Pathology

Subject : Pathology

Lec no : 6

Done By : Jana Alqhaiwi Hala Shmari

وقل رب زدني علماً

للوصول الى guidance الباثو و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الباثو على موقع النادي :

كتب المادة

ROBBINS

PATHOMA

شرح المادة

شرح المادة كاملة

يوجد شرح للمادة كاملة من أرشيف دفعة أثر ، مع العلم ان الوحدة الثالثة كانت تعطى من قبل الدكتورة عادة

PATHO ATHAR

شرح لاب الباثو

PATHO LAB

شرح الفريق العلمي

شرح قديم للفريق العلمي

PATHO - SCIENTIFIC TEAM

تفاريغ

يمكن الاستفادة من تفاريغ الدفع السابقة

تفاريغ دفعتي اثر و ورود قويات جدا

ATHAR PATHOLOGY NOTES

VEIN PATHO NOTES

QUIZZES

كويزات للدكاترة

Download File

Download File

Apoptosis : pathological و physiological في منه

- Is a form of cell death based on sequential activation of "death genes "and suicide pathway enzymes . Also called "programmed cell death " . انتحار
  the body should remove the cell from tissue as the role of the cell ends
- This is one method the body uses to get rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells
  has DNA damage / misfolded protein
  - **Apoptosis** is initiated by two most important pathways :

1 **Extrinsic pathway** : which is activated by the activation of the so-called death receptors on the surface of cell membrane . روابط
Ligands for such receptors are proteins such as tumor necrosis factor or Fas ligand . مثال

2 **Intrinsic mitochondrial pathway** : which is initiated by increased mitochondrial permeability & the release of pro-apoptotic molecules such as cytochrome C that acts on initiator caspases which are capable of degrading the cell's own nuclear DNA & nuclear & cytoplasmic proteins .

مواد تحفز ال opoptosis

Key enzyme of opoptosis

damage to mitochendria + opening conductive channels

Apoptosis is a pathway of cell death in which cells acti- vate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins

The death receptor (extrinsic) pathway of apoptosis. Many cells express surface molecules, called death receptors, that trigger apoptosis.

Caspases are a family of endoproteases (enzymes) that provide critical links in cell regulatory networks controlling inflammation and cell death

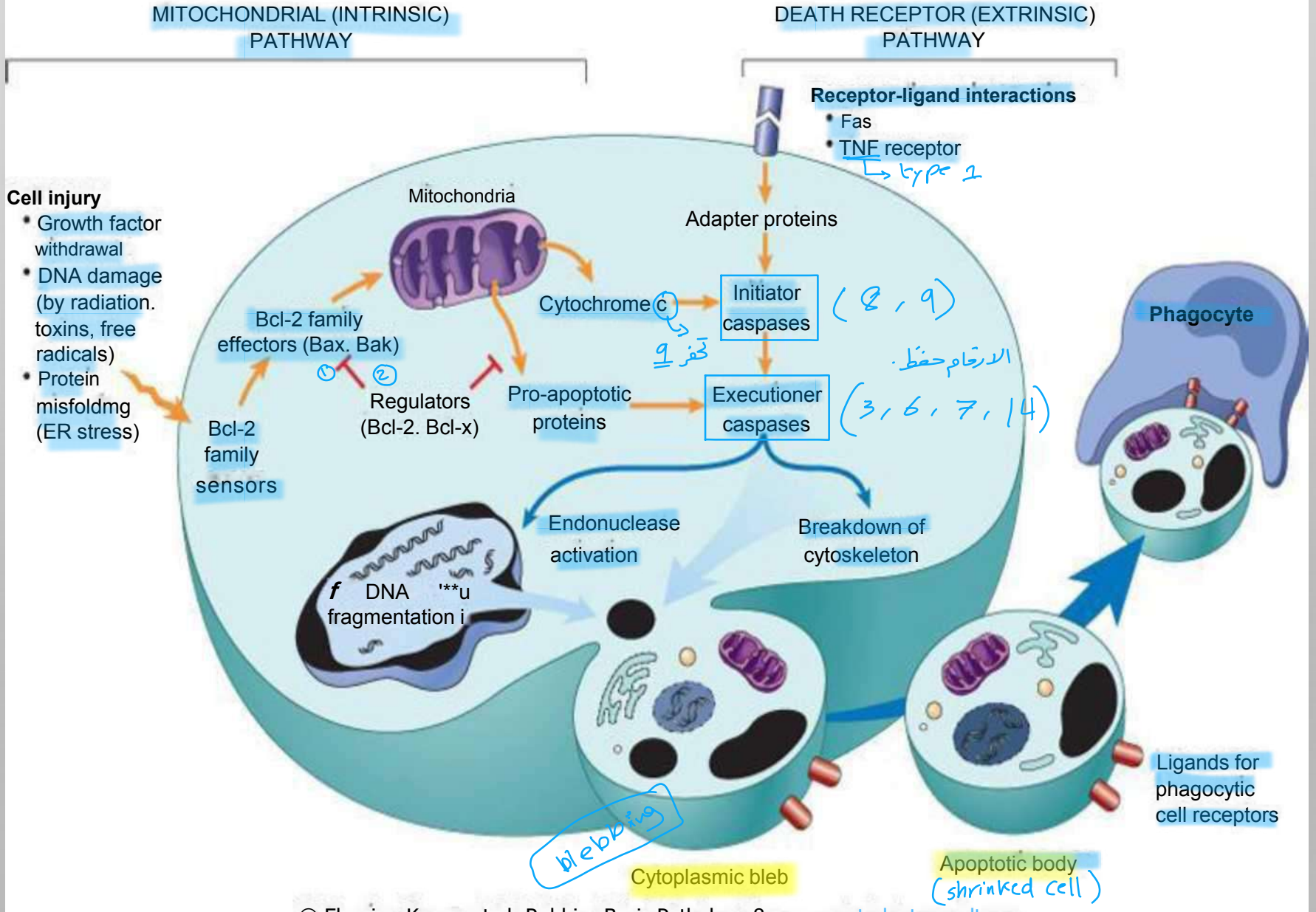
ما الفرق بين ال **pathways** تاعة ال **opoptosis** ؟
هي عمليه الابتداء اشي ببلش من **receptors** او **ligands**
والثاني ببلش من ال **mitochondria** وبطلع منها اشياء مثل ال **cytochrome**
الي بحفز ال **caspases**

اهم معلومه انو اهم انزيم في عمليه ال **opoptosis** هو ال **caspases**

- **APOPTOSIS** CAN BE TRIGGERED BY **BOTH INTERNAL AND EXTERNAL FACTORS**. INTERNAL FACTORS INCLUDE **MISFOLDED PROTEINS** AND **DEREGULATED SIGNALING**, WHILE **NUTRIENT LOSS, RADIATION, HEAT, AND ACTIVATION OF CELL SURFACE RECEPTORS, SUCH AS TNF AND FAS3, ARE EXTERNAL TRIGGERS.**
- **APOPTOSIS** IS INITIATED BY THE INTERACTION OF **PRO-APOPTOTIC AND ANTI-APOPTOTIC MEMBERS OF THE BCL-2 FAMILY,** INCLUDING BAD AND BCL-2. THIS LEADS TO THE ACTIVATION OF CASPASE PROTEINS, A FAMILY OF PROTEOLYTIC ENZYMES, WHICH ACTIVATE OTHER PROTEINS THAT DISMANTLE THE CYTOSKELETON, ORGANELLES, AND DEGRADE DNA. THIS CONTROLLED PROCESS ALLOWS ADJACENT TISSUE TO SUFFER MINIMAL DAMAGE

BCL-2 family has pro-opoptic gene and anti-opoptic gene

86 :Mechanisms of Apoptosis



- Apoptosis is mediated by **proteolytic enzymes called caspases**, which trigger cell death by cleaving specific proteins in the cytoplasm and nucleus. **Caspases** exist in all cells as inactive precursors, or **procaspases**, which are usually activated by cleavage by other caspases, producing a proteolytic caspase cascade.

كيف بصير **activation** في ال **caspases** ؟ عن طريق **cleavage** ل **caspases** ثانيين

- The initiation of apoptosis is tightly regulated by activation mechanisms, because once apoptosis has begun, it inevitably leads to the death of the cell

حتمًا

ال **opoptosis** مجرد ما بدأ لا يتوقف لازم يكمل

Necrosis سمات ال؟

Apoptosis differs from necrosis which is characterized by:

(1) loss of membrane integrity → rapture of cell membrane.

(2) enzyme digestion of cell **By lysosome contents**

(3) leakage of cellular contents, with inflammation

(4) always pathologic, → **Leads to digestion of the cell and degradation of it's products**

while apoptosis is usually physiologic, & rarely pathologic .

However, apoptosis & necrosis sometimes coexist.

Opoptosis maintains homeostasis,preserve membrane integrity , shrinkage of cell

CAUSES OF APOPTOSIS

Apoptosis occurs normally, as a physiological phenomenon, but pathologically, when irreparable DNA damaged cells are eliminated by apoptosis.

Apoptosis in Physiologic Situations

serves to eliminate cells that are no longer needed & maintain a steady number of various cell populations in tissues.

It is important in the following physiologic situations :

1. **The programmed destruction of cells during embryogenesis**, including implantation, organogenesis, developmental involution, metamorphosis.

2 .**Hormone deprivation** : resulting in involution of hormone-dependent tissue such as

(a) **endometrial cell breakdown during the menstrual cycle.** حيض المرأه بسبب نقصان الاستروجين

(b) **regression of the lactating breast after weaning.** فطام رجوع الصدر الى حجمه الطبيعي

hyperplasia لانو صارله

3. **Cell loss in proliferating cell populations, as in intestinal crypt epithelia, so as to maintain a constant number.**

4. **Death of cells** that have served their useful purpose such as neutrophils in an **acute inflammation**, & lymphocytes at the end of an immune response.

It will be eliminated by opoptosis

Body response to the cell injury

نقص

Apoptosis occurs in these cells because they are deprived of necessary survival signals, such as growth factors.

Apoptosis in Pathologic Conditions

Apoptosis eliminates cells that are genetically altered or injured beyond repair without eliciting host reaction.

(I) DNA damage: Radiation, Cytotoxic anticancer drugs, extreme of temperature, & hypoxia can damage DNA, either directly or via production of FR.

Free radicals: موجود بأخرها active بتخليها Free مع النواة و مكونات الخلية.

- If the damage is irreparable, cell triggers apoptosis .
- Inducing apoptosis of cancer cells is a desired effect of chemotherapeutic agents, many of which work by damaging DNA .

2. Accumulation of misfolded proteins → ممكن يجي سؤال case

Improperly folded proteins may arise because of mutations in the genes encoding these proteins, or damage caused by FR. **Free radicals, inflammation and radiation**

3. Cell injury in certain viral infections, in which loss of infected cells is largely due to apoptotic death that may be induced either by

(1) by the virus itself (as in adenovirus & HIV infections), or

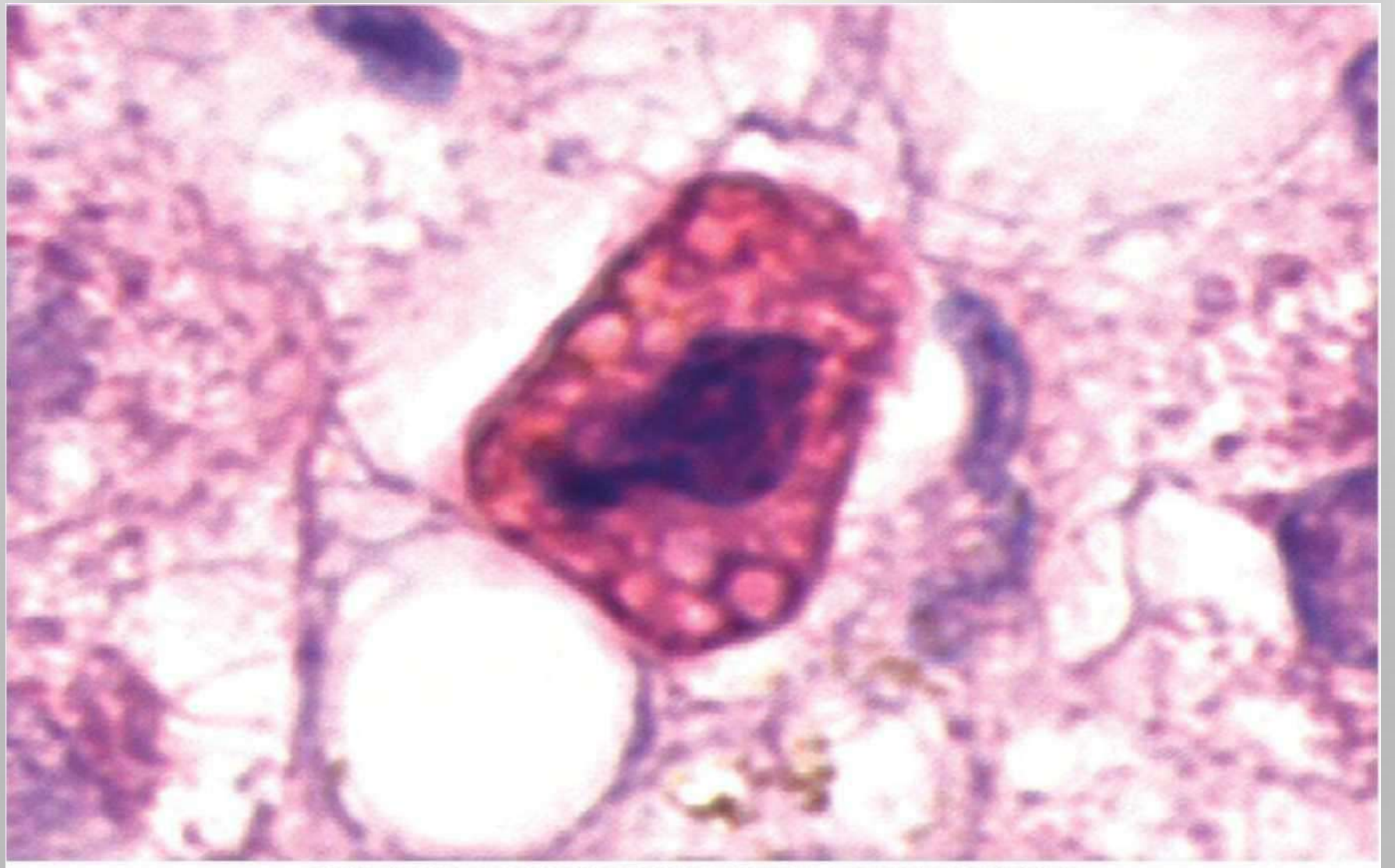
(2) by the host immune response (as in viral hepatitis) . عدوى فايروسيه للكبد بعدين بصيرة **opoptosis**

4. Pathologic atrophy in parenchymal organs after duct obstruction , such as occurs in the pancreas, parotid gland, and kidney . duct أي عضو فيه

Morphology of apoptosis:

- Apoptotic cells appear as: a **rounded or oval masses**, with intensely eosinophilic cytoplasm. Dark orange colour in necrosis and opoptosis — يعني متكتل او مرصوص عبعضه
- Nuclei show **chromatin condensation** & ultimately, Karyorrhexis . fragmentation.
- The cells are **rapidly shrink** , form cytoplasmic **buds** & fragment into **apoptotic bodies** composed of membrane-bound vesicles of cytosol & organelles. — براعم
- Because these apoptotic bodies are quickly extruded (projected through cell wall) & **phagocytosed** with out eliciting an inflammatory response ... — خارج/مقذوفا — مثل العقلة

F 80 : Apoptosis of a liver cell in viral hepatitis. The cell is reduced in size & contains brightly eosinophilic cytoplasm & a condensed nucleus.



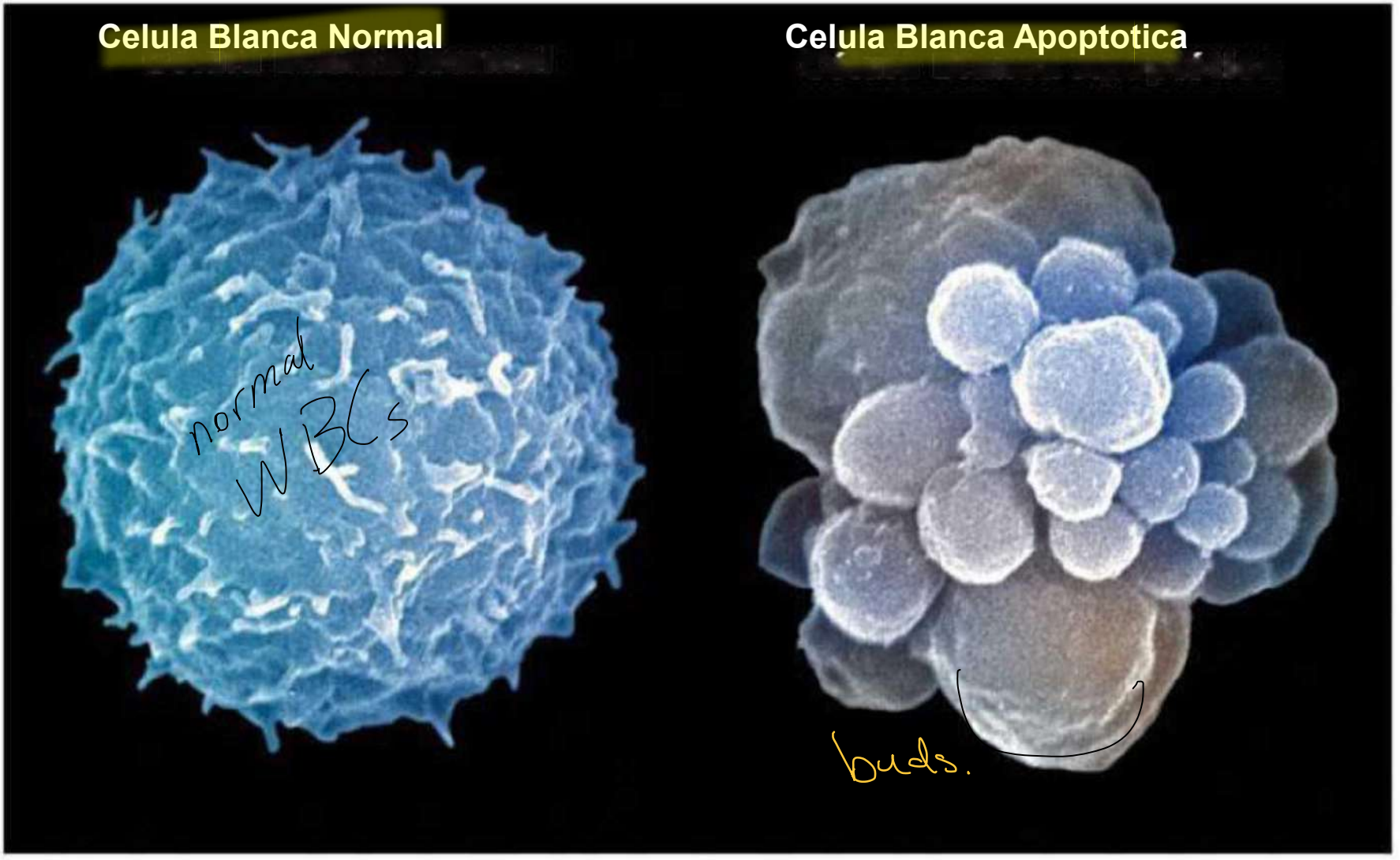


Figure 81 - Electron Microscopic (EM) appearance of normal(left) & apoptotic white Blood Cell (right).

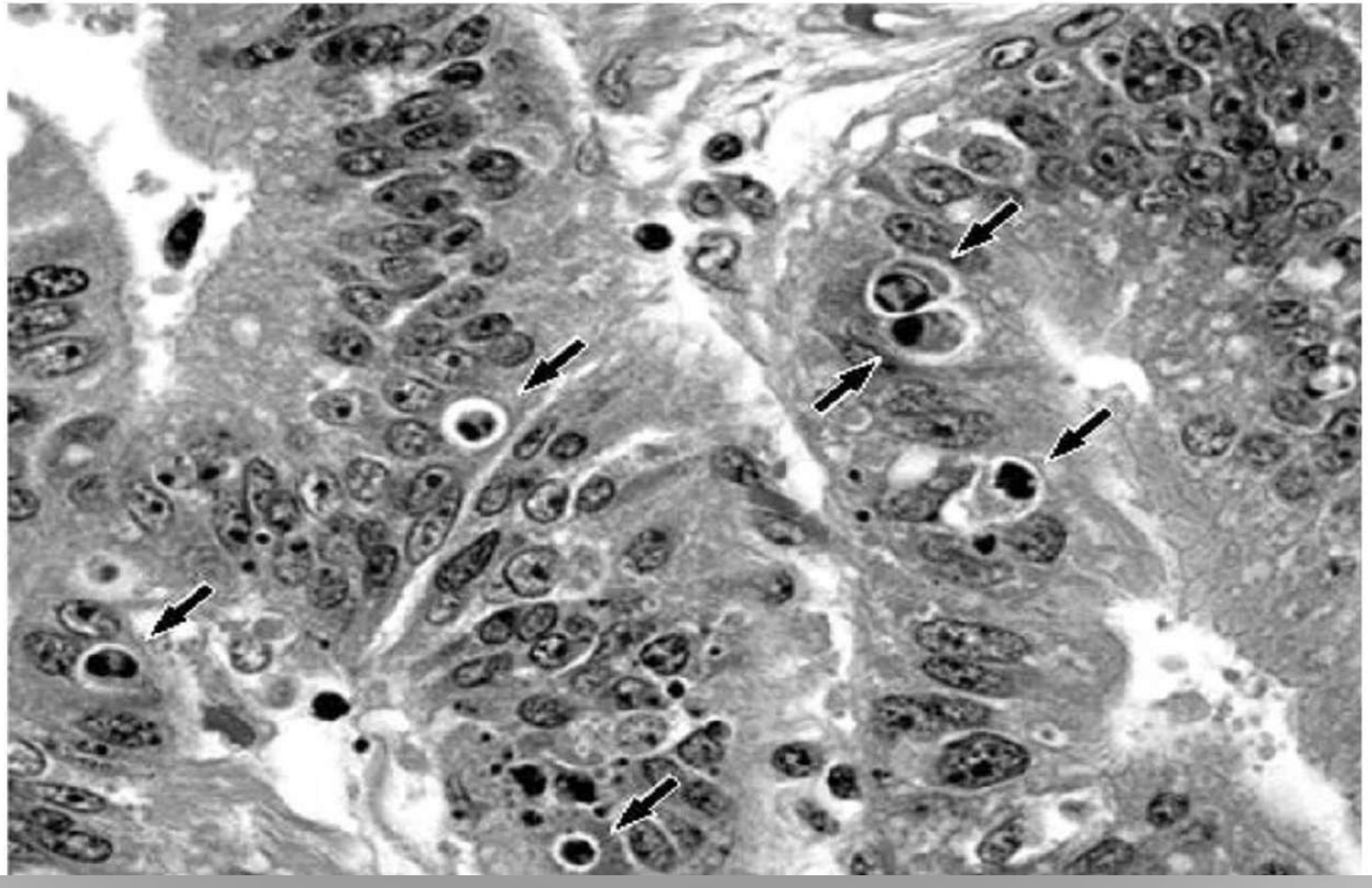


Fig. 82 : Microscopic view of apoptosis (arrows)

الخلايا صارلها shrinkage

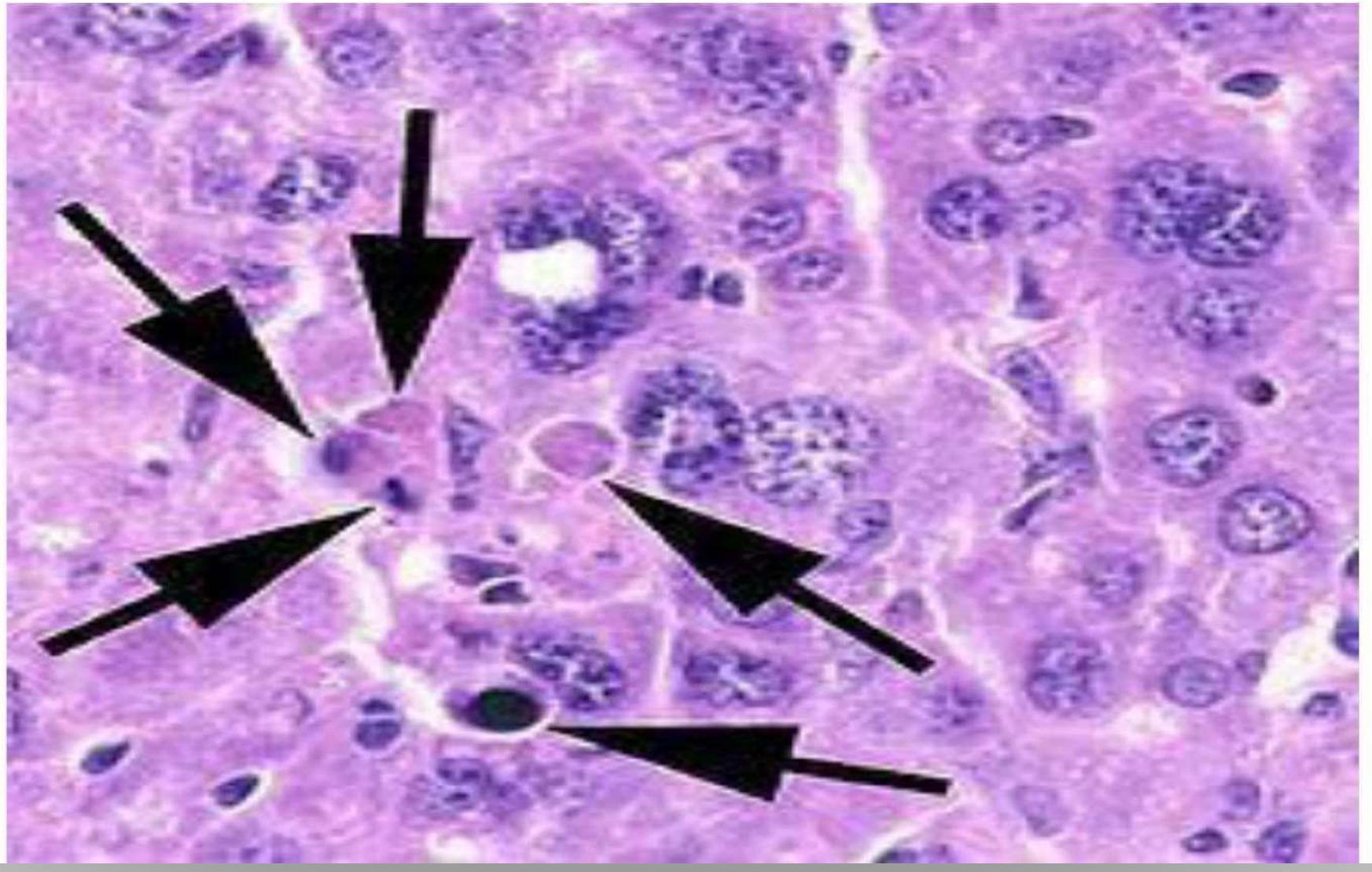


Figure 83 : Apoptotic cells (Arrows) as reddish spots of dead cells in livertissue. اختفاء النواه

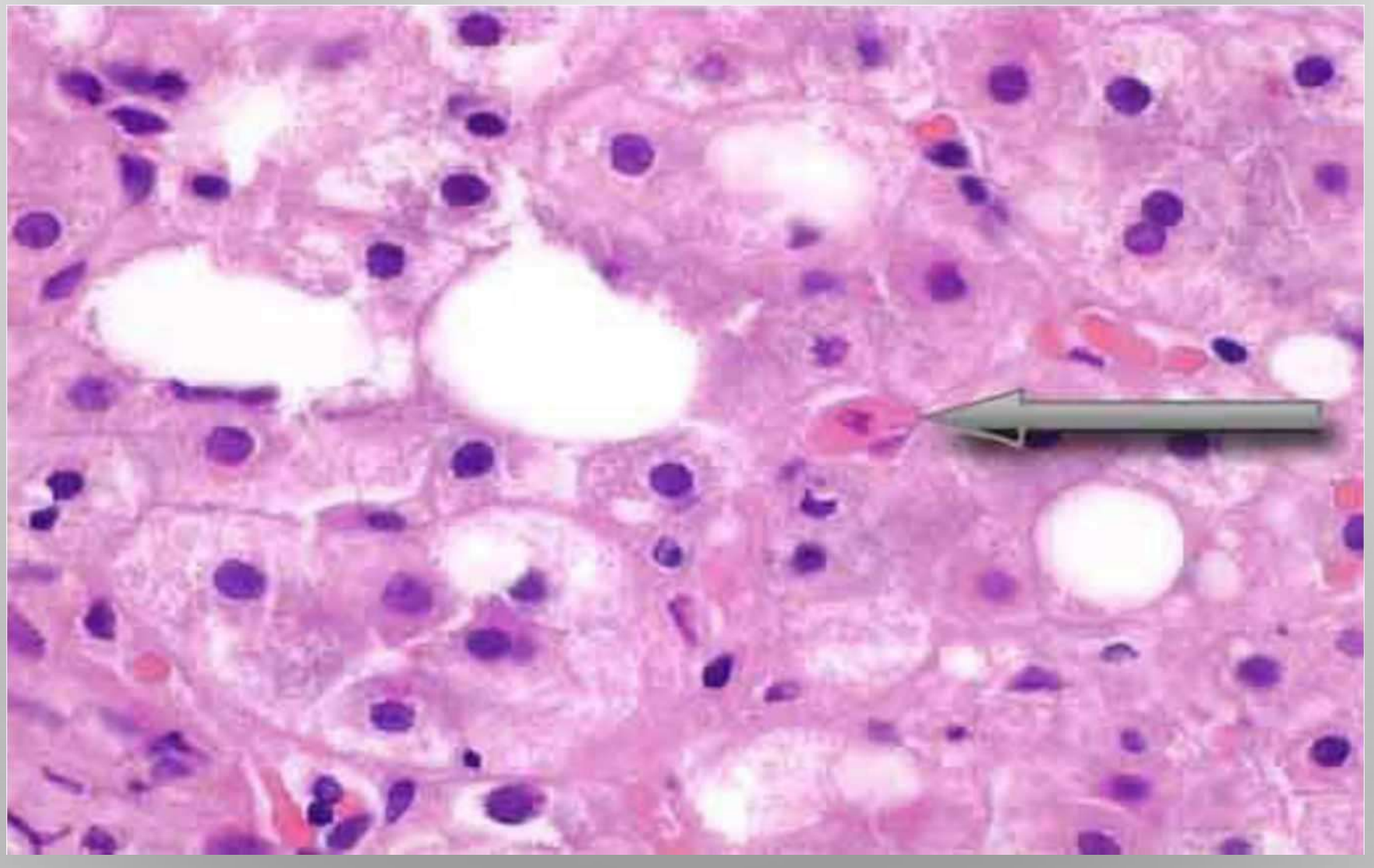
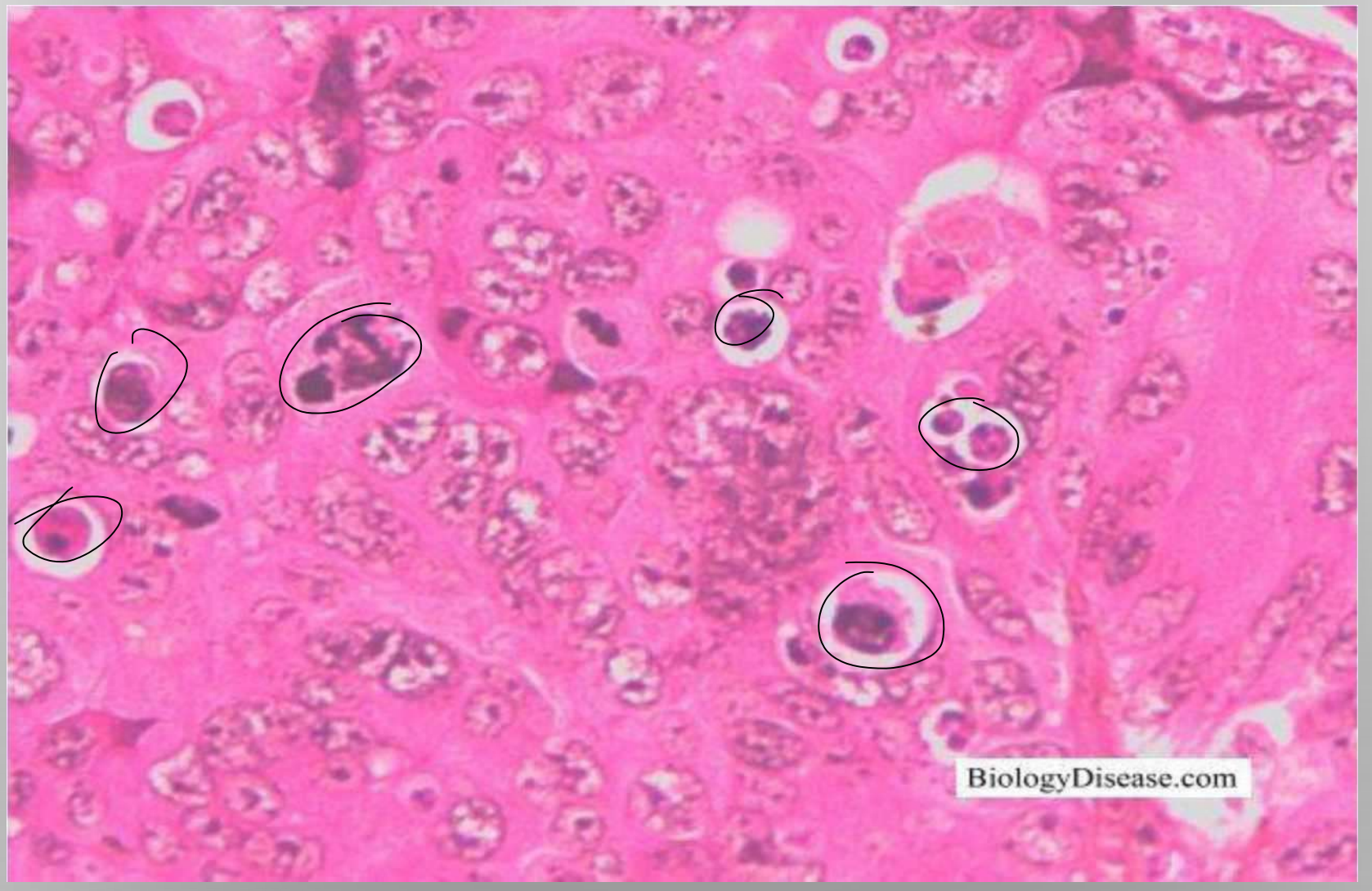


Figure 84 : Liver biopsy : Apoptotic cells (arrow) in viral hepatitis.



Apoptotic cells in a malignant tumor appearing as reddish dots of apoptotic cells surrounded by empty spaces.

Role of P53 gene in apoptosis :

Normally, P53 gene first arrests cell cycle at G1, to allow time for repair of the damage, if the repair is successful P53 allow the cell cycle progression from G1 to S phase .

But, if the damage is irreparable, the P53 triggers apoptosis, by activating Bax & Bak, i.e., → pro-apoptosis.

P53 order damaged cell : To Stop ^ Repair Or Die!

Not functional

when P53 is mutant or absent (as in 70% of human cancers), it is incapable of inducing apoptosis, so that cells with damaged DNA are allowed to survive.

In such cells, the DNA damaged may result in mutations or translocations that lead to neoplastic transformation

Cancer

INTRACELLULAR ACCUMULATIONS Of substances

- **Under some circumstances, cells may accumulate abnormal amounts of various substances.**
  - Substance may be harmless or may cause injury
    mild / لا تؤذي يعني لا تأثير
    Induce body reactions
  - Substance may locate either within organelles (typically lysosomes), in the cytoplasm, or in the nucleus .
    Reversible or irreversible
  - Substance may be endogenous synthesized by the affected cells, or may be exogenous , produced elsewhere.

CO2 / fatty.

General pathways by which cells can accumulate abnormal intracellular material are illustrated in

steatosis

1- Abnormal metabolism : as in fatty change in the liver.

2- Protein mutation causing alteration in protein folding & transport, with defective protein accumulation in the cytoplasm . (e.g. alpha 1- antitrypsin deficiency).

in liver

Acute reactant protein

autosomal recessive نقصه

3- Lack of enzyme responsible for breaking down certain compounds causing substrates to accumulate in lysosomes, as in e.g. lysosomal storage diseases

lung + liver بعمل امراض بال

خيرقابلة للهضم

4- Ingestion of indigestible materials e.g. accumulations of carbon or silica particles.

Fatty change = Steatosis

Normally, free fatty acids from adipose tissue or ingested food are transported into hepatocytes where they are...

a. Esterified to triglycerides
b. Converted into cholesterol or phospholipids or
c. Oxidized to ketone bodies

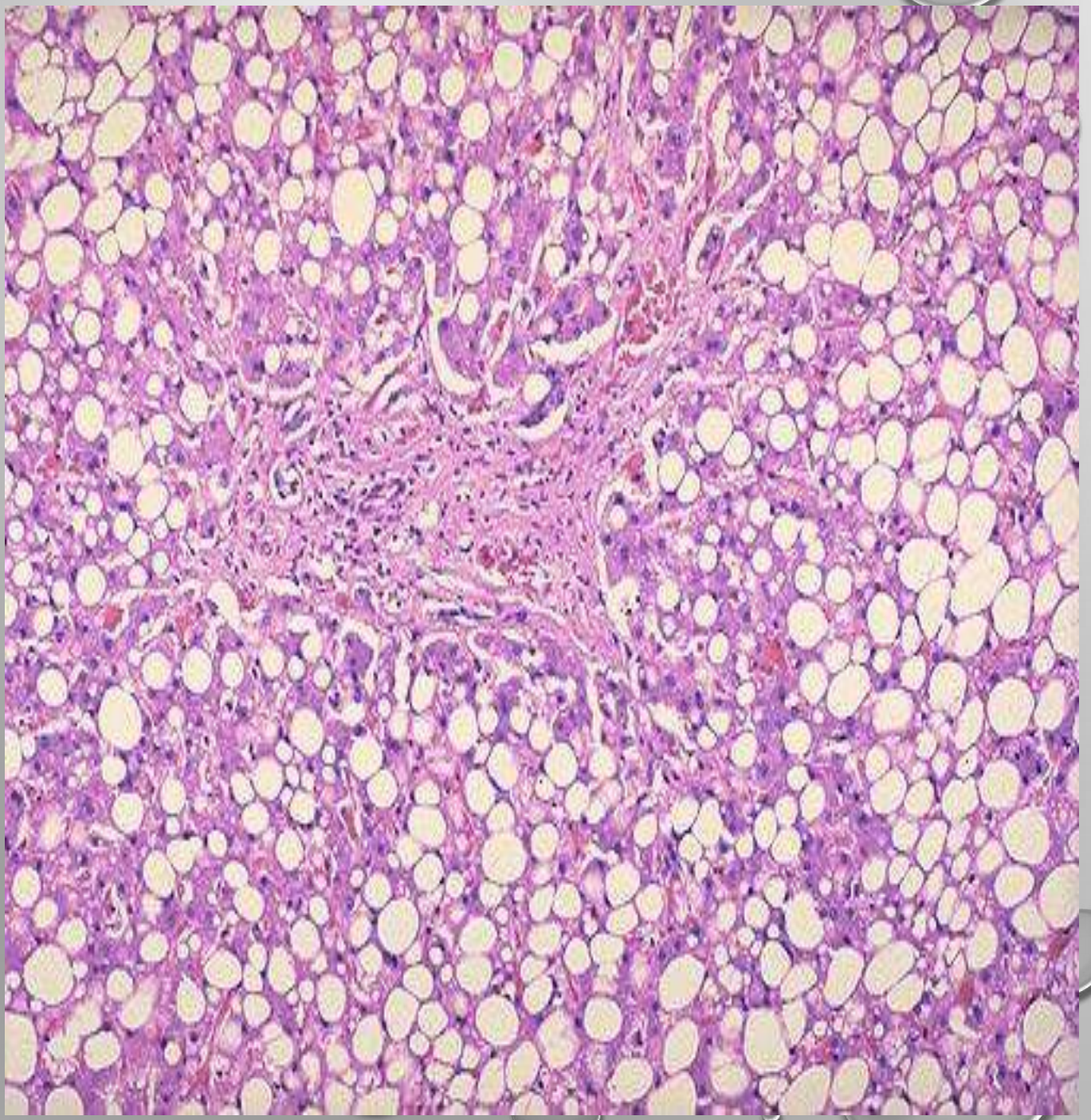
- Transport of the triglycerides from the hepatocytes requires complexing with Apo-proteins to form lipoproteins, which then traverse the circulation. (HDL/LDL)
- Excess accumulation of triglycerides may result from defects at any step from fatty acid entry to lipoprotein exit .
- Steatosis is an abnormal accumulation of triglycerides within parenchymal cells.
- Steatosis mostly seen in the liver , the major organ involved in fat metabolism , it may also occur in heart , skeletal muscle, kidney & other organs.

Main site of metabolism

Fatty changes are reversible unless chemicals appear that effect on vital cellular substances
Like CCL4 / CCL3 which cause irreversible fatty changes

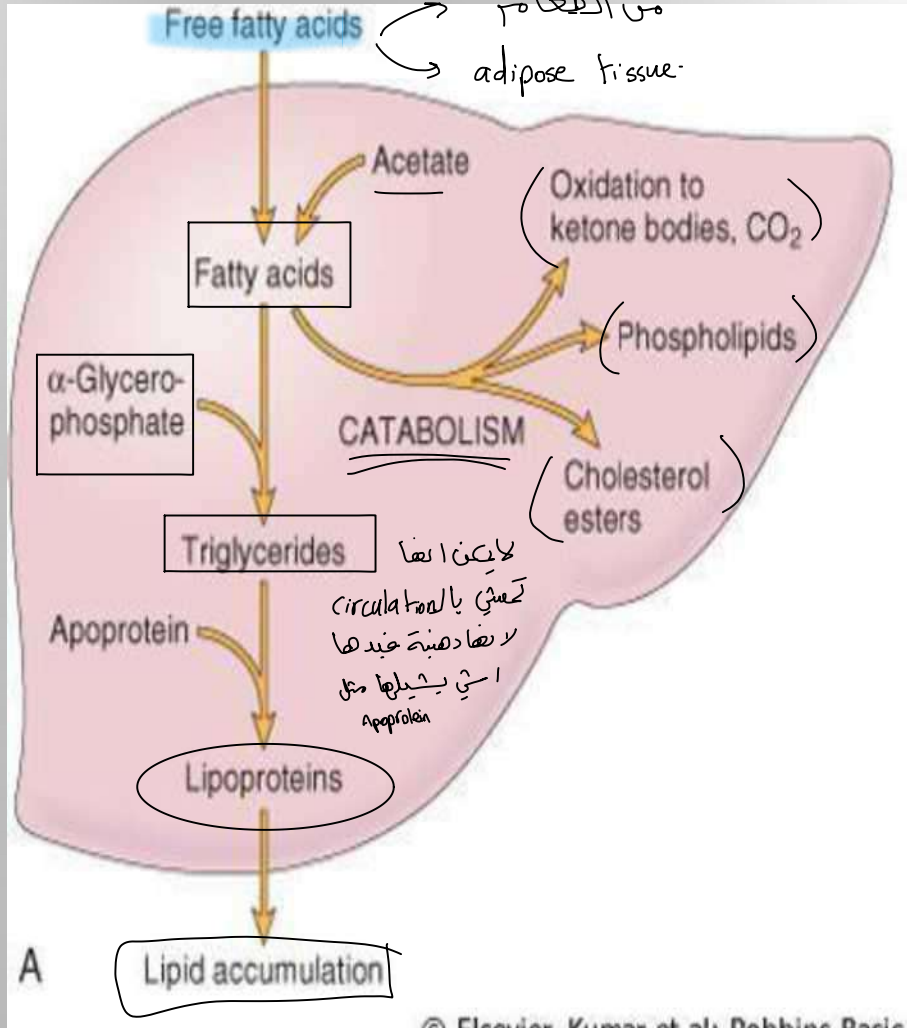
Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is steatosis, or fatty **metamorphosis (fatty change) of the liver in which deranged lipoprotein metabolism from injury leads to accumulation of lipid in the cytoplasm of hepatocytes.** Note the large, clear lipid droplets that fill the cytoplasm of many hepatocytes.

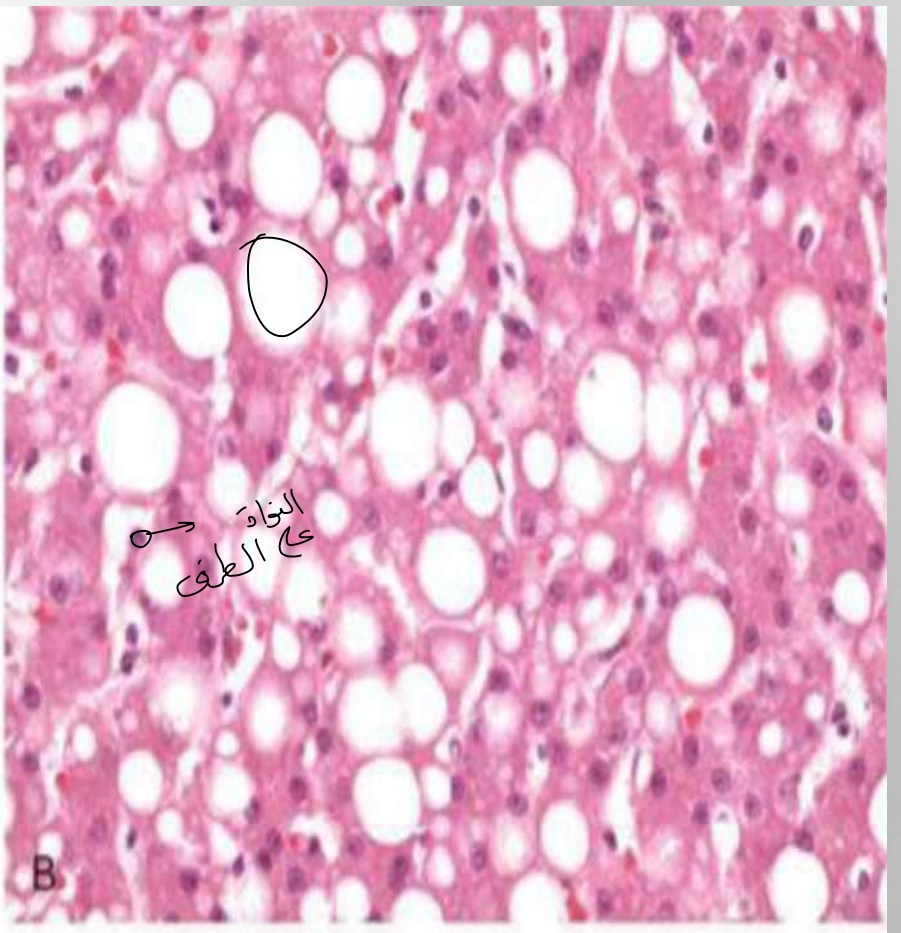
By oil o stain can be detected



Fatty Liver. A, The mechanisms leading to accumulation of triglycerides in fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can lead to Steatosis. B, Microscopically, the fat vacuole in the cytoplasm displace & squeeze the nucleus to the periphery of the cell.

Signet ring shape





The liver injury with chronic alcoholism leads to fibrosis and regeneration of the hepatocytes in nodules. This firm, nodular appearance of the liver as seen here is called cirrhosis.

تشمع كبد سببه
fatty accumulation or fatty changes
وبتكون عند الي يشربو كحول كثير

Start's reversible , but end's irreversible

- **Alcohol abuse** is the most common cause of fatty change in the liver in industrialized nations .
- **Protein malnutrition ,obesity, diabetes mellitus, anemia, anoxia,& toxins are other causes of fatty change .**
- CCL4 & protein malnutrition decrease the synthesis of Apo proteins.
- Anoxia inhibits fatty acid oxidation .
- Starvation increase fatty acid mobilization from peripheral stores.

❑ Effects of fatty change depend on the cause & the severity of accumulation.

- When mild, it may have no effect on the cellular function.
- More sever fatty change may transiently impair cellular function, but unless some vital intracellular process is irreversibly impaired (e.g., in CCL4 poisoning) , fatty change is reversible.
- In a severe form, fatty change may precede cell death .

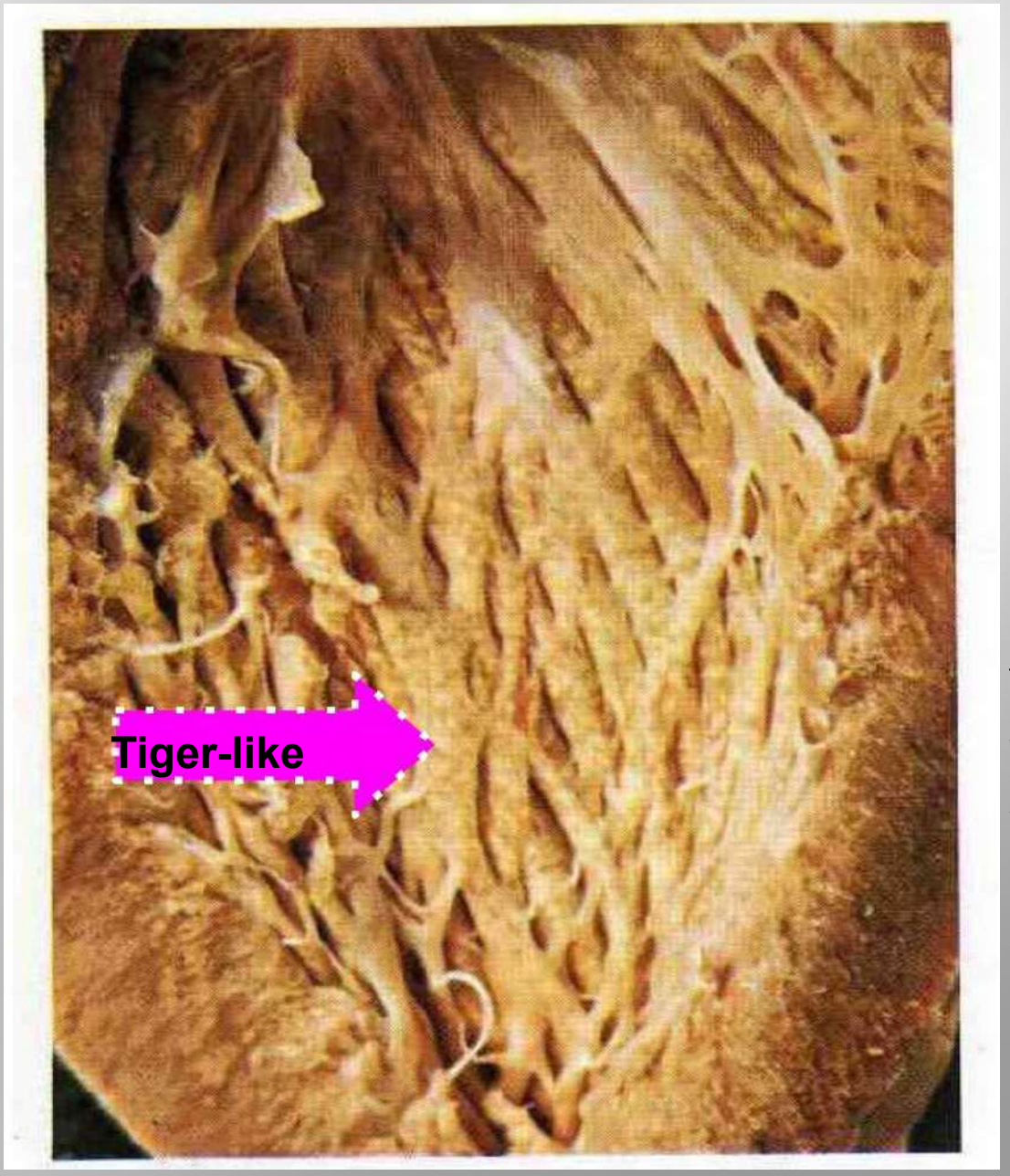
- GROSSLY : in the liver , mild fatty change may not affect the gross appearance. With accumulation, the liver *becomes* yellow, *enlarges,* in extreme cases, it may weigh 3 to 6 Kg (normal weight 1.5 Kg) & appears *bright yellow, soft & greasy.*
- Microscopically : early fatty change is seen as small fat vacuoles in the cytoplasm around the nucleus. Later, the vacuoles coalesce (unite together) to create cleared large space that displace the nucleus to the cell periphery .
- In the heart , prolonged moderate hypoxia (as in severe anemia) result in focal intracellular fat deposits, with a characteristic ('tiger-like, tabby-cat' pattern) , while more severe hypoxia or toxic myocarditis (e.g., diphtheria infection) result in diffuse fatty change .

السؤال في السنة الماضية

- in severe anemia

Fatty change: liver. The patient was chronic alcoholic. The presence of large quantities of neutral fat within the liver cells result in a uniform yellow appearance of the liver section.

5.4 Fatty change: liver



F 90 : Fatty change:
Heart . The muscles of the LV shows patchy mottling as yellow streaks & lines (due to focal fatty change) alternating with unaffected muscle to produce : A ‘tiger-like , tabby-cat’ pattern characteristic of heart fatty change in anemia.

Fatty change: heart

Cholesterol & Cholesteryl Esters

- Normally, cellular cholesterol metabolism is tightly regulated to ensure normal cell membrane synthesis without significant intracellular accumulation.
- Phagocytic macrophages in contact with the lipid debris of necrotic cells may become stuffed with lipid, imparting a foam appearance to their cytoplasm, called foam cells .

Because of the accumulation of cholesterol and LDL insid them

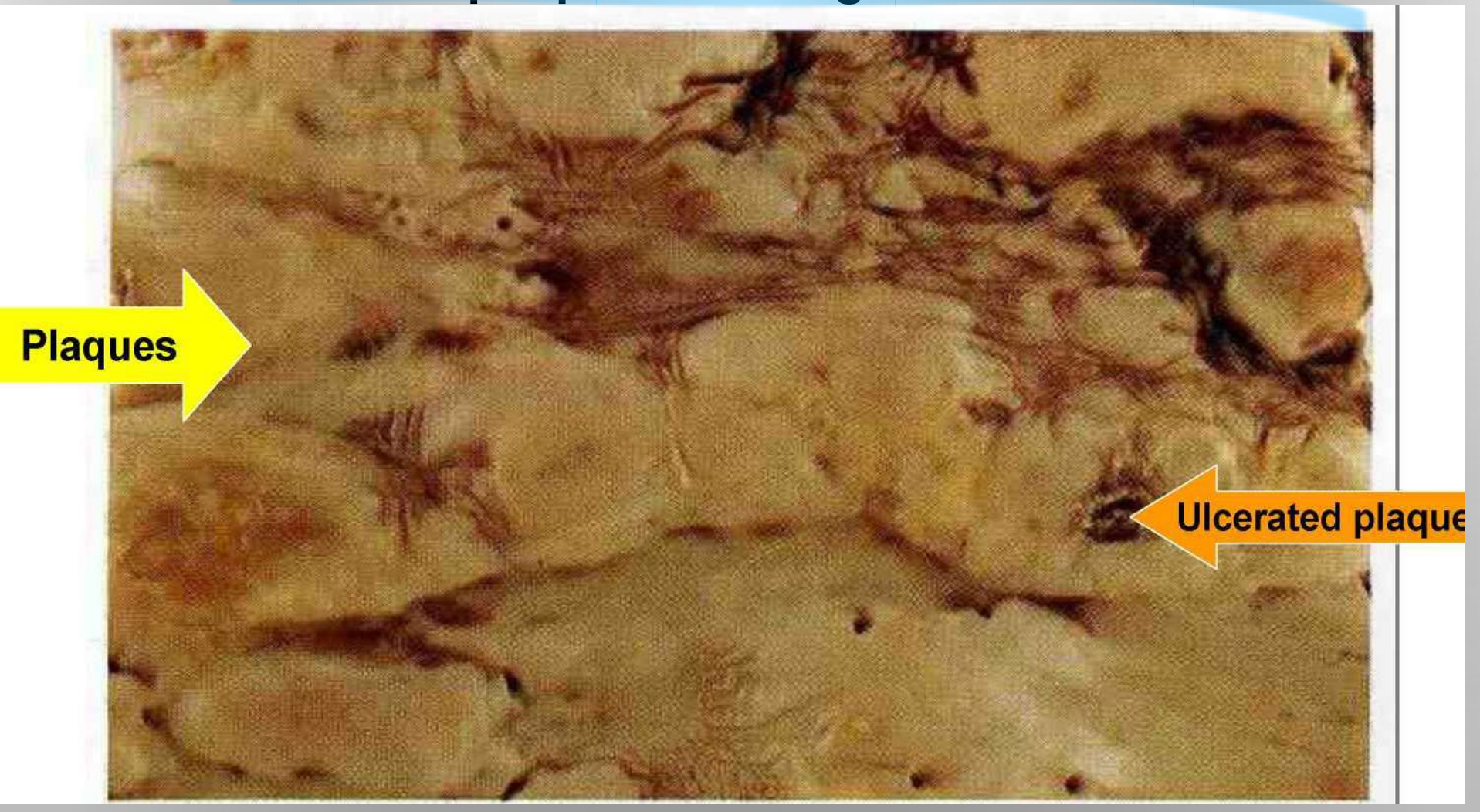
- **In atherosclerosis** , smooth muscle cells & macrophages are filled with lipid vacuoles composed of cholesterol & cholesterol esters; these give atherosclerotic plaques their characteristic yellow color

Cholesterol accumulates in the blood vessels and makes them harder and the clot form around them and make blockage

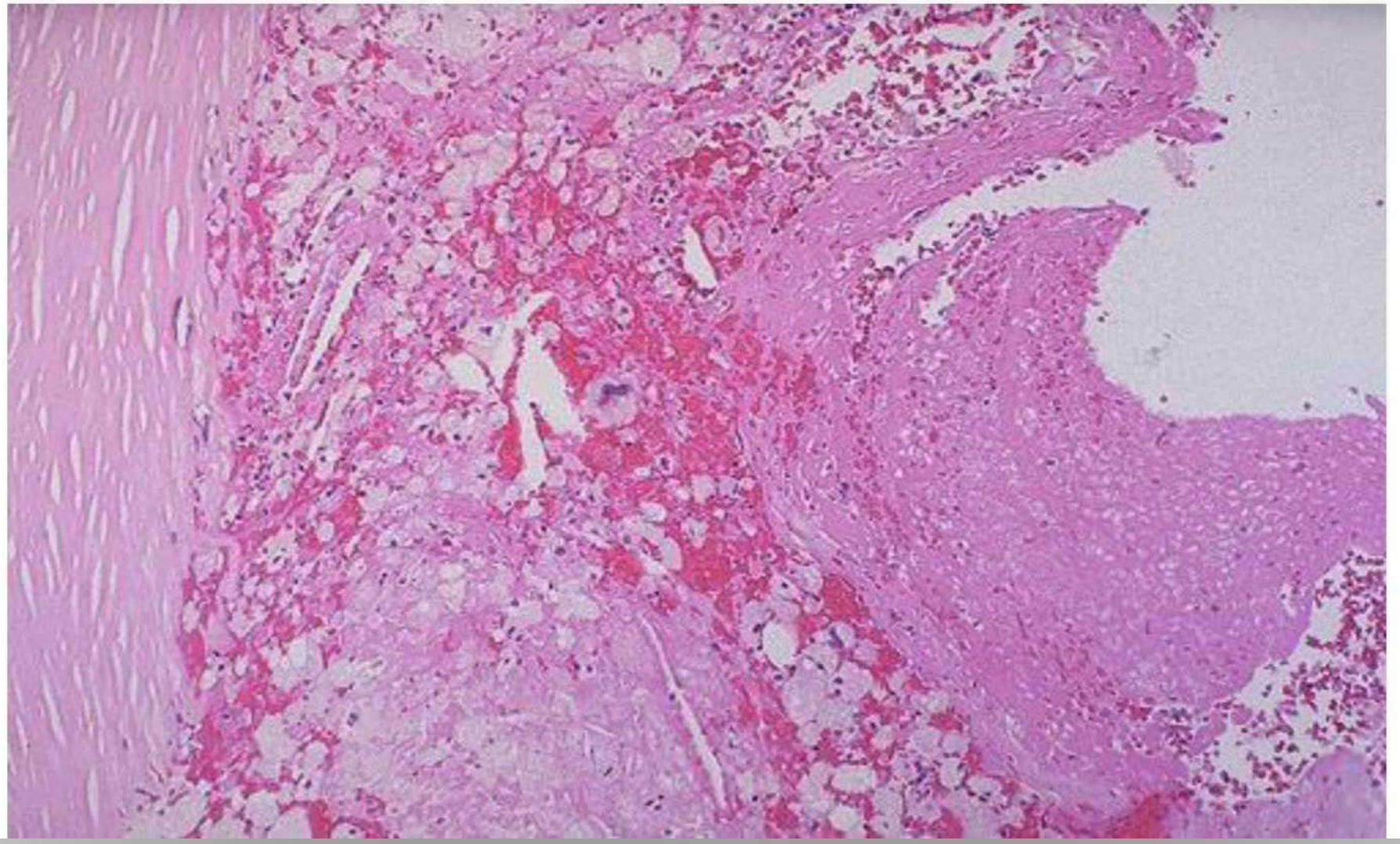
Abnormal high fat concentration

- In hereditary & acquired hyperlipidemic syndromes , macrophages accumulates intracellular cholesterol in the skin
- or in tendons, forming masses called Xanthomas .

Abundant fat within large atheromatous plaques, as confirmed by the yellow color of the lesions shown. The plaque on the right has ulcerated.



Atherosclerosis: aorta



Atherosclerosis in aorta: microscopic view shows deposition of cholesterol & cholesterol esters appear as white vacuoles within macrophages & smooth muscle cells in the wall of blood vessel.

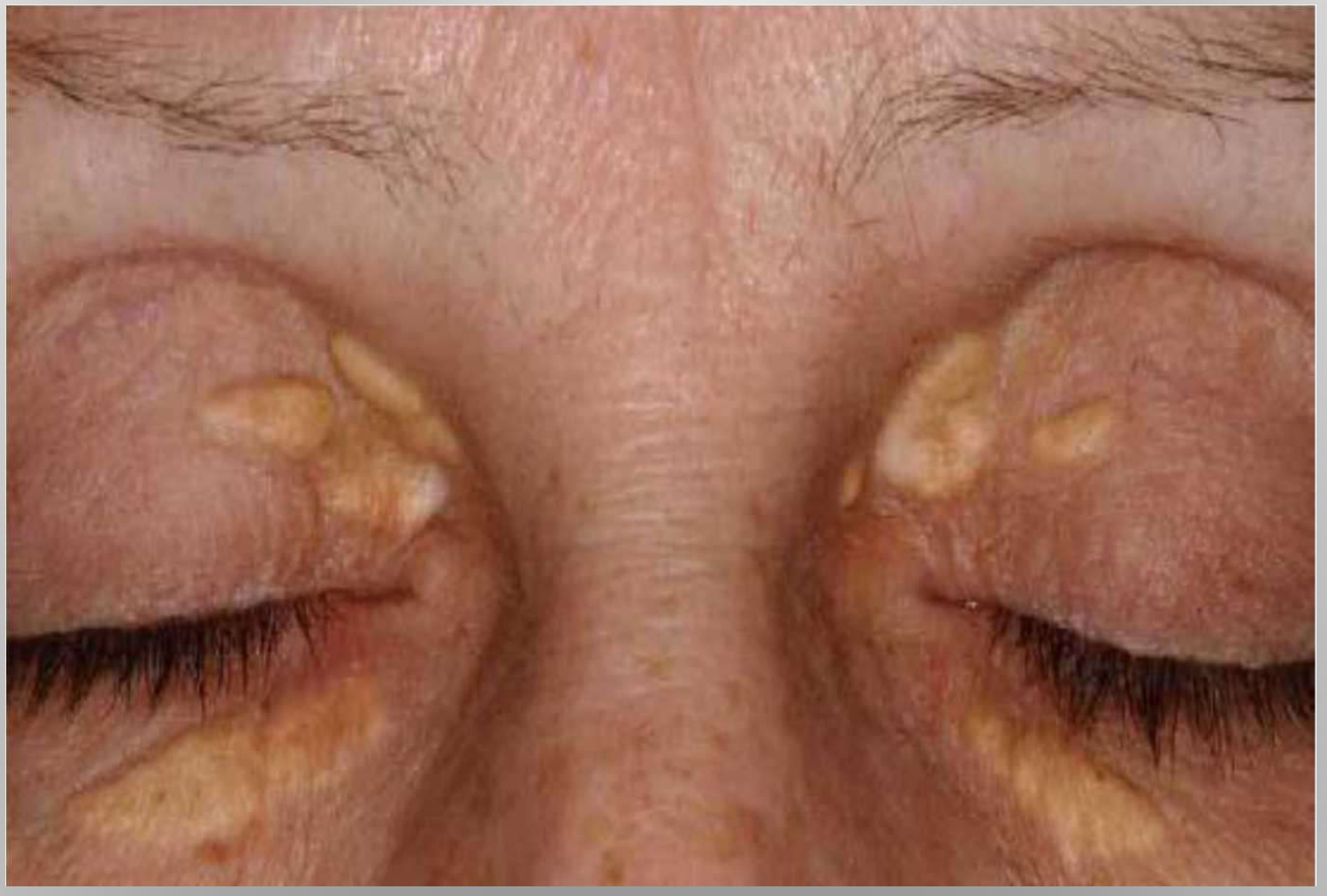


Figure 93 : Xanthelasma : Yellowish skin nodules , consisting of cholesterol filled subcutaneous lesions .

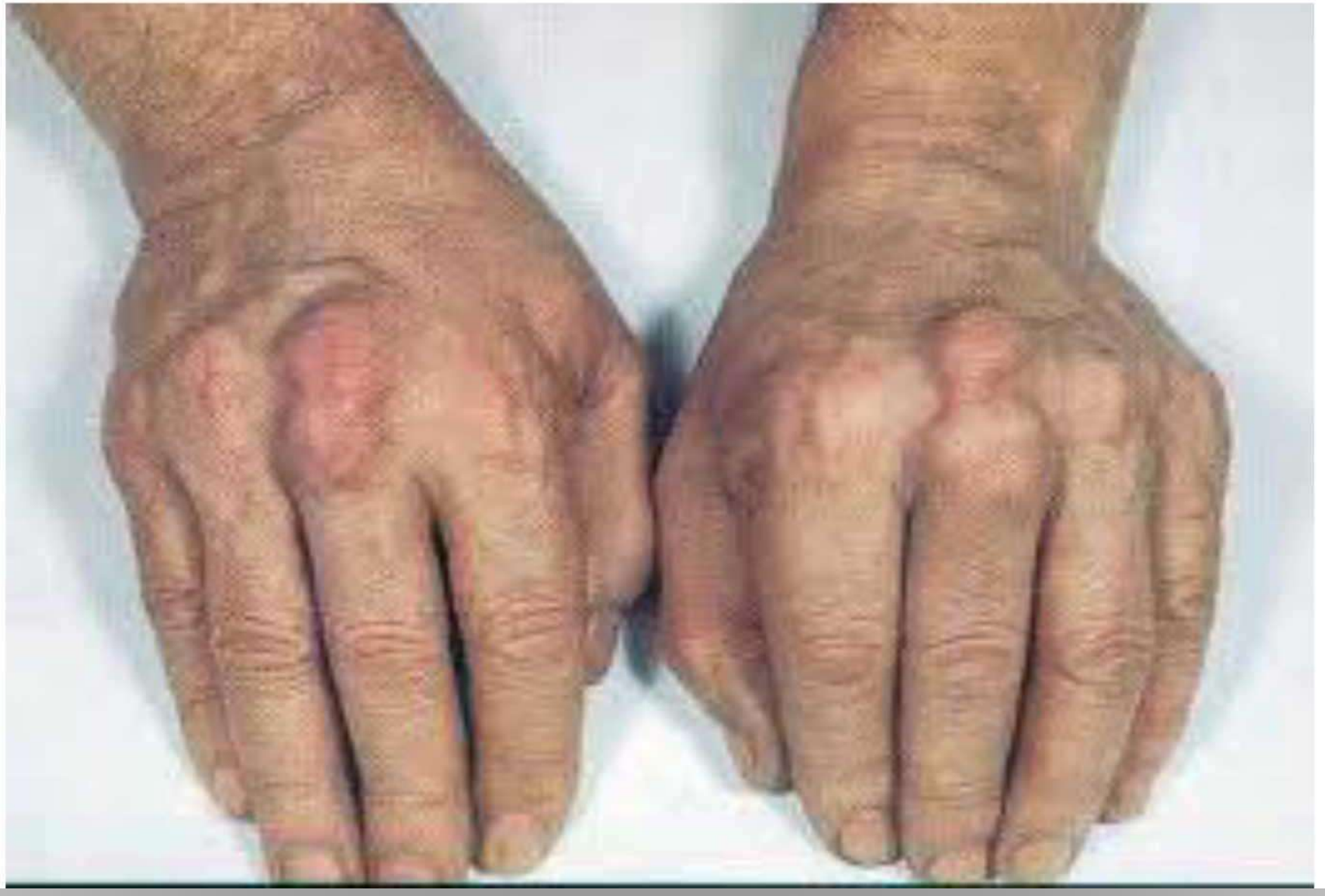


Figure 94 : Xanthoma of hands.

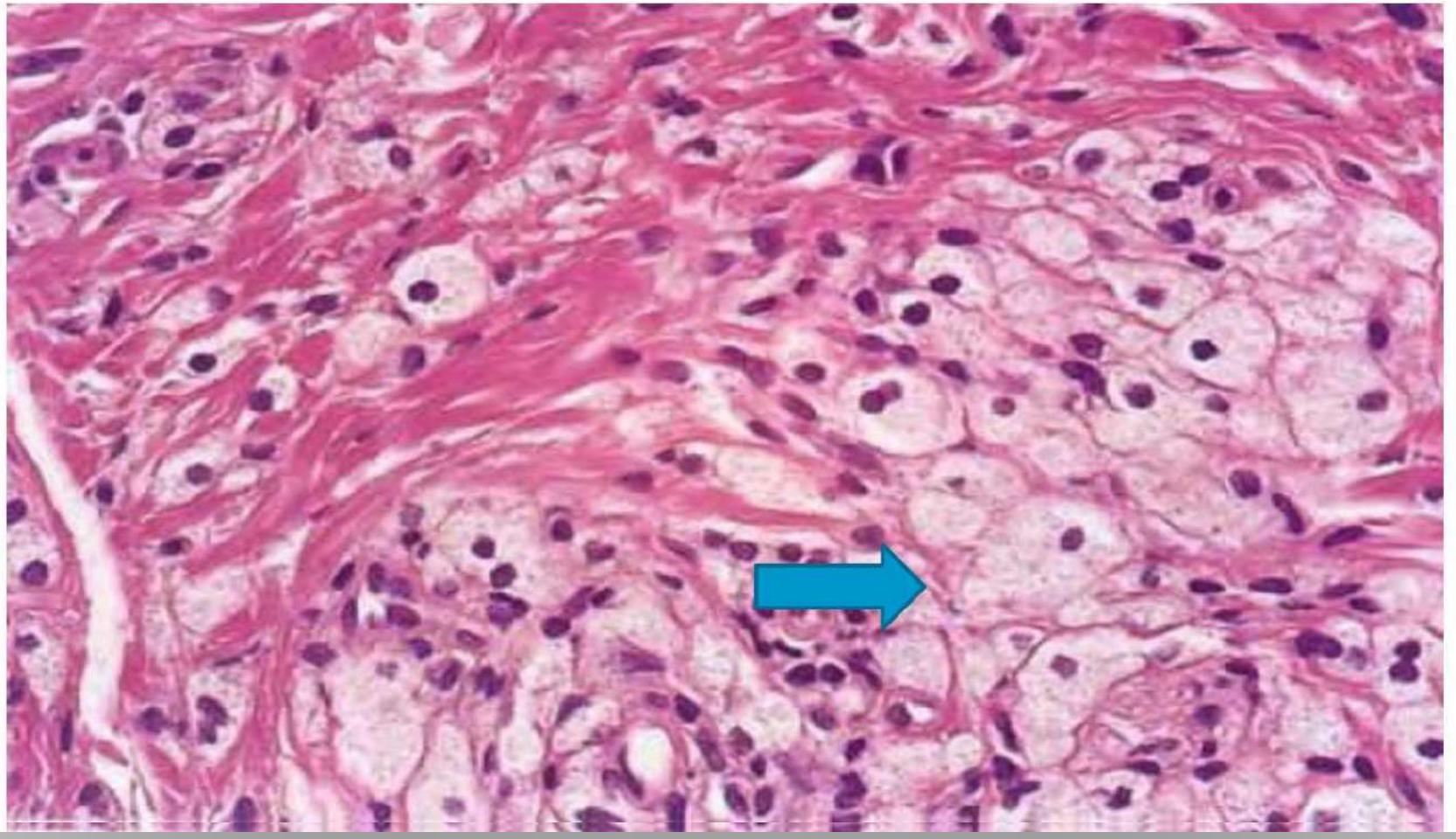


Figure 95 : Skin biopsy in xanthoma : showing foamy lipid-laden macrophages filled with cholesterol (arrow) .