Cell Injury Lecture Summary

This is a summary of the most important concepts from Dr. Dolan's Cell Injury I and II lectures. Exam questions will come from this summary – so if you understand this stuff, you should be good for the exam.

The four main types of cellular adaptations

When cells are injured, they respond by either adapting or by dying. In the area of adaptations, there are four words you should be able to define in your sleep:

1. **Hyperplasia**: an *increase in the number of cells* in a particular organ. For example, in pregnancy, the uterus gets a lot bigger, in part due to an increase in cell number (but also due to an increase in cell size!). Note: sometimes, cancer can develop in an area of hyperplasia. But this is a RARE occurrence. Most of the time, hyperplasia is just physiologic – meaning that it's a normal response to stress and that's it.

2. **Hypertrophy**: an *increase in cell size*. For example: the aforementioned uterus. Also, the heart: when there is excess stress on the heart, the individual cells get bigger (cardiac muscle cells can't make more of themselves - so they just get bigger).

3. **Atrophy**: decrease in cell size and metabolic activity. For example, when muscles are not used, they atrophy; the individual muscle cells shrink in size. Tell me about it; I need to get to the gym.

4. **Metaplasia**: a change from one cell type to another. For example, in some cigarette smokers, the bronchial epithelium may change from normal ciliated columnar epithelium to squamous epithelium.

Apoptosis vs. necrosis

Both apoptosis and necrosis are types of cell death. So what are the important differences?

Apoptosis is programmed cell death. The cell decides to kill itself, and that's that. The mechanisms for doing so are already programmed into the cell's DNA; it just needs the right signal. It's usually a tightly-regulated and controlled process. It can occur in pathologic processes, like tumors, but it is also a part of certain physiologic processes, like embryogenesis (the hand starts out as a little paddle, then parts of the tissue undergo apoptosis, and what remains becomes the baby's fingers).

Necrosis, on the other hand, is always pathologic and never physiologic. It is the result of irreversible injury to a cell. It's not tightly controlled - the cell just dies because it's been injured by lack of blood supply, free radical damage, infection, toxins, or other nasty things.

The six types of necrosis

Coagulative necrosis

- Cell outlines preserved, but cells look "ghostly."
- Most common type of necrosis.
- See this in most infarcts (except brain infarcts!). An infarct, by the way, is just an area of tissue death caused by lack of blood supply.

Liquefactive necrosis

- Tons of neutrophils and cell debris; the tissue is literally "liquefied."
- See this in infections and brain infarcts.

Caseous necrosis

- Fragmented cells and debris surrounded by macrophages. These lesions are called "caseating" granulomas (they're just regular old granulomas that have a bunch of fragmented, dead cells in their centers).
- Caseous is from the Latin *caseus*, meaning cheese – and this type of necrosis really does look like cheese to the naked eye (think feta).
- See this in tuberculosis.

Fat necrosis

- Shadowy, bluish, dead fat cells.
- See this in acute pancreatitis (inflammation of the pancreas). In acute pancreatitis, damaged pancreatic cells leak lipase, which rips apart the fat cells around the pancreas. Fatty acids from the fat cells combine with calcium (this is called "saponification," or soap formation!), forming chalky white deposits you can see grossly.

Fibrinoid necrosis

- Bright pink, stringy ("fibrin-like" or "fibrinoid") deposits in vessel walls.
- See this in diseases with type III (immune complex) hypersensitivity reactions (like lupus).

Gangrenous necrosis

- This type of necrosis is diagnosed grossly (meaning by just looking at the tissue with your naked eye, as opposed to the microscope).
- It usually occurs in limbs or digits that have lost blood supply ("gangrene" refers to a dead body part resulting from inadequate blood flow), usually as a result of severe diabetic complications, or frostbite.
- When you look at gangrenous tissue under the microscope, you usually see coagulative necrosis, sometimes with superimposed liquefactive necrosis (if there's secondary infection).

What happens in cell injury, super-short-attention-span version

Cell injury often starts with depletion of ATP. When that happens, cell membrane pumps don't work well, and calcium accumulates in the cell, doing all sorts of bad things.

The four structures that are most vulnerable to cell injury are:

1. mitochondria
2. cell membranes
3. the protein synthesis apparatus
4. DNA

Too much cytoplasmic calcium is bad for 3 reasons:

1. It denatures proteins
2. It poisons mitochondria (makes them open little channels in their membranes which makes oxidative phosphorylation fail; also activates pathways that make the cell kill itself)
3. It activates a bunch of nasty cellular enzymes (like phospholipases, which break down membranes).

Cell injury can also be induced by free radicals (molecules that have a single, vicious unpaired electron). Several types of processes can increase the production of free radicals. Get enough free radicals, and the cell membrane will be damaged.

The bottom line is that there are two main reasons a cell dies:

1. Cytoplasmic calcium accumulation, and
2. Membrane damage.

Morphological changes seen in reversible and irreversible injury

When a cell is injured, you can often see signs under the microscope. The earliest changes are only visible with an electron microscope – but pretty soon, you can see that something is wrong even with a regular light microscope.

Changes you can see in **reversibly injured** cells include:

- Mitochondrial densities
- Cellular swelling
- Cytoskeletal disruption (e.g., loss of microvilli, blebs)

Once you see any of the following things, a cell is considered **irreversibly damaged**:

- Increased eosinophilia (pink color) in cells. Check out the image above of a myocardial infarction: the myocytes are brightly eosinophilic (remember: “red is dead!”).
- Great big mitochondrial densities

- Nuclear changes, such as pyknosis (a shrunken, dark nucleus), karyolysis (a fading of the nucleus), and karyorrhexis (fragmentation of the nucleus into little cookie-crumb-like pieces).

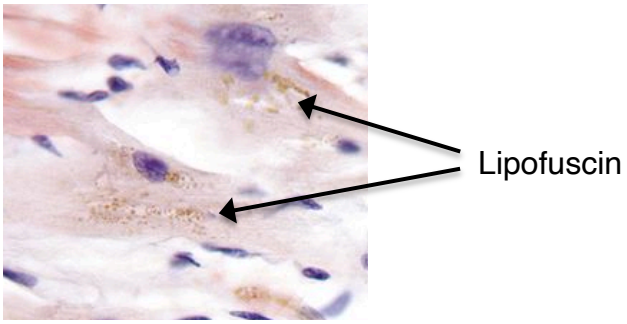
The five main tissue pigments

Pigments (colored substances) are sometimes seen in histologic sections. They can be normal or abnormal, and they may be from the outside (exogenous) or made inside the body (endogenous). There are five main pigments seen within tissues.

1. Carbon (coal dust)
This is the most common exogenous pigment. It's seen in urban dwellers, coal miners and smokers. The official name for the blackening of the lungs seen in these patients is anthracosis.

2. Tattoo pigment
Tattoo pigments are often composed of metal salts (like iron oxide), but vegetable dyes and plastic-based dyes may be used too. The pigment is phagocytosed by dermal macrophages which retain the pigment for the person's lifetime.

3. Lipofuscin
This pigment, known as the wear-and-tear pigment, is composed of a bunch of lipids and proteins and has a yellow-brown appearance. The name is derived, in part, from the Latin word fuscus, which means dingy, brown, or dark. That's probably why "obfuscate" means "to make unclear or obscure." Lipofuscin accumulates with age and is of no clinical significance.



4. Melanin
Melanin comes from the Greek word for black (*melas*). It is a deep brown-black pigment that is seen, not surprisingly, in melanocytes.

5. Hemosiderin
This yellow-brown pigment is one of the major storage forms of iron. It is normally seen in macrophages in the bone marrow, spleen and liver (which are actively breaking down red cells). It is also seen when there is a local excess of iron (as in a bruise) or systemic excess of iron (for example, in patients with repeated blood transfusions).

Metastatic vs. dystrophic calcification

Tissues can undergo calcification in a couple of different settings. The important things to remember are:

- whether the affected tissue is normal or damaged
- whether the serum calcium level is normal or elevated

In **dystrophic calcification** the tissue is the problem. This type of calcification occurs in damaged or necrotic tissue; the serum calcium level is normal. For example, the calcification that occurs in atherosclerotic plaques, or on damaged heart valves, is considered dystrophic.

In **metastatic calcification**, the problem is the serum calcium level. This type of calcification occurs in normal tissues in patients who have a high serum calcium level. There are lots of potential causes of hypercalcemia – a common one is chronic renal failure. In this type of calcification, the calcium "metastasizes" (bad word! this isn't a malignant process!) all around the body, often landing in the kidney, lungs, or arteries.