Sublethal Cell Injury: Lysosomes

APPROVED

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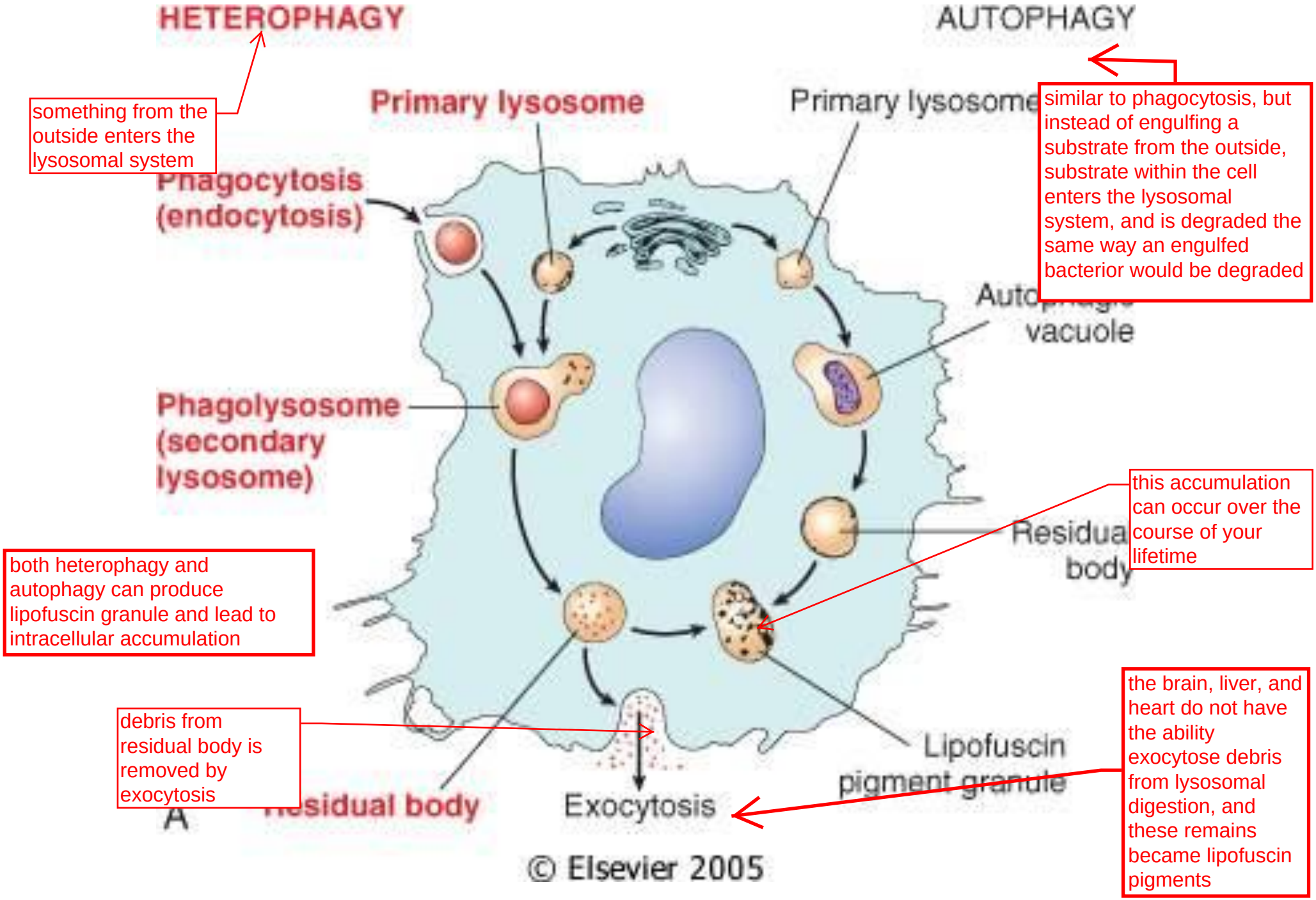
HETEROPHAGY
AUTOPHAGY
something from the outside enters the lysosomal system
Primary lysosome
Primary lysosome
similar to phagocytosis, but instead of engulfing a substrate from the outside, substrate within the cell enters the lysosomal system, and is degraded the same way an engulfed bacterior would be degraded
Phagocytosis (endocytosis)
vacuole
Phagolysosome (secondary lysosome)
Residua body
this accumulation can occur over the course of your lifetime
both heterophagy and autophagy can produce lipofuscin granule and lead to intracellular accumulation
debris from residual body is removed by exocytosis
Lipofuscin pigment granule
the brain, liver, and heart do not have the ability exocytose debris from lysosomal digestion, and these remains became lipofuscin pigments
Residual body
Exocytosis
A
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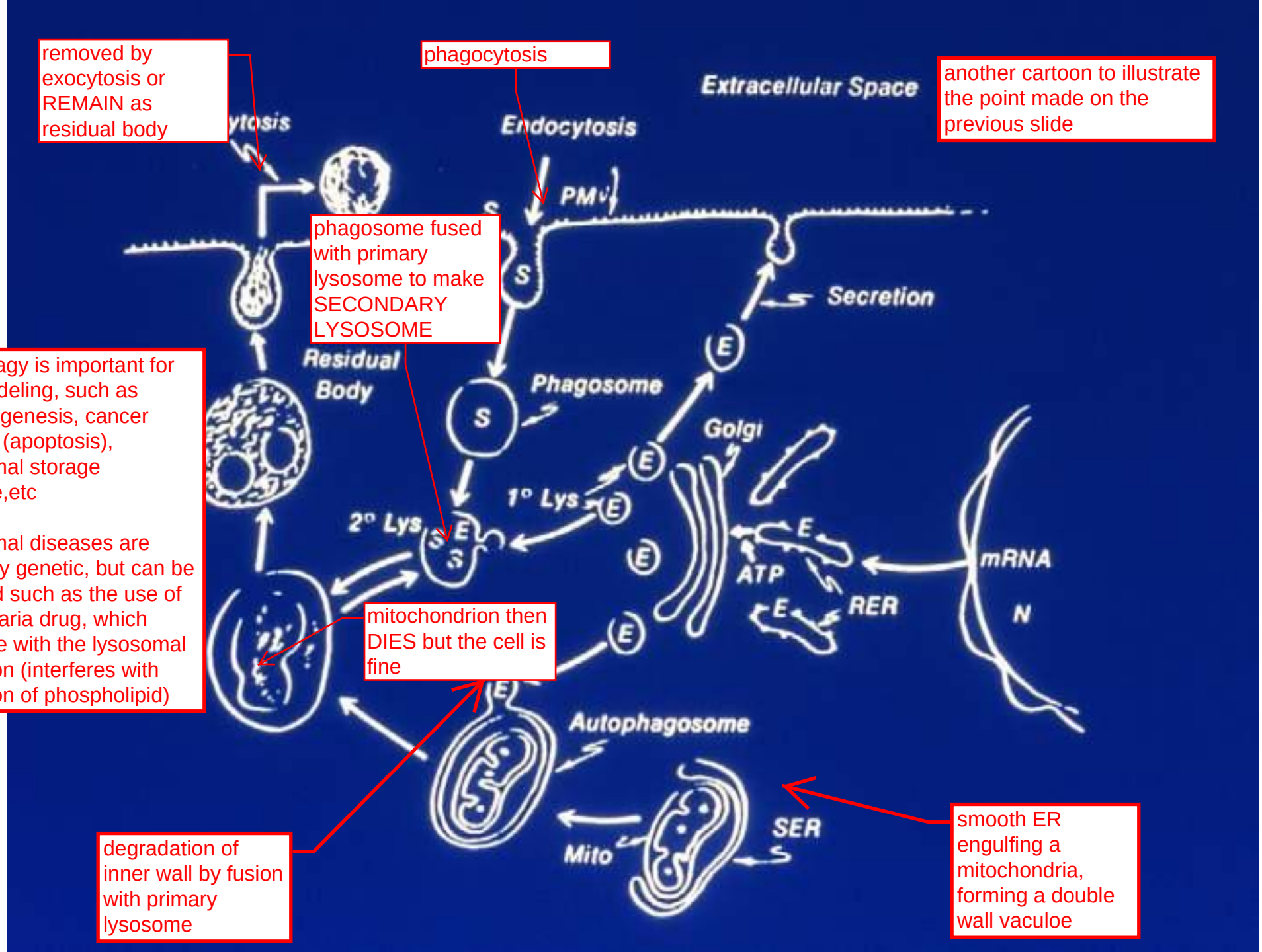
removed by exocytosis or REMAIN as residual body
phagocytosis
Extracellular Space
another cartoon to illustrate the point made on the previous slide
Endocytosis
PM
phagosome fused with primary lysosome to make SECONDARY LYSOSOME
Secretion
Residual Body
Phagosome
Golgi
autophagy is important for cell modeling, such as embryogenesis, cancer biology (apoptosis), lysosomal storage disease,etc
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lysosomal diseases are normally genetic, but can be induced such as the use of antimalaria drug, which interfere with the lysosomal digestion (interferes with digestion of phospholipid)
1° Lys
2° Lys
ATP
RER
mRNA
N
mitochondrion then DIES but the cell is fine
Autophagosome
degradation of inner wall by fusion with primary lysosome
Mito
SER
smooth ER engulfing a mitochondria, forming a double wall vaculoe

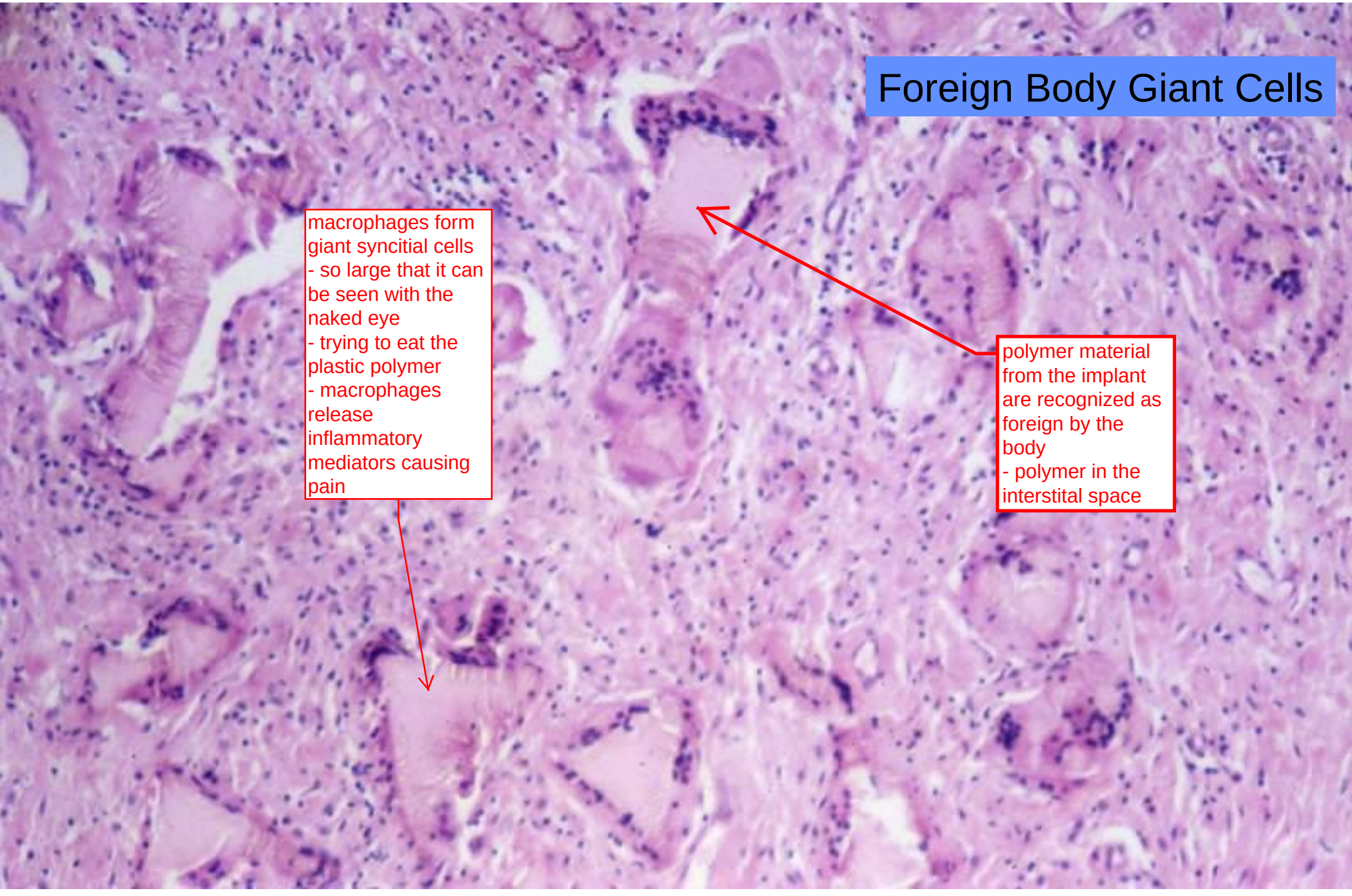
Lysosomes: Sublethal Changes

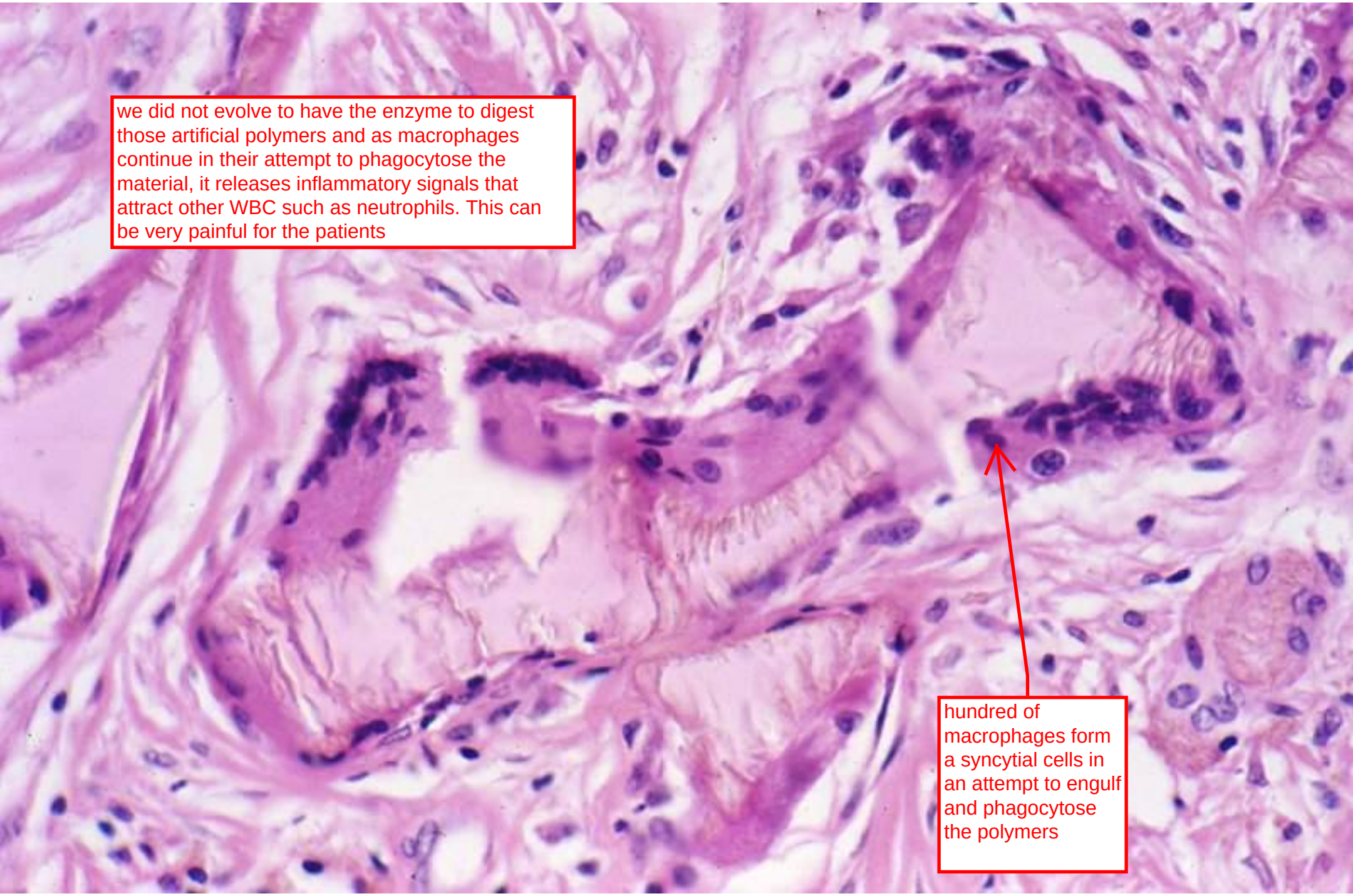
now we will examine each of the following

- Heterophagy - exogenous material or endogenous material
- Autophagy - endogenous material - role in storage diseases
- Aging pigment - lipofuscin

Heterophagy:
Exogenous Material

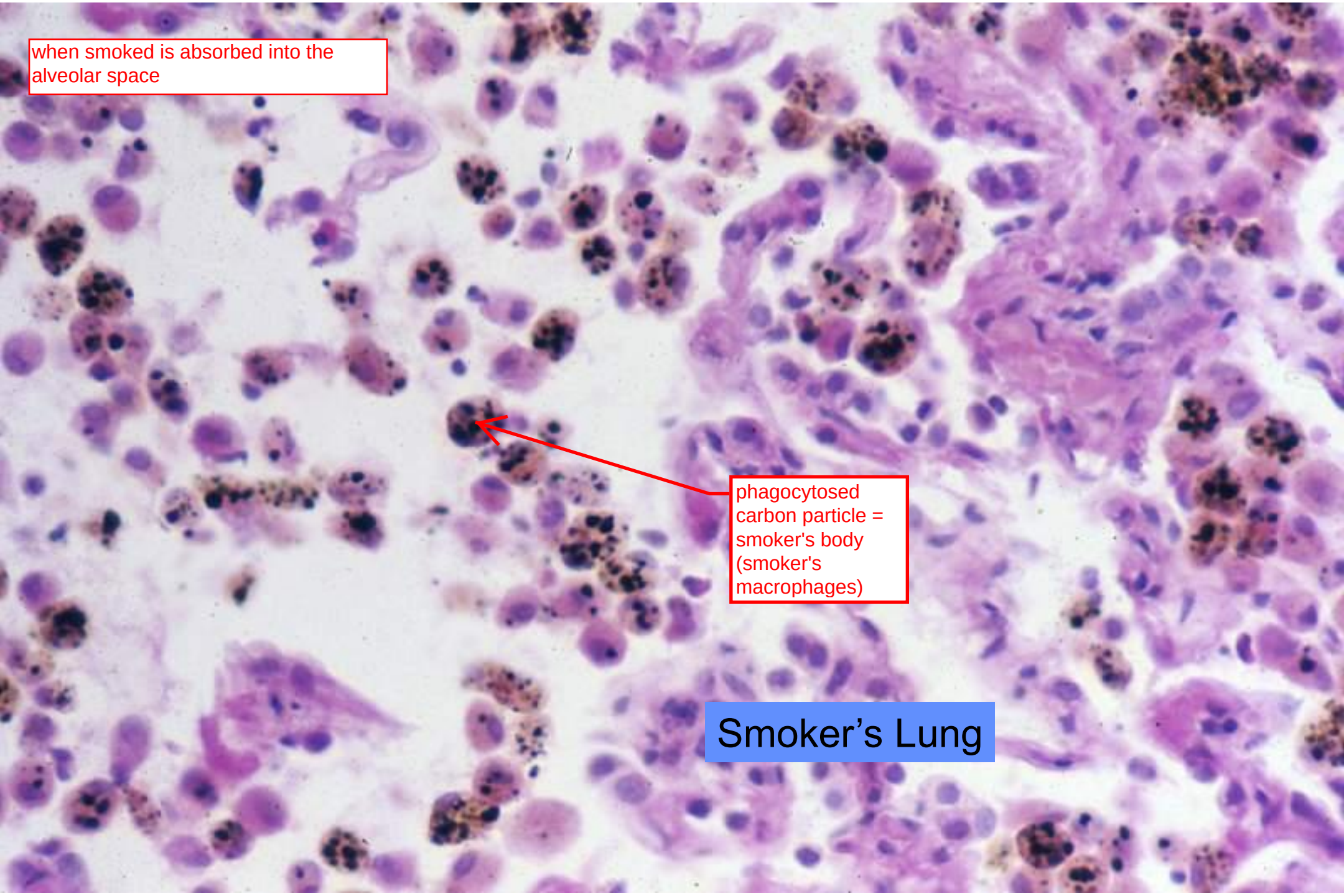
Ruptured Breast Implant

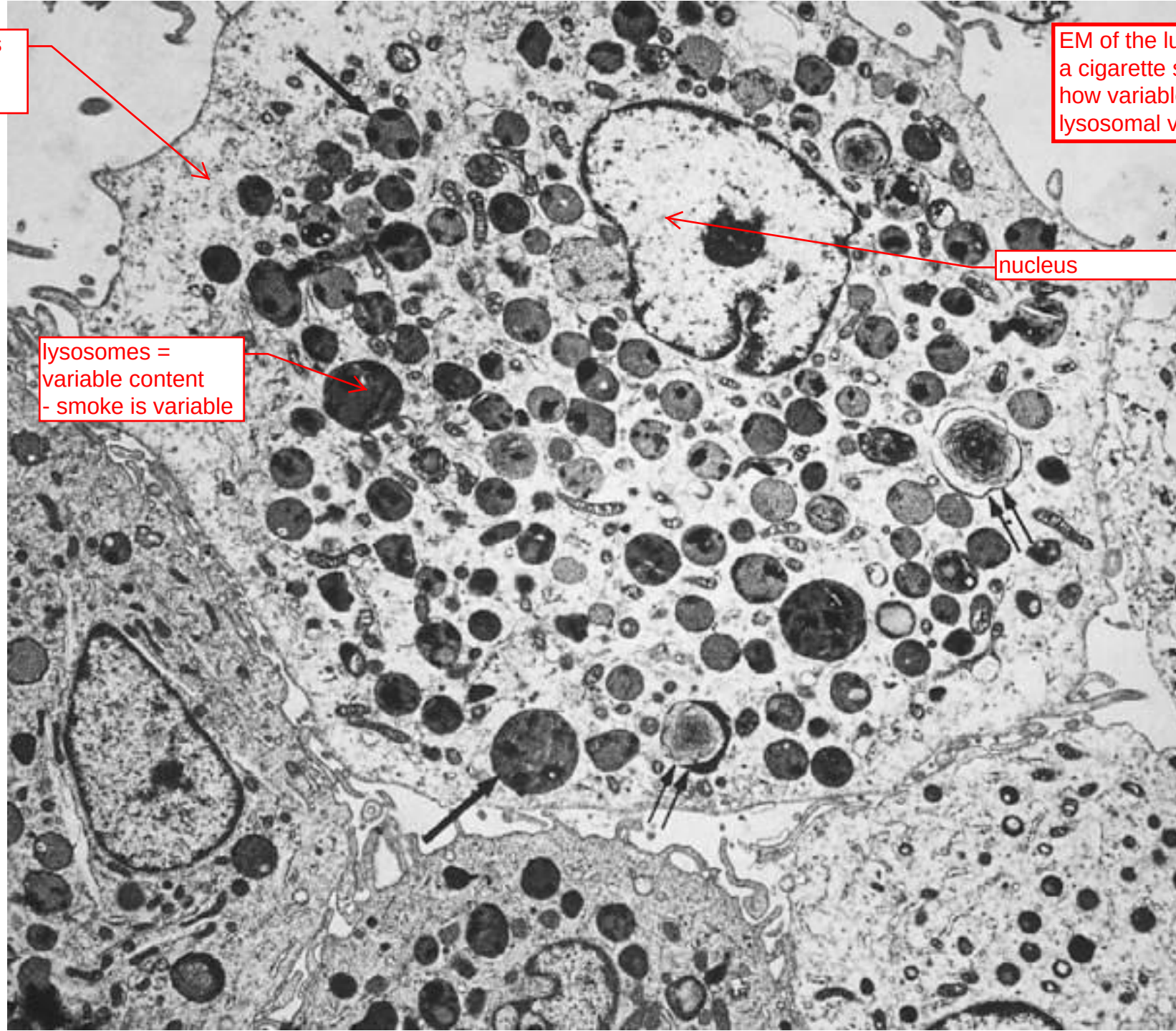

Foreign Body Giant Cells
macrophages form giant syncitial cells
- so large that it can be seen with the naked eye
- trying to eat the plastic polymer
- macrophages release inflammatory mediators causing pain
polymer material from the implant are recognized as foreign by the body
- polymer in the interstital space

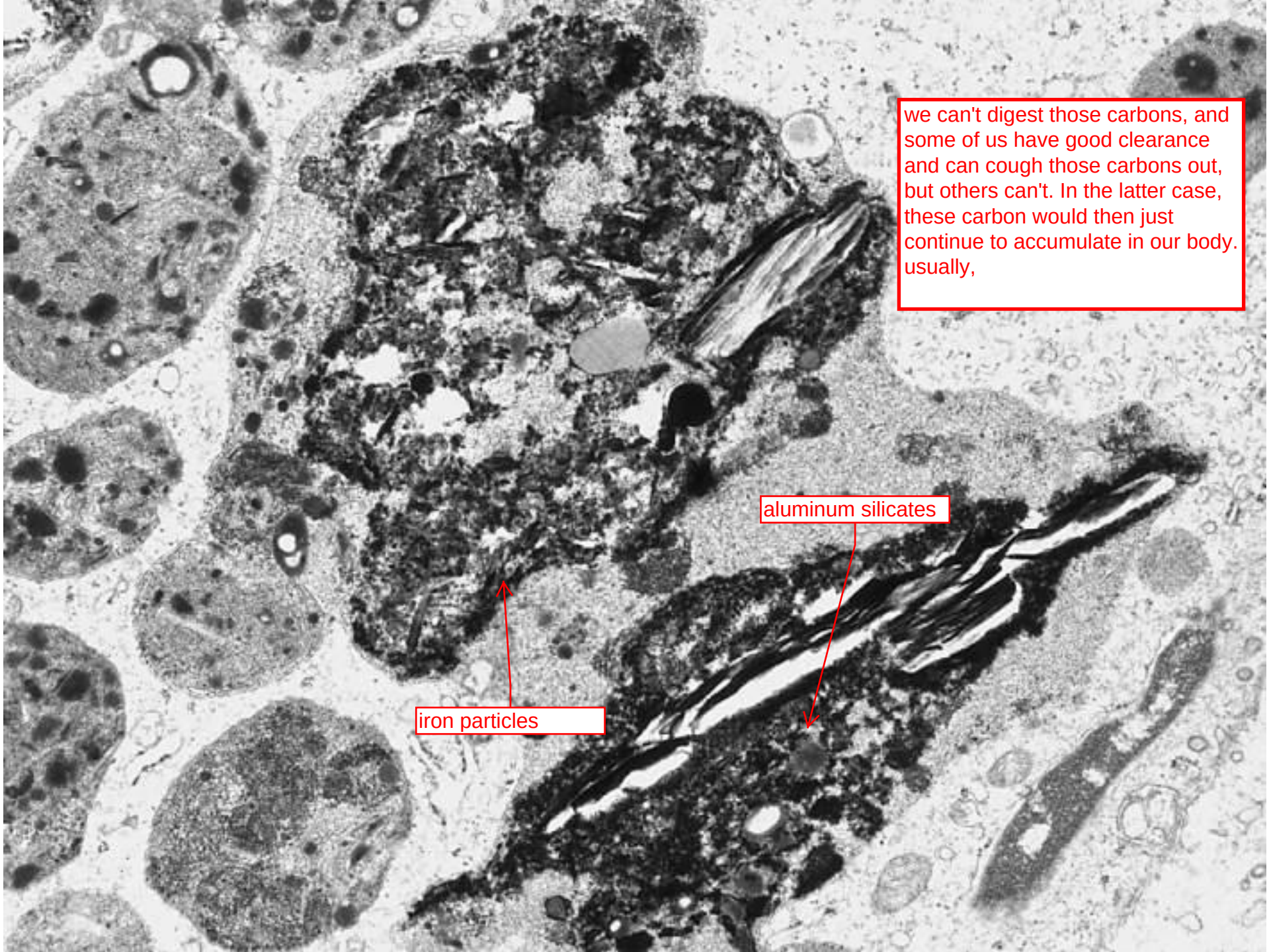

we did not evolve to have the enzyme to digest those artificial polymers and as macrophages continue in their attempt to phagocytose the material, it releases inflammatory signals that attract other WBC such as neutrophils. This can be very painful for the patients
hundred of macrophages form a syncytial cells in an attempt to engulf and phagocytose the polymers

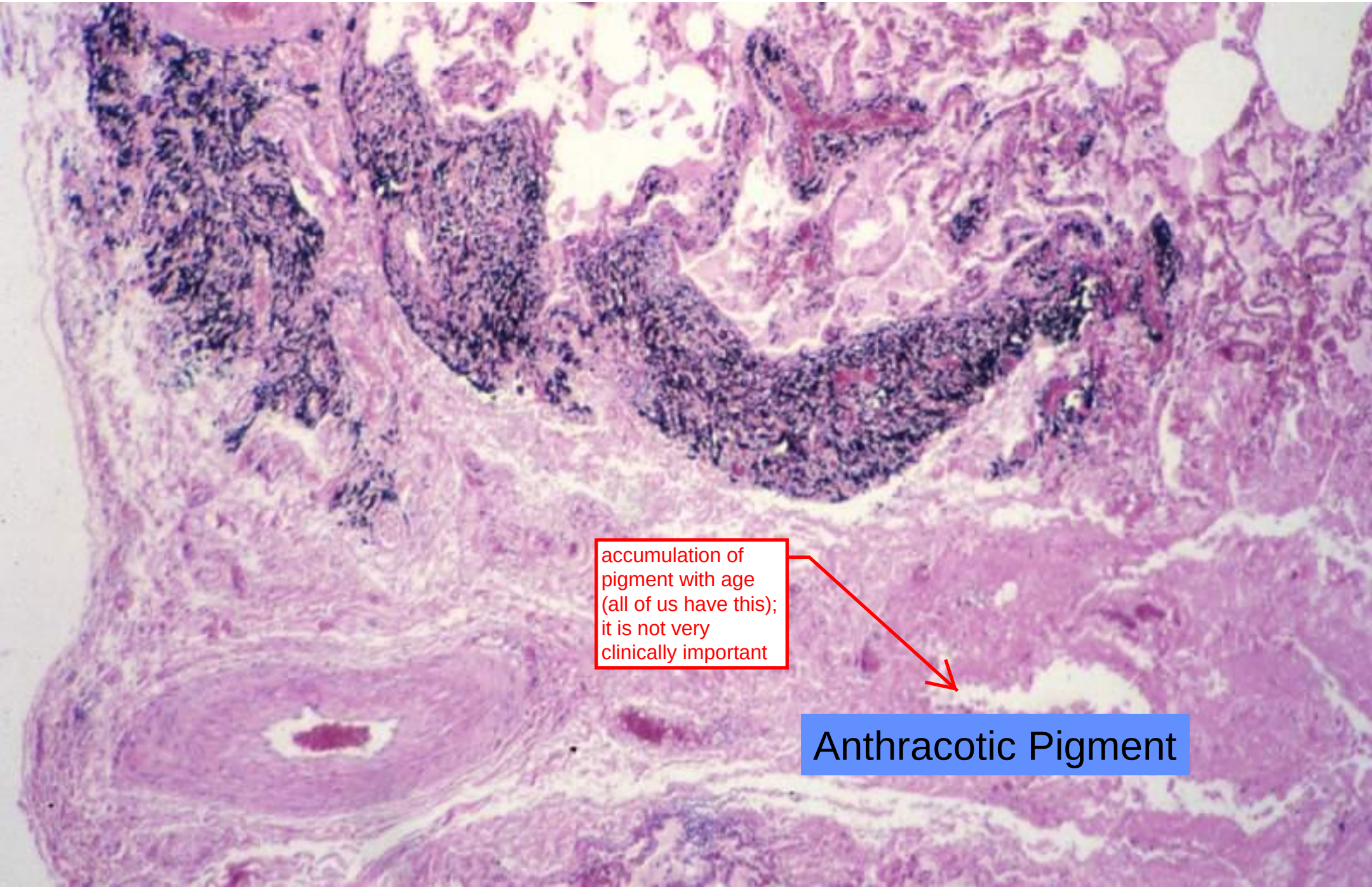
Heterophagy: Exogenous Material

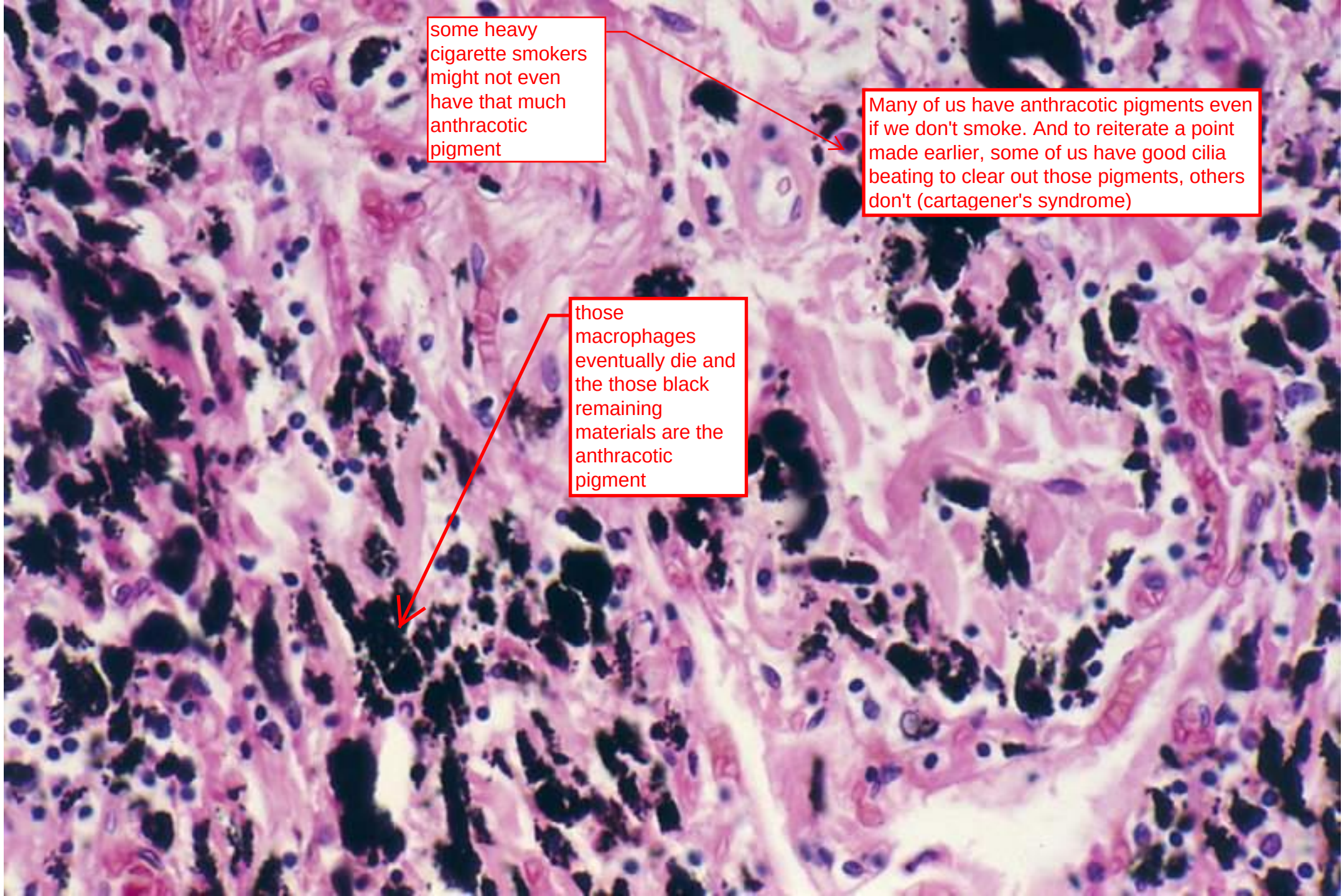
Cigarette Smoke


when smoked is absorbed into the alveolar space
phagocytosed carbon particle = smoker's body (smoker's macrophages)
Smoker’s Lung


whole big thing is alveolar macrophage
EM of the lung tissue from a cigarette smoker, note how variables the lysosomal vacoules are.
nucleus
lysosomes = variable content - smoke is variable

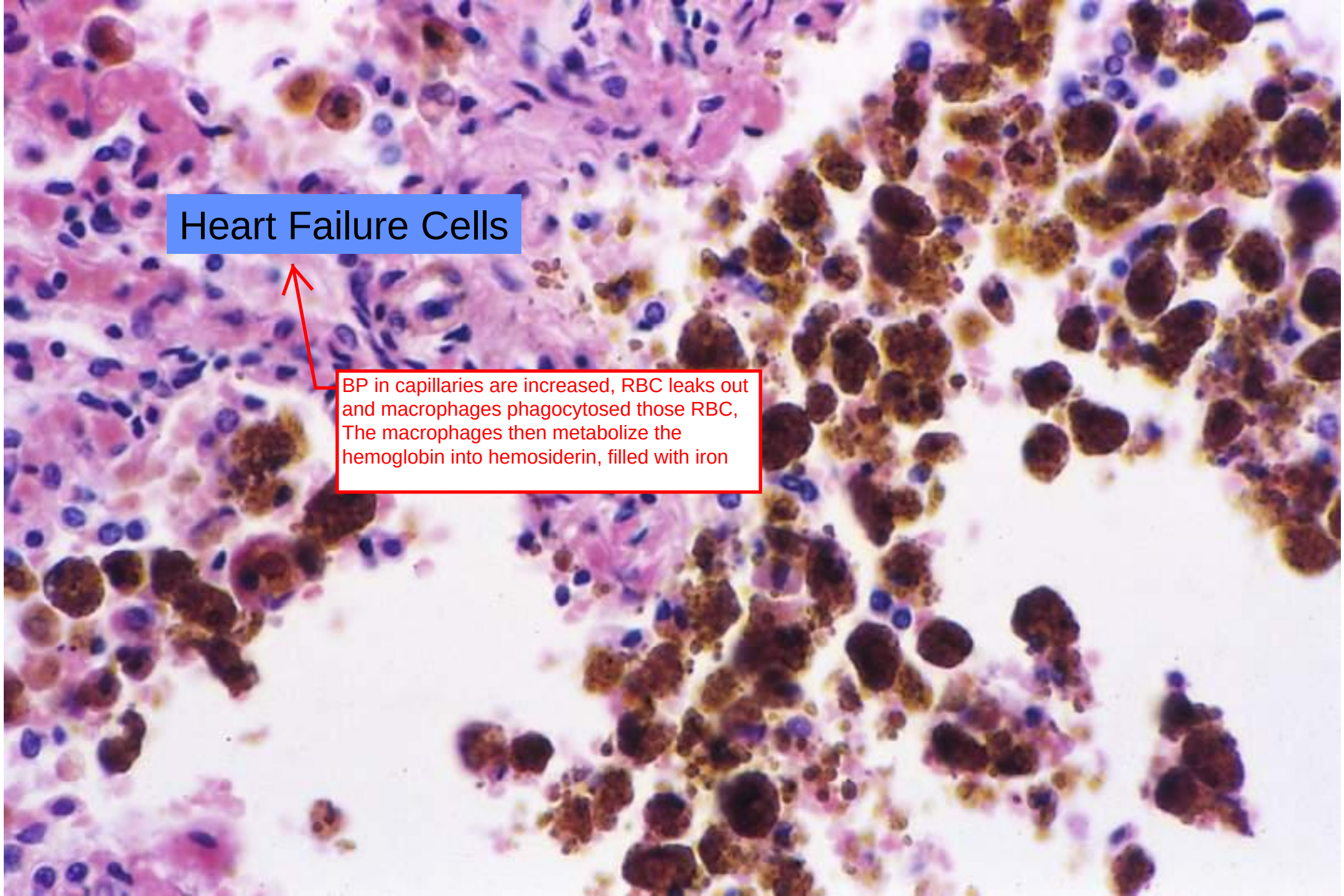

we can't digest those carbons, and some of us have good clearance and can cough those carbons out, but others can't. In the latter case, these carbon would then just continue to accumulate in our body. usually,
aluminum silicates
iron particles

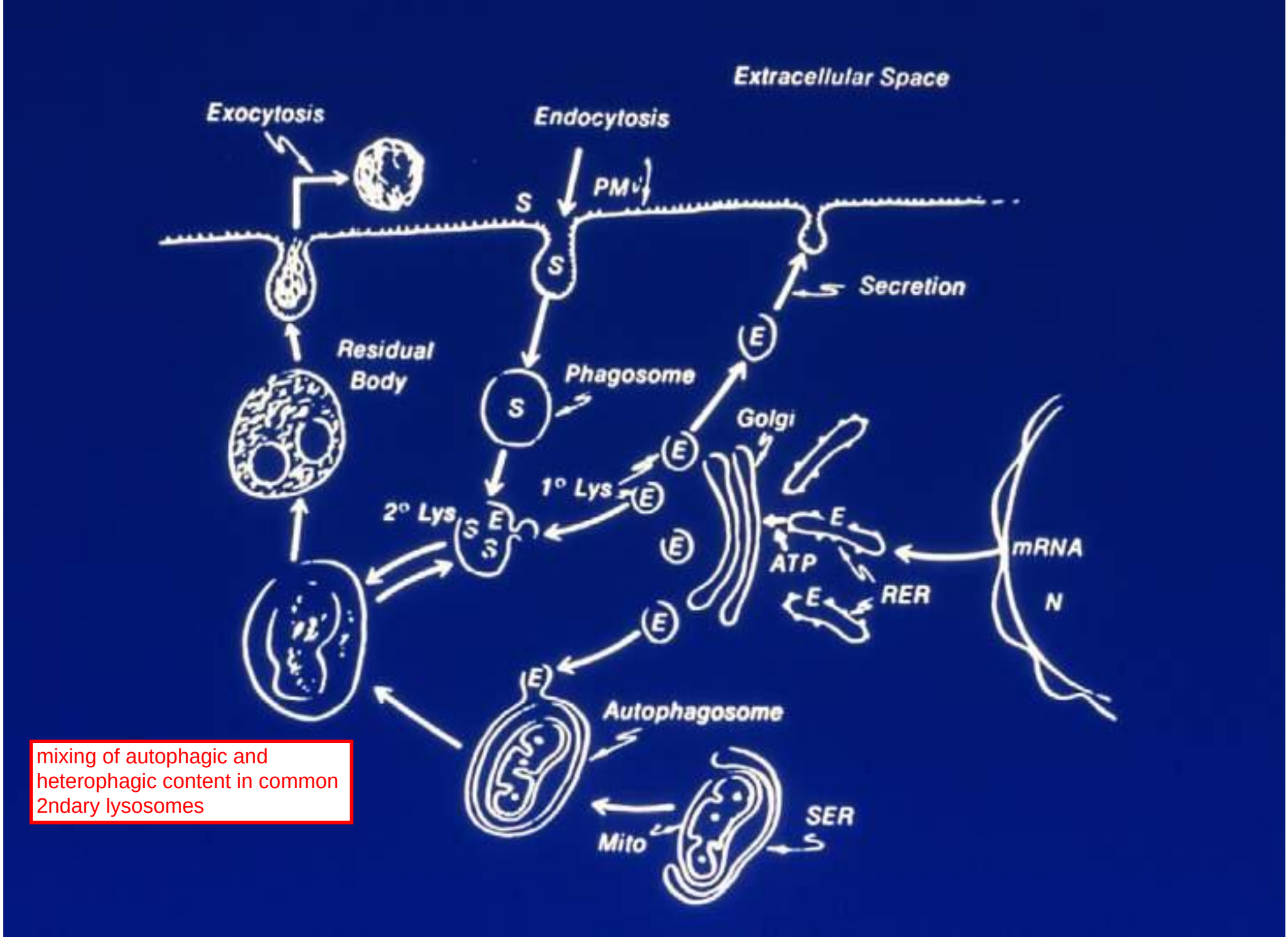

accumulation of pigment with age (all of us have this); it is not very clinically important
Anthracotic Pigment


some heavy cigarette smokers might not even have that much anthracotic pigment
Many of us have anthracotic pigments even if we don't smoke. And to reiterate a point made earlier, some of us have good cilia beating to clear out those pigments, others don't (cartagener's syndrome)
those macrophages eventually die and the those black remaining materials are the anthracotic pigment

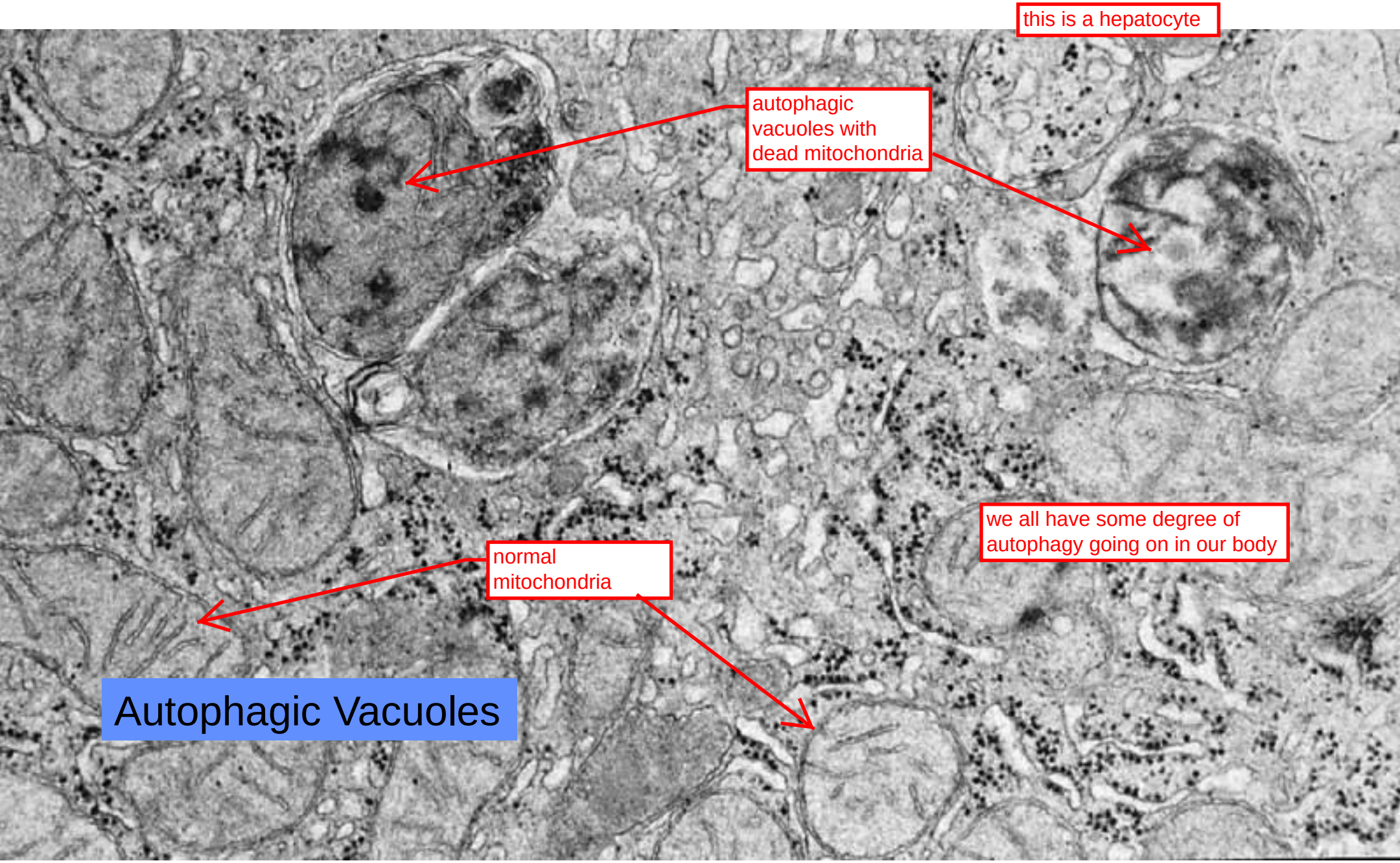
Heterophagy:
Endogenous Material

Heart Failure Cells
Hemosiderin


Heart Failure Cells
BP in capillaries are increased, RBC leaks out and macrophages phagocytosed those RBC, The macrophages then metabolize the hemoglobin into hemosiderin, filled with iron

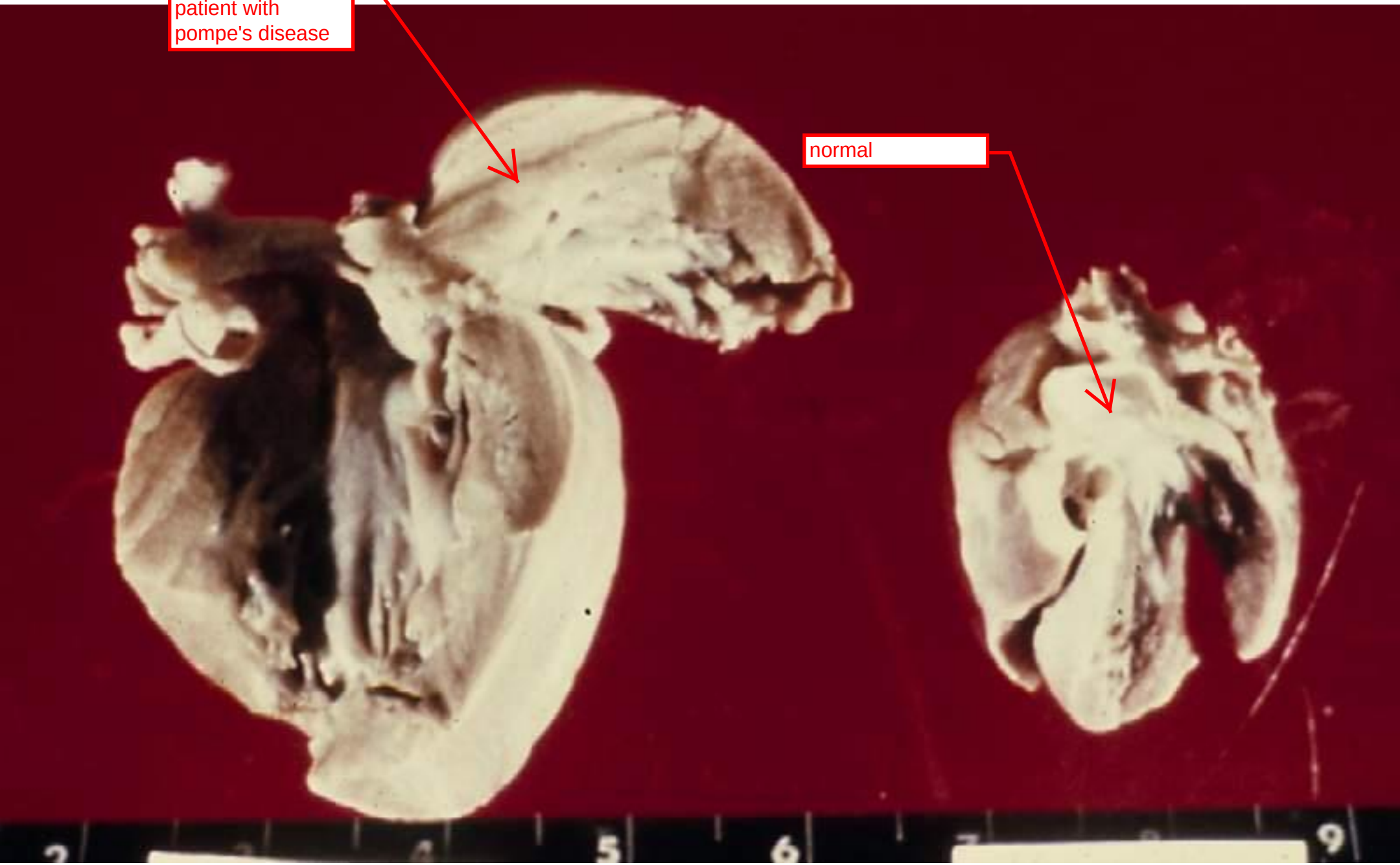


mixing of autophagic and heterophagic content in common 2ndary lysosomes

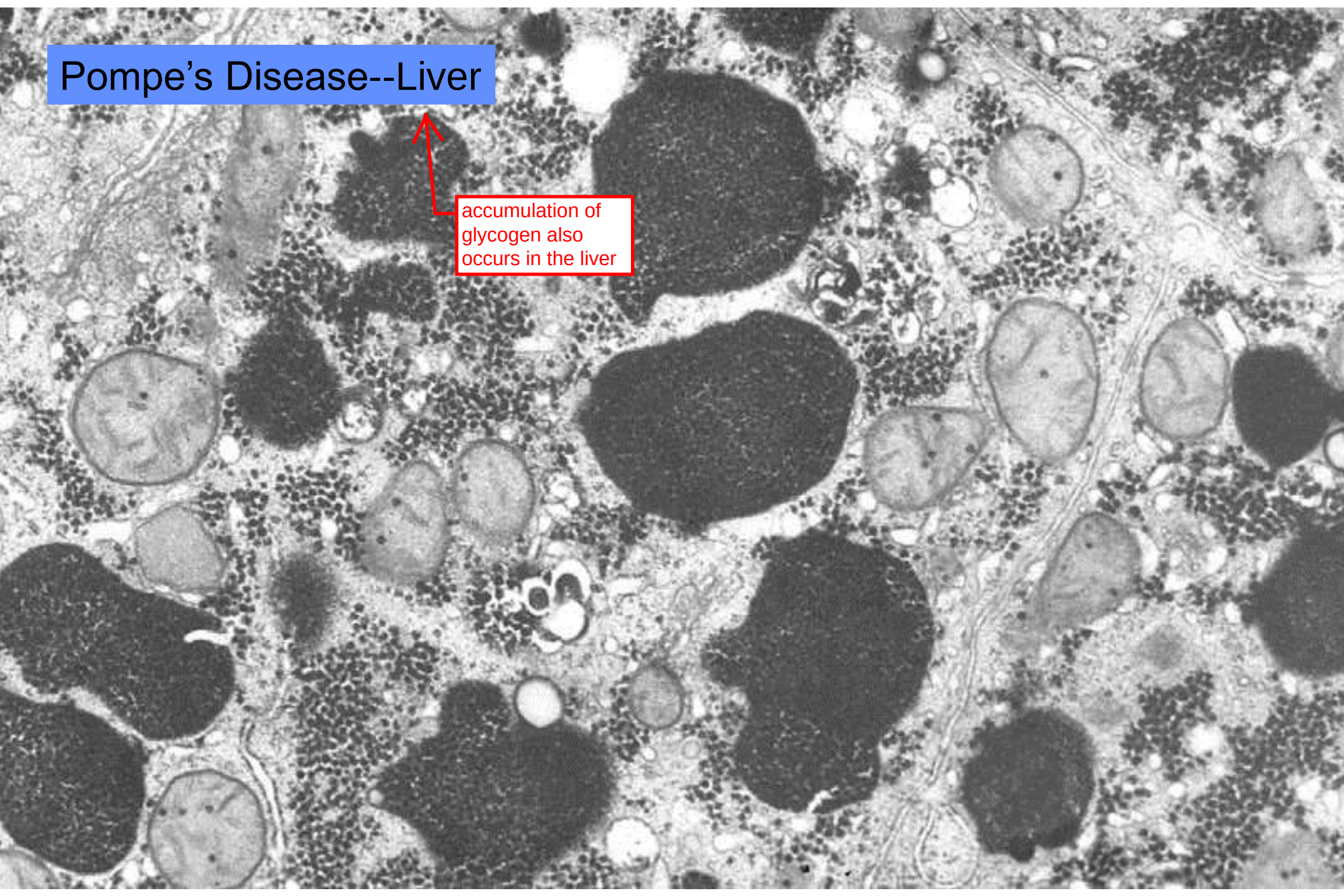

this is a hepatocyte
autophagic vacuoles with dead mitochondria
we all have some degree of autophagy going on in our body
normal mitochondria
Autophagic Vacuoles

Lysosomal Storage Diseases

- Pompe's Disease genetic defect
- Lack of lysosomal glucosidase results in glycogen accumulation

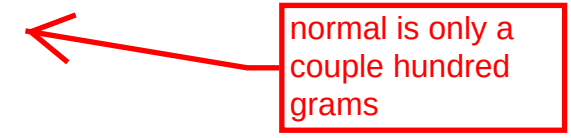

neonatal heart of patient with pompe's disease
normal

Pompe's Disease--Heart


Pompe's Disease--Liver
accumulation of glycogen also occurs in the liver

Lysosomal Storage Diseases

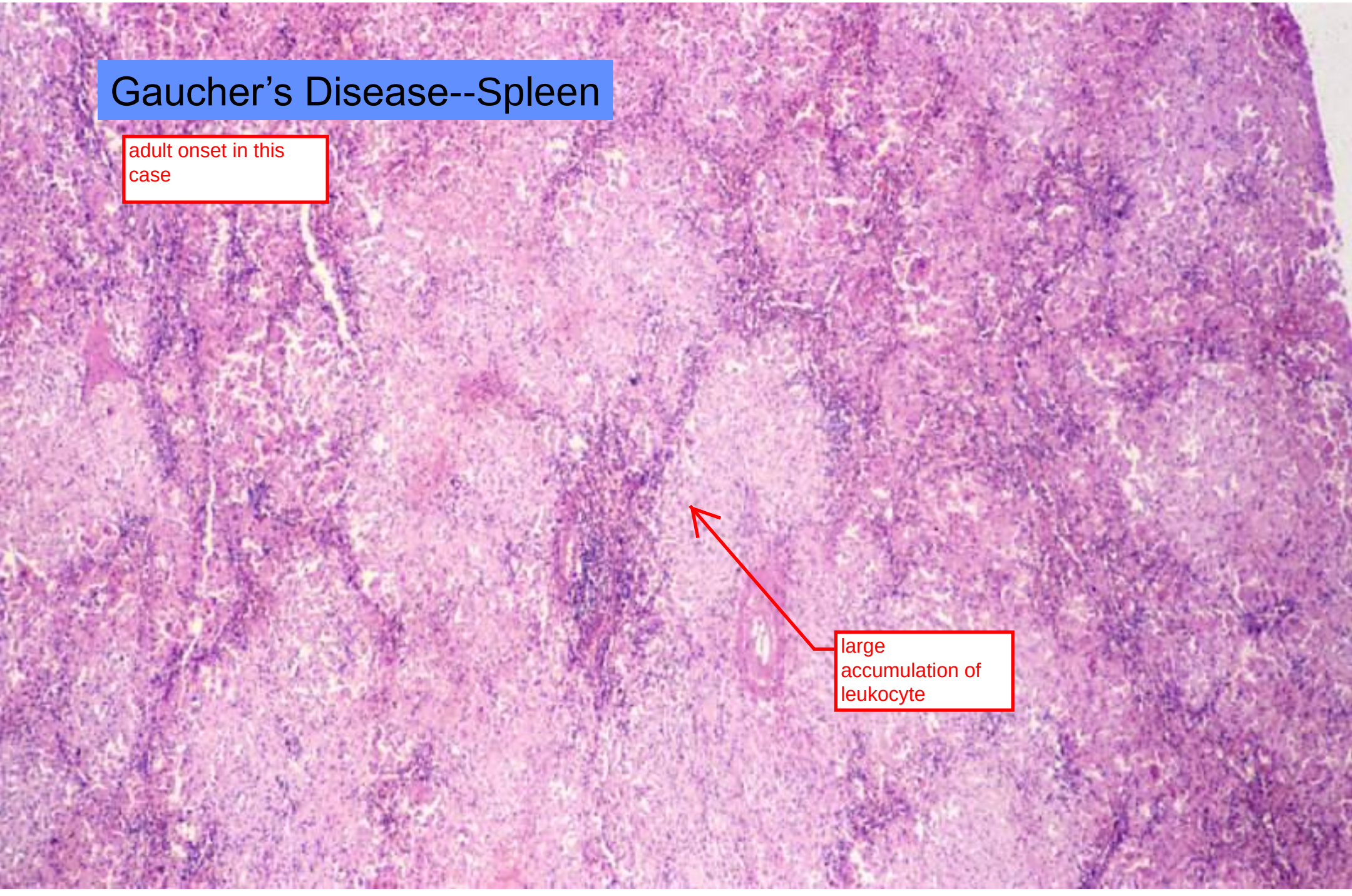
- Gaucher's Disease
- Lack of lysosomal glucocerbrosidase
- Cerebroside accumulation
- Slide 404 – 5,050 gm spleen

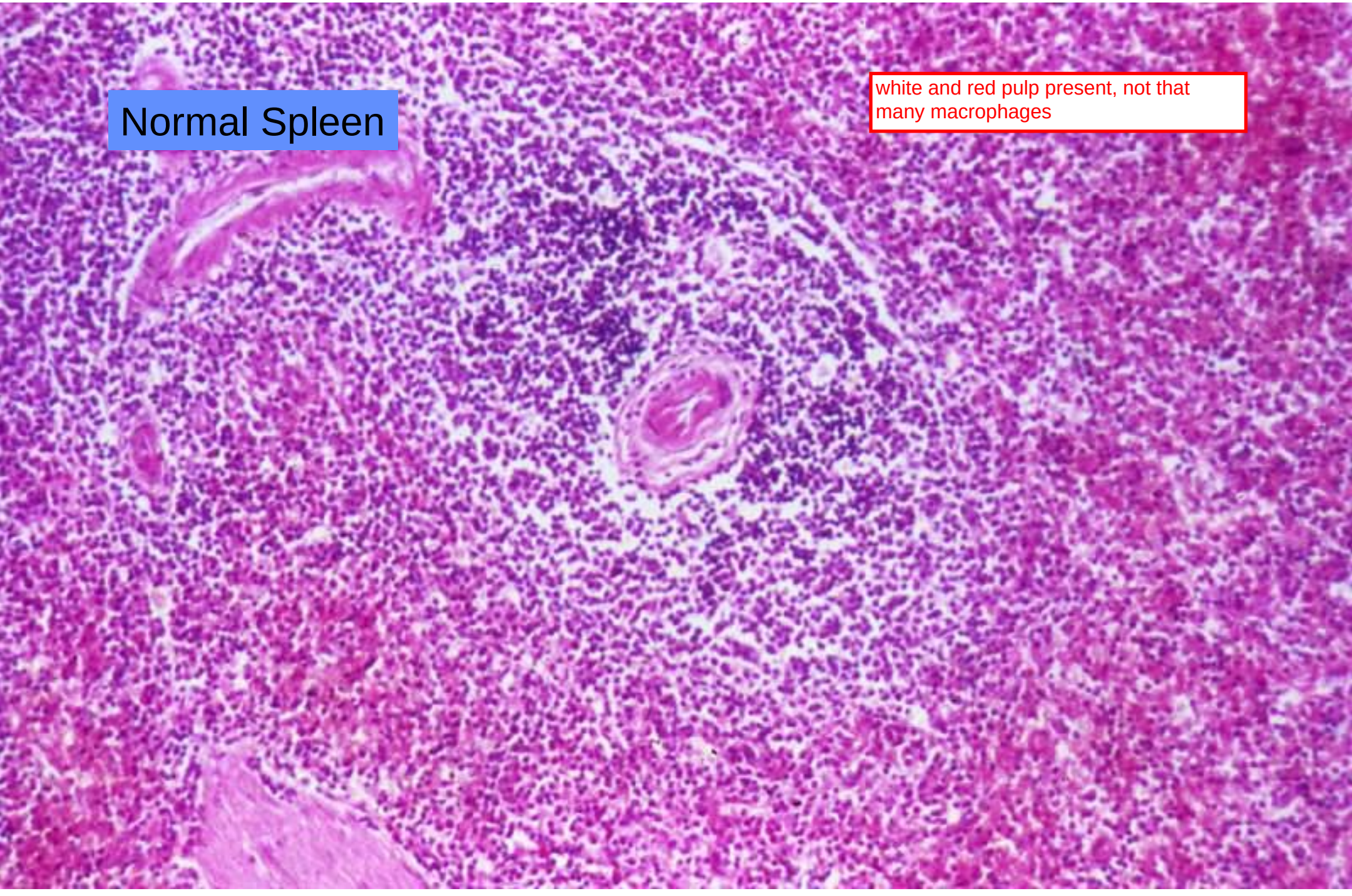


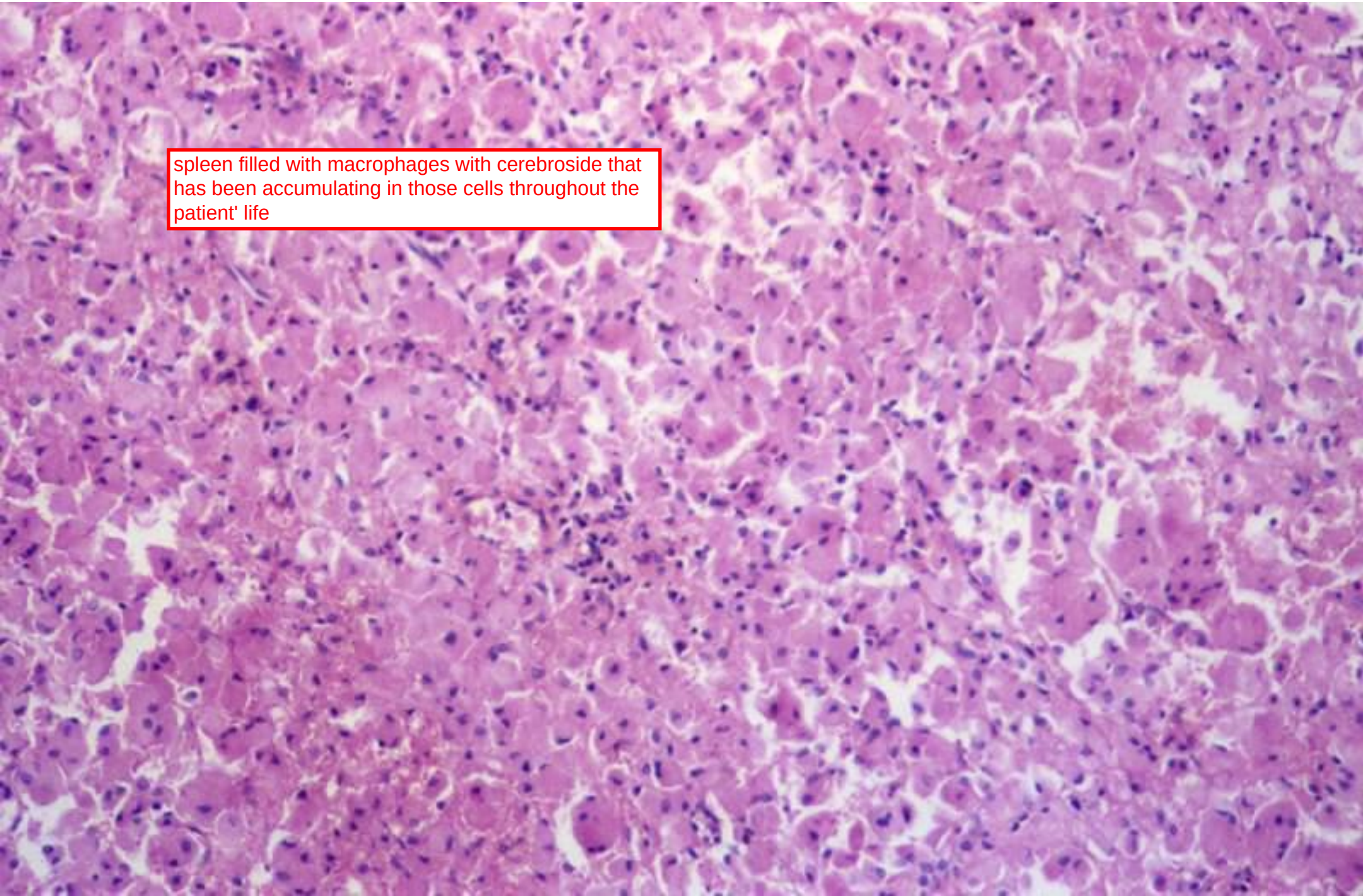
Gaucher's Disease

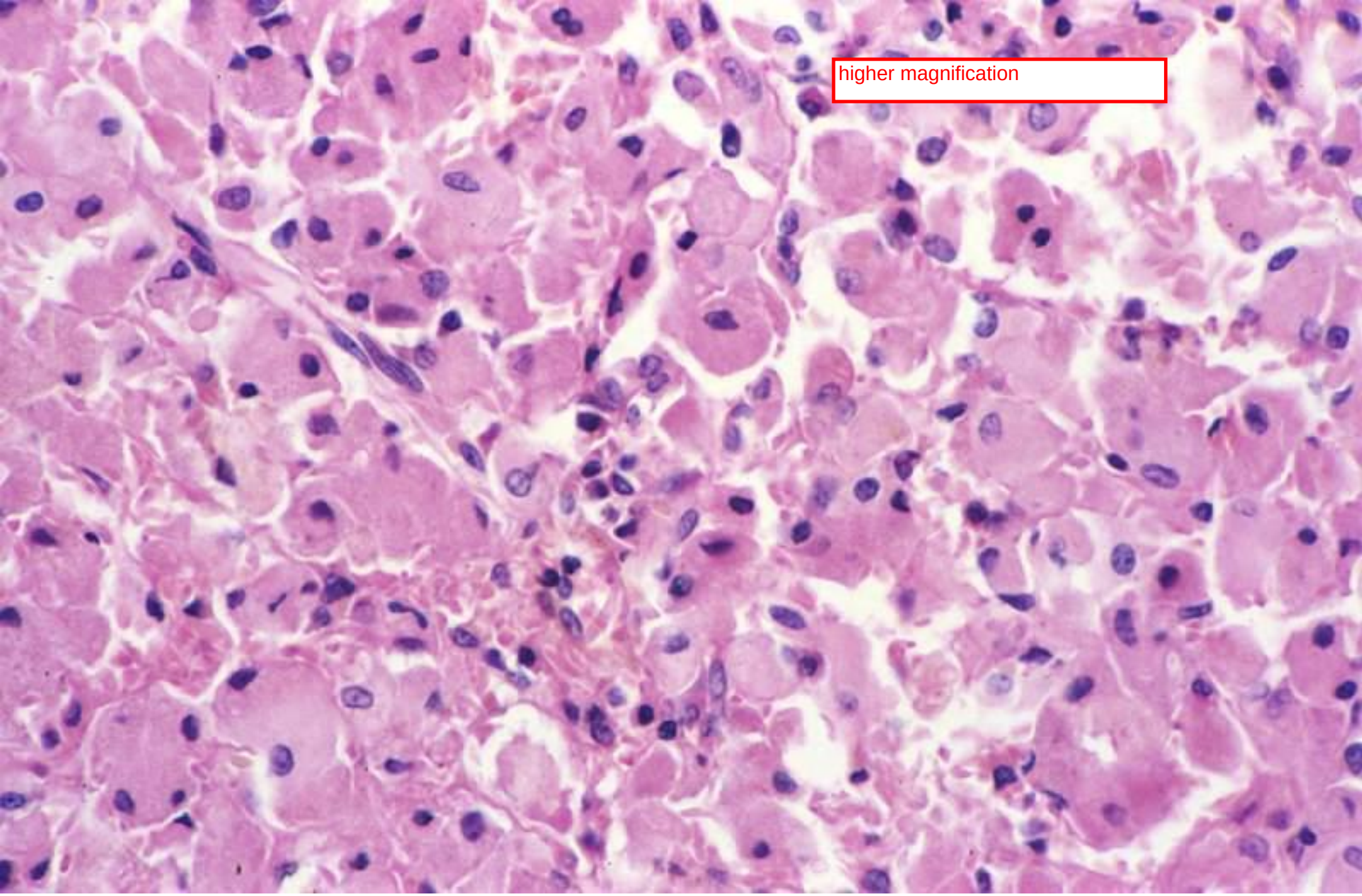
- 35 yo male presented for inguinal hernia repair
- Hx of fatique, bone pain
- W/U - anemia, leukopenia
- Imaging - enlarged spleen, liver

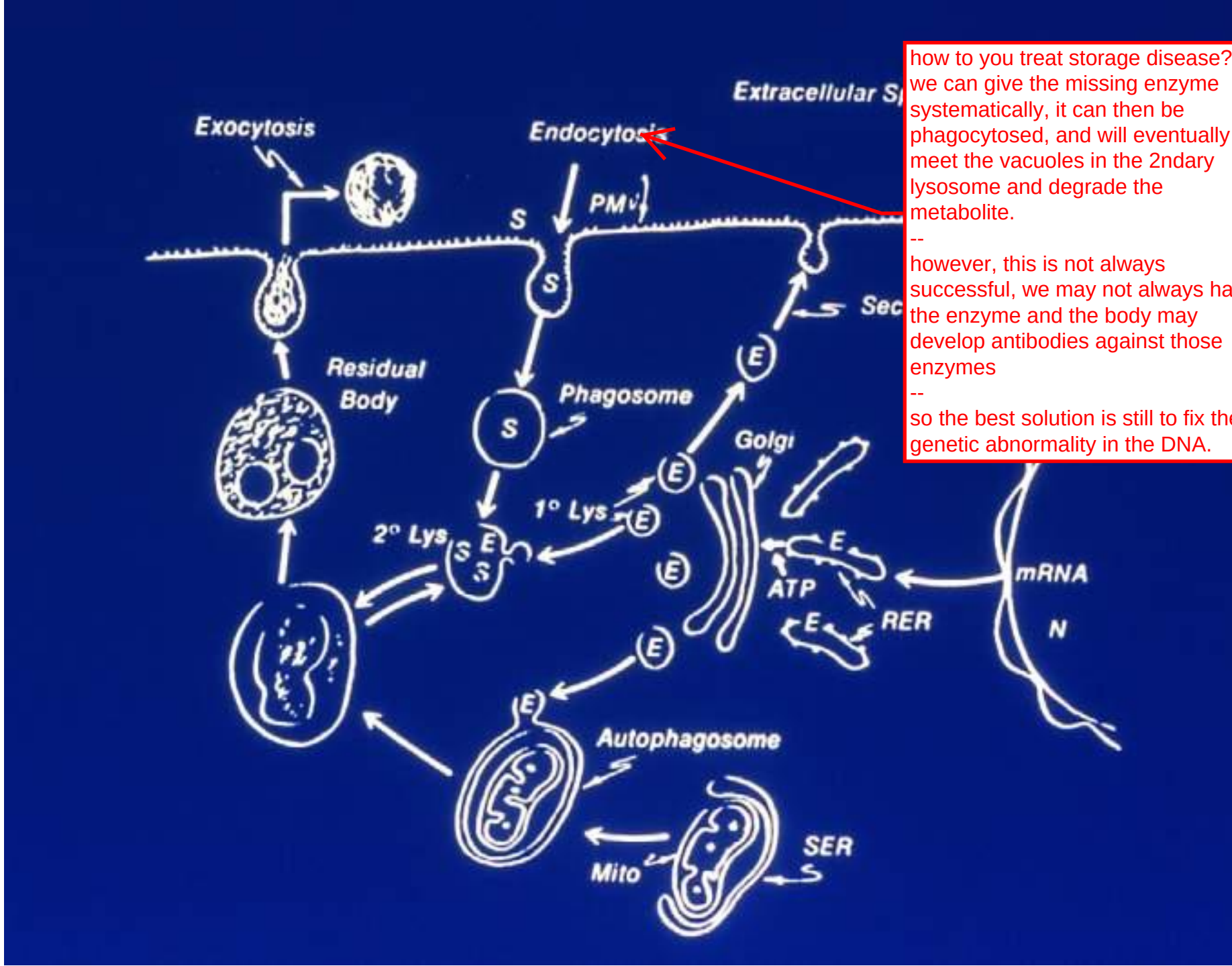
Gaucher's Disease--Spleen




Normal Spleen
white and red pulp present, not that many macrophages


spleen filled with macrophages with cerebroside that has been accumulating in those cells throughout the patient' life


higher magnification



how to you treat storage disease?
we can give the missing enzyme systematically, it can then be phagocytosed, and will eventually meet the vacuoles in the 2ndary lysosome and degrade the metabolite.
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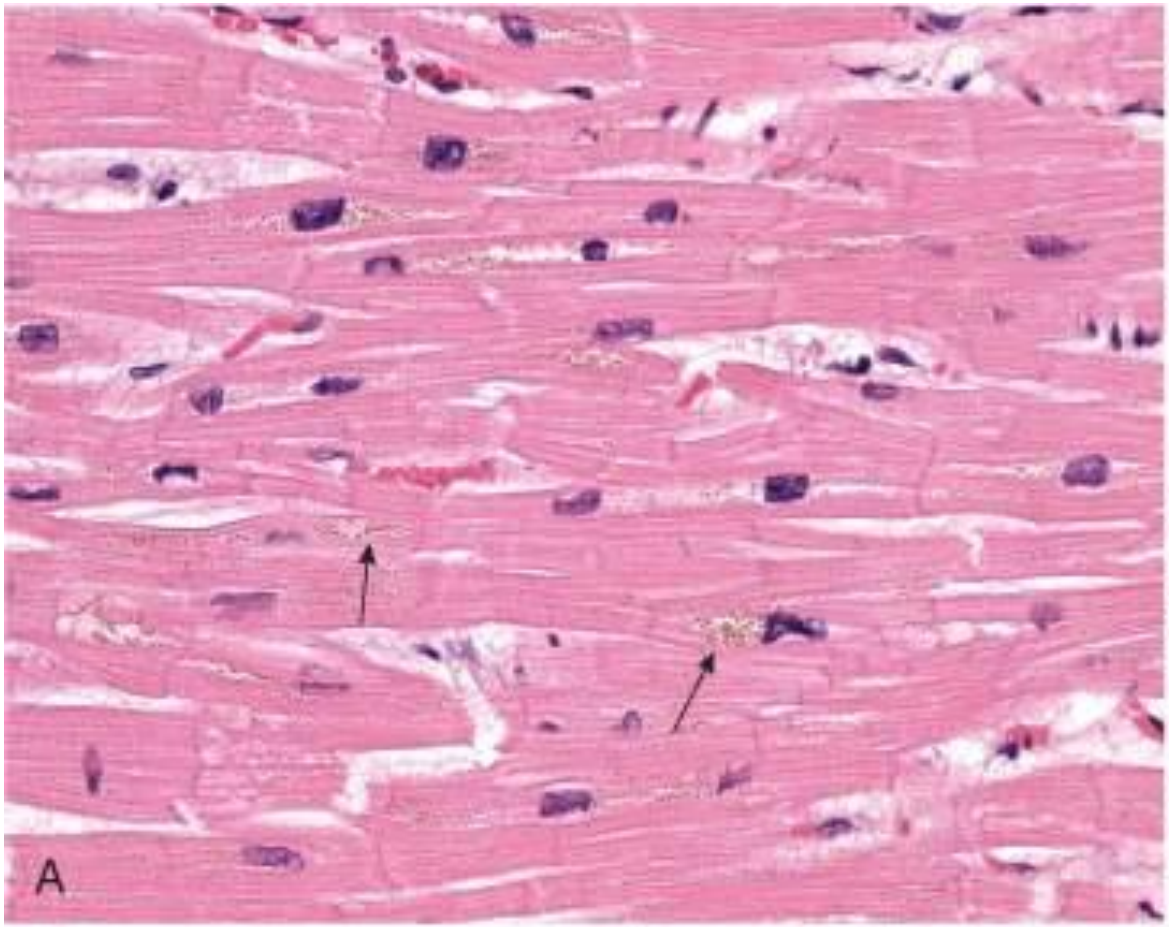
however, this is not always successful, we may not always have the enzyme and the body may develop antibodies against those enzymes
--
so the best solution is still to fix the genetic abnormality in the DNA.

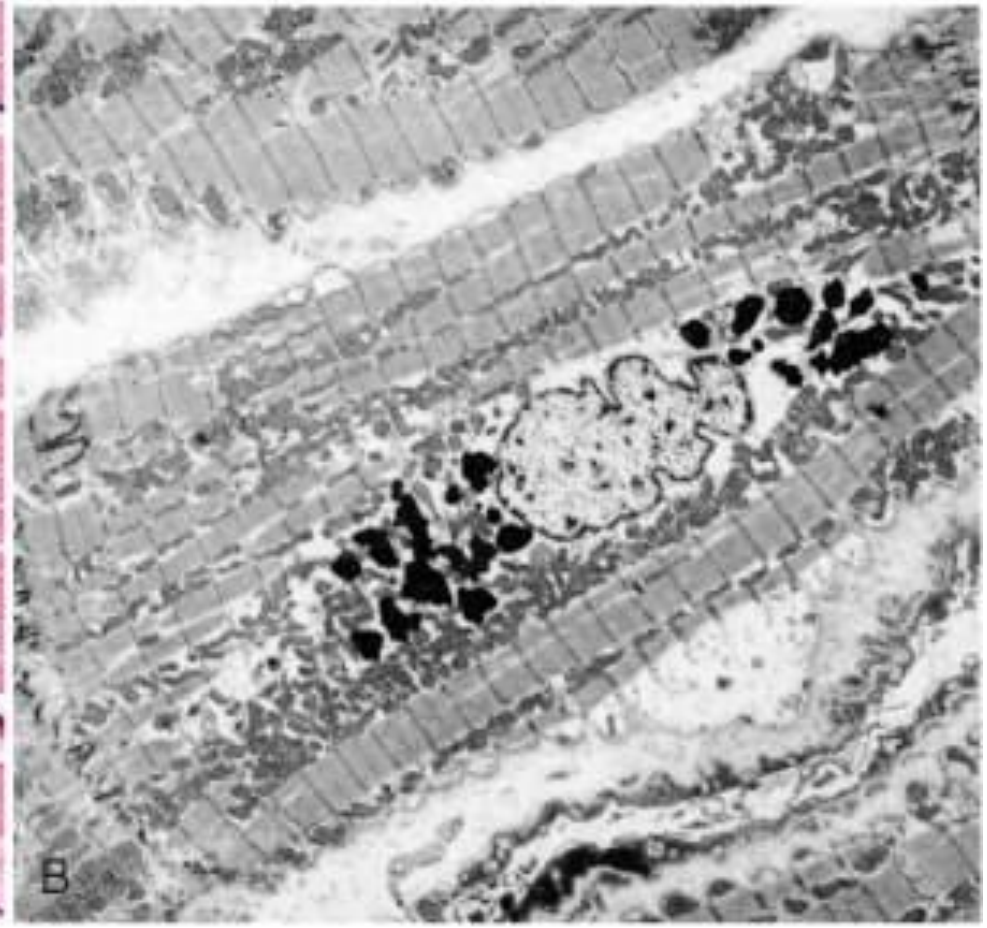
he just read the slide

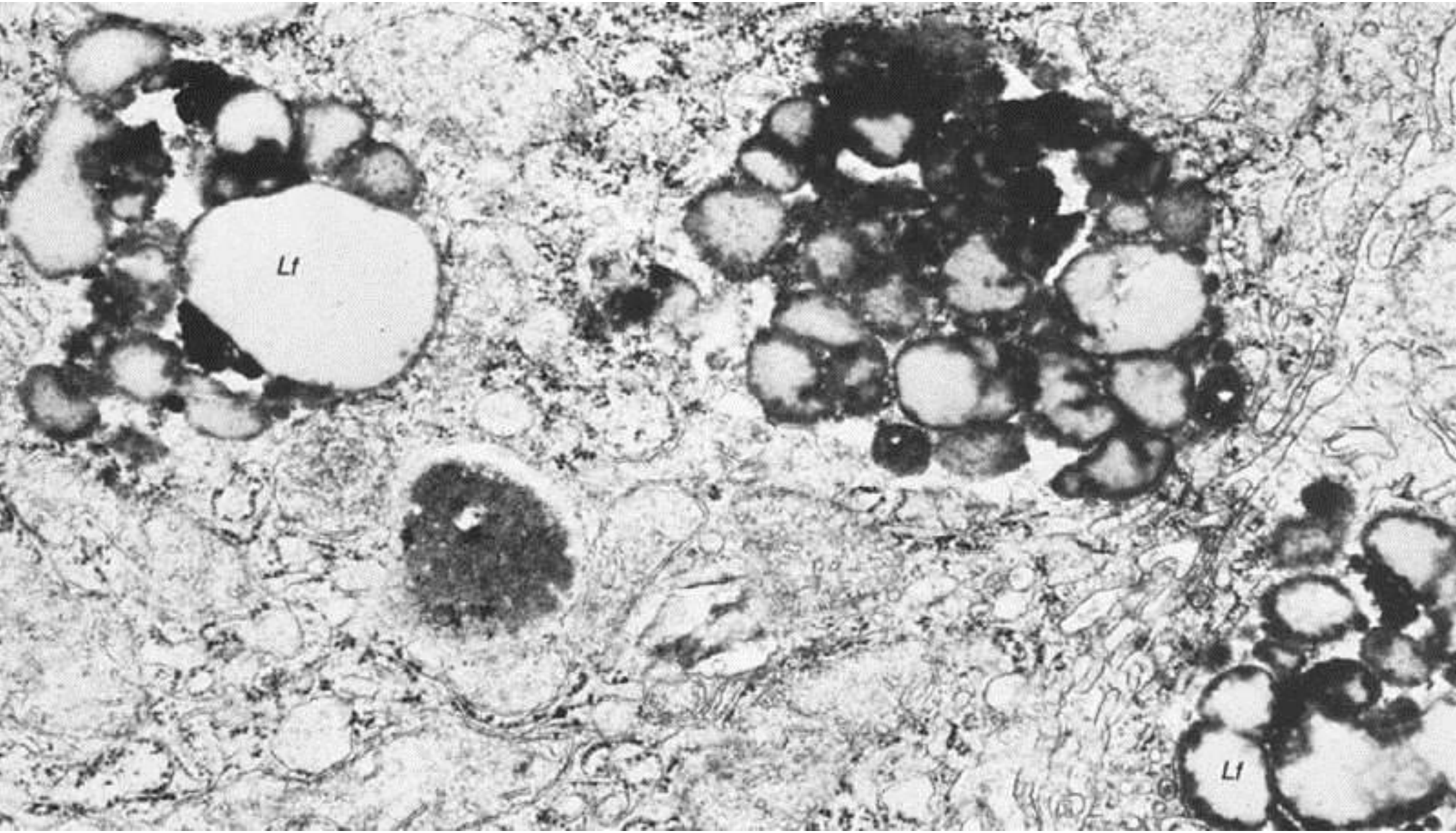
Lipofuscin

- Insoluble, brownish-yellow intracellular pigment
- Accumulates with age
- Complexes of lipid and protein derived from peroxidation of polyunsaturated lipids of subcellular membranes

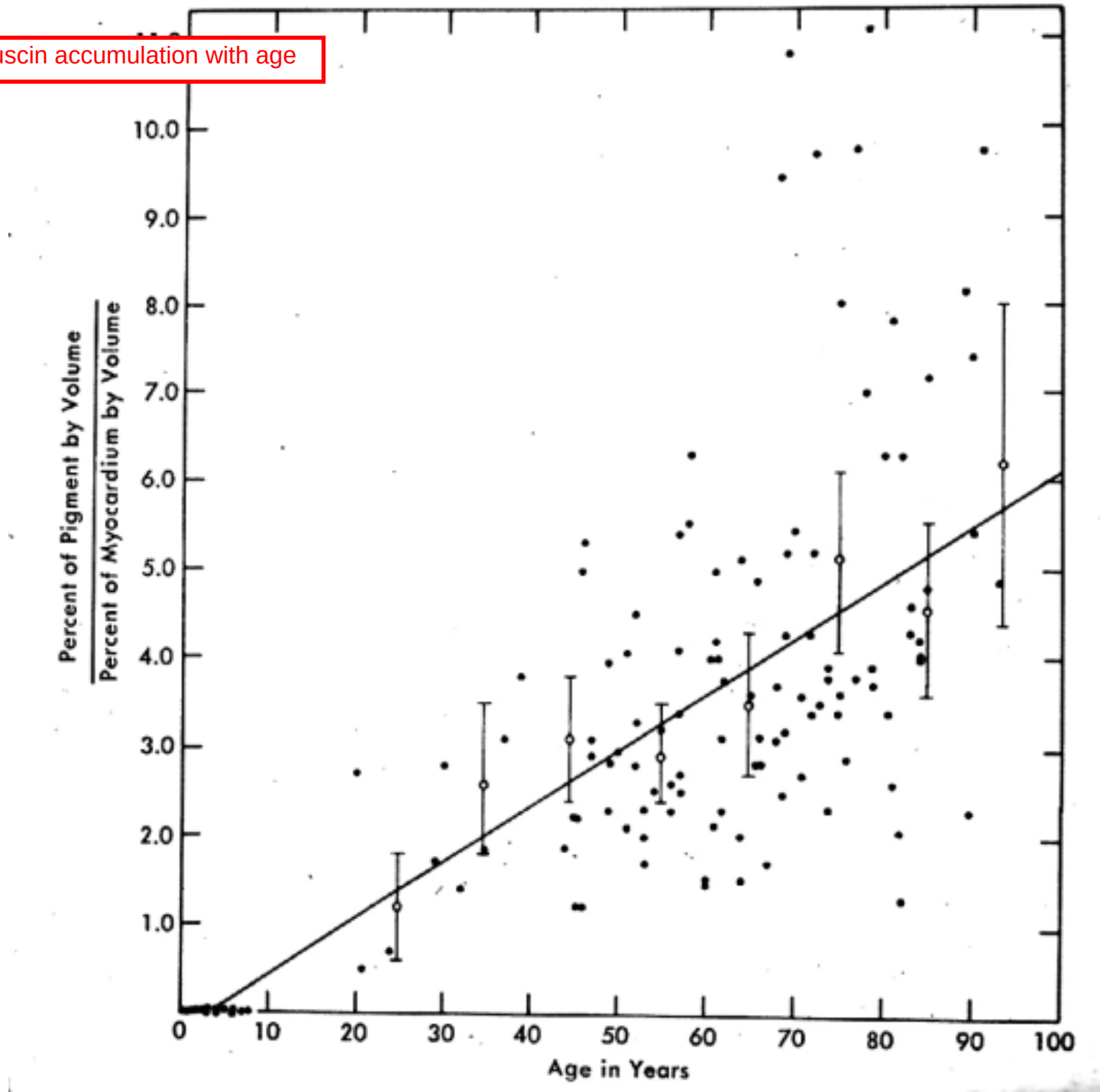
those lipofuscin bodies look yellow in H & E.
They are usually not harmful.



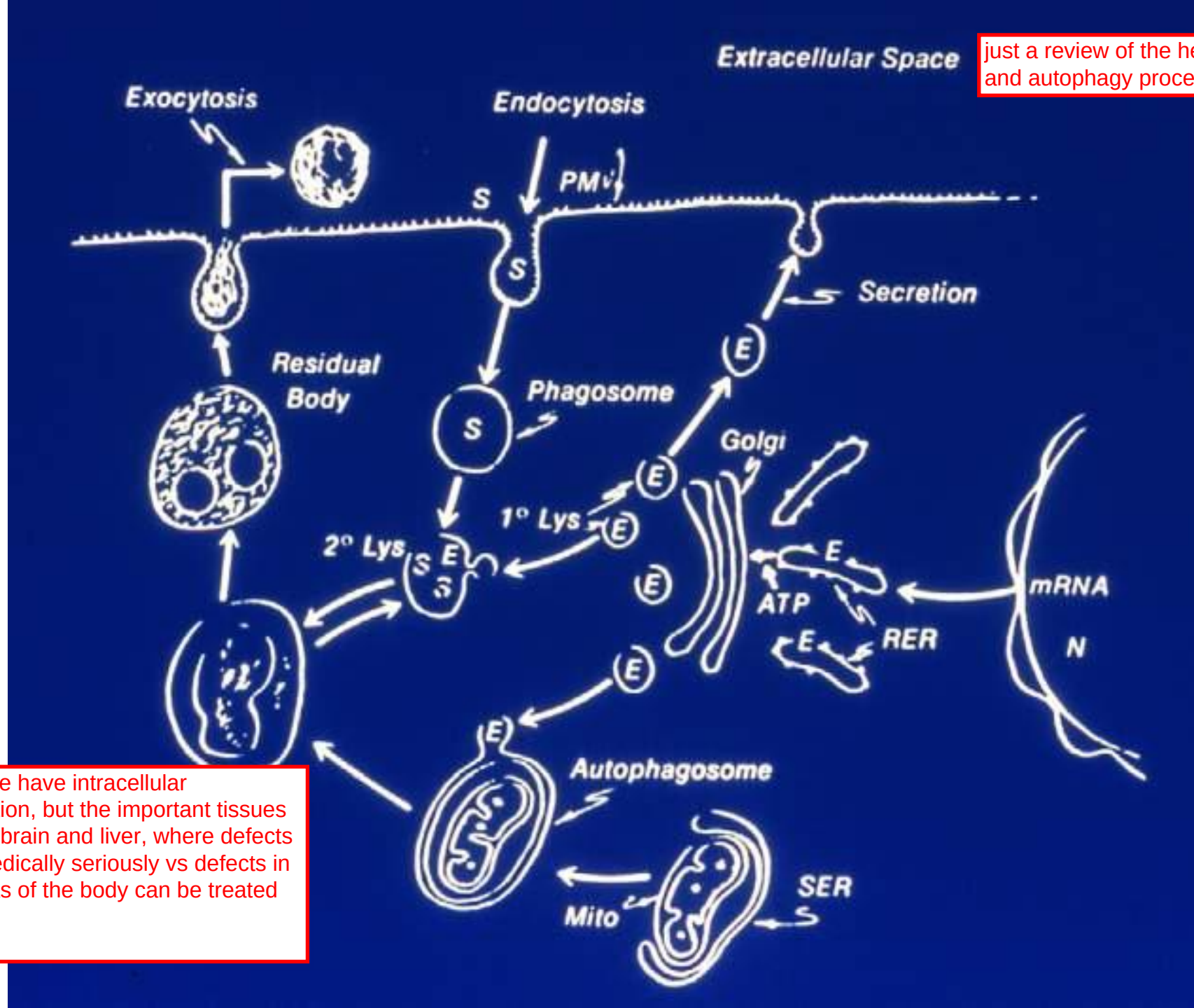



Lf
Lf

trend: more lipofuscin accumulation with age



just a review of the heterophagy and autophagy processes



most tissue have intracellular accumulation, but the important tissues are heart, brain and liver, where defects can be medically seriously vs defects in other areas of the body can be treated or fixed.