

CONNECTIVE TISSUE PROPER

FUNCTION OF CONNECTIVE TISSUE

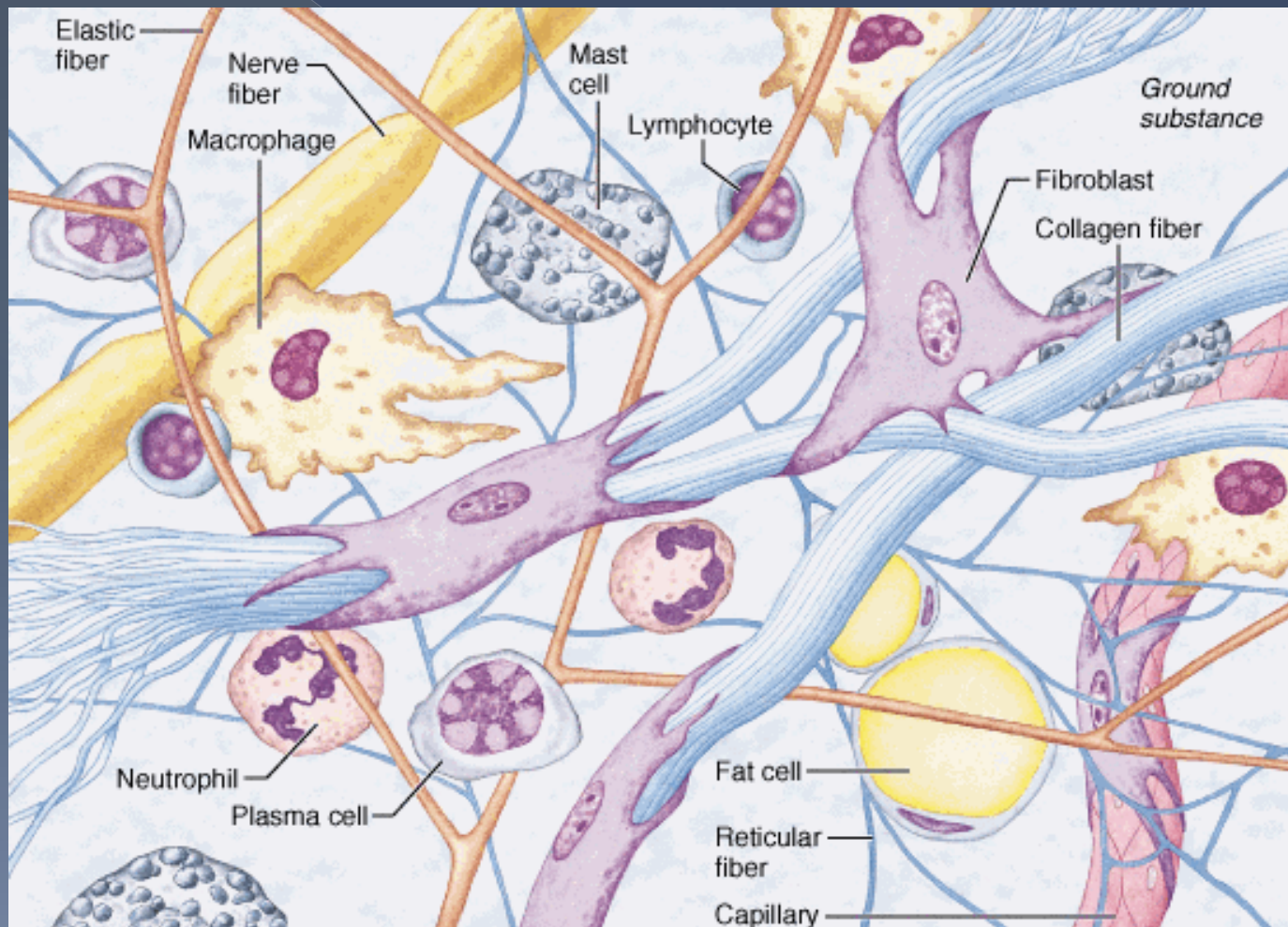
- maintaining an integrity of the body by forming a continuum with the other tissues (epithelial tissue, muscle, nervous tissue) and with other elements of connective tissues.
- providing structural support
- serving as a medium for substance exchange
- forming a site for storage of fat

Connective tissue is classified as connective tissue proper, embryonic connective tissue and specialized connective tissue (cartilage, bone, blood)

Connective tissue proper - cells

Fixed cells: fibroblasts, adipose cells, histiocytes (macrophages), mast cells, pericytes.

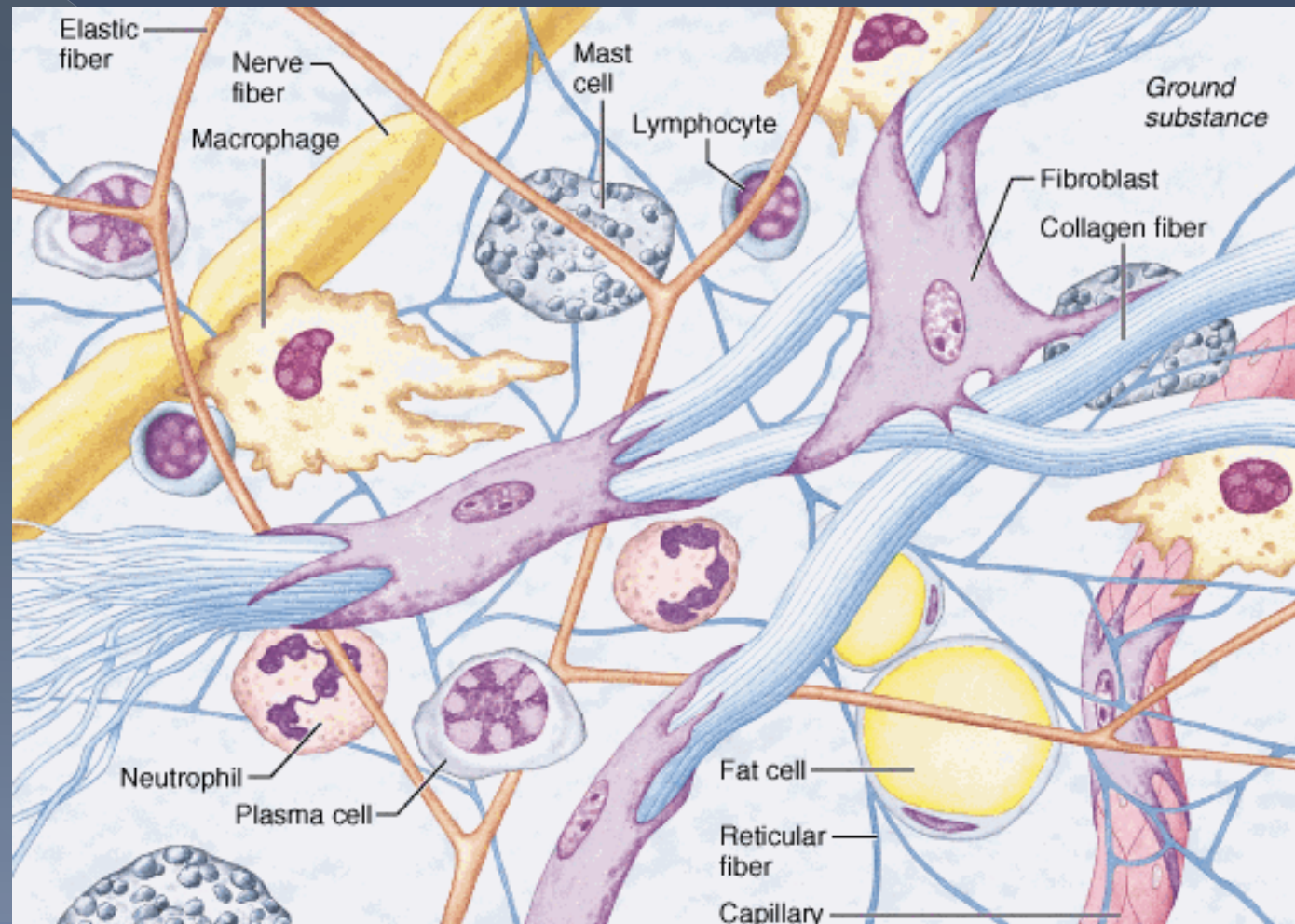
Transient cells: plasma cells, migratory leukocytes, macrophages



Connective tissue proper - extracellular matrix (ECM)

Fibers: collagen fibers (type I), reticular fibers (type III), elastic fibers

Ground substance: glycosaminoglycans, proteoglycans, glycoproteins

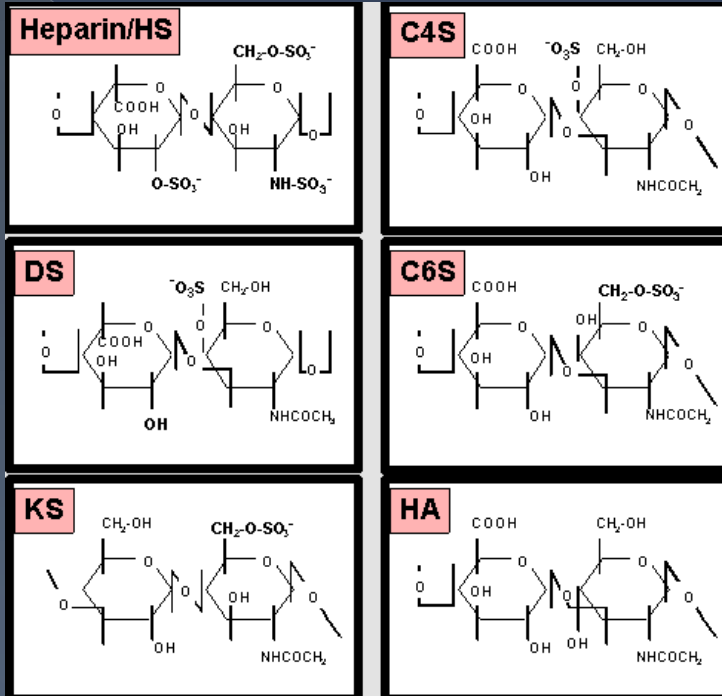


GROUND SUBSTANCE

amorphous gel-like material composed of glycosaminoglycans (GAGs), proteoglycans and glycoproteins.

GLYCOSAMINOGLYCANS – negatively charged, long unbranched polysaccharides consisting of repeating disaccharide units. The repeating unit usually consists of an amino sugar (N-acetylglucosamine or N-acetylgalactosamine) and a uronic sugar (glucuronic acid or iduronic acid) or galactose.

GAGs



SULFATED GAGS:

keratan sulfate KS
heparan sulfate HS
heparin HS

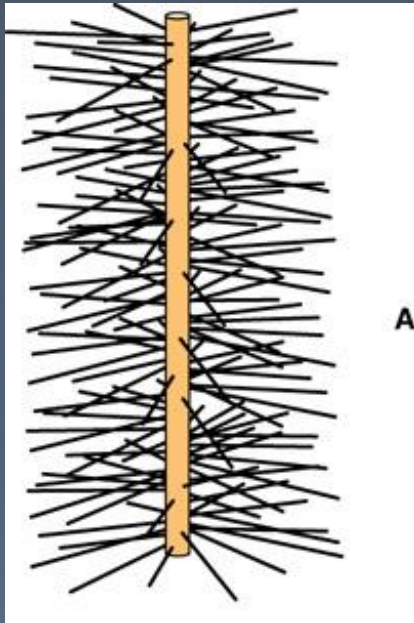
chondroitin 4-sulfate C4S
chondroitin 6-sulfate C6S
dermatan sulfate DS

These GAGs are covalently linked to protein molecules to form proteoglycans.

Only nonsulfated GAG is hyaluronic acid (HA) – very large (10 000 disaccharide units) macromolecule.

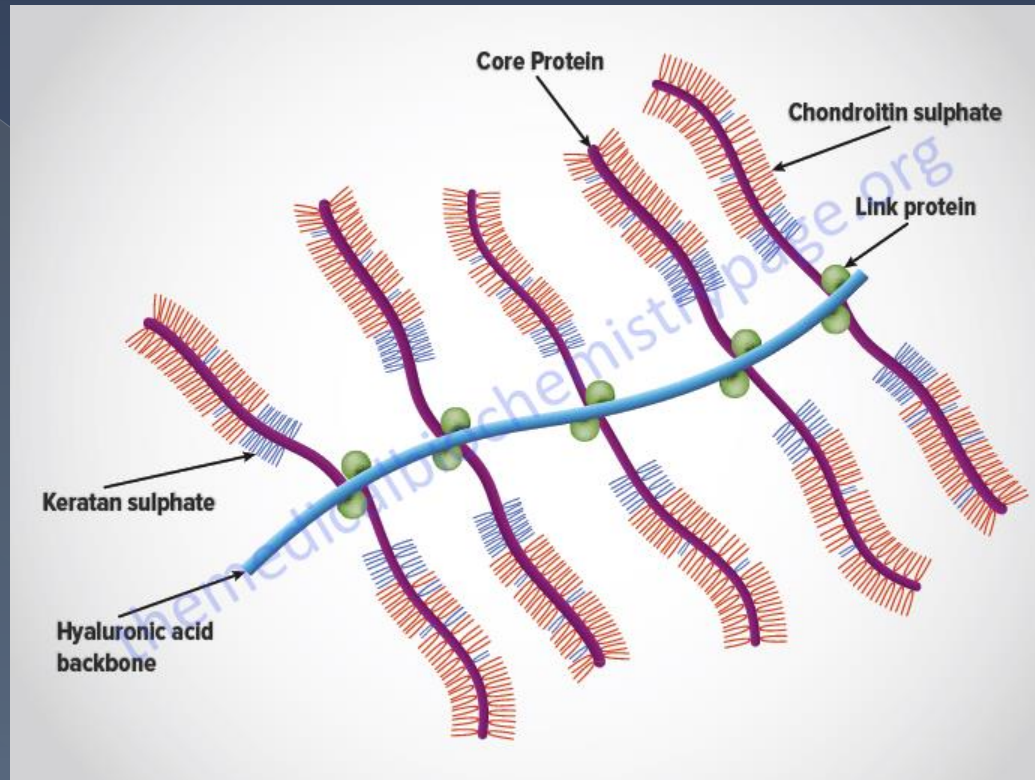
Proteoglycans (PGs)

Proteoglycans contain protein core with covalently bonded glycosaminoglycans (GAGs).



Disaccharides of GAGs are able to bind large quantities of water, and because of their negative charges attract cations (sodium ions) and extracellular fluid (resistance to forces of compression). As the water is squeezed from spaces between GAGs, these molecules repel each other. The size of proteoglycans varies from 50 000 Da (e. g. decorin) to 3 million Da (aggrecan, versican).

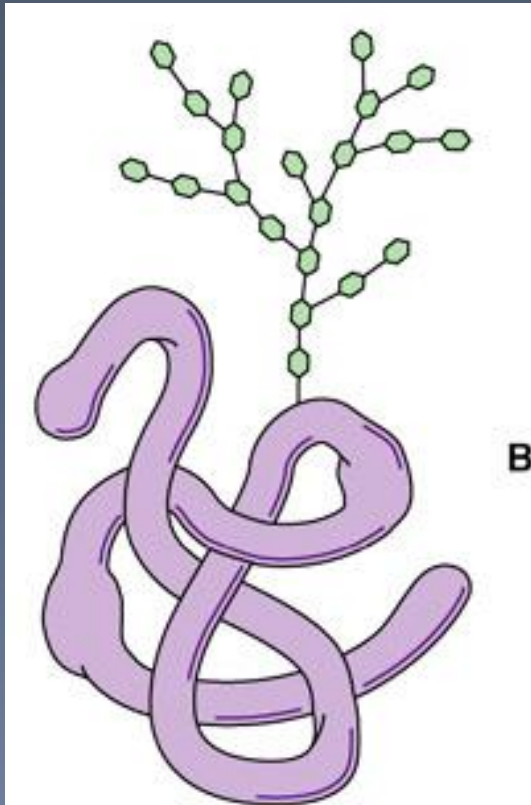
Proteoglycans



Many proteoglycans (aggrecan, versican) attach to hyaluronic acid with small link proteins that form bonds between the core protein of PG and HA. Because hyaluronic acid is very long, such macromolecule occupies very large volume and is responsible for the gel state of ECM.

Glycoproteins

Glycoproteins contain globular protein molecule with attached branched chains of monosaccharides. They have binding sites for the components of ECM and for cell membrane integrins that allows the attachment of cells to the ECM.



The major types of glycoproteins:

Fibronectin – present in connective tissue and blood

Laminin - present in basal lamina

Entactin (nidogen)- connects laminin and collagen IV

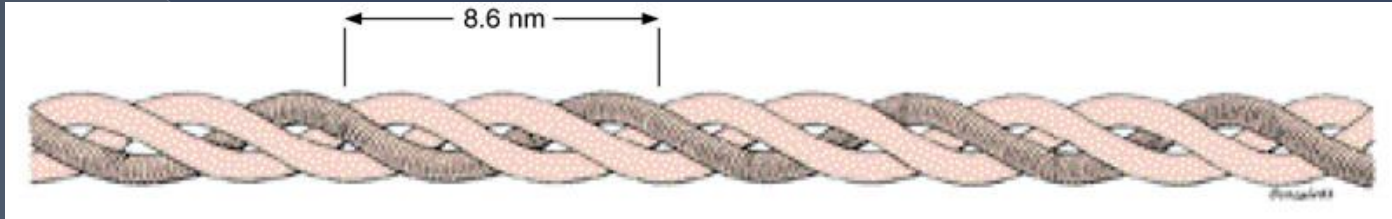
Tenascin – present in embryonic tissues

Chondronectin – present in cartilage

Osteonectin – present in bone

COLLAGEN FIBERS

Inelastic fibers possessing great tensile strength.

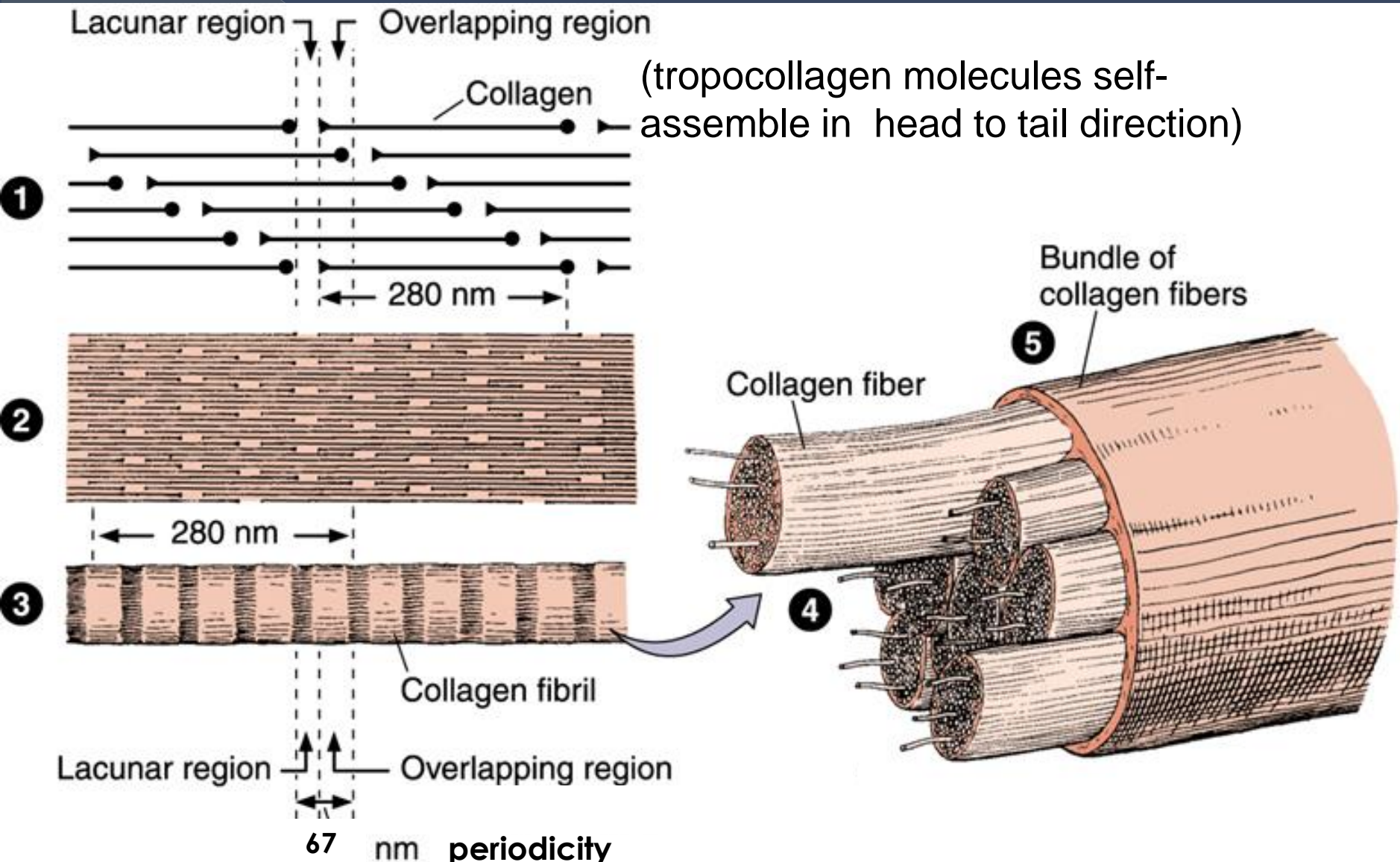


Collagen type I and III molecule. Each molecule (tropocollagen) is composed of **three alpha** peptide chains forming a helix and held together by hydrogen bonds and hydrophobic interactions. **The main amino acids of collagen are glycine and proline, but characteristic for collagen are hydroxylated amino acids – hydroxyproline and hydroxylysine.**

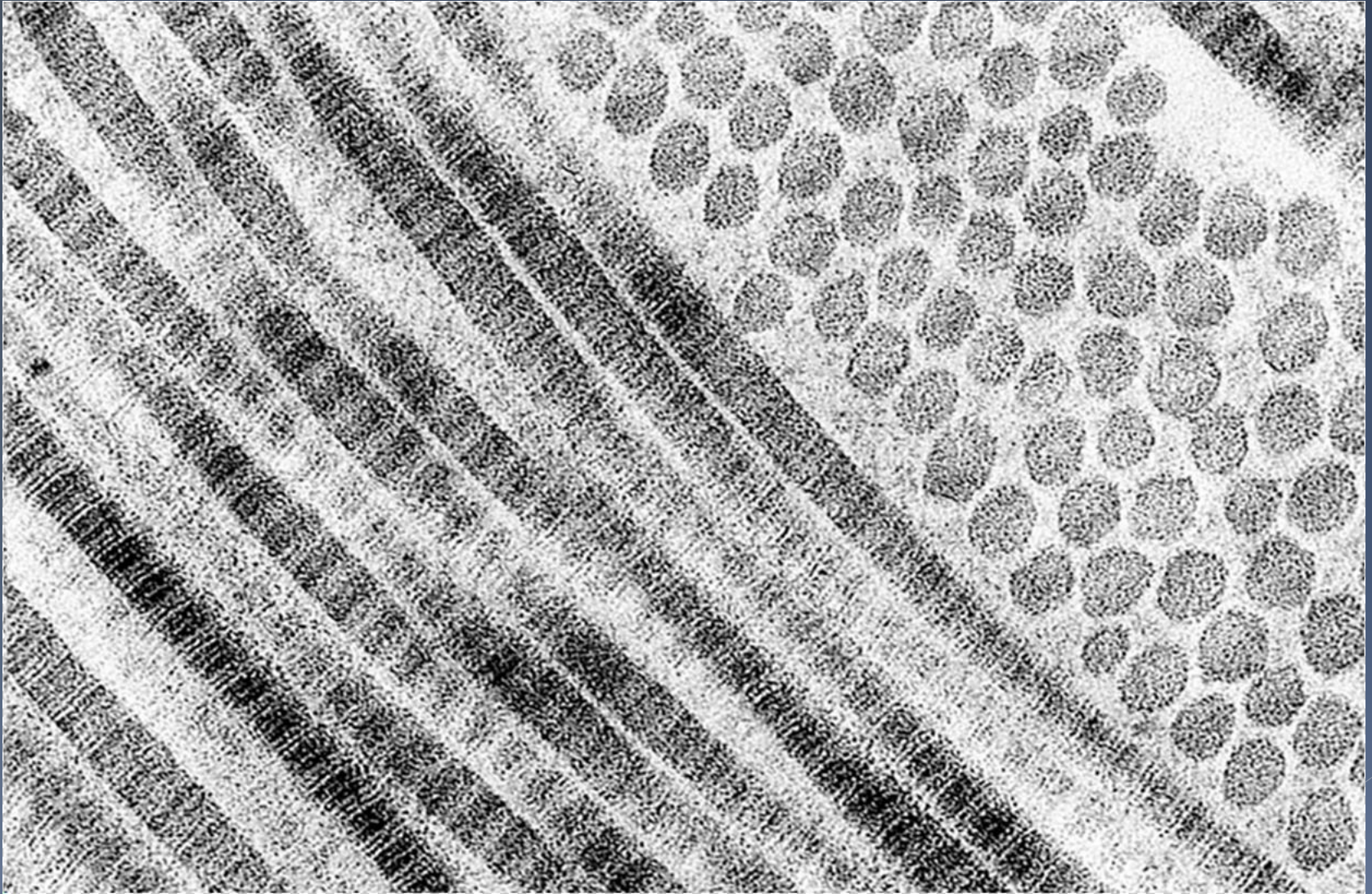
Collagen type I forms collagen fibers of dermis, tendons, ligaments and capsules of organs.

Collagen type III forms reticular fibers in framework of spleen, liver, lymph nodes, smooth muscles, adipose tissue, in cardiovascular system, lung and skin.

Organization of tropocollagen, formation of collagen fibrils, fibers and bundles



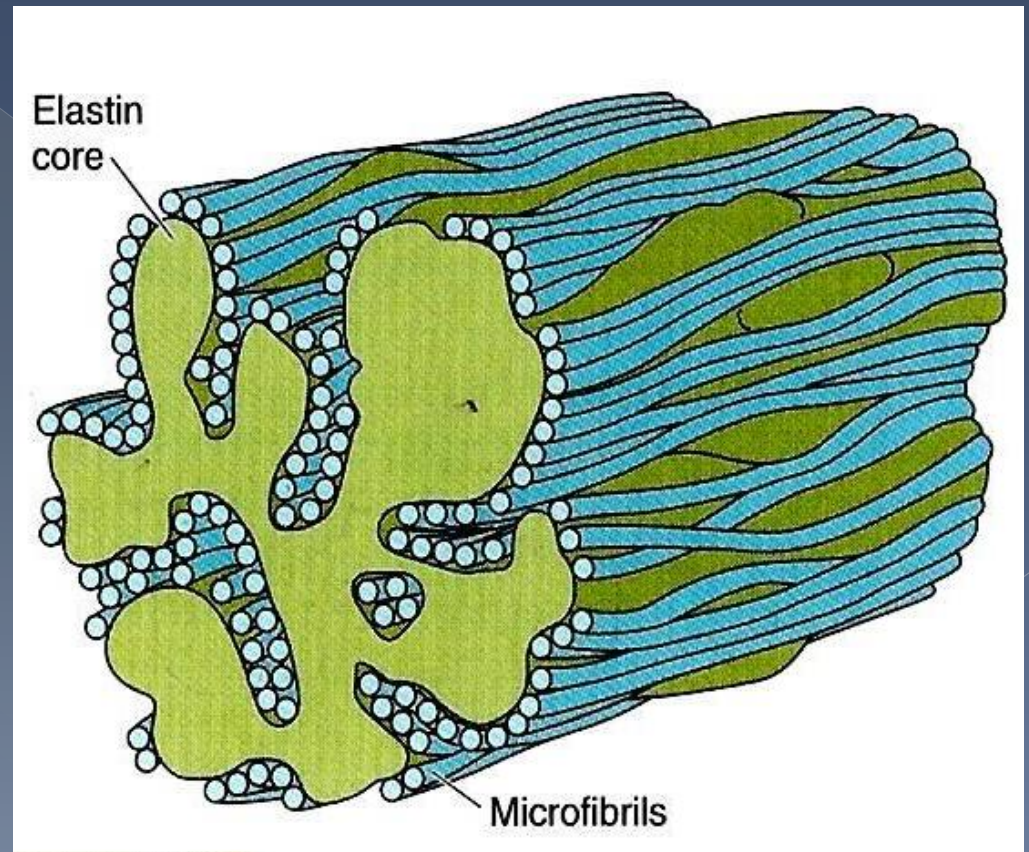
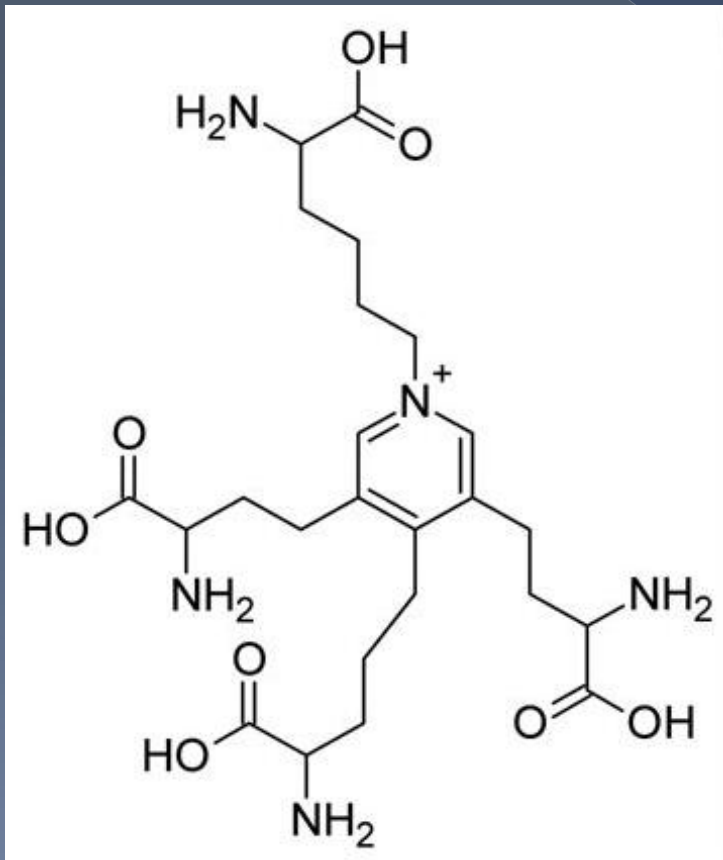
Collagen fibers (EM)



Visible cross-striations with 67 nm periodicity

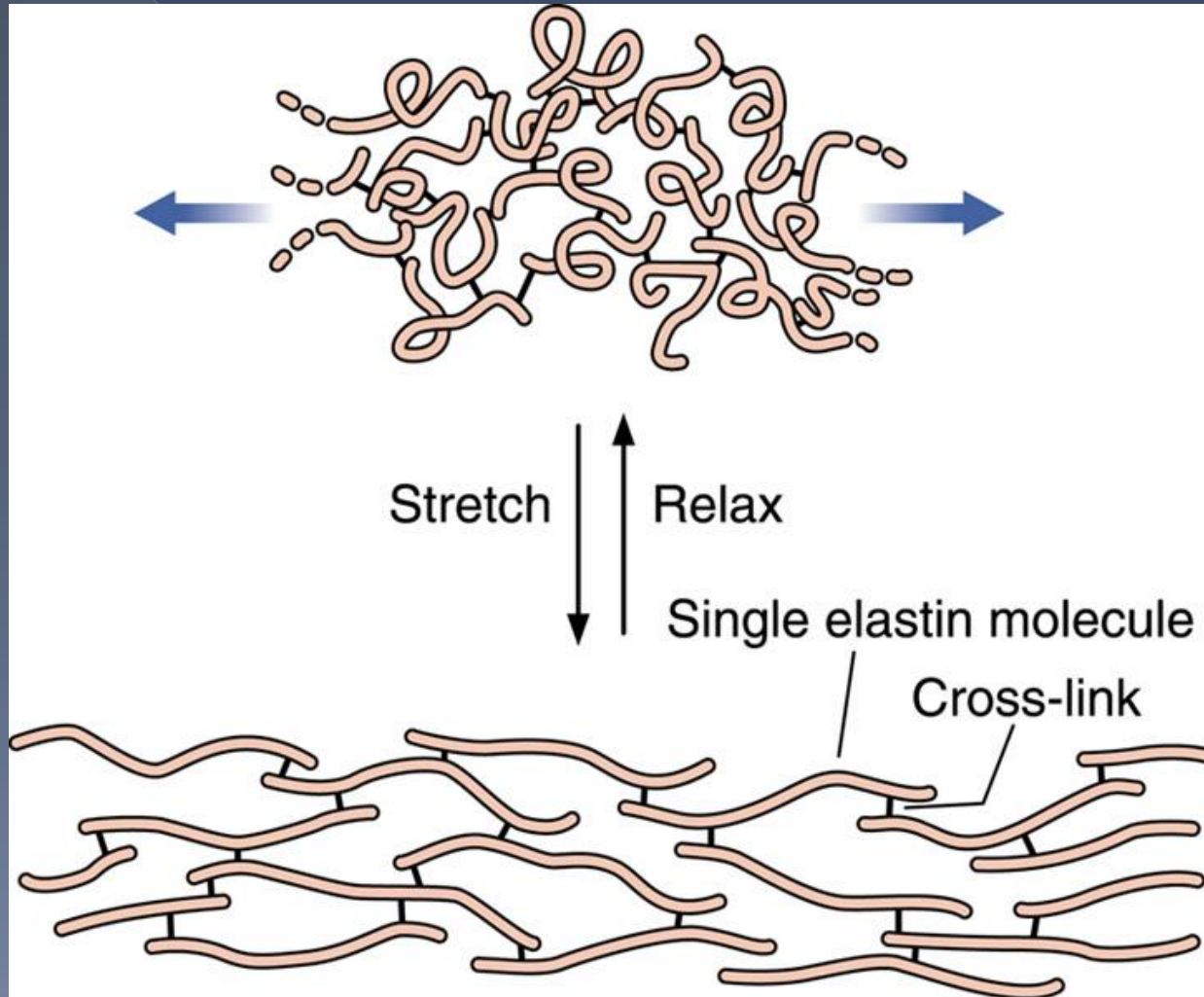
ELASTIC FIBERS

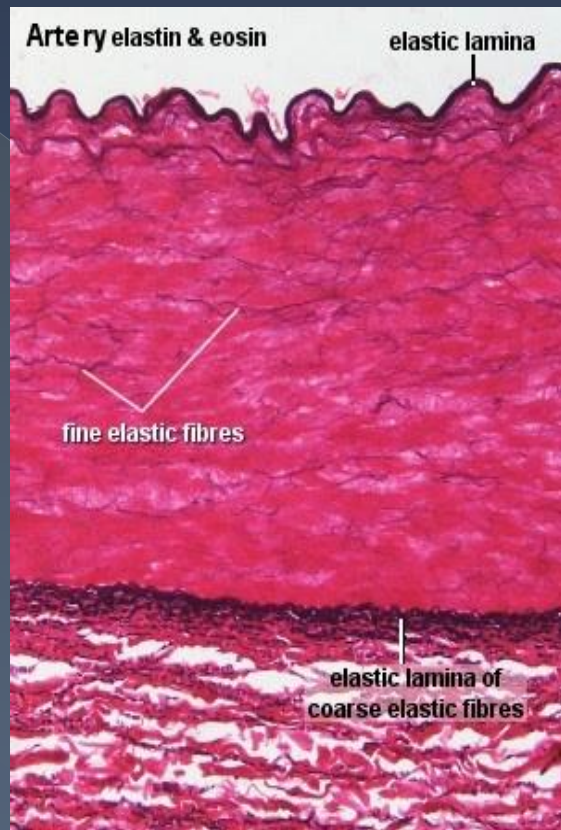
formed from the elastic microfibrils (fibrillin 1) and amorphous elastin. Elastin is rich in **glycine and proline**, which form mobile hydrophobic regions bounded by crosslinks between lysine residues belonging to four different elastin chains (**desmosine crosslinks**).



ELASTIC FIBERS

An extensively interconnected, rubbery network formed by elastin molecules can stretch and bend in any direction giving connective tissue elasticity.



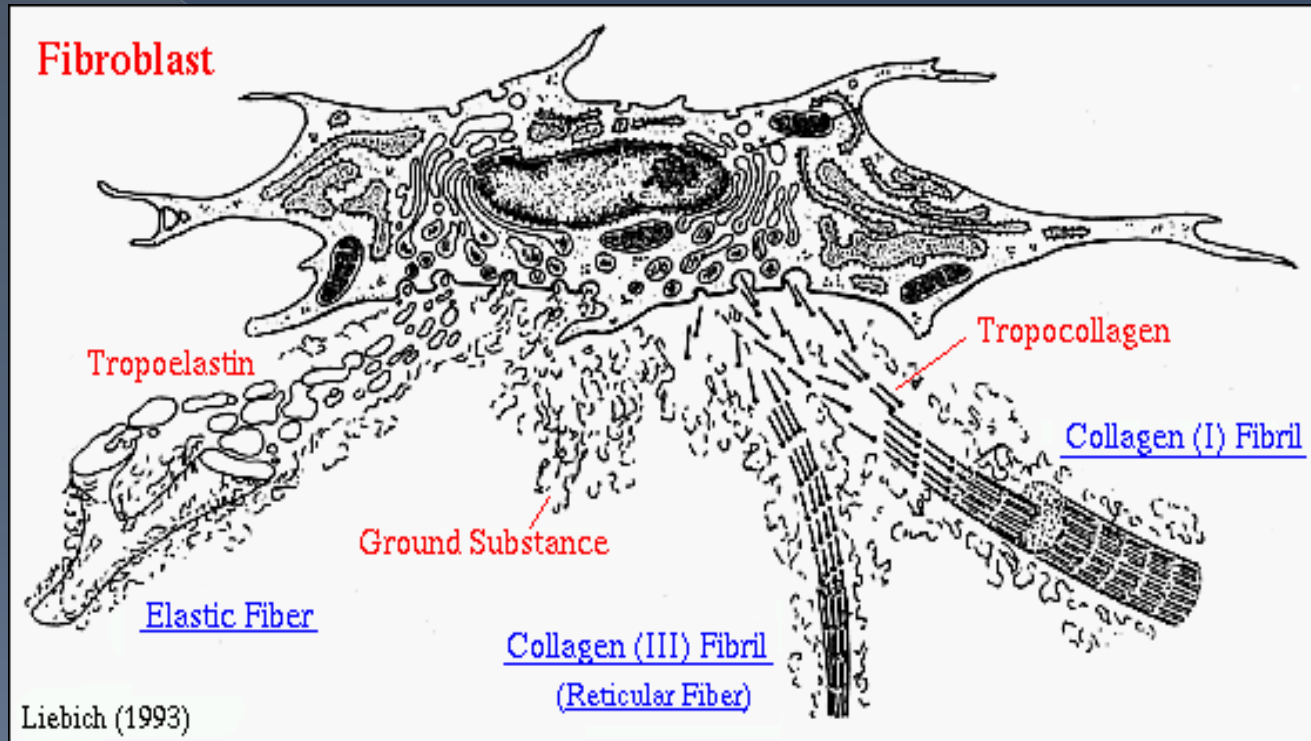


Elastic fibers are usually slender (in loose connective tissue) but may form bundles (e. g. in ligaments), and concentric sheets in the walls of larger blood vessels

Fibroblasts (fibrocytes – quiescent fibroblasts)

the most abundant cell type

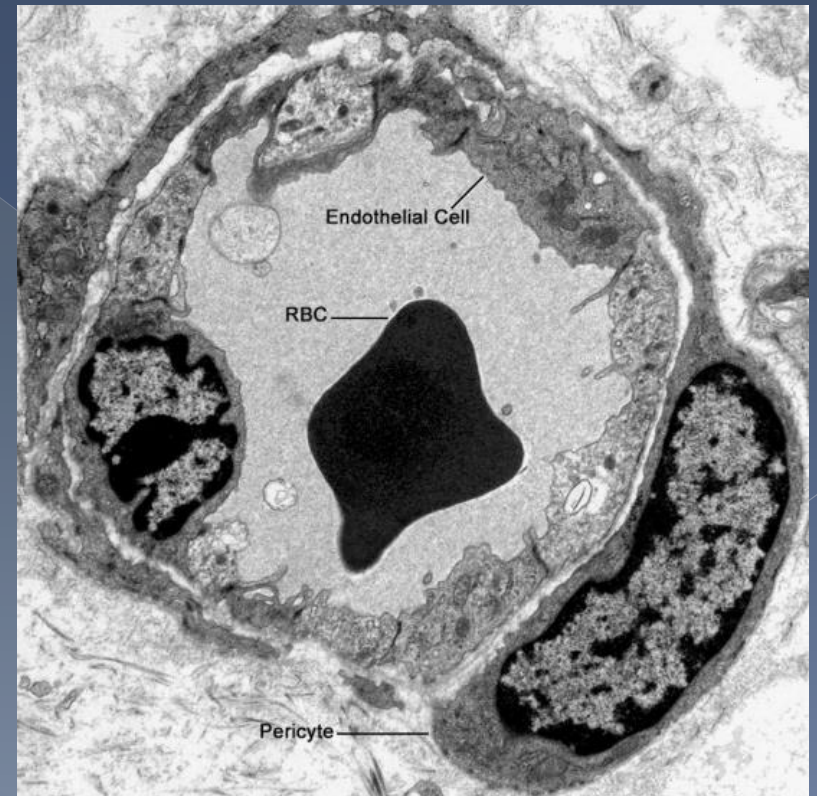
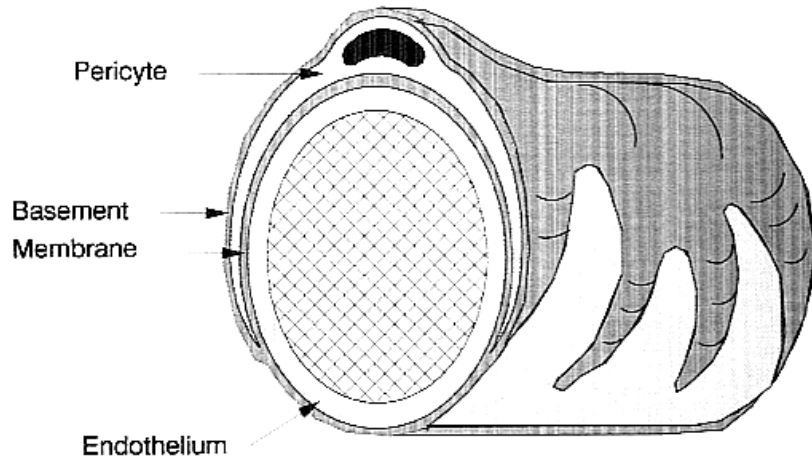
Produce fibers, ground substance (ECM) and proteolytic enzymes



Special form: myofibroblasts abundant actin and myosin filaments (contractile elements) similarly to smooth muscle cells, but external lamina is absent. They participate in wound healing (wound contraction)

PERICYTES

surround endothelium of capillaries and small venules, possess their own basal lamina, contain actin, myosin and tropomyosin, may function in contraction. They regulate the dimension of the lumen of capillary vessels



MAST CELLS (mastocytes, labrocytes)

Functions: wound healing, inflammation.

Participate in allergy and anaphylaxis.

Tissue mast cells

In various organs
along blood vessels
in fluid of body cavities

Mucosal mast cells

In mucosa of alimentary
and respiratory tract

Granules (metachromatic):

Heparin (anticoagulant, inactivate histamine) chondroitin sulfate

Histamine (↑vascular permeability, vasodilation, bronchospasm)

Neutrophil chemotactic factor (NCF)

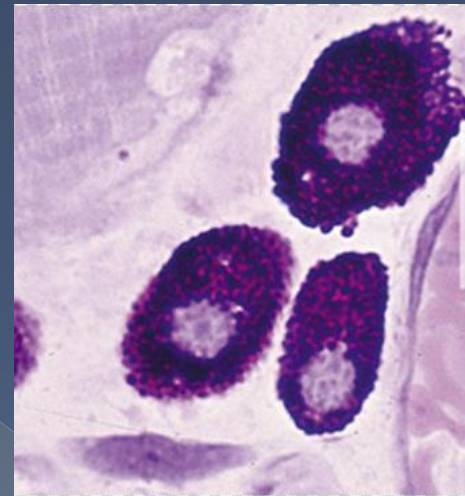
Eosinophil chemotactic factor (ECF)

Proteolytic enzymes

MAST CELLS

Release also leukotrienes, prostaglandins and thromboxanes not present in granules. They are produced by phospholipase A2, which acts on cell membrane phospholipids to form arachidonic acid (AA). AA is converted (*via* lipoxygenase and cyclooxygenase activity) into the secondary mediators. These mediators act similarly to histamine but more intensively.

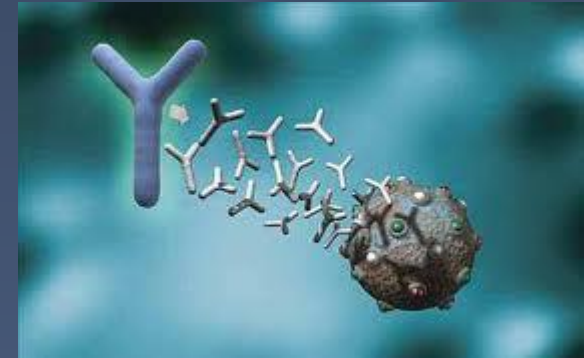
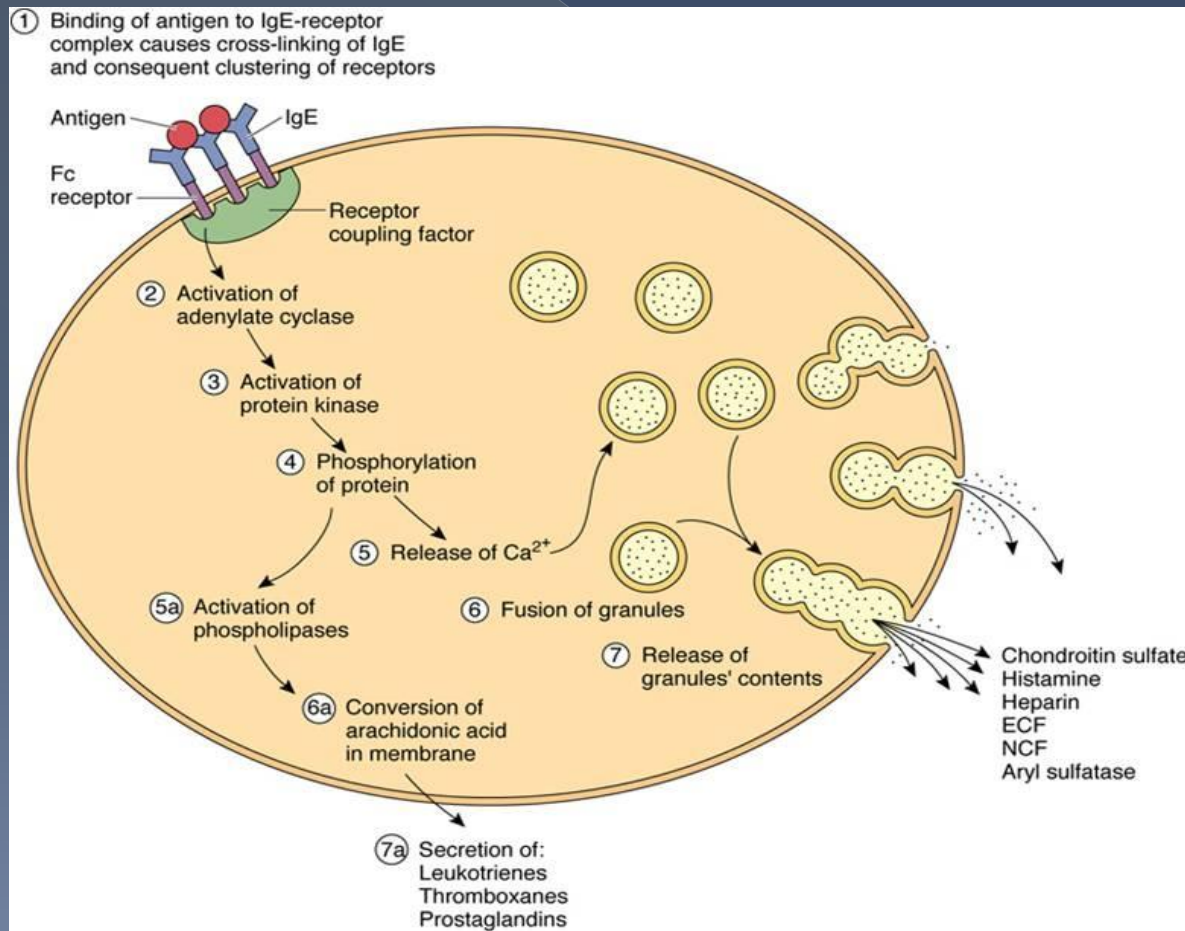
Contain high affinity receptors for immunoglobulin E



Mediate allergic reaction known as immediate hypersensitivity reactions, in most developed form leading to anaphylactic shock

Mast cell activation and degranulation.

When the first exposure to the antigen elicits formation of IgE antibodies, the inflammatory response termed immediate hypersensitivity reaction or their systemic form an anaphylactic reaction develops.

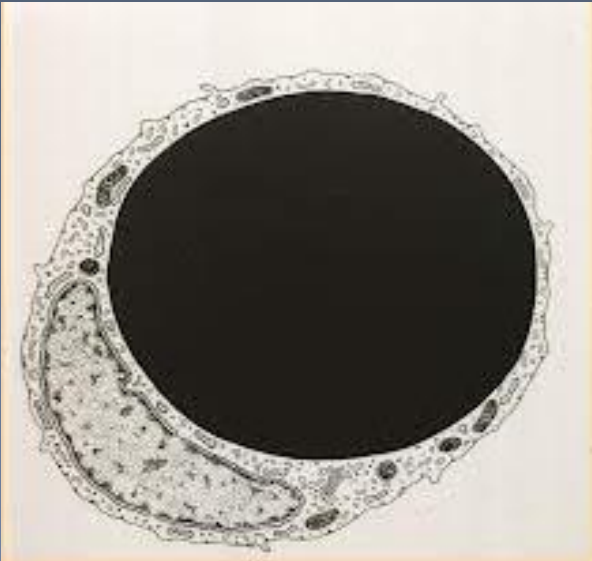


ADIPOSE CELLS

Fully differentiated cells that function in the synthesis, storage and release of fat.

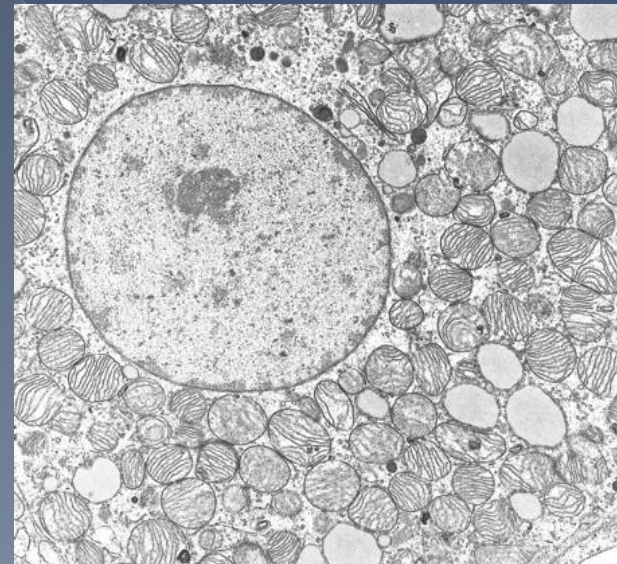
UNILOCULAR FAT CELLS

Large, spherical cells forming white adipose tissue
Storing of fat in a single droplet
Cytoplasm and nucleus peripherally displaced (signet ring)

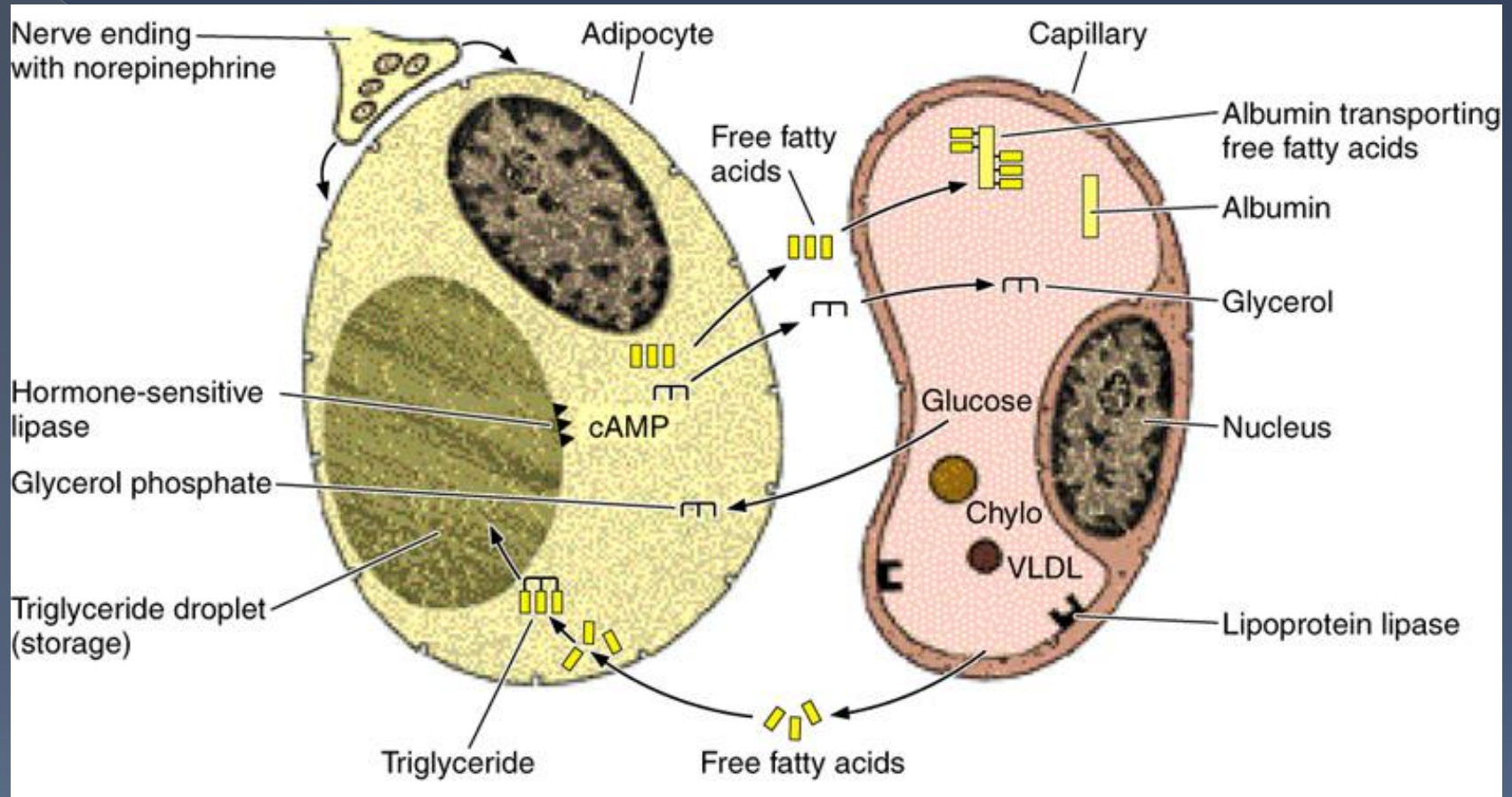


MULTILOCULAR FAT CELLS

Smaller, more polygonal cells forming brown adipose tissue
Storing of fat in several small droplets
Spherical nucleus
More mitochondria than unilocular cells
Brown fat occurs mainly in children



UNILOCULAR FAT CELL (WHITE ADIPOSE TISSUE)

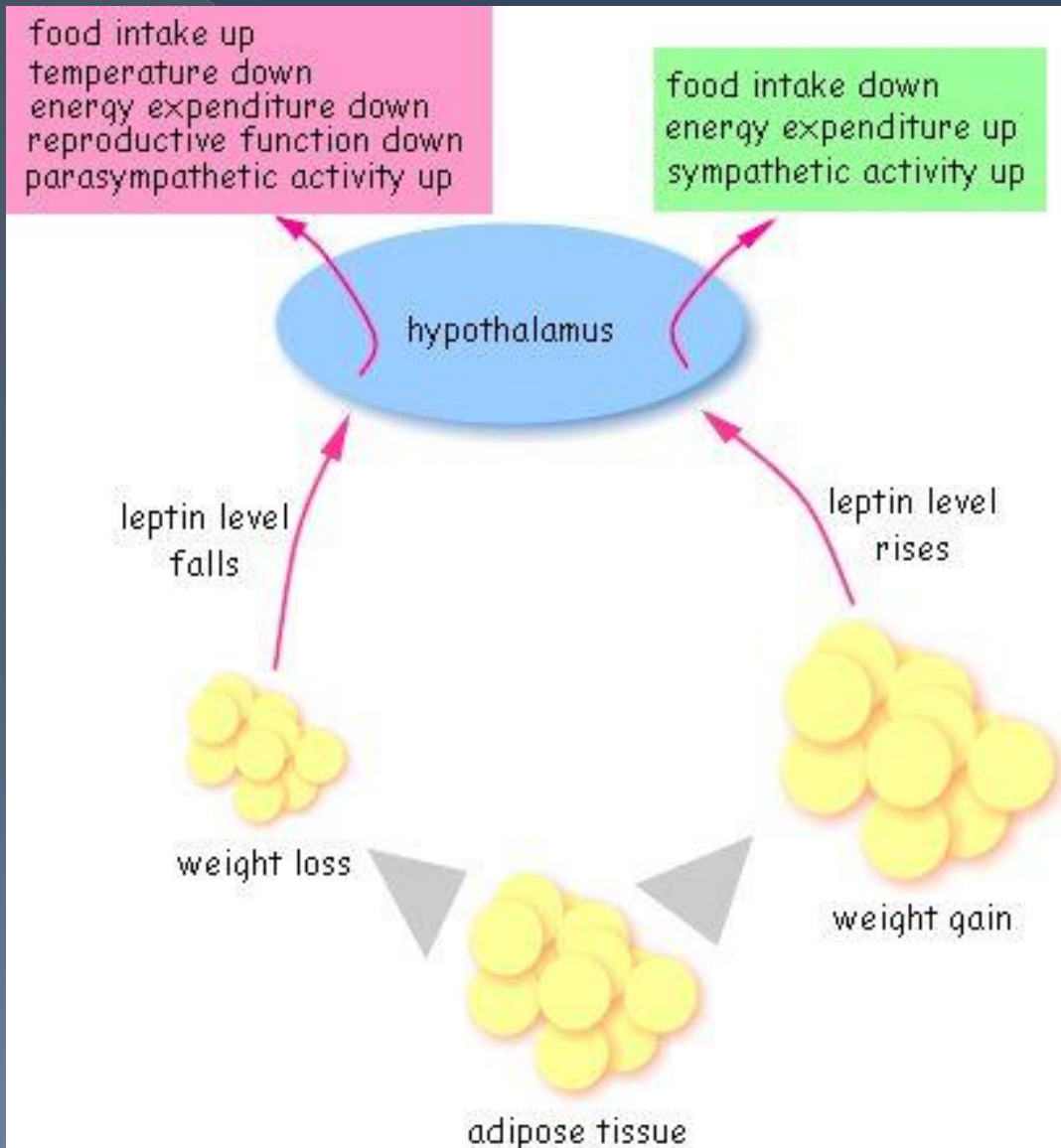


Lipoprotein lipase hydrolyzes fats into free fatty acids. They diffuse into adipocytes, are converted into triglycerides and stored in fat droplets

Norepinephrine stimulates the cyclic AMP system which activates hormone-sensitive lipase. This enzyme hydrolyzes triglycerides and fatty acids are released from cells.

Adipokines

substances that control the the body's fatty acid equilibrium



Leptin – satiety hormone, fat-burning hormone, reduces appetite by inducing activity of lipases that results in release of fatty acids from adipocytes and by inhibiting of neuropeptide Y which trigger the appetite.

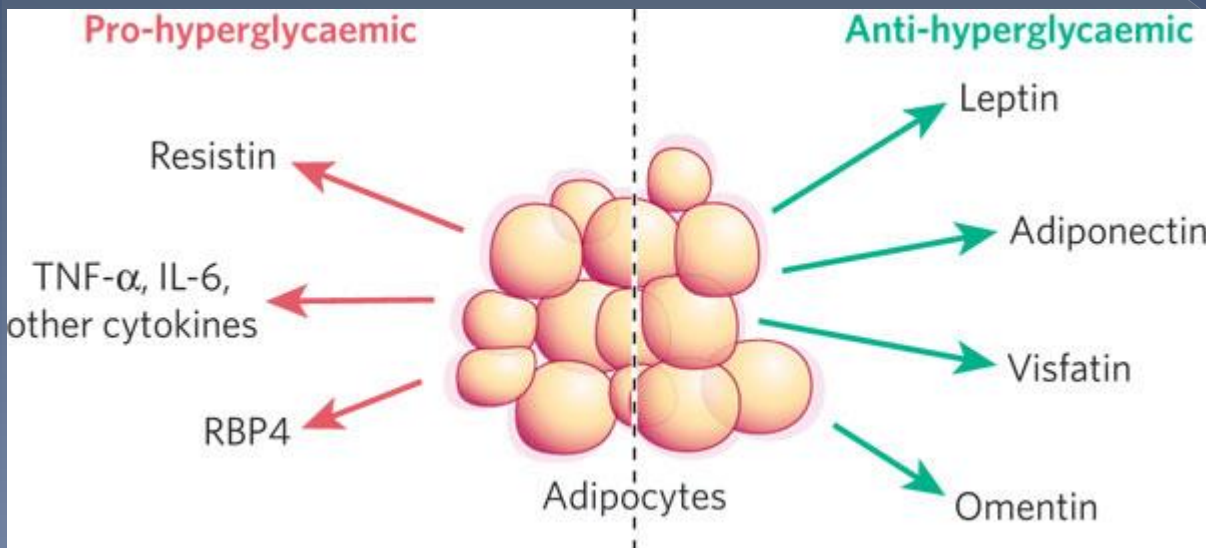
Adipokines

Adiponectin – increases the insulin sensitivity of skeletal muscle cells, increases the gluconeogenesis in liver, represses hunger.

Retinol-binding protein 4 (RBP4) increases insulin resistance and participates in development of chronic inflammation.

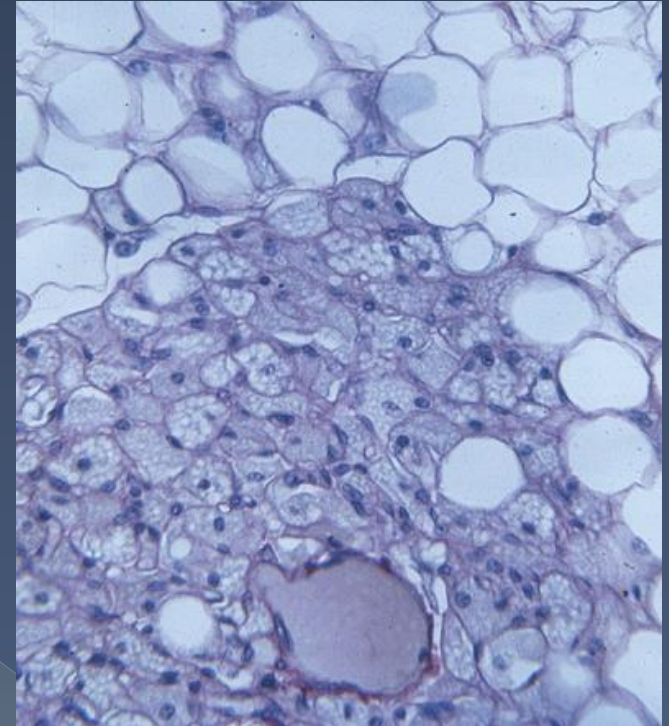
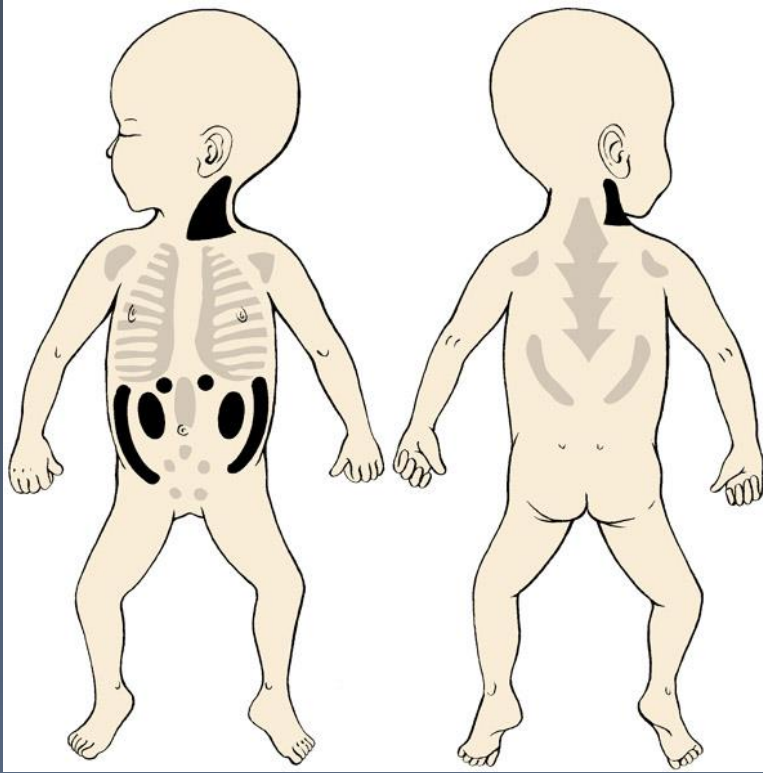
Resistin – increases of insulin resistance and participates in development of chronic inflammation.

TNF – produced by macrophages of adipose tissue – primary cause of insulin resistance.



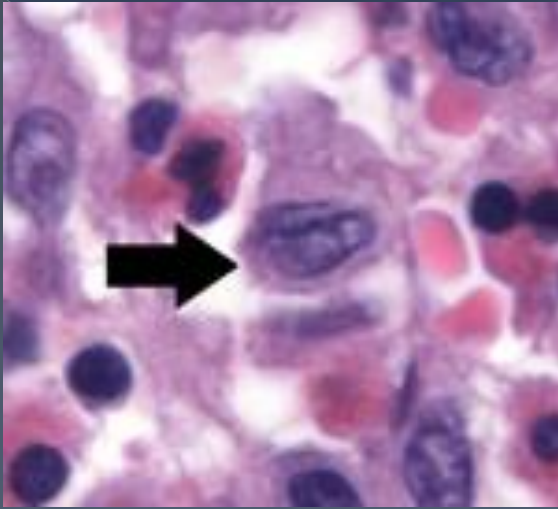
IL-6 - produced by macrophages of adipose tissue increases insulin resistance.

MULTILOCULAR CELLS (BROWN ADIPOSE TISSUE).



Thermogenin is a 33 kDa inner-membrane mitochondrial protein exclusive to brown adipocytes in mammals that functions as a proton transporter, allowing the dissipation as heat. ATP is not produced and energy is dispersed as heat.

Macrophages (histiocytes)



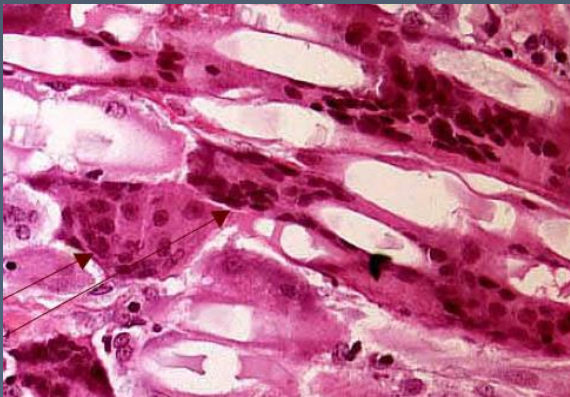
Originate from monocytes passing into blood from bone marrow. Tissue macrophages survive for several months.

Functions:

Phagocytosis of microorganisms, foreign substances, cell debris and senescent cells; when the particulate matter is extremely large macrophages fuse and form foreign body giant cells.

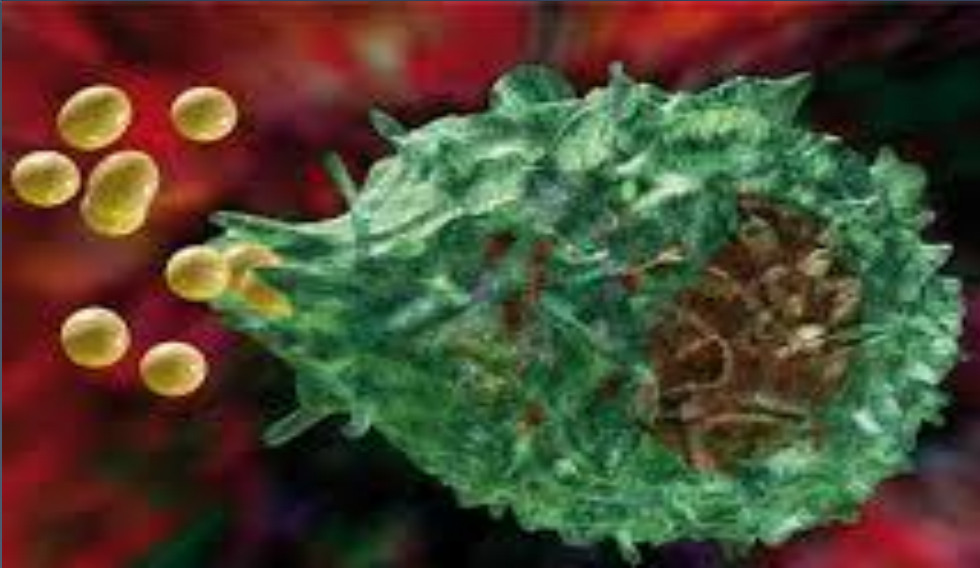
Participation in initiation of immune response

Immunophagocytosis

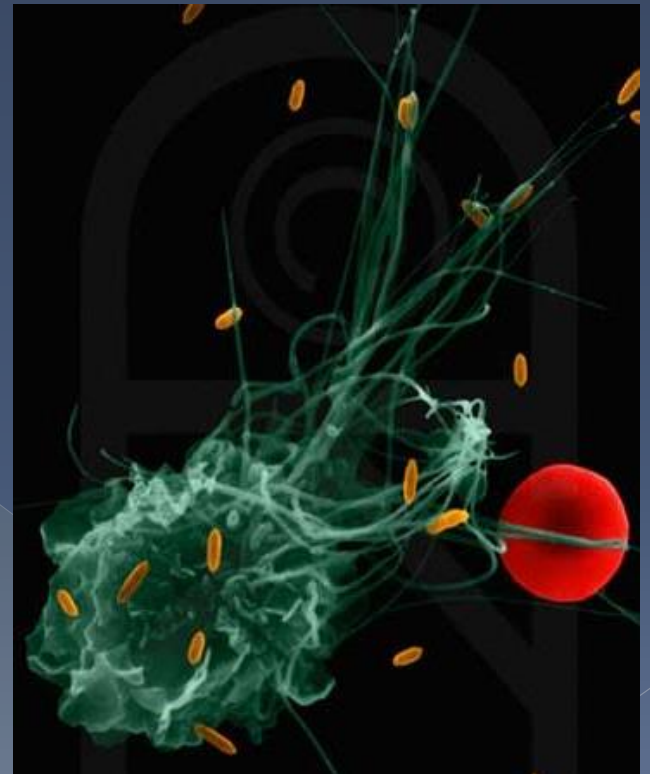


Foreign body giant cells in suture granuloma

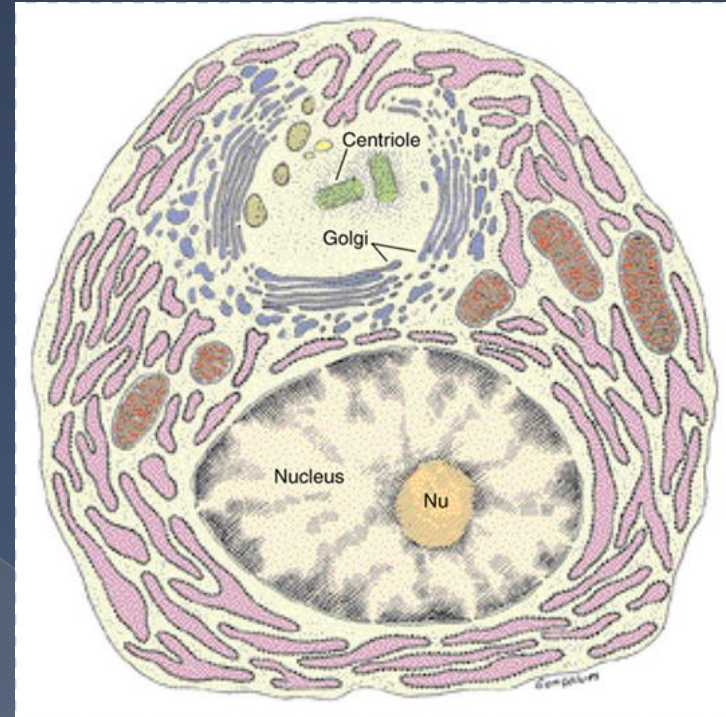
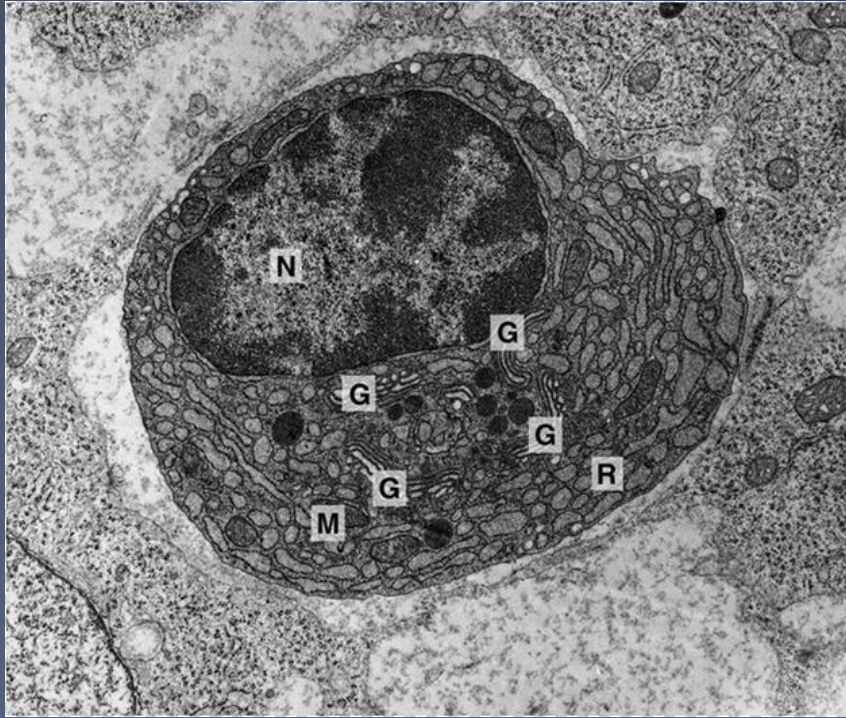
Produce: hydrolytic enzymes, interleukins (IL-1, IL-4, IL-6, IL-8, IL-10, IL-12) and other cytokines (TNF, PDGF, TGF-beta).



Macrophages and bacteria

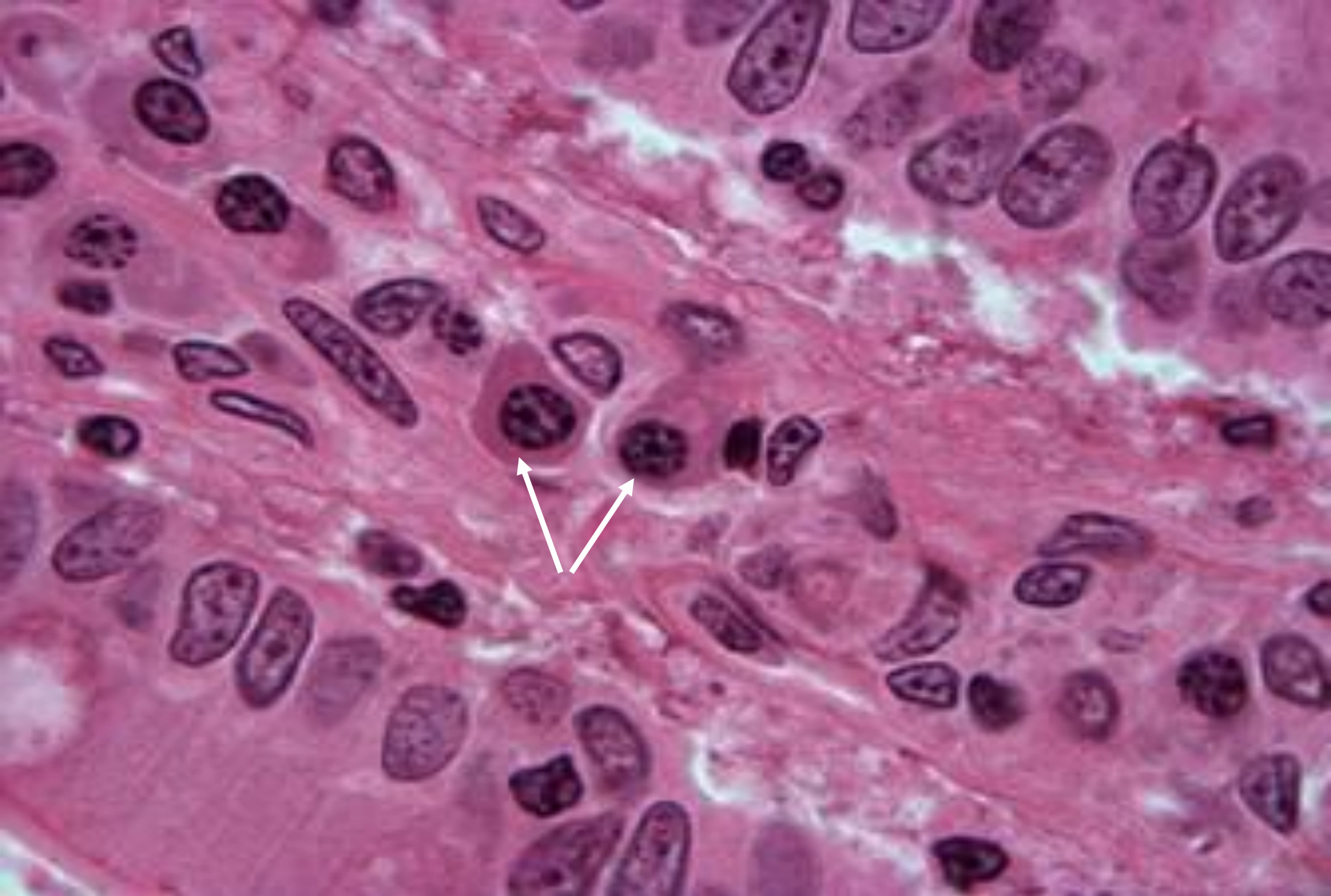


PLASMA CELLS



Differentiate from B lymphocytes. Produce and secrete immunoglobulins (antibodies) **IgA**; **IgD**; **IgE**, **IgG**, **IgM** and are responsible for humorally mediated immunity.

Dilated cisternae of RER filled with immunoglobulins which are not stored in granules, clock face or spoked nucleus.



Intestinal villous – plasma cells

LEUKOCYTES

White blood cells migrating to the connective tissues during inflammation to perform various functions connected with the immune response.

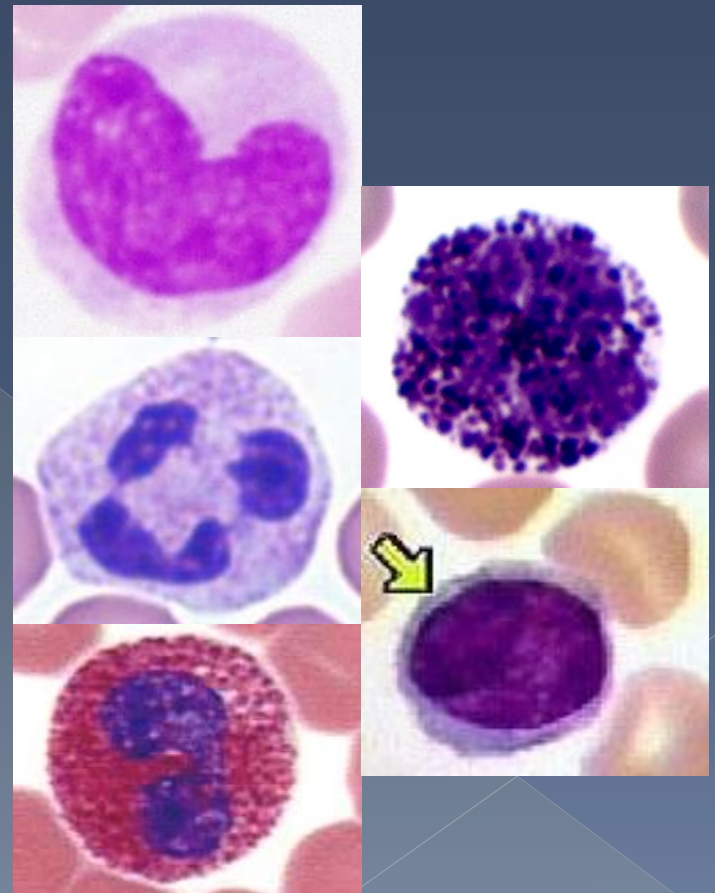
MONOCYTES – transform into macrophages

NEUTROPHILS – (microphages)
phagocytose and digest bacteria in areas of inflammation, participate in formation of pus – accumulation of dead neutrophils and debris.

EOSINOPHILS – combat parasites, moderate the allergic reactions, phagocytose the antibody-antigen complexes.

BASOPHILS – similar to mast cells

LYMPHOCYTES – humoral and cellular mediated immunity.



EMBRYONIC CONNECTIVE TISSUE

MESENCHYMAL CT

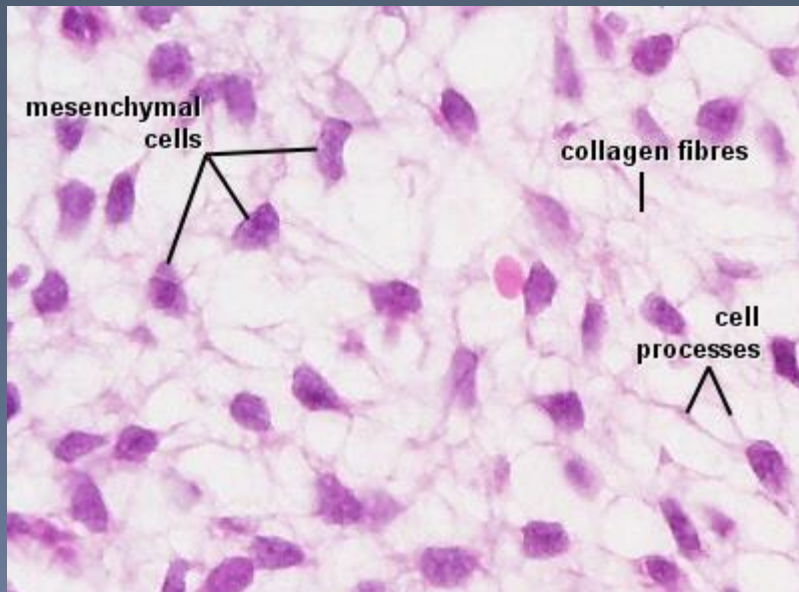
Present in embryo and in pulp of teeth

Mesenchymal cells

Amorphous ground substance

Scattered reticular fibers

High mitotic activity



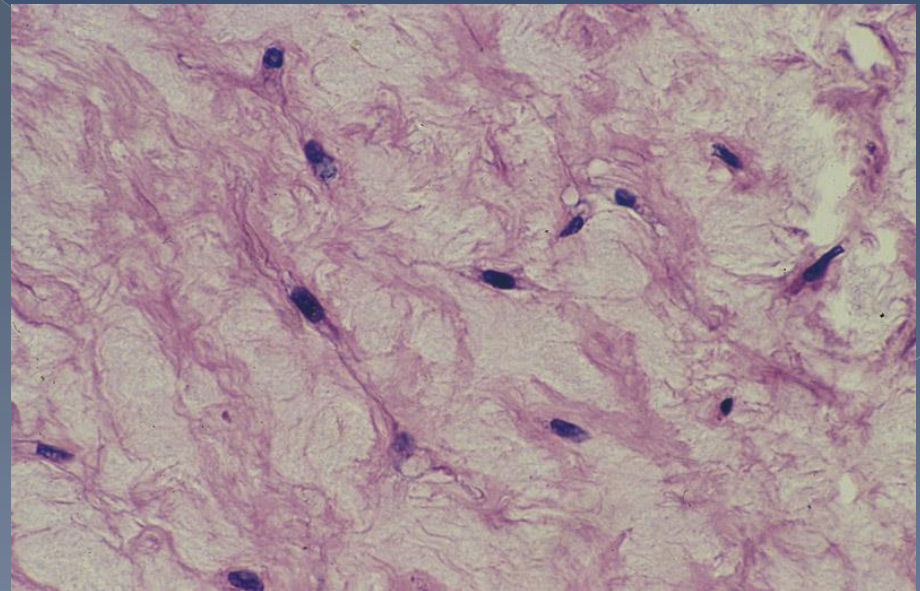
MUCOUS CT

Present in umbilical cord (Wharton's jelly)

Fibroblasts

Amorphous, jelly-like ECM (HA)

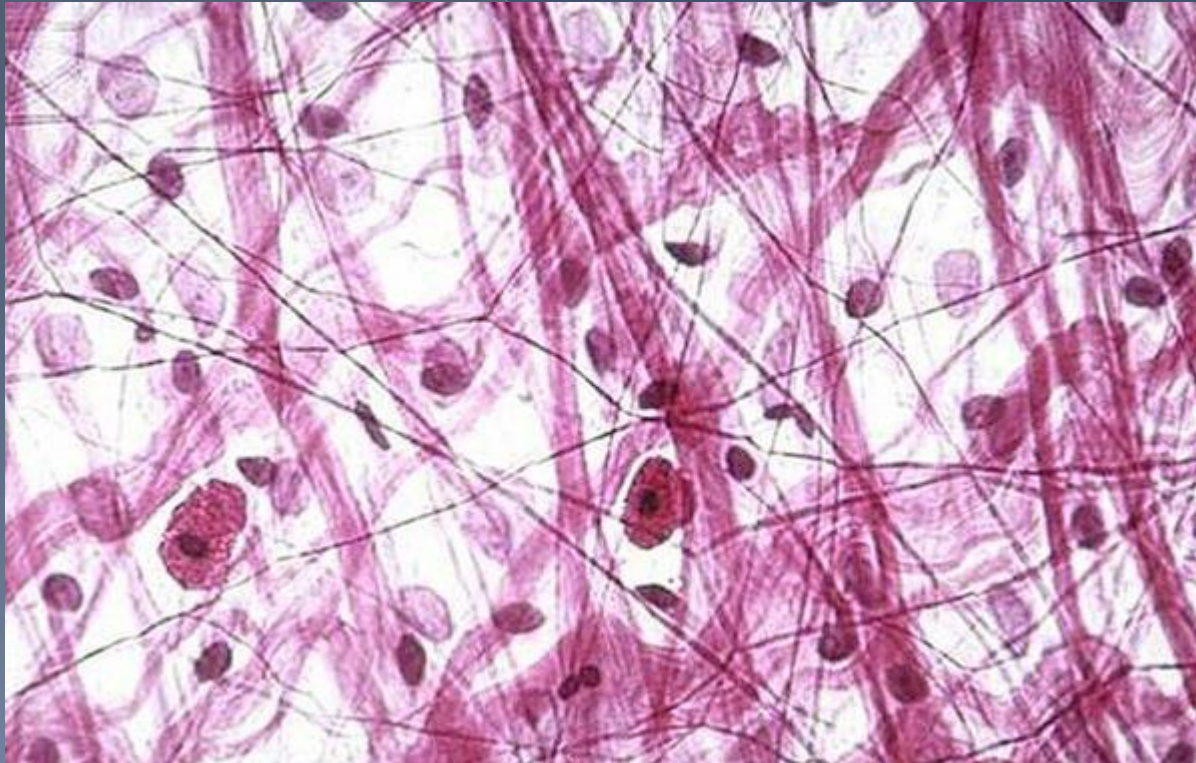
Few type I and III collagen fibers



CLASSIFICATION OF CONNECTIVE TISSUE PROPER

LOOSE CONNECTIVE TISSUE

Areolar CT, fills the spaces in the body, forms lining of internal body cavities, adventitia of blood vessels, surrounds parenchyma of glands
Abundant ground substance and tissue fluid, loose arrangement of fibers (collagen type I, type III and elastic fibers), fibroblasts, mast cells, macrophages, adipose cells, undifferentiated cells, transient cells



DENSE CONNECTIVE TISSUE

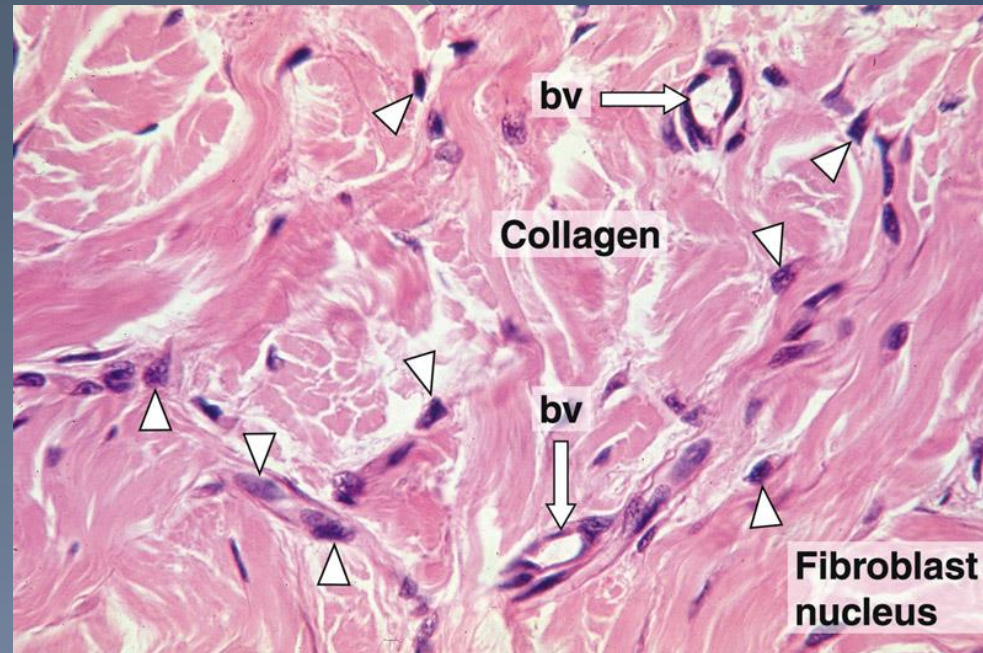
abundance of fibers, few cells

a) DENSE IRREGULAR CONNECTIVE TISSUE

randomly arranged fibers

Dermis of the skin, the sheaths of nerves, capsules of the spleen, testes, ovary, kidneys, lymph nodes

Coarse collagen fibers interwoven into a meshwork, scattered elastic fibers, all types of cells



DENSE CONNECTIVE TISSUE

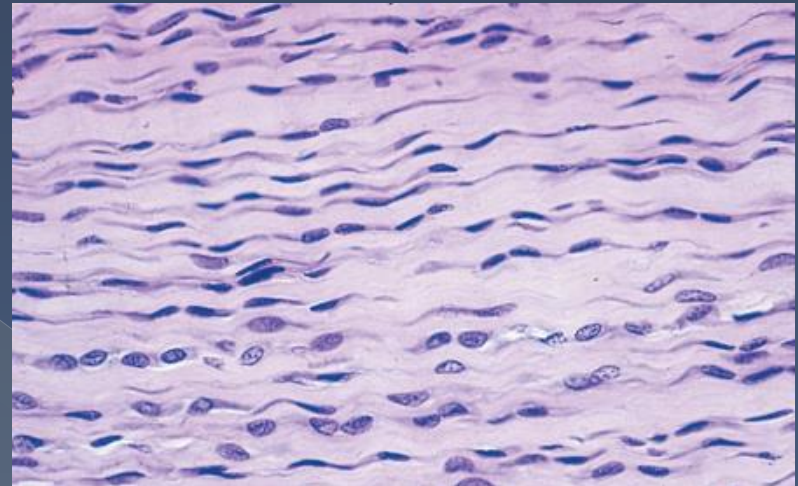
abundance of fibers, few cells

b) DENSE REGULAR CONNECTIVE TISSUE

organized arrangement of fibers (e.g. parallel)

DENSE REGULAR COLLAGENOUS CONNECTIVE TISSUE

coarse collagen bundles of fibers
Tendons, ligaments, aponeuroses
Thin, sheet like fibroblasts



DENSE REGULAR ELASTIC CONNECTIVE TISSUE

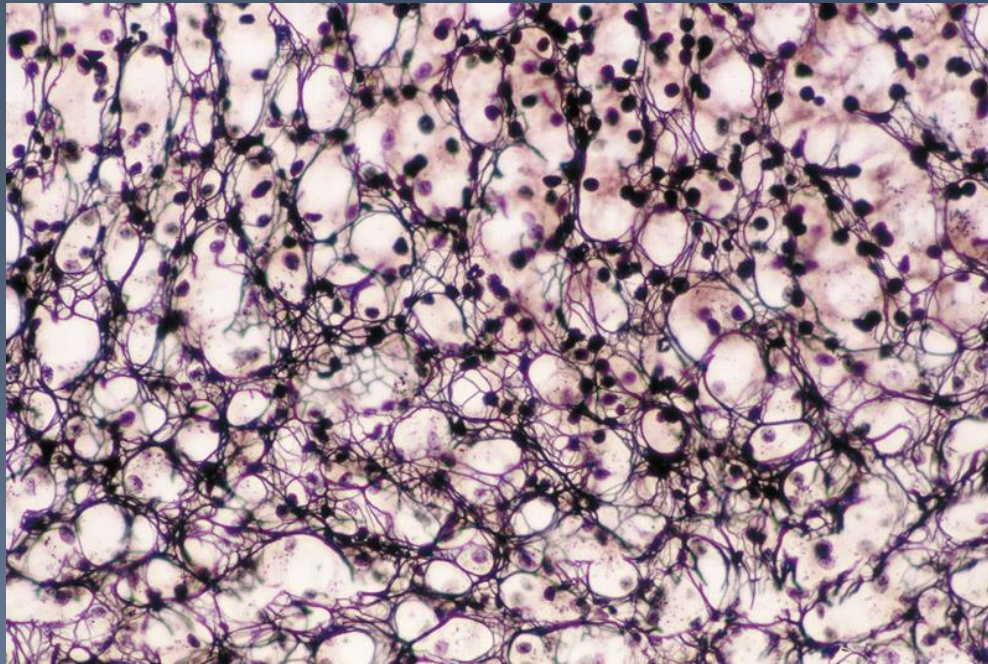
coarse elastic fibers
Walls of large blood vessels,
ligamenta flava in vertebral
column, fibroblasts



RETICULAR TISSUE

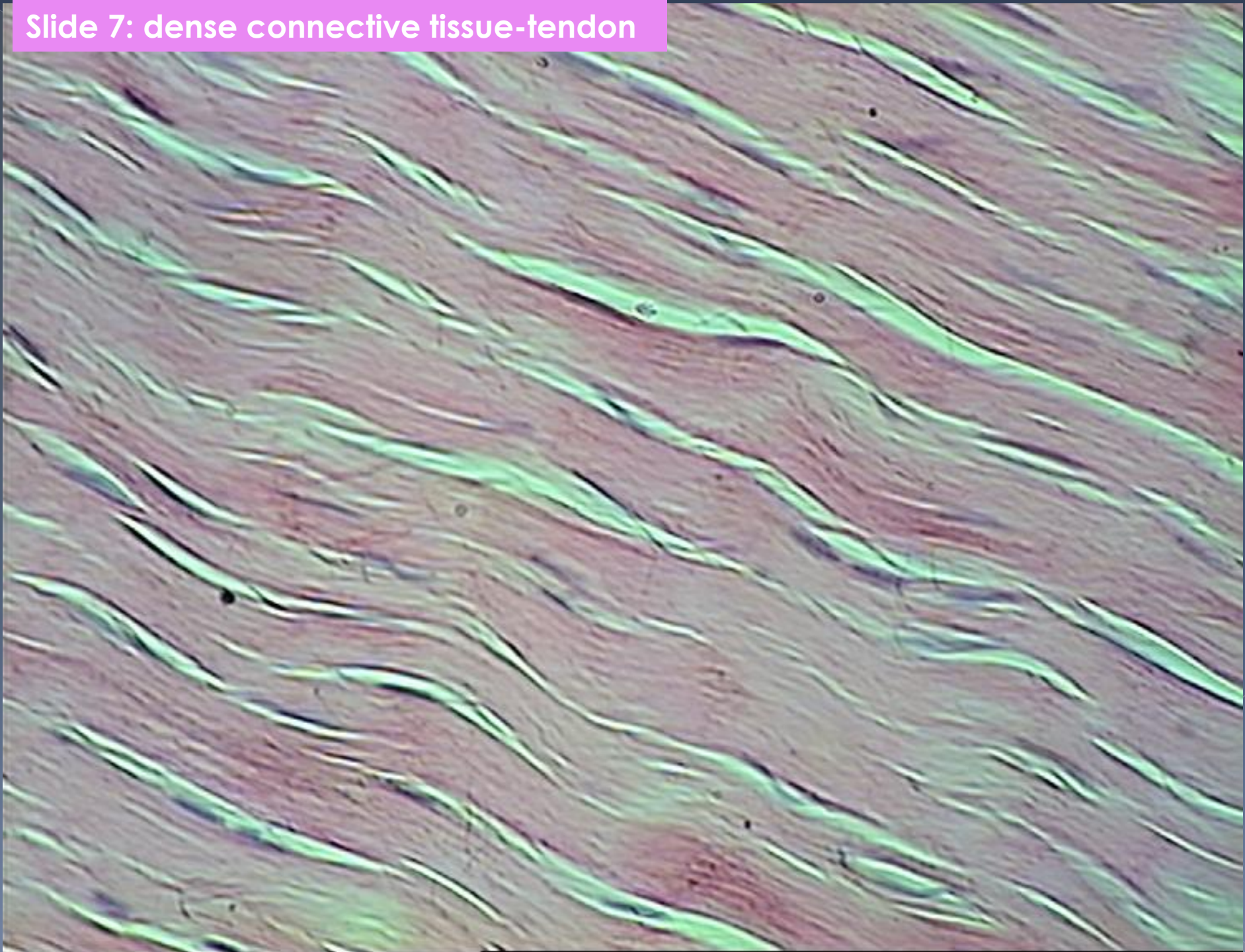
type III collagen fibers

Framework of liver sinusoids, adipose tissue, bone marrow, lymph nodes, spleen, smooth muscles, islets of Langerhans
Network of reticular fibers, fibroblasts, macrophages

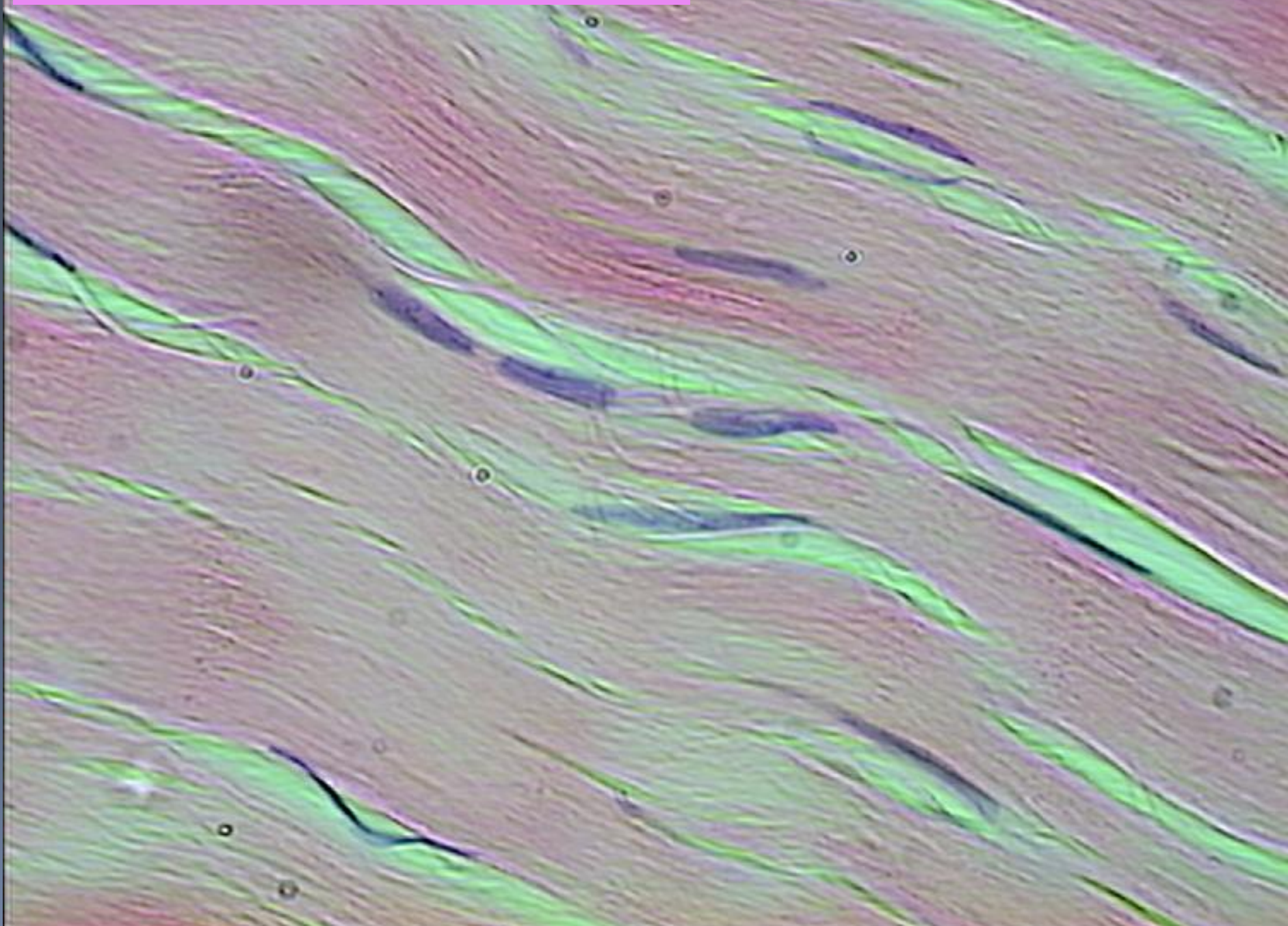


Reticular fibers – silver impregnation

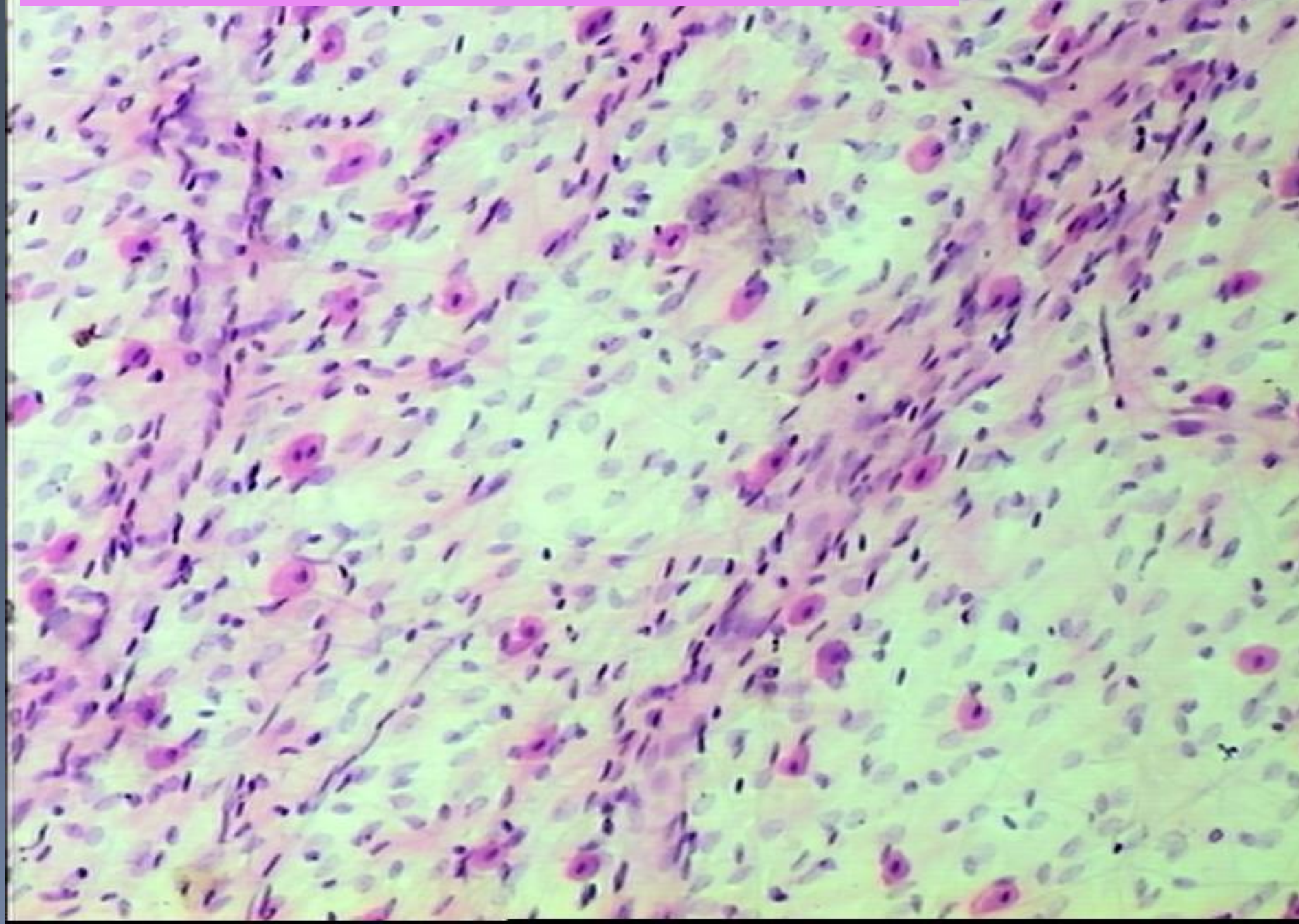
Slide 7: dense connective tissue-tendon



Slide 7: dense connective tissue-tendon



Slide 9: loose connective tissue-mesentery



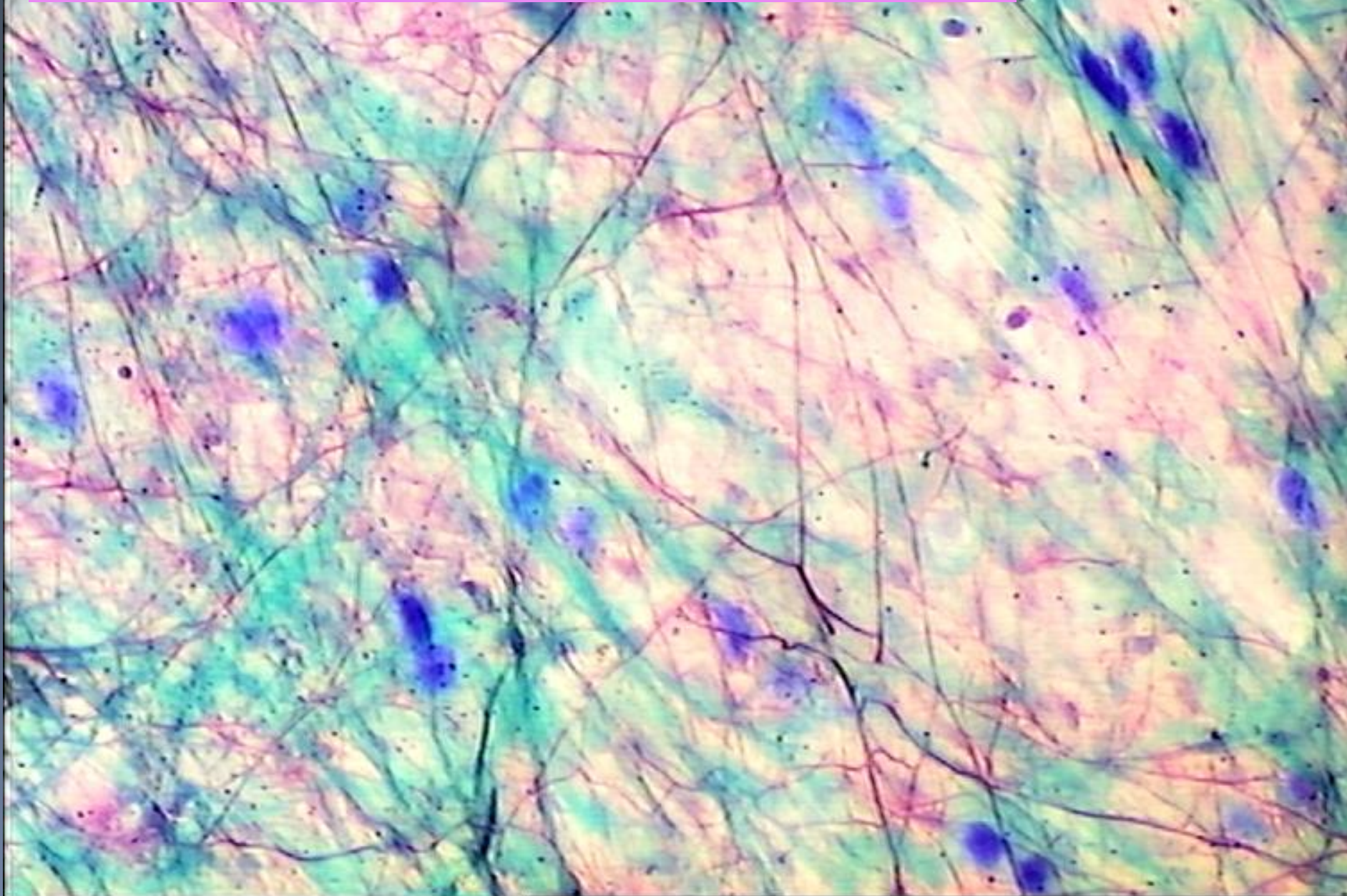
Slide 9: loose connective tissue-mesentery



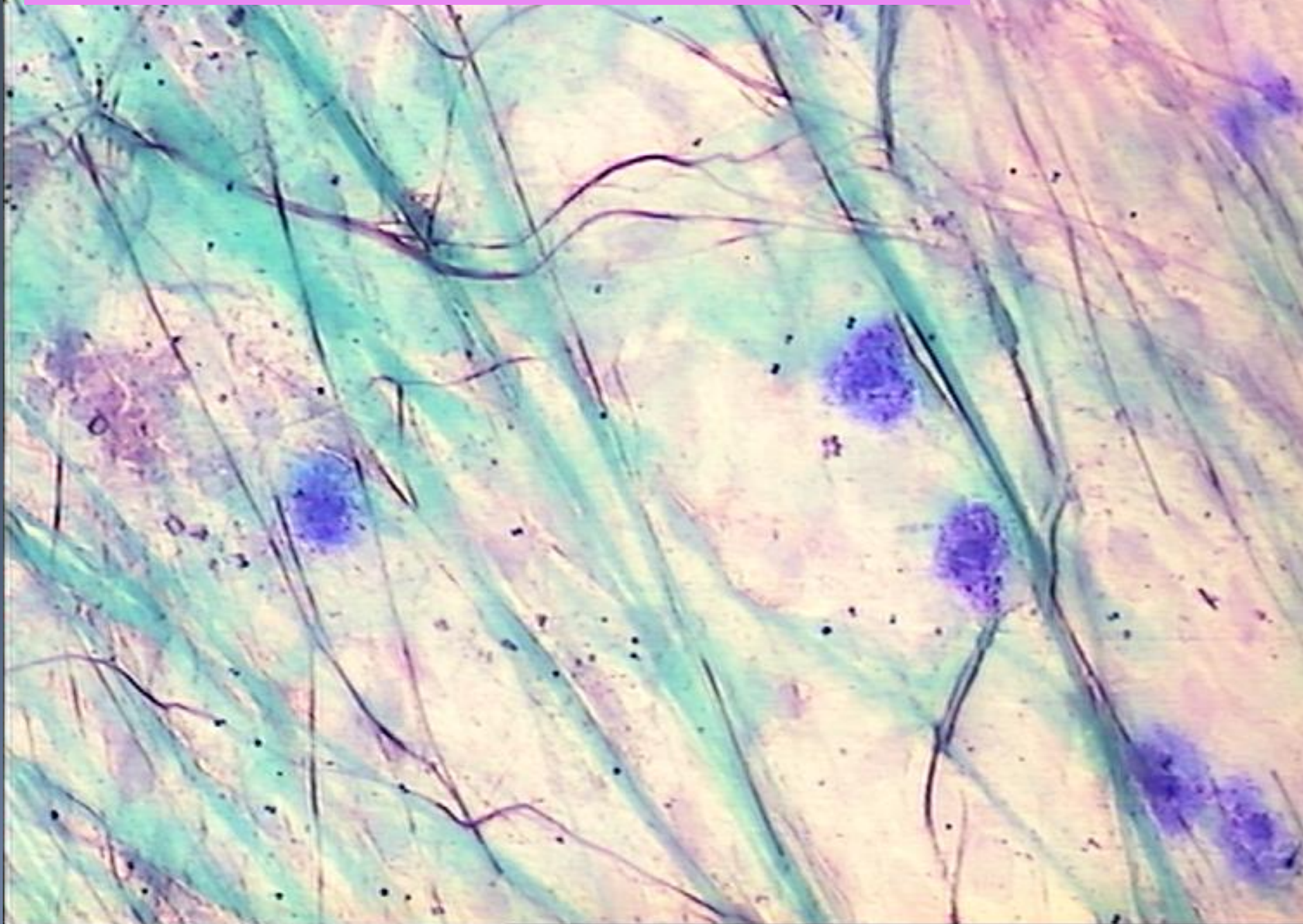
Collagen fibers, elastic fibers, mast cells, fibroblasts (nuclei)

This histological micrograph displays loose connective tissue from a mesentery. The field is filled with numerous spindle-shaped fibroblasts, their nuclei stained dark purple. Interspersed among these cells are bundles of pink-stained collagen fibers and thin, dark-stained elastic fibers. Several mast cells are also present, characterized by their large, reddish-orange granules and centrally located nuclei. The overall appearance is that of a loose, cellular connective tissue matrix.

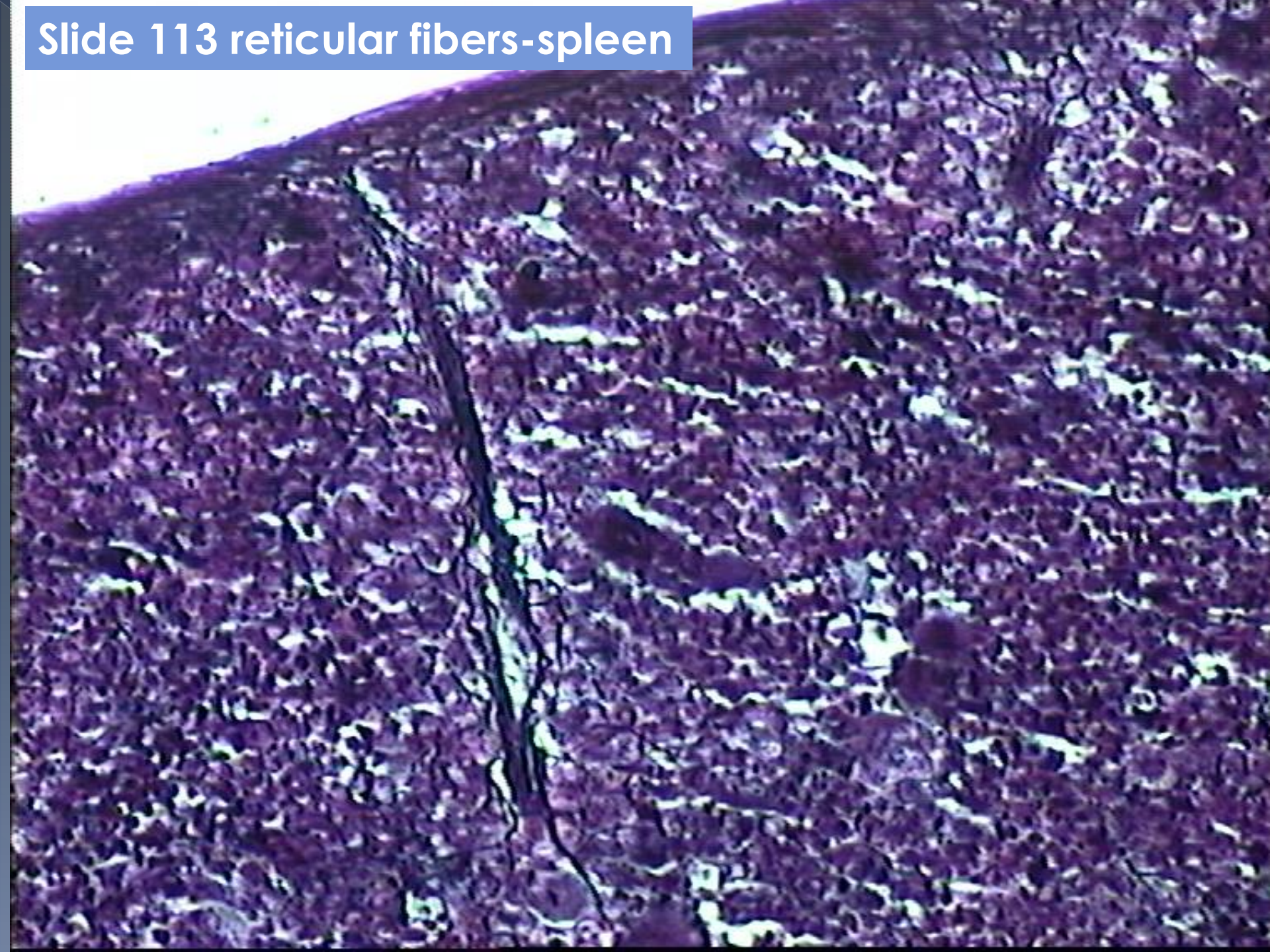
**Slide 9: loose connective tissue-mesentery
(stained with light green and hematoxylin)**



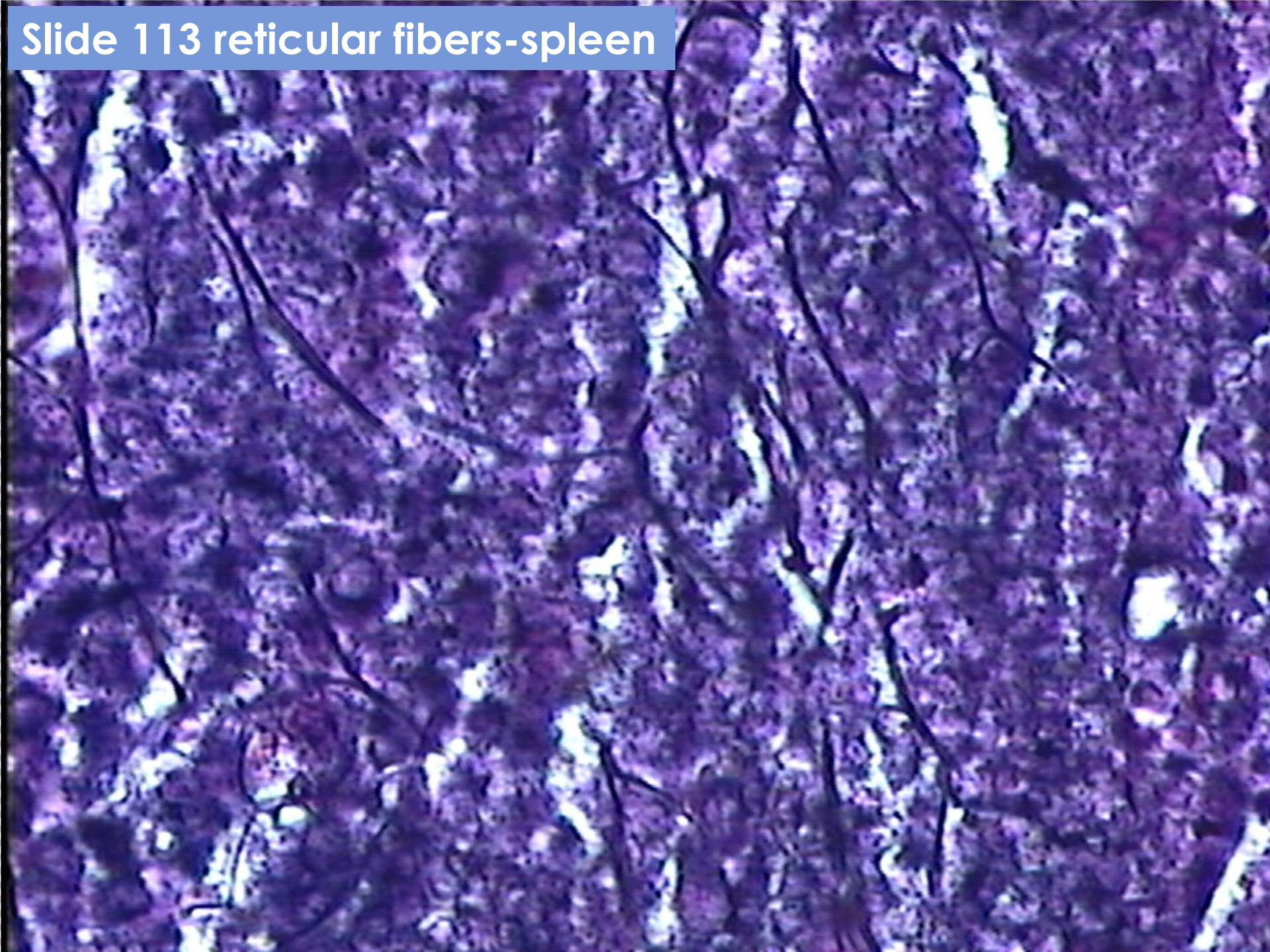
Slide 9: loose connective tissue-mesentery



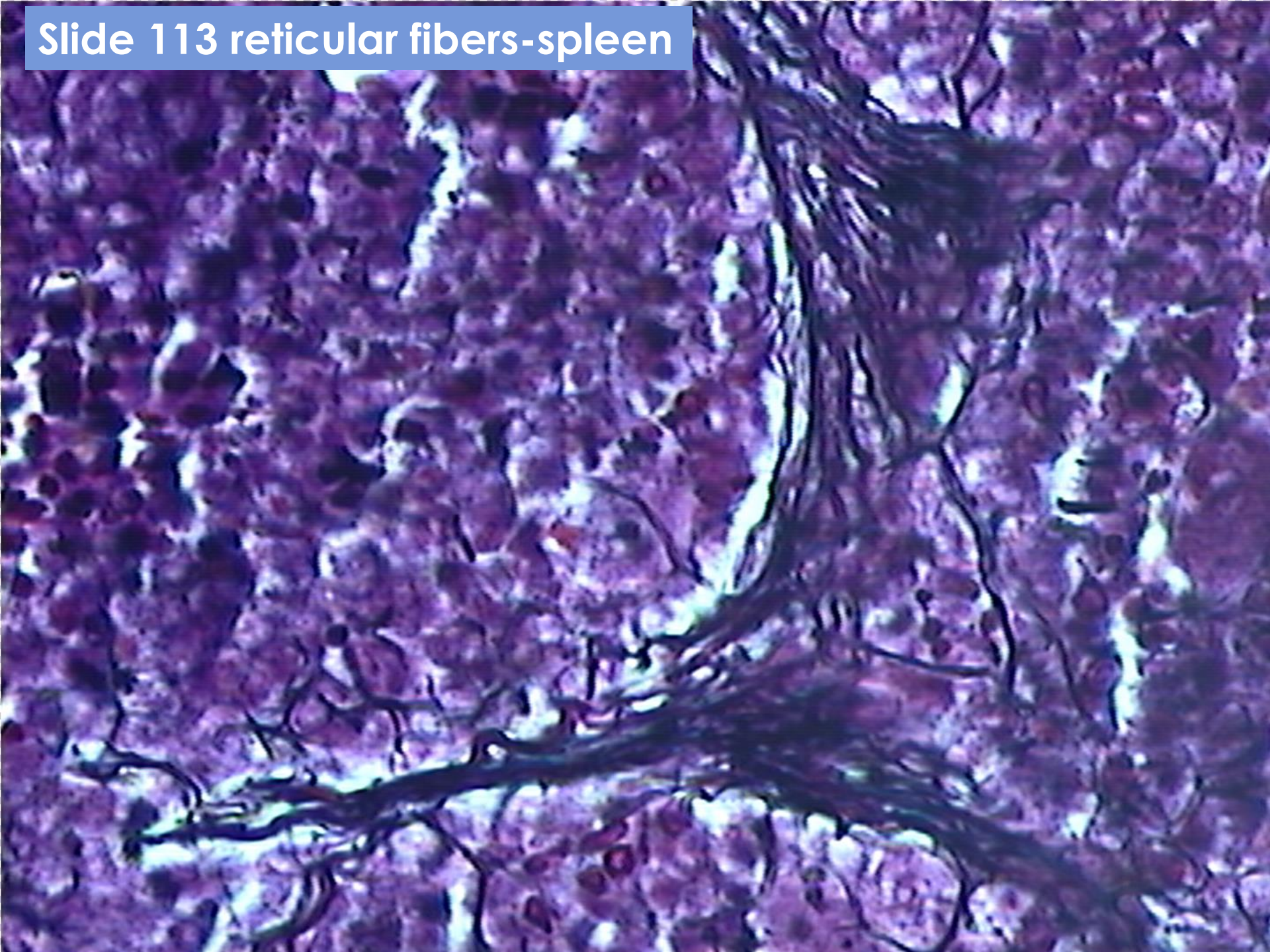
Slide 113 reticular fibers-spleen



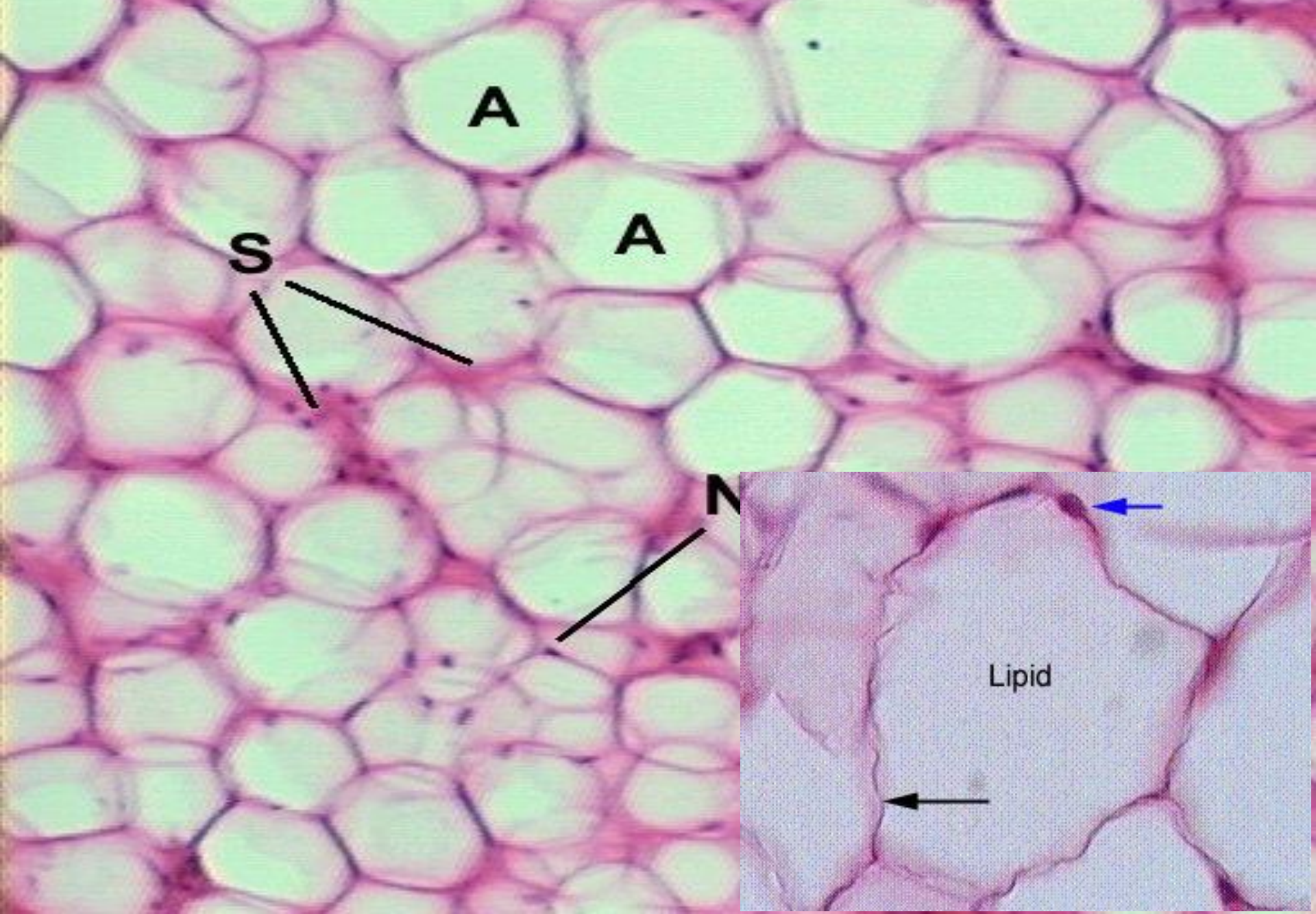
Slide 113 reticular fibers-spleen



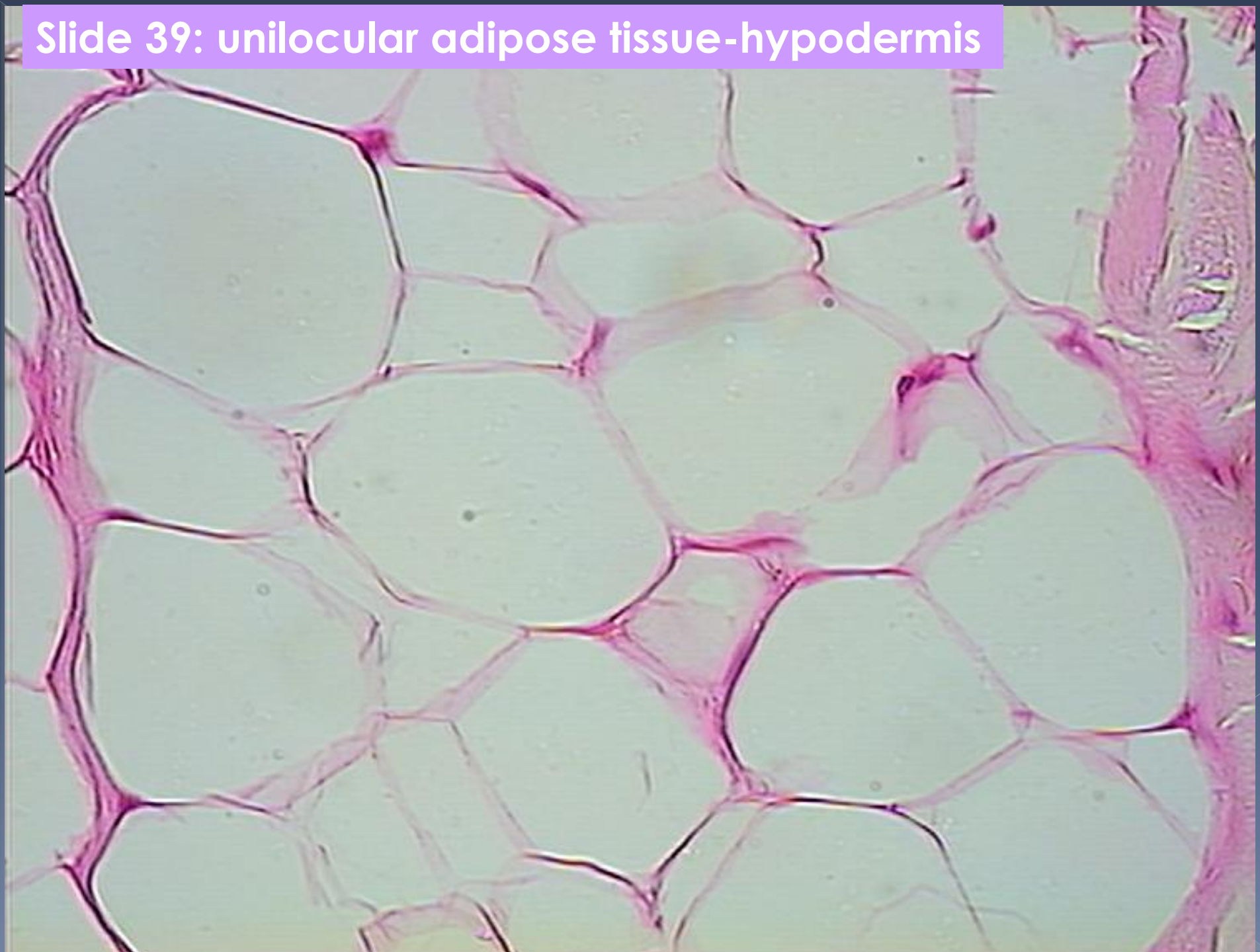
Slide 113 reticular fibers-spleen



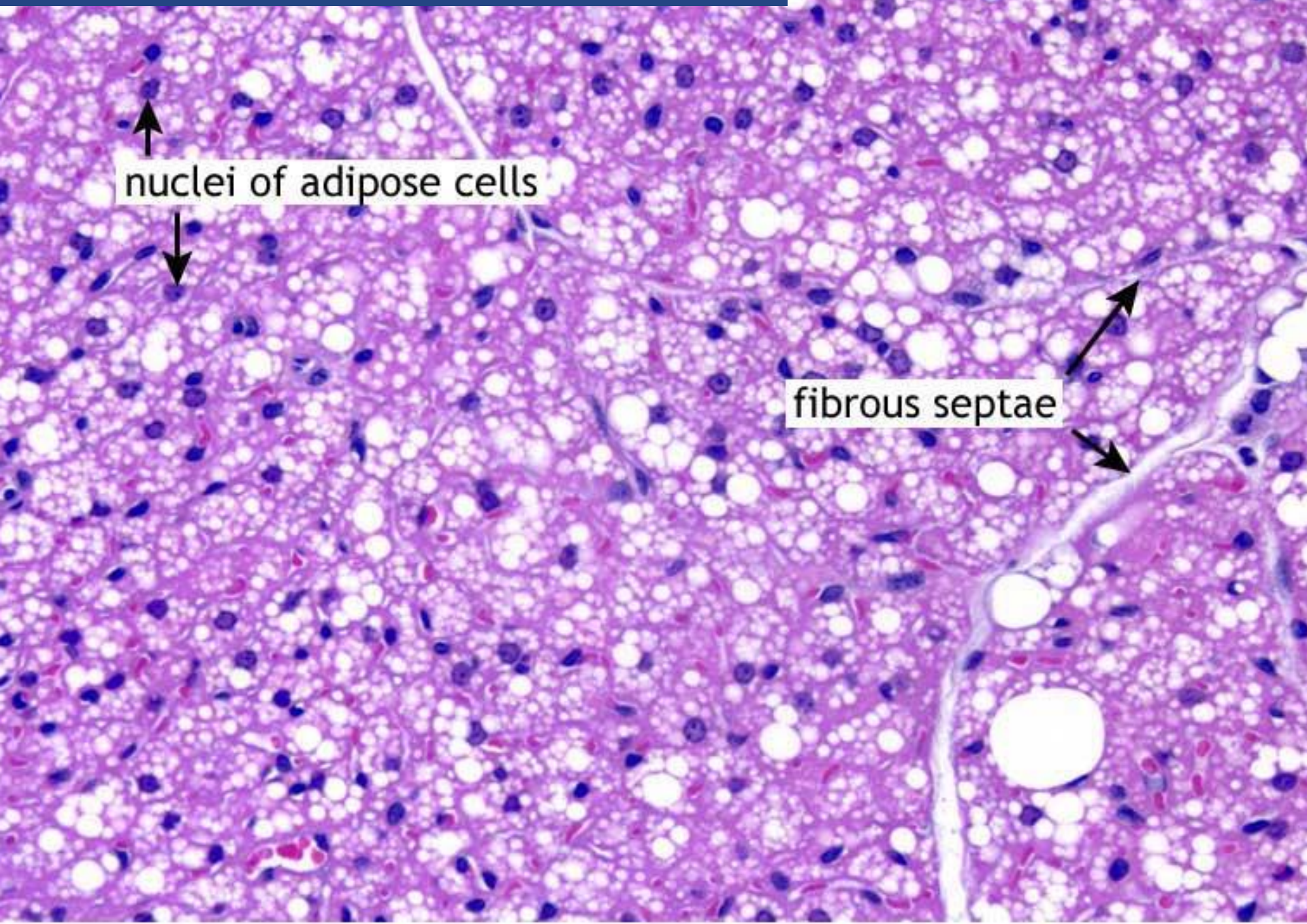
Slide 39: unilocular adipose tissue-hypodermis



Slide 39: unilocular adipose tissue-hypodermis



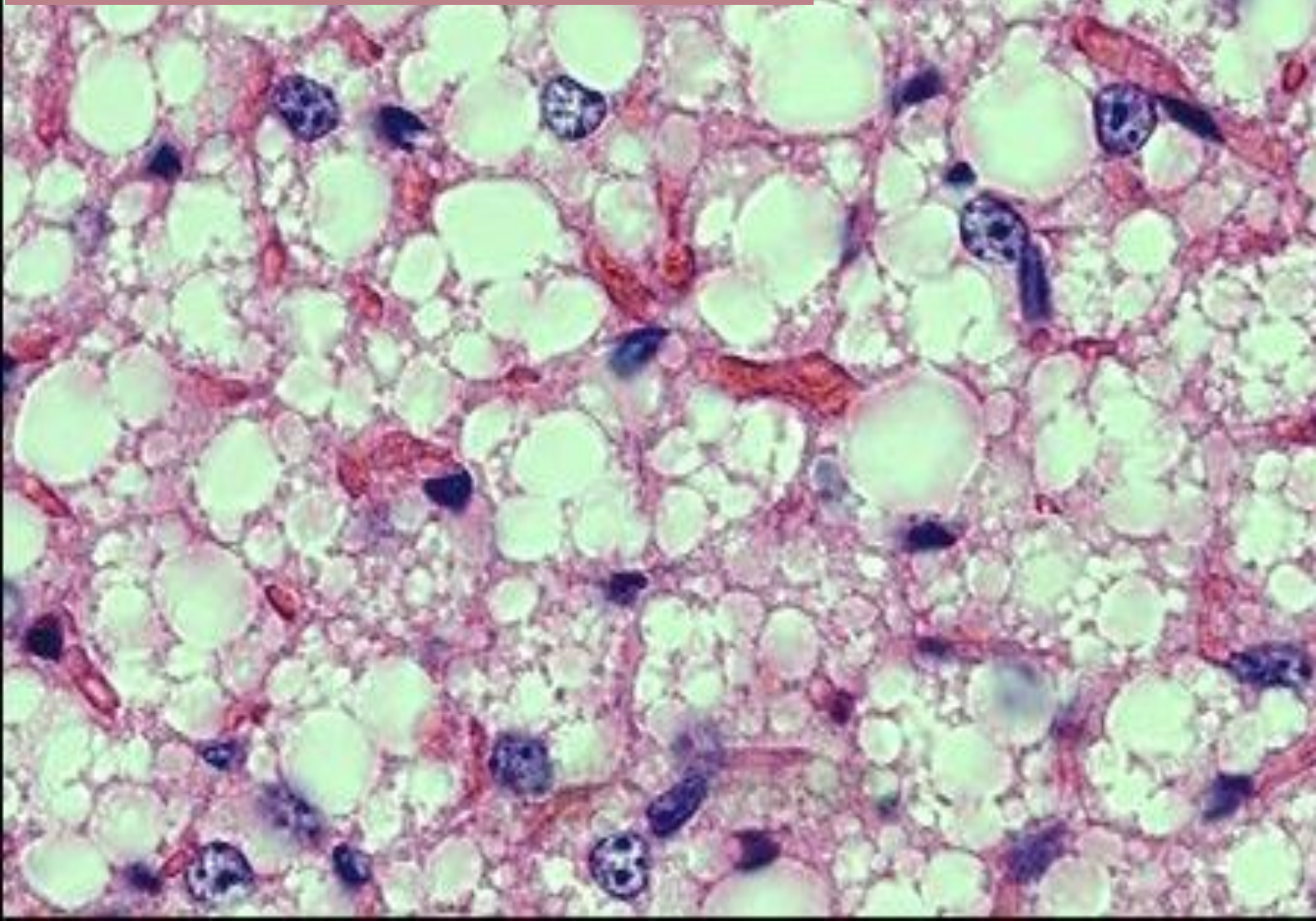
Slide 110: multilocular adipose tissue



nuclei of adipose cells

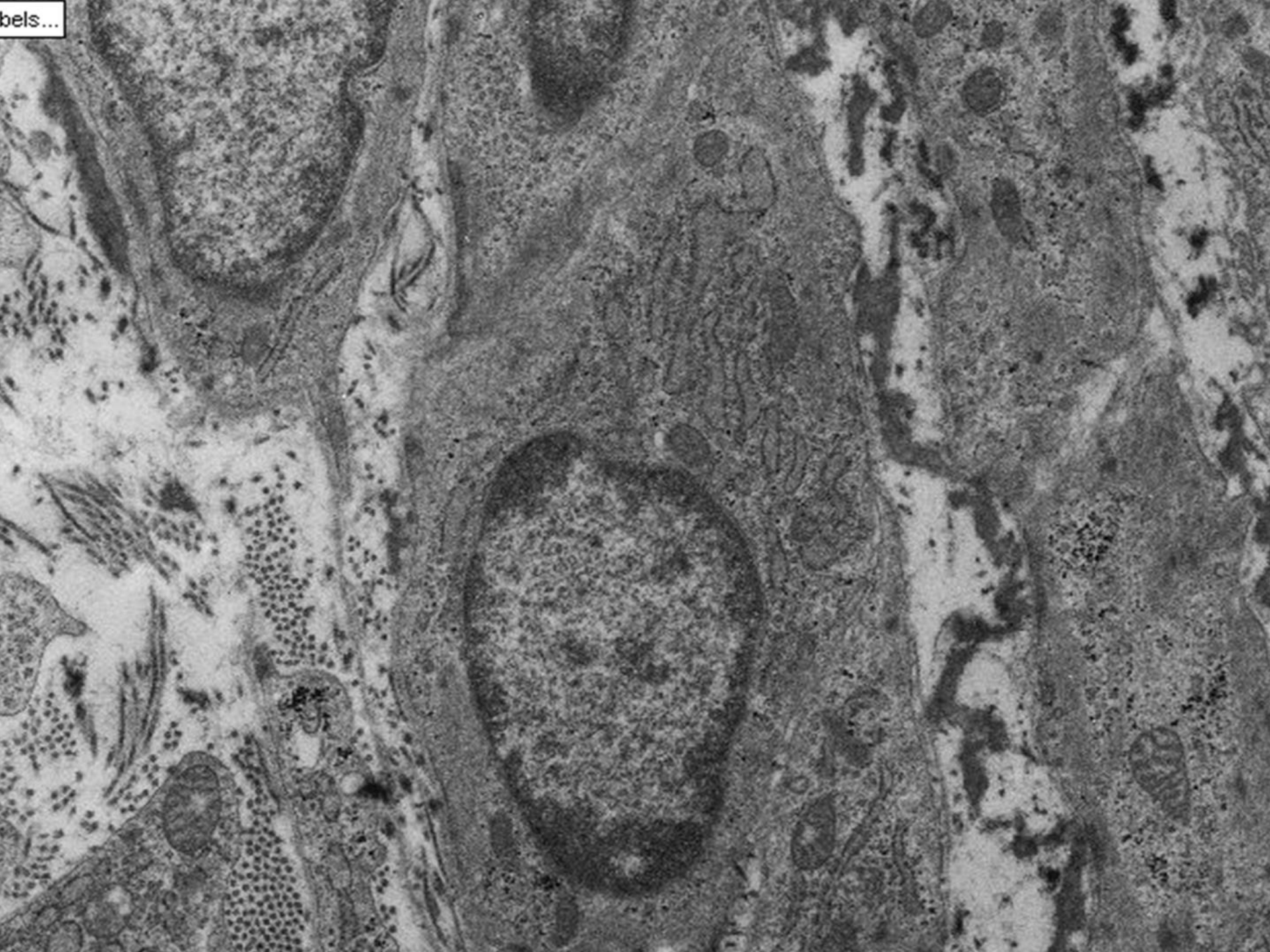
fibrous septae

Slide 110: multilocular adipose tissue

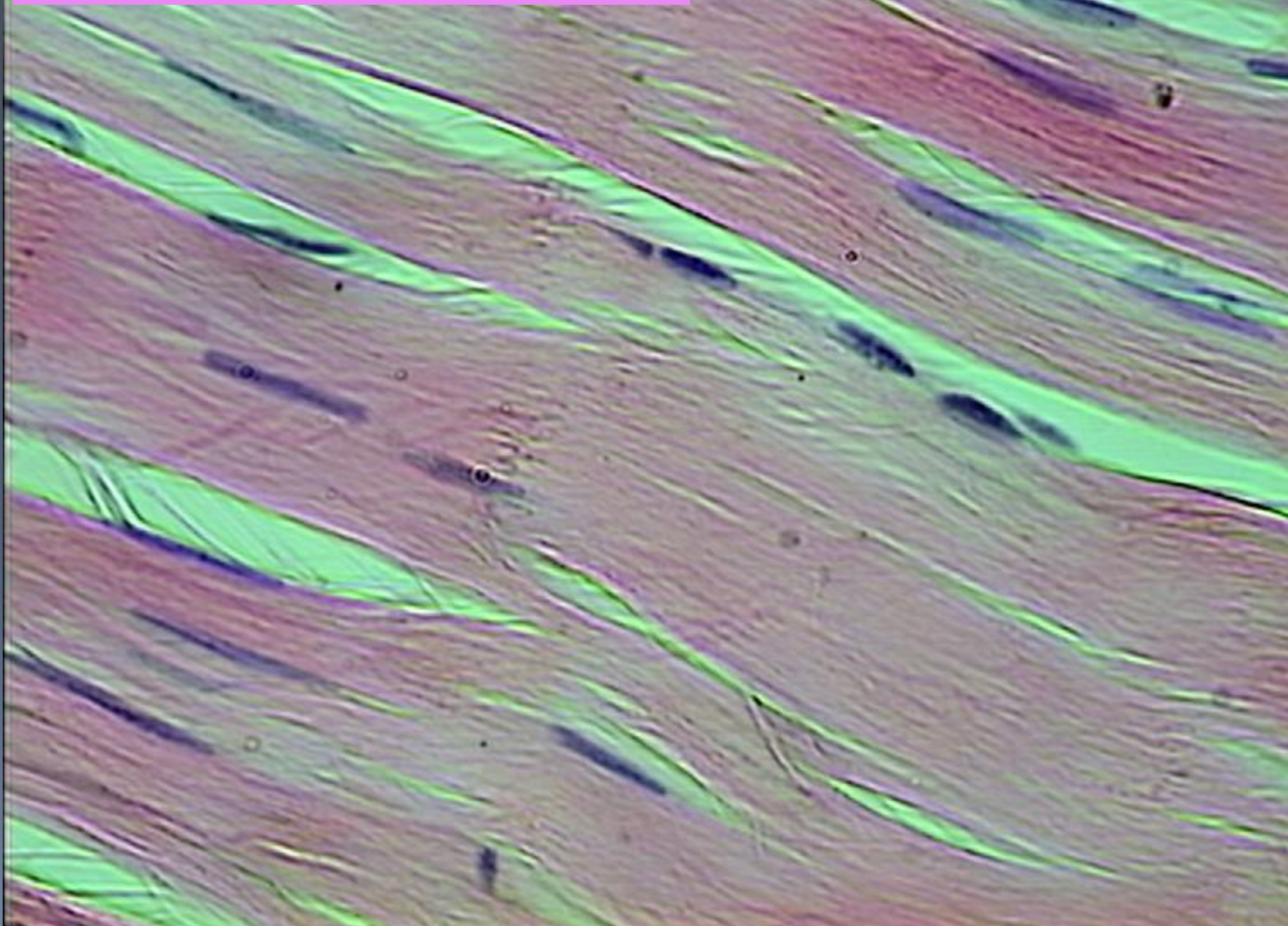


Next chapter –
Cartilage and bone

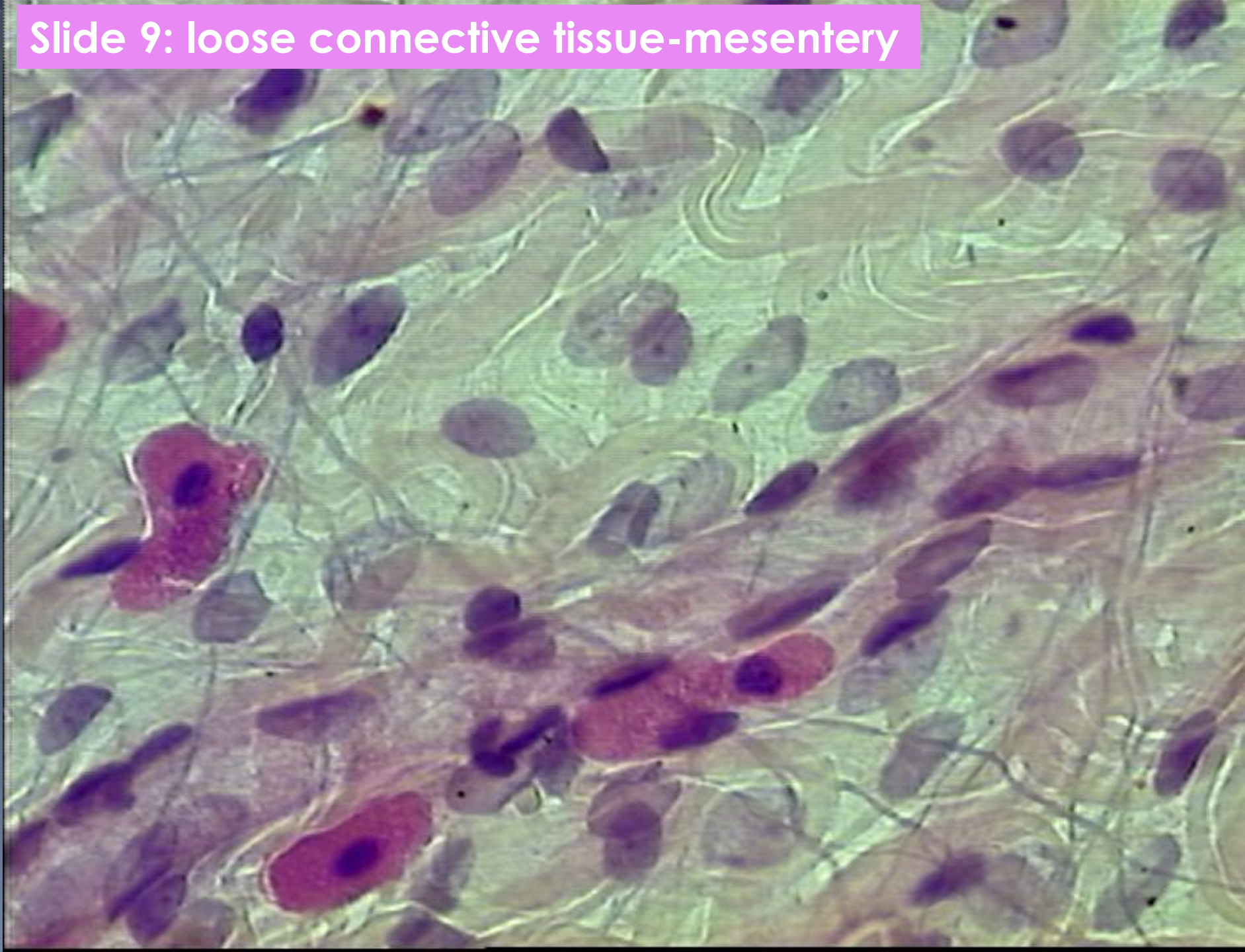
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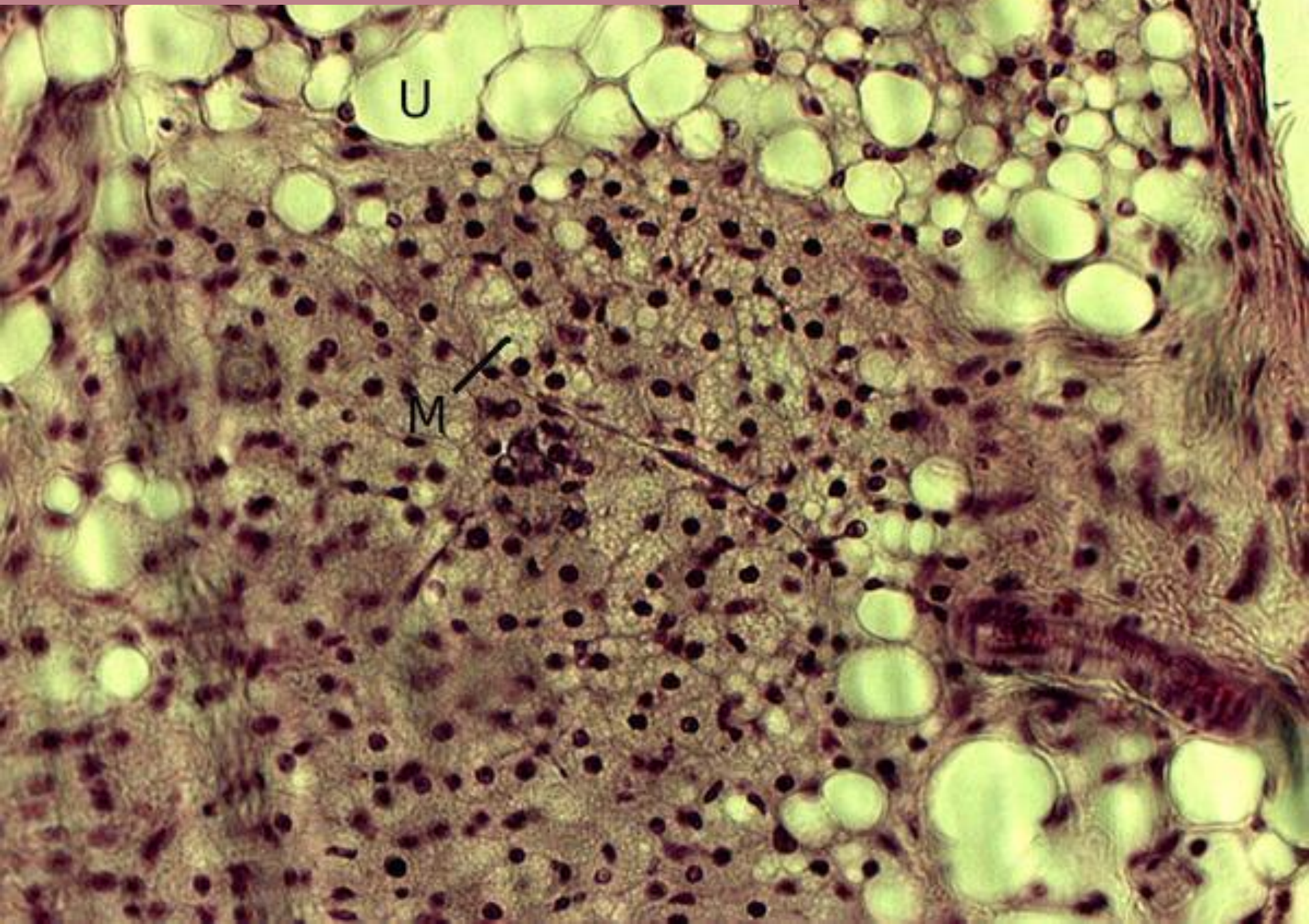
Slide 7: dense connective tissue-tendon

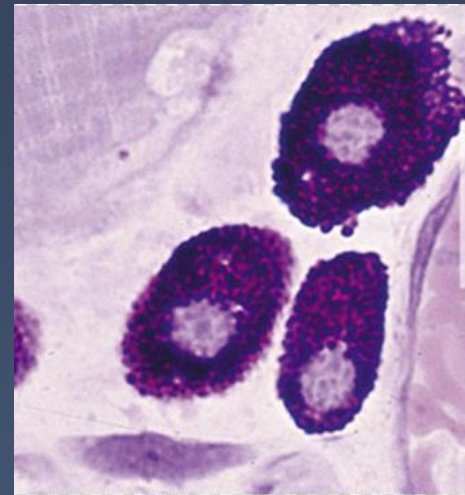
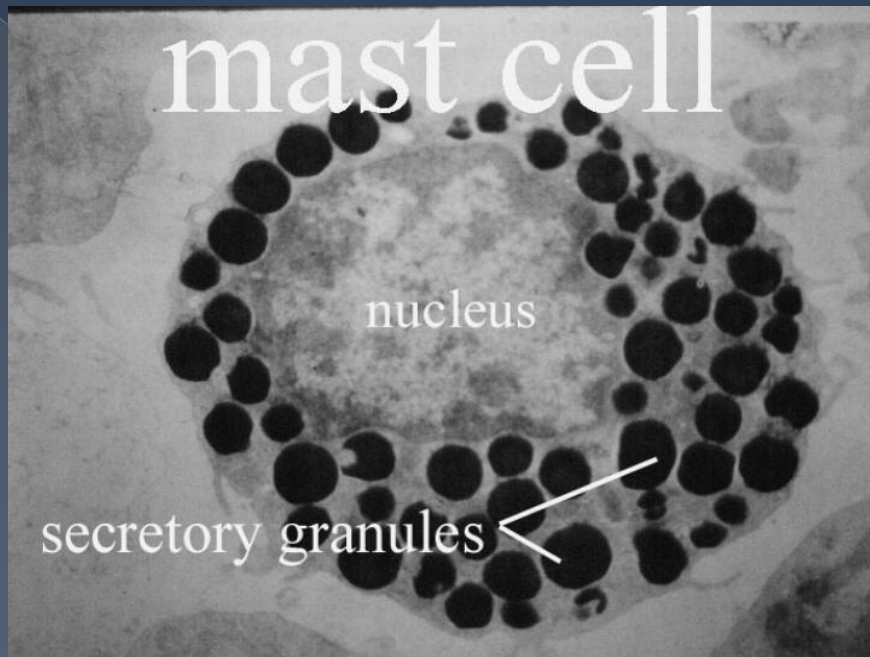


Slide 9: loose connective tissue-mesentery



Slide 110: multilocular adipose tissue





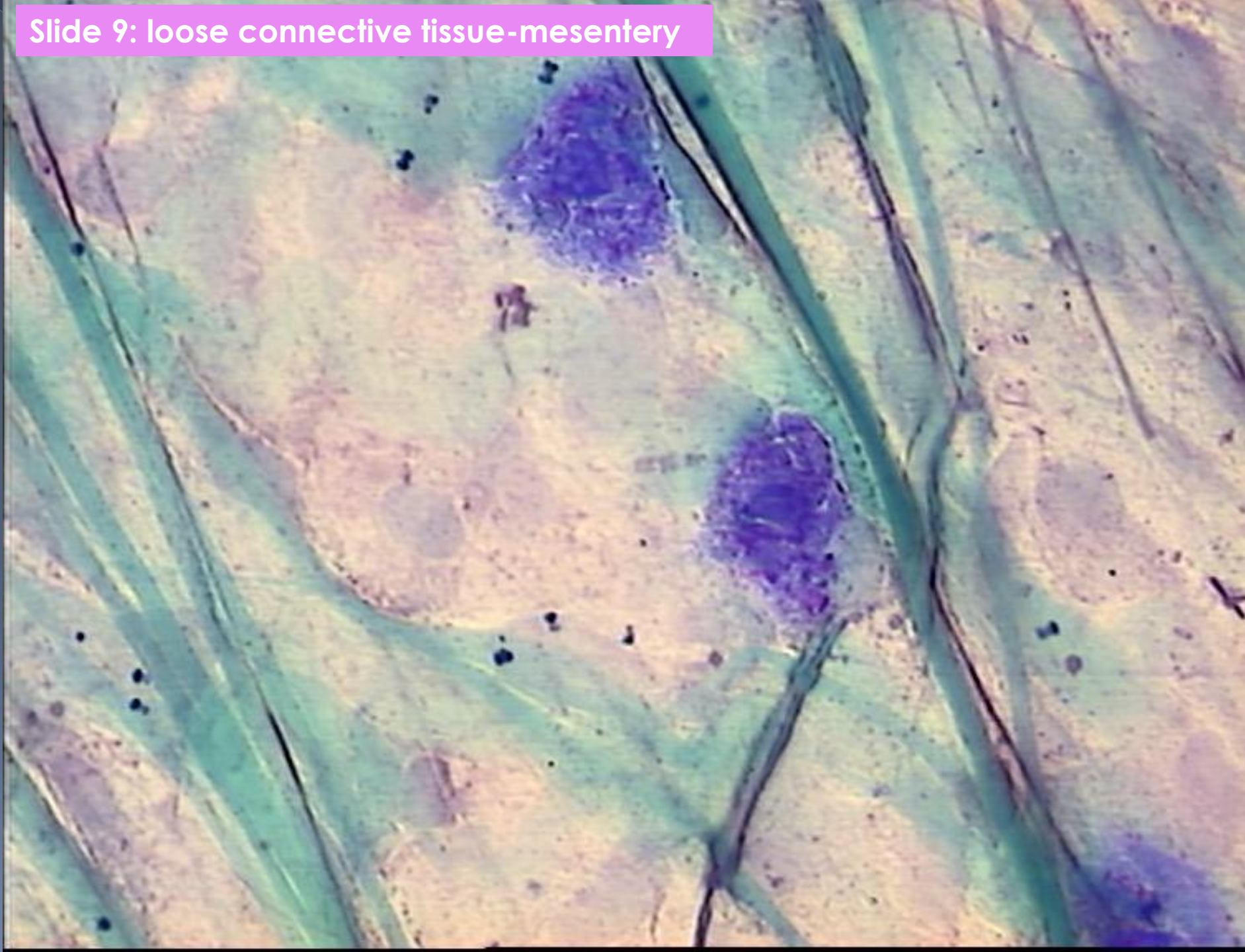
METACHROMASIA

Characteristic change in the color of staining carried out in biological tissues, exhibited by e. g. toluidine blue when it binds to particular substances.

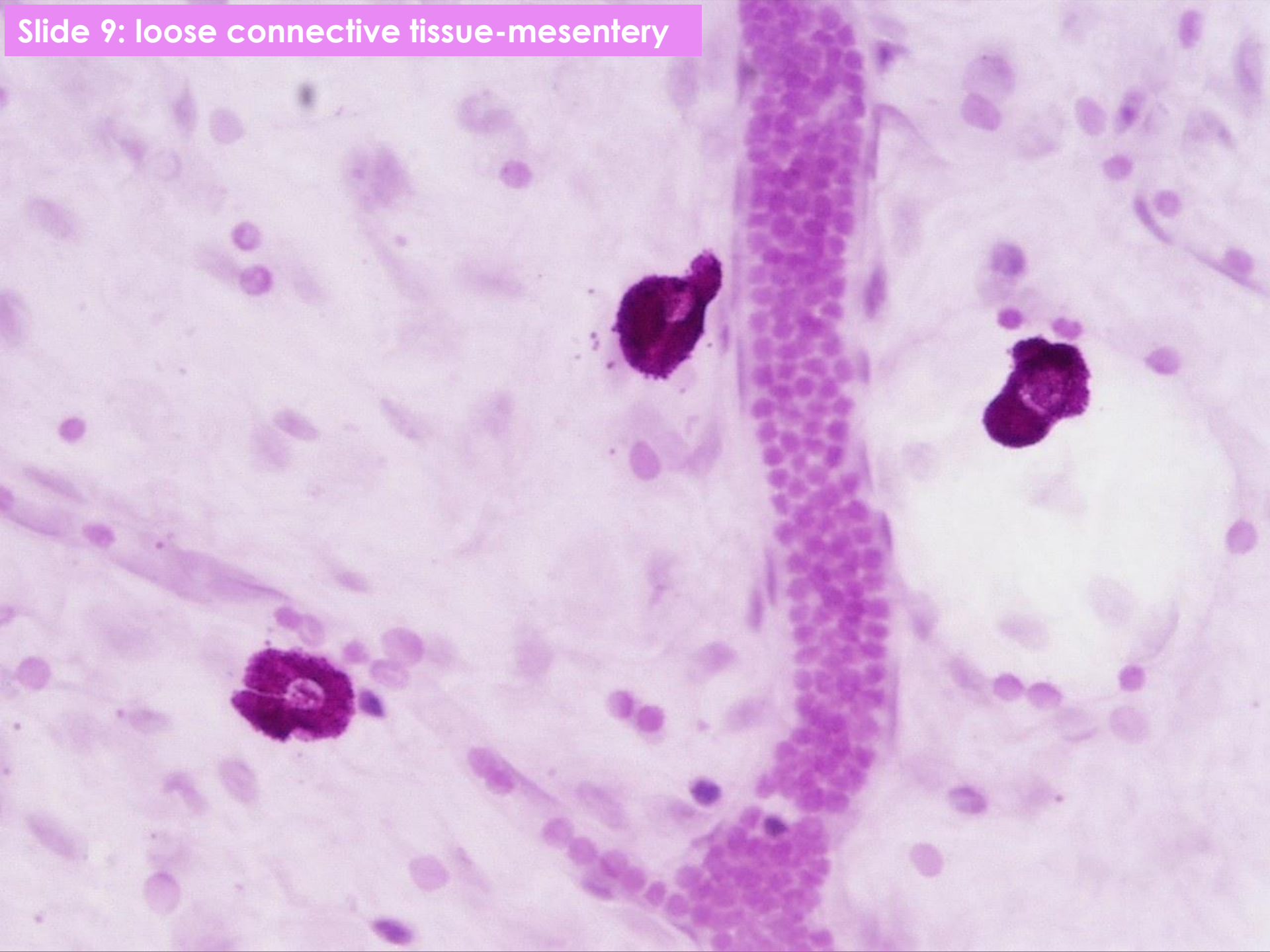
The molecules of concentrated basic dye polymerize in the presence of polyanions within the tissue. The absorption properties of these aggregations differ from those of the individual dye molecules.

Cell and tissue structures that have high concentrations of ionized sulfate and phosphate groups-such as the ground substance of cartilage, heparin-containing granules of mast cells, exhibit metachromasia.

Slide 9: loose connective tissue-mesentery

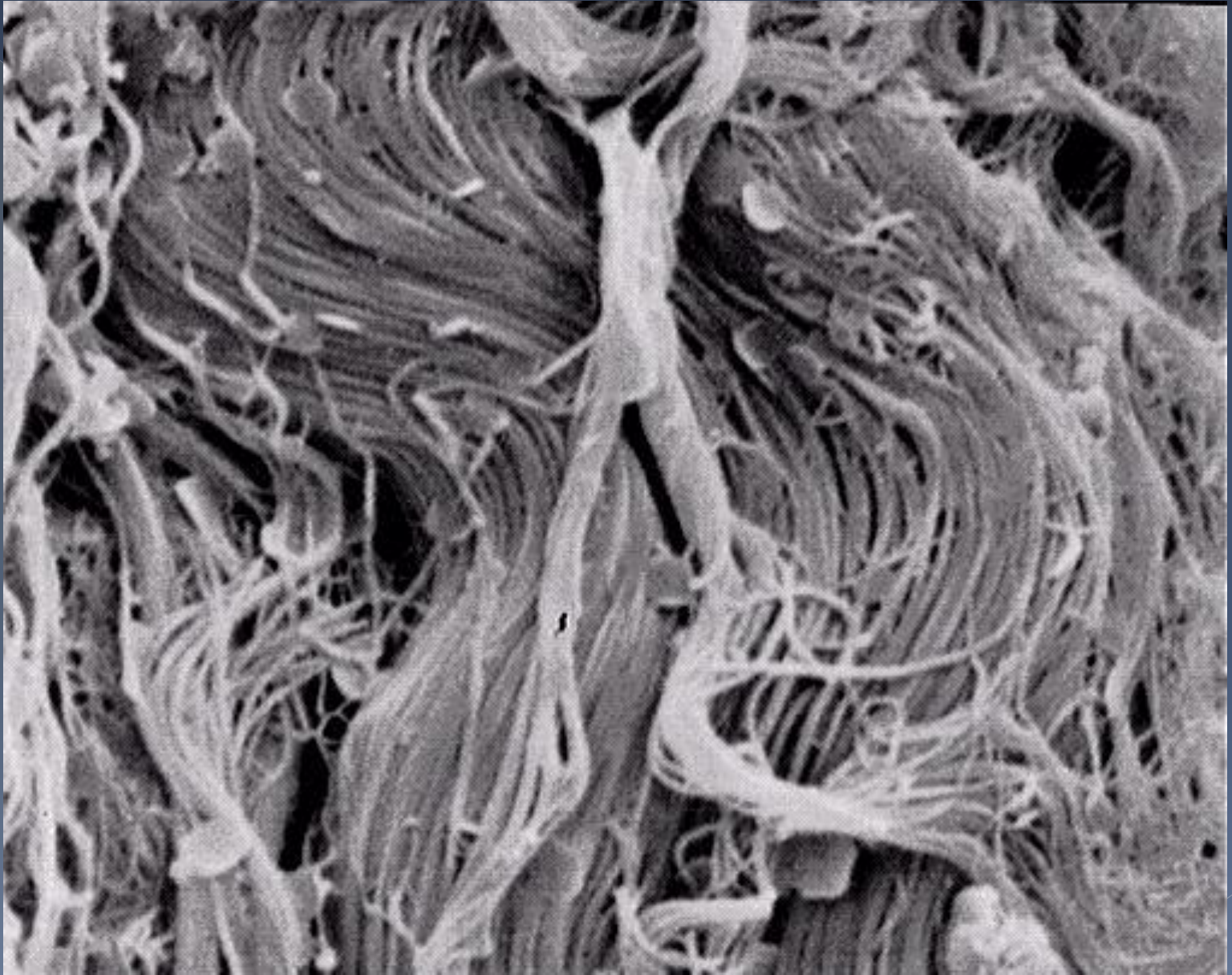


Slide 9: loose connective tissue-mesentery



Slide 39: unilocular adipose tissue-hypodermis



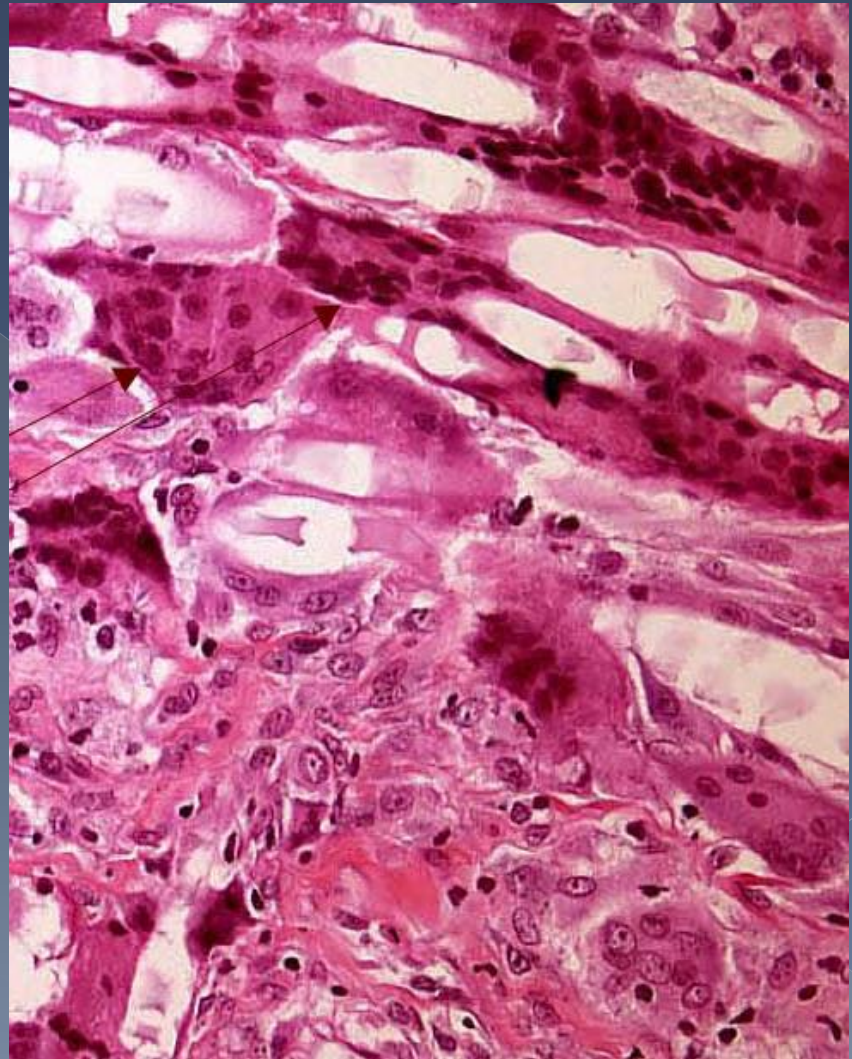


A bundle of collagen fibers, scanning electron microscope

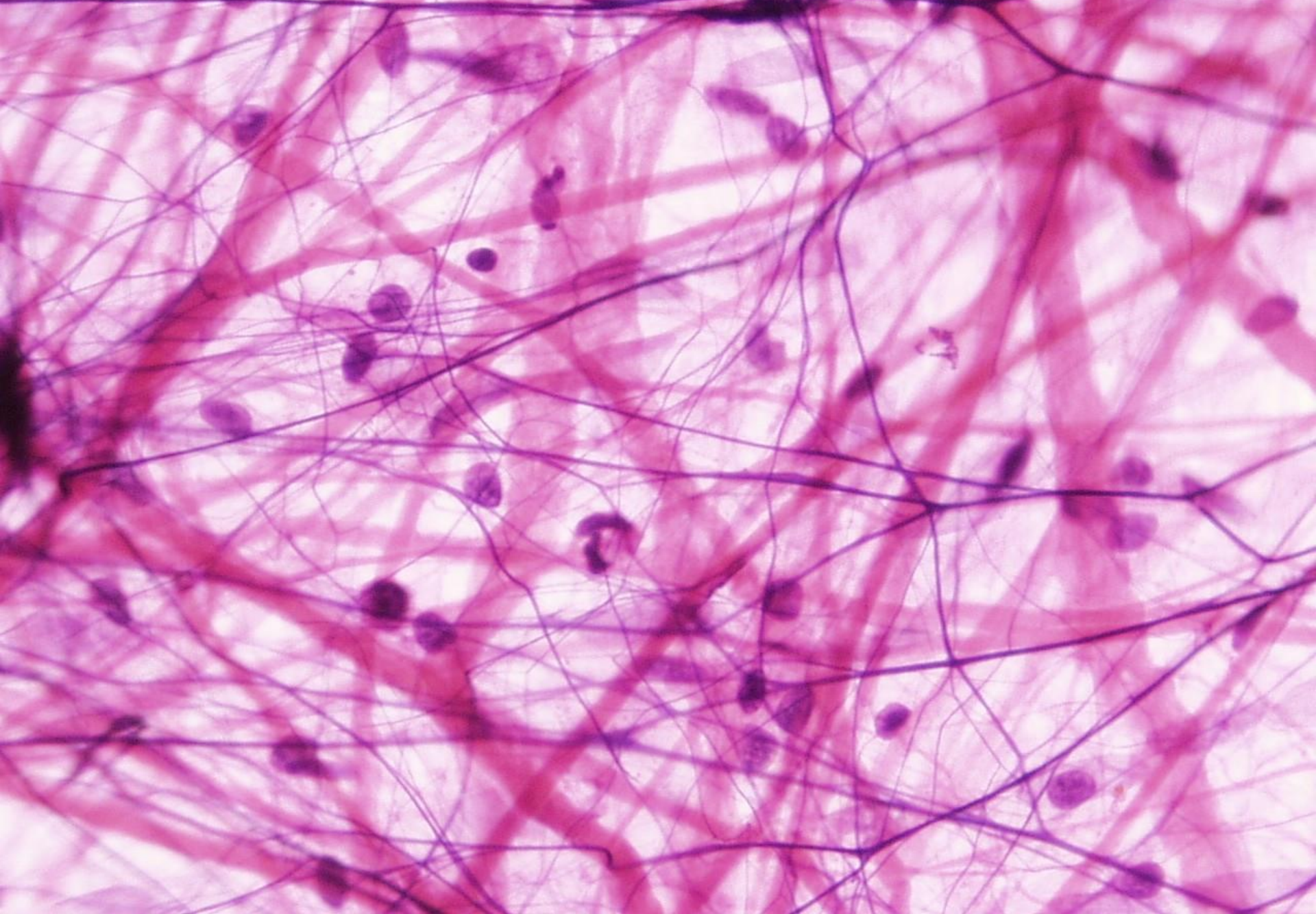
FOREIGN BODY GIANT CELLS

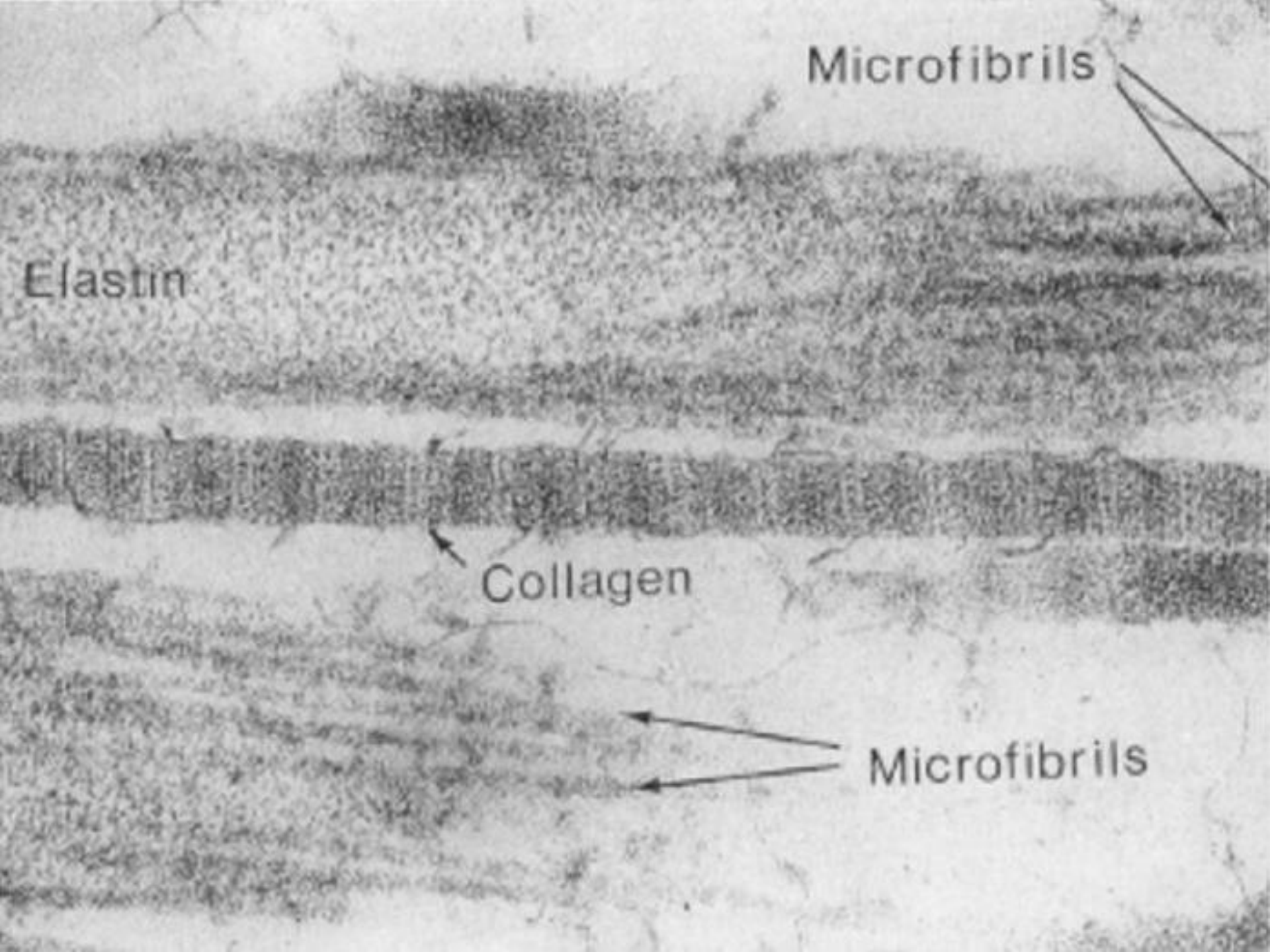
in suture granuloma

Foreign body giant cells



Slide 9: loose connective tissue-mesentery





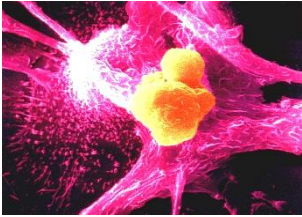
Microfibrils

Elastin

Collagen

Microfibrils

**Seminar: Structure and function of connective tissue proper and adipose tissue.
Practical class: Connective tissue proper and adipose tissue.**



phagocytosis of cancer cell
by macrophage (pink)

- loose connective tissue – mesentery, mast cells, elastic fibers (slide # 9),
- dense connective tissue – tendon (slide # 7),
- unilocular (yellow) adipose tissue – hypodermis or synovial membrane of joint capsule (slide # 38),
- multilocular (brown) adipose tissue (slide # 110),
- reticular fibers - spleen (slide # 113),
- leptin, the hormone of satiety, secreted by adipocytes (text # 22).
- “Crocodile people” - photo # 24

photo # 24



**Ornamental keloids on the skin of inhabitants
of New Guinea “Crocodile people”. From the special correspondent of the
Department of Histology & Embryology, Prof. dr hab. Marek Kamiński.**

Text # 22

LEPTIN, THE HORMONE OF SATIETY, SECRETED BY ADIPOCYTES

Adipocytes secrete the protein hormone (mol. mass 16 kD) termed leptin. The latter appears in the blood plasma at the concentration of 5-50 nmoles and its concentration depends upon the overall mass of adipose tissue of the body. Leptin binds to the specific receptors of the cellular membrane of hypothalamic neurons and choroid plexus cells. The role of the leptin is not clear since it was discovered few years ago. One of the hypothesis assumes that leptin is a kind of "adipostatic signal" that carries the information on the adipose tissue mass to the brain. Accordingly, the increase of leptin level triggers the nerve and hormonal mechanisms yielding in the reduction of adipose tissue mass (negative feedback). Pivotal role in that mechanism seems to be played by neuropeptide Y (neurotransmitter) that is very potent stimulator of appetite. Leptin inhibits secretion of neuropeptide Y and thereby reduces the appetite.

Both the discovery of leptin and our knowledge of adipose tissue homeostasis have emerged as a result of research of mutations in *obese (ob)* gene of the mice. Homozygous *ob/ob* mice fail to produce leptin and occur to be obese. Moreover, *ob/ob* mice cured with the leptin lost the weight and became slim. The results of those experiments were the source of a presumption that the human obesity could result in the mutation in the gene *ob*. However, the analysis of DNA obtained from obese people failed to confirm such an assumption.

Mouse obesity can also be a result of the mutation in *diabetes (db)* gene that codes for the leptin receptor. The similar mutation in human *db* gene of patients suffering of obesity was so far not found.

The starvation of mice can lead to the decrease of leptin level. On the other hand, the starvation results in malfunction of endocrine glands (reduction of secretion of LH and thyroxine as well as the increase of secretion of corticosterone and ACTH); the injection of leptin restores, at least partially, the normal function of endocrine glands disturbed by starvation. Therefore, leptin may be suspected to be one of the factors participating in the adaptation of starving organisms.

Leptin and its receptors constitute one of the systems controlling the adipose tissue homeostasis. Although the mechanisms causing the obesity continue to be an enigma, some pharmaceutical companies make contemporarily attempts to apply leptin as a drug for treatment of obese people.