Module II: Cells and Tissues: Injury and Repair

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The body has many complex systems that help maintain health and well-being. Malfunction of any component can result in disease.

At sufficient doses, toxic agents, also known as toxicants, can damage cells, tissues, organs, or organ systems so that these cannot function properly, thus leading to sickness or death (for example, liver or kidney failure) of the organism.

Typically, the toxicant exerts its harmful effect (adverse effect) directly on specific cells or their chemical constituents, or on biochemical pathways within the affected organ. These cellular and chemical changes in turn cause the tissue or organ to malfunction. Sometimes the tissue or organ can repair itself. In other cases, structure and function are affected to a greater or lesser extent.

Before exploring toxicology principles in depth, a basic understanding of the unit of life, the cell, is helpful. In Part B of this module, the basic components of cells will be reviewed. Cells of a similar type make up a tissue, and one or more tissues can form an organ, a structure that carries out a specific function. Toxic effects may disrupt the normal functioning of cells, as well as tissues and organs.

Parts C and D will review ways in which cells and tissues might be affected by toxicants and how these structures and biochemical pathways would respond. The following pages will introduce a few of the general concepts more fully discussed in Parts B-D.

Certain toxicants may affect only a specific type of cell or biochemical reaction. For example:

- The toxicity of carbon monoxide specifically targets the red blood cell where it binds to the hemoglobin molecule and displaces oxygen in the process.
- Carbon monoxide has a greater affinity for hemoglobin than does oxygen and binds nearly irreversibly to it. This prevents the red blood cells from delivering life-sustaining oxygen to the cells and tissues.

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Terms in bold are defined in the IUPAC Glossary of Terms used in Toxicology found at http://sis.nlm.nih.gov/enviro/iupacglossary/frontmatter.html
Components of the body subjected to toxic effects are often referred to as target tissues, target organs, or generically as target sites. Nervous tissue, for example, is a target site for pesticides.

The target site affected by a given chemical may change depending on the amount (dosage, see dose) of toxicant present or the duration (i.e., length of time) of the exposure.

For example, acute (or short-term) exposure to a chemical, such as ethanol which is present in alcoholic beverages, may affect the central nervous system. Chronic (long-term) exposure, such as long term drinking, may result in further injury to the liver.

Toxicity can result from adverse effects on cells, chemical constituents of cells (macromolecules) such as proteins or DNA, or biochemical pathways. Examples are:

- Formation of fibrous connective tissue (i.e., fibrosis or scarring) within organs
- Modifying an essential biochemical activity or physiological function
  - Certain pesticides disrupt the biochemical activities of neurons, thus interfering with the transmission of signal between them
  - Tetanus toxin causes a breakdown in communication between nerve endings and muscles, resulting in the muscle spasms and paralysis of lockjaw
  - Chemicals can damage an enzyme system such as that regulating protein synthesis

Some toxicants may also exert their effects by:

- Breaking down into chemicals that damage cellular components
  - Examples: hydrogen peroxide, free radicals
- Directly damaging DNA
  - Examples: ultraviolet radiation, nitrosamines, anticancer agents like doxorubicin
• Interfering with nutrition
  o Example: aluminum hydroxide, which is a constituent of some antacids, can bind to phosphorus in food, thus preventing phosphorus absorption and use by bones. Over time, this could result in phosphorus depletion. Mild phosphorus depletion causes weakness in muscles and bones. Serious cases can cause osteomalacia (softening of the bones) and severe pain in walking.

Part B. Cells, Tissues, and Organs

Objectives

Upon successful completion of this part of Module II you will be able to:
• Define what a cell is
• Name some ways that cells are categorized
• Name the basic parts of the cell and explain their functions
• Describe five important types of molecules in cells and their functions
• List the four tissue types
• Define what an organ is
• Provide examples of how toxicants affect cells and tissues

What is a Cell?

Part B of Module II will focus on animal, especially human, cells. These fall into the broader category of eukaryotic cells (as distinct from the more primitive prokaryotic cells). The cell is the smallest living unit of the body. The human body is made up of several trillion cells.

Each cell performs specialized functions and works in concert with other cells to promote the health and vitality of the organism, thus playing a role in the maintenance of homeostasis.

Homeostasis is the ability of the body to maintain relative stability and a steady state, and continue to function, even though disturbances occur in the external environment or in a portion of the body. While each cell is an independent entity, and is subject to its own internal homeostasis, it is also affected by the environment around it.

The body contains approximately 200 types of cells, differing greatly in size, appearance, and function. Like types of cells cluster together and work in concert as tissues performing specific functions. The neuron, or nerve cell, for example, is a component of nervous tissue.
Groups of tissues with a specific function form an organ, such as the heart or stomach. For example, the heart contains muscle and connective tissues. Cell structure varies according to function.

Cells vary greatly in size. Although all cells are small, ova (eggs), for example, are quite large in comparison to sperm.

Cells can be classified in a variety of ways. Shape is a distinguishing feature. Some cells are cube-shaped, including ones in the skin and intestine, and others are rectangular or flat, also found in the skin and intestines. Others are more disc shaped (blood cells) or irregularly shaped (nerve cells).

Cells also are classified by the type of tissue they form, such as nerve cells or heart muscle cells.

Another way to characterize cells is by whether they are germ-line cells (that is, ova and sperm) or somatic cells (the non-reproductive cells of the body). The effects a toxic agent may have on a germ-line cell can differ from those observed in a somatic cell.

Germ-line cells are involved in the reproductive process. Male germ-line cells give rise to sperm and female germ-line cells develop into ova (ova is plural, ovum is singular). When an egg and sperm unite, a new organism can result. A germ-line cell has only a single set of chromosomes (23 in human germ-line cells) derived from its specific parent.
Toxic effects on germ-line cells may result in injury to the developing embryo or fetus, such as lack of implantation or spontaneous abortion, or to birth defects.

Somatic cells are all the cells in the body except the reproductive germ-line cells. Although they vary in shape and function, each human somatic cell has two sets (or pairs) of chromosomes (46 total in human somatic cells). Toxicity to somatic cells may result in various toxic effects, ranging from mild (dermatitis) to serious (cancer, death).

Parts of a Cell

Despite their differences, all cells (except the cells of simpler prokaryotic organisms like bacteria) have many common features including:

- **Cell membrane** – the structure that encloses the contents of the cell.
- **Cytoplasm** – the cell matrix containing organelles and other cell contents.
- **Organelles** – small structures that carry out various functions within the cell. Cells of humans (with the exception of the mature red blood cell) and other eukaryotic organisms contain a nucleus.

Toxicants can injure any of the components of the cell, causing cell damage, malfunction, or death.

While toxicants have the potential to affect all components of a cell, the sites typically targeted are the cell membrane and organelles such as the nucleus, ribosomes, peroxisomes, lysosomes, and mitochondria. These primary components of a typical cell will be described next, with examples of what might happen when they become targets of toxicity.

Parts of a Cell: Cell Membrane

Cell membrane – Containing cholesterol and protein, this structure consists of two layers of phospholipids and is thus referred to as a phospholipid bilayer. Phospholipids are fatty organic compounds with two or more phosphate groups attached.
Functions:
- Provides structural support
- Precisely controls the movement of substances into and out of the cell to maintain homeostasis

Toxicants that cause membrane damage lead to changes in permeability (the extent to which substances can migrate into and out of cells) and structural integrity of the cell.

Alterations in either structural integrity or permeability may directly cause cell death. These may also cause changes in cell function or render the cell more susceptible to the entry of other toxicants, causing a breakdown in cellular homeostasis. If too many cells are out of balance the tissue or organ will not function normally.

For example, ethanol can interact with cell membranes in the brain. Cellular changes cause the drinker to suffer from incoordination and other adverse effects.

*Parts of a Cell: Nucleus*

Nucleus – This membrane-encapsulated structure contains various materials but most importantly the genetic material of the cell. The genetic material is contained in structures called chromosomes, which consist of deoxyribonucleic acids (DNA) and proteins including histones. Genes are sections of DNA; differences in genes make each of us unique.

The nucleus controls overall cellular activity, such as protein synthesis and storage and processing of genetic information in cooperation with ribonucleic acid (RNA).

RNA (ribonucleic acid) is a version of the genetic information which is able to move from the nucleus into the cytoplasm. While both DNA and RNA are nucleic acids, DNA is a double stranded helix, while RNA is single stranded. Both molecules twist into three dimensional shapes. There are additional relevant chemical differences between the two. DNA provides the template to make RNA. There are several types of RNA; some have complex twisted shapes that are related to function. One type of RNA provides the template to make proteins, another assists in the assembly of the subunits that make up the proteins, and others regulate processes within the cell.
Mustard gas (also known as sulfur mustard) is an example of a toxicant that can cause damage to the nucleus.

This agent has been used in chemical warfare. In addition to nuclear damage, exposure can affect tissues such as the skin, eyes, and respiratory tract. Blisters often develop. In World War I, although deaths were infrequent, many victims suffered serious and irreversible damage, including blindness and chronic respiratory disorders.

Survivors of exposure can develop cancer from DNA changes caused by mustard gas. Mustard gas very strongly cross-links (covalently binds) to DNA, RNA, proteins, and components of cell membranes. This binding can ultimately result in disruption of cellular functions, causing gene coding errors, DNA strand breaks, low fidelity DNA repair, inhibition of DNA replication and translation, and slowing down of cell division.

Similar binding with RNA molecules can result in altered function, blocking of protein synthesis, and cell death. Binding to critical proteins and enzymes leads to altered metabolism and general breakdown of the vital functions of the cell.

Members of the nitrosamine group of chemicals can also be toxic to cell nuclei, and exposure may result in genetic alternations and, sometimes, cancer. We can be exposed to nitrosamines environmentally via tobacco smoke, air pollution, and auto exhaust, for example.

Nitrosamines can also be produced in a variety of foods, including meats which undergo curing and cooking. Ironically, this happens when nitrates or nitrites are added to them as preservatives to extend shelf life and inhibit microbial growth.

*Parts of the Cell: Ribosomes*

Ribosomes – These are very small structures in the cell cytoplasm involved with protein manufacturing. They are made up of RNA and proteins.

RNA makes proteins via a two step process, transcription and translation. In the nucleus, the gene sequence is copied into messenger RNA (mRNA), in what is known as the transcription process. Translation occurs in the ribosome. There the mRNA is used as a template and transfer RNA (tRNA) brings amino acids to assemble along the template to build proteins.

More about RNA follows in the section on nucleic acids.

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Cells differ in the type of proteins that they manufacture with the assistance of ribosomes. For example, liver cells manufacture blood plasma proteins such as fibrinogen and albumin. In fat cells, ribosomes are involved in the production of triglycerides.

Structural elements such as membranes are found inside the cytoplasm of the cell to compartmentalize processes and assist with transport of cellular materials. Some membranes have ribosomes attached. These have a bumpy appearance and are known as rough endoplasmic reticulum (rough ER). The presence of ribosomes is an indication that rough ER plays a role in protein synthesis. Ribosomes are also scattered throughout the cytoplasm.

A second type of membrane is smooth endoplasmic reticulum (smooth ER), which lacks ribosomes. Functions of smooth ER include activities related to carbohydrate and lipid synthesis. In the liver, smooth ER produces enzymes which help in the detoxification of certain chemicals.

Toxicants can affect structures inside the cell or processes in the cell. Direct action of toxicants which change rough ER and smooth ER will interfere with cell function. If toxic agents damage ribosomes or nucleic acids (DNA and RNA), protein synthesis will be disrupted, and damage can cascade through the organism.

For example, damage to liver cell ribosomes may result in a decrease in production of the protein albumin, which is found in the blood. Reduction in albumin impairs transport of drugs and other molecules that bind to albumin. It may also interfere with acid-base balance and coagulation, among other possible effects.

Toxicants can be used to help us better understand cell function. Ethyl methanesulfonate, for example, a chemical that transfers groups of atoms from one part of a molecule to another, is used to study biomolecular processes.

Parts of a Cell: Lysosomes

Lysosomes – These are membrane-bound organelles which are vesicles containing powerful digestive enzymes that normally defend against disease. They can break down bacteria or damaged cellular organelles.

When lysosomes are damaged by xenobiotics or other agents, their digestive enzymes can be released into the cytoplasm where they can rapidly destroy cellular constituents, a process known as autolysis.
Parts of a Cell: Peroxisomes

Peroxisomes - These are smaller vesicles than lysosomes. They contain a large variety of metabolic enzymes, including some that oxidize lipids such as fatty acids.

Peroxisomes may destroy toxicants such as hydrogen peroxide (H2O2) and alcohol. Liver cells contain numerous peroxisomes that remove and neutralize toxicants absorbed from the intestinal tract.

Some xenobiotics can stimulate liver and other cells to increase the number and activity of their peroxisomes, which in turn can stimulate the cell to divide. These xenobiotics are known as peroxisome proliferators, and have a role in liver cancer in some species.

For example, Clofibrate, a cholesterol-lowering drug, has been shown to induce an increase in peroxisome proliferation in rodents.

Parts of a Cell: Mitochondria

Mitochondria – These bean-shaped organelles have a double membrane with inner folds enclosing important metabolic enzymes. Each mitochondrion provides the energy that cells require for survival.

The energy production process involves the synthesis of the molecule ATP (adenosine triphosphate). ATP stores and transports the energy we need to carry out vital functions, such as muscle contractions and transmission of nerve messages. If a xenobiotic interferes substantially with the energy production process, the cell will rapidly die.

Chemicals which interfere with mitochondrial function include:

- Cyanide
- Hydrogen sulfide
- Cocaine
- Organochlorine pesticides such as DDT
- Carbon tetrachloride
- Drugs such as acetaminophen, doxorubicin (adriamycin), cocaine
- Toxic metals such as mercury
**Parts of the Cell: Summary**

In summary, important organelles that can be affected by xenobiotics include:

- Cell membranes
- Nuclei
- Ribosomes
- Endoplasmic reticulum
- Lysosomes
- Peroxisomes
- Mitochondria

**Cellular Compounds**

Now that we have reviewed the structure of a cell, we will learn about the different types of chemicals within a cell.

A foreign chemical (an exogenous substance) or physical agent may interfere with or damage biochemicals normally present in the body (endogenous chemicals). This type of interaction results in the body chemical being unable to carry out its function in maintaining homeostasis.

Homeostasis can be disrupted in several ways. For example:

- interference with absorption or disposition of an essential nutrient
- interference with nerve transmission
- damage to components of a cell organelle which prevents it from functioning

The following contains a brief description of important cellular chemicals and how toxic agents can affect them.

There are five types of organic chemical compounds found in the cell. Organic chemicals, by definition, contain carbon atoms attached to hydrogen atoms, sometimes with other elements. Usually, they are covalently bonded (i.e., they share electrons). The science of biochemistry is largely concerned with the structure and function of these carbon-based compounds and the chemical and biological processes in which they are involved.
These five types (with examples of each) are:

- Carbohydrates (glucose, glycogen)
- Lipids (high density lipoproteins (HDL), low density lipoproteins (LDL), and cholesterol)
- Proteins (enzymes, structural components)
- Nucleic Acids (DNA, RNA)
- Energy molecules (ATP)

Each of these compounds is made up of specific molecular building blocks.

Cellular Compounds: Carbohydrates

Many carbohydrates play a key role in providing ready energy to cells. The characteristic atoms in carbohydrates include carbon, hydrogen, and oxygen. Types include sugars, starches, and cellulose. Plants produce sugars through photosynthesis. Sugars are stored in plants as starches, more complex assemblages of the basic sugar units. Other carbohydrates provide structure. Cellulose is a specific combination of sugars which makes a strong material found in structural components of plant cells.
Animals derive energy from consumed sugars and starches. Digestive processes release energy from the many bonds of these compounds. In animals, the sugars not used immediately for energy are stored as glycogen in the liver and in muscles. The processes responsible for the formation, breakdown, and conversion of one type of carbohydrate into another are known as carbohydrate metabolism.

Trichloroethylene (TCE) is an industrial solvent. It is an example of a chemical which can alter carbohydrate metabolism. TCE increases the storage of glucose as glycogen in the liver. As glycogen storage in the liver reaches its limit, glucose may then be converted to fatty acids. In addition, this interruption of normal glucose metabolism can affect insulin signaling, which is essential for regulation of blood sugar levels.

**Cellular Compounds: Lipids**

Lipids are essential substances of all cells. They serve as a major energy reserve and also are important structural components of cells. Lipids are generally soluble in solvents such as acetone and benzene, but not in water. Lipids include fatty acids, fats and oils, phospholipids, and steroids; each has a characteristic chemical nature.

Cholesterol is an example of a lipid. It is a component of cell membranes and is utilized in the production of steroids, such as the sex hormones testosterone and estrogen. Phospholipids serve as the main components of the phospholipid bilayer cell membrane discussed previously.

Because lipids are an integral part of cell membranes, toxicant-induced damage of lipids will affect the integrity of the cell.

Carbon tetrachloride is a solvent and an example of a toxicant that can cause lipid damage. Within cells, especially those in the liver and kidney, carbon tetrachloride is metabolized or converted into a more reactive form. This more reactive form can extract electrons from the lipids that make up cell membranes and release free radicals, atoms with unpaired electrons. This process, often called lipid peroxidation, can be very damaging to membranes as the free radicals are unstable and highly reactive. Such damage affects the functioning of the cell membrane and other membrane-bound structures like the endoplasmic reticulum and mitochondria. Damage to individual cells can affect the entire organ, such as the liver or kidney, and extend to the system level, for example, affecting the nervous system.
Safety decisions are based on understanding of toxicology. Carbon tetrachloride was once widely used in fire extinguishers, cleaning products, and pesticides. Due to its potential toxicity, other chemicals are now used instead. Other solvents, such as auto antifreeze, rubbing alcohol, and halogenated anesthetic, also affect lipids in cells.

**Cellular Compounds: Proteins**

Proteins are the most diverse and abundant group of organic compounds in the body. There may be over 100,000 human proteins, accounting for some 20% of body weight.

There are 20 kinds of amino acids, the building blocks of proteins. Each contains carbon, hydrogen, oxygen, nitrogen, and sometimes sulfur. Most protein molecules are large polypeptides consisting of 50-1000 amino acids bonded together in a very precise 3-dimensional structural arrangement. Even the slightest change in the structure of the protein molecule can alter its function.

Proteins perform many important functions. Some proteins are primarily structural, such as the protein pores in cell membranes, keratin in skin and hair, collagen in ligaments and tendons, and myosin in muscles. However, other proteins such as hemoglobin and albumin have important other functions including transporting oxygen, nutrients, and other biochemicals in the blood. Antibodies and nonsteroidal hormones are also proteins.

A particularly important group of proteins are the enzymes. Enzymes are catalysts that accelerate chemical reactions without themselves being permanently changed. Enzymes tend to be quite specific and any given enzyme typically catalyzes only one type of reaction. Enzymes participate in reactions by binding to specific molecules called substrates. Enzyme denaturation (change in shape) and enzyme inhibition are examples of toxic effects which xenobiotics can cause.

Ions of metals such as cadmium, mercury, and lead have been shown to cause toxicity by inhibiting the action of enzymes. These ions block important functional groups on the enzyme, altering its shape and ability to catalyze chemical reactions.

**Cellular Compounds: Nucleic Acids**

Nucleic acids are large organic compounds that store and process information at the molecular level inside virtually all body cells. The two main types of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).
DNA and RNA are very large molecules composed of smaller nucleotides. A nucleotide consists of a pentose (containing 5 carbon atoms) sugar, a phosphate group, and one nitrogenous base. The sugar in DNA is deoxyribose, while the bases are Adenine, Guanine, Cytosine and Thymine, often labeled as A, G, C, and T respectively. RNA, on the other hand, consists of the sugar ribose and the four bases Adenine, Guanine, Cytosine and Uracil.

**DNA and RNA**

DNA exists as two strands shaped like a double helix held together by bonds between hydrogen atoms on the adjacent strands. RNA is a single strand.

DNA and RNA are very important biological molecules. Because of their unique structure, cells can divide accurately and pass along genetic information. DNA and RNA are composed of specifically arranged bases connected with sugar phosphates.

DNA, located within the cell nucleus and in the mitochondria in eukaryotes, is packaged into units known as chromosomes. Sections of DNA containing the bases A, T, C, and G, make up genes. The genes are the hereditary units that give instructions for making and operating all parts of our bodies.

Genes direct the highly regulated process of protein synthesis. This begins with copies of sections of the DNA being made via a mechanism known as transcription. The copies are referred to as messenger RNA (mRNA). The transcribed molecules move into the cytoplasm of cells where ribosomes translate the coded sequence of bases to systematically produce a protein.

Chromosomes contain the genetic material that provides instructions for cell activities such as making of proteins.

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Some substances can damage DNA and result in cell death. Other possible outcomes of such damage are cancer, birth defects, and hereditary changes in offspring.

Tobacco contains substances known to damage DNA. Components of tobacco smoke can bond with nucleotides, altering the configuration of the DNA molecule. This may lead to genetic mutations and initiate the carcinogenesis process. Ionizing radiation can also alter DNA.

Damage to RNA causes impaired protein synthesis, and is responsible for many types of diseases. Ultraviolet light, which damages DNA and can contribute to skin cancer, has also been shown to alter normal functioning of RNA.

*Cellular Compounds: Energy Molecules*

ATP, an important nucleotide, is involved in the storage and release of cellular energy at the molecular level.

ATP stores and transports the energy we need to carry out vital functions, such as muscle contractions and transmission of nerve messages.

In eukaryotic cells, ATP is synthesized aerobically in the mitochondria and anaerobically in the cytoplasm by a process called glycolysis.

ATP is formed from adenosine diphosphate (ADP) when a large amount of energy is used to add a third phosphate group.

This energy is released for processes in the cell by the breaking of the bond connecting the third phosphate group.

Pentachlorophenol is a chemical used in pesticides and as a disinfectant that interferes with ATP synthesis.

*Tissues and Organs*

The beginning of Part B featured various types of cells, the basic parts of a cell, and the molecules involved with cellular function. Now we look at how cells combine. Cells of a particular type are organized into tissues. These cells work together to carry out specific activities of the body. Animal cells are arranged into four main tissue types.
Tissues of different types combine together to form organs, such as the liver or kidney. We have already seen that toxic agents can affect the cell, which in turn can result in damage to tissues and organs. The remaining sections of Part B of this module will explore how cells, tissues, and organs respond to toxicity.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Description</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>line inner and outer surfaces</td>
<td>based on shape (squamous, cuboidal, columnar) and number of layers (simple, stratified, pseudostratified)</td>
</tr>
<tr>
<td>Connective</td>
<td>provide structure and connection; characterized by noncellular matrix outside the cells</td>
<td>loose, dense, fibrous, cartilage, bone, blood, adipose</td>
</tr>
<tr>
<td>Nervous</td>
<td>coordinate receipt of and response to stimuli</td>
<td>neurons, glial cells</td>
</tr>
<tr>
<td>Muscle</td>
<td>movement is a consequence of contraction of these cells results in movement</td>
<td>smooth, striated, cardiac</td>
</tr>
</tbody>
</table>

Many toxicants can be stored in the body. For example, TCDD and DDT are stored in fat. Other common storage sites are organs such as the liver, kidney, and bone. Blood is the main avenue of distribution for toxicants, while the lymph also plays a role in their transport.

The distribution of toxicants and toxic metabolites throughout the body ultimately determines the sites where toxicity occurs. A major determinant of toxicity is lipid solubility, since a lipid-soluble toxicant readily penetrates lipid-containing cell membranes.

Most toxicants cause effects specific to particular tissues (such as connective tissue) or organs, which are thus referred to as the target tissues or target organs, respectively, or generically as target sites.

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Some toxicants affect processes specific to a tissue type. For example, the highly specific effect of organophosphate pesticides is to inhibit a cholinesterase enzyme (acetylcholinesterase) that is responsible for affecting transmission of impulses at nerve endings. Normally, acetylcholinesterase acts to break down the neurotransmitter acetylcholine, so as to reduce the level of transmission at nerve endings.

Communication between two neurons begins when an electrical impulse called an action potential travels along the axon of a presynaptic neuron toward the axon terminal. The action potential cannot cross the synaptic space. When it reaches the axon terminal, it causes membranous sacs, called vesicles, to move toward the membrane of the axon terminal.

The membrane of the vesicle fuses with the membrane of the axon terminal, enabling the vesicle to release its contents into the synaptic space. The molecules released from the vesicles are chemicals called neurotransmitters. They drift across the synaptic space and bind to special proteins called receptors on the postsynaptic neuron. The binding of a neurotransmitter to its receptor can trigger an action potential in the postsynaptic neuron. That electrical signal then moves toward the cell body of the postsynaptic neuron.

Now that the neurotransmitter has relayed its message, it releases from the receptor into the synaptic space. Some of the neurotransmitter is degraded by enzymes in the synaptic space, and some of the neurotransmitter is carried back into the presynaptic neuron through transporter proteins. The neurotransmitter that is taken back up into the presynaptic neuron is then repackaged into vesicles that can be released the next time an action potential reaches the axon terminal. The entire process repeats each time an action potential reaches the axon terminal of the presynaptic neuron.

However, with the organophosphate pesticides acting as a cholinesterase inhibitor, there is an overabundance of the neurotransmitter and thus, over-stimulation of nerve endings.

The drug cocaine also acts to over-stimulate transmission at nerve endings, but through a different mechanism. Typically, the degree of transmission is regulated by the amount of neurotransmitters in the synapse between the transmitting and receiving neurons. The amount of neurotransmitters in the synapse is regulated in part by transport or reuptake of the neurotransmitters back into the transmitting neuron.
However, cocaine acts to block this reuptake mechanism, thus increasing the levels of neurotransmitter in the synapse, and by extension, the degree of transmission at the nerve ending.

Target sites affected by exposure to a given chemical may be different depending upon dosage. Thus, alcohol (specifically ethanol in alcoholic beverages), targets the nervous system after acute (short-term) exposure, but additionally targets the liver after chronic (long-term) exposure.

**Summary**

In exploring toxicology, understanding the basics of the cell is important.

The cell contains many critical structures (such as cell and organelle membranes) and undergoes processes (energy generation, protein production, DNA replication, cell division) that are necessary for normal function and survival. There are five types of organic compounds that make up and carry out functions for the cell; these are carbohydrates, lipids, proteins, nucleic acids, and energy compounds.

Cells are organized into tissue types (epithelial, connective, muscle, nervous). Tissues combine into organs, structures such as the heart, liver, and kidney, which carry out a particular function.

Any compound that disrupts cellular structures or processes may cause dysfunction of the cell, which in turn can lead to cytotoxicity and more generalized damage to tissues and organs.

**Part C. Principles of Cell Damage and Tissue Repair**

**Objectives**

Upon successful completion of Part C you will be able to:

- Identify and discuss the major outcomes of cellular toxicity
- Identify and discuss physiological and pathological changes in response to toxic agents
- Identify and discuss two types of reversible cell damage: cellular swelling and fatty change
- Describe apoptosis and necrosis and their significance
- Identify and discuss the two mechanisms of tissue repair: regeneration and replacement
Introduction

The body is a remarkable, complex living machine consisting of trillions of cells and multitudes of chemical reactions. The number and types of possible toxic responses of cells and tissues are likewise very large.

The following diagram summarizes the types of toxic damage to cells and how this damage can affect tissues and organs. The general principles relating to cellular responses to toxic agents will be discussed in this section of Module II and these principles will be applied to specific types of damage in the last part of the Module.

As shown in the diagram above, possible outcomes of cellular toxicity include:

- Complete repair of the tissue and return to normal functioning
- Incomplete repair of the tissue, with maintenance of sustained function at a reduced capacity
- Complete loss or sufficient irreparable loss of a tissue or organ, which may lead to the death of the organism or the need for medical treatment. Examples of restoring health despite such loss include:
  - After the death or loss of function of cells in the pancreas, medical administration of insulin may restore health by compensating for the insulin that would have been produced by the dysfunctional cells.
  - Sometimes an organ can be replaced by transplantation.

Another possible effect is the induction of a neoplasm (i.e., cancer). This might be medically cured or managed or result in the death of the organism.
Physiological and Pathological Changes

Cells and tissues adapt in order to maintain homeostasis in the face of environmental challenges such as exposure to toxic agents.

Such adaptation and the specific responses may be beneficial (physiological) or detrimental (pathological) to health.

Examples of beneficial or physiological cellular adaptations include increases in the

- Size of individual skeletal muscle cells in athletes due to exercise
- Number and size of milk-secreting cells in breasts of women during pregnancy in response to hormone stimulation
- Amounts of enzymes in liver cells which are used to detoxify certain chemicals or poisons

There are times when, ironically, the response or adaptation to a toxicant is detrimental to the health of the individual. The body naturally attempts to adapt by repairing or replacing the affected cells or limiting the harmful effects. However, when these changes result in cells or organs that cannot function normally, the adaptation is referred to as pathological.

For example, pathological changes can result from excessive exposure to substances such as cigarette smoke and alcoholic beverages.

- Cigarette smoke, which contains many chemicals, produces changes in lung cells, called squamous metaplasia.
- Excessive consumption of alcoholic beverages may result in cirrhosis of the liver.

The extent of the pathological damage will determine whether the changes become life-threatening.

Reversible Cell Damage

The pathological response of cells to toxic injury may be transient and reversible once the stress has been removed or the compensatory cellular changes made. In some cases the full function of the damaged cells returns.

In other cases, some degree of diminished cellular or tissue capacity may persist.

Two commonly encountered reversible cell changes associated with toxic exposures are cellular swelling and fatty change.

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Cellular swelling is associated with hypertrophy (enlargement). It can be caused by electrolyte imbalances or cellular hypoxia (low oxygen levels), which damages the sodium-potassium membrane pump. The sodium-potassium pump keeps a balance of chemicals inside and outside the cells. Damage to it alters intracellular electrolyte balance, resulting in an influx of fluids into the cell, causing it to swell. Cellular swelling may be reversed if the cause is eliminated.

Epithelial cells of the kidney line tube-like structures called the renal tubules. Toxicants such as diethylene glycol, a solvent that has historically adulterated pharmaceutical and personal care products, can injure these cells and disrupt kidney function.

Fatty change is more serious and occurs with severe cellular injury. In this situation, the cell becomes damaged and is unable to adequately metabolize fat. The result is that small vacuoles (droplets) of fat accumulate and become dispersed within the cytoplasm. While fatty change can occur in several organs, it is usually observed in the liver as most fat is synthesized and metabolized in liver cells. Fatty change can be reversed but it is a much slower process than the reversal of cellular swelling.

Fatty change in the liver is commonly associated with chronic excess alcohol consumption. Alcoholic fatty liver is a clinical condition characterized by an accumulation of lipids in and around the hepatocytes of the liver. The metabolism of ethanol in the liver produces acetaldehyde which results in the production of more lipids than usual. At the same time, less lipids are used by the mitochondria of the hepatocytes. Thus, an excess production of lipids combined with a decrease in their use result in an abnormally high concentration within the liver.
**Lethal Cell Damage**

In some situations, the damage to a cell may be so severe that the cell cannot survive. There are multiple pathways to cell death, and toxicologists use various terms to describe the different processes. Two pathways most widely studied in toxicology are necrosis and apoptosis. Necrosis involves cell swelling and membrane damage. Apoptosis is a type of naturally occurring cell death that is programmed into cell processes, and during which the cell membrane remains intact.

Necrosis involves a progressive failure of essential metabolic and structural cell components, usually in the cytoplasm, causing cell death in tissues. This generally involves a group of adjacent cells or occurs at the tissue level. Such progressive deterioration in structure and function rapidly leads to cell death or necrotic cells. The presence of dead tissues or cells in a living organism is also referred to as necrosis.

Cell necrosis begins with a reduction in protein production, changes in electrolyte gradient, or loss of membrane integrity (especially increased membrane permeability). Some cytoplasmic organelles, such as the mitochondria and endoplasmic reticulum, swell, while others, especially ribosomes, disappear.

This early phase progresses to fluid accumulation in the cells. Fluid accumulation makes the stained cells appear pale. Pathologists call this cloudy swelling or hydropic degeneration.

An example of necrosis is the damage to the liver that can result from large doses of acetaminophen, a frequently used over-the-counter pain medication. Poisoning from acetaminophen is common and the most frequent cause of acute liver failure in the United States.

The top portion of this image shows healthy liver cells unaffected by acetaminophen (arrow A). These cells stain purple because of their glycogen content. Glycogen is a form of carbohydrate storage in animals that is synthesized from glucose and stored mainly in the liver.

In the final stages of necrotic cell death the nucleus becomes shrunken or fragmented. Total cell breakdown, called lysis, then occurs.

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The second form of lethal cell damage, known as apoptosis, is a type of programmed cell death. It is a process of self-destruction of the cell nucleus and the death of single cells. The dying cells are not adjacent but are scattered throughout a tissue.

Apoptosis is a normal process in cell turnover, as cells have a finite lifespan. During embryonic development, certain cells are programmed to die and are not replaced (such as the cells in the webbing between each developing finger). If this process is interrupted and the programmed cells do not die, the fetus ends up with incomplete fingers or fingers joined together in a webbed fashion. However, apoptosis (or its inhibition) can also be the result of a toxic insult.

During apoptosis, the cells shrink from a decrease of the fluid of the cytoplasm and nucleus. Other than the nucleus, the organelles appear normal during apoptosis. The cell disintegrates into fragments referred to as apoptotic bodies, each containing a range of intact organelles. These apoptotic bodies are readily phagocytosed (engulfed) by the adjacent cells and local macrophages (white blood cells that take in cell debris). Unlike during necrosis, this occurs without the initiation of an inflammatory response (see inflammation). The deleted cells just appear to fade away.

Earlier, acetaminophen overdose and its ability to induce necrosis in hepatocytes of the liver was discussed. However, both apoptosis and necrosis can be observed in liver hepatocytes after acetaminophen overdose.
Some toxicants can induce apoptosis, while others inhibit the process. Also, apoptosis depends on the energy production of the cell and the availability of the energy molecule adenosine triphosphate (ATP). Some toxicants can induce apoptosis at low concentrations. However, at higher concentrations, when insufficient ATP is present to fuel the normal apoptotic processes, cell death may occur by necrosis. Apoptotic cell death usually results in cell proliferation, whereas necrosis of a tissue leads to inflammation and even more tissue injury.

Cyclosporine A is a drug sometimes used to suppress the immune system to prevent organ rejection after transplantation. An unintended side effect of cyclosporine A is renal toxicity. Studies show that low dose exposure to cyclosporine A can result in apoptosis of kidney cells, while high dose exposure results in necrosis. This underscores the importance of carefully establishing the effective dose of a drug relative to the possible side effects.

Following cell death, the tissue attempts to regenerate the same type of cells that have died. When the injury is limited, the tissue may be able to replace the damaged or lost cells. In severely damaged tissues or long-term chronic situations, the tissue may be unable to regenerate the same cell types and tissue structure, resulting in an imperfect repair.
**Tissue Repair**

Pathological changes in cells, tissues, and organs may lead to their destruction. Other times repair is possible.

Tissues and organs consist of different types of cells that work together to function in a particular way. Therefore responses of tissues and organs to toxic insults may be quite different from responses of individual cells. Interactions between cells lead to complex responses of tissues to cellular damage. For example, damage to one cell type may lead not only to death of that cell type but also to changes within the tissue to compensate for the injury.

There are two basic mechanisms of tissue repair, regeneration and replacement.

Regeneration is the process by which new cells, identical to those that have been damaged, are formed in tissues. The repair may or may not be complete.

Replacement, on the other hand, is the formation of new cells, different in type from those that have been damaged. Since the new cells are not functionally identical to those they replace, the repair of the tissue is incomplete. Scarring is an example.

Organs contain two basic types of tissues, parenchymal and stromal. The parenchymal tissues contain the functional cells (for example, squamous dermal cells, liver hepatocytes, and pulmonary alveolar cells). Stromal cells form the supporting connective tissues such as in blood vessels and elastic fibers, and provide structure.

As indicated previously, repair of damaged tissue can occur by regeneration or replacement. The type of cell affects how readily damage to toxic insult is repaired by regeneration of cells.

Tissue repair by regeneration occurs in the parenchymal cells. Tissue repair by replacement occurs through the formation of new stromal cells.

Regenerating cells come from the proliferation of parenchymal cells near the damaged cell(s). The ability to regenerate varies greatly with the type of parenchymal cell. There are three types, stabile cells, labile cells, and permanent cells. The type of cell therefore affects how readily damage to toxic insult is repaired by regeneration of cells.

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Stable cells usually have a long lifespan with a normally low rate of division, but can rapidly divide upon demand. Thus stable cells can also respond and regenerate, but to a lesser degree than labile cells. This cell type is quite dependent on the supporting stromal framework. When the stromal framework is damaged, the regenerated parenchymal cells may be irregularly dispersed in the organ resulting in diminished organ function.

Examples
- liver hepatocytes
- alveolar cells of the lung
- epithelium of kidney tubules

Labile cells routinely divide and replace cells that have a limited lifespan. Labile cells have a great potential for regeneration by replication and repopulation with the same cell type, so long as the supporting structure remains intact. These cells are more likely to repair when exposed to toxic insult.

Examples
- Squamous epithelium of the skin, mouth, vagina, and cervix
- Columnar epithelia, which replace rapidly, cover the surface of villi, small finger-like projections of the intestinal lining
- Transitional epithelium of the urinary tract
- Bone marrow cells (hematopoietic stem cells)

Permanent cells show little evidence of cell division, even when stressed or some cells die.

Examples
- Nerve cells
- Cardiac muscle

A tissue normally attempts to regenerate the cells that are damaged. However, in many cases, this cannot be accomplished. Replacement with stromal connective tissue is the best means for at least achieving structural continuity.
Several examples of replacement with fibrous tissue follow.

Example 1
Chronic alcoholic damage to liver tissue is an example of a toxicity in which repair tends to be imperfect. When alcoholic fatty liver disease progresses to more detrimental forms of injury, such as fibrosis and cirrhosis, the body loses the ability to replace dead hepatocytes. Instead, connective tissue, which serves as a kind of structural substitute, is formed.

Fibrocytes containing collagen replace the liver cells (hepatocytes) and normal liver tissue is replaced with scar tissue. The fibrotic scar tissue fills the space but cannot replace the function of the lost hepatic tissue. As more and more fibrotic change occurs, the function of the liver is continually reduced until eventually it can no longer maintain homeostasis. This fibrotic replacement of the liver results in cirrhosis.

Example 2
4,4’-methylenedianiline (MDA) is a chemical which targets bile duct cells.

Example 3
After a heart attack (cardiac infarct), cardiac muscle cells do not regenerate. These cells are replaced by fibrous connective tissue. The scar that is formed cannot transmit electrical impulses or participate in contraction of the heart. The efficiency of the heart in circulating blood is correspondingly reduced.

Example 4
Chemotherapy with doxorubicin, a drug used to treat breast and other types of cancers, can injure the heart. Studies show that doxorubicin exposure adversely affects mitochondria within cardiac myocytes (cells within heart tissue responsible for generating electrical impulses). Mitochondrial injury leads to myocyte apoptosis. Eventually the cells are replaced by connective tissue, causing a deterioration and weakening of the heart muscle (cardiomyopathy).
Example 5
Pulmonary fibrosis, a typically irreversible disease, is lung damage in which damaged or dead epithelial cells lining the pulmonary alveoli are replaced by fibrous tissue. Gases cannot diffuse across the fibrous cells easily, so gas exchange in the lungs is drastically reduced. Inhaling asbestos or silica particles can cause pulmonary fibrosis years after the original exposure.

Another example of pulmonary fibrosis appears in infants with bronchopulmonary dysplasia (BPD). BPD can sometimes occur in infants born prematurely with poorly developed lungs and in infants who have received high levels of oxygen from a ventilator for a long period of time. This type of tissue damage is termed hyperoxic lung injury. With treatment, the fibrosis can sometimes be reversed.

The previous examples illustrate potential effects at the tissue and organ levels as a result of cellular damage.

To review, toxic effects on cells and subsequent damage to tissues and organs may be reversible, with either return of normal organ function or impaired function, or else irreversible resulting in the complete loss of organ function.
We will go on to explore how toxicity can affect the shape of cells and tissues.

Summary
In summary:
- Cell damage can be reversible or irreversible and can lead to a variety of impacts on tissues and organs.
- Reversible cell damage includes cellular swelling and fatty change.
- Irreversible damage leads to cell death, which occurs by:
  - Necrosis - deterioration of cell function and structure leading to lysis
  - Apoptosis - controlled cell disintegration without the inflammation accompanying necrosis
- Tissue repair can occur with labile and stable parenchymal cell types but not with permanent cell types.
- The two mechanisms of tissue repair are regeneration and replacement.

In Part D, Types and Outcomes of Cell Damage, we will review changes related to shape (morphology). Cancer and the related damage of cells is the subject of a separate module.

Part D. Types and Outcomes of Cell Damage
Objectives
Upon successful completion of this Part D you will be able to:
- Identify and discuss biochemical responses of cells to toxic agents
- Identify and discuss morphological responses of cells to toxic agents

Introduction
Part C focused on the general responses, both reversible and irreversible, of cells to toxicants, and subsequent effects on tissues and organs. After a brief look at biochemical cell damage, Part D will focus on changes in the form and structure (i.e., morphology) of cells resulting from toxic insults. The morphological changes discussed are atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia, anaplasia, and neoplasia.

Biochemical Cell Damage
Toxic effects due to xenobiotics may cause visible damage to a cell or its organelles. In other cases, the effects are on specific biochemical interactions.
For example, xenobiotics may cause interference with a chemical that transmits a message in the nervous system.

Nerve cells have gaps between them called synapses. Acetylcholine is a neurotransmitter that carries impulses across the synapse from neuron to neuron or across the junction from neuron to muscle. Acetylcholinesterase is an enzyme that breaks down acetylcholine in the gap, thus preventing the uncontrolled transmission of the signal.

Organophosphate pesticides such as malathion result in toxicity by causing inhibition of the enzyme acetylcholinesterase.

The pesticide molecule binds to acetylcholinesterase and prevents it from breaking down acetylcholine. Thus, with the transmitter remaining in the synapse, electrical signals continue to fire from cell to cell without regulation.

This can result in effects in humans such as twitching, paralysis, labored breathing, convulsions, and in extreme cases, death.

Substances can also affect biochemical processes by replacing an essential chemical with a toxic one or by inhibiting its activity.

Hemoglobin is the protein molecule in red blood cells which transports oxygen from the lungs to tissues throughout the body. Carbon monoxide displaces oxygen in hemoglobin, thus preventing the blood from supplying tissues with this vital element.

The U.S. Centers for Disease Control and Prevention reports that about 15,000 emergency department visits and 500 unintentional deaths occur each year in the United States due to unintentional carbon monoxide exposure.

Morphological Cell Damage

Cell and tissue damage can also result from alterations in the morphology (that is, form and structure) of cells. The seven types of morphological changes are:

- Atrophy - decrease in size or number of cells
- Hypertrophy - increase in size of individual cells
- Hyperplasia - increase in number of cells
- Metaplasia - change in the cell from one type to another
- Dysplasia - cells have abnormal form and contents
- Anaplasia - cells don’t develop the normal specialization of that cell type
- Neoplasia - cells lose the ability to regulate their growth

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**Morphological Cell Damage: Atrophy**

Atrophy of cells is a decrease in the size of the cells. If a sufficient number of cells is involved, the organ itself may also decrease in size (i.e., organ atrophy).

When cells atrophy

- Their need for oxygen is reduced
- They synthesize less protein
- They have fewer and smaller organelles

Atrophy of an entire organ can also occur due to the combination of smaller cells and decreased numbers of cells.

Toxicants may induce cell atrophy by:

- Reducing use of cells (for example, muscle deterioration)
- Interrupting hormonal or nerve stimulation to an organ
- Inhibiting absorption or utilization of nutrients
- Reducing blood flow to the tissue
- Accelerating aging

For example, long-term or high doses of estrogens or estrogen-like chemicals will interfere with the normal hormonal balance in males and result in atrophy of the cells involved in reproduction. Environmental and occupational exposures to dioxin-like chemicals have been associated with lower levels of testosterone; gonadal atrophy and lowered testosterone levels have been observed in animal studies. Estrogens used in the treatment of prostate cancer can also have these side effects.

**Morphological Cell Damage: Hypertrophy**

Hypertrophy is an increase in the size of individual cells.

This frequently results in an increase in the size or weight of an organ and increased metabolic needs. When cells undergo hypertrophy, the organelles within the cell increase in number or size. These larger cells increase their functional capacity in an attempt to meet increased cell needs or in response to other stimuli.

Hypertrophy can occur in any organ; however, it is a common response in organs that have limited ability to produce more cells, such as cardiac and skeletal muscle. In the heart, this hypertrophy can be pathological, that is, lead to heart enlargement and less effective beating of the heart. In skeletal muscle, the physiological adaptation is beneficial in increasing strength and endurance.
Examples of hypertrophy due to chemicals/toxicants

- Phenobarbitol, commonly used to treat convulsions or as a sedative, can result in hypertrophy of smooth endoplasmic reticulum, and increase in this membrane structure inside the cell can increase cell size.
- Some chemicals are called peroxisome proliferators because they produce an increase in peroxisomes, organelles involved in lipid metabolism. These organelles can become so numerous that hepatocyte size increases.
- Ciprofibrate, a lipid modifying drug for treating high levels of the low-density lipoprotein cholesterol, is a peroxisome proliferator in rats.

Morphological Cell Damage: Hyperplasia

Tetralogy of Fallot is a complex congenital (present at birth) heart disease associated with a number of heart defects, including hypertrophy. These result in insufficient blood reaching the lungs to get oxygen, and oxygen-poor blood flowing to the body.

Alcoholism and thalidomide use in expectant mothers have been identified as possible risk factors for the development of Tetralogy of Fallot in their newborn infants.

Hyperplasia is an increase in the number of cells in a tissue. When this occurs, the size or weight of an organ might increase.

Only tissues capable of producing new cells demonstrate hyperplasia, such as epithelial cells lining the surface of the skin, intestines, and glands, some cells, such as muscle and nerve cells, do not divide and thus cannot undergo hyperplasia.

Hyperplasia is often a compensation to meet an increase in body demands as well as in response to toxicant-induced changes.

Hyperplasia may result from wounds or trauma. In wound healing, hyperplasia of connective tissue (such as fibroblasts and blood vessels) contributes to the wound repair.

Hyperplasia is a frequent response to toxic agents. However, when the toxic stress is removed the tissue may return to normal.
One way toxicants can cause hyperplasia is by affecting the normal balance of hormones in the body.

Some chemicals have been found to cause hyperplasia in mammary glands. In one study, for example, New Zealand white rabbits (both female and male) developed this condition when exposed to cyclosporine A, an immunosuppressive agent. The hyperplasia regressed, though, when administration of the drug was discontinued. Gynecomastia (breast enlargement) due to hyperplasia of glandular breast tissue is a known side effect of Premarin, flutamide, and other hormonal treatments for humans.

As an adaptive response to toxicant damage, hyperplasia can also serve to regenerate or repair cells.

Biliary epithelial cells form the tubes that transport bile from the liver to the intestines. PCB and dioxin, two environmental contaminants, have been shown to cause damage to these cells in animals. In response to the injury, these cells multiply to repair the damage, resulting in biliary hyperplasia. Dogs also can show this type of hyperplasia when treated with atorvastatin (Lipitor), a drug for the treatment of high cholesterol.

Furan, an industrial solvent that is also used to manufacture other chemicals, is sometimes found in heat-treated foods. It is classed as a possible carcinogen by the International Agency on Research in Cancer. Rat studies have demonstrated that the solvent causes biliary hyperplasia.

*Morphological Cell Damage: Metaplasia*

Metaplasia is a change that occurs when an organ replaces existing cells with new cells that would otherwise not exist in that same organ.

Chemicals or toxicants can produce metaplasia by causing chronic irritation, inflammation, and/or by interfering with the normal development of cells. Replacement cells form which can better handle the stressful environment. However, these metaplastic changes usually result in a loss of the function that was performed by the original cell type.

Sometimes metaplasia progresses to the cancerous growths defined as neoplasia. A future module will focus on chemically-induced cancers.

An example of chemically-induced metaplasia is pulmonary metaplasia due to cigarette smoke.
Epithelial cells line the airways into the lungs, including the trachea, bronchi, and bronchioles. These cells can be adversely affected by tobacco smoke.

The non-ciliated squamous epithelium produced by pulmonary metaplasia can better withstand the irritation of cigarette smoke. However, the replacement cells lack the defense mechanism performed by the cilia, which is to move foreign particles trapped in mucus up and out of the trachea. These metaplastic sites are also sites for neoplastic changes (that is, abnormal tumor growth) and with time the epithelial cells can develop into a carcinoma.

In cirrhosis of the liver, which is a common condition of chronic alcoholics, the normal functional hepatic cells are replaced by cells which form nonfunctional fibrous tissue. This disrupts the architecture of the liver. The fibrotic tissue does not perform the many metabolic functions of normal liver cells. Because the liver is the site of many detoxifying chemical reactions, a reduction in the number of functional cells severely affects the ability of the liver to process metabolic wastes and xenobiotics.

**Morphological Cell Damage: Dysplasia**

Dysplasia is a condition of abnormal cell changes or growth in which the cells are structurally altered in size, shape, and appearance. Cellular organelles also become abnormal. Metaplasia involves normal cells, but dysplastic cells are abnormal.

A common feature of dysplastic cells is that the nuclei are larger than normal. The dysplastic cells also divide at a rate higher than the original normal cells, so upon examination, many cells are undergoing mitosis.

Causes of dysplasia include chronic irritation and infection. In many cases, the dysplasia can be reversed if the stress is removed. Then normal cells return. In other cases, dysplasia may be permanent or represent a precancerous change.
Exposure to PCBs can lead to dysplastic mammary gland proliferation. Another example is cancer chemotherapy. The use of chemotherapeutic alkylating agents or radiation, which inhibit cell division, can cause dysplasia in intestinal epithelium.

An interesting example of cross-generational dysplasia occurred with the synthetic female hormone diethylstilbestrol (DES), which had been prescribed between 1938 and 1971 to help women with morning sickness during pregnancy. Prenatal exposure to DES has been linked with cervical and other dysplasias in the daughters of the women who took the drug during pregnancy. The daughters were also at increased risk of developing uncommon cervical and vaginal cancer.

Mustard agents have been used as chemical weapons during combat in World War I and World War II. More recently, in a study of soldiers exposed to mustard gas during the Iraq-Iran war, dysplasia of the eye’s conjunctiva, the mucous membrane covering the white part of the eye and lining the inside of the eyelids, was observed.

**Morphological Cell Damage: Anaplasia**

Anaplasia refers to cells that are undifferentiated, that is, these cells do not have the characteristics of a specific cell type.

Cells showing anaplasia
- Are not well developed.
- Lack a characteristic structure or function
- Tend to multiply quickly
- Have irregular nuclei and cell structure
- Are often in the midst of cell division

Anaplasia is frequently associated with malignancies and serves as one criterion for grading the aggressiveness of a cancer.

For example, an anaplastic carcinoma is one in which the cell appearance has changed from the highly-differentiated original cell to a cell type lacking the normal characteristics of the original cell. In general, anaplastic cells have lost the normal cellular controls which regulate division and differentiation.

Anaplastic carcinoma of the thyroid is the most aggressive thyroid gland malignancy, and tends to occur in people in iodine-deficient areas.
Anaplastic meningiomas are tumors originating in the meninges, or the lining of the surface of the brain and other nervous tissue. These are the second most common type of neoplasm in the central nervous system. Most are benign. Patients who have undergone radiation to the scalp have a higher risk of developing meningiomas.

**Morphological Cell Damage: Neoplasia**

Neoplasia is the unregulated growth of cells and commonly leads to the formation of a tumor. This may be benign or malignant, the latter type of tumor is known as a cancer. Neoplasia may occur, in part, when toxicants create permanent damage to the DNA of cells and interfere with the ability of cells to regulate their growth. There are many types of cancers, some caused by exposure to chemical agents, and they present a significant challenge to medicine.

Cancer cells may exhibit changes such as dysplasia or anaplasia.

**Summary**

To maintain homeostasis in the presence of a toxic event, cells or tissues undergo cellular responses.

The two types of cell damage caused by toxicants are biochemical and morphological.

- Biochemical damage can involve any of the very large number of chemicals that make up cells and tissues
- Morphological changes can be divided into seven categories based on the types of cell changes that occur, affecting cell size, cell number, cell type, and cell structure.

These morphological changes include:

- Atrophy, a decrease in cell size and/or number
- Hypertrophy, an increase in individual cell size
- Hyperplasia, an increase in cell number in a tissue
- Metaplasia, the replacement of one cell type for another
- Dysplasia, abnormal cell changes or deranged cell growth
- Anaplasia, cells remain undifferentiated or lose their differentiation
- Neoplasia, growth of new tissue to form a tumor
Credits
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