CELLULAR INJURY

(CHAPTER 10)

QUESTION 1

Describe hydropic swelling.

Hydropic swelling or **hydropic degeneration** results from a malfunction of the Na^+/K^+ exchange pump, causing an osmotic gradient and pulling water **into** the cell.

Normally, the Na^+/K^+ pump uses ATP to throw 3 Na^+ ions out of the cell and pull 2 K^+ ions back in.

When this process slows down, more sodium stays **inside** the cell, increasing the **colloidal concentration** of the intracellular environment.

We will talk about osmosis more in the next unit (Fluid/Electrolyte Balance,) but just remember for now that different concentrations of solutes will always try to **balance themselves out**.

In this case, that occurs by water moving from the **less-concentrated** area outside the cell to the **more-concentrated** area inside.

QUESTION 2

Can cells recover from hydropic swelling?

Yes, absolutely! This imbalance is usually only a temporary (**reversible**) injury, unless it reaches an extreme point that results in cell death.

When the root cause is addressed and the Na^+/K^+ pump resumes working, it will work in "overdrive" to correct the electrolyte imbalance.

As sodium is exported from the cell in exchange for a **smaller amount** of potassium, the colloidal concentration of the cell will **decrease**.

This results in the excess fluid inside the cell **leaving** to follow the exported sodium ions.

QUESTION 3

What could cause hydropic swelling?

Hydropic degeneration can be caused by anything that interferes with the normal operation of the Na^+/K^+ exchange pump.

Remember that, because the action of Na^+/K^+ ATPase is an **active transport** process, it requires ATP to function!

This means that anything that causes a **decrease** in **ATP production** (such as **hypoxia**) can cause hydropic swelling to occur.

ATP is produced most effectively through **aerobic metabolism**, so an insufficiency of **oxygen** will result in lower ATP availability.

QUESTION 4

What are some types of cellular inclusions?

Cellular inclusions occur when a substance accumulates in abnormal amounts **inside** a cell.

In theory, this can be anything, but certain types of inclusion are **more common**...

Fatty liver disease (FLD) occurs when intracellular inclusions of **lipids** develop due to impaired export of **lipoproteins** (VLDL.)

Glycogen storage disease (GSD) occurs when **glycogenolysis** is disrupted, leading to a buildup of **glycogen** in cells.

Lipofuscin (a byproduct of lysosomal digestion of fatty acids) tends to build up in many types of cells as a normal part of aging.

Tau tangles are an intracellular accumulation of **tau protein** seen in **Alzheimer's disease**.

QUESTION 5

Which cellular process is disrupted when inclusions occur?

Inclusions are usually caused by some form of disruption to cellular **metabolism** or **transport** of molecular products.

Either the cell isn't **breaking down** something properly, or it isn't **getting rid of it** fast enough.

QUESTION 6

Where does lipid often accumulate?

As we mentioned before, lipids can accumulate inside the **hepatocytes**, the main functional cells of the **liver**.

Normally, the liver exports lipids and cholesterol inside of **very low-density lipoprotein** (VLDL,) but when liver damage occurs, this process is often **slowed**.

Over time, this extra lipid content gets **trapped** inside the cell and slowly builds up **inside** the hepatocytes.

Remember that the fat is **not** building up in **deposits** within the liver; the fatty inclusions are present in **every cell** throughout the liver!

QUESTION 7

Where does pigment accumulate as lipofuscin?

Lipofuscin can accumulate in many types of cells throughout the body:

- **liver** and **kidneys**
- **myocardium** (a.k.a. "heart muscle")
- **eyes** (macular degeneration)
- **nerves** (Parkinson's, ALS, etc.)

QUESTION 8

An enzyme is a cellular protein. Why do you think misfolding of proteins is a serious problem for the cell?

The key point is that a protein's **function** is a direct product of its **structure**, which includes **both** molecular bonds and **folding**.

Remember that a molecule's shape is influenced by the **hydrophobic effect**, **van der Waals forces**, etc. as well as the actual bonds.

In short, enzymes need to be assembled and folded **exactly right** or they **won't work**.

Every enzyme in the body has a distinct **purpose**, so if some problem is causing a protein to become misfolded, that means some cellular process is **blocked** or **impeded**.

QUESTION 9

How is protein damage limited?

One of the strategies employed by the body to moderate protein folding is the use of **molecular chaperones**.

These are proteins that assist with the assembly and folding of other proteins, ensuring that molecules such as enzymes are correctly constructed during DNA translation.

QUESTION 10

How does the ubiquitin-proteasome system function?

Ubiquitin and **proteasome** are two other proteins that contribute to the **management** of enzymes and other proteins in the body.

Proteasome is a very **large** protein that functions as a "shredder," breaking up proteins when they are no longer needed, or if they are tagged for disassembly.

Ubiquitin has a few roles in the body, but one is to **tag** proteins that are incorrectly assembled or folded, allowing them to be targeted by proteasome for disassembly.

QUESTION 11

Why are the phases of cellular injury and homeostasis equated?

In **reversible injury**, homeostatic mechanisms are **strained** but not yet overwhelmed. The body is capable of adapting to keep the injured cells alive.

In **irreversible injury**, the cells are pushed to the point where they are permanently killed, either through programmed cell death (**apoptosis**) or "unintentional" cell death (**necrosis**.)

Before we go on, let's cover some definitions related to **cellular adaptation**...

a- (not)

trophé (nourishment)

ATROPHY

"reduction in the **size** or **number** of cells to decrease resource consumption"

hupér (excessive)

trophḗ (nourishment)

HYPERTROPHY

"an increase in the **size** of individual cells"

hupér (excessive)

plásis (formation)

HYPERPLASIA

"an increase in the total **number** of cells"

metá- (succession, change)

plásis (formation)

METAPLASIA

"an adaptive change in which cells **change form** to become another type of cell"

dus- (bad)

plásis (formation)

DYSPLASIA

"an increased number of **abnormal** cells"

(Also called **atypical hyperplasia**—technically **not** adaptive!)

aná (backward)

plásis (formation)

ANAPLASIA

"the **de-differentiation** of dysplastic cells, commonly seen in malignancy"

(**Definitely** not adaptive! Anaplasia serves **no** physiologic purpose!)

QUESTION 12

Compare hyperplasia and hypertrophy.

Hyperplasia and **hypertrophy** both result in an increase in the size of **tissues**.

The important distinction between the two is at the **cellular level**!

Hyperplasia ("over-growth") – **too many** cells, but **normal** cell size

Hypertrophy ("over-nourishment") – **normal number** of cells, but individual cells are **bigger**!

QUESTION 13

Give examples of hyperplasia and hypertrophy.

Physiologic **hyperplasia**:

- Growth of the breasts during pregnancy/puberty
- Thickening of the endometrium during ovulation

Pathologic **hyperplasia**:

- Hepato(spleno)megaly
- Benign prostatic hyperplasia (BPH)

Physiologic **hypertrophy**:

- Muscle growth following exercise

Pathologic **hypertrophy**:

- Left ventricular hypertrophy (LVH)
- Hypertrophic cardiomyopathy (HCM)

QUESTION 14

Describe the cause of atrophy.

Atrophy is a decrease in the **size** or **number** of cells, either due to **disuse** or the inability to **support** their needs.

Cells either die, resulting in fewer cells, or make themselves smaller through **autophagy**.

Caused by a deficit of resources, or by those resources being intentionally "bugdeted" elsewhere.

QUESTION 15

Give some examples of atrophy.

Can be caused by:

- Disuse
- Denervation
- Ischemia
- Nutrient starvation
- Hormonal changes
- Persistent cellular injury

EXAMPLES OF ATROPHY

Disuse: Muscle cells use a LOT of protein and are expensive for the body to maintain

If not in use, protein will be budgeted to more important things, e.g. energy for the brain

EXAMPLES OF ATROPHY

Denervation: Similar concept. Muscles without good nerve control aren't worth maintaining, resources will be budgeted elsewhere instead.

Think paraplegia, carpal tunnel syndrome, etc.

EXAMPLES OF ATROPHY

Ischemia: Every cell in the body needs O_2 for aerobic metabolism. If they don't get enough, growth is impaired and some cells may die.

This can happen anywhere in the body, especially due to poor circulation!

EXAMPLES OF ATROPHY

Nutrient starvation: Cells also need other resources (protein, glucose) for normal function, and can atrophy if there is a systemic deficit of these nutrients.

Caloric malnutrition → **marasmus**

Protein malnutrition → **kwashiorkor**

EXAMPLES OF ATROPHY

Hormonal changes: Many tissues' growth rate signaled by hormones—change in hormone level results in change in tissue growth.

Decreased androgens → muscular atrophy

Decreased estrogen → endometrial atrophy

EXAMPLES OF ATROPHY

Persistent cellular injury: Atrophy can also be caused by direct damage to the cells themselves.

Good example: Duchenne muscular dystrophy (DMD.) Lack of a specific structural protein causes sarcolemma to lose adherence, resulting in damage.

QUESTION 16

How can cells respond to persistent injury?

Generally speaking, **cellular adaptation** can take any of the forms we talked about earlier:

- **atrophy** – **abandon** cells in the injured tissues
- **hypertrophy** – **bulk up** cells to compensate for the injury
- **hyperplasia** – produce **more** cells to compensate for the injury
- **metaplasia** – convert **epithelial cells** to a more resilient type

(Remember that **dysplasia** and **anaplasia** are not considered adaptive.)

QUESTION 17

The lining of the trachea of a smoker changes from ciliated pseudostratified columnar epithelium with goblet cells to stratified squamous epithelium. Why would this be a problem?

The secretions of the respiratory tract normally function to **clean** the airways.

Goblet cells are responsible for **producing** these secretions, which trap any airborne particles in the airways, and the **cilia** work to **move** these secretions up and out of the respiratory tract.

In response to repeated noxious stimuli, such as tobacco smoke, the epithelium of the trachea can **change** to stratified squamous, developing a thick "shield" of many layers of smaller cells.

This new epithelium is more resilient to smoke damage, but **lacks** goblet cells and cilia.

As a result of this change, the respiratory tract becomes **dry**, and any secretions that are produced have no way of being cleared from the airways, often leading to even worse respiratory problems.

QUESTION 18

Is the process described in the previous question reversible? What is it called?

Yes! The cells survive and adapt, meaning that this is a **reversible** injury.

As we mentioned previously, this protective change between two types of epithelial cells is called **metaplasia**.

FYI: This can also happen in the **esophagus** as a result of repeated exposure to stomach acid from **gastroesophageal reflux disease** (GERD.)

The normal **stratified squamous** tissue will change to **simple columnar**—this is referred to as **Barrett's esophagus**.

QUESTION 19

Describe dysplasia.

Dysplasia (atypical hyperplasia) occurs when a **localized mutation** causes particular cells to over-proliferate in an **abnormal pattern**.

Like in **hyperplasia**, there is an abnormally large **number** of cells, but the individual cells are also **abnormal**.

Their shapes and sizes will vary (known as **pleomorphism**,) and their arrangement will be **disorganized**.

Despite the fact that dysplasia is not adaptive, it is considered a **reversible** injury and may sometimes go away on its own.

In other cases, it may progress to **anaplasia**, which is indicative of malignancy. For this reason, dysplasia can be considered "pre-malignant."

QUESTION 20

Cervical dysplasia is commonly seen in human papilloma virus (HPV) infection. What is the cause of this injury?

Viruses, such as HPV, replicate by **injecting their DNA** into a host cell to "trick" it into producing more virions.

These infected cells then begin to **hyperproliferate**, resulting in the production of **even more** infected cells.

The ultimate result is **dysplasia**—the infected cells are both **abnormal** and **excessively numerous**.

QUESTION 21

When adaptation is ineffective, the process that results is known as ___.

Remember the two stages of cellular injury: **reversible** and **irreversible** injury.

In **reversible** injury, the cells are able to adapt and survive depsite the stressor.

In **irreversible** injury, the homeostasis of the cell is overwhelmed and the cell dies, a process known as...

nékrōsis (death)

NECROSIS

"unintentional (non-physiologic) cell death due to external factors"

Technically, irreversible injury may occur in another way—the body **intentionally** killing the injured cells.

For example, a cell infected by a virus may "choose" to explode to prevent the virus from proliferating.

This process may originate within the cell or from outside, and is known as...

apó (away from)

ptôsis (falling)

APOPTOSIS

"programmed (intentional) cell death"

QUESTION 22

Describe the different types of necrosis.

Six basic types of necrosis:

- Coagulative
- Liquefactive
- Caseous (a type of coagulative necrosis)
- Gangrenous (a type of coagulative necrosis)
- Fat (a type of liquefactive necrosis)
- Fibrinoid (immune-mediated; not covered in this course)

Coagulative necrosis: Most common type, occurring in many tissues as a result of ischemia. Cells die, but the tissues maintain their original structure.

Liquefactive necrosis: After cell death, enzymes liquefy the dead cells resulting in a viscous liquid abcess.

Occurs primarily in the **brain** but can also occur in the **lungs** as well.

Caseous necrosis: Literally means "cheese-like". Most commonly associated with tuberculosis and found at the center of granulomas.

Gangrenous necrosis: Caused by infection or ischemia, most commonly in the hands and feet. Most common cause is poor peripheral blood supply.

Fat necrosis: Occurs after the death of adipose tissue, most commonly in the breast and around the pancreas. Enzymes break down extracellular fat, resulting in "soapy" accumulation.

QUESTION 23

In which tissues do each type of necrosis commonly occur?

Coagulative necrosis can occur essentially anywhere in the body (for example, necrosis of the heart can occur after a prolonged **myocardial infarction**.)

Gangrenous necrosis tends to occur in the extremities due to impaired perpipheral circulation (diabetes, frostbite, etc.)

General **liquefactive** necrosis occurs most commonly in the **brain**.

Caseous necrosis is often seen in the **lungs** of TB patients.

Fat necrosis occurs where there are significant amounts of adipose tissue, such as in the **breasts** and around the **pancreas**.

QUESTION 24

What causes the difference in presentation seen in wet vs. dry gangrene?

The primary difference between wet and dry gangrene is the presence of **infection**. Dry gangrene represents tissue that is dead, but uninfected.

Wet gangrene can occur **spontaneously**, or as a **progression** of dry gangrene when an infection develops.

Don't get **wet** gangrene confused with **liquefactive** necrosis. All gangrene is **coagulative** necrosis!

QUESTION 25

Why would reperfusion of tissues lead to cellular injury?

Reperfusion (the sudden **restoration** of blood flow to previously unperfused tissues) can actually be harmful!

The sudden rush of **white blood cells** into the area can trigger inflammation, and the return of oxygen supply can lead to the creation of free radicals that cause **oxidative stress**.

This can be a concern any time there is a transient period of poor perfusion to an area: **myocardial infarction** (heart attack,) **ischemic stroke**, or after an **organ transplant**.

QUESTION 26

Why would hypoxia of tissues lead to cellular injury? How would this lead to hydropic swelling?

Every cell in the body needs a **consistent supply** of oxygen in order to fuel cellular metabolism!

Remember that the Na^+/K^+ exchange pump is an **active** process which requires the expenditure of **ATP**.

Insufficient oxygen supply leads to **decreased** ATP production, which can slow down the Na^+/K^+ pump and lead to hydropic degeneration.

QUESTION 27

Name some physical agents that cause cellular injury.

Three categories of agents capable of causing injury to cells are **chemical agents**, **physical factors**, and **radiation**.

QUESTION 28

Give examples of some of these agents and how they harm tissues.

Chemical agents – Lots of these! Cyanide, arsenic, asbestos, etc.

Physical factors – heat, cold, acidity, etc.

Radiation – sunburn/radiation burns, cancer, etc.

QUESTION 29

How is aging distinct from disease?

Aging is a **normal physiologic process**, distinct from any particular pathology.

Whereas disease represents some **imbalance** or **external stressor**, aging occurs gradually along with the body's normal physiologic functions.

QUESTION 30

How are the changes observed in aging described?

Aging is characterized by a decrease in **functional reserve** and a reduced ability to **adapt to environmental demands**.

Essentially, as we age, our internal homeostasis becomes more of a **fragile balance** and our bodies are no longer as **resilient** to injury and disease.