DEGENERATION, ACCUMULATION, PIGMENTS,CALACIFICATION

Degenerations

Endogenous pigments

Exogenous pigments.

Calcifications, lithiasis, amyloidosis.

Livia Vida 2018

Theoretical questions

5. The definition and types of degenerations. Parenchymal and fatty degeneration. Organ examples

6. Pathomorphology, pathogenesis and complications of atherosclerosis. Aneurysm types

7. Exogenous and endogenous pigments. Histochemical characteristics of the different pigments. Anthracosis.

8. Hemoglobinogenic pigments I. Different forms of jaundice and cholostasis, morphology, differential diagnostics.

9. Hemoglobinogenic pigments II. Pathological forms of iron storage Endogenous nonhemoglobinogenous pigments: lipofuscin, melanin, homogentisinic acid.

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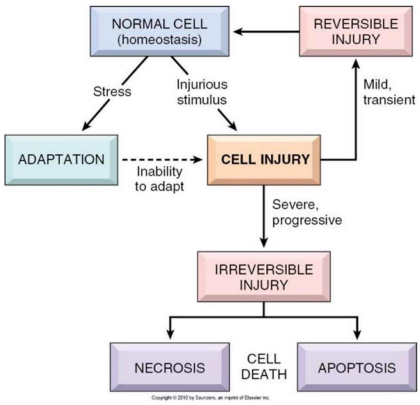
Cellular Responses to Stress and Noxious Stimuli

- The normal cell is confined to a fairly narrow range of function and structure.
- It is nevertheless able to handle physiologic demands, maintaining a steady state called **homeostasis.**
- **Adaptations** are reversible functional and structural responses to changes in physiologic states and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.



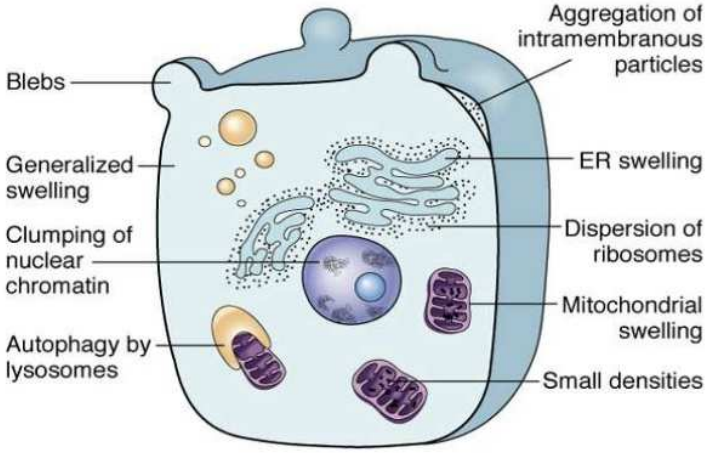
Pathological adaptation

- Left ventricular hypertrophy can develop in response to some factor — such as high blood pressure or aortic stenosis — that causes the left ventricle muscle to work harder.
- In response to this pressure overload inside the left ventricle, heart muscle cells **ADAPT** by getting thicker along the inner walls of the heart. This thickened wall can cause the left ventricle chamber to weaken, stiffen and lose elasticity, which may prevent healthy blood flow.
- Left ventricular hypertrophy is a strong independent predictor of cardiovascular deaths.

Cellular swelling

The hallmarks of reversible injury are reduced oxidative phosphorylation with resultant depletion of energy stores in the form of ATP, and cellular swelling caused by changes in ion concentrations and water influx.

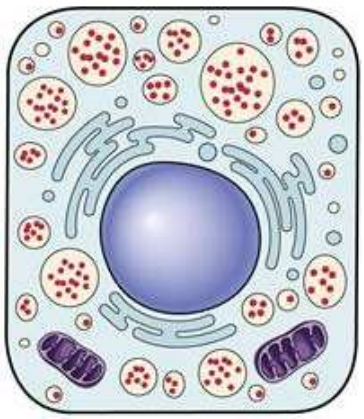
In addition, various intracellular organelles, such as mitochondria and the cytoskeleton, may also show alterations.

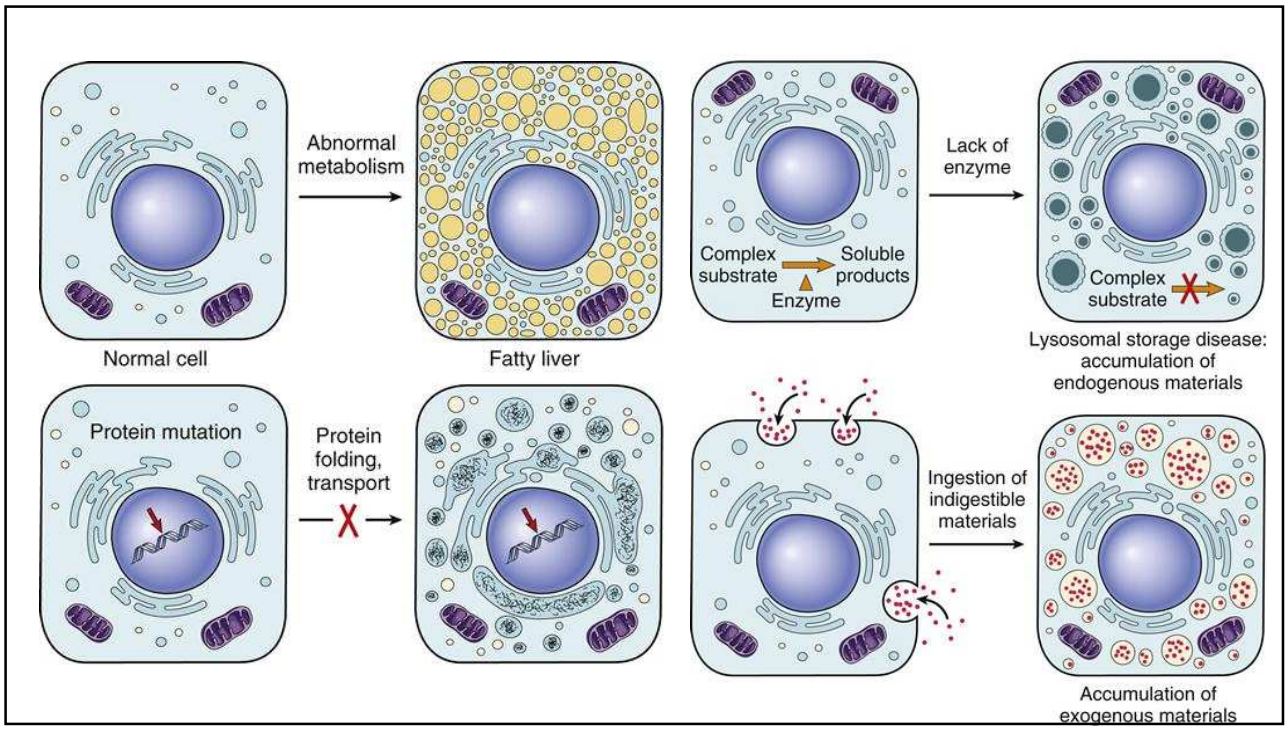


B. Reversible injury

Intracellular Accumulations

- One of the manifestations of metabolic derangements in cells is the intracellular **accumulation of abnormal amounts of various substances** that may be harmless or associated with varying degrees of injury. The substance may be located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere.
- There are **four main pathways** of abnormal intracellular accumulations.





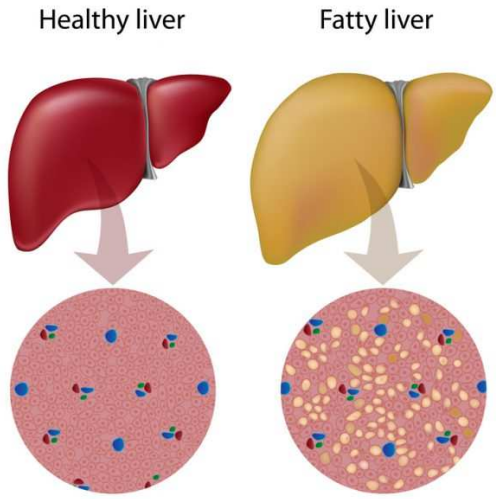
Intracellular accumulations

- There are four main pathways of abnormal intracellular accumulations:
- Inadequate removal of a normal substance, as in fatty change
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects, as in hemosiderosis, amyloidosis
- Failure to degrade a metabolite due to inherited enzyme deficiencies, as in Gaucher's disease
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade it, as in anthracosis

Fatty change, fatty degeneration, steatosis

- Definition: the terms steatosis and fatty change describe abnormal accumulations of triglycerides within parenchymal cells.
- 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.
- Etiology: the causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia.

In developed nations, the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease, which is often associated with diabetes and obesity.



Pathogenesis

- Short-term ingestion of as much as 80 gm of alcohol produces mild, reversible hepatic steatosis.
- Daily intake of 160 gm or more for 10 to 20 years is associated more consistently with severe injury.
- Only 10% to 15% of alcoholics, however, develop cirrhosis.

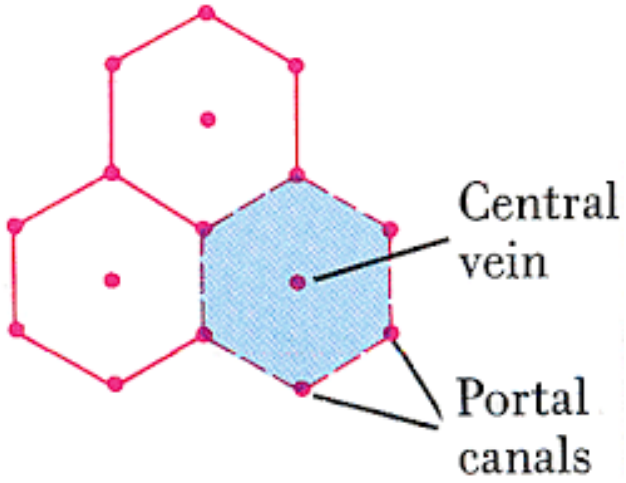
Morphology - macroscopy

- Macroscopically, the fatty liver of chronic alcoholism is a large (as heavy as 4 to 6 kg), soft organ that is yellow and greasy. Although there is little or no fibrosis at the outset, with continued alcohol intake fibrous tissue develops around the terminal hepatic veins and extends into the adjacent sinusoids.
- Liver enlargement: hepatomegaly
- Severe liver fibrosis: hepatic cirrhosis

Morphology - microscopy

Hepatic Steatosis (Fatty Liver). After even moderate intake of alcohol, **microvesicular** lipid droplets accumulate in hepatocytes.
With chronic intake of alcohol, lipid accumulates creating large, clear **macrovesicular** globules that compress and displace the hepatocyte nucleus to the periphery of the cell.
The fatty change is completely reversible if there is abstention from further intake of alcohol.

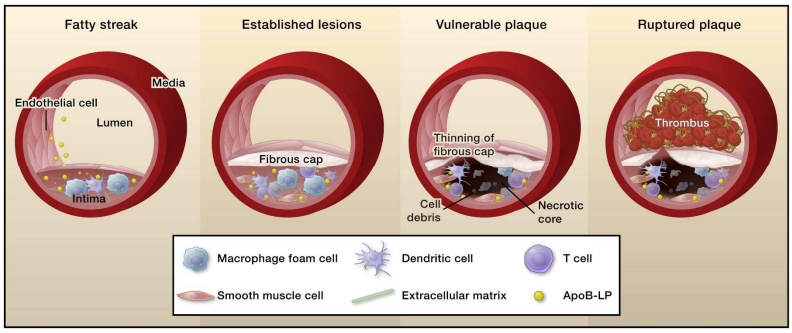
Micromorphology



Fat accumulation is partial first (centrolobular or peripherolobular), finally it becomes panlobular.

What is atherosclerosis?

Atherosclerosis, from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern. **Atherosclerosis underlies the pathogenesis of coronary, cerebral and peripheral vascular disease, and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder.**



Etiology

The likelihood of atherosclerosis is determined by the combination of **acquired** (e.g., cholesterol levels, smoking, hypertension) and **inherited** (LDL receptor gene mutations) risk factors.

Risk factors:
Age
Gender
Hyperlipidemia
Diet
Lifestyle
High blood pressure
Smoking
Diabetes mellitus
Inflammation!

Pathogenesis of atherosclerosis

1. Endothelial injury and dysfunction, increased vascular permeability, leukocyte adhesion.
2. Accumulation of lipoproteins (LDL) in the vessel wall.
3. Monocyte adhesion to the endothelium, followed by migration into the intima and transformation into foam cells.
4. Smooth muscle cell activation.

Pathogenesis of atherosclerosis

5. Smooth muscle cell proliferation, extracellular matrix production, and recruitment of T cells.
6. Lipid accumulation both extracellularly and within cells(macrophages and smooth muscle cell)

Morphology

- **Fatty streaks** begin as minute yellow, flat macules that coalesce into elongated lesions.
- They are composed of lipid-filled foamy macrophages, they are only minimally raised and do not cause any flow disturbance.
- Fatty streaks can appear in the aortas of infants younger than 1 year of age and are present in virtually all children older than 10 years.

- **Atherosclerotic plaques** are patchy, usually involving only a portion of any given arterial wall.
- Local flow disturbances, such as turbulence at branch points, make certain parts of a vessel wall susceptible to plaque formation.

Atherosclerotic plaques have three principal components: (1) cells, including smooth muscle cells, macrophages, and T cells; (2) extracellular matrix, including collagen, elastic fibers, and proteoglycans; and (3) intracellular and extracellular lipid.

Morphology

- The proportion and configuration of each component varies from lesion to lesion.
- Most commonly plaques have a superficial fibrous cap composed of smooth muscle cells and relatively dense collagen.
- Deep to the fibrous cap is a necrotic core, containing lipid (primarily cholesterol and cholesterol esters), necrotic debris, lipid-laden macrophages and smooth muscle cells (foam cells), fibrin, variably organized thrombus, and other plasma proteins.
- The extracellular cholesterol frequently takes the forms of crystalline aggregates that are washed out during routine tissue processing, leaving behind empty "cholesterol clefts." The periphery of the lesions shows neovascularization.
- Atheromas also often undergo calcification.

Clinical consequences

The principal pathophysiologic outcomes depend on the size of the affected vessel, the size and stability of the plaques, and the degree to which plaques disrupt the vessel wall:

- ACUTE Occlusion of smaller vessels can compromise tissue perfusion.
- ACUTE Plaque rupture can expose atherosclerotic debris, leading to acute (and frequently catastrophic) vascular thrombosis or (with shedding of debris) distal embolization.
- CHRONIC Destruction of the underlying vessel wall can lead to **aneurysm** formation, with secondary rupture and/or **thrombosis.**

Aneurysms

- Aneurysms are congenital or acquired dilations of blood vessels or the heart.
- Aneurysms can be classified by shape. *Saccular* aneurysms are discrete outpouchings ranging from 5 to 20 cm in diameter, often with a contained thrombus.
- *Fusiform* aneurysms are circumferential dilations up to 20 cm in diameter; these most commonly involve the aortic arch, the abdominal aorta, or the iliac arteries.

Pathogenesis: **The two most important causes of aortic aneurysms are atherosclerosis and hypertension.**

Aneurysm types

Atherosclerosis is the more dominant factor in abdominal aortic aneurysms, while hypertension is associated with ascending aortic aneurysms.

Saccular aneurysm: The most frequent cause of clinically significant non-traumatic subarachnoid hemorrhage is rupture of a saccular (berry) aneurysm. Rupture can occur at any time, but in about one third of cases it is associated with acute increases in intracranial pressure.
Although they are sometimes referred to as congenital, they are not present at birth but develop over time because of underlying defects in the vessel media.

Atherosclerotic aneurysms occur most frequently in the abdominal aorta, but the common iliac arteries, aortic arch, and descending thoracic aorta can also be involved. Abdominal aortic aneurysm (AAA) occurs more frequently in men and in smokers and rarely develops before the age of 50 years.

Clinical Consequences

The clinical consequences of AAA may include

- **Obstruction of a vessel branching off the aorta** (e.g., the renal, iliac, vertebral, or mesenteric arteries), resulting in distal ischemia of the kidneys, legs, spinal cord, or gastrointestinal tract, respectively.
- **Embolism from atheroma** or mural thrombus.
- **Rupture** into the peritoneal cavity or retroperitoneal tissues, leading to massive, often fatal hemorrhage
- The risk of rupture is determined by size.

Theoretical questions

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Definition of pigments

Pigments are colored substances that are either exogenous, coming from outside the body, such as carbon, or endogenous, synthesized within the body itself, such as lipofuscin, melanin, and certain derivatives of hemoglobin.

Carbon

- The most common exogenous pigment is carbon (an example is coal dust), a ubiquitous air pollutant of urban life.
- When inhaled, it is phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional tracheobronchial lymph nodes. Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma (anthracosis).

Lipofuscin

Lipofuscin, or "wear-and-tear pigment," is an insoluble brownish-yellow granular intracellular material that accumulates in a variety of tissues (particularly the heart, liver, and brain) as a function of age or atrophy.

Lipofuscin represents complexes of lipid and protein that derive from the free radical–catalyzed peroxidation of polyunsaturated lipids of subcellular membranes.

It is not injurious to the cell but is a marker of past *free radical* injury.

The brown pigment, when present in large amounts, imparts an appearance to the tissue that is called *brown atrophy*.

One of the most common endogenous pigments found in human tissues.

Melanin

- Melanin is an endogenous, brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation.
- Although melanocytes are the only source of melanin, adjacent basal keratinocytes in the skin can accumulate the pigment (e.g., in freckles), as can dermal macrophages.

Hemosiderin

Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or systemic excess of iron.

Iron is normally stored within cells in association with the protein apoferritin, forming ferritin micelles.

Hemosiderin pigment represents large aggregates of these ferritin micelles.

The iron can be identified by the Prussian blue histochemical reaction.

Although hemosiderin accumulation is usually pathologic, small amounts of this pigment are normal in the mononuclear phagocytes.

Excessive deposition of hemosiderin, called hemosiderosis, and more extensive accumulations of iron seen in hereditary hemochromatosis.

Bilirubin

- Bilirubin is the non-iron-containing, yellow-orange pigment that results from breakdown of porphyrin rings (mostly hemoglobin).
- Bilirubin by itself is insoluble in water and is carried on albumin to the liver, where hepatocytes conjugate it with glucuronic acid and pour it into the bile.
- Elevated levels of bilirubin in the blood mean jaundice.
- You may see bile plugs (bile in distended canaliculi; big ones that ruptured are "bile lakes") or intracellular bilirubin in the liver in obstructive jaundice.

Alkapton (homogentisic acid)

Patients with the hereditary alkaptonuria accumulate homogentisic acid, a breakdown product of tyrosine / phenylalanine (one enzyme is missing due to mutation), which polymerizes into black pigment in their cartilages (nose, ears) and joints.

The accumulation itself is called ochronosis.

Patients are asymptomatic as children or young adults, but their urine may turn brown or even inky black if collected and left exposed to open air. They develop arthritis symptoms later in life.

It is an autosomal recessive hereditary condition. Google Archibald Garrod!

Exogenous vs. Endogenous pigments

Exogenous: inhaled or digested pigments or traumatic entry (injury, tattoo).

Endogenous:

- Non-hemoglobinogenic pigments: melanin, lipofuscin, homogentisic acid
- Hemoglobinogenic pigments: hemosiderin and bilirubin

Hemoglobin is a complex protein made of heme and globin. During brakedown of scenecent erthrocytes, pigments are made.

Bilirubin

Hemoglobinogenic pigments. Causes and forms of jaundice.

Jaundice

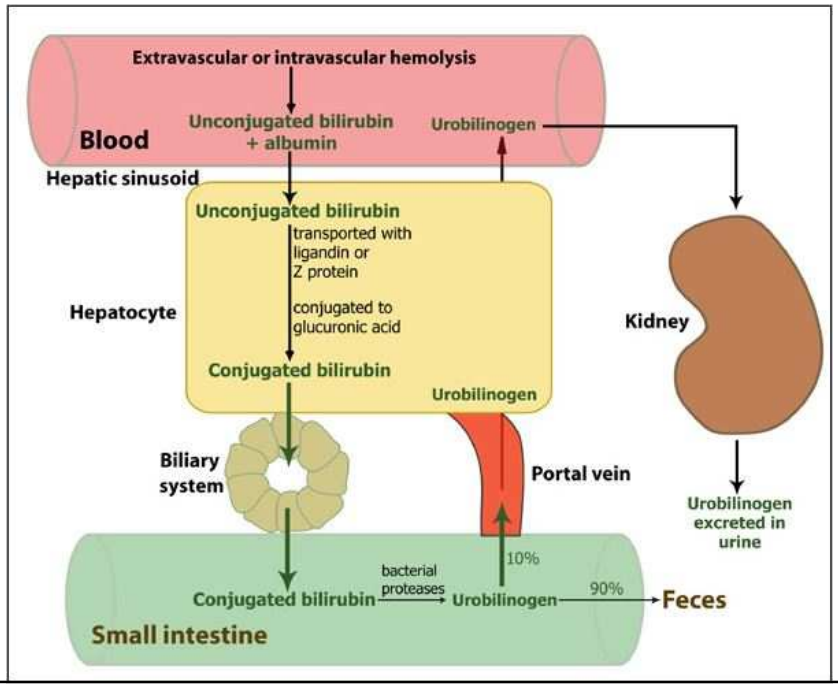
Bilirubin is the end product of heme degradation.

Elevated levels of bilirubin in the blood mean jaundice.

Jaundice results from the retention of bile.

Bile formation is a complex process and is readily disrupted **by a variety of hepatic insults**. Thus, *jaundice,* a yellow discoloration of skin and sclerae (*icterus*).

Cholestasis is defined as systemic retention of not only bilirubin but also other solutes eliminated in bile (particularly bile salts and cholesterol).



Etiology

Jaundice occurs when the equilibrium between bilirubin production and clearance is disrupted.

Most common causes of icterus:

- Hemolytic anaemia
- Hepatitis (liver inflammation)
- Blockage of bile flow

Neonatal icterus: transient, enzymes are not ready yet.

Gilbert syndrome: benign „non disease”, harmless hyperbilirubinemia

Dubin-Johnson syndrome results from an autosomal recessive defect in a hepatic transport protein. Hepatomegaly and hyperbilirubinemia, benign.

Clinical consequences

- Cholestasis, which results from impaired bile flow due to hepatocellular dysfunction or intrahepatic or extrahepatic biliary obstruction, also may manifest as jaundice. However, sometimes pruritus is the first presenting symptom.
- Skin xanthomas (focal accumulations of cholesterol) also may appear in cholestasis.
- Extrahepatic biliary obstruction frequently is amenable to surgical correction.
- Intrahepatic cholestasis cannot be treated surgically (maybe transplantation), and the patient's condition may be worsened by an operative procedure.
- Thus, there is always urgency in identifying the cause of jaundice and cholestasis.

Hemosiderin

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Generalized Hemosiderosis

Too much iron in the whole body:

many red cell transfusions without blood loss
(i.e., diseases that ruin red cell precursors)

problems using the iron:

- ineffective erythropoiesis (thalassemia, myelodysplasia)
- "sideroblastic" anemia

Transfusion blood red cells live shorter, repeated transfusions are necessary. Iron is accumulating with every transfusion.

Local hemosiderosis

Localized hemosiderosis

Local excesses of iron and hemosiderin

result from:

1. **gross hemorrhages** - bruise
2. **minute hemorrhages** due to vascular congestion

lung: induratio brunea pumonis

Liver: hepar moschatum

spleen: fibroadenia**/** Fibrosiderotic plaques

Skin: lower extremities: venous congestion

Brown induration of the lung

Due chronic left-sided heart failure severe congestion occurs.

We see “heart failure cells”, ie alveolar macrophages with hemosiderin granules (appear as brown cytoplasmic granules with H&E staining).

Note, when phagocytosed erythrocytes are broken down in macrophages the iron is removed and is bound to stored as hemosiderin granules.

Long standing congestion in the lung will lead to fibroblast activation and pulmonary fibrosis.

Induration is due to fibrosis

Brunea: due to hemosiderosis

Hemochromatosis

- Hereditary hemochromatosis refers to a genetic disorder characterized by excessive accumulation of body iron, most of which is deposited in the liver, pancreas, and heart.
- The total body content of iron is tightly regulated.
- There is no excretory pathway for excess absorbed iron.
- The hereditary hemochromatosis gene, responsible for the most common form of this disorder, is called *HFE.*
- Expression of the mutated HFE protein leads to upregulated absorption of iron.

In hereditary hemochromatosis, iron accumulates over the lifetime of the affected person from excessive intestinal absorption.

Pathogenesis

Regardless of source, excessive iron seems to be directly toxic to tissues by the following mechanisms:

- Lipid peroxidation, protein oxidation by iron-catalyzed free radical reactions
- Stimulation of collagen formation= fibrosis=scar tissue
- Direct interactions of iron with DNA

Morphology

The morphologic changes in hereditary hemochromatosis are all responses to the **deposition of hemosiderin** in the following organs (in decreasing order of severity):

- liver
- pancreas
- myocardium
- pituitary
- adrenal
- thyroid and parathyroid glands
- joints and skin

In the liver, iron becomes evident as golden-yellow hemosiderin granules in the cytoplasm of periportal hepatocytes and Kupffer cells. Iron is a direct hepatotoxin.

The liver typically is larger than normal (hepatomegaly), dense, and brown. Fibrous septa develop slowly, leading ultimately to **cirrhosis** in an intensely pigmented (very dark brown) liver.

Importance of screening

Screening involves demonstration of very high levels of serum iron and ferritin, exclusion of secondary causes of iron overload, and liver biopsy if indicated.

Also important is screening of relatives.

The natural course of the disease can be substantially altered by phlebotomy and the use of iron chelators (Desferal®)to decrease total body iron.

Patients diagnosed in the subclinical, precirrhotic stage and treated by regular phlebotomy have a **normal life expectancy**.

Heterozygotes may show a mild increase in iron absorption and accumulation.