Regressive lesions - 2/2021

1 - Fatty liver

2 - Haemochromatosis (liver)

3 - Caseous necrosis (tbc)

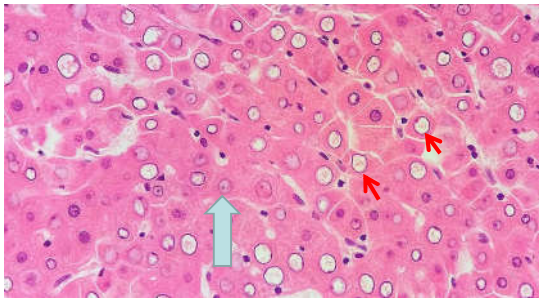
4 - Enzymatic necrosis of pancreatic fat tissue (Balser type)

5 - Apoptosis (viral hepatitis)

Degeneration=accumulation

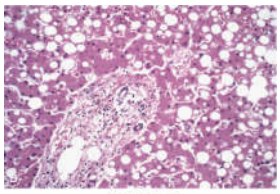
- Cells may accumulate abnormal amounts of substances (harmless or causing injury)
- The substance is located in the cytoplasm (lysosomes) or in the nucleus and it may be synthetized by the affected cells or may be produced elsewhere

Intranulcear glycogen accumulation with chromatine margination - liver



1- Fatty liver

- **Steatosis (fatty degeneration, fatty change)** it is a particular type of intracellular degeneration which consists in extensive accumulation of lipids in parenchymal cells of affected organ



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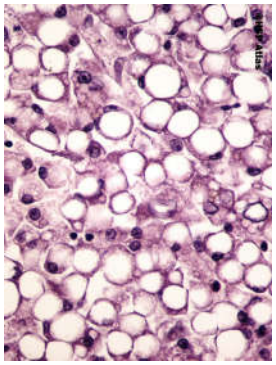
Fatty change of the liver. In most cells, the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole

- **Adiposity (interstitial fatty infiltration)** it is abnormal increase in adipocytes in stroma of affected organ (hyperplasia of adipose tissue)

Hepatocellular steatosis/fatty liver

patologia.cm.uml.pl



- nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole

1 - Fatty liver

The causes of steatosis include:

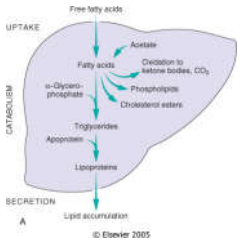
- drugs (e.g. corticosteroids, salicylates, tetracyclines)
- **ethanol**
- protein malnutrition,
- diabetes mellitus,
- obesity,
- anoxia,
- insulin resistance
- dyslipidemia (hypertriglicerinemia, low high density lipoprotein cholesterol, high low density lipoprotein cholesterol)

toxins (e.g. mushroom- Amanita phalloides - toadstool) (Irreversible!)

1 - Fatty liver

Fatty change is often seen in the **liver** because it is the major organ involved in fat metabolism, but it also occurs in heart, muscle, and kidney

In normal circumstances no lipids are histologically demonstrable within hepatocytes

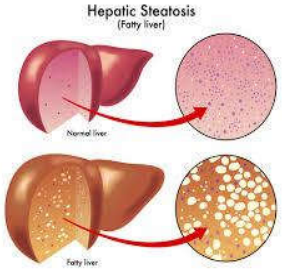


Excessive accumulation of lipids in hepatocytes may arise from:

- Increase in mobilization of fatty acids from adipose tissue
- Increase in intensity of hepatic lipogenesis
- Decrease in fatty acids utilization (oxidation)
- Reduction in secretion of lipoproteins

Schematic diagram of the possible mechanisms leading to accumulation of triglycerides in fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can result in **lipid accumulation**.

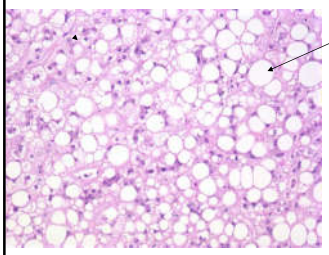
Fatty liver change (steatosis)



practical-tips-in-sonography-17-638.jpg. https://sugarytooth.wordpress.com/tag/fatty-liver/

Fatty liver

pathology outlines.com



- This is the histologic appearance of hepatic macrovesicular steatosis (fatty change). The lipid accumulates in the hepatocytes as vacuoles.

Alcoholic fatty liver disease

- 90-100% of alcoholics develop fatty liver, and of those 10-35% develop alcoholic hepatits
- Alcoholic fatty liver disease can manifest histologically as **steatosis, steatohepatitis and cirrhosis**

NAFLD *(non-alcoholic fatty liver disease)* with NASH *nonalcoholic steatohepatits* (overt clinical features of liver injury)

(In industrialized nations, by far the most common cause of significant fatty change in the liver (fatty liver) is alcohol abuse !

but

the entity called NAFLD can mimic the entire spectrum of hepatic changes associated with alcohol abuse

- **NAFLD** (non-alcoholic fatty liver disease) first described in 1980; liver disease developes in individuals who do not drink alcohol
- **NAFLD** is most consistently associated with *insulin resistance* and *metabolic syndrome; type 2 diabetes, obesity and dyslipidemias*

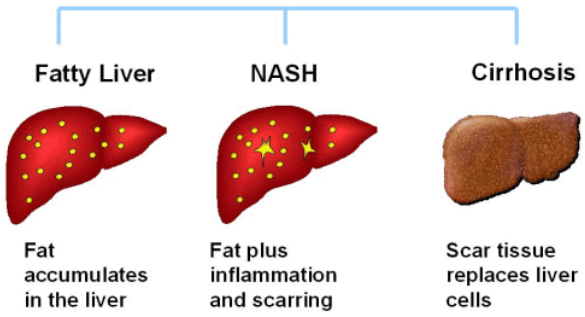
Non-alcoholic fatty liver disease

- NAFLD is an umbrella term that encompasses a spectrum of disease: simple steatosis (where there is only fat in the liver), NASH (non-alcoholic steatohepatitis, where there is a combination of hepatic fat as well as hepatocyte inflammation or fibrosis), or cirrhosis.
- NAFLD is often diagnosed incidentally when patients are found to have elevated liver enzymes; often asymptomatic, although patients with hepatomegaly may complain of right upper quadrant pain.
- It is currently the most common cause of elevated liver enzymes in the North American population, although it can coexist with other liver diseases, such as viral hepatitis, hereditary diseases (ie hemochromatosis, Wilson Disease, etc), as well as alcoholic liver disease.

Risk factors for NAFLD

- central obesity, insulin resistance and diabetes mellitus type II, hyperlipidemia (especially hypertriglyceridemia), and the presence of metabolic syndrome.
- A weight loss of 10% from baseline weight over the period of a year has been shown in various studies to reduce not only hepatic steatosis and inflammation, but also to reverse fibrosis in some studies.
- Patients with simple steatosis are thought to have a very low risk of progression to the development of cirrhosis, whereas patients who have NASH are at higher risk

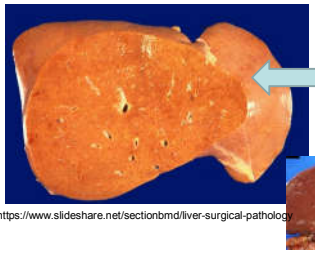
The Spectrum of NAFLD



http://www.calgarygi.com/index.php?mode=webpage&id=735&pp=730

1 - Fatty liver (Steatosis hepatis)

MA: fatty change may be either asymptomatic or present with mild enlargement and tenderness of the liver. In the case of severe chronic fatty change liver is enlarged, with stretched out capsule, rounded edges, and decreased concistency. In diffuse panlobular steatosis, cut surface is uniformly yellowish with blurred lobular pattern

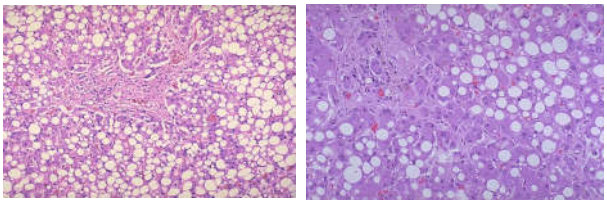


https://www.slideshare.net/sectionbmd/liver-surgical-pathology

Fatty liver / versus unchanged one
This liver is slightly enlarged and has a pale yellow appearance, seen both on the capsule and cut surface.

1 - Fatty liver

MI: microscopically, hepatic fatty change can be subdivided into **micro- and macrovesicular ones**. The former is observed for example in Reye's syndrome. Macrovesicular we can see in alcohol abuse, obesity, acute mushrooms poisoning. Macrovesicular (large droplet) steatosis hepatocytes show large fat globule in central area of cytoplasm. They are frequently enlarged with nucleus pushed towards stretched fat.
Because of presence of large, apparently empty round cells with peripheral nuclei, at first sight fatty liver microscopically resembles adipose tissue. In fact lipids are absent on presented slides, being dissolved out by routine tissue processing



Reye syndrome

a rare disese; the most severe forms are fatal

- Acute noninflammatory encephalopathy and fatty degenerative liver failure
- Affects children 1 - 14 years of age
- The pathogenesis: loss of mitochondrial function
- Typically occurs after a viral illness, particularly an upper respiratory tract infection, influenza, varicella, or gastroenteritis, and is associated with the use of aspirin during the illness (in persons with inborn errors of metabolism/IEM?)
- MI: changes within hepatocytes (microvesicular steatosis) and astrocytes
- Sceletal muscle, kidneys and heart may reveal mitochondrial alteration

2. Haemochromatosis (liver)

Hemochromatosis is a severe iron-storage disorder arising from abnormal increase in intestinal iron absorption
Inborn or acquired damage to the barrier results in higher intestinal iron absorption which surpasses the amount necessary for the synthesis of heme.
Hereditary hemochromatosis – 4 genetic variants

The most common – an autosomal recessive disease caused by mutation in HFE gene. (The **HFE gene** provides instructions for producing a protein that is located on the surface of cells, primarily liver and intestinal cells.)

2 most common mutations – C282Y – 80% of hemochromatosis patients are homozygous for the C282Y.

10% of hereditary hemochromatosis patients are compound heterozygotes for the C282Y/H63D or homozygotes for H36D mutation

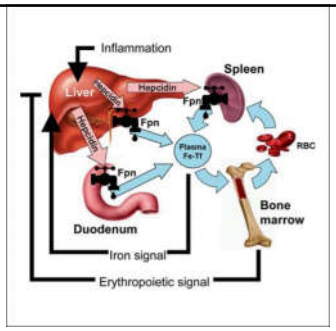
The remainder comprise variants of hereditary hemochromatosis that do not involve the HFE gene

Acquired forms are known as secondary iron overload: multiple transfusion, ineffective erythropoiesis (sideroblastic anemia, beta-thalasemia) and increase iron intake (Bantu siderosis).

Hepcidin- an amino-acid peptide

the principal regulator of iron absorption and its distribution to tissues

- HFE influences iron absorption by modulating the expression of hepcidin
- Hepcidin is synthetized predominantly in hepatocytes
- Hepcidin is the central regulator of systemic iron homeostasis. Dysregulation of hepcidin production results in a variety of iron disorders.
- Hepcidin deficiency is the cause of iron overload in hereditary hemochromatosis, iron-loading anemias, and hepatitis C.



- Hepcidin-ferroportin (Fpn) interaction determines the flow of iron into plasma. Hepcidin concentration is in turn regulated by iron, erythropoietic activity and inflammation.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2855274/

2 - Haemochromatosis (liver)

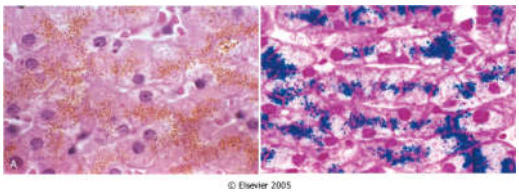
- Iron is collected in form of **haemosiderin** in parenchymal cells of various organs (predominantly liver, pancreas, endocrine glands, heart).
- It leads to cell damage.

Clinically the disease is mainly characterized by:

- hepatic cirrhosis
- diabetes mellitus due to the damage of beta cells
- gray to bronze skin pigmentation due to overproduction of ACTH and MSH secondary to adrenal gland insufficiency
- heart failure

2 - Haemochromatosis (liver)

MI: cirrhotic or non cirrhotic liver with numerous hepatocytes loaded with golden brown haemosiderin granules. This deposits we can also see in fibrous tissues, Kupffer cells or bile duct epithelium



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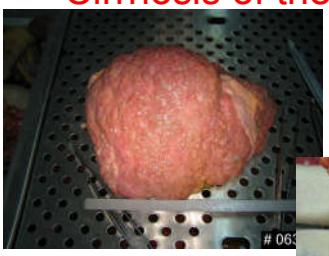
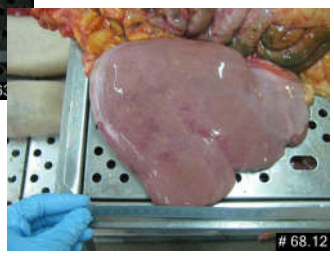
Hemosiderin granules in liver cells. *A*, H&E section showing golden-brown, finely granular pigment. *B*, Prussian blue reaction, specific for iron.

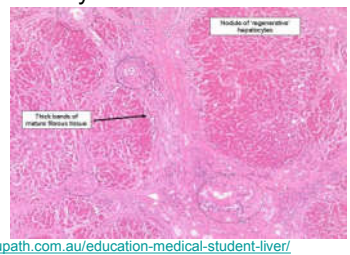
Cirrhosis of the liver/normal





Cirrhosis

- **Cirrhosis** is the widespread distortion of the liver's structure
- it refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands



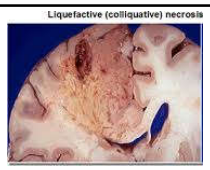
- https://tissupath.com.au/education-medical-student-liver/

Necrosis

- The type of cell death that is associated with loss of membrane integrity and leakage of cellular contents
- The leaked cellular contents elicit a local host reaction (inflammation), that attempts to eliminate the dead cells
- Patterns of tissue necrosis: coagulative and liquefactive

Necrosis

- Coagulative: a form of tissue necrosis in which the cells are dead but the tissue architecture is preserved for several days;
- is characteristic of infarcts (ischemic necrosis) in solid organs;
- similarity to coagulation of proteins that occurs upon heating

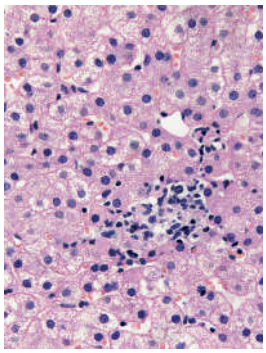


- Liquefactive: dissolution of the necrotic cells;

Seen in

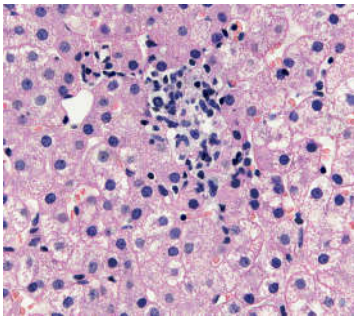
- 1. bacterial infections-microbes stimulate leukocytes to digest (liquefy) the tissue
- 2. brain strokes

Chronic hepatitis.

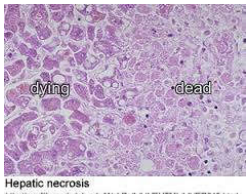


- Spotty necrosis is a term used to describe necrosis of minute clusters of hepatocytes, usually in association with lymphocytes. Necrosis involving larger groups of hepatocytes within a lobule may be referred to as focal necrosis. These terms describe a continuum of lobular injury

Chronic hepatitis. Spotty necrosis



The leaked cellular contents elicit a local host reaction (inflammation)



Hepatic necrosis

http://medlib.med.utah.edu/WebPath/UVEHTML/LIVER045.html

Patterns of Hepatic Injury

Necrosis and Apoptosis

- *Distribution:*
  1. Centrilobular – most common; immediately around terminal hepatic vein
  2. Mid-zonal and periportal – rare
- *Degree of involvement:*
  1. Focal or spotty – limited to scattered cells within hepatic lobules
  2. Interface hepatitis – between periportal parenchyma & inflamed portal tracts
  3. Bridging necrosis – span adjacent lobules
  4. Submassive necrosis – entire lobules
  5. Massive – most of the liver

- www.slideshare.net/specialclass/liver-1

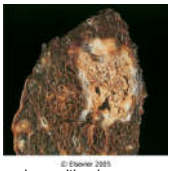
3 - Caseous necrosis (tbc)

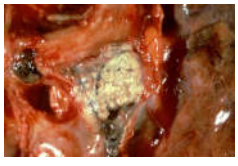
It constitutes a distinctive subtype of **coagulative necrosis**.
Adjective „caseous" refers to the gross appearance of necrosis. Changed areas are namely fragile, whitish-yelowish, similar to white cheese (Lat. „caseus" – cheese)

C.n. appears in non- or poorly vascularized, cell-rich tissues which are subdued to the effect of endogenous toxins.

These conditions are fulfilled only by pathologic tissues: tuberculous and luetic granulomas and malignant neoplasms.

MA: necrotic masses resemble white-yellowish cheese, are matt and brittle





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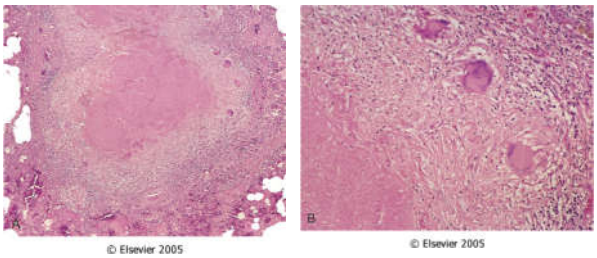
A tuberculous lung with a large area of **caseous necrosis**. The caseous debris is yellow-white and cheesy.

Caseous necrosis (tbc)

MI: focus of caseous necrosis appears as amorphous, granular debris (without even any shadow of underlying structure of organ) enclosed within a distinctive inflammatory border known as granulomatous reaction



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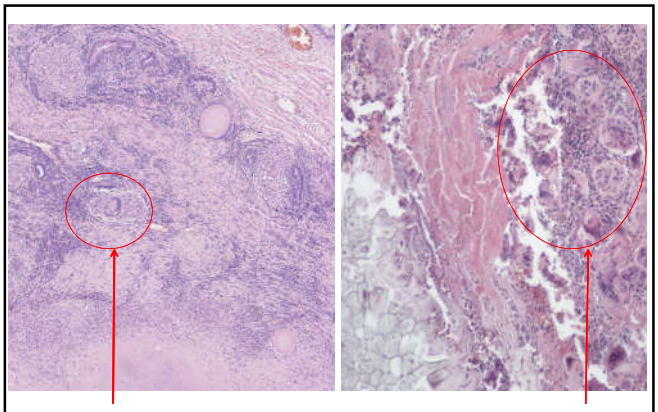
Characteristic tubercle at low magnification (*A*) and in detail (*B*) illustrates **central caseation** surrounded by: epithelioid and multinucleated giant cells (Langhans cells - derive from numerous fused macrophages –their nuclei form peripheral circle or horse-shoe) and lymphocytes.



Multinucleated giant cel, Langhans type
Nuclei form „horse-shoe" structure

Multinucleated giant „foreign-body type"cell. Irreguralery placed nuclei

Enzymatic necrosis of pancreatic fat tissue (Balser type) – Balser's fat necrosis

Balser's fat necrosis is a hallmark of severe form of **acute pancreatitis** which is characterized by acinar cell necrosis and foci of haemorrhage.

Acute necrotizing/haemorrhagic pancreatitis is most commonly associated with:
- **alcohol abuse and cholelithiasis**. Less common factors include:
- trauma, abdominal surgery, metabolic abnormalities.

➢ Damage of acinar cells leads to activation of pancreatic enzymes, especially lipase, tripsin, chymotrypsin.

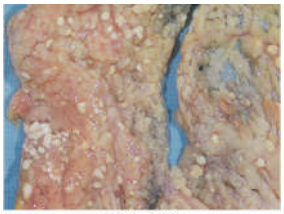
➢ Action of lipase leads to injury of adipose tissue located in and around affected pancreas.

➢The enzyme hydrolyses triglycerides (from fat tissue) with release of **fatty acids** and **glycerol**. The latter is absorbed into bloodstream but **fatty acids bind calcium and magnesium ions to form insoluble soaps (fat saponification).** Active lipase circulating with blood may cause extrapancreatic and extraabdominal fat necrosis as well.

Enzymatic necrosis of pancreatic fat tissue (Balser type) – Balser's fat necrosis

MACROSCOPICALLY:

The resulted foci (of insoluble soaps) are chalky white, well discrete on yellow background of unchanged adipose tissue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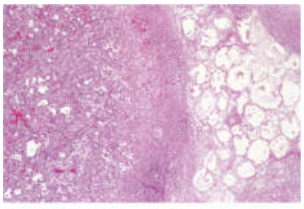
Foci of fat necrosis (Balser's fat necrosis) with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

4 - Enzymatic necrosis of pancreatic fat tissue (Balser type) – Balser's fat necrosis

Microscopical examination of adipose tissue affected with Balser's necrosis reveals „ghosty" adipocytes with blurred cell membranes and bluish, granular cytoplasm. Additionaly amorphous basophilic extracellular depositions of calcium can be observed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Acute pancreatitis.
The microscopic field shows a region of fat necrosis on the right and focal pancreatic parenchymal necrosis (*center*).

Apoptosis

- derives from a Greek word which means „the falling down of leaves".

5 - Apoptosis (viral hepatitis)

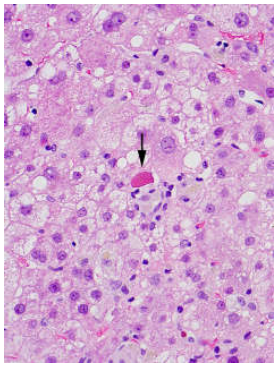
Apoptosis means genetically programmed, spontaneous death of cells (suicide of cells)

The term „apoptosis" derives from a Greek word which means „the falling down of leaves". They become detached one after another, never all simultanously. The same is true for apoptosis and it is a difference with necrosis which usually involves the majority of cells of a given area.

Apoptosis fails to secrete any mediators – there is no inflammatory reaction (on the contrary to necrosis). Necrosis almost always induced the inflammation which leads to phagocytosis of necrotic mass.

Apoptosis is physiological but also results from pathogen for example viruses

A cell undergoing apoptosis is variably referred to as "apoptotic body," "acidophil body," or "Councilman body"



- Apoptotic body (arrow).
- Note the condensation and dark staining of the cytoplasm and absence of nucleus.

Liver injury

- Liver injury can be caused by different stimuli such as alcohol intake, viral infection, cholestasis, steatosis, drug abuse, and autoimmunity
- In the damaged liver, cell death modes include apoptosis and necrosis
- Apoptosis is an early, chronic, and temperate response subsequent to injury induction, whereas necrosis is an acute and severe reply.

Hepatic apoptosis

- Apoptosis is a prominent feature of liver diseases. Causative factors such as alcohol, viruses, toxic bile acids, fatty acids, drugs, and immune response, can induce apoptotic cell death *via* membrane receptors and intracellular stress.
- Apoptotic signaling network, including membrane death receptor-mediated cascade, reactive oxygen species (ROS) generation, endoplasmic reticulum (ER) stress, lysosomal permeabilization, and mitochondrial dysfunction, is intermixed each other, but one mechanism may dominate at a particular stage.
- Mechanisms of hepatic apoptosis are complicated by multiple signaling pathways
- The acute liver injury involves much necrosis, but the chronic infection of HCV and HBV exhibits abundant apoptosis. Only human and chimpanzee hepatocytes are naturally able to support HCV entry

- *Cell Death and Disease* (2014) **5**, **Molecular mechanisms of hepatic apoptosis** K Wang-

5 - Apoptosis (viral hepatitis)

Apoptotic hepatocytes are typicall for viral hepatitis. They are called acidophilic bodies (**Councillman's bodies**)

Morphologically apoptosis is represented by a sign of necrosis in the single cells.

In single hepatocytes we can find the signs of (coagulative) necrosis:

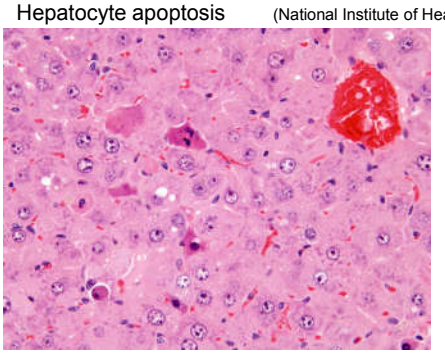
-pyknosis -condensation of chromatin

-kariorhexis – fragmentation of nuclei with margination of chromatin followed by its encapsulation and formation apoptotic bodies

-in the end cells disappear

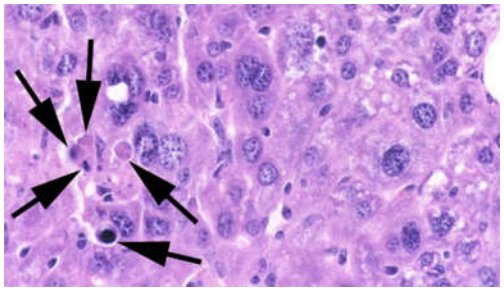
Apoptotic hepatocytes are deeply pink and their nuclei are condensated

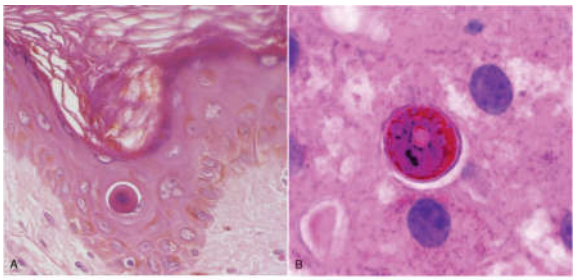
Hepatocyte apoptosis (National Institute of Health)



- Hepatocytes have hypereosinophilic cytoplasm and are surrounded by a clear halo resulting from fragmentation and contraction of the dying hepatocyte

Apoptotic bodies





Apoptosis of epidermal cells in an immune-mediated reaction. The apoptotic cells are visible in the epidermis with intensely eosinophilic cytoplasm and small, dense nuclei. H&E stain