Pigments and Accumulations
Intracellular Accumulations

- Normal cellular constituent vs. abnormal substance
- Transient vs. permanent
- Harmless vs. toxic
- Cytoplasm vs. nucleus
- Cell produced vs. produced other place in body
1. Abnormal metabolism
   - Normal cell
   - Fatty liver

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

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

4. Ingestion of indigestible materials
   - Accumulation of exogenous materials

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Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.
**FIGURE 1–30A** Fatty liver. A, Schematic diagram of the possible mechanisms leading to accumulation of triglycerides in fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can result in lipid accumulation.

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B, High-power detail of fatty change of the liver. In most cells the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole.

(Courtesy of Dr. James Crawford, Department of Pathology, University of Florida School of Medicine, Gainesville, FL.)
Cholesterol

- Athersclerosis
- Xanthomas
- Cholesterolosis
- Niemann-Pick disease, type C

- Triglycerides
- Cholesterol
**FIGURE 11–13A** Histologic features of atheromatous plaque in the coronary artery.  

**A**, Overall architecture demonstrating fibrous cap (F) and a central necrotic (largely lipid) core (C). The lumen (L) has been moderately compromised. Note that a segment of the wall is free of plaque (arrow); the lesion is therefore “eccentric”. In this section, collagen has been stained blue (Masson’s trichrome stain). **B**, Higher power photograph of a section of the plaque shown in A, stained for elastin (black), demonstrating that the internal and external elastic membranes are attenuated and the media of the artery is thinned under the most advanced plaque (arrow). **C**, Higher magnification photomicrograph at the junction of the fibrous cap and core, showing scattered inflammatory cells, calcification (arrowhead) and neovascularization (small arrows).
Xanthoma

Normal Skin:

![Image of normal skin structure]

- Stratified squamous epithelial tissue type
- Cornified layer (flattened, fused cell remnants)
- Collagen fibers
- Basement membrane

![Image of xanthoma structure]

http://dermatology-s10.cdlib.org/123/case_presentations/xanthoma/1.jpg

http://www.ajronline.org/content/188/5/1380/F19.large.jpg

Normal

**FIGURE 1–31** Cholesterolosis. Cholesterol-laden macrophages (foam cells, arrow) in a focus of gallbladder cholesterolosis.

(Courtesy of Dr. Matthew Yeh, Department of Pathology, University of Washington, Seattle, WA.)
Proteins

• Pink in H&E staining
• Proteins may accumulate as aggregates in vacuoles or in extracellular spaces
• Protein droplets may stain brightly in proximal tubules
• Secretory granules budded from ER may stain brightly as Russell bodies
• Misfolded proteins aggregate, such as $\alpha_1$-antitrypsin in hepatocytes
Russell Body

http://www.atlasbloodcells.es/imagenes_atlas/thumbm_11263233826_4.jpg

http://imagebank.hematology.org/Content%5C10939%5C10939_full.JPG
Hyaline

- Histologic appearance of pale, glassy, diffuse pink in H&E staining
- Eosine binds free amino groups
  - N-ends, Lys, Arg
  - May indicate protein breakdown or influx of plasma proteins
- Accumulation of staining, not itself a pigment
Amyloid

- Amyl = starch
- Misfolded proteins in B-pleated sheet formation that resist digestion and accumulate as inclusions
- Amyloid accumulations in glomeruli stain brown with iodine, similar to the iodine reaction with glycogen
- Amyloid and glycogen stain pink under white light with Congo red, but polarized light bounces off amyloid and looks green
Glycogen

- Glycogen is a readily available energy source stored in the cytoplasm of healthy cells.
- Excessive intracellular deposits of glycogen are seen in patients with an abnormality in either glucose or glycogen metabolism.
- Glycogen dissolves in aqueous fixatives; for its localization, tissues are best fixed in absolute alcohol.

<table>
<thead>
<tr>
<th>Type</th>
<th>Defective enzyme</th>
<th>Organ affected</th>
<th>Glycogen in the affected organ</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Von Gierke</td>
<td>Glucose 6-phosphatase or transport system</td>
<td>Liver and kidney</td>
<td>Increased amount; normal structure.</td>
<td>Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.</td>
</tr>
<tr>
<td>II Pompe</td>
<td>α-1,4-Glucosidase (lysosomal)</td>
<td>All organs</td>
<td>Massive increase in amount; normal structure.</td>
<td>Cardiorespiratory failure causes death, usually before age 2.</td>
</tr>
<tr>
<td>III Cori</td>
<td>Amylo-1,6-glucosidase (debranching enzyme)</td>
<td>Muscle and liver</td>
<td>Increased amount; short outer branches.</td>
<td>Like type I, but milder course.</td>
</tr>
<tr>
<td>IV Andersen</td>
<td>Branching enzyme (α-1,4 → α-1,6)</td>
<td>Liver and spleen</td>
<td>Normal amount; very long outer branches.</td>
<td>Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.</td>
</tr>
<tr>
<td>V McArdle</td>
<td>Phosphorylase</td>
<td>Muscle</td>
<td>Moderately increased amount; normal structure.</td>
<td>Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.</td>
</tr>
<tr>
<td>VI Hers</td>
<td>Phosphorylase</td>
<td>Liver</td>
<td>Increased amount.</td>
<td>Like type I, but milder course.</td>
</tr>
<tr>
<td>VII</td>
<td>Phosphofructokinase</td>
<td>Muscle</td>
<td>Increased amount; normal structure.</td>
<td>Like type V.</td>
</tr>
<tr>
<td>VIII</td>
<td>Phosphorylase kinase</td>
<td>Liver</td>
<td>Increased amount; normal structure.</td>
<td>Mild liver enlargement. Mild hypoglycemia.</td>
</tr>
</tbody>
</table>

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.
Pigments

- Exogenous
- Endogenous

Tattoo

Exogenous Pigments

• Lipofuscin
• Melanin
• Hemosiderin
Lipofuscin

- Fuscus = brown
- Inclusions of lipid peroxides, phosphates, proteins
- Not harmful
- Accumulates in liver, heart from normal “wear and tear”
- Sign of free radical damage
- Pigment accumulates near nucleus
- Indicative of age, oxidative damage
- Does not stain blue with Prussian blue or Perl’s iron
Melanin

- Melas = black
- Synthesized from tyrosine by tyrosinase
- Reaction confined to melanosome compartment of melanocytes in dermis
- Whole melanosome is transferred to keratinocytes in epidermis
- Blocks UV radiation
- Benign accumulations (freckles, moles) are called nevi (pl., singular: nevus or naevus = from birth; birthmark)
- Alternative name, lentigo, like a lentil or pea
• Hemochromatosis
• Bilirubin

Figure 1. Distribution of Iron in Adults.
In the balanced state, 1 to 2 mg of iron enters and leaves the body each day. Dietary iron is absorbed by duodenal enterocytes. It circulates in plasma bound to transferrin. Most of the iron in the body is incorporated into hemoglobin in erythroid precursors and mature red cells. Approximately 10 to 15 percent is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes). Iron is stored in parenchymal cells of the liver and reticuloendothelial macrophages. These macrophages provide most of the usable iron by degrading hemoglobin in senescent erythrocytes and re-loading ferric iron onto transferrin for delivery to cells.
**Oxyhemoglobin**
- Oxygen-bound hemoglobin, Hb or HbO2, is red
- Mucous membranes and nail beds look pink

**Deoxyhemoglobin**
- Reduced hemoglobin, HHb is dark purple-red
- Mucous membranes and nail beds look blue (cyan)

http://medsci.indiana.edu/a215/virtualscope/images/blood4_b.jpg

Colors of bruising
Colors of bruising

• Initial hemorrhage of RBCs into tissue is cleared by macrophages, which process Hb
  ▪ Oxyhemoglobin and Deoxyhemoglobin
  ▪ Deoxyhemoglobin and Biliverdin
  ▪ Biliverdin and Bilirubin
  ▪ Bilirubin and Hemosiderin
  ▪ Hemosiderin

• When iron is completely cleared, tissue resumes normal color

• Accumulation of hemosiderin is hemosiderosis

• Hemochromatosis is severe, chronic accumulation
Bilirubin Metabolism

Sinusoid → Hepatocyte → Cannalicular

- Bilirubin (B) → B-L → B + UDP-GU
- Ligandin (L)
- Glucuronyl Transferase (GT)
- Glucuronyl Transferase (GT)
- UDP-Gu = Uridine diphosphoglucuronic acid

80% excreted, 20% reabsorbed
Hepatic bile ducts
Jaundice, icterus

• Bilirubin build-up in tissues
  ▪ Prehepatic or hemolytic: due to excessive hemolysis
    • build-up of unconjugated bilirubin
  ▪ Hepatic or hepatocellular: due to failure of at least 80% of liver function
    • both conjugated and unconjugated bilirubin accumulates
  ▪ Posthepatic or obstructive: due to failure of bile to drain into GI tract
    • Conjugated bilirubin accumulates
Excessive accumulation of iron

- Accumulation of hemosiderin is hemosiderosis
- Hemosiderin is normally found in marrow, spleen, liver
- Hemosiderosis in tissues is secondary to:
  - iron intake overload (enteral or parenteral), long-term hemodialysis or transfusions, blood disorders
- Hemochromatosis is severe, chronic accumulation in liver, pancreas, myocardium
  - Primary, genetic hemochromatosis most frequent in men of northern European descent
- Hemochromatosis results in oxidative damage and inflammation
Hemosiderosis, hemochromatosis
Pathologic Calcification

- Dystrophic Calcification
- Metastatic Calcification
Dystrophic calcification

- Associated with necrosis, aging or damaged heart valves
- Precipitated calcium salts look white
- Basophilic when stained with H&E
- Blue granular crystals
Calcified bicuspid
Psammoma body

Histologically, with the usual hematoxylin and eosin stain, calcium salts have a basophilic, amorphous granular, sometimes clumped appearance.

On occasion single necrotic cells may constitute seed crystals that become encrusted by the mineral deposits.

The progressive acquisition of outer layers may create lamellated configurations, called psammoma bodies because of their resemblance to grains of sand.
Metastatic calcification

• Associated with imbalances in phosphorous equilibrium or hypercalcemia
  ▪ Hyperparathyroidism stimulates resorption of Ca from bone
  ▪ Accelerated bone turnover due to immobility, metastatic cancer, leukemia, Paget disease
  ▪ Vitamin-D intoxication, sarcoidosis
  ▪ Renal failure
    • Phosphate retention
    • Hyperparathyroidism

• Principally affects acid secreting cells
  ▪ Gastric mucosa, kidneys, lungs, systemic arteries, pulmonary veins
Metastatic Calcification Lung