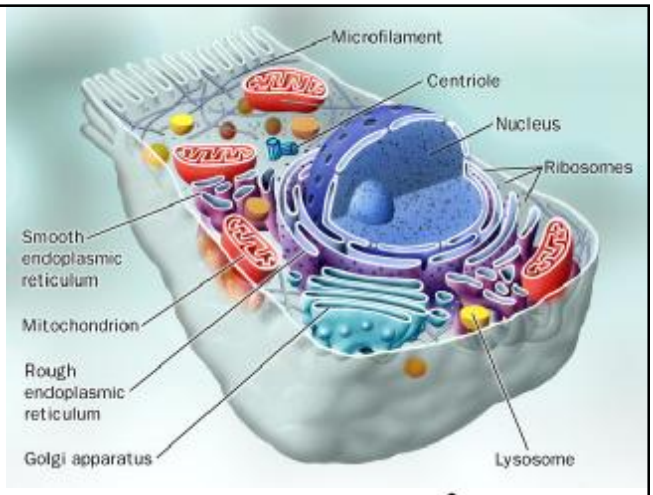
Intracellular accumulation & Pathologic Calcification



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Intracellular accumulation

- **Accumulation of abnormal amounts** of various substances either in the **cytoplasm**, within **organelles** (typically lysosomes), or in the **nucleus**.
- May be harmless or may cause varied degrees of injury.
- The substance may be synthesized by the affected cells or may be produced elsewhere.

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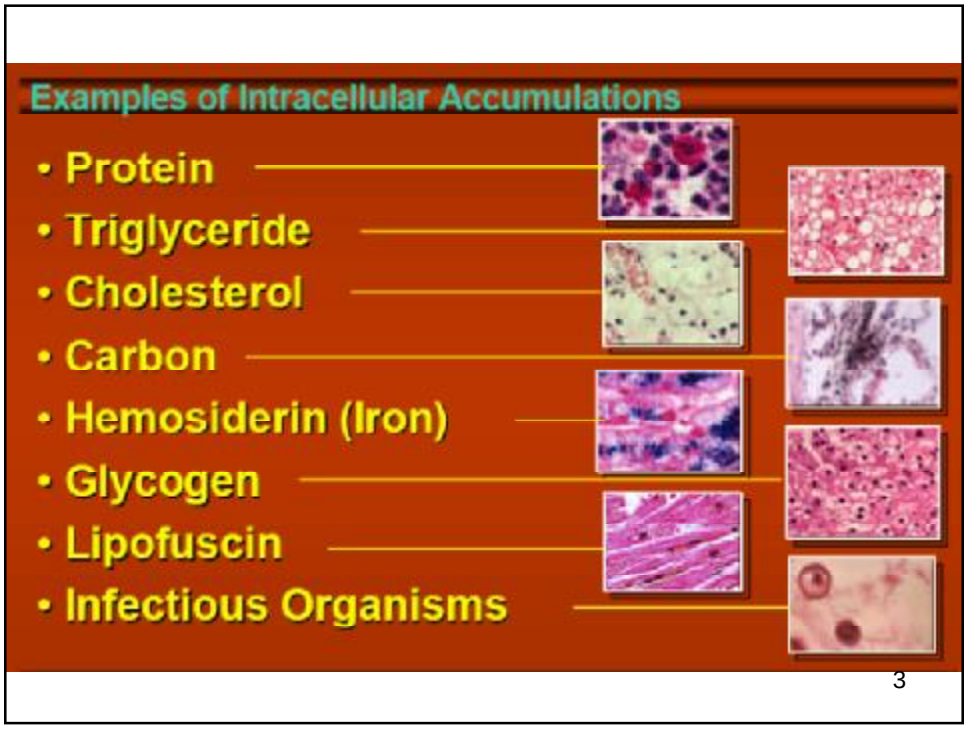

General pathways for intracellular accumulation

1. **Abnormal metabolism of substances**

   e.g. fatty liver

2. **Defective folding and transport of proteins**

   e.g. alpha-1 antitrypsin deficiency.

3. **Genetic or acquired lack of enzyme**

   e.g. storage diseases.

4. **Accumulation of exogenous indigestible material**

   e.g. carbon

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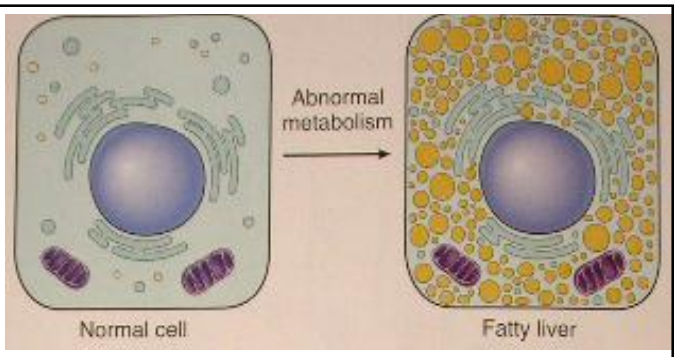
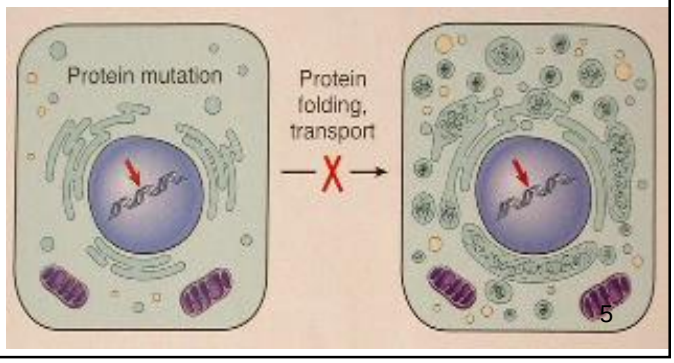
Causes:

1) **Abnormal metabolism** of substances
e.g. **fatty liver**



2) **Defective folding & transport of proteins**
e.g. **alpha-1 antitrypsin deficiency**.



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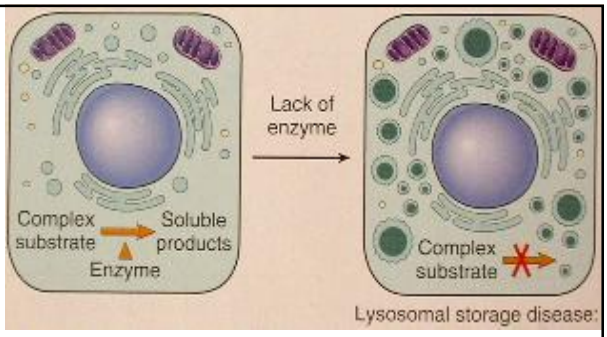
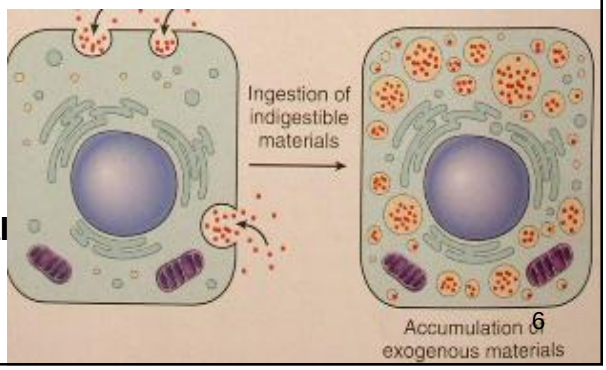
3) **Genetic or acquired lack of enzyme**
e.g. **storage diseases**.



4) **Accumulation of exogenous indigestible material**
e.g. **carbon**



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Fatty changes: Steatosis

- Defined as **abnormal accumulation of triglycerides** within parenchymal cells.
- **Liver** is the most common organ affected, but heart, skeletal muscles and kidney may be affected.
- Fatty changes are **reversible**.

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Causes of Fatty changes

- **Toxins**: **alcohol** is the most common cause.
- **Protein malnutrition**: due to decrease in the synthesis of apolipoproteins.
- **Diabetes mellitus**
- **Obesity**
- **Anoxia and starvation**

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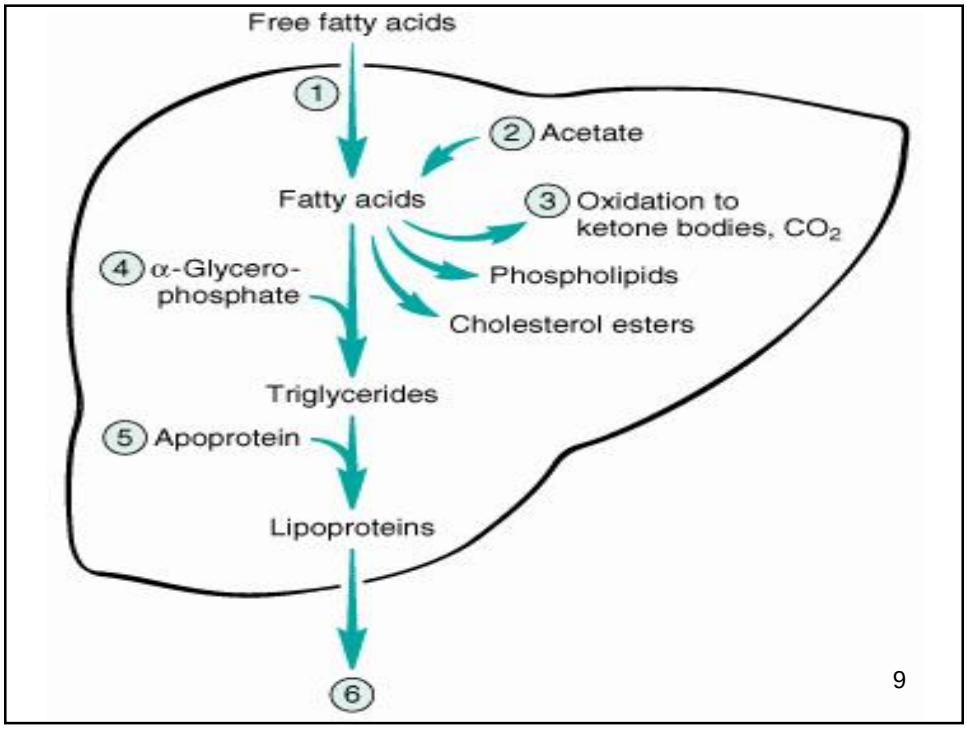
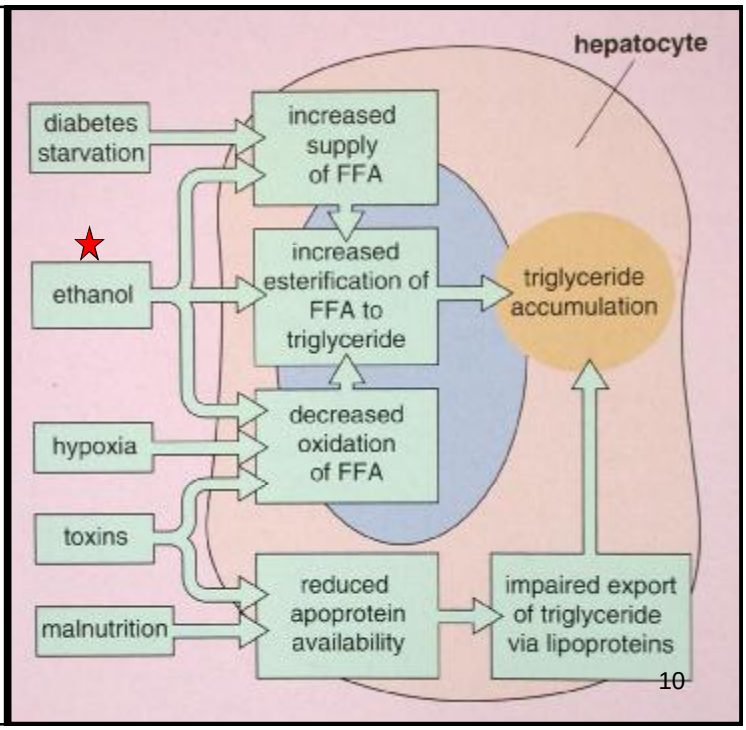
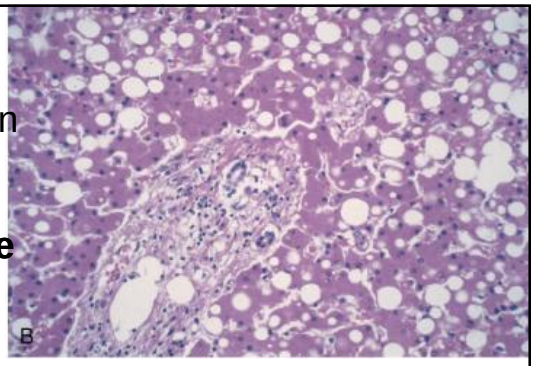


Causes of Fatty changes



MORPHOLOGY:

Early fatty change is seen by light microscopy as small **fat vacuoles in the cytoplasm** around the nucleus.



With accumulation, **the organ enlarges** and becomes progressively **yellow**, **greasy** & **soft**.

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Cholesterol & cholesterol esters

- Mainly **accumulates in macrophages**, leading to the formation of **foam cells**.

- **Example 1:**

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

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Cholesterol & cholesterol esters

Example 2:

In hereditary and acquired hyperlipidemic syndromes, macrophages accumulate intracellular cholesterol; when present in the subepithelial connective tissue of skin or in tendons, clusters of these foamy macrophages form masses called **xanthomas**.

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Proteins

1. **In nephrotic syndrome**, there is an increased pinocytic reabsorption of the protein. Fusion of these **pinocytic** vesicles with lysosomes results in the histologic appearance of pink, **hyaline cytoplasmic droplets**
2. **Russell bodies**; accumulation of newly synthesized **immunoglobulins within the RER in plasma cells**.

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Proteins

3. **Mallory bodies** or "**alcoholic hyaline**"; accumulation of **eosinophilic intracytoplasmic inclusions** (**prekeratin filaments**) in liver cells in alcoholic liver disease.
4. **Neurofibrillary tangle** found **in the brain** in **Alzheimer** disease; **aggregated protein** inclusion contains microtubule-associated proteins and neurofilaments.

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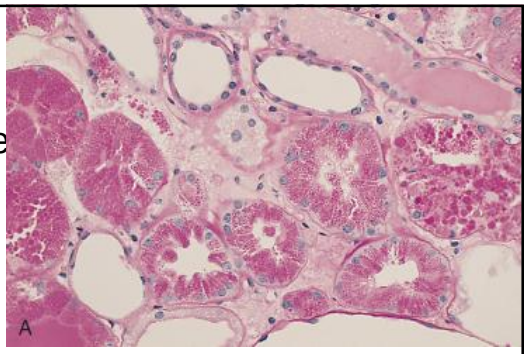
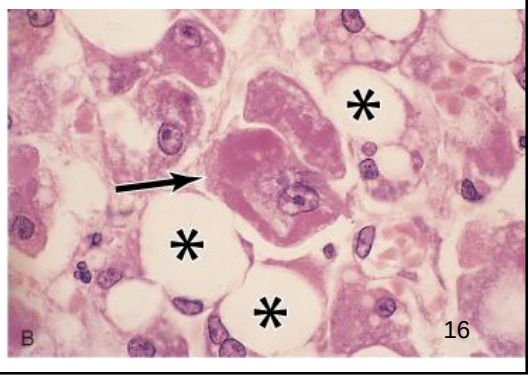
A, **Protein reabsorption droplets in the renal tubular epithelium**; the droplets are contained within pinocytic vacuoles and within lysosomes.

B, **Mallory bodies** (arrow). Also note the intracellular fat accumulation (asterisks), associated with acute alcohol intake.





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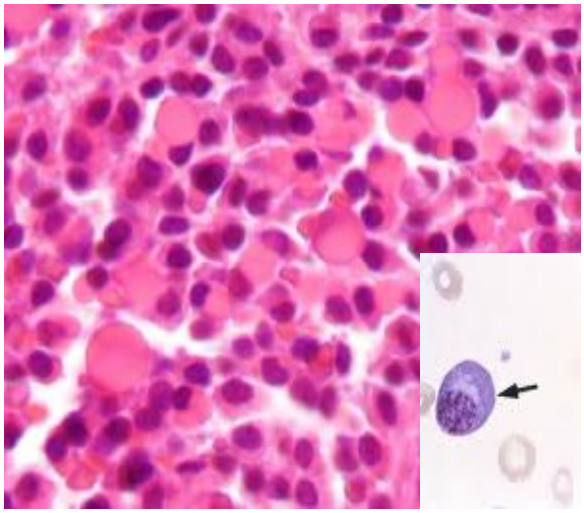
Russell bodies



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Glycogen

- Associated with abnormalities in the metabolism of either glucose or glycogen.
- **Examples:**

1) In **diabetes mellitus**; glycogen accumulates in renal tubular epithelium, cardiac myocytes, and beta cells of the islets in the pancreas.

2) **Glycogen storage diseases** due to enzymatic defects

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Pigments

- **Colored substances** that are either exogenous or endogenous.
- **Carbon** is the most common exogenous pigment. In the **lung** and the **hilar lymph nodes** carbon aggregates are called **anthracosis**.

- **Endogenous pigments include:**

  lipofuscin, **melanin**, and **hemosiderin**

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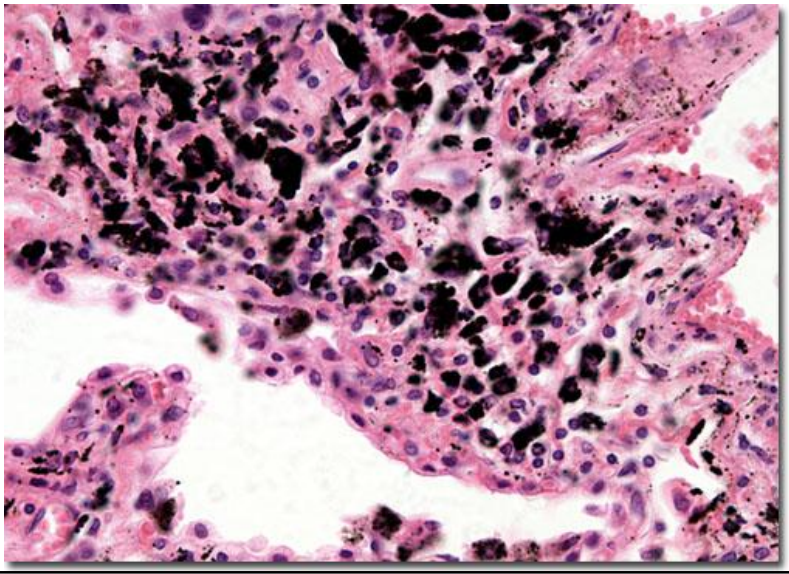
Anthracosis



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Pigments: Lipofuscin

- an **insoluble, brownish-yellow granular intracellular material** that accumulates as a function of **age or atrophy**.
- also called "**Wear and tear pigment**".
- represents **complexes of lipid and protein** that **derive from the free radical-catalyzed** peroxidation of polyunsaturated lipids of subcellular membranes.
- **not injurious to the cell** but is important marker of past free radical injury.

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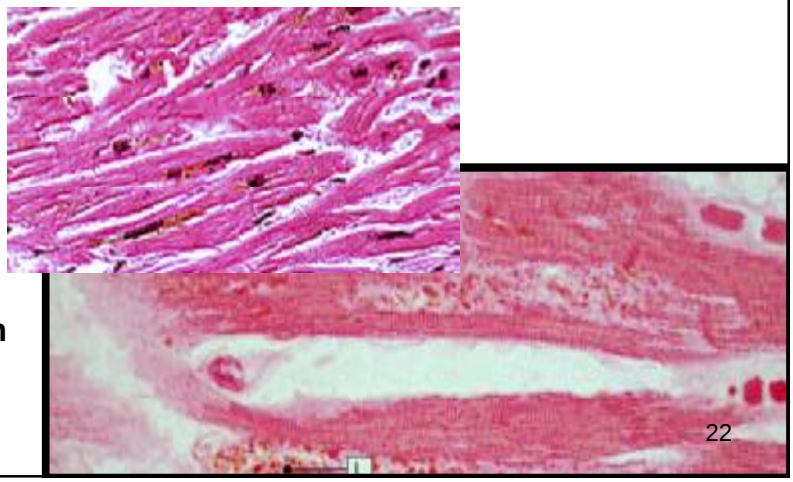
Pigments: Lipofuscin

- the pigment appears as perinuclear electron-dense granules
- called "**brown atrophy**" if apparent grossly



Lipofuscin granules in cardiac myocyte

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Pigments: Melanin

- an **endogenous**, **brown-black pigment formed by melanocytes**.
- adjacent basal **keratinocytes in the skin can also accumulate the pigment** (e.g., in **freckles**), or it may be accumulated in dermal macrophages.

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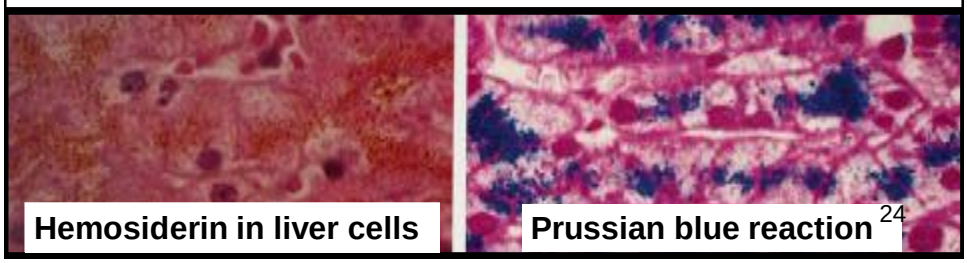
Pigments: Hemosiderin

- Hemoglobin derived golden-yellow to brown pigment.
- accumulates in tissues when there is a local or systemic **excess of iron**
- Hemosiderin pigment represents **large aggregates of ferritin**
- Detected by special stain called “Prussian blue”.



Hemosiderin in liver cells

Prussian blue reaction

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Pathological calcification

- **Definition:** abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium and other minerals.
- **Types of pathological calcification:**
  - **Dystrophic calcification.**
  - **Metastatic calcification.**

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Dystrophic calcification

- **Deposition of calcium on dead or dying cells**.
- **Normal levels of serum calcium**.
- Associated with clinical organ dysfunction.
- **Grossly** appears as fine white granules.
- **Microscopically**: intracellular or extracellular basophilic deposits.

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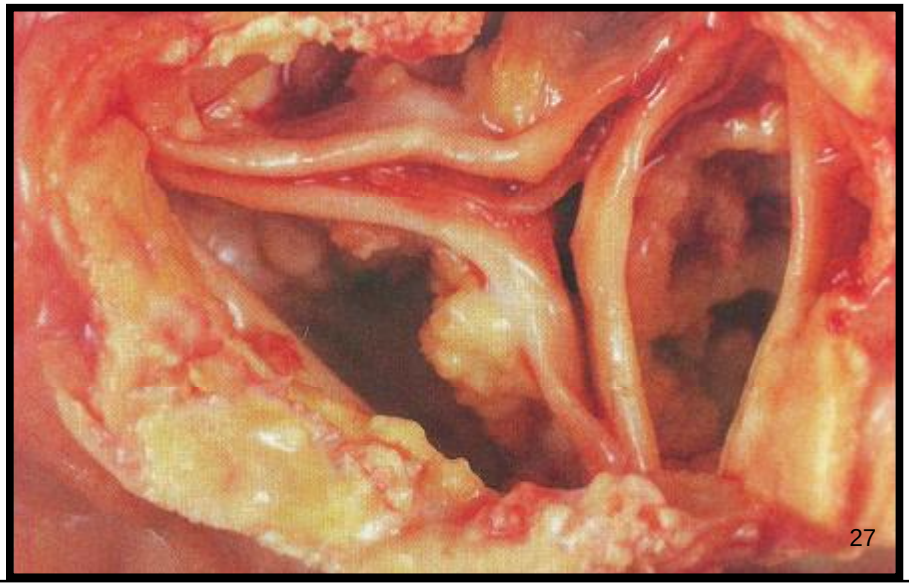
Dystrophic calcification in aortic valve is an important cause of aortic stenosis in the elderly



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Metastatic calcification

- **Deposition of calcium in normal tissue in the presence of hypercalcemia.**
- **Causes of hypercalcemia:**
  1. Increased secretion of parathyroid hormone.
  2. Destruction of bone by tumors.
  3. Vitamin-D related disorders.
  4. Renal failure.

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Metastatic calcification

- Affects mainly the interstitium of blood vessels, kidneys, lungs, and gastric mucosa.
- Does not generally cause clinical dysfunction, unless the process is severe

  e.g. **nephrocalcinosis**

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