Intra- and Extracellular Accumulations

Accumulated substances can either be
• **Endogenous** – generated within
• **Exogenous** – generated outside

Intracellular accumulations
• A normal cellular constituent accumulates in excess: water, proteins, lipids, carbohydrates
• An abnormal substance accumulates
  – **Exogenous**: infectious agents, metals, etc.
  – **Endogenous**: products of faulty synthesis or metabolism
• Pigments (will cover in another lecture)
  – Melanin
  – Hemosiderin
  – Many others
Intracellular accumulations - Mechanisms

- A normal **endogenous** substance is produced at normal or increased rate but metabolism is inadequate.
Atherosclerosis – accumulation of fat laden cells in the walls of arteries; with atherosclerosis, there is also extracellular deposition of fatty substances.

Kidney – Hyalin droplet change

Glucocorticoid liver – canine Cushing’s disease

Accumulation of fat and other substrates such as glycogen
Intracellular accumulations - Mechanisms

- An abnormal endogenous substance accumulates due to faulty synthesis – α1-antitrypsin deficiency

- Accumulation of endogenous substances due to faulty catabolism – lysosomal storage disease
Mannosidosis in a calf

Intracellular accumulations -
Mechanisms
- Exogenous substance accumulate because it can not be catabolized - *anthracosis*

Coal miners lung –
Inhalation of carbon dust
Lead poisoning – kidney
Inset – acid-fast stain

Other intracellular accumulations
Microorganisms – Viral inclusions

Other intracellular accumulations
Microorganisms – bacteria & others
Amyloidosis refers to a heterogeneous group of disorders characterized by the deposition of abnormally folded (β-sheet) glycoproteins that resist degradation in various tissues.
Amyloidosis

Amyloid develops from a variety of precursor proteins

Classification of Amyloidosis

Immunocyte-associated

- Neoplasms
  - Usually multiple myeloma: Systemic
  - Plasmacytomas – Localized
- Precursor protein
  - Immunoglobulin light chain
- Fibril protein
  - AL

Classification of Amyloidosis

Reactive systemic

- Associations
  - Chronic inflammatory processes
  - Non-immunocytic neoplasms
  - Idiopathic
- Precursor protein
  - Acute phase protein designated SAA synthesized in liver and released during systemic inflammatory reactions
- Fibril protein
  - AA is a proteolytic cleavage fragment of SAA
Classification of Amyloidosis

Familial - localized & systemic

- Associations
  - Abysinnian cat – mainly renal glomerular
  - Siamese cat – mainly liver deposits
  - Shar-pei dog – mainly renal medullary interstitium
  - Humans – polyneuropathy

- Precursor protein
  - Acute phase protein designated SAA synthesized in liver and released during systemic inflammatory reactions - veterinary
  - Transthyretin - humans

- Fibril protein
  - AA is a proteolytic cleavage fragment of SAA
  - ATTR

Classification of Amyloidosis

Other Forms of Amyloidosis

- Amyloid of aging
  - Brain (senile dementia and Alzheimers); consist of Aβ derived from amyloid precursor protein (APP)
  - Senile Amyloid

- Endocrine related
  - Thyroid C-cell tumor; calcitonin peptide
  - Pancreatic islets (cats, primates, humans); islet amyloid peptide; associated with diabetes mellitus

- Prion diseases
  - Abnormal conformational form of prion protein
  - Will be covered in another lecture

Amyloidosis

No matter the chemical composition or protein precursor, the appearance of amyloid and its staining characteristics are similar
Amyloid (meaning starch) reacts with Lugol's iodine followed by weak sulfuric acid forms a color reaction typical of starch-containing substances. One affected organ is the kidney where amyloid is commonly deposited in glomeruli.

With H&E stains, amyloid forms hyalin to somewhat fibrillar amorphous eosinophilic (pink) extracellular deposits.

The most commonly used stain for amyloid is Congo red but this alone is not specific.
When Congo red stained sections are viewed with polarized light, one can observe apple-green birefringence.

Feline pancreas – islets obliterated by amyloid deposits

Apple-green birefringence in pancreatic islets with Congo red staining

Other tissues

Liver (above) and spleen (right)
Extracellular accumulations
Fibrinoid change
• Deposition of amorphous to fibrillar eosinophilic material in blood vessel walls
• Deposits consist of immunoglobulin, complement, and/or other proteins including fibrin
• Associated with immune-mediated infectious and non-infectious inflammation of blood vessels
• Is also a lesion that may be seen in the brain with malignant hypertension

Significance
Hemorrhage
Thrombosis
Ischemia

Gout
OUCH!

Available from Amazon
Gout – one of the older afflictions of mankind

**Primary gout**

- Uric acid is the endpoint of purine metabolism
- With abnormal metabolism (for 85-95% unknown), uric acid accumulates in blood leading to hyperuricemia
  - Can be due to overproduction with normal excretion
  - Defective excretion with normal production
  - Hypoxanthine guanine phosphoribosyl transferase deficiency (enzyme in the purine salvage pathway); an absolute deficiency of this enzyme causes X-linked Lesch-Nyhan syndrome

**Secondary gout**

- Increased nucleic acid turnover leads to hyperuricemia – an example of a disease would be leukemia
- Renal disease leading to decreased excretion
  - Gout in veterinary medicine is a disease of birds and reptiles
  - Is associated with vitamin A deficiency, high-protein diets, and renal disease

**Gout - mechanisms**

- < 7.0 mg/dl is considered the upper limit of normal for uric acid in the blood
- When hyperuricemia reaches a threshold, uric acid (as uric acid monohydrate) precipitates out of the blood and is deposited in tissues as fine needle-like crystals
- Intense pain and inflammation
Gout - pathology

- Two forms
  - Gouty arthritis
  - Visceral gout
- In reptiles and birds, the visceral form is most common

Gouty tophus - snake

Cholesterol

- Cholesterol deposits are the bi-products of
  - Hemorrhage
  - Necrosis
  - Inflammation
Sample Question #1
Which of the following statements is true concerning Parkinson’s disease?
1. An abnormal exogenous substance accumulates due to faulty synthesis
2. A normal endogenous substance produced in excess accumulates
3. An abnormal endogenous substance accumulations due to faulty synthesis
4. An exogenous substance accumulates due to faulty catabolism.

Sample Question #2
• Briefly explain the pathogenesis of reactive systemic amyloidosis.