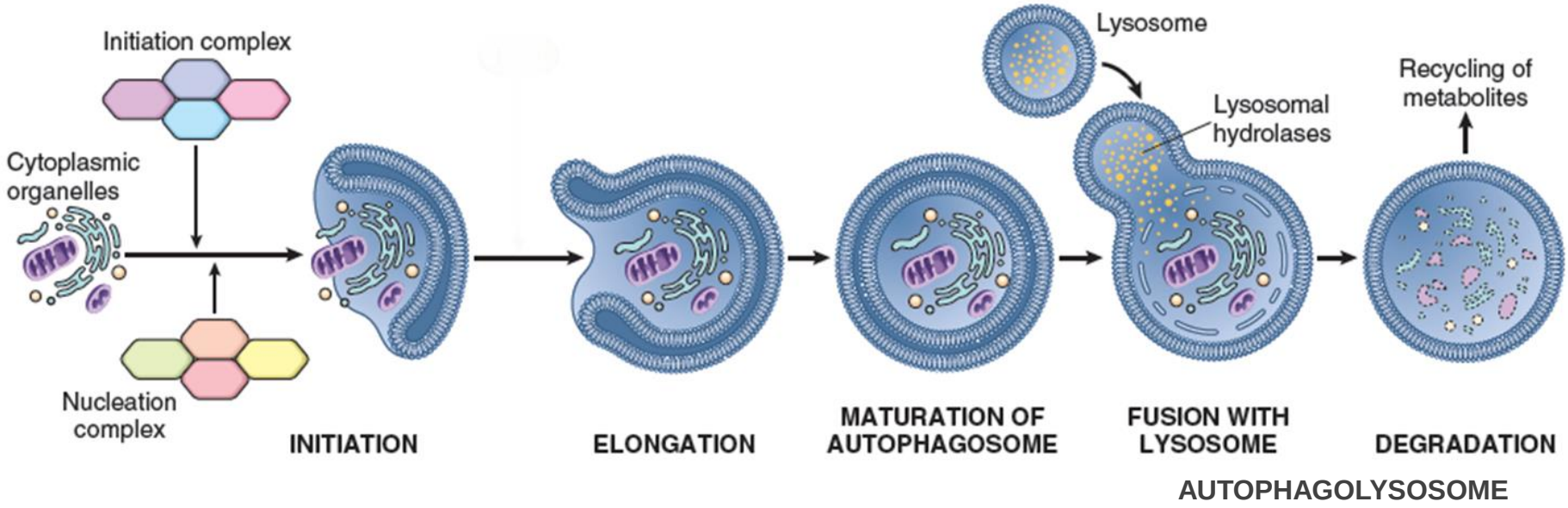
Autophagy

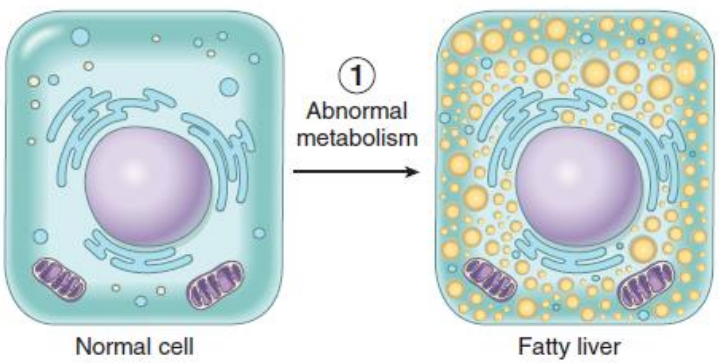
Greek: **auto,** *self;* **phagy,** *eating*

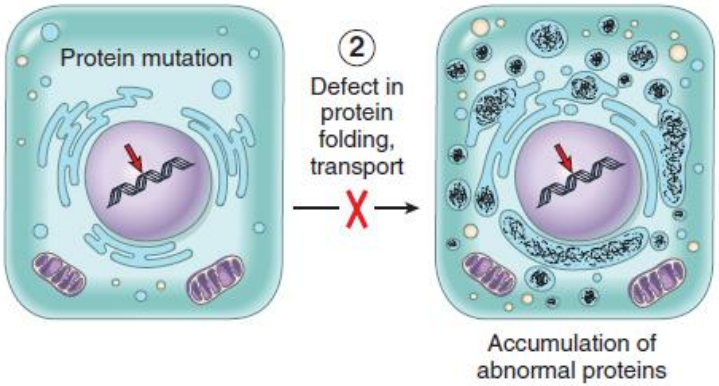


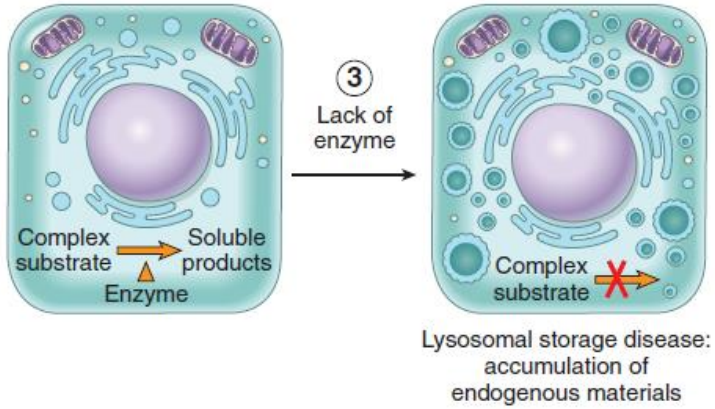
- Survival mechanism/nutrient deprivation
- Organelle turnover
- Adaptation failure → autophagy signals a unique type of cell death
- Clearance of misfolded proteins (neurons, hepatocytes)
- IBD link?
- Has a role in cancer

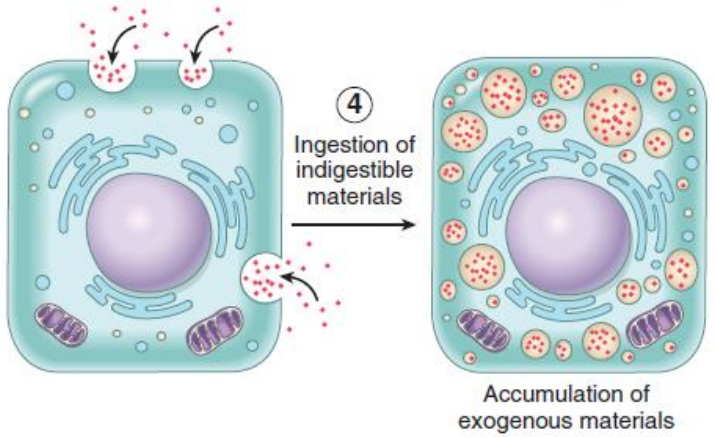
Intracellular accumulations

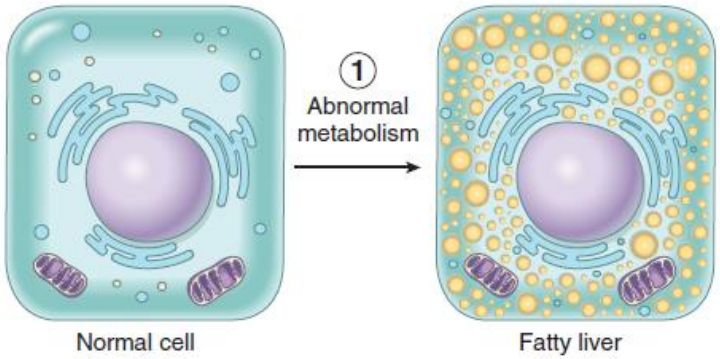
Types

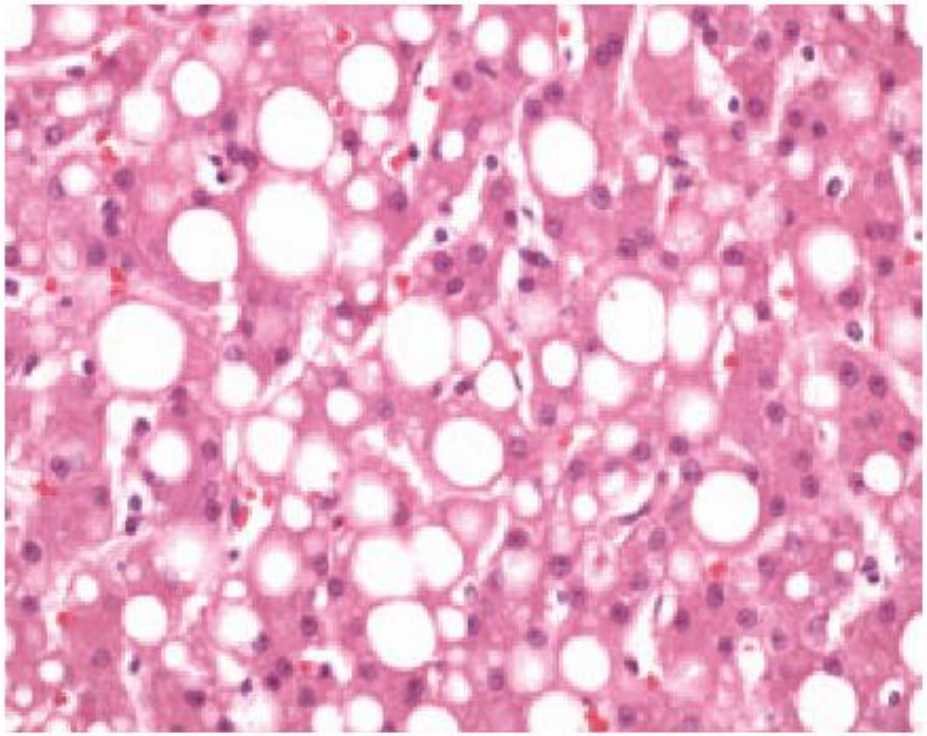

1
Abnormal metabolism
Normal cell
Fatty liver


Protein mutation
2
Defect in protein folding, transport
Accumulation of abnormal proteins


3
Lack of enzyme
Complex substrate
Soluble products
Enzyme
Complex substrate
Lysosomal storage disease: accumulation of endogenous materials


4
Ingestion of indigestible materials
Accumulation of exogenous materials





Lipids

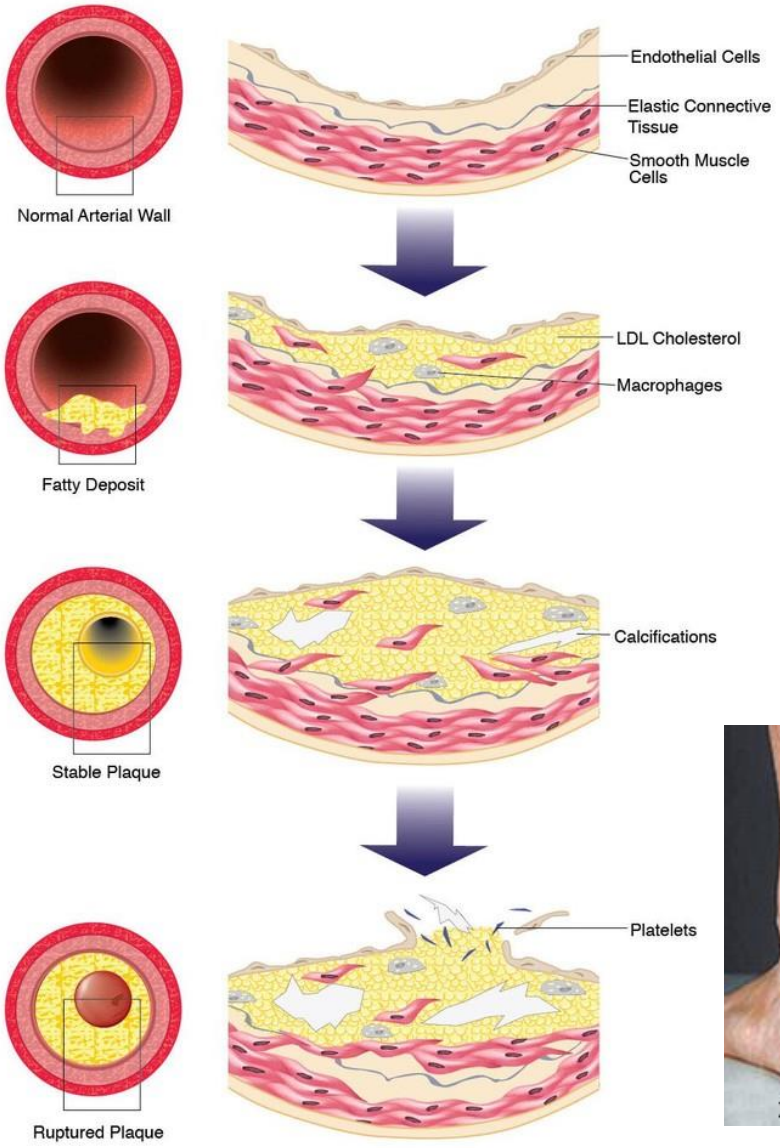
TAG (fatty change)

Most common in liver

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



Lipids

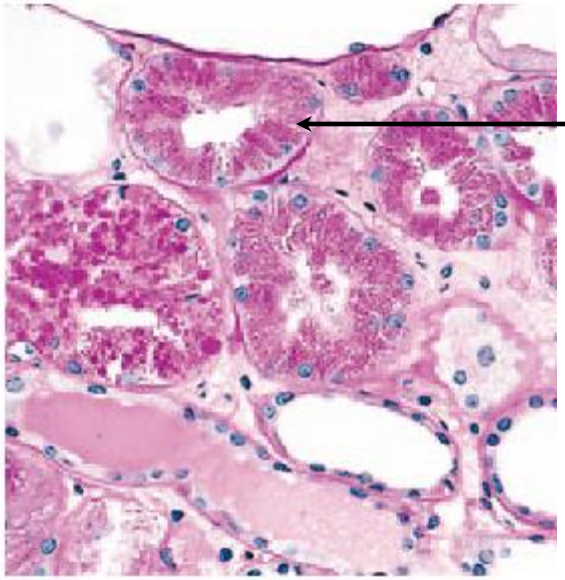
Cholesterol

Atherosclerotic plaques:

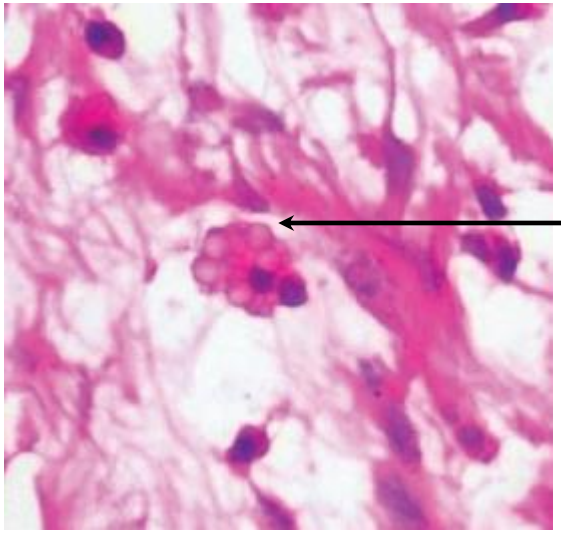
muscle cells and macrophages + C,CE (foam cells)

Xanthomas:

Cholesterol within macrophages characteristic of acquired and hereditary hyperlipidemias



Example of excess external protein. Accumulated reabsorbed albumin in the proximal renal tubules in proteinuria



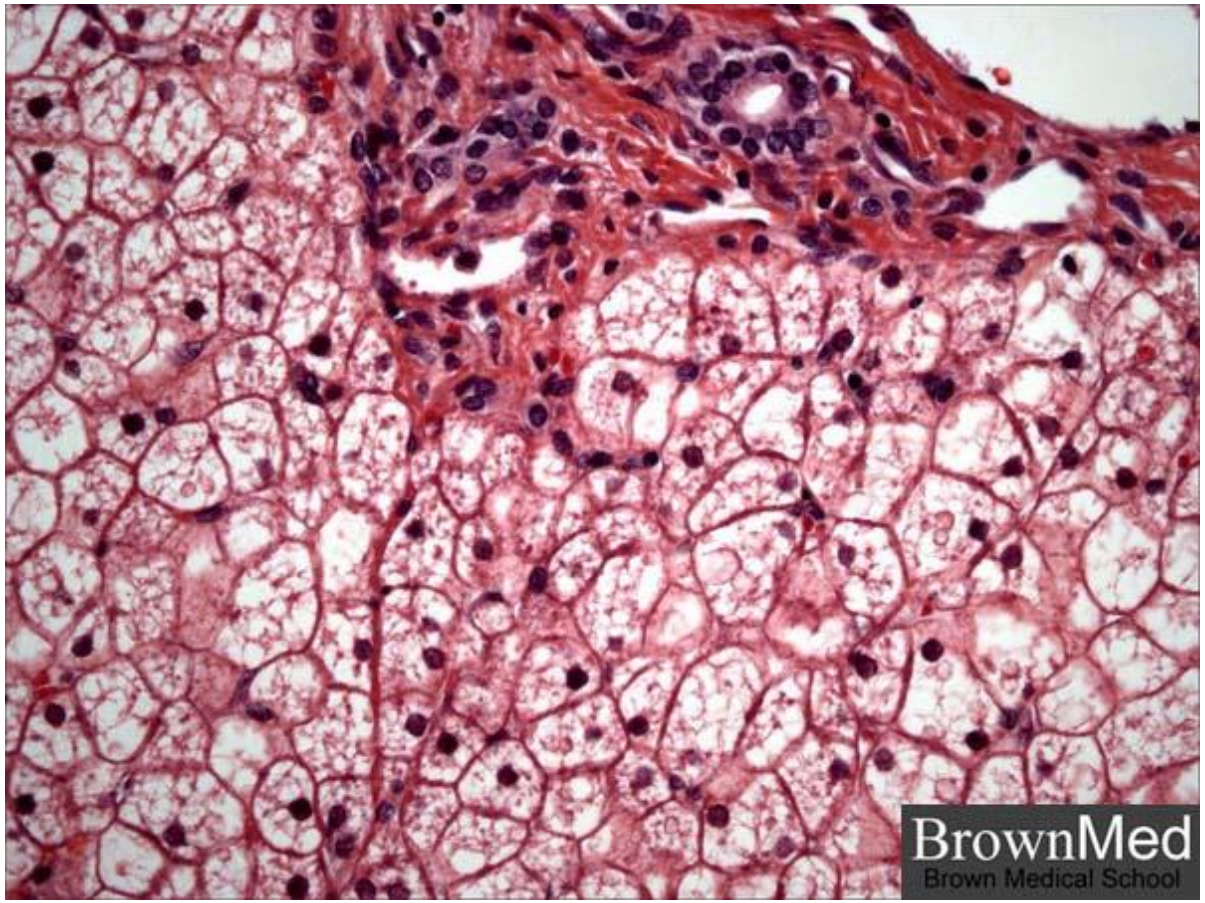
Russell bodies

Example of excess internal protein synthesis. Accumulated Ig's

Protein

Much less common than lipid accumulations

Either excess external or internal synthesis



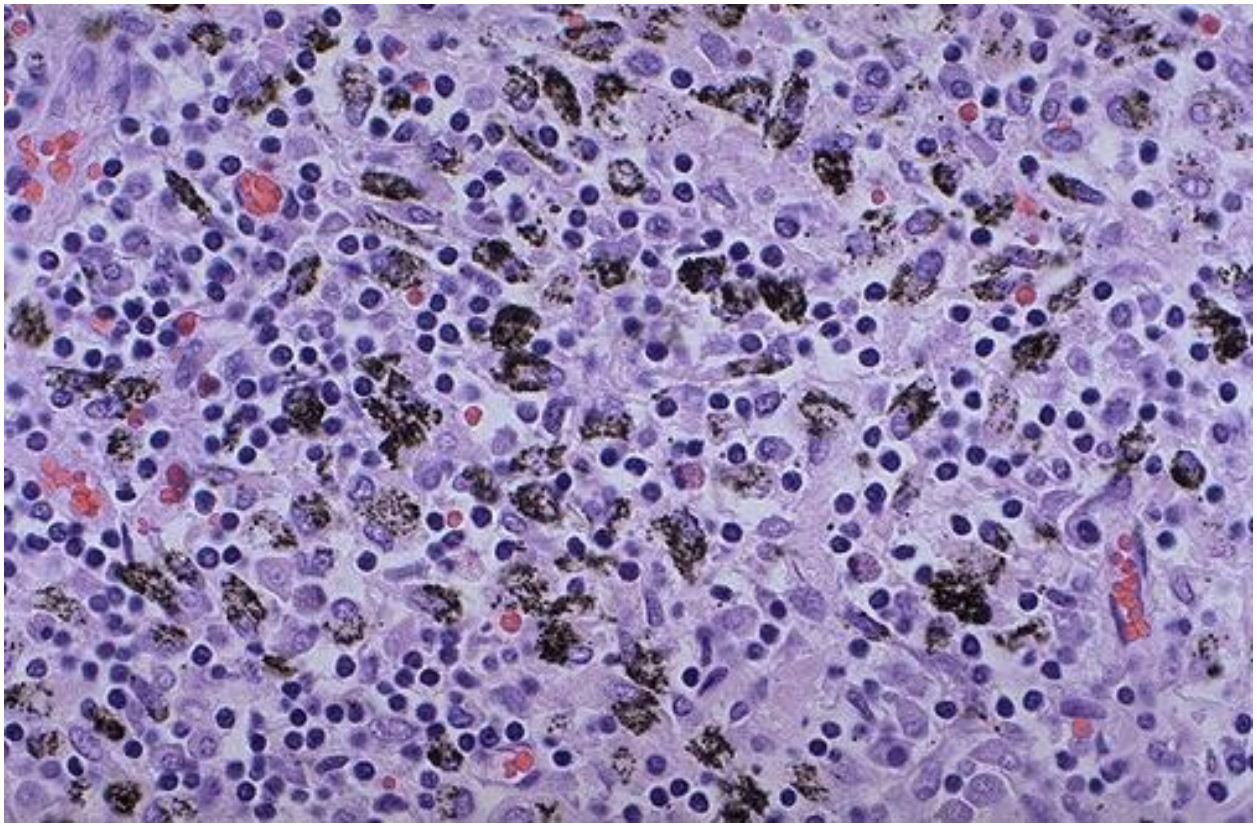
Example of G6Pase deficiency showing typical mosaic pattern in the swollen hepatocytes

Glycogen

Abnormality in glucose or glycogen metabolism

DM

Glycogen storage diseases



Pigments

Exogenous

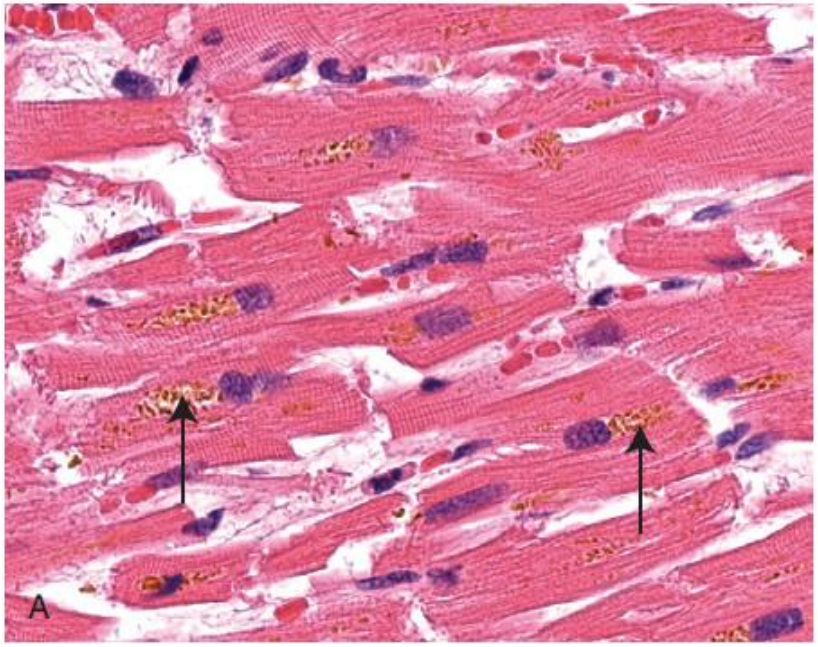
Most common exogenous, carbon (coal dust, air pollution)

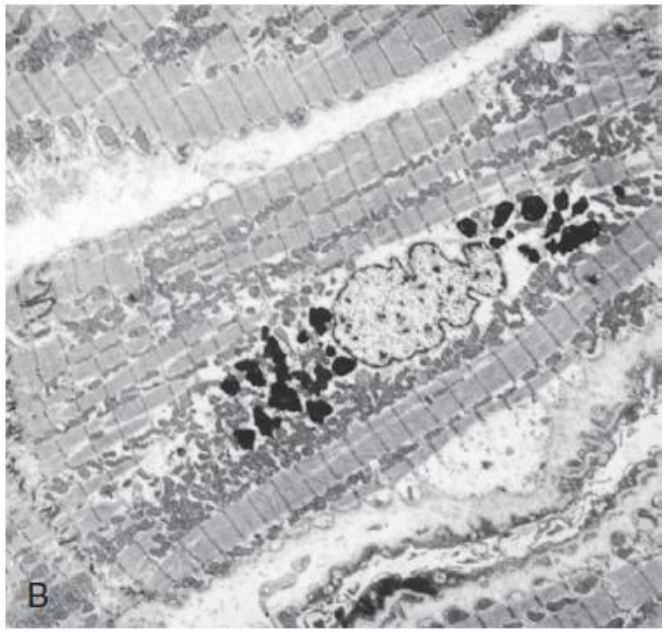
Alveolar macrophages → lymphatic channels → tracheobronchial LN

Anthracosis

Tatoos

(dermal macrophages)





Pigments

Endogenous

Lipofuscin

“wear-and-tear pigment”

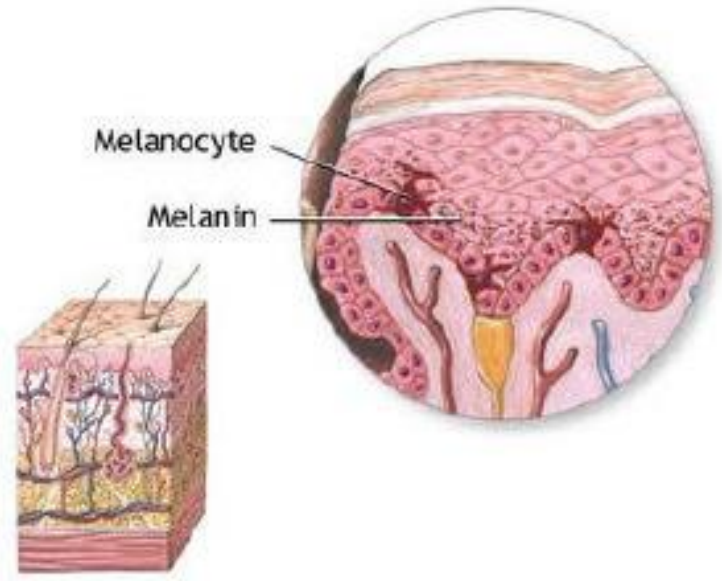
Age/atrophy

Heart, liver, and brain

Lipid and protein

Marker of past free radical injury

brown atrophy



Pigments

Endogenous

Melanin

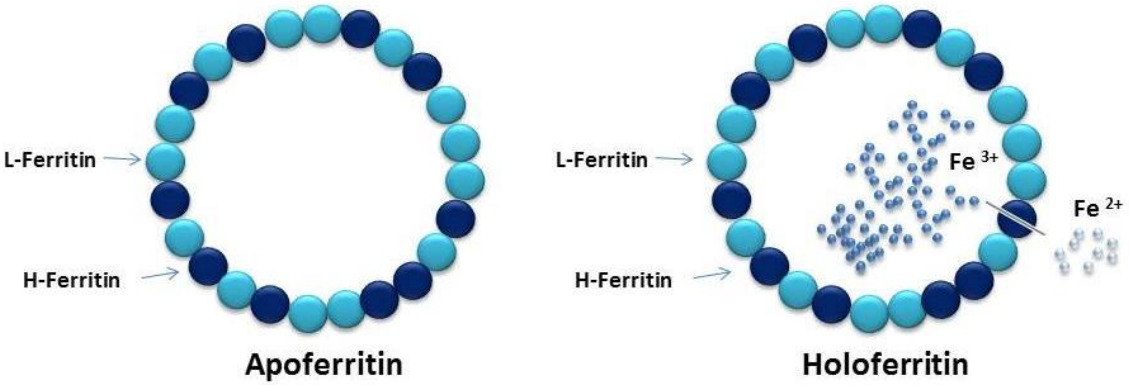
Source: melanocytes

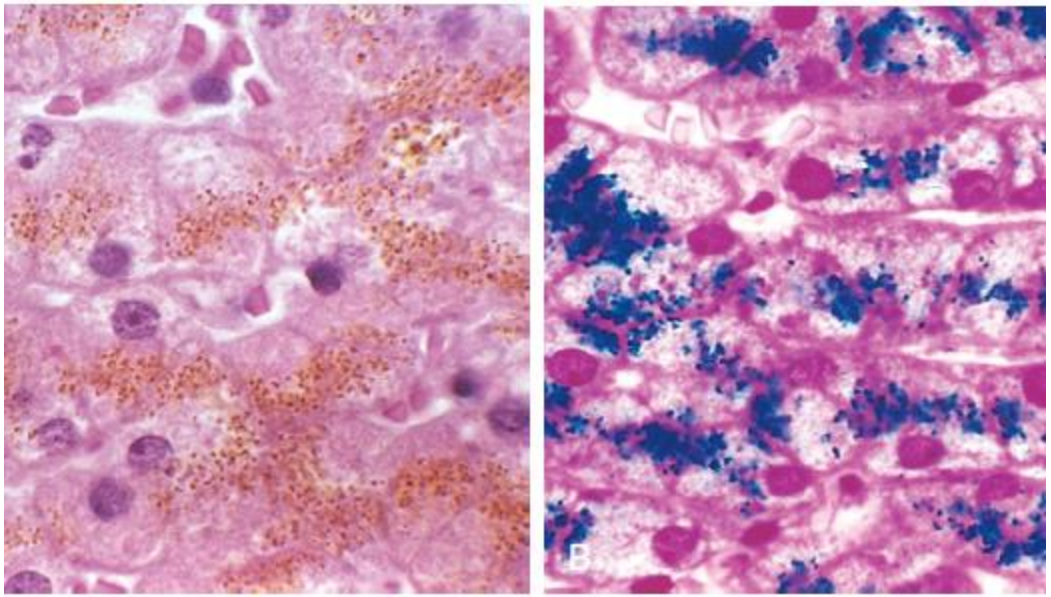
UV protection

Accumulates in dermal macrophages and adjacent keratinocytes

Skin tan

Freckles





Hemosiderin

Hb-derived granular pigment

Accumulation of 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

Definition

"Abnormal deposition of mostly calcium salts, with iron, magnesium, and other minerals"

Dystrophic Calcification

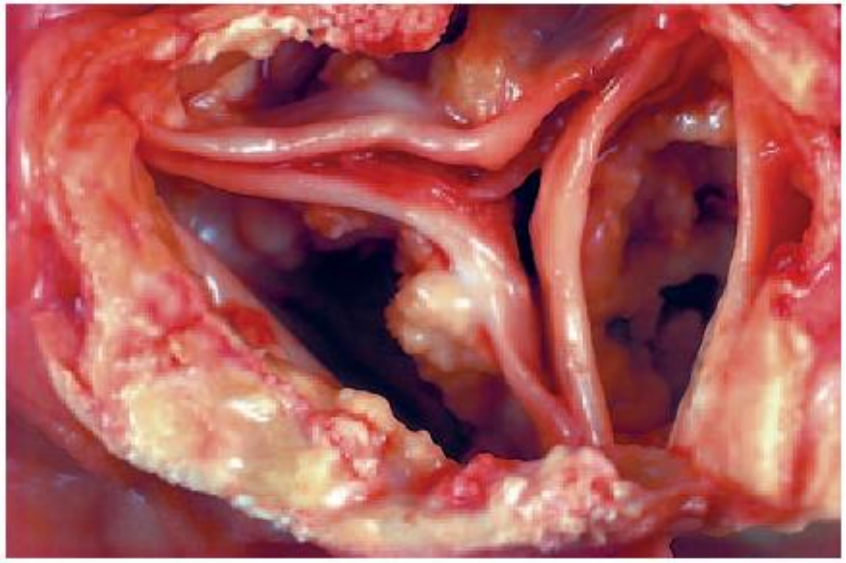
- Deposition in dead/dying tissues
- Normal Ca^{2+} metabolism
- Exacerbated by Hypercalcemia

Metastatic Calcification

- Deposition in normal tissues
- Almost always abnormal Ca^{2+} metabolism (hypercalcemia)

Dystrophic Calcification

- Necrosis of any type (e.g. atheromas, damaged cardiac valves)
- Initiation → propagation
- Intracellular/extracellular
- Calcium phosphate crystals



Metastatic Calcification

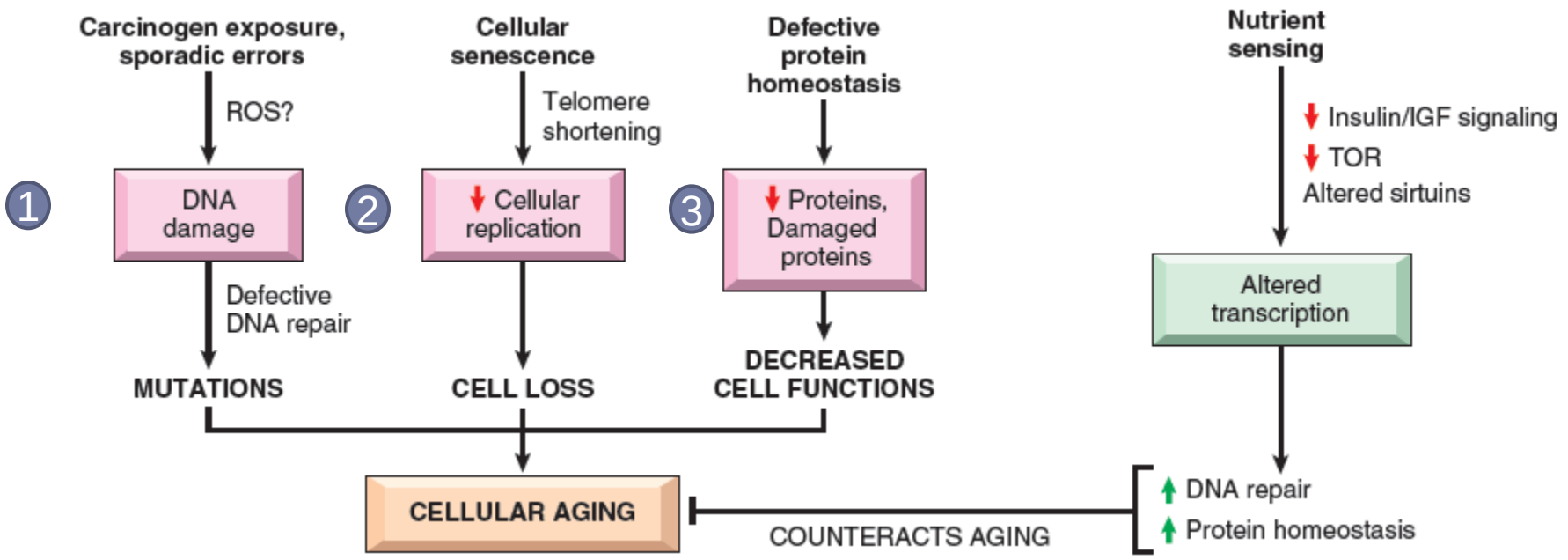
- Hyperparathyroidism (1ry/2ry)
- Bone destruction (metastasis, MM, leukemia, Pagets)
- Vit-D intoxication, Sarcoidosis

Cellular Aging

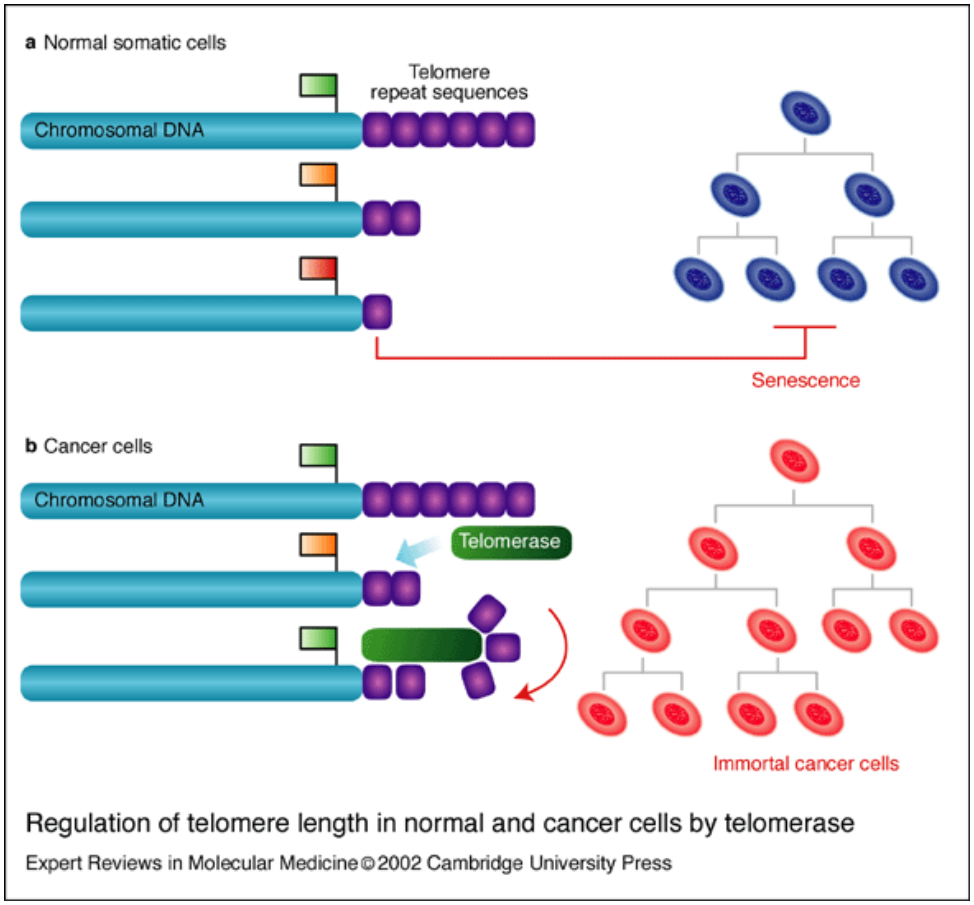
"If I don't go to the doctor, he can't find anything wrong with me. That's how I stay healthy!"

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

Mechanisms


Carcinogen exposure, sporadic errors
ROS?
1
DNA damage
Defective DNA repair
MUTATIONS
Cellular senescence
Telomere shortening
2
Cellular replication
CELL LOSS
Defective protein homeostasis
3
Proteins, Damaged proteins
DECREASED CELL FUNCTIONS
Nutrient sensing
Insulin/IGF signaling
TOR
Altered sirtuins
Altered transcription
CELLULAR AGING
COUNTERACTS AGING
DNA repair
Protein homeostasis

Cell Senescence & Telomeres



Regulation of telomere length in normal and cancer cells by telomerase

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press