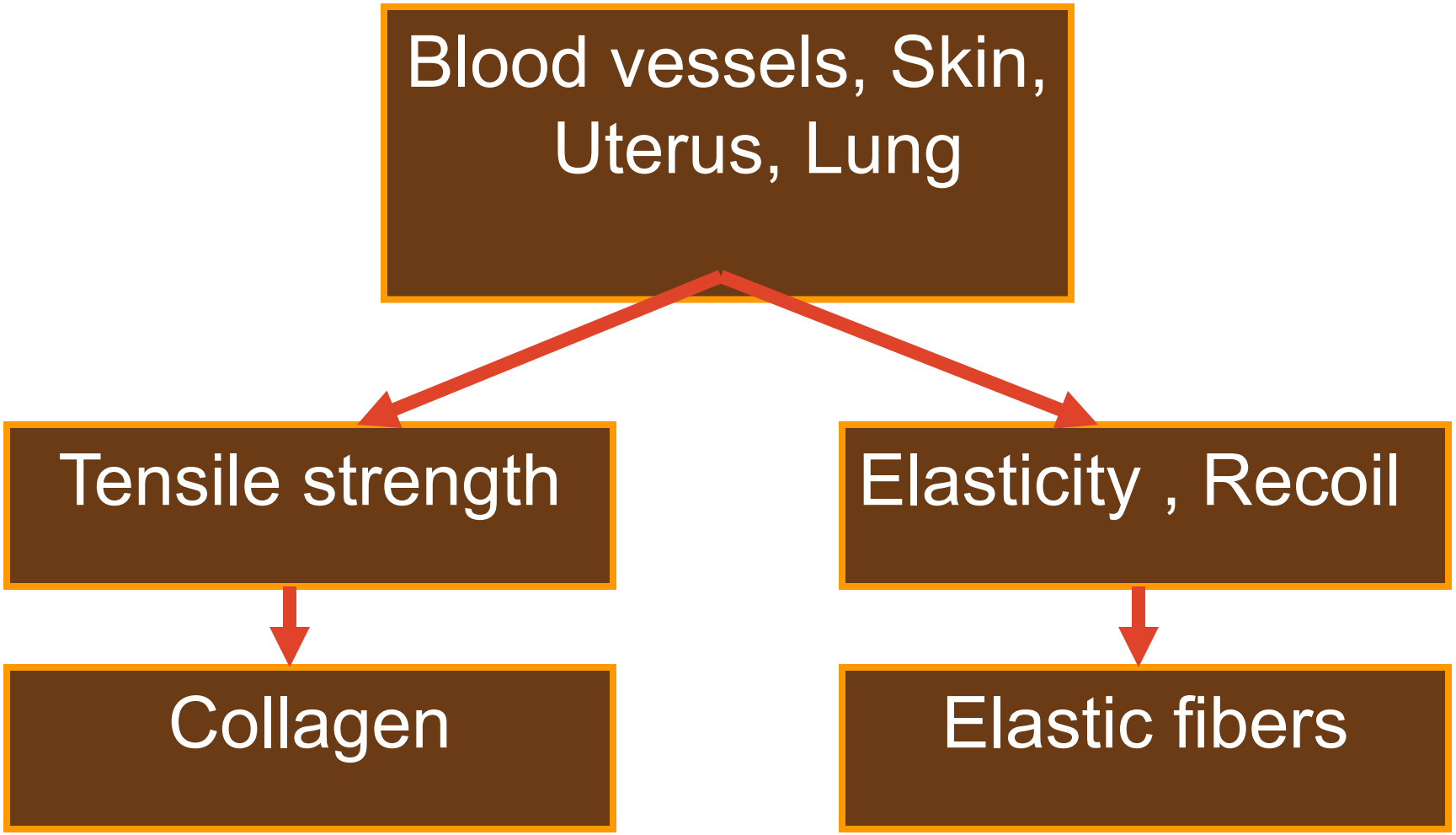

CELL
DNA
mRNA
Splicing
Mature mRNA
A. NUCLEUS
Translation
NH_2
Hydroxylation
OH
OH
NH_2
OH
O-Gal-Glu
Gal-O
NH_2
Glycosylation
O-Gal
NH_2
HO
OH
OH
Chain selection
C
NH_2
OH
O-Gal-Glu
OH
OH
NH_2
B. ENDOPLASMIC RETICULUM
C
N
Helix formation
GOLGI
EXTRACELLULAR SPACE
PROCOLLAGEN
N
Cleavage of propeptides
COLLAGEN
(Lysyl hydroxylysyl oxidation)
Cross-linking
tensile strength



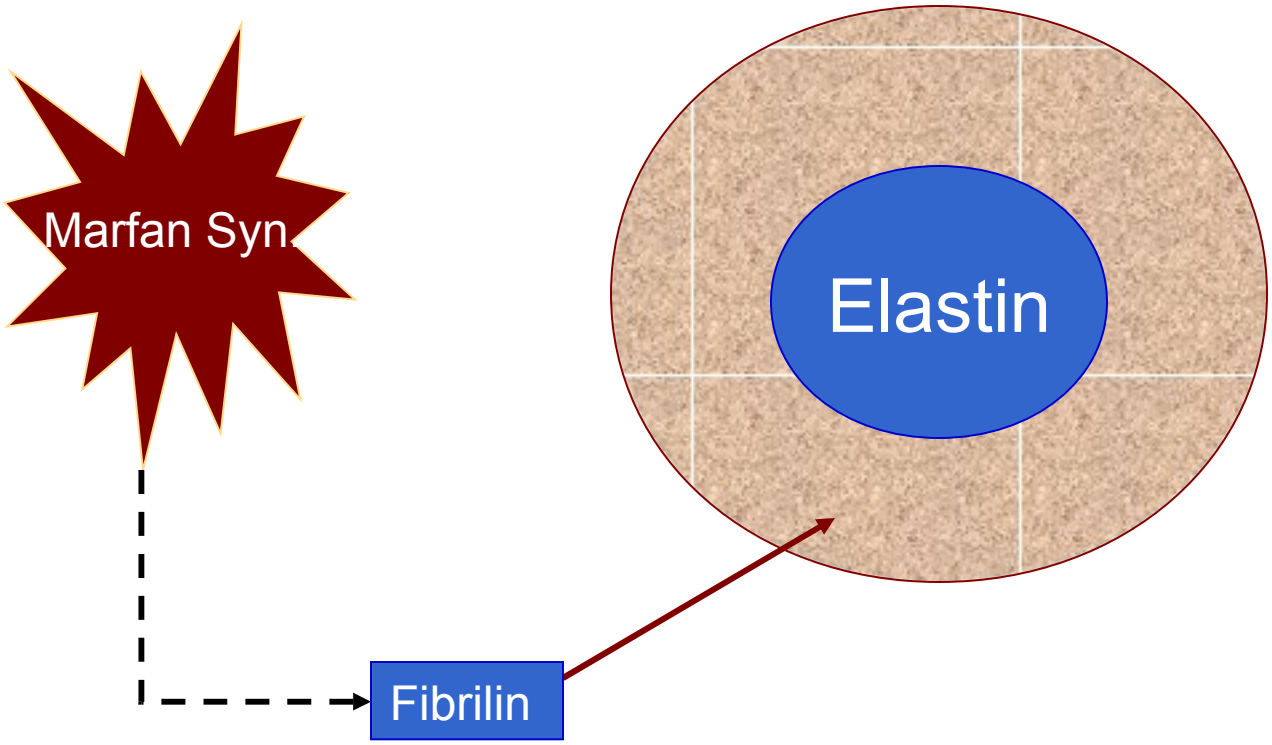
Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St Laurent.

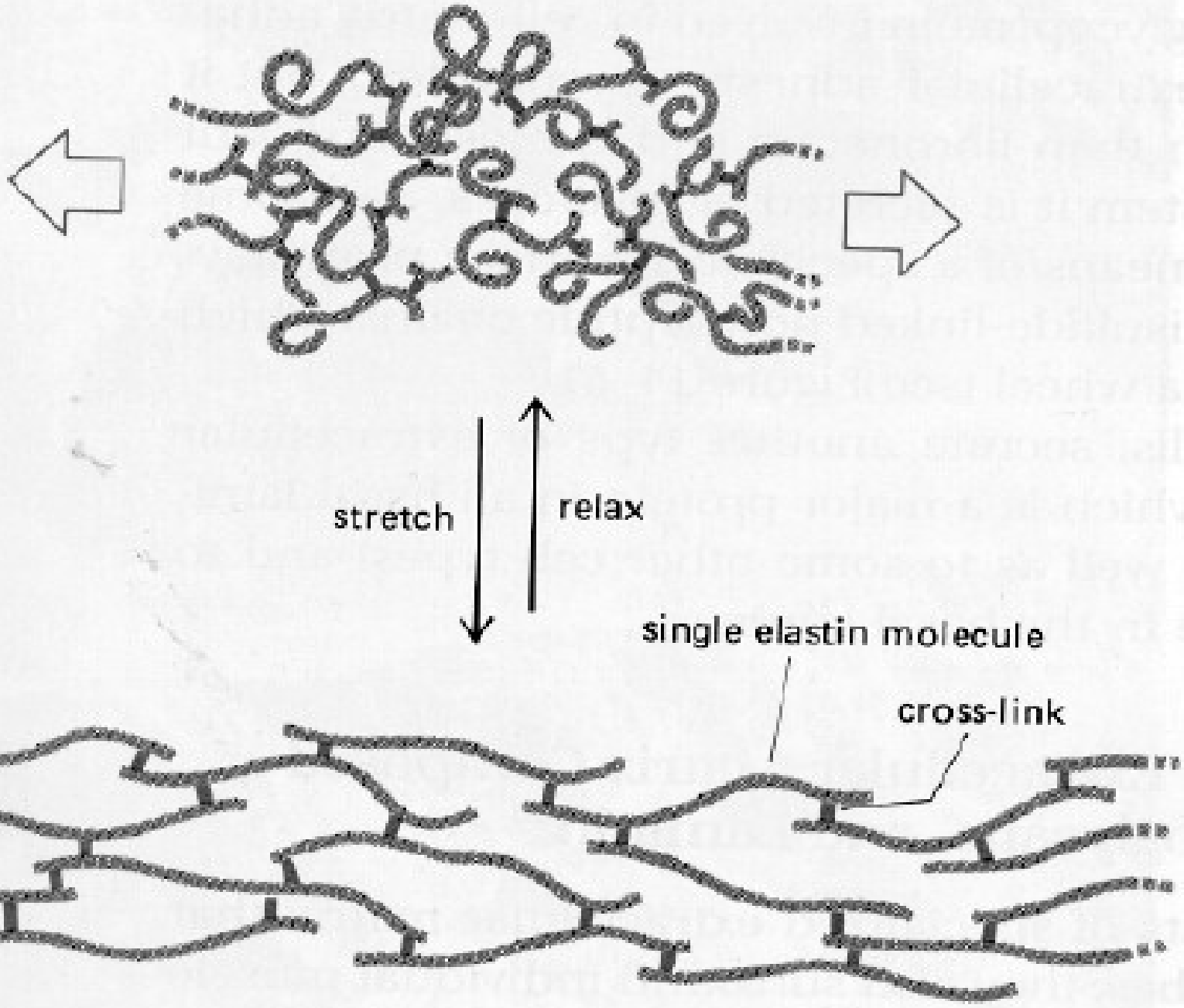
Collagen Type	Tissue Distribution
Fibrillar Collagens	
I	Ubiquitous in hard and soft tissues
II	Cartilage, intervertebral disk, vitreous
III	Hollow organs, soft tissues
V	Soft tissues, blood vessels
IX	Cartilage, vitreous
Basement Membrane Collagens	
IV	Basement membranes
Other Collagens	
VI	Ubiquitous in microfibrils
VII	Anchoring fibrils at dermal-epidermal junctions
IX	Cartilage, intervertebral disks
XVII	Transmembrane collagen in epidermal cells
XV and XVIII	Endostatin-forming collagens, endothelial cells

ELASTIN, FIBRILLIN, AND ELASTIC FIBERS

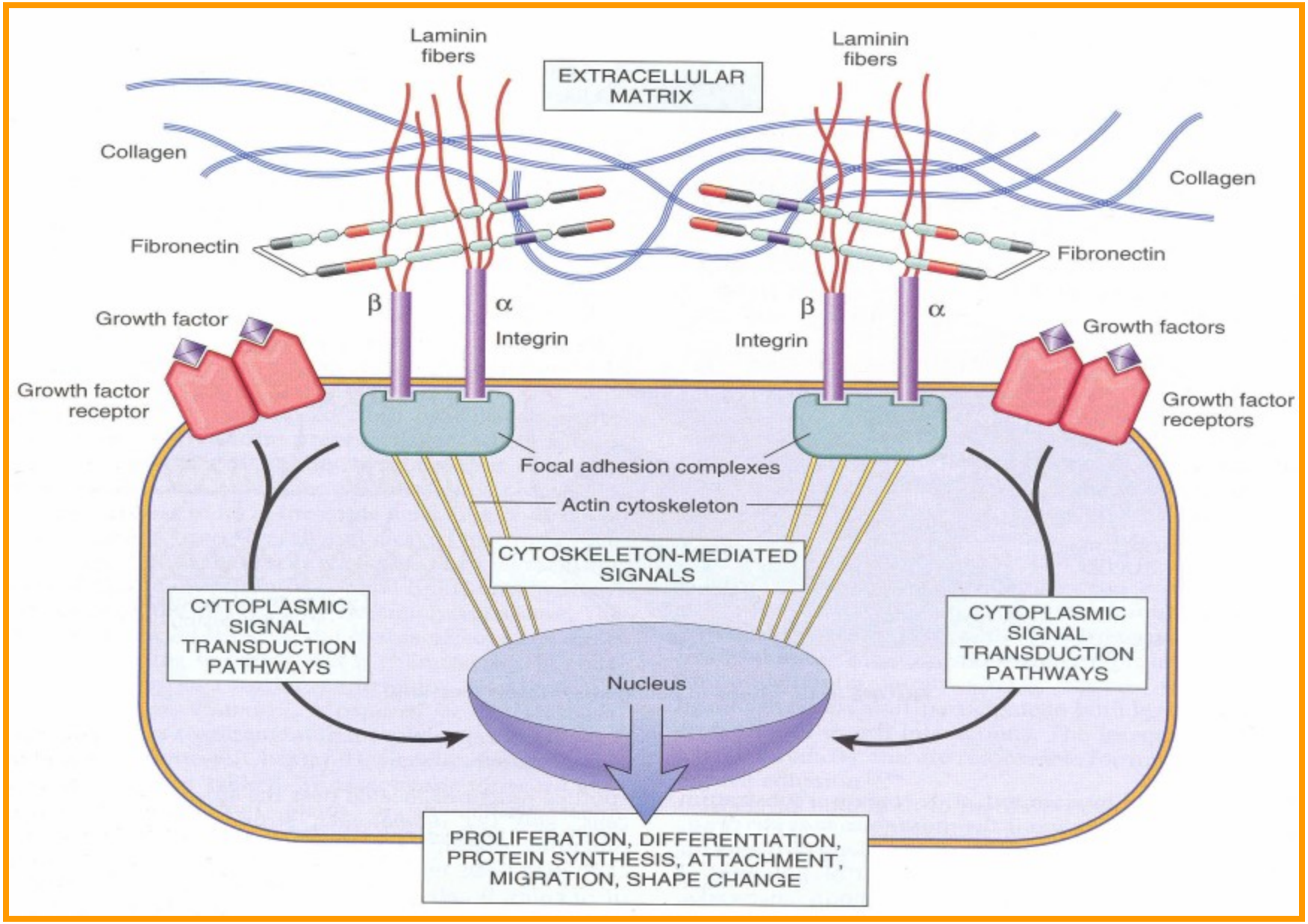


Elastic fibers




stretch
relax
single elastin molecule
cross-link

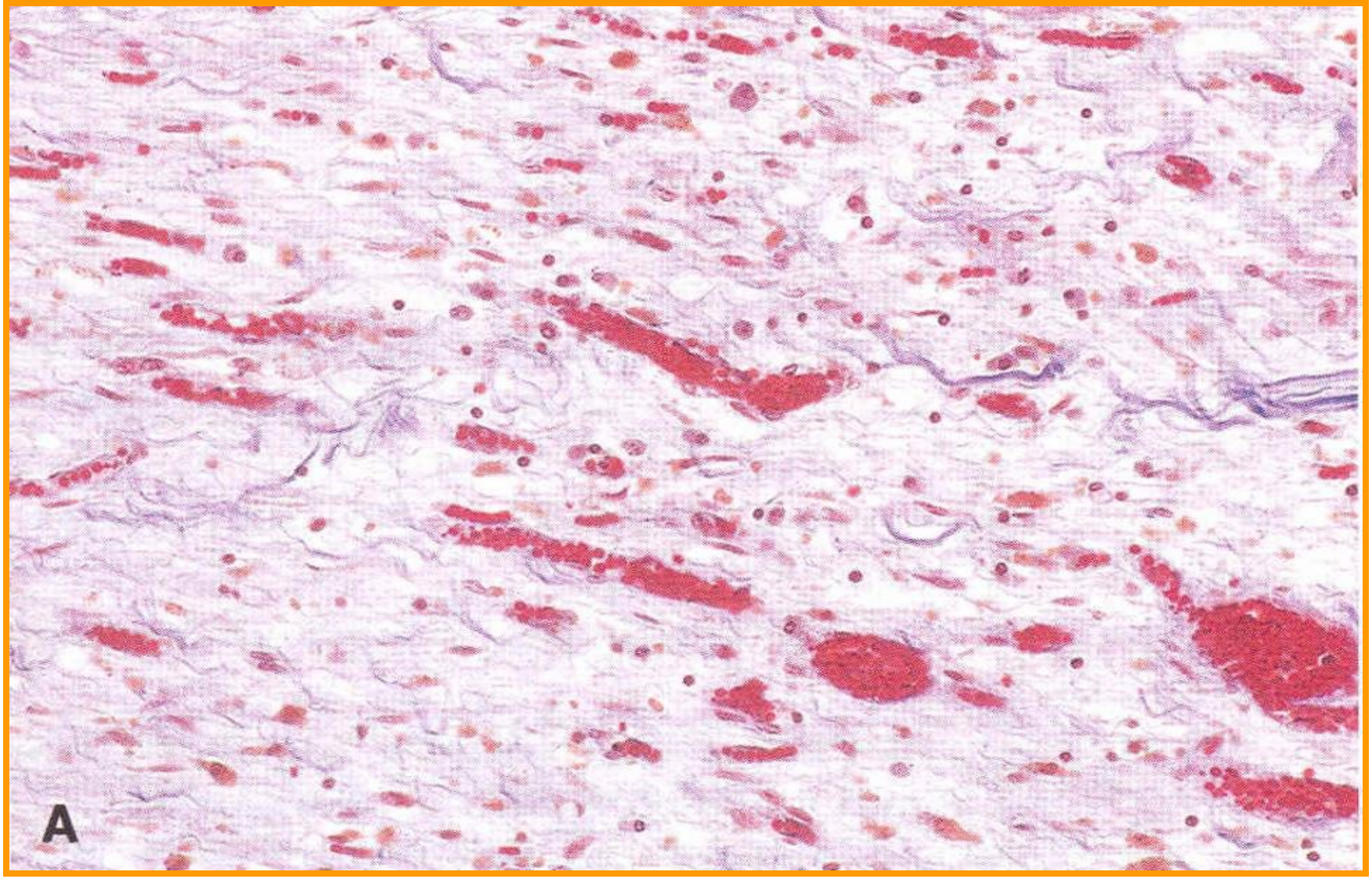
CELL ADHESION PROTEINS



Repair by Healing, Scar Formation and Fibrosis

1. inflammatory process
2. Proliferation and migration of parenchymal
3. angiogenesis and granulation tissue
4. Synthesis of ECM proteins and collagen deposition
5. Tissue remodeling
6. Wound contraction
7. Acquisition of wound strength

Granulation tissue

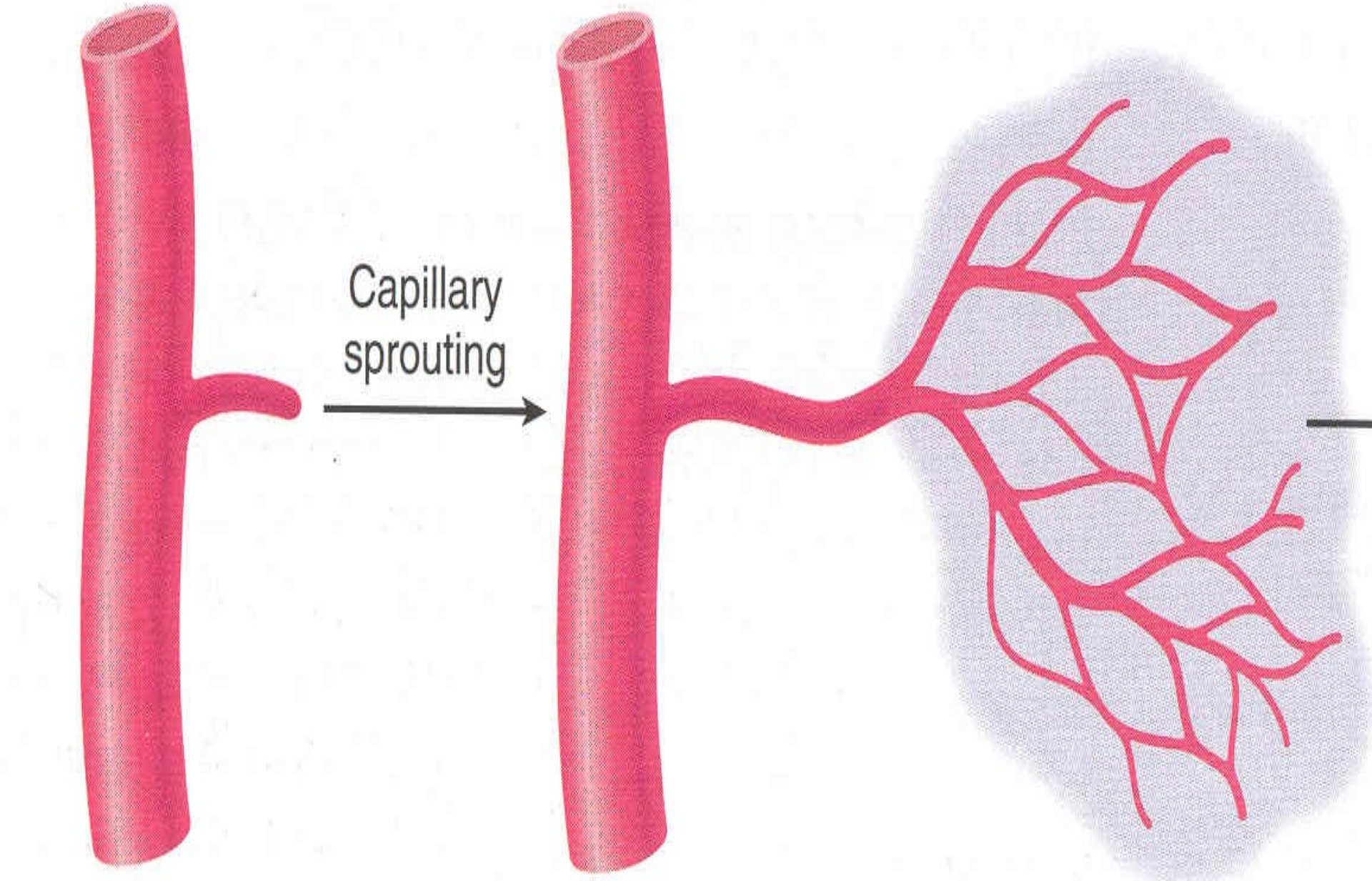


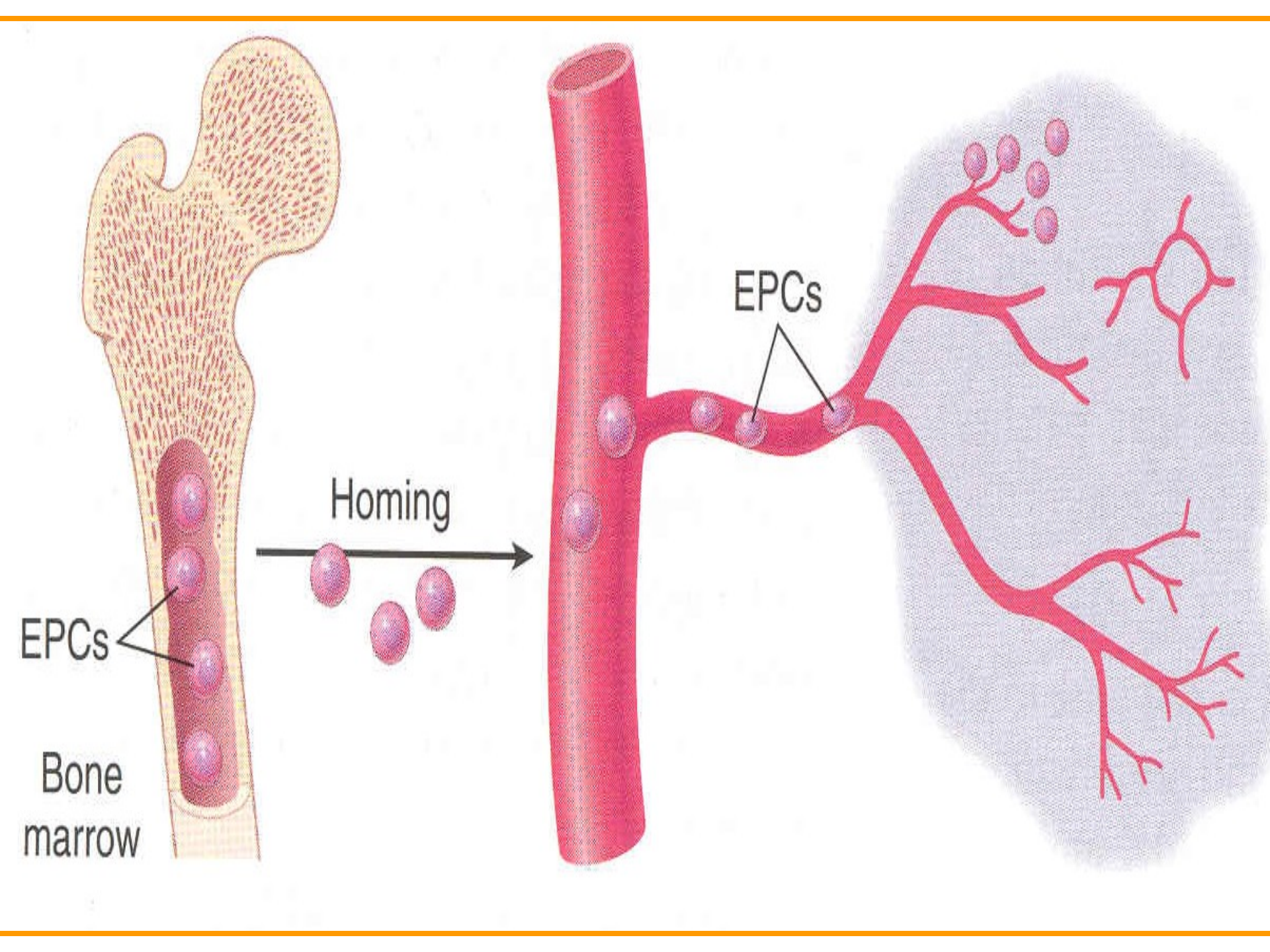
- Hallmark of healing
- The formation of new small blood vessels (angiogenesis) and the proliferation of fibroblasts
- new granulation tissue is often edematous, why?

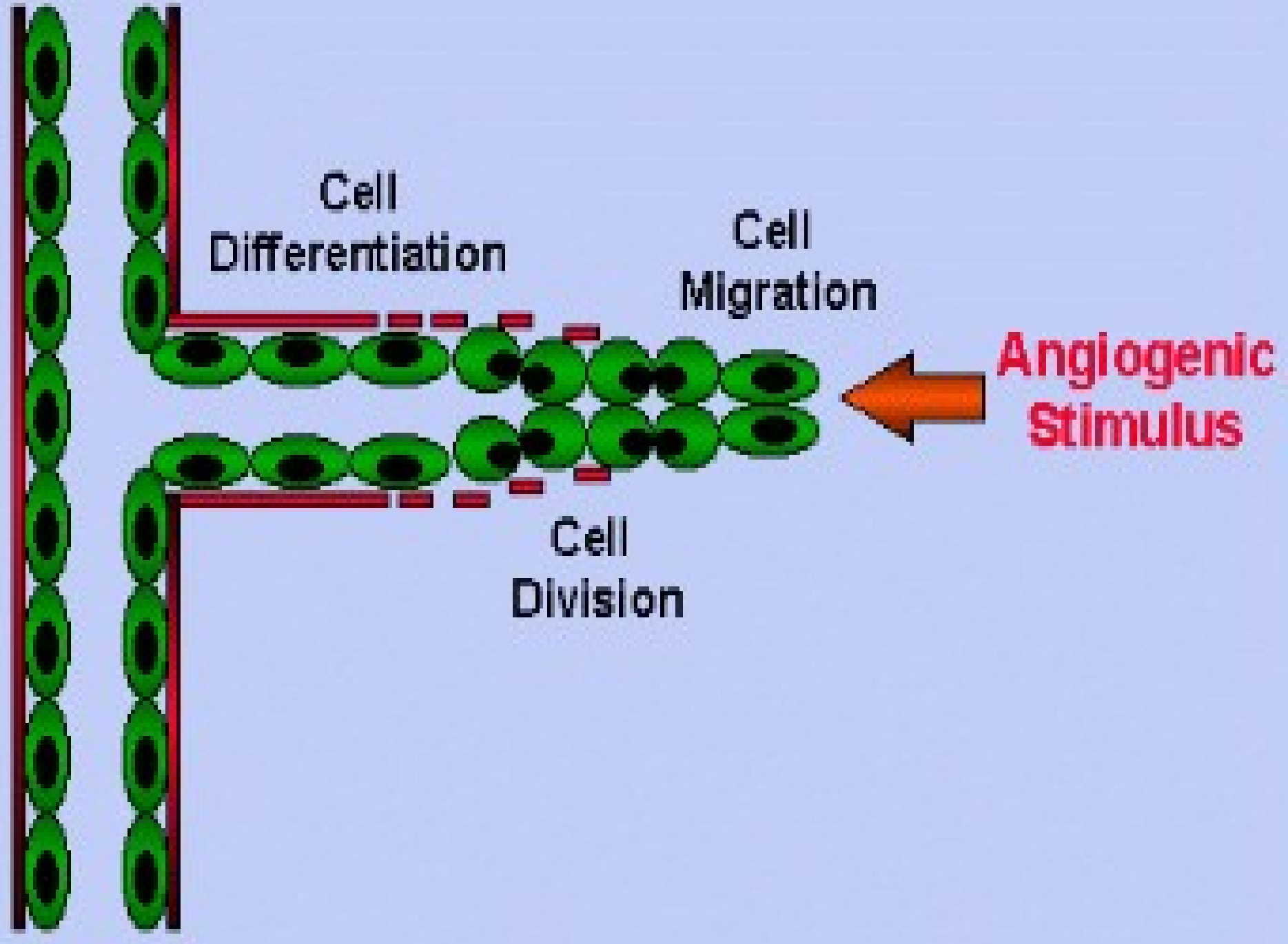
ANGIOGENESIS

- Angiogenesis & Vasculogenesis
- Angiogenesis = neovascularization :

branching and extension of adjacent blood vessels or ?

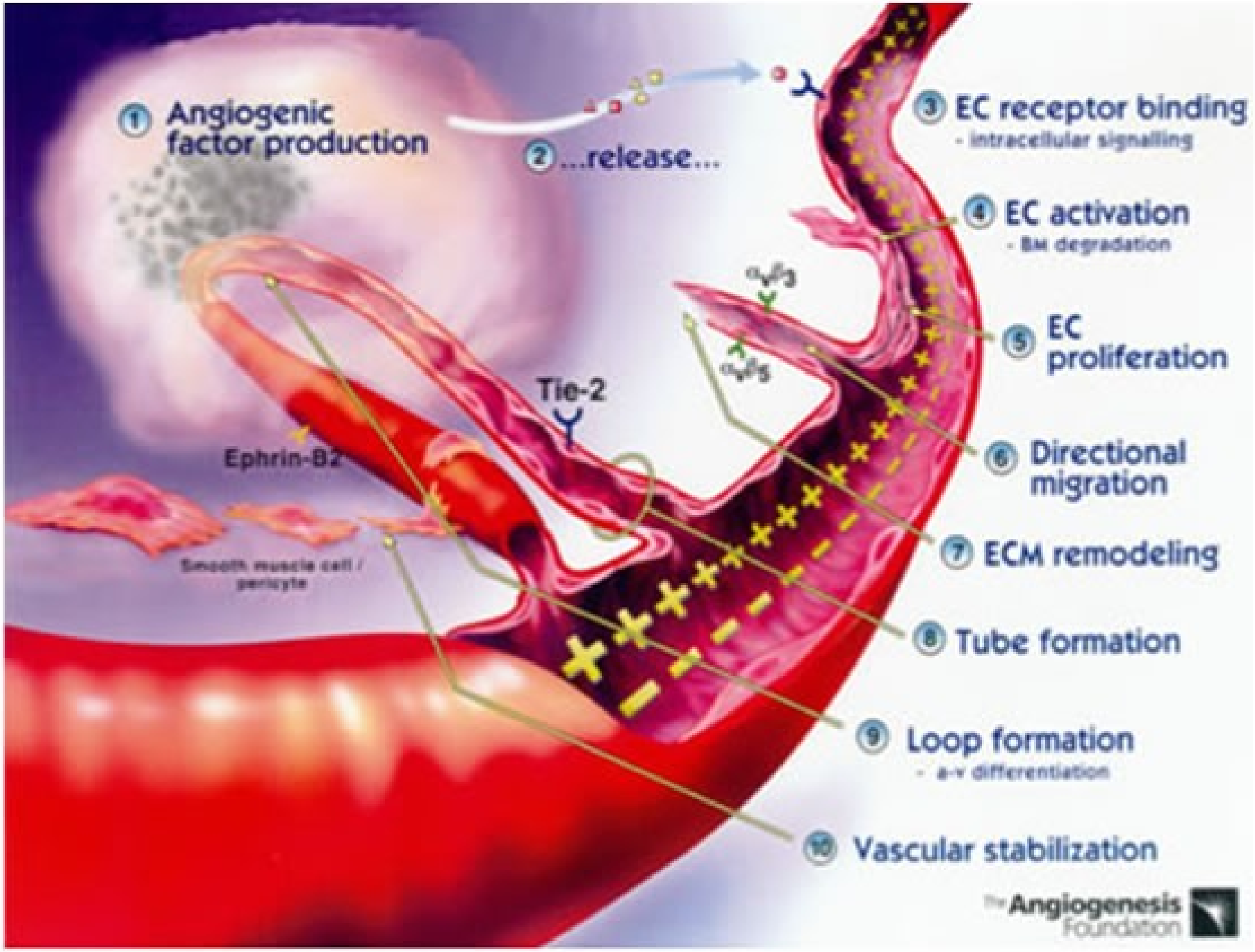

Capillary
sprouting

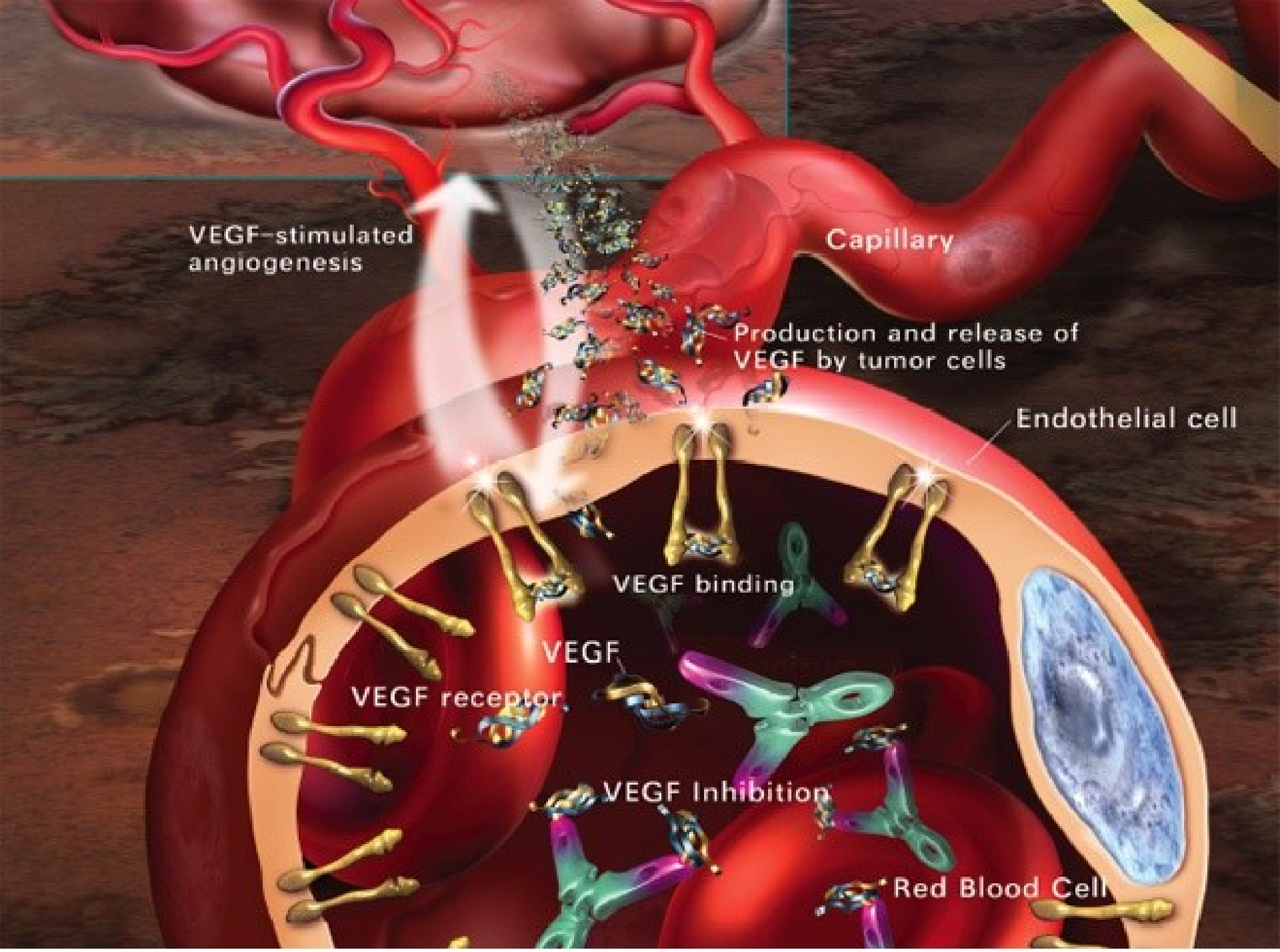

EPCs
Homing
EPCs
Bone
marrow


Cell
Differentiation
Cell
Migration
Angiogenic
Stimulus
Cell
Division

Angiogenesis from Pre-Existing Vessels

1. Vasodilation
2. Proteolytic degradation of the BM
3. Migration of endothelial cells
4. Proliferation of endothelial cells
5. Maturation of endothelial cells
6. Recruitment of periendothelial cells (including pericytes for small capillaries and vascular smooth muscle cells for larger vessels)


1 Angiogenic factor production
2 ...release...
3 EC receptor binding
- intracellular signalling
4 EC activation
- BM degradation
5 EC proliferation
6 Directional migration
7 ECM remodeling
8 Tube formation
9 Loop formation
- a-v differentiation
10 Vascular stabilization
Tie-2
Ephrin-B2
Smooth muscle cell / pericyte
The Angiogenesis Foundation


VEGF-stimulated
angiogenesis
Capillary
Production and release of
VEGF by tumor cells
Endothelial cell
VEGF binding
VEGF
VEGF receptor
VEGF Inhibition
Red Blood Cell

Angiogenesis

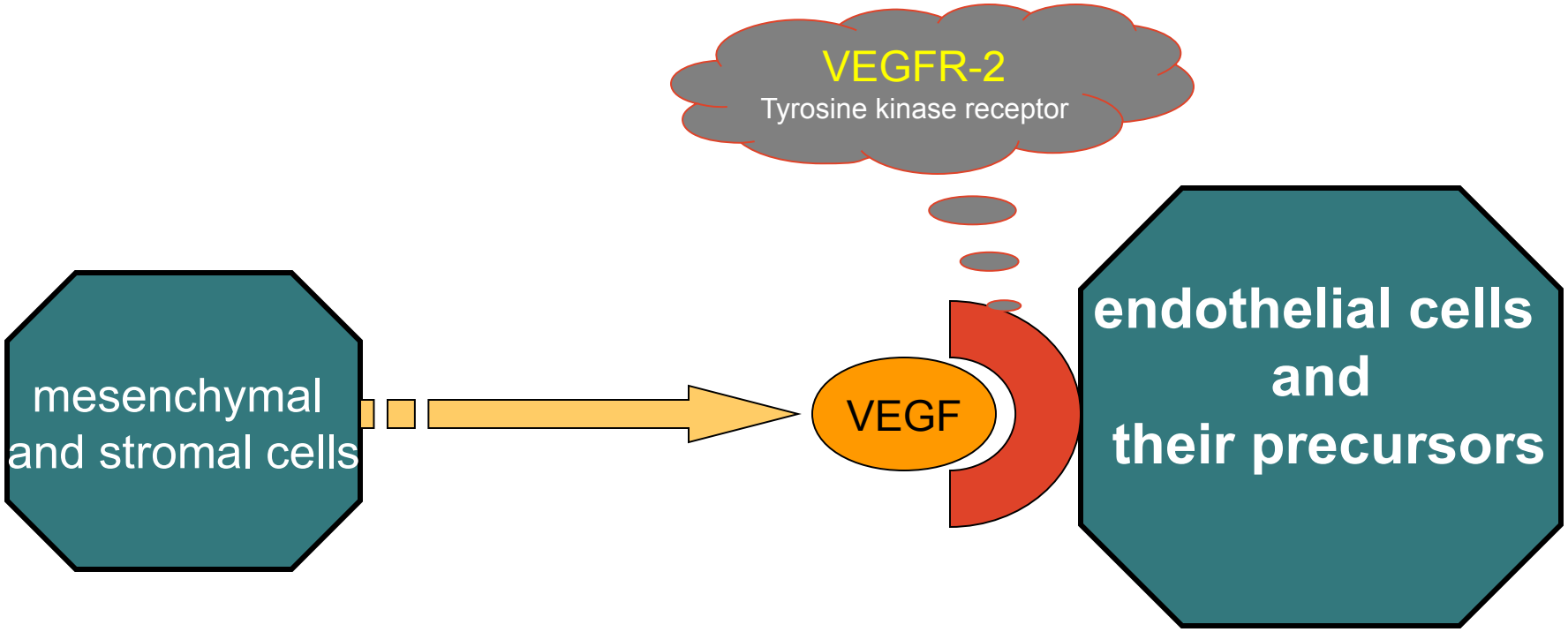
is critical to

1. chronic inflammation
2. fibrosis
3. tumor growth
4. vascularization of ischemic tissues

Growth Factors and Receptors Involved in Angiogenesis

- Many growth factors exhibit angiogenic activity

VEGF & Angiopoietins



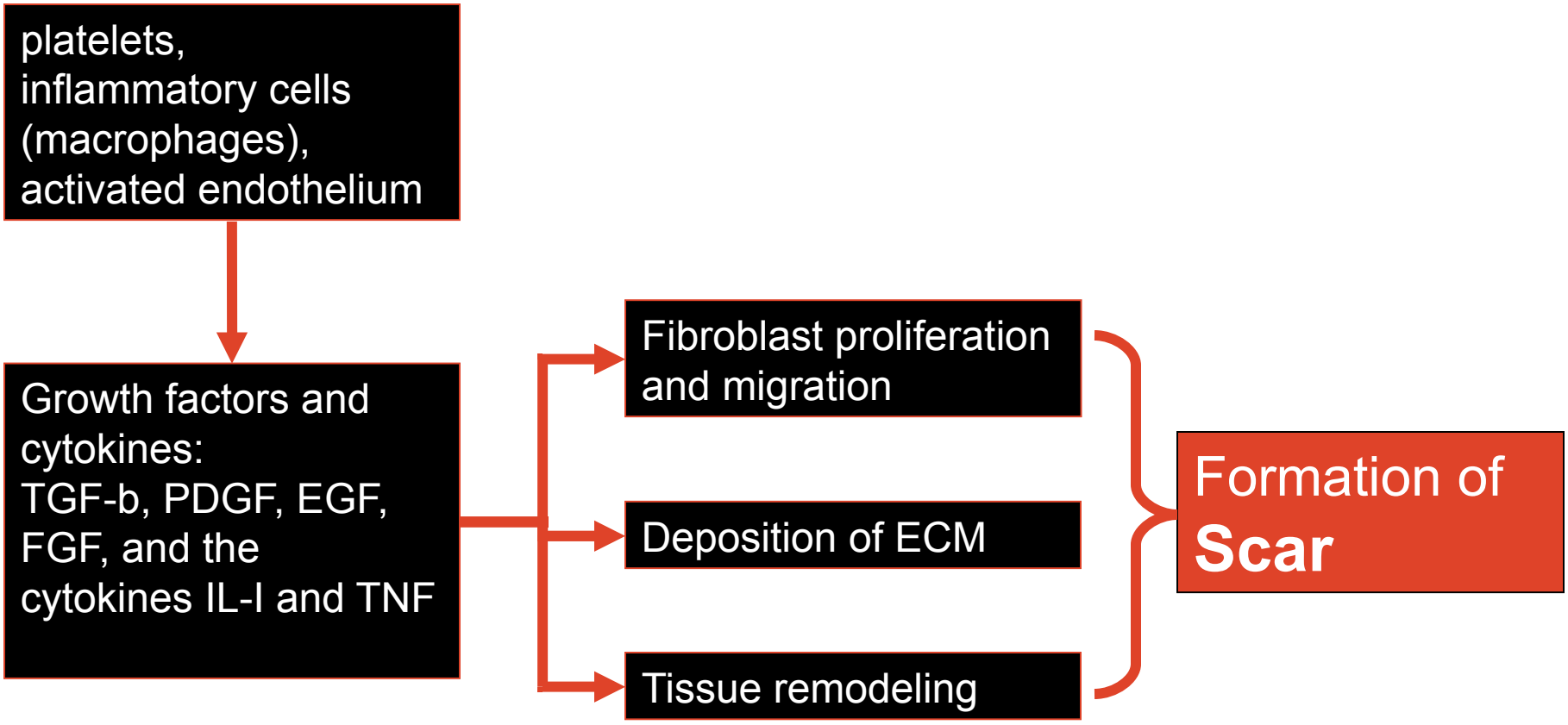
Angiogenesis from Endothelial Precursor Cells:
mobilization of endothelial cell precursors from the bone marrow and enhances the proliferation and differentiation of these cells

Angiogenesis from Pre-Existing Vessels:
VEGF stimulates both proliferation and motility of endothelial cells, thus initiating the sprouting of new capillary

Stabilization process

- Recruitment of pericytes and smooth muscle cells and the deposition of ECM proteins
- Angiopoietins 1 and 2, PDGF, TGF-b

SCAR FORMATION

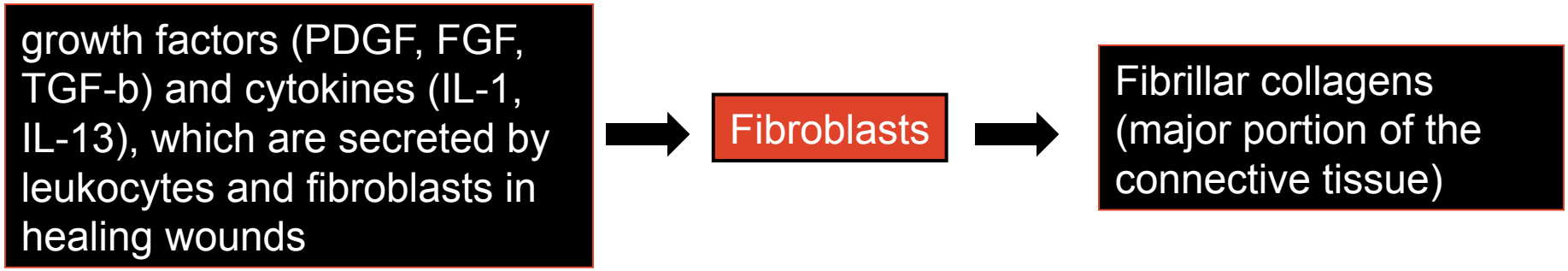


TGF-β

the most important because of the multitude of effects that favor fibrous tissue deposition

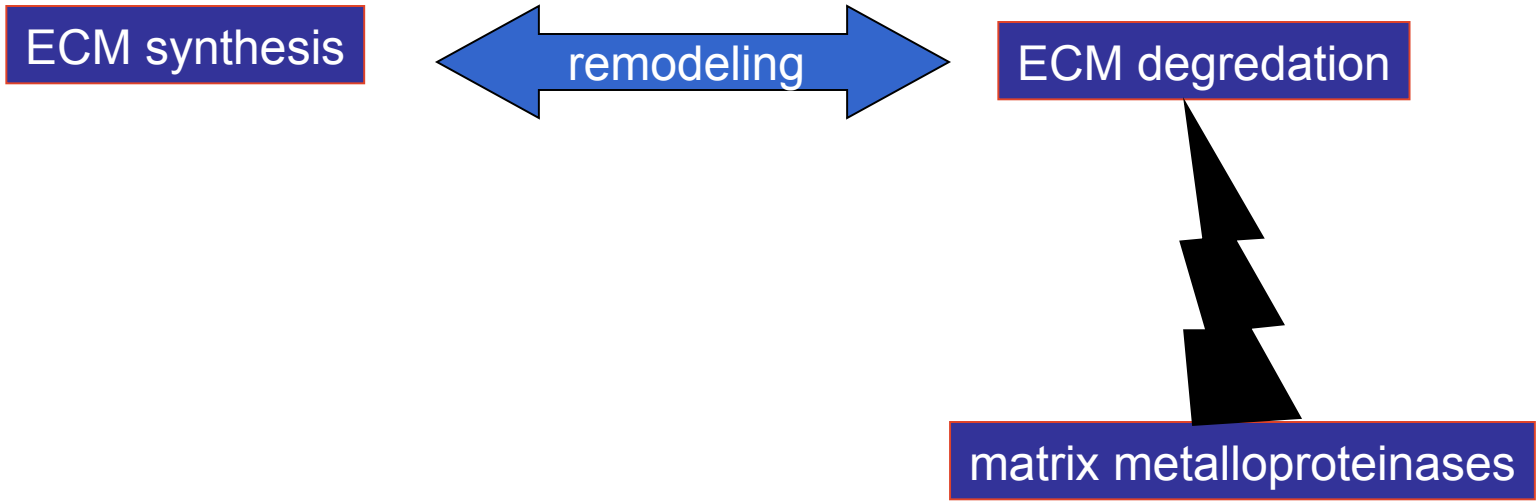
- causes fibroblast migration
- proliferation
- increased synthesis of collagen and fibronectin
- decreased degradation of ECM by metalloproteinases
- chemotactic for monocytes and causes angiogenesis

ECM Deposition and Scar Formation

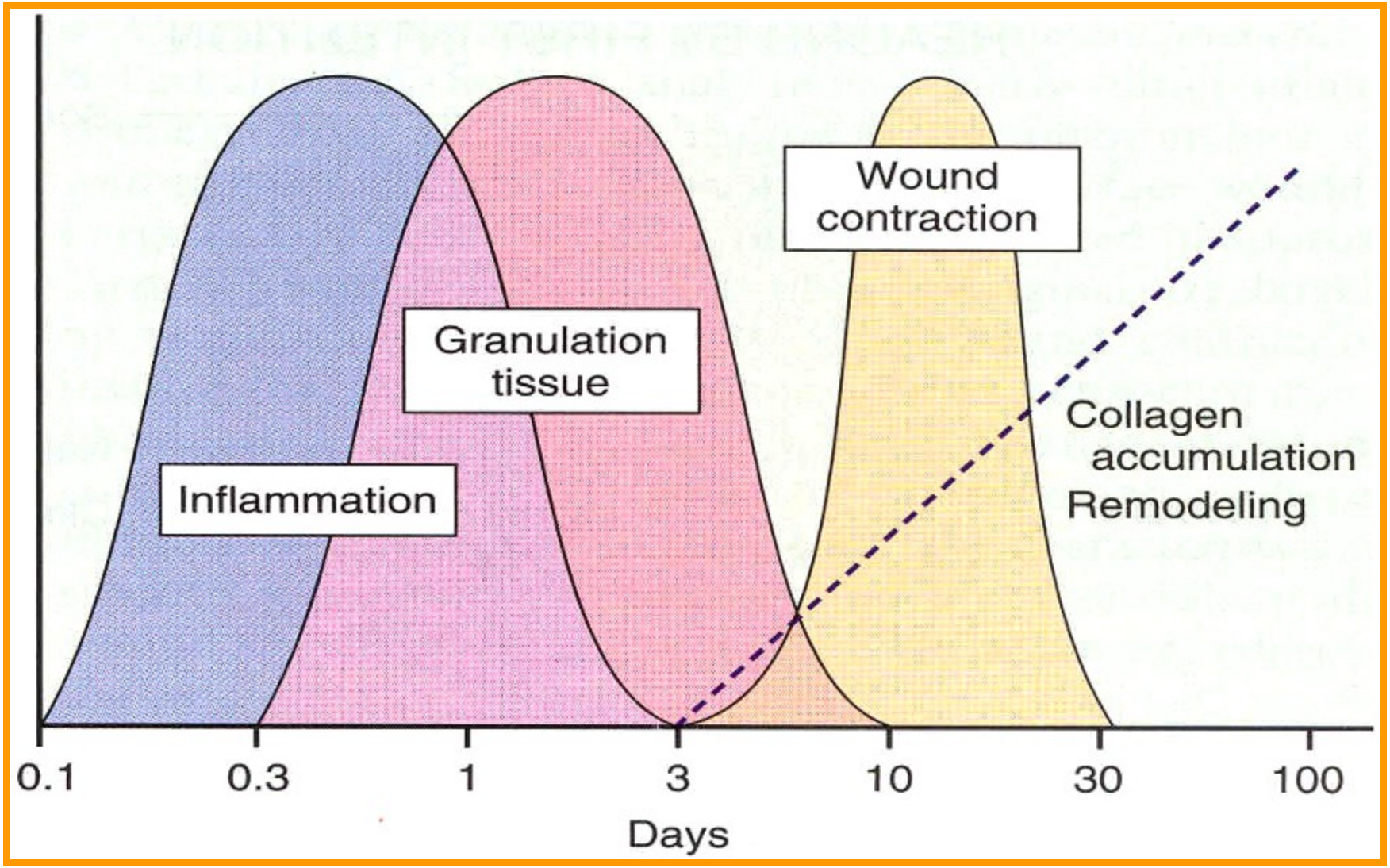


Tissue Remodeling

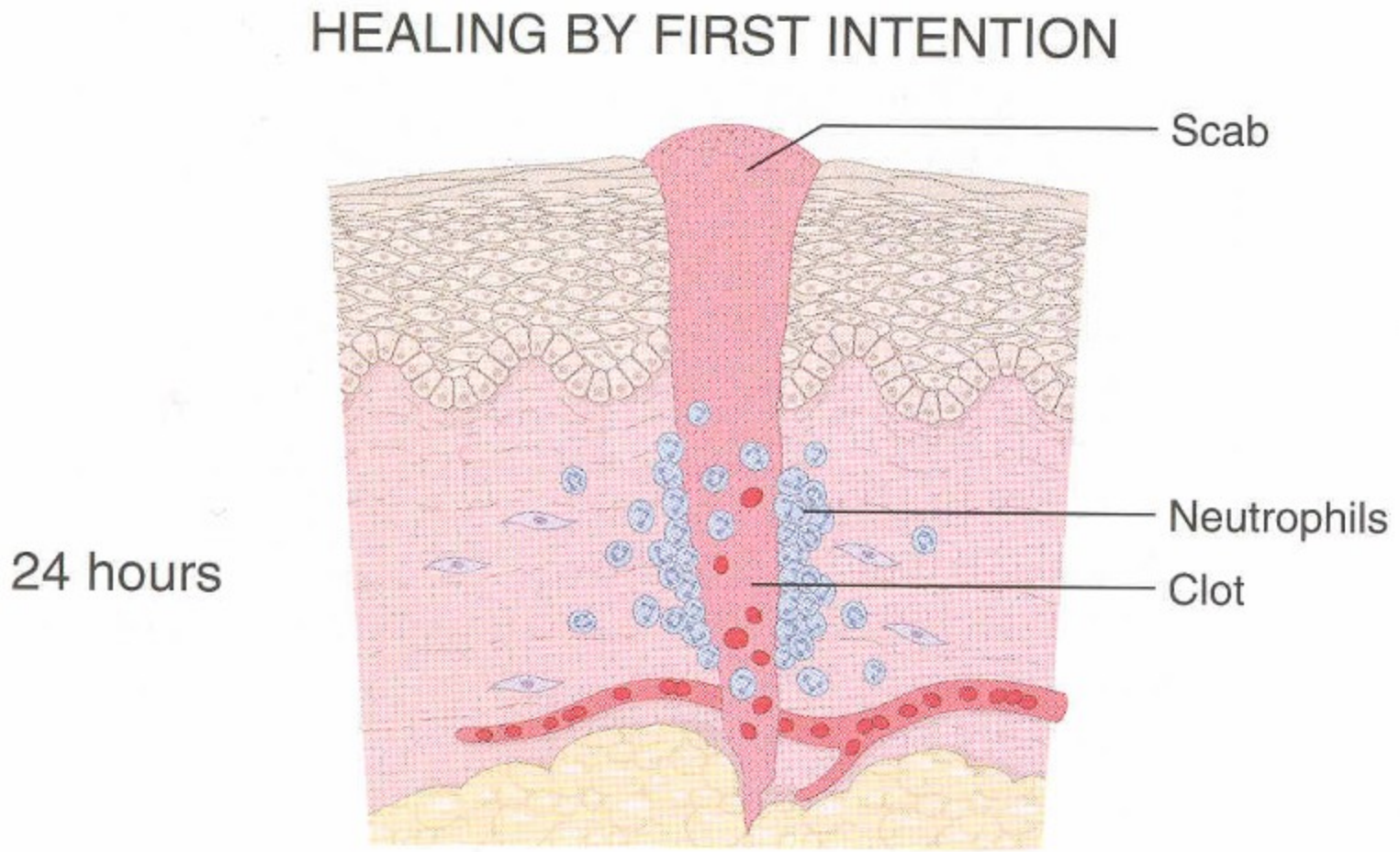
replacement of granulation tissue with a scar



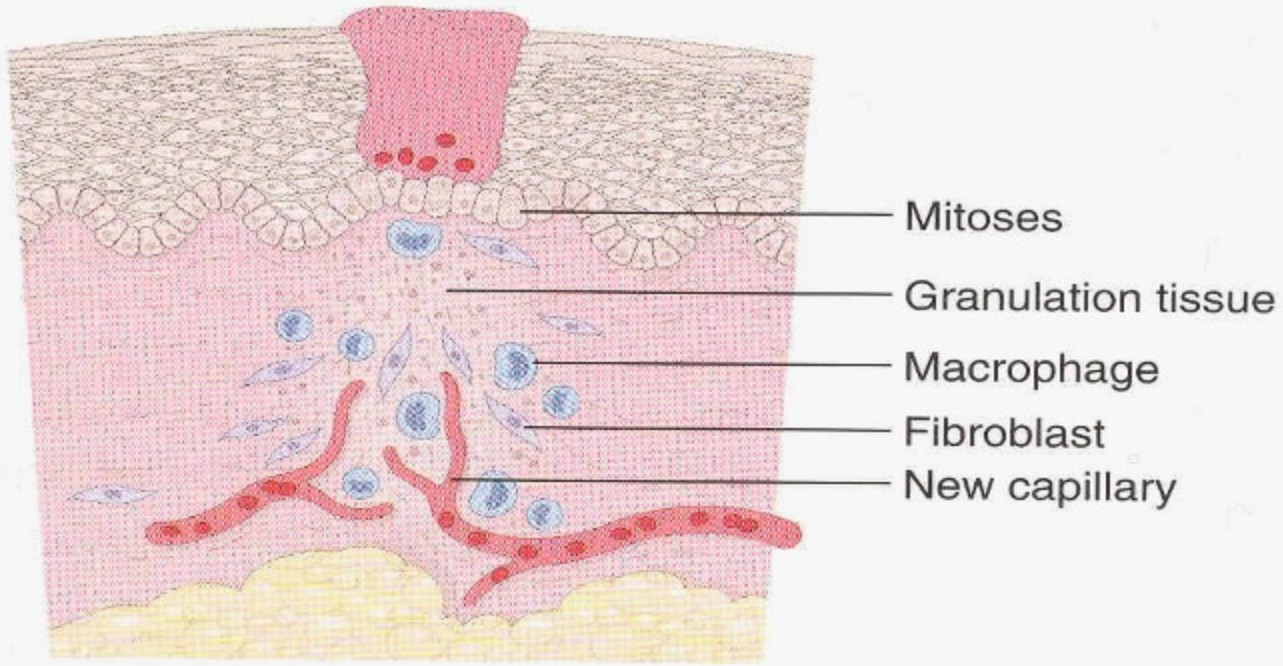
Cutaneous Wound Healing



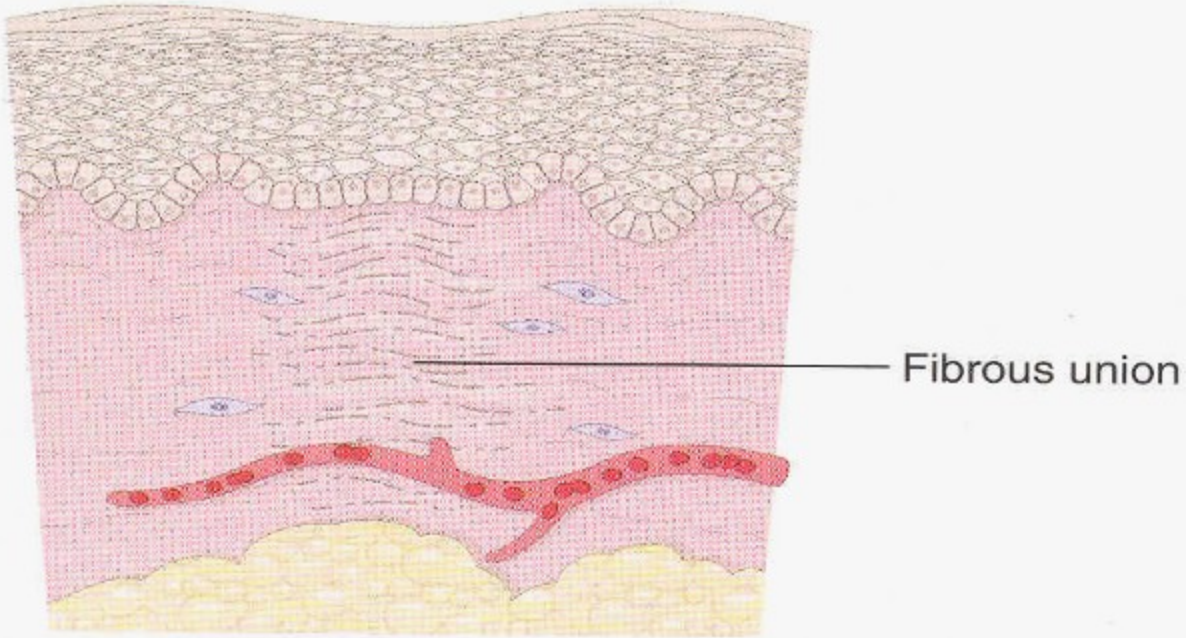
HEALING BY FIRST INTENTION (WOUNDS WITH OPPOSED EDGES)



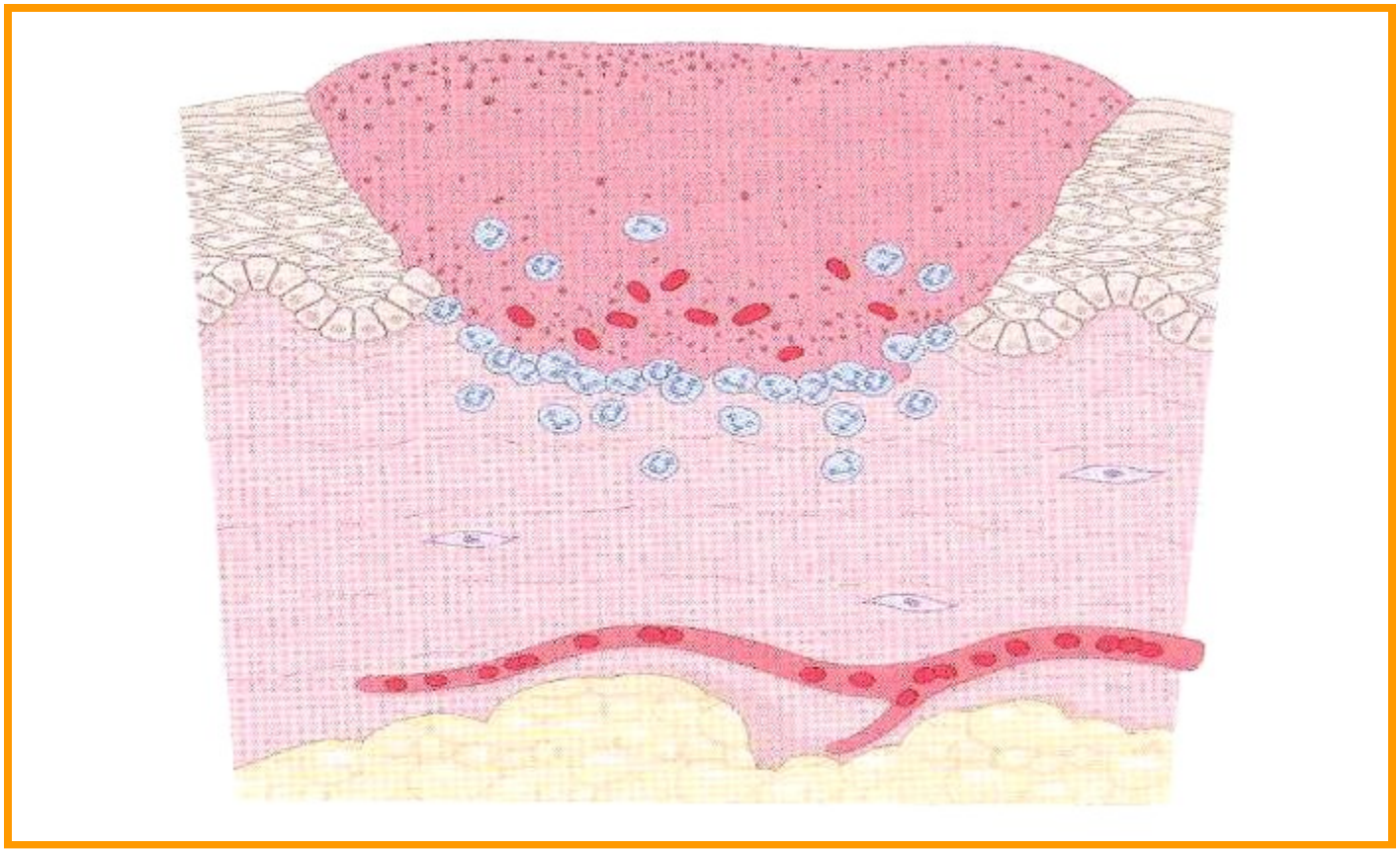
3 to 7 days

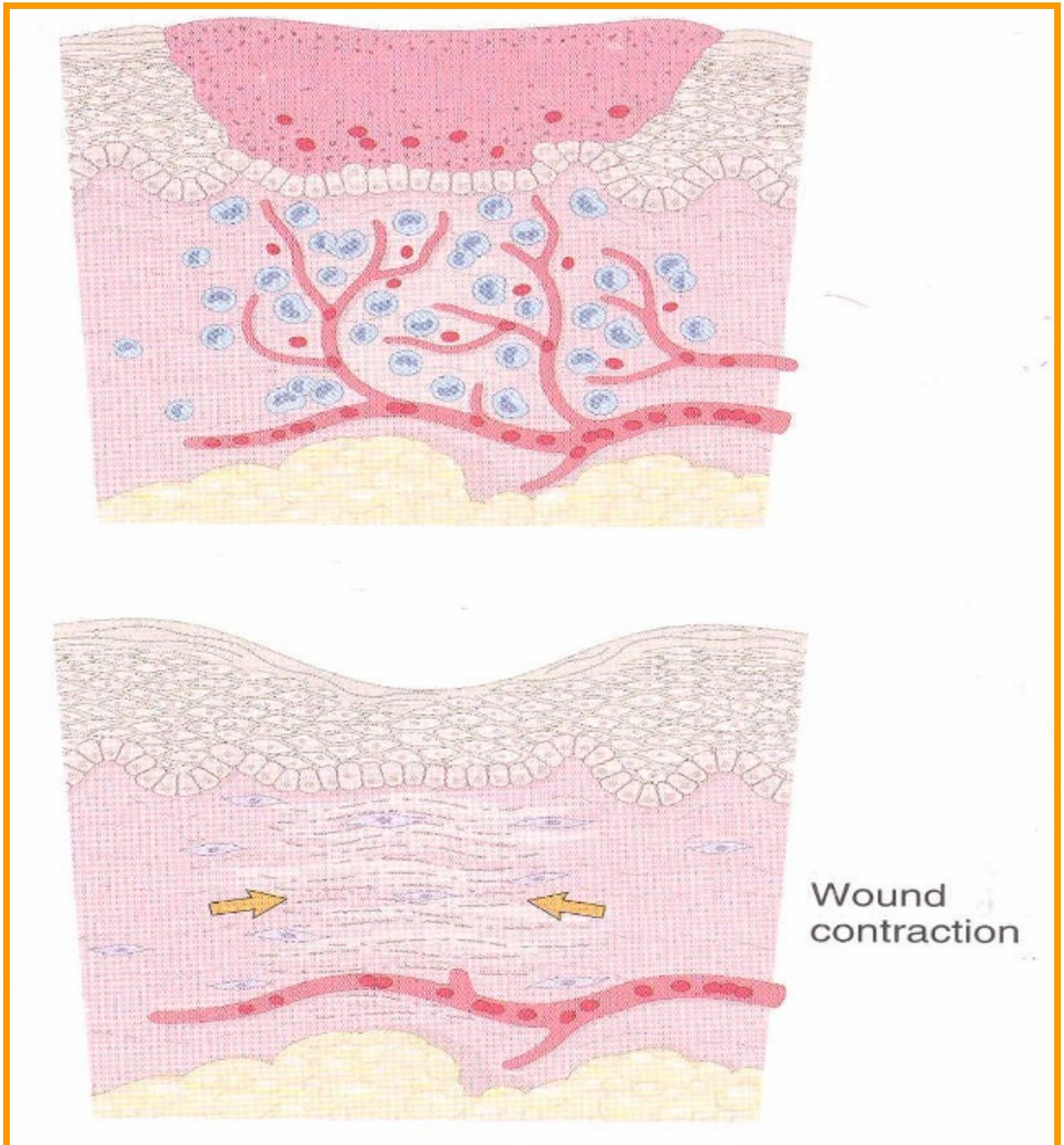


Weeks



HEALING BY SECOND INTENTION (WOUNDS WITH SEPARATED EDGES)




Wound
contraction

WOUND STRENGTH

first week= 10% → **third month=70-80%** → **…**

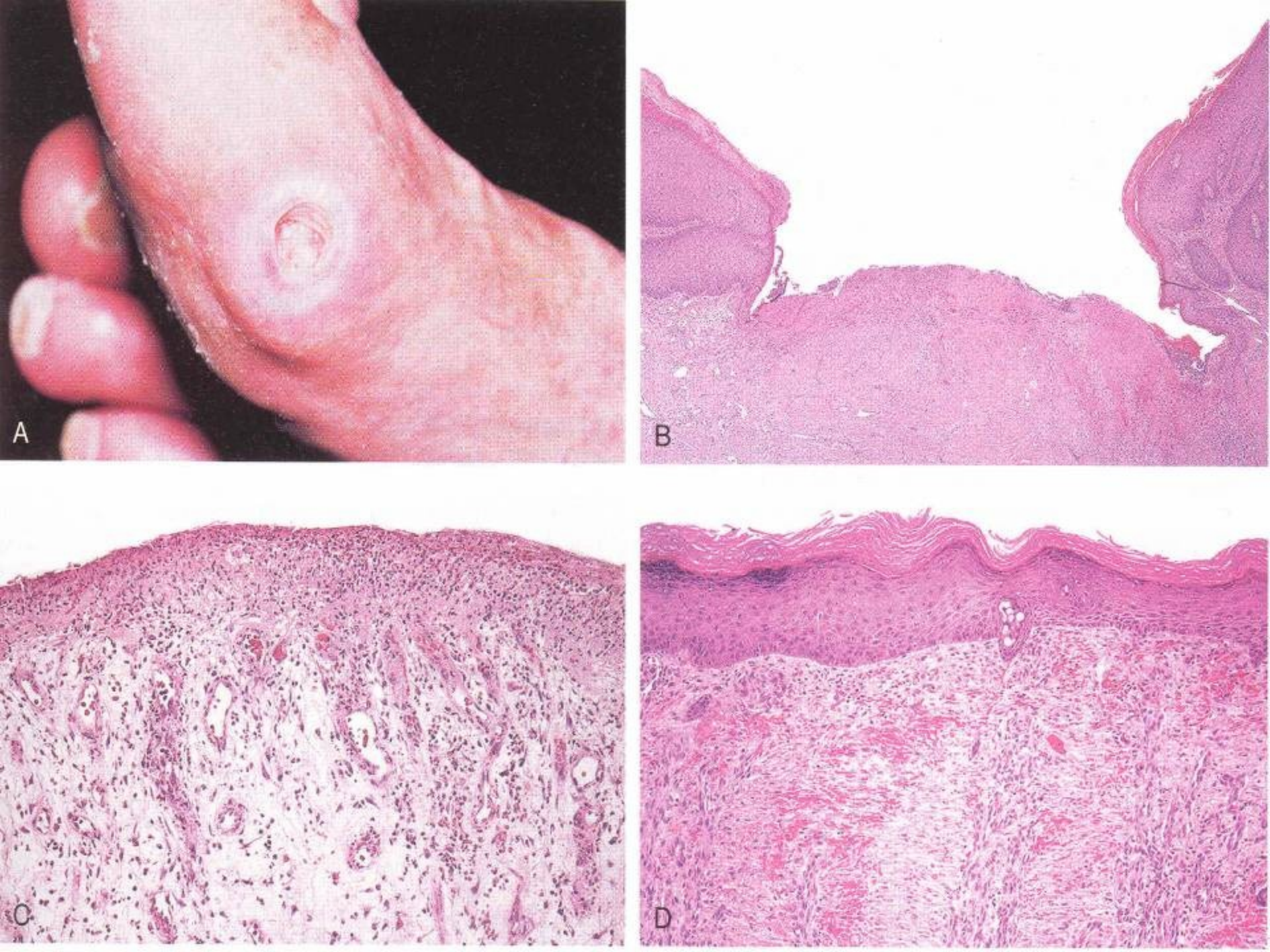

A
B
C
D

TABLE 3–5 Factors That Retard Wound Healing

Local Factors	
Blood supply	Mechanical stress
Denervation	Necrotic tissue
Local infection	Protection (dressings)
Foreign body	Surgical techniques
Hematoma	Type of tissue
Systemic Factors	
Age	Malnutrition
Anemia	Obesity
Drugs (steroids, cytotoxic medications, intensive antibiotic therapy)	Systemic infection
	Temperature
	Trauma, hypovolemia, and hypoxia
Genetic disorders (osteogenesis imperfecta, Ehlers-Danlos syndromes, Marfan syndrome)	Uremia
	Vitamin deficiency (vitamin C)
Hormones	Trace metal deficiency (zinc, copper)
Diabetes	
Malignant disease	

Adapted from Schwartz SI: Principles of Surgery. New York, McGraw Hill, 1999.

COMPLICATIONS IN CUTANEOUS WOUND HEALING

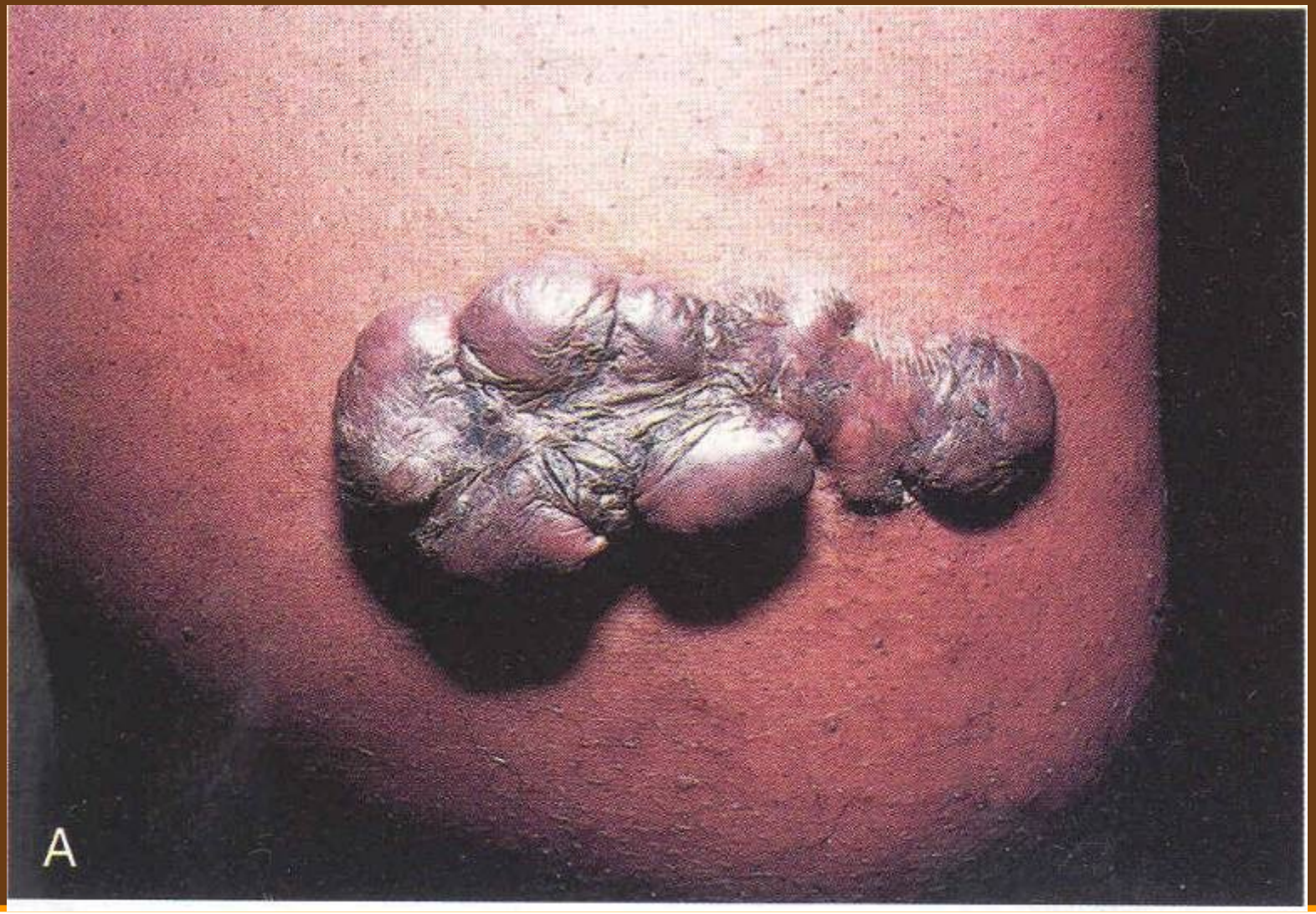
(1) Deficient scar formation

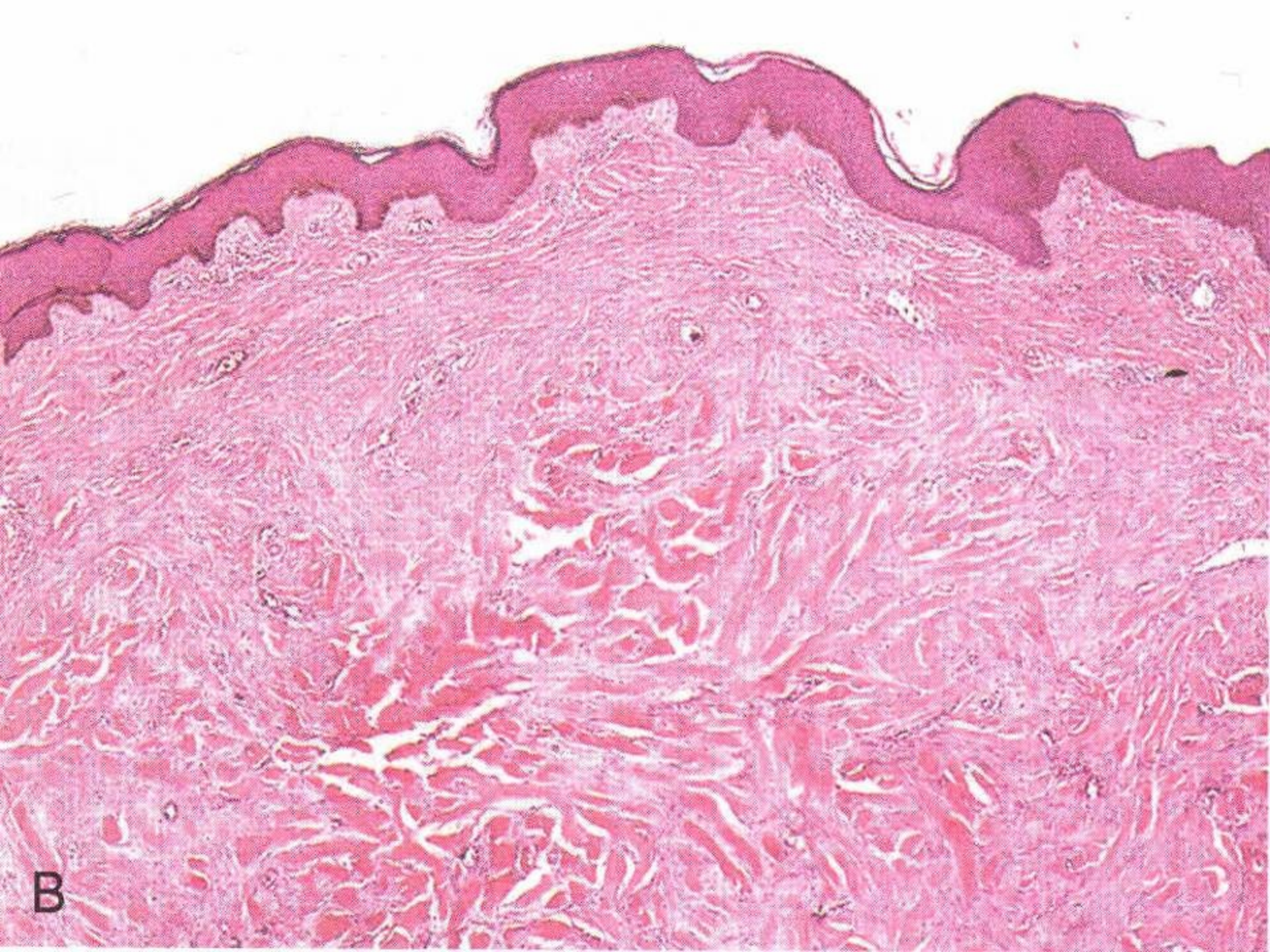
- Dehiscence
- Ulceration

(2) Excessive formation of the repair components

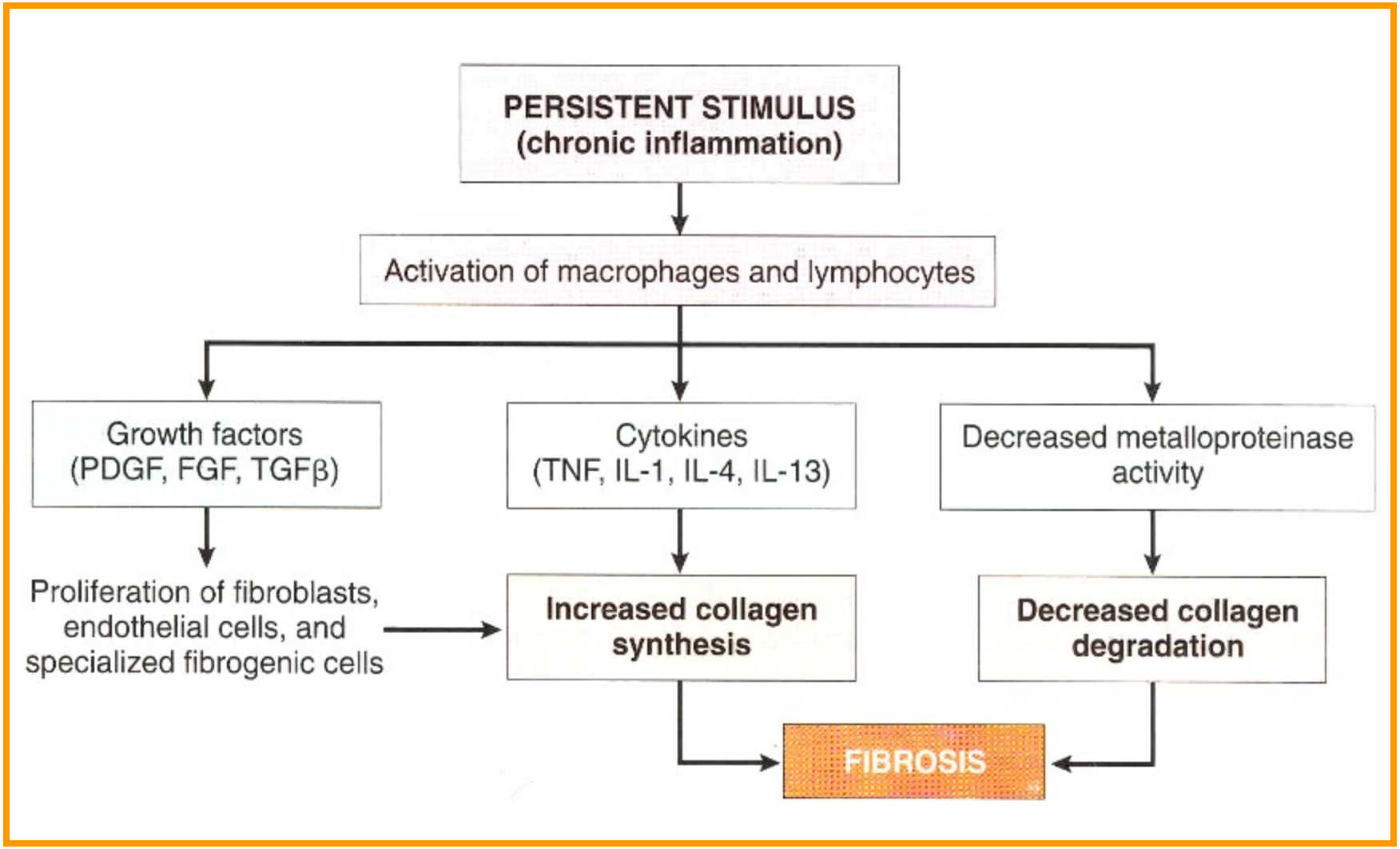
(3) Formation of contractures

hypertrophic scar & keloid

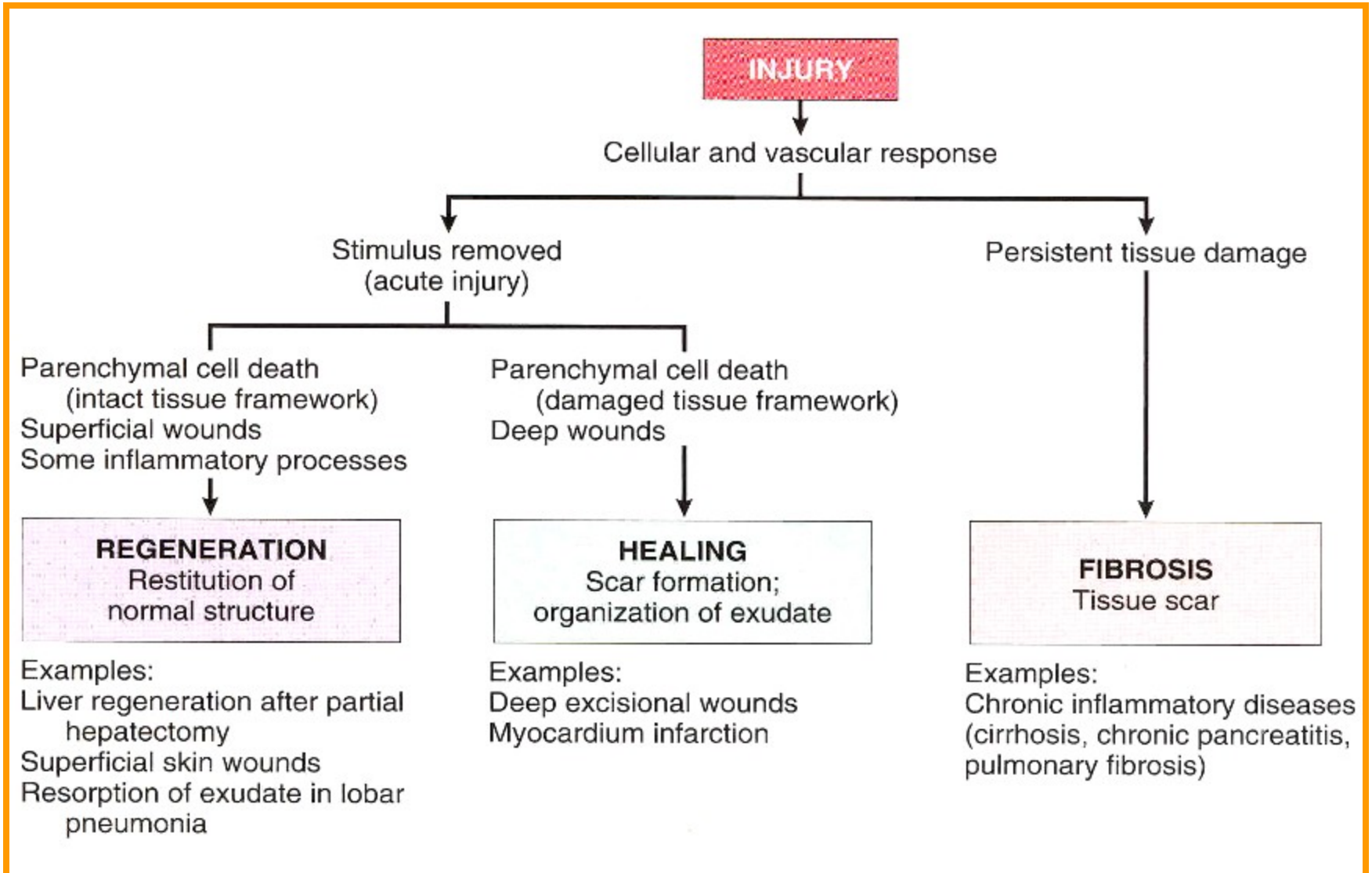


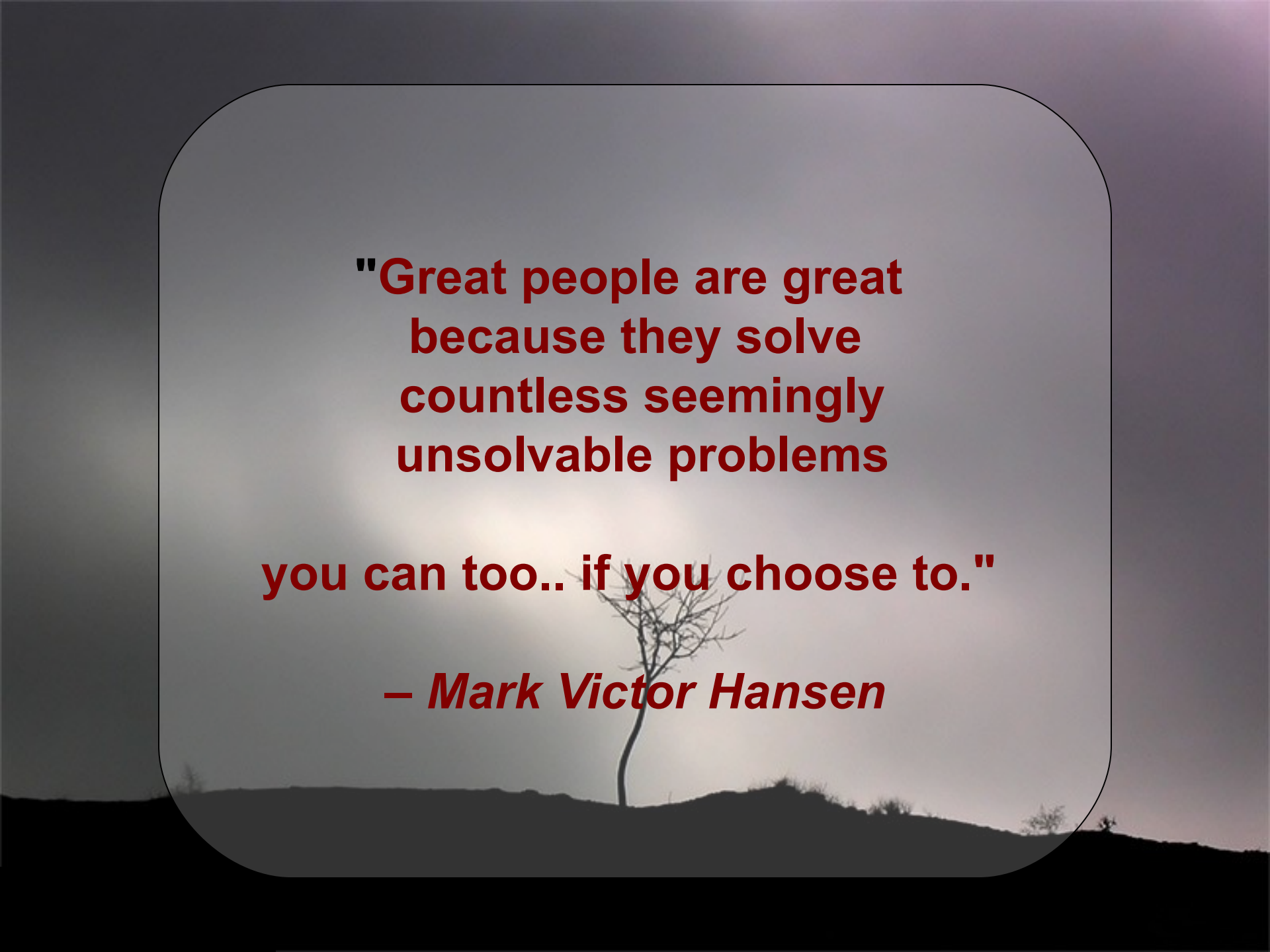

B

Fibrosis


PERSISTENT STIMULUS
(chronic inflammation)
Activation of macrophages and lymphocytes
Growth factors
(PDGF, FGF, TGFβ)
Cytokines
(TNF, IL-1, IL-4, IL-13)
Decreased metalloproteinase
activity
Proliferation of fibroblasts,
endothelial cells, and
specialized fibrogenic cells
Increased collagen
synthesis
Decreased collagen
degradation
FIBROSIS

Overview


INJURY
Cellular and vascular response
Stimulus removed (acute injury)
Persistent tissue damage
Parenchymal cell death (intact tissue framework)
Superficial wounds
Some inflammatory processes
Parenchymal cell death (damaged tissue framework)
Deep wounds
REGENERATION
Restitution of normal structure
HEALING
Scar formation; organization of exudate
FIBROSIS
Tissue scar
Examples:
Liver regeneration after partial hepatectomy
Superficial skin wounds
Resorption of exudate in lobar pneumonia
Examples:
Deep excisional wounds
Myocardium infarction
Examples:
Chronic inflammatory diseases (cirrhosis, chronic pancreatitis, pulmonary fibrosis)


"Great people are great
because they solve
countless seemingly
unsolvable problems
you can too.. if you choose to."
– Mark Victor Hansen