Intracellular accumulations
calcifications
cellular aging

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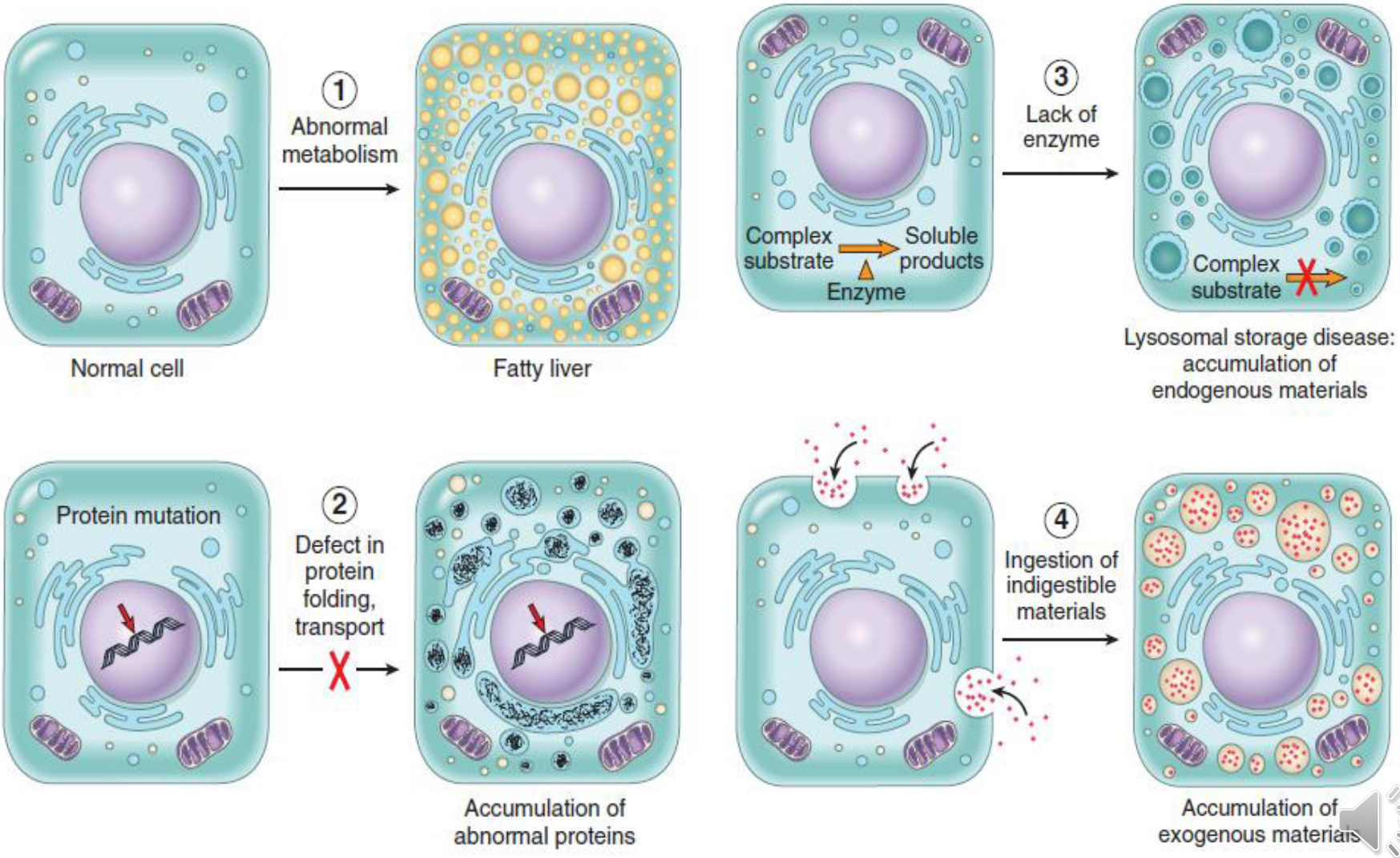
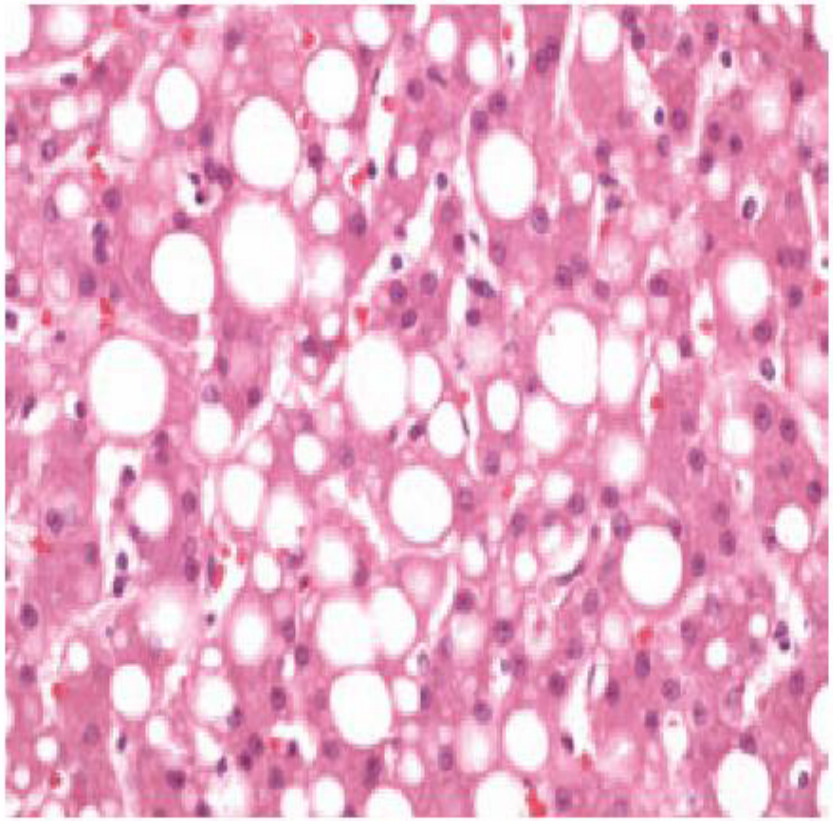
INTRACELLULAR ACCUMULATIONS

- 1)Inadequate removal of a normal substance (fatty change in the liver)
- 2)Accumulation of an abnormal endogenous proteins due to folding defect (α1-antitrypsin defficiency)
- 3)Failure to degrade a metabolite due to inherited enzyme deficiencies (lysosomal *storage diseases)*
- 4)Deposition and accumulation of an abnormal exogenous substance (carbon and selica)


1
Abnormal metabolism
Normal cell
Fatty liver
Complex substrate
Soluble products
Enzyme
3
Lack of enzyme
Complex substrate
Lysosomal storage disease: accumulation of endogenous materials
Protein mutation
2
Defect in protein folding, transport
Accumulation of abnormal proteins
4
Ingestion of indigestible materials
Accumulation of exogenous materials

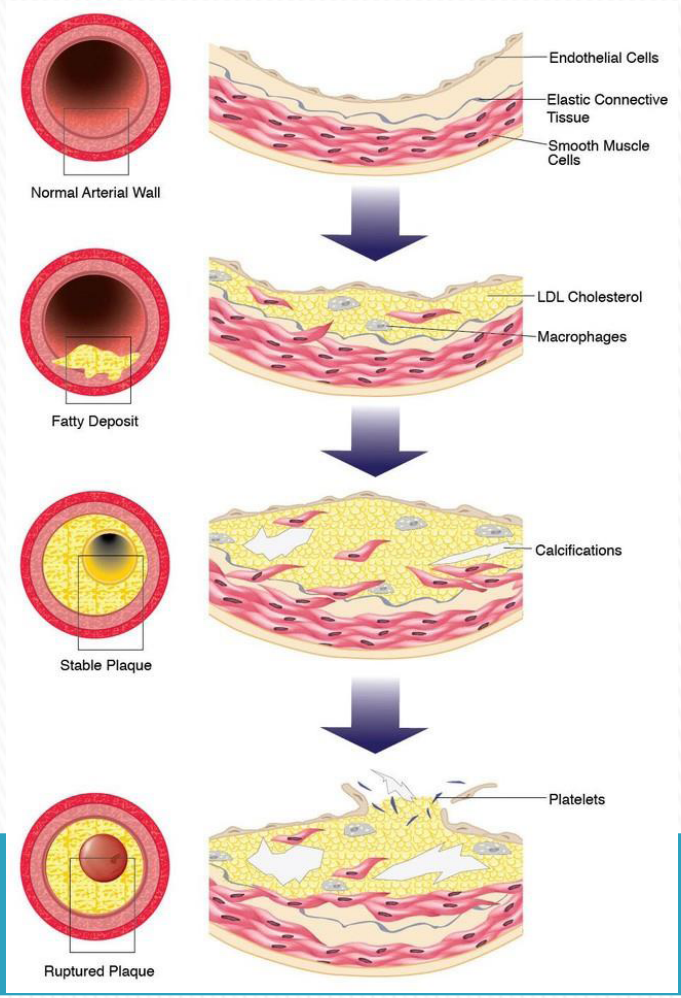
fatty change: steatosis

- Most common in liver
- Triglycerides
- Also in heart, kidney, muscle
- Causes: toxins, protein malnutrition, DM, obesity, anoxia
- Alcohol abuse and DM+obesity are the most common causes of fatty liver



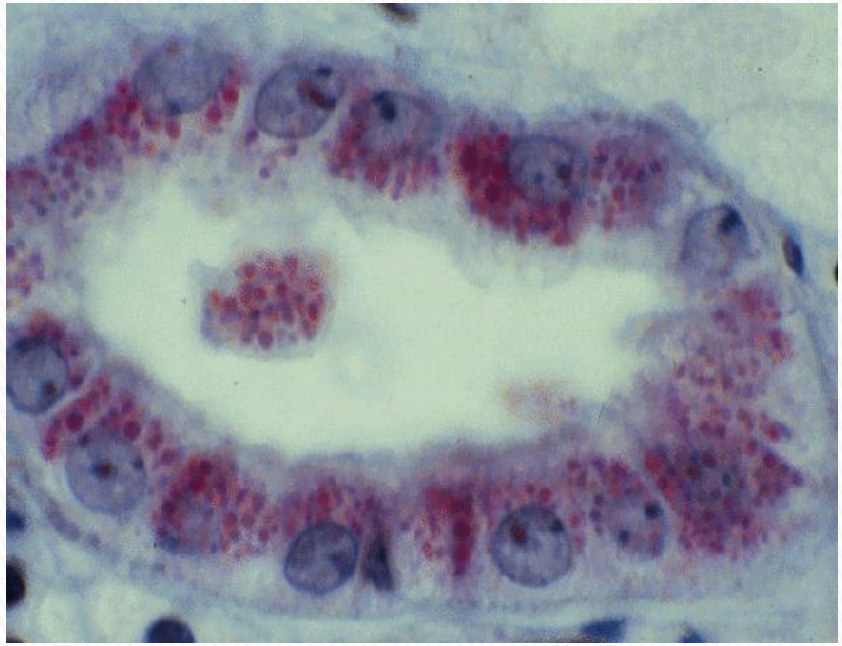
Cholesterol and Cholesteryl Esters

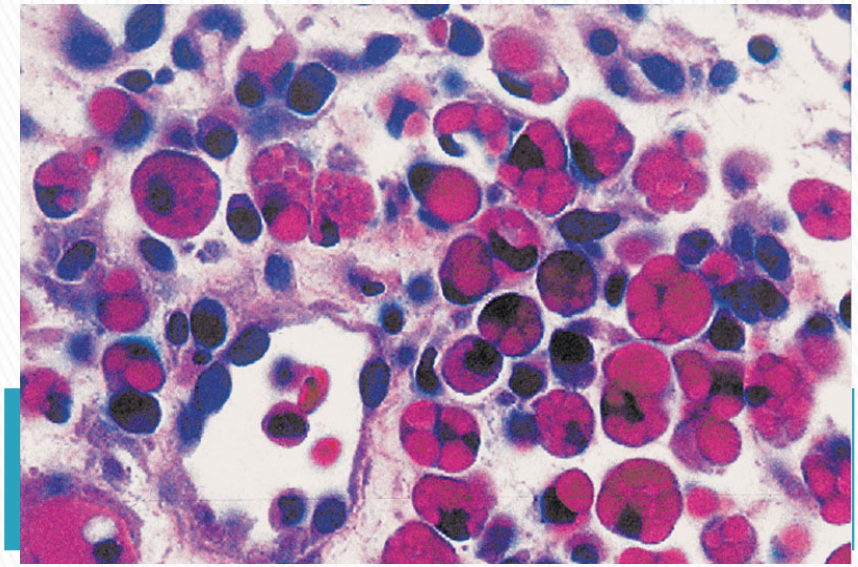
- Phagocytic cells become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters)
- Increased intake or decreased catabolism
- Atherosclerosis



Proteins

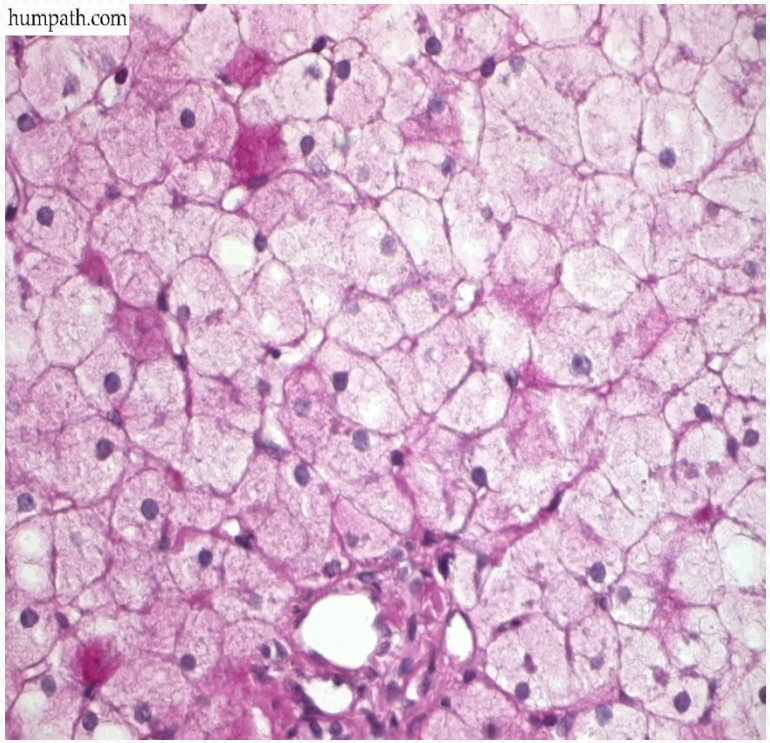
- Much less common than lipid accumulations
- Either excess external or internal synthesis
- Proximal renal tubules in nephrotic syndrome
- Russell bodies in plasma cells.
- Alcoholic hyaline in liver.
- Neurofibrillary tangles in neurons





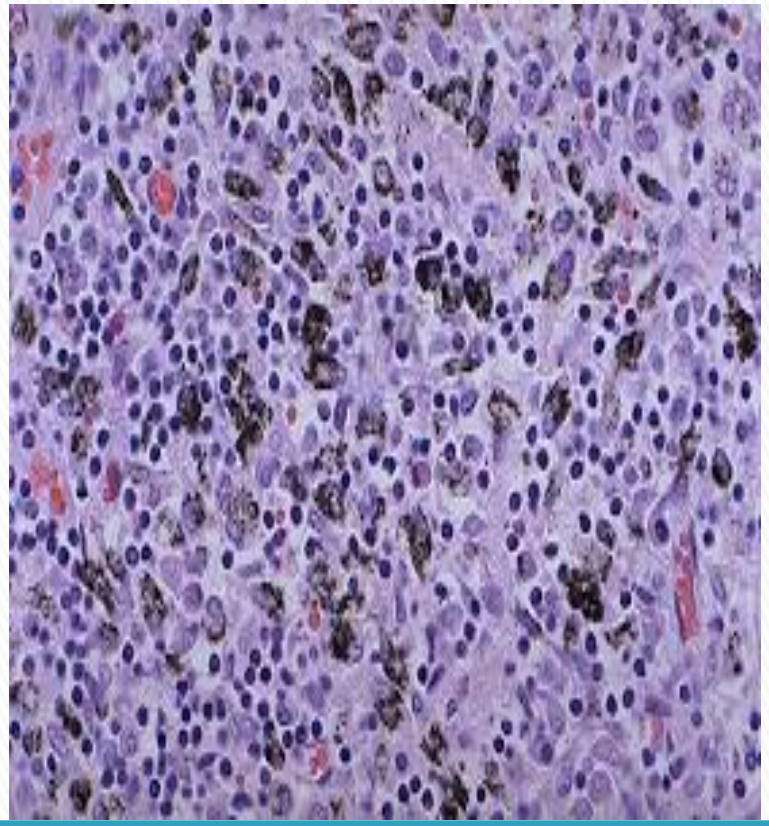
Glycogen

- Abnormality in glucose or glycogen metabolism
- **DM** (in renal tubules, heart, B cells of pancreas).
- **Glycogen storage diseases**



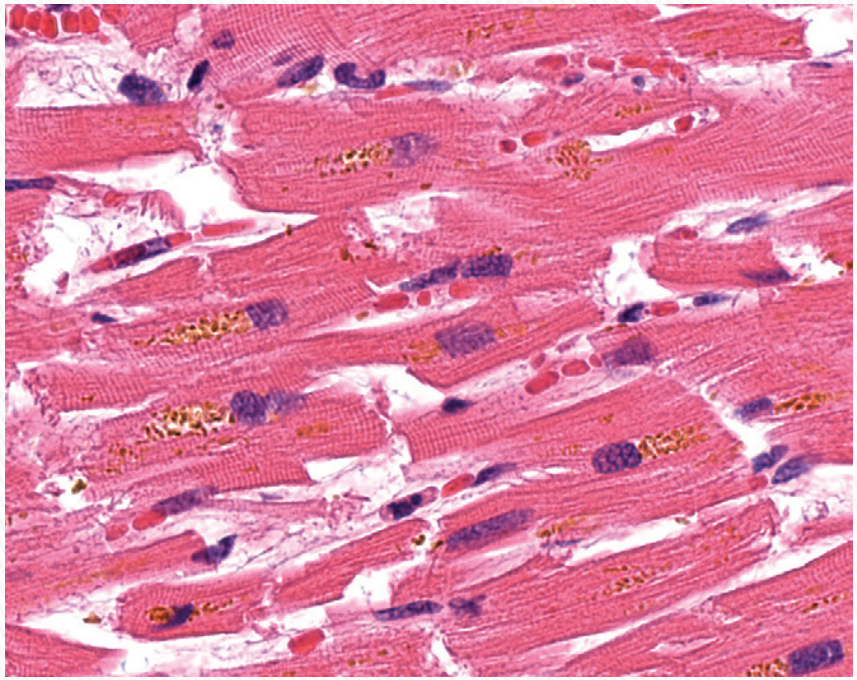
Pigments

- **Exogenous**
- Most common exogenous, **carbon** (coal dust, air pollution)
- Alveolar macrophages → lymphatic channels → tracheobronchial LN
- *Anthracosis*



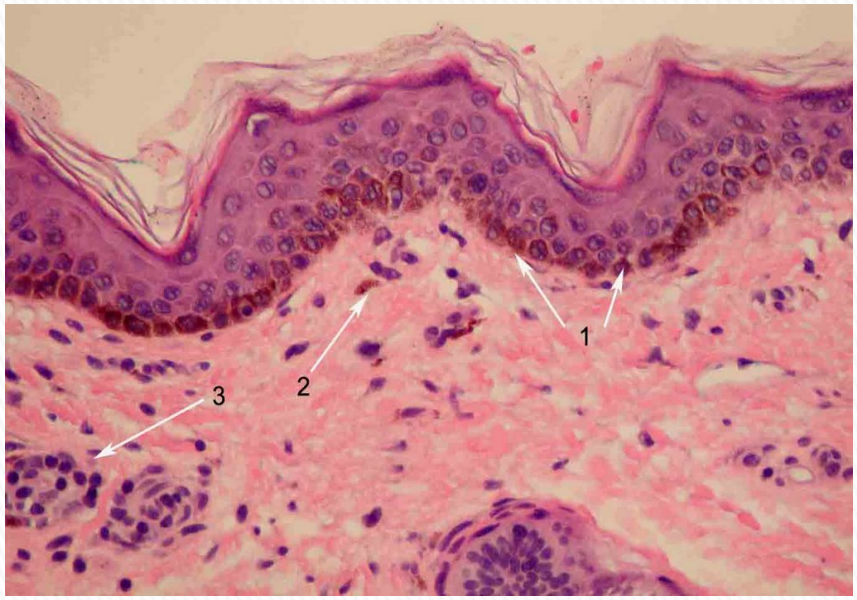
Pigments

- **Endogenous**
- **Lipofuscin**
- “wear-and-tear pigment”
- Age/atrophy
- Heart, liver, and brain
- Lipid and protein
- Marker of past free radical injury
- *brown atrophy*



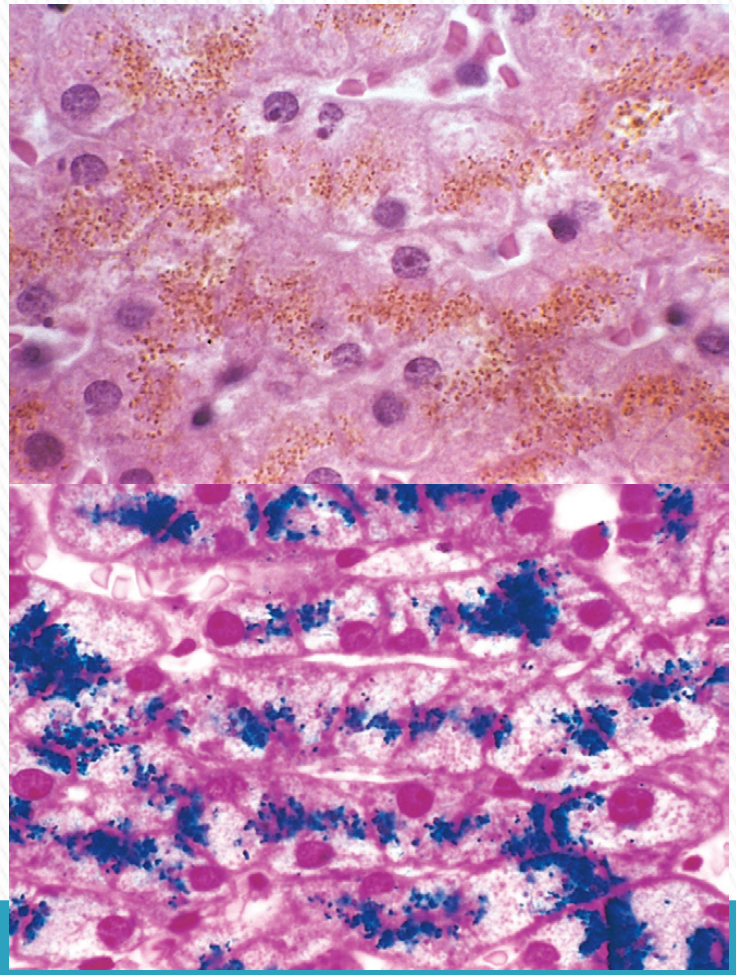
Pigments

- **Endogenous**
- **Melanin**
- Source: melanocytes
- UV protection
- Accumulates in dermal macrophages and adjacent keratinocytes
- Freckles



pigments

- **Hemosiderin**
  - Hb-derived granular pigment
  - Iron +apoferritin==ferritin micelles
  - Physiologic in the mononuclear phagocytes of the BM, spleen, and liver, from RBC turnover
  - Bruise: local pathologic deposition from hemorrhage
  - Hemosiderosis: systemic pathologic deposition of hemosiderin (hemochromatosis, hemolytic anemias, repeated blood transfusions)



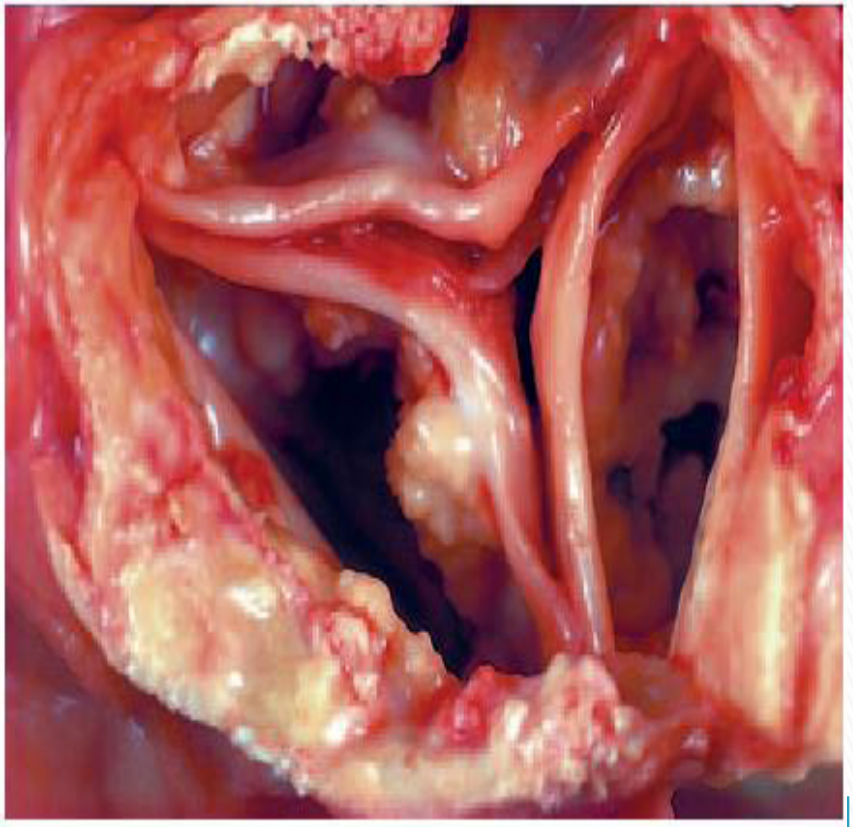
PATHOLOGIC CALCIFICATION

- Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral

- **Dystrophic Calcification**
- Deposition in dead/injured tissues
- Normal Ca2+ metabolism
- Exacerbated by Hypercalcemia

- **Metastatic Calcification**
- Deposition in normal tissues
- Almost always abnormal Ca2+ metabolism (hypercalcemia)

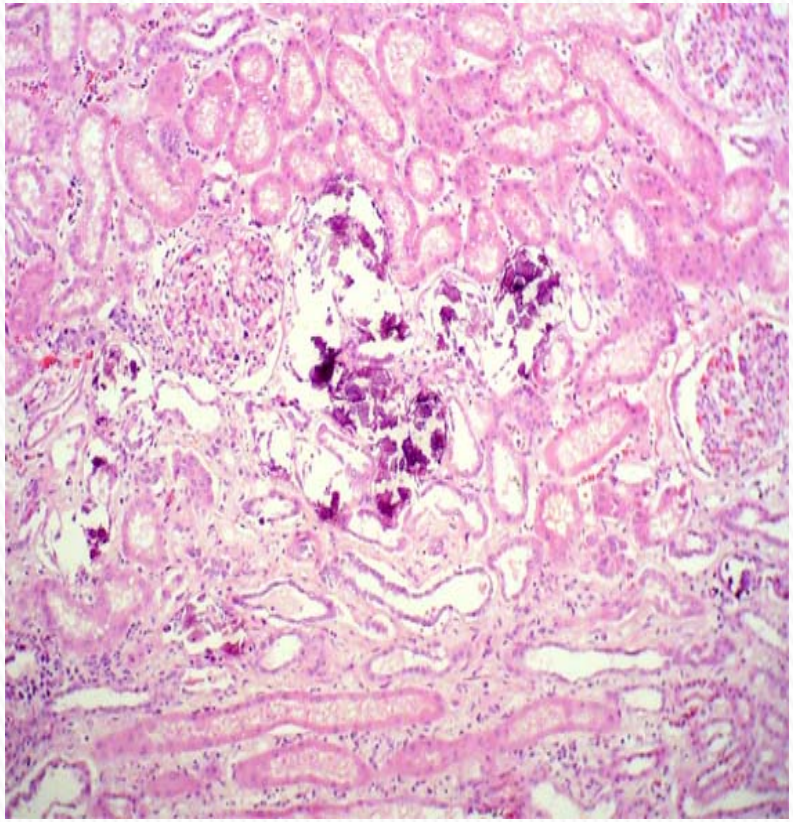
Dystrophic calcification



- **Necrosis of any type (e.g. atherosclerosis, aging or damaged heart valves, aortic stenosis, tuberculosis)**
- **Incidental finding indicating insignificant past cell injury**
- **May be a cause of organ dysfunction.**

Metastatic Calcification

- Hyperparathyroidism (primary and parathyroid hormone related protein)
- Bone destruction (metastasis, MM, leukemia, Pagets, immobilization)
- Vit-D intoxication,
- Sarcoidosis.
- Renal failure with 2ry hyperparathyroidism.
- **VESSELS, LUNG, KIDNEY**



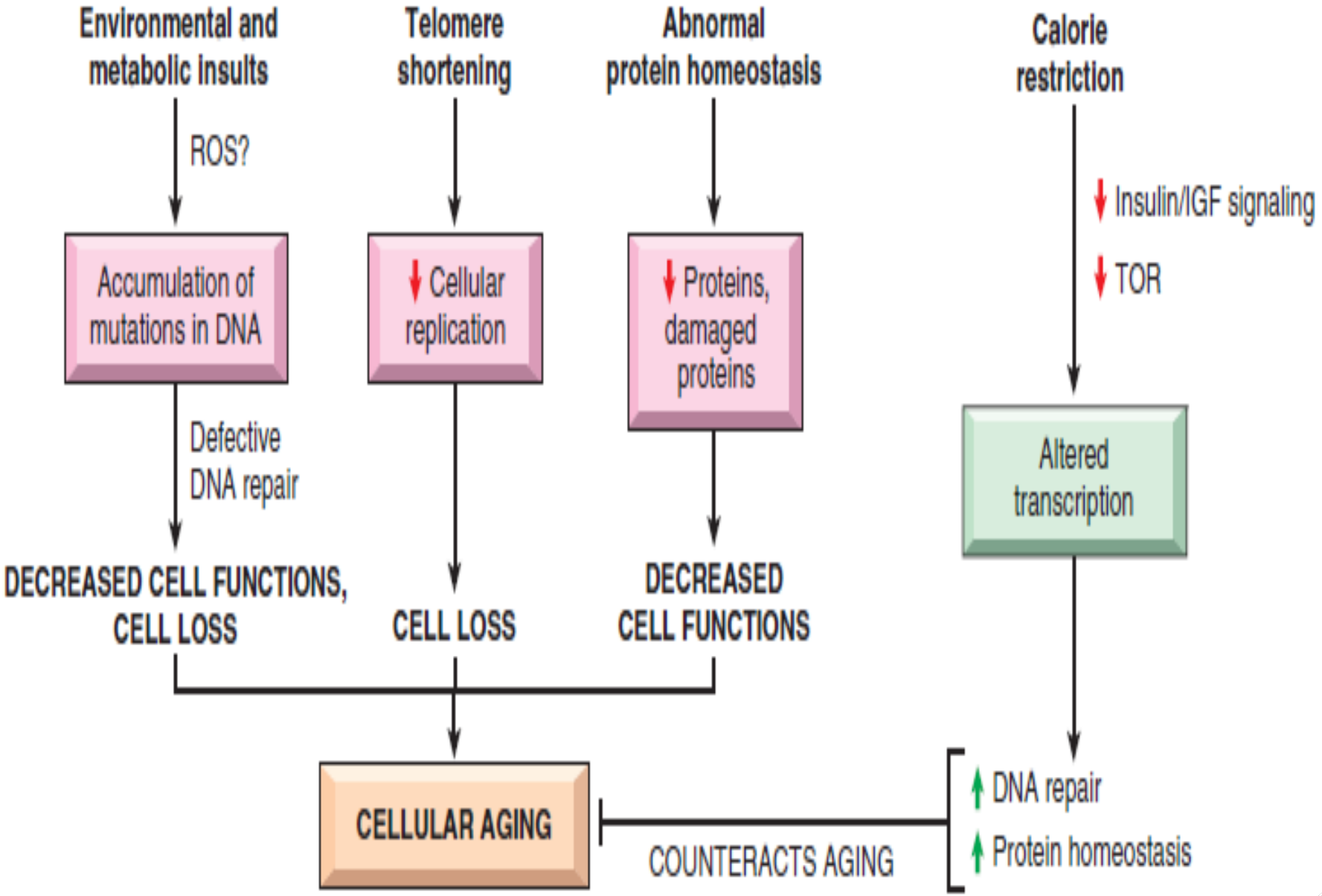
CELLULAR AGING

- Age is one of the strongest independent risk factors for many chronic diseases, such as cancer, Alzheimer disease, and ischemic heart disease

- Progressive decline in the life span and functional capacity of cells.

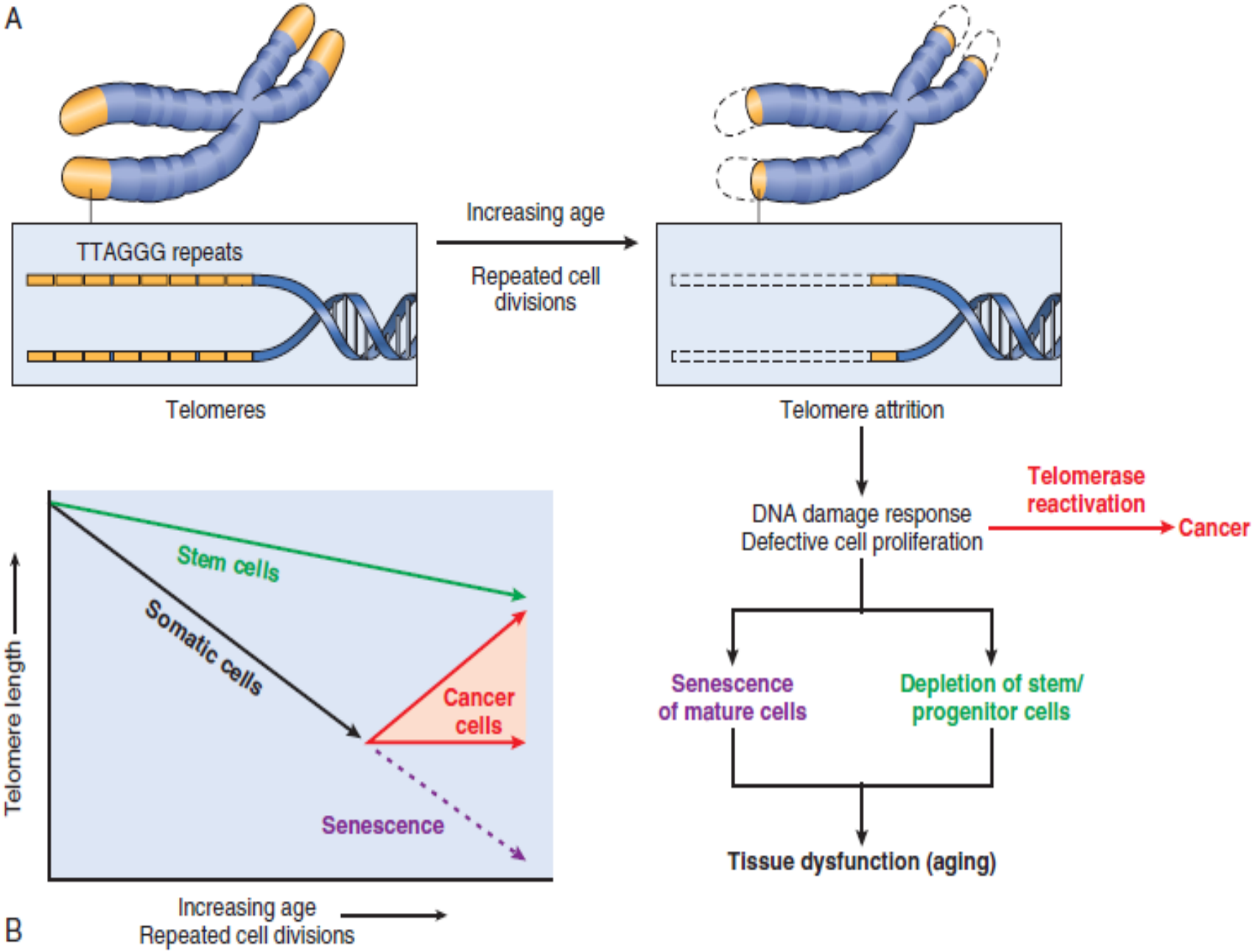
- **Several mechanisms :**
- **Accumulation of mutations in DNA.**
- **Decreased cellular replication (replicative senescence)**
- **Defective protein homeostasis**

- **Replicative senescence**: progressive shortening of telomeres which ultimately results in cell cycle arrest.


Environmental and metabolic insults
ROS?
Accumulation of mutations in DNA
Defective DNA repair
DECREASED CELL FUNCTIONS, CELL LOSS
Telomere shortening
Cellular replication
CELL LOSS
Abnormal protein homeostasis
Proteins, damaged proteins
DECREASED CELL FUNCTIONS
Calorie restriction
Insulin/IGF signaling
TOR
Altered transcription
CELLULAR AGING
COUNTERACTS AGING
DNA repair
Protein homeostasis

Telomeres

- Short repeated sequences of DNA at both ends of chromosomes
- Ensure complete replication of chromosome ends and protecting them.
- Progressively shortened upon replication (aging).
- Signals cell cycle arrest
- Telomere length is maintained by telomerase.
- Telomerase expressed in germ cells, low levels in stem cells, but absent in most somatic cells.
- Telomerase is reactivated in cancer cells.


A
TTAGGG repeats
Telomeres
Increasing age
Repeated cell divisions
Telomere attrition
DNA damage response
Defective cell proliferation
Telomerase reactivation
Cancer
Senescence of mature cells
Depletion of stem/ progenitor cells
Tissue dysfunction (aging)
Telomere length
Stem cells
Somatic cells
Cancer cells
Senescence
Increasing age
Repeated cell divisions
B

Defective protein homeostasis

- Increased turnover
- Decreased synthesis
- Defective activity of chaperones and proteasomes
- Overall decrease in intracellular proteins
- Accumulation of misfolded proteins can trigger apoptosis.

Anti aging- slowing of aging (elixir of youth)

Calorie restriction

Improve immunity

reduce IGF

Physical activity

Stress accelerates aging

Precise mechanisms underlying these effects remain to be defined

Persistent inflammation, chronic metabolic diseases, accelerates aging