Bio 381 Lesson #1

Cellular injury

With some basic knowledge under our belts we are ready to discuss some cellular and genetic mechanisms of disease. We need to understand pathology on a cellular level in order to understand it on an organ or organ system level. Let’s begin with several (potentially) reversible mechanisms of cellular injury. Mostly we will discuss examples of substances that can accumulate inside cells: 1. water, 2. excessive amounts of normal intracellular substances, 3. abnormal substances produced by faulty cell metabolism, and 4. accumulation of pigments or particles that the cell is unable to degrade.

1. **Hydropic swelling** occurs when water accumulates in the intracellular space due to loss of function of the Na\(^+\)-K\(^+\) ATP pump, usually because of a deficiency of ATP needed to fuel the pump. If you recall, an electrochemical gradient exists between the intracellular and extracellular space. (A gradient is just a difference. For instance, there is an age gradient between teachers and students at BYU-Idaho.) Cells at rest have a relatively negative intracellular electrical charge as well as a higher potassium concentration and lower sodium concentration than the extracellular space. These conditions are reversed in the extracellular space. To transmit information (like action potentials), sodium and potassium change places. The Na\(^+\)-K\(^+\) ATP pump functions to restore and maintain this gradient. Cells may be able to tolerate 24 hours or so of hydropic swelling before they die.

Like many of the concepts we will soon discuss, hydropic swelling is not exclusively a cellular mechanism—it can also apply to organs or the entire body. “Hydropic” is essentially synonymous with “edema:” to swell or take on fluid. This illustration of an infant depicts an infant suffering from hydrops fetalis; it is a “swollen fetus.” Hydropic swelling is one cause of organomegaly: an increase in the size of an organ.

2. **Excessive amounts of normal intracellular substances.** The liver is a very dynamic, resilient organ that can handle lots of abuse before it is permanently damaged. One example of such abuse is
drinking alcohol (ethanol). Career heavy drinkers first develop a fatty liver in which abnormally large amounts of lipids accumulate inside hepatocytes. If the patient with this condition can stop pouring ethanol down the hatch, this condition is totally reversible. People that drink that much, however, tend not to stop. Eventually, permanent damage (fibrosis) appears, and if drinking continues the liver is even more severely and irreversibly damaged and destroyed—a process known as cirrhosis.

Another example of an intracellular storage disease in which lipids accumulate inside cells is Tay Sachs disease. This is a genetic disease (autosomal recessive—more below) in which both parents must contribute a defective gene on chromosome 15 to have an affected child. These children lack hexosaminidase A, an enzyme that breaks down normal fatty constituents of nerve cells called gangliosides that need to be recycled and replaced on a continual basis. Perhaps we can think of the hexosaminidase A as city garbage men. We all tend to take them for granted, but when they go on strike things get really ugly. In the case of the garbage, things tend to eventually get sorted out. In the case of Tay Sachs disease, the affected children die—usually by age 4 or 5. There is no effective treatment.

The population most at risk to carry the Tay Sachs gene is Ashkenazi Jews, whose roots lie in Eastern Europe. In this population 1 out of every 27 people carry the defective gene. For those of you up-to-date on your statistical probability calculations, this computes to about 1 out of every 729 conceived fetuses. Notice that I didn’t say 1 out of every 729 births. Many of these fetuses are diagnosed prenatally and aborted.

3. Accumulation of abnormal substances produced by faulty cell metabolism. Mucopolysaccharides, molecules now known as glycosaminoglycans, are large carbohydrate complexes that are important constituents of extracellular matrix in connective tissues. Not unlike the gangliosides in Tay Sachs disease, glycosaminoglycans also need to be recycled and replaced on a continual basis, a task typically performed by a group of 11 lysosomal enzymes. Deficiency of these enzymes is responsible for the group of cellular metabolic diseases known as the mucopolysaccharidoses, one example of which is Hunter Syndrome. Mucopolysaccharidoses are part of the lysosomal storage disease family of diseases. They share many clinical
characteristics, but have varying degrees of severity. This list of signs and symptoms to the right are fairly nonspecific, and the underlying diagnosis can easily be missed.

A very similar group of diseases is the **glycogen storage diseases.** These are also known as **inborn errors of metabolism** and involve defective glycogen metabolism. The etiology of these conditions can be either genetic or acquired, and the manifestations are also variable. Coincidentally, there are also currently 11 recognized forms of these diseases—just like the mucopolysaccharidoses

4. **Accumulation of pigments and particles that the cell is unable to degrade.** Hemoglobin is the oxygen-carrying molecule within red blood cells (RBCs). These cells circulate between 90-120 days, and then are recycled by phagocytic cells. Heme is the actual oxygen-carrying portion of the hemoglobin molecule, and the breakdown product of heme is a yellowish-organ pigment known as **bilirubin.** Bilirubin is conjugated in the liver, a process that basically involves binding a molecule anchor that carries the bilirubin out from the liver and into the gut for disposal. Because RBCs are constantly being recycled and replaced, we all have small amounts of bilirubin in circulation. However, when excessive bilirubin is produced, for example in some newborns, or the liver is unable to keep up with bilirubin processing the pigment accumulates throughout the body, causing **jaundice.** In adults any lasting damage caused by high bilirubin levels is the result of the underlying disease process. However, in infants’ developing brains high bilirubin levels can be taken up by developing neurons, permanently damaging the brain—a condition called **kernicterus.**

**Cellular adaptation**

Cells respond to these and other mechanisms of injury in a variety of ways. This is going to be mainly a vocabulary exercise, but this is terminology that we will use throughout the rest of the semester (as well as in your future medical careers). We will consider these terms from the perspective of cellular injury and adaptation, but much like “hydropic” above, they may also be used to refer to changes in body tissues or organs. For instance, when cells undergo **atrophy** they shrink, but Alzheimer’s disease causes atrophy of the entire brain.
There are many varieties of atrophy, and the following list is not exhaustive, but covers what we need to know. Disuse atrophy may occur in skeletal muscles (or brains) that are not utilized, denervation atrophy occurs when skeletal muscles lose their motor nerve supply, hormonal atrophy occurs when hormonally sensitive tissues lose the necessary chemical input, and physiological atrophy may occur when structures stop functioning as we age. For instance, menopause, the cessation of menstruation, is a form of physiological atrophy that occurs when ovaries can no longer produce female reproductive hormones such as estrogen. Another potential cause of atrophy is ischemia: lack of blood supply. Of course, total lack of blood supply ultimately results in cell death, a process known as infarction. A myocardial infarction is death of heart muscle cells due to loss of blood supply and is also commonly known as a heart attack.

Hypertrophy is just the opposite of atrophy and means an increase in mass or size. Perhaps visualizing the typical BYU-Idaho instructor’s bulging biceps will be a vivid mental image of the hypertrophy that occurs in response to resistance exercise stimulating increased protein synthesis within the affected muscle cells. The end result is hypertrophy of both the individual muscle cells and the entire muscle itself. This image portrays a hypertrophic left ventricle of the heart.

Hyperplasia is an increase in cell number. This process often occurs simultaneously with hypertrophy. For instance, during the proliferative phase of the uterine (menstrual) cycle the lining of the uterus (the endometrium) undergoes both hypertrophy and hyperplasia in preparation for implantation—cells increase in both size and number.

Metaplasia (Greek: “change in form”) is the replacement of one fully differentiated cell type by another. This often occurs as a protective mechanism. If the injurious stimulus is removed, metaplasia is usually reversible and is not typically carcinogenic. A common example of metaplasia occurs in the respiratory tract of smokers. The normal epithelium in the upper respiratory tract is pseudostratified ciliated columnar (respiratory) epithelium. The irritant effect of cigarette smoking transforms this normal respiratory epithelium into stratified squamous epithelium. If the smoker quits, the process reverses in time. Probably.

There are occasions in which cellular adaption goes awry. Dysplasia (Greek: “malformation; to create or form”) is an abnormality of development—typically consisting of an expansion of immature cell
numbers and a corresponding decrease in mature cell numbers. Microscopically\textsuperscript{xii} what is seen is an abnormality of shape, size, and/or arrangement of cells. Dysplasia is often pre-cancerous ("preneoplastic").

Pap smears are probably the best example of successful cancer screening. Cervical cancer at one time was the most common cause of death of American women, but early recognition of the presence of dysplasia allows treatment before frank cancer becomes invasive and threatens life.

The most extreme example of dysplasia is \textit{carcinoma in situ}\textsuperscript{xiii} (Greek: “cancer in its place”) and is defined by the presence of severely dysplastic cells but with the absence of invasion of the surrounding tissue. These lesions typically progress to frankly invasive cancers, so treatment usually involves either complete removal or destruction of the affected tissue.

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**Irreversible cell injury**

**Necrosis**

\textit{Necrosis} is abnormal, irreversible cellular death caused by external injury. Necrosis frequently causes systemic (body-wide) signs and/or symptoms like fever, malaise, elevated white blood cell counts, anorexia, etc. The various types of necrosis usually depend on the type of body tissue involved, the length of time, and the specific mechanism that causes the necrosis.

\textit{Coagulative necrosis} causes extensive \textit{denaturation}\textsuperscript{xiv} of proteins and results in the area of necrosis remaining relatively solid for some weeks. The typical architecture of the tissue is preserved because the lysosomal enzymes are \textit{denatured}, making them nonfunctional.\textsuperscript{xv}

\textit{Liquefactive necrosis}\textsuperscript{xvi} is characteristic of local severe bacterial or fungal infections, but also commonly occurs in brain. In this variety of necrosis the affected cells are completely digested by a variety of enzymes, resulting in formation of liquid.

\textit{Fat necrosis}\textsuperscript{xvii} involves death of adipose tissue and is typically seen in trauma or inflammation of the pancreas. The pancreas’s \textit{lipase} enzymes release fatty acids from triglycerides, which then react with
calcium to form soaps (no kidding). The areas of fat necrosis take on a white, chalky appearance. This type of necrosis can be seen anywhere fat cells are present.

*Caseous necrosis* is typical of tuberculosis. The necrotic material looks much like cottage cheese (but doesn’t taste good with fruit on it). This type of necrotic material may persist indefinitely. The most common variety of tuberculous affects the lung, but the leprosy organism is also of the same genus. We do have some leprosy in the area—most common among Basque shepherders in a small community west of Idaho Falls.

**Gangrene**

Now on to a truly happy subject: *gangrene* or *gangrenous necrosis*. This term refers to cellular death involving a large area of tissue. “Gangrene” is often used to refer to not only the cellular death but also the decomposition and putrefaction that occurs after necrosis is included in the meaning. *Dry gangrene* is a form of coagulative necrosis, generally only seen on the extremities. It characteristically has a clear line of demarcation between the viable and the necrotic tissue. Surgery for this condition basically involves using a big set of scissors to amputate proximally—kind of like sequentially clipping off pieces of a pencil—until bleeding is seen from the stump. (If tissue bleeds it isn’t gangrenous.) Once the gangrenous tissue is removed the final closure is accomplished.

*Wet gangrene* involves liquefactive necrosis, typically in internal organs. *Gas gangrene* occurs when anaerobic bacteria of the *Clostridium* genus produce gas inside tissues. If the affected area is close enough to the surface, an effect much like popping bubble wrap occurs when pressure is applied. This is a medical emergency, and every second counts. These patients are taken directly to the operating room, where nonviable tissue is removed and incisions are left open to eliminate the anaerobic environment.

**Apoptosis**

While necrosis refers to abnormal cell death, *apoptosis* is cell death triggered by intracellular signaling cascades. Apoptosis is a *normal physiological phenomenon* that does not cause inflammatory changes or damage to surrounding tissue. Synonyms for this word include “programmed cell death” or “cell suicide.” When cells evolve an ability to “evade” apoptosis, then defective cells can do undesirable things like transform into cancer, a process called *malignant*
transformation. Cancer cells are immortal, having the ability to evade apoptosis. It is thought that malignant cells that die in response to radiation or chemotherapy do so through an apoptotic mechanism.

There are times that apoptosis is implicated in pathological processes. For instance during a heart attack or myocardial infarction, approximately 20% of the cells that necrose do so in response to ischemia. The remaining 80% die because of apoptosis. Obviously, if we could inhibit the apoptotic cells from dying we could greatly decrease the mortality rate in heart attacks.

If we consider apoptosis as being similar to suicide, then the actual molecular “weapons” are a group of digestive enzymes known as caspases. Actually, one group of these enzymes is actually called executioner caspases, which always elicits a rather vivid mental image for me: a hangman’s noose around the neck or a pistol held to the cellular “head.”

Apoptosis is always a balancing act for the cell. There are numerous internal and external chemical cascades and metabolic pathways that regulate cell survival or death, and the final outcome of life or death depends on the strength and magnitude of the various stimuli.

Let’s discuss three apoptosis “triggers:”

1. Cells are rather social organisms and many of them rely on “survival” signals from neighboring cells or extracellular materials (called matrix). These survival signals normally suppress apoptosis, and withdrawal of these signals triggers cell suicide. Cancer cells evolve the ability to survive despite lack of these signals.

2. The second mechanism of triggering apoptosis involves extracellular signals, such as the Fas ligand, which binds to cellular receptors and activates “death receptors.”

3. P53 is an intracellular protein (which of course means that it is a product of the p53 gene) that increases in concentration in response to DNA damage inside the cell. P53 can act as a repairman as well as an executioner. If it can repair the DNA damage it does, but in cases in which the damage is too severe it triggers execution caspaces and subsequent apoptosis. The p53 gene is ubiquitous and necessary for normal cellular function, and it also is an important mechanism by which cells undergoing malignant transformation evade apoptosis. Over half of all human cancers have mutant (damaged) p53! There is currently
a drug in early development called nutlin-3 that functions to repair p53 which holds great promise—I hope.

**Comparison of Cellular Death by Necrosis and Apoptosis**

Cell necrosis is *usually caused by cell damage* and does not require gene activity. The membrane is the major site of damage—it loses its ability to regulate osmotic pressure. Cell contents are released and result in an inflammatory reaction. Think of it as stepping on a grape and squishing it.

**Apoptosis** also results in cell death, but *occurs as a result of gene activity*. It can be prevented either by activation of survival genes or by external signals. Apoptotic cells kind of shrivel up like a raisin being produced from a grape. Cell contents are not released into the environment, and no inflammation occurs. Once the “raisin” is nicely dried out, phagocytic cells (think “garbage men”) engulf and digest the apoptotic cell. Necrosis is messy, but apoptosis is neat and tidy. Hopefully your roommates resemble apoptosis rather than necrosis.

**Etiology of cellular injury**

*Hypoxia* is cellular lack of oxygen and results in cellular “power failure.” As you may recall, aerobic cellular respiration produces 36 to 38 ATP molecules per molecule of glucose burned for fuel, but anaerobic respiration produces only 2 ATP and *lactate*. Cells can survive using anaerobic respiration for only short periods of time. Think of it as cells “holding their breath.” Hypoxia is usually caused by *ischemia*—interruption of blood flow. As a broad generalization, ischemia is probably the most common cause of cellular damage in clinical medicine.

Now we are confronted with a truly ironic situation. Cell death due to hypoxia is actually fairly slow to develop. Most cellular damage and death actually occurs when blood supply is re-established, a phenomenon known as *reperfusion injury*. If we could eliminate the reperfusion injury we could prevent 70-80% of cellular death in situations like heart attacks and strokes. Lots of lives could be saved.

Let’s discuss this next diagram, *Fundamentals of Reperfusion Injury* for the Clinical Cardiologist which addresses reperfusion injury specifically in the heart. Similar diagrams exist for other cell types.
including brain cells. The black terms at the top of the diagram represent three methods by which blood flow is restored to ischemic heart muscle cells (myocardium). Once blood flow is restored, the five blue ovals represent metabolic changes seen in reperfused myocardium:

1. **Oxygen free radicals**, also known as **reactive oxygen species**, are atoms, molecules, or ions with unpaired electrons in their outer orbital shells. Most of these particles contain oxygen atoms, and there isn’t enough oxygen around to form these free radicals until the ischemia is relieved and oxygen atoms again become available. Reperfusion also stimulates **neutrophils** (a type of white blood cell) and **platelets** (also known as **thrombocytes**, which are critical in blood clotting) to become active, which in turn also stimulates more reactive oxygen species production. The free radicals react with lipids in the cell membrane, which damages membrane-bound enzymes, which also in turn cause still more free radical production. The reactive oxygen species also quench cellular production of nitric oxide (NO), which further damages the endothelium and small blood vessels that supply the heart. These activated cells in turn activate metabolic cascades, such as the **complement cascade**, which in turn does more damage to cellular membranes.

2. **Alterations in calcium handling**—Ischemia and reperfusion also result in increased intracellular calcium levels. Calcium is necessary for muscle cells to contract, and these high levels interfere with cardiomyocyte function. Ironically, drugs known as calcium channel blockers have successfully blocked at least some of this calcium influx, but do not seem to have an impact clinically. Obviously, there is more to this whole situation than we understand currently.

3. **Altered myocardial metabolism**—myocardial cells normally function primarily through aerobic respiration, but during ischemic episodes **lactate** is, of course, produced. We would expect that when perfusion is re-established this lactate would be metabolized by aerobic cellular respiration, but in fact lactate release persists throughout reperfusion. Obviously, the normal cellular metabolic pathways are damaged.
Risk factors for cardiovascular disease, including high cholesterol levels, diabetes, and hypertension, have been reported to increase reperfusion injury. So, these patients that are at an increased risk of ischemia are also more likely to have a greater reperfusion injury.

So, what can be done to decrease reperfusion injury? Over the past 3 decades, well over 1,000 different interventions have been studied in this effort. Aggressive body cooling (hypothermia)\textsuperscript{xxiv} has shown some promise, but is still quite cumbersome and expensive. A myriad of medications have at best yielded mixed results, and even treatment with antioxidants (which scavenge reactive oxygen species produced during normal metabolism) have been disappointing. This doesn’t stop the nutritional supplement industry from earning billions of dollars each year from sales of antioxidants. Again, we have lots more to learn, and this whole scenario also shows us once again that what seems to make sense (like antioxidant effectiveness) is not necessarily true.

\textbf{Other causes of cellular injury}

Nutritional deficiencies (and excesses) are common. The last few years have shown, for instance, that vitamin D deficiency is much more common than previously known. Patients with obesity are at increased risk of a multitude of health problems. Infections and immunological injuries, chemical injuries, physical and mechanical injuries are all common. The list is almost endless.

\textbf{Aging}

This is also a huge subject, but it is worthwhile considering whether aging is a manifestation of normal physiology or a disease state? Once a person is older than 60 years of age, their risk of death doubles every eight years, so a person that is 68-years-old has a risk of dying twice as great as a 60-year-old. Aging is universal, but what causes it? An abundance of theories include:

1. Gradual accumulation of genetic mutations from chronic exposure to background radiation;

2. Gradual damage from free radicals—but the existence of increased free radical levels in the aged have not been documented;
3. The so-called error theory: an accumulation in random errors in gene transcription and translation;

4. Programmed senescence theory: basically, most cells only have so many cell divisions before they undergo apoptosis. This is true, and is called the Hayflick limit, but the association with aging of the entire body has never been proven.

5. Telomere shortening: telomeres are caps on the ends of chromosomes, and do shorten with increased numbers of cell divisions. The typical human telomere is about 8,000 base pairs in length at birth, and telomeres shorter than 3,000 base pairs increase all-cause mortality by at least five-fold. The Rate of Telomere Shortening Predicts Mortality from Cardiovascular Disease in Men, Telomeres do shorten as we age, but is this a cause of aging or a manifestation of aging? Cancer cells are immortal, and overcome the Hayflick limit through the enzyme telomerase which rebuilds telomeres.

6. Inadequate exercise—I have always thought it very ironic that James F. Fixx, who almost single-handedly started the running craze in the United States died at age 52 while running. This has sparked my “fixed heart beat theory of aging.” We only have so many heartbeats during our lives, so why waste them in pointless exercise? (This theory may appropriately be filed in the garbage can along with the “Donut Deficiency Theory of Aging.”)

7. President Gordon B. Hinckley gave some perspective on aging when he said that, “I am the last leaf on the tree, and the wind is blowing.” Death will come to us all, regardless of age, so “Through all of living have much joy and laughter, life is to be enjoyed, not just endured.” If we are prepared we have nothing to fear.
Genetics

First, let’s review

For those of you who need a review, here is my summation I have entitled, “Genetics in 5 Easy Minutes:”

The genetic “code” is contained within long strings of a molecule called DNA that is contained in our cells’ nuclei bundled into packages called chromosomes. Chromosomes come in pairs—like socks—and each pair of chromosomes is referred to as homologous chromosomes. This image is that of a karyotype—a technique by which photos of all 46 chromosomes are cut out of the nucleus and arranged in homologous pairs.

Each chromosome is basically a big recipe book that the body uses to make (synthesize) proteins and the specific region in each chromosome that contains the code (the recipe) for a specific protein is called a gene. There are a variety of different genes that code for a specific protein, and these different varieties of genes are known as alleles. Think of them as slightly different recipes for the same cake. Because we inherit one of each homologous chromosomal pair from each parent, we inherit one allele of each gene from each parent.

Our variability in phenotype (body appearance, both inside and out) occurs due to a combination of genotype (our genetic make-up) and environment. Gametes all contain a different genotype because during meiosis (one form of cell division that results in gamete production) a process called crossing over occurs: homologous chromosomal pairs randomly exchange genetic material. You may think of crossing over as chromosomes studying together and sharing notes in preparation for a big test. Crossing over is the critical step in meiosis that allows every gamete (and therefore every non-identical offspring) to be genetically unique. What happens is that the homologous chromosomal pairs line up and then exchange genetic material between themselves.

Mitosis is cell division resulting in 2 genetically identical (clone) cells that are both 2n, somatic, or diploid cells—different ways of saying the same thing.
Autosomes are the non-sex chromosomes: chromosome pairs 1 through 22. In the karyotype image above, the autosomes are the first 22 pairs of chromosomes. Sex chromosomes comprise the 23rd pair of chromosomes: “X” is female, “Y” is male. If a Y chromosome is present, it is dominant—the individual is male. So, males are “XY” and females are “XX.”

The “X” chromosome is large, so there are a number of genes on it beyond what is necessary to determine female sex. The “Y” chromosome is really small, so the only genes of note on it are the ones that determine male sex.

An organism’s ploidy number is the number of chromosomes that particular organism normally possesses. The haploid number (n or 1n) is the number of chromosomes in a gamete or germ cell—sperms cells and eggs—the cells produced by meiosis. Germ cells combine during fertilization to produce a zygote: a fertilized egg.

Somatic cells (all the non-reproductive cells), have the same number of chromosomes as the zygote, therefore somatic cells have twice as many chromosomes—they possess a diploid (2n) number of chromosomes—the full complement. Aneuploid cells (“an” – “without”) do not contain a ploidy number of chromosomes. Things went wrong during meiosis. Many cancer cells are aneuploid.

If a cell actually uses a certain gene, we refer to that gene as being expressed. (Like cells and their genes, I don’t use all the recipes in my cookbooks. Do you? If the answer is yes, then I want to be invited to dinner.)

If a gene on both homologous chromosomes is identical, we refer to that person as being homozygous for that gene. (“Homo” means “same,” “zygote” refers again to a fertilized egg.) If each homologous chromosome contains different alleles of a certain gene, then that person is heterozygous for that gene. (“Hetero” means “different.”)

Alleles (which when we talk about inheritance are often referred to as traits) come in two basic varieties—dominant and recessive. If a dominant trait (allele) is present, it will be expressed—even if the other allele is different. A recessive trait will be masked by the presence of a dominant allele, and will only be expressed if a person is homozygous for that recessive allele. It is possible, but less common, for two different alleles to BOTH be expressed. This is known as codominance.
Polygenic traits—are phenotypic manifestations resulting from the interactions between several different genes. Most traits are polygenic: beauty, intelligence, athletic ability, hypertension, etc.

Expressivity is the degree to which a particular gene produces a given effect. For instance, both of the above individuals possess the same genetic trait (neurofibromatosis). I think we’d all agree that this gene is certainly variably expressed as evidenced in the photo directly above. We will discuss neurofibromatosis later in this week’s material.

Mendelian genes—are genes that code for a single trait; the name comes from Gregor Mendel, the monk who we credit as the father of genetics.

Genetic disorders

Chromosomal abnormalities—aberrant structure of chromosomes

Abnormalities in chromosomal structure involve breakage and loss of DNA or faulty rearrangement of pieces of chromosomes during either meiosis or mitosis.

Deletions involve loss of a portion of a chromosome. All three of these ladies have a partial deletion of chromosomes number one. In this photograph they all look phenotypically pretty normal, but they have a long list of both signs and symptoms associated with their genotype. These include behaviors such as overeating, temper outbursts, throwing objects, striking people, and episodes of violent physical activity.

Cri du Chat syndrome (“cry dew shaw,” French for “cry of the cat”) involves deletion of the short arm of chromosome 5. The syndrome is named because their high-pitched cry sounds like a cat’s “meow.” Their clinical manifestations involve mental retardation, microcephaly, low birth weight, poor growth, webbing of the fingers and toes, wide-set eyes, poor motor skills, skin tags in front of the ear, and a single line in the palm of the hand known as a Simian crease, and heart anomalies. The circled chromosome in this karyotype is the one with the deletion. If no major organ defects or other critical medical conditions exist their lifespan is potentially normal.

Translocation is a chromosomal rearrangement in which a segment of genetic material from one chromosome breaks away and becomes
linked to a different, non-homozygous chromosome. *Balanced translocations* occur in an even exchange of genetic material with no genetic information lost or duplicated. These individuals are usually phenotypically normal, but their offspring often inherit an abnormal genotype and are therefore phenotypically abnormal. Translocations occur because of faulty crossing over, and are quite common. Estimates of incidence range from about 1 in 500 to 1 in 650 human newborns.

A specific example of a chromosomal translocation is the *Philadelphia chromosome*, which involves a balanced translocation between chromosomes 9 and 22. The presence of the Philadelphia chromosome is a highly specific and sensitive test for one type of leukemia: *chronic myelogenous leukemia* or *CML*.

A *gene duplication* is basically the opposite of a deletion. It is thought that duplications play a vital role in evolution.

**Chromosomal abnormalities — aberrant numbers of chromosomes**

*Numerical* chromosomal abnormalities are more common than *structural* abnormalities. *Monosomy*—“mono” — “one”; “somy” — refers to the state of having only one copy of a somatic (non-sex) chromosomal pair. Somatic monosomy (complete loss of one autosome) is not compatible with extrauterine life. These fetuses are pretty much doomed.

*Polysomy*—“poly” — “many” occurs when three (instead of two) copies of a homologous autosomal pair are present. The bottom line is that *generally it is better to have too much genetic material rather than not enough*.

The most common chromosomal disorder of any variety is *Down Syndrome*. These individuals have 3 copies of chromosome #21, thus are also known as *trisomy 21* or *47XY+21* (or *47XX+21* if they are female). The incidence of Down syndrome is around 1 in 700 live births. Clinical manifestations include mental retardation, hypotonia, short stature, macroglossia, almond-shaped eyes caused by an epicanthic fold of the eyelid, up slanting palpebral fissures, short limbs, a simian palmar crease, increased susceptibility to infections, recurrent ear infections often leading to hearing loss, and gastroesophageal reflux. One-half or so of these patients has congenital heart disease, and they also have a shortened life expectancy. Three-quarters of Down Syndrome fetuses spontaneously abort or are stillborn, and 20% of the survivors die by age 10. Those
who survive past age 10 have a life expectancy of approximately 60 years, but by age 40 most develop deterioration in mental faculties similar to Alzheimer Syndrome.

A woman’s chances of giving birth to a Down child increases with increasing maternal age. At age 35 the risk is 1 in 400 births, but by age 45 the risk is 1 in 35. However, most Down syndrome infants are born to young mothers because younger women have far more babies. If a mother already has one Down child she has about 1 percent chance of having another. Both men and women can parent Down syndrome infants if they carry a genetic translocation, even though the parents are usually normal. Increasing paternal age does somewhat increase the risk of a Down child if the mother is 35 or older, but the paternal effect is much less marked than the maternal effect.

Story Time

When I was in my residency I met a young man at Primary Children’s Medical Center with trisomy 21 that was in middle school and was at the top of his class. It took a while to convince me of his underlying diagnosis. It just goes to show that there are exceptions to every rule.

Other trisomies also exist. Edwards Syndrome is trisomy 18 and Patau Syndrome is trisomy 13. They are both much less common and more severe than Down syndrome. These syndromes also occur more commonly with increasing maternal age.

Chromosomal abnormalities — sex chromosome abnormalities

Kleinfelter syndrome patients are male, but have an extra “X” chromosome (47, XXY), there are Kleinfelter patients that have more than two “X” chromosomes (48, XXY; 49, XXXY; 50 XXXXY; etc.). Their body proportions are abnormal, with long legs and a short trunk. They are generally infertile, have small firm testicles, suffer from other sexual problems, and have less than the expected amount of pubic, armpit, and facial hair. They have gynecomastia, which increases their risk of developing breast cancer. Mentally they are moderately impaired, a high percentage of them suffer from Attention Hyperactivity Deficit Disorder (ADHD). Treatment with testosterone can be helpful in treating some of the clinical manifestations. I knew of a young man with this disease who attended school at BYU-Idaho. It wasn’t easy for him, but he managed to graduate.

Turner Syndrome patients are female, but possess only one sex chromosome. These girls have near-normal IQ and have a short
stature, droopy eyelids, low-set ears, a low hairline, a webbed neck, and widely spaced nipples. Instead of ovaries they have what are called “gonadal streaks,” but with donated eggs and intensive hormonal therapy some of these individuals have successfully carried infants to term. Without hormonal therapy they don’t go through puberty, and also would not menstruate. Turner is highly lethal during pregnancy. Only 0.5% of these conceptions and 3% of embryos that make it to the fetus stage (8 weeks gestation) survive.

Story Time

When I was in my third year of medical school I spent an afternoon during my pediatric rotation with a wonderful pediatric endocrinologist, Dr. Marv Rallison. I met one of his Turner patients and was able to visit with her and her mother and examine her. Dr. Rallison’s summation was, “Michelle can do anything she wants in this life except bear her own children” (and even that may well be possible now). Dr. Rallison was obviously good friends with this young lady. It was a great lesson for me in compassion and truly caring for a patient as a person.

Concepts in single-gene (or Mendelian) disorders

These disorders arise from abnormal or mutated single genes. Pedigrees are very useful in tracing these genes through families, and Punnett squares are helpful in understanding their inheritance patterns. Thousands of these disorders have been described, but it is still worth knowing the details of a select few of these conditions in order to understand these inheritance patterns. To begin, let’s first discuss Punnett squares.

Punnett squares are all about genotype. The genotype of both the mother and the father are listed outside the squares, and the genotype of all their potential offspring are listed inside the squares. This example above involves the sex chromosomes. Obviously, the mother (listed at the top) is “XX,” and the father (listed at the left) is “XY.” Each potential offspring (in each of the inner squares) inherits one sex chromosome from each parent.

Punnett squares are a way to understand the genotypical probabilities of each offspring. They cannot accurately be used to predict the
genotype outcome in a particular family. For instance, statistically speaking about half of the human race is female and half is male. However, I have a colleague who has 10 children—all girls.

Although, it’s kind of entertaining, I still wouldn’t recommend tattooing basic concepts of biology onto our body to commemorate graduation. However, this image of a Punnett square depicting a single gene is fairly memorable. The convention in Punnett squares is that dominant alleles are capitalized, and recessive alleles are depicted in lower case letters. You can readily see that both of the parents on this wrist are heterozygous (Ee) for this gene, while 50% of the potential offspring are likely to be heterozygous just like the parents. The statistical probabilities dictate that 25% of the offspring would be homozygous dominant (EE) and 25% would be homozygous recessive (ee). What percentage of the offspring is likely to be affected (express the “E” trait)? * What percentage of the offspring would be carriers of the recessive trait?

As we can see from this cartoon, Punnett squares can also be very destructive to biologists’ social lives.

**Concepts in Mendelian single-gene disorders**

Single-gene disorders are classified according to:

1. The *location* of the defective gene (autosome or sex chromosome), and
2. The *mode of transmission* (dominant or recessive).

Substances known as *mutagens* are capable of causing mutations—permanent changes in DNA structure—and mutagenic agents include radiation, tobacco, innumerable chemicals, viruses, etc. Mechanisms of mutation include:

1. Point mutations—single nucleotide base-pair substitutions, or
2. Frame shift mutations—in which the *reading frame* of the DNA *codon* is changed or shifted.

A codon is a 3-molecule segment of nucleic acid (DNA or RNA). Each possible codon dictates or is the “code” for a specific amino acid.

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1 *(75%)** *(50%)**
Mutations permanently change a codon, so alter the protein that a specific gene controls.

Let’s consider this example of a point mutation. Hemoglobin, of course as we already discussed, is the oxygen-carrying molecule within our red blood cells. Sickle-cell disease is caused by a single nucleotide substitution as we can see to the left. The middle nucleotide ("T" or thymine) in the DNA molecule (the top aqua-colored molecule) is replaced by an "A" (adenine). This causes an incorrect amino acid (valine in the purple lower-right-hand of the diagram) to be inserted into the sickle-cell hemoglobin molecule. The mutation makes the sickle-cell hemoglobin much less durable and effective.

Frame shift mutations usually involve an insertion or deletion of a nucleotide. This radically changes the entire gene. Think of it as a broken zipper. It only takes a single broken tooth to make a zipper totally useless.

**Autosomal dominant disorders**

The characteristics of these disorders include:

1. Males and females are equally affected,
2. Affected individuals typically have an affected parent,
3. Unaffected individuals do not transmit the disease, and
4. Offspring of affected individuals have a 50% chance of inheriting the disease.

Spend a minute with this Punnett square and make sure you understand these concepts. I suggest you understand rather than memorize this list.

The father is heterozygous and affected with the “D” disease. The chances are that 50% of his offspring will inherit the “D” gene and also be affected. The other 50% will inherit the normal “d” gene from both parents and not be affected. There is no carrier state (possessing the gene but not being affected by the disease) in autosomal dominant disorders.

Please also look at this pedigree for an autosomal dominant disorder. The squares represent males (I remember that men are blockheads,
but don’t quote me) and the circles represent females. The blue filled-in individuals are affected with the disease.

Speculation exists that President Abraham Lincoln had Marfan syndrome. This is a disorder of connective tissue—specifically their connective tissue is inadequately cross-linked and therefore weaker. The specific defect is in the Fibrillin-I gene on chromosome 15. Fibrillin-I is a glycoprotein secreted by fibroblasts. Affected patients are typically tall and slender with long, thin arms and fingers—
arachnodactyly or “spider fingers.” There are certainly musculoskeletal manifestations of the disease, but the life threatening manifestations are cardiovascular. Because their blood vessels are weak, arteries like the aorta are at a greatly increased risk of dilation and rupture. Other manifestations include an abnormal chest wall shape, hypotonia, micrognathia, nearsightedness, retinal detachments, and a high probability of dislocation of the lens of the eye.

The gene for Huntington disease is located on chromosome 4. The abnormal protein, huntingtin, accumulates in brain tissue, causing relentless neural deterioration—including mental deterioration and involuntary, writhing movements of the extremities known as chorea. It is an ugly, prolonged death, typically taking about 10 years. This condition is high on most physicians’ lists of diseases they don’t want to have. Typically, symptoms don’t appear until about age 40—when most peoples’ reproductive age is about over. So, before people realize they have the disease they may have already passed it on to their children. The gene was characterized in 1993 making genetic testing of family members possible.

Neurofibromatosis (NF) or von Recklinghausen’s disease is a variably expressed condition that stimulates tumor growth. (We mentioned it briefly under gene expression.) These neurofibromas arise because of a mutation in the neurofibromin gene found on chromosome 17. This gene is a tumor suppressor gene (more later) whose normal function is to inhibit production of a particular protein known as the \( p21 \) ras oncoprotein. In the absence of this gene’s inhibition cellular proliferation is erratic and uncontrolled. Most of these tumors arise within the skin and most are benign. In some individuals NF may produce only pigmented skin lesions called \( \text{café au lait} \) (coffee and cream) spots, but when tumors arise they may occur anywhere—including the brain, eyes, and nervous system. Neurofibromas can originate from any cells arising from the embryological structure known as the neural crest. The disease is autosomal dominant, but 30-50% of patients have no family history of the disease. In these
individuals NF arises because of a mutation of the neurofibromin gene, and the gene then acts like any other autosomal dominant gene.

The eye lesions in NF are known as Lisch nodules.iii

Story Time

During my residency I served in an Elders’ Quorum Presidency with a man whose wife’s parents had a condominium at Snowbird, in Little Cottonwood Canyon above Salt Lake City. They were kind enough to offer to let us hold a party at their condo, and we, of course, quickly accepted. While we were up there we noticed that the mom would occasionally exhibit a combination huddering/shivering/writhing type motion for a few seconds and then look OK. It wasn't too much later that she was diagnosed with Huntington disease. My counselor and his wife already had one little boy, and of course were worried about whether or not the wife could pass the gene on to their children. It was a difficult decision for her whether or not she wanted to be tested for the gene. An early diagnosis could help them in their family planning, but the disease is untreatable so would do nothing for my counselor’s wife. If she had the gene, health and life insurance would effectively not be available to her. (There is some legal protection in place now, however.) She ended up getting the test ordered, then got cold feet and cancelled. They have ended up with three children. As far as we know everybody is doing fine.

Autosomal recessive disorders

Let’s now consider autosomal recessive disorders. Again, understanding, not memorizing this material will enable you to quickly recall the characteristics of these disorders, which include:

1. Again, males and females are equally likely to be affected;
2. For an individual to be affected (in this example, the “dd” genotype) both parents must be carriers;
3. Unaffected individuals may transmit the disease to offspring (which is the definition of a carrier state) if they mate with another carrier; and
4. The mating of two heterozygous carriers results in a 25% risk of affected offspring and a 50% risk that the offspring are carriers themselves (“Dd”).
Nearly everybody carries several undesirable recessive mutant genes, but affected children can only be born if both parents have the gene. The practice of *consanguinity* (mating with a close relative) increases the risk of having children that express autosomal recessive disorders. I would not recommend this practice. It really is best not to marry your brother or sister.

The next condition is known as *albinism*. Individuals with this condition lack color in the hair, skin, or iris of the eye because of a lack of the ability to produce or distribute the pigment known as *melanin*. These pigment producing cells, known as *melanocytes*, lack the enzyme *tyrosinase*, which metabolizes the amino acid *tyrosine* into melanin.

Some of the albinism support groups are upset because albinos are frequently portrayed in movies as the bad guys. What is definitely bad, however, is that these patients are very likely to develop skin cancers because they lack protective pigment. They also have visual challenges because they also lack functional pigment cells normally found in the retina.

Even African-American individuals may be affected by albinism. This young lady is posing with her mother.

*Phenylketonuria (PKU)* is the inability to metabolize the amino acid phenylalanine. This amino acid’s metabolites build up in the body and nervous system, affecting nervous system development. The syndrome is named for the presence of these metabolites (*phenylketones*) in the urine. PKU is one of several *inborn errors of metabolism* that by law are screened for in every live birth in most states. (Do some states not care if they have a bunch of brain damaged kids hanging around? Why don’t all state require screening?) It is desirable to make the diagnosis at birth because if *phenylalanine* is excluded from the diet normal neurological development occurs. An idea of what the diet for PKU entails is included in this next graphic.

There are different degrees in severity in PKU patients. Some children and adults exhibit few or no symptoms while only loosely maintaining a diet while others suffer terribly with minimal exposure. It is critical for *pregnant mothers* with PKU to maintain an extremely strict diet. There was a drug released in 2008 (Kuvan®), which increases to some extent activity of the enzyme *phenylalanine hydroxylase*, but strict dietary control is still important.
**Cystic fibrosis**, CF, or *mucoviscidosis* is the most common single-gene lethal recessive disorder in Caucasians. 5% or so of white Americans carry this gene. CF is present in about 1 out of every 2500 live births, and affects all exocrine glands in the body. Recall that glands exist in both endocrine and exocrine varieties. Exocrine glands are gland with ducts and include sweat glands, sebaceous glands, mucous glands, and the exocrine (digestive) portion of the pancreas. Endocrine glands are ductless and release products called hormones.

The name cystic fibrosis refers to the characteristic scarring (fibrosis) and cyst formation within the pancreas. Measuring the chloride levels in sweat—the **sweat chloride test**, makes the diagnosis. Nutrition is a problem because of the lack of digestive enzymes from the pancreas, but usually death is brought on because of pulmonary damage. The prognosis has improved recently such that as of 2008 the life expectancy of these patients was 37 years—a big increase.

**Story Time**

We have some good friends that have four children—all with CF. We all figured that they just had incredibly bad luck, but a visit with a geneticist at the University of Utah revealed that they didn’t have the typical autosomal recessive inheritance pattern. The expectation was that all of their children would have CF. It probably would have been nice to have known that earlier. We should all remember that there are exceptions to every rule.

**Sex-linked (X-linked) disorders**

**Sex-linked disorders** are recessive and the gene is on the “X” chromosome. Characteristics of these disorders include:

1. Affected individuals are male (except in the very rare homozygous state),
2. Fathers transmit the gene to none of their sons, but all of their daughters,
3. Unaffected males do not carry the gene, and
4. A carrier female has a 50% chance of producing an affected son and a 50% chance of producing a carrier daughter.

As an example of a sex-linked disorder let’s discuss hemophilia A, a bleeding disorder associated with a deficiency of clotting factor VIII. Affected individuals bleed spontaneously or excessively with minimal injuries. Several European royal families were afflicted because of their fondness of consanguinity—still a bad idea. There is a variant of the disease, hemophilia B, that worldwide affects about 10% of hemophiliacs, but we have a disproportionately higher percentage of
“B” patients in the intermountain west because a polygamist in the 1800’s carried the gene and had lots of children. (Polygamists tend to do that.)

The hallmark of the disease is hemoarthrosis—bleeding into joints. The blood serves as an excellent medium for fibrosis to occur, and even new bone formation, which severely deforms and limits the motion of the joint.

Story Time

Not long after I started my private practice I saw a young man in his 20’s that had hemophilia and (unsurprisingly) was having problems with nose bleeds. As I began the examination he quickly stopped me and told me to be careful because he had AIDS. It used to be the case that hemophiliacs received human clotting factors pooled from about 60 different donors, and one of his donors turned out to have the HIV virus. The patient died about 6 months after I first met him from AIDS. Currently, the missing clotting factors are available through recombinant DNA technology. This means that the factors are synthesized in the lab and there is no risk of transfusion-associated conditions like AIDS.

My parents’ second mission together was a medical and humanitarian mission in Hanoi, Vietnam. Part of their calling was to identify worthy projects for the Church’s humanitarian services to address. There was a hospital specifically for hemophiliacs that wanted the Church’s assistance, so my parents visited to look the place over. My Dad, a pediatrician, noticed that about half of their patients were female—an obvious red flag for a disease that is usually sex-linked. He asked the director how this could be, and was told that blood testing wasn’t really necessary. If my Dad had as much experience with hemophilia as he did, you would be able to diagnose the females with the disease. Needless to say, the project wasn’t approved.

Multifactorial (polygenic) disorders—the rule, not the exception

Our discussion thus far may lead unwary students to believe that every disease known to mankind can be categorized under one of these inheritance patterns. However, it turns out that a single gene does not cause most diseases with a genetic component of their etiology. Examples include hypertension, cancer, diabetes, heart disease, and many more.

As an example, let’s briefly discuss breast cancer. In the United States, as a generalization, the risk of a female being diagnosed with breast cancer is about 1 in 8 or 12.5%. The risk doubles (to 25%) if a woman has a close relative—mother or sibling—with breast cancer. Of all women with breast cancer, about 7% are associated with one of two
breast cancer genes—**BRCA1 or BRCA2**. These acronyms stand for breast cancer susceptibility gene 1 and 2. A woman’s lifetime risk of developing breast or ovarian cancer is greatly increased if she has one of these genes. For instance, BRCA1 positive women have a lifetime risk of 60-85%! BRCA2 is common among men that develop breast cancer (which does happen) and also increases the risk of prostate cancer. The lifetime risk for most women of developing ovarian cancer is about 1.4% (14 out of every 1000 women) compared with a 15 to 40% risk in women with either gene.

Now that your confidence in the field of genetics has been shaken, let me remind you that the principles of genetics you have learned thus far are very important and worth remembering. Recalling the inheritance patterns and basic of each of these representative conditions should aid your understanding of the genetics of disease.

**Environmentally induced congenital disorders**

Congenital disorders are present at birth, but many are NOT associated with genetic disorders. Let’s discuss other causes of congenital disorders.

*Teratology* is the branch of embryology and pathology that deals with abnormal development and congenital malformations. Agents that cause the conditions are known as *teratogens*. These agents are particularly likely to cause fetal damage during *periods of fetal vulnerability*. Let’s consider a few examples.

Topiramate (Topomax®) is an anti-seizure drug that increases the risk of cleft palate in infants exposed to the drug during the first trimester of pregnancy. The prevalence of clefts in exposed fetuses is 1.4% compared to a prevalence less than 0.55% in infants exposed to other antiepileptic drugs. The prevalence of clefts in infants in the general population is 6.39 out of 10,000 births or 0.00639%.

The **congenital rubella syndrome** is a classic triad: sensorineural deafness, eye abnormalities (like cataracts), and congenital heart disease (like atrial septal defects). If a mother is infected 0-28 days before conception there is a 43% chance the infant will be affected. If the infection occurs 0-12 weeks after conception the infant has a 51% risk of being affected. 13-26 weeks after conception induces a 23% change, but if rubella occurs after 20 weeks gestation the infant is not usually affected.
Other teratogens include:

1. *Diethylstilbesterol (DES)* is an estrogen analog previously given to prevent miscarriage (known as spontaneous abortion). Female infants exposed to the drug have a much higher risk of vaginal cancer and other reproductive disorders.

2. *Thalidomide* is a sedative drug marketed in Europe in the late 1950’s. Prenatal exposure to this drug can cause several abnormalities in limb development. Interestingly enough, this drug is available in the US and is being studied as a treatment of a particularly vicious cancer known as multiple myeloma and a complication of leprosy. Intrauterine alcohol exposure can result in the *fetal alcohol syndrome*.

3. Abnormal facial growth and development; central nervous system problems including mental retardation; abnormalities in the heart, kidneys, bones, and hearing; and a host of others.

4. The *TORCH syndrome* is an acronym for several infectious organisms: toxoplasmosis, others, rubella, cytomegalovirus, and herpes. These organisms cause similar teratologic phenomena similar to the congenital rubella syndrome described above. This infant has the typical (but not universal) “blueberry muffin rash” of the TORCH syndrome. Measuring antibody levels against the various organisms usually makes the diagnosis.

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**Neoplasia (tumor development)**

**Basic terminology in neoplasia**

*Neoplasia* (“neo”-new; “plasia”-growth) refers to the development of tumors. The word tumor actually means “swelling,” but it is also accurate to use this term to describe an uncontrolled growth of abnormal cells. We will use “tumor” interchangeably with “neoplasm.”

Neoplasms exist in two broad categories: *benign* and *malignant*. Benign tumors do not *metastasize* or spread distantly. Malignant tumors are more invasive locally and can metastasize.

As a broad generalization benign tumors are less life threatening than malignant ones, but we shouldn’t assume that benign tumors are not problematic. I often think of neoplasms like this as benign tumors in a malignant location.
Other characteristics of benign and malignant neoplasms are summarized here

**Characteristics of Benign and Malignant Tumors**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microscopic</strong></td>
<td>Similar to tissue of origin; few mitoses</td>
<td>Anaplastic; pleiomorphic; many mitoses; nucleus relatively larger compared to cell size;</td>
</tr>
<tr>
<td><strong>appearance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>None</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Growth rate</strong></td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td><strong>Tumor necrosis</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Strictly local, often encapsulated</td>
<td>Invasive; no capsule</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Usually good</td>
<td>Dependent on tumor type and treatment, stage, grade, etc.</td>
</tr>
</tbody>
</table>

During development, all of our cells arise from one zygote, and then gradually undergo a process of *differentiation*—the development of specialized structure, organization, and/or function. To one degree or another neoplastic cells undergo a process called *anaplasia* in which they lose their differentiation. This is particularly true in malignant neoplasms. In general, the more anaplastic the tumor cells are the more threatening is the neoplasm.

**Priorities in treatment**

As a general approach to treatment of tumor patients there are several priorities:

1. **Early diagnosis.** The only way to definitively diagnose a tumor is to perform a *biopsy*—remove at least part of the lesion and send it to a pathologist (a specially trained physician). The pathologist will prepare the specimen for microscopic analysis, examine it, and then render the ultimate diagnosis. Pathology is a challenging specialty, and pathologists aren’t perfect. However, they generally do a
good job. Early diagnosis allows treatment to begin at an early stage.

2. **Complete staging.** Cancer stage is a description of how widespread the cancer is at the time of diagnosis and pretty much always matters. Each cancer type has a unique staging method, but a simple and quite universal staging system is stage 1-4. Stage 1 cancers are early and usually well localized. In stage 4 the cancer is not only large, but also widespread. Patients with higher stage cancers tend to be treated with multiple modalities of therapy. For example, surgery and radiation or radiation and chemotherapy.

3. **Timely, scientific treatment.** The cancer type and stage are critical in making a treatment plan. As time goes on and science progresses our understanding of various cancers improves and the outcome generally improves as well. In our current information age many (most?) cancer patients can be treated close to home. This is a good thing both in cost savings and convenience.

4. **Close follow up.** Cancers tend to recur (return). In the instances where it does we are better off knowing about the recurrence earlier rather than later. For instance, I treated many patients with cancer of the mouth and throat. I told them that if their cancer was going to recur it would be most likely to do so in the first year, with numbers like 80% or so being a good generalization. A further 10% or so would recur in the second year, and then occasional recurrences are seen further down the line. My routine for most of these patients was to see them every month for the first year, about every other month for the second, and then gradually less frequently as time progressed. I would tell them that I wanted to see them regularly for as long as I stayed in practice and they stayed here on earth.

**Nomenclature (naming) of neoplasms**

*Carcinomas* cancers that arise from epithelial tissues. Characteristics of epithelial tissues are: they line body surfaces, both inside and out; they lie on basement membranes; their cells are tightly packed together, enough so that no blood vessels are present.

*Carcinoma in situ* is a term that refers to carcinomas that have not yet invaded the basement membrane.
Sarcomas arise from connective tissues like bone, muscle, nerve sheaths, etc. This image is a photograph during surgery of a large sarcoma (not a large baby frog).

Lymphomas\(^\text{ix}\) are of lymphatic tissue origin like lymphocytes (one variety of white blood cells), lymph nodes, spleen, thymus, or other similar lymphoid tissues.

Gliomas arise from glial cells, which are supporting or helping cells in the nervous system. Glia include myelin-producing cells like oligodendrocytes (in the central nervous system or CNS) and Schwann cells (in the peripheral nervous system or PNS).

Leukemias\(^\text{ixi}\) arise from blood forming tissues like bone marrow. The malignant bone marrow produces overwhelming numbers of malignant non-functioning cancer cells, which crowd out and replace functional blood cells.\(^\text{ixii}\) The diagnosis is made by biopsying bone marrow or a microscopic examination of peripheral blood. 90% of leukemia patients are adult, with the remaining 10% children.

Melanoma\(^\text{ixiii}\) is a cancer of melanocytes (pigment producing cells). They are very threatening cancers, occurring most commonly on the skin. These neoplasms are strongly associated with exposure to sunlight.

Genetic mechanisms of cancer

Cancer is predominantly a disorder of gene expression—it is a genetic disease. We have already discussed mutagens—substances capable of inducing genetic mutations. Mutagens that induce cancer-forming mutations are called carcinogens, and carcinogenic mutations occur in two basic classes of genes—proto-oncogenes and tumor suppressor genes.

Proto-oncogene mutations are usually expressed in a dominant fashion, and the mutated version of a proto-oncogene is known as an oncogene. ("Onco-" means "cancer." ) A recent study\(^\text{ixiv}\) examined over 1,000 different tissue samples in 17 different types of cancer. This study showed that mutations in 14 different proto-oncogenes (see above figure) are associated with a high likelihood of developing cancer.
To clarify the terminology, oncogenes are cancer-causing genes. **Proto-oncogenes are normal genes** that mutate and cause normal cells to become cancerous. **Proto-oncogenes** encode proteins that function to stimulate cell division, halt cell death, and inhibit cell differentiation. These are all functions that normal cells need; but when these proteins are over-expressed cells divide at excessive rates, resist apoptosis, and exhibit decreased cellular differentiation—all characteristics of cancer cells.

Historically, oncogenes were discovered first. As the normal, unmutated versions of oncogenes were discovered they came to be called proto-oncogenes. ("Proto-" means "before.") Today, more than 40 different human proto-oncogenes are known. Proto-oncogenes are typically turned off once the developmental processes they regulate are completed. However, if proto-oncogene activity either remains high, or these genes are inappropriately re-activated, cancer can result.

Probably the best-known example of proto-oncogenes is the family of genes known as ras. We will refer to this family of genes as if they were one. (I suppose that is the same as referring to everybody in the Jones family as a Jones.) Ras is a G-protein that relays growth signs from outside the cell into the cell’s nucleus. If the cell is a car, ras represents the ignition switch. Activation of ras stimulates cell growth, differentiation, and survival. Cells in which ras is mutated and remain in the “on” position have a high likelihood of becoming cancerous. Ras mutations are caused by a single point mutation, and are common enough in malignancies as to be present in over 1/3 of all human cancer patients!

Let’s now discuss a specific mechanism by which proto-oncogenes are transformed into oncogenes. **Retroviruses**, the most notorious of which is the HIV virus, are RNA viruses that carry a unique enzyme called reverse transcriptase that directs the synthesis of a DNA copy of the viral RNA. This viral DNA is then transported to the nucleus, where another viral enzyme called integrase inserts it into the cell’s native
DNA. The normal sequence in an uninfected cell is DNA→RNA→protein. When retroviruses are involved the sequence changes into RNA→DNA→RNA→protein. There are many retroviruses that have permanently been inserted into human DNA, and are thought to constitute 5-8% of the total human genome!

If the viral DNA happens to be inserted near a *promoter sequence* (“on” signals that tell a cell to use a particular gene) the viral genes are continuously transcribed and used to make new viral RNA. The tendency of retroviruses to slip in and out of host genomes allows them to pick up some of the host’s genes, particularly growth-promoting proto-oncogenes. Reverse transcription is a fairly imprecise process in which proto-oncogenes are often mutated into oncogenes. Retroviruses then carry these genes into neighboring cells, inducing malignant transformation.

*Tumor suppressor genes* also inhibit cellular proliferation. Loss of function of these genes predisposes to cancer formation. The first tumor suppressor gene discovered was the *Rb gene*. Rb stands for retinoblastoma, an unusual malignancy of the retina. The normal function of Rb is to suppress excessive cell growth until a cell is ready to divide. Interestingly, it is not known why an eye cancer results from a mutation in a gene that is important all of the body. Fairly recent data suggests that the *Rb gene* is also important in development of the placenta—the organ connecting a developing fetus to the mother’s uterus.

*P53* is probably the most important tumor suppressor gene because, as already stated, over half of all human malignancies contain mutant p53. The BRCA1 and BRCA2 genes are also tumor suppressor genes in their normal, healthy state.

**Carcinogenesis**

Carcinogenesis is the process by which cancers develop. Let’s spend a few minutes on this subject so that you don’t come away with a false impression that it is a simple, one-step process. Simply mutating a proto-oncogene or knocking out a tumor suppressor gene is generally not enough to do the job. However, as a simplification we could say that the three basic steps in carcinogenesis are:

1. Initiation,
2. Promotion, &
3. Progression.
Most of our recent discussion in the section “genetic mechanisms of cancer” involved the initiation process. For instance, mutations that begin the transformation of proto-oncogenes into oncogenes and inactivate tumor suppressor genes involve initiation. Carcinogens come into play in this step; and in many cancers this initiation process involves not just one, but multiple mutations.

During the promotion stage the mutant cells proliferate. There are often additional mutations that occur here, but nonmutating factors also play a role. For instance, infection, nutritional factors, hormonal growth factors, and additional noxious substances all may play a role. In patients with breast, ovarian, and endometrial cancers estrogens play an important promoter role. Women that begin menses at an early age and complete menopause at a later age have a longer exposure to reproductive hormones. These women are at an increased risk to develop reproductive cancers. A similar relationship exists between prostate cancer and testosterone. Most patients with throat cancers are not only heavy smokers, but heavy drinkers as well. It is thought that alcohol plays the role of a promoter.

Finally, these damaged and mutated cells undergo progression. More mutations occur, and cells that develop a growth advantage over their neighbors win the evolution race. The phenotype of these cells change in many ways, including cellular morphology, metabolism, and biochemical composition. Some cells evolve lytic enzymes that allow them to invade surrounding tissues. Most cancer cells contain telomerase, which allows them to rebuild their telomeres and overcome the Hayflick limit. Malignant cells also lose sensitivity to crowding that normally inhibits proliferation, and also often produce angiogenesis factors which stimulate formation of new blood vessels to nourish the developing neoplastic cells. A common example of an angiogenesis factor is vascular endothelial growth factor (VEGF).

Aneuploidy, the presence of an abnormal number of chromosomes, is also common in cancers.\textsuperscript{lxxxi} Jacquelyn L. Banasik: Genetic and Developmental Disorders. In Copstead, Lee-Ellen and Banasik, Jacquelyn Pathophysiology 4th Ed. 2010, St. Louis, Saunders Elsevier p. 144. This occurs not because of mutation, but because of errors in mitosis. Through autocrine stimulation\textsuperscript{lxxxii} many malignant cells actually produce their own growth hormones and factors, decreasing their reliance on external stimulation. The final product is fully developed neoplastic cells with many abnormal behaviors and characteristics.
Metastasis and cancer behavior

Distant spread of cancer (metastasis) can occur by many routes: through blood vessels; through lymphatic vessels (which is the most common route); or invading through serous membranes and then spreading through body cavities—a process known as seeding.

Although not always predictable, certain cancers tend to spread to certain locations, a phenomenon called organ tropism. For example, prostate cancer, a malignancy primarily of older men, typically spreads first to lymph nodes in the pelvis. It next usually spreads to bone, and this is reliable enough that in an elderly man with a bony metastasis (typically manifesting as a pathological fracture) the most likely diagnosis is metastatic prostate cancer.

Tumor markers are substances that are produced by some cancer cells that may be useful in several ways:

1. Identifying the tissue of origin of poorly differentiated cancers.
2. Screening individuals at high risk for a certain cancer.
3. Following the clinical course of certain cancer patients.

For example, common practice is to measure levels of prostate specific antigen or PSA in the bloodstream of older men. If the PSA level is rising, a vigorous search for prostate cancer is often indicated. Successful treatment would be expected to drop the PSA level. Such patients usually have periodic PSA levels checked after treatment, and if the PSA level rises later there is a high possibility of a cancer recurrence. There are a multitude of tumor markers, but the majority of cancers do not produce them.

We previously discussed cancer stage, but cancer grade is sometimes useful as well. Where stage is a description of how widespread a cancer is at the time of diagnosis, cancer grade is a description of how closely a cancer’s cells resemble their tissue of origin (how abnormal they appear under a microscope). High grade cancers may look nothing like the parent tissue, and low grade cancers sometimes hardly appear to be malignant when viewed microscopically. Cancer stage is essentially always relevant and important, but in many cancers the grade does not carry anywhere near the significance of stage.
Effects of cancer on the body

Pain\textsuperscript{lxxxvii} doesn’t occur often in early stage cancers, but \textit{most terminal cancer patients have significant pain.}

\textit{Fatigue} is the \textit{most common symptom} both because of the cancer itself and also because of the cancer treatment.

\textit{Cachexia} is profound weight loss and the most severe form of malnutrition. It occurs because of multiple factors:

- \textit{Anorexia} – not eating, often due to loss of appetite;
- \textit{Early satiety} – getting “full” more quickly than usual;
- \textit{Asthenia} – weakness;
- \textit{Altered metabolism} – the cancer can “steal” necessary nutrients that would normally be available to the rest of the body;
- \textit{Altered taste} – which contributes to anorexia;
- \textit{Increased metabolic rate} – which also contributes to the cachexia; and
- \textit{Nutrient mobilization from normal body tissue} – the cancer stimulates normal body tissues to be broken down, which may occur both during metastasis and also so the necessary raw materials can be supplied to the tumor.

\textit{Immune system deficits} may occur due to a variety of mechanisms including as a side effect of treatment, and also because many neoplasms are immunosuppressive in their behavior. No matter the mechanism, however, the prognosis worsens when the immune system is depressed.

\textit{Suppression of bone marrow activity} has many consequences. Bone marrow is where blood cells are formed, and clinical manifestations of marrow suppression include:

- \textit{Anemia}\textsuperscript{lxxxviii} — deficiency in either numbers of red blood cells and/or deficiency in RBC hemoglobin content. In either situation the oxygen carrying capacity of blood is decreased.\textsuperscript{lxxix} \textit{Erythropoietin} is a hormone produced by the kidney that stimulates RBC production. It is commercially available (and really expensive) and is sometimes used to treat anemia.

- \textit{Leucopenia} – is a deficiency in white blood cell (WBC) numbers that may lead, in turn, to:
  - \textit{Opportunistic infections} – infections due to microorganisms that would not be threatening to immunocompetent hosts;
Infections from any pathogenic organism.

- **Thrombocytopenia** – deficiency in platelet (thrombocyte) numbers – predispose the cancer patient to hemorrhage (like this hand).
- **Paraneoplastic syndromes** – manifestations that cannot be explained by the presence of the cancer cells themselves. These occur in 10-15% of cancer patients.

Cancer therapy

Options to treat cancers include surgery, radiation therapy, chemotherapy, and immunotherapy as well as several adjunctive measures. As a generalization, lower stage (1 & 2) cancers are often treated with one modality of therapy while higher stage malignancies often require multiple methods of treatment.

*Surgery* is often employed for solid tumors and can be curative in localized (early stage) disease. Cancer surgery is challenging for many reasons, not the least is which that it often distorts the expected normal anatomy. An expert cancer surgeon not only is skilled at resection (removal) but also at a variety of reconstructive techniques. Useful adjunctive measures in surgery include *frozen section margin control*, which involves sending grossly normal-appearing tissue from the borders of the resection for immediate examination, looking for microscopic foci of cancer by a surgical pathologist. This image above was taken immediately after resection of a tongue cancer that was reconstructed by harvesting tissue from the forearm and transferring it to the surgical defect in the tongue—a “radial forearm free flap.”

*Radiation therapy* can be useful in killing tumor cells that have escaped surgery or chemotherapy or destroying tumors in areas that are not surgically accessible. It damages cellular DNA and also may attack the blood supply of tumors. It is useful in monotherapy for certain localized tumors or to treat the regional lymph nodes where there is a reasonably high likelihood of microscopic metastasis may be present. It does damage surrounding normal tissues to some extent, so in order to minimize this damage radiation is usually delivered gradually over a period of several weeks, and precise aiming of the radiation is critical. Radiation may be delivered by directing a beam of ionizing energy into the body from an external machine—*external*
beam radiation therapy. It may also be accomplished by implanting radioactive substances (like these pellets placed into the pelvis to treat prostate cancer) into the body in or near cancers—brachytherapy. It is also possible to injection radioactive isotopes into the bloodstream or lymphatic system to treat cancers that takes up these isotopes. For instance, many thyroid cancer patients are treated with an injection of radioactive iodine.

Chemotherapy involves the systemic administration of anti-cancer chemicals. Because chemo treats the entire body it is often used in wide-spread (poorly localized or high stage) malignancies. In general they interrupt some vital part of cellular life and metabolism, so are often referred to as being cytotoxic. Common targets involve interrupting DNA, RNA, or protein synthesis. The previously discussed nutlin-3 acts to restore the normal function of the p53 gene. The DNA/RNA effect is usually apparent during cell division, and any and all dividing cells are affected. Thus, hair loss, bone marrow suppression, or skin and mucous membrane toxicity is common because these normal body tissues replicate fairly rapidly under normal circumstances.

Important concepts to understand regarding chemotherapy include:

1. Chemotherapeutic medications are usually delivered in multiple-drug combinations in order to attack multiple metabolic targets. If cancer can be likened to a criminal that needs to be killed, we might shoot, stab, bludgeon, shock, drown, and strangulate the intended victim in order to make sure the job gets done. (I can recommend the chemo, but don’t condone the violence.)
2. The principle of dose intensity dictates that the highest tolerable dosages of the chemo drugs be utilized. The dilemma is to maximize the possibility of a cure while minimizing toxicity. Hopefully the cancer will be killed without ending the patient’s life.
3. The timing of chemotherapy administration is also important. Adjuvant chemotherapy is given after local treatment (like surgery or external beam radiation therapy) to “sterilize” potential micrometastases. This is a common strategy, for instance, in breast cancer. Primary or neoadjuvant chemotherapy is given before local therapy to shrink the primary tumor site as well as to control microscopic metastatic disease.
4. A complete response or remission is defined as the disappearance of all malignant cells after treatment.
Unfortunately, CR is not synonymous with cure. Only patients that have been in remission for some period of time (months to years, depending on the cancer) are considered likely cures.

5. A *partial response* is a 50% decrease in the burden on cancer cells. There are patients that respond in lesser ways, like 30% for instance, but from a strict response standpoint these patients are considered non-responders.

*Immunotherapy* for cancer treatment\(^\text{xcviii}\) involves using the immune system to reject the malignancy. Cancer cells generally display abnormal surface markers (antigens), and harvesting cancer cells and synthesizing antibodies against these antigens can be very effective—but expensive, cumbersome, and for the most part impractical with our current technology. There are a half dozen or so monoclonal antibodies that are available commercially, but these are not tailored to each individual patient. Even though this mode of cancer therapy is not widely available it does show immense promise. My personal bias, despite the fact that I think and hope that this will be the cancer therapy of the future, immunotherapy is the *least likely to be currently available or useful*. I hope to be eating my words soon.

*Gene therapy* may hold the same promise for the future, but the drawbacks and limitations match those of immunotherapy.

*Stem cell transplantation*, commonly called *bone marrow transplantation*,\(^\text{xcix}\) involves either “rescuing” patients who have had their bone marrow destroyed by either the cancer or the cancer treatment, or replacing bone marrow that has been overtaken by malignant cells. It turns out that hematopoietic stem cells do circulate to some extent in the peripheral bloodstream. It is possible to harvest these cells, save them, administer aggressive cytotoxic chemotherapy and/or radiation therapy, then re-infuse the patient’s own stem cells to repopulate their bone marrow. This is not an uncommon therapy, for instance, in some advanced cases of breast cancer.

**Epidemiology and risk factors of cancer**

Cancer accounts for 25% of all deaths, which is second only to heart disease. Men’s risk of developing some form of cancer over the course of their lives is about 1 in 2. Women have about a 1 in 3 risk. Overall, the 5-year survival rate for all cancers is about 62%. One-third of all cancers are caused by lifestyle choices—tobacco, poor nutrition, sun
exposure, unsafe sexual behavior, etc. We will discuss more details later in the course.

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**Vocabulary for Bio 381 Lesson 1**

*There are lots of terms here, but don’t despair—it will definitely be worth the effort. We’ll be using these terms the entire remainder of the semester—and even your entire careers.*

1) **Aberration**—a departure from the norm; an abnormality
2) **Abortion**—termination of pregnancy
3) **Adjuvant**—serving to help or assist; auxiliary
4) **Aging**—is a matter of the mind. If you don’t mind, it doesn’t matter.
5) **Albinism**—the state of being an *albino*: a person without pigment
6) **Alleles**—or traits come in two basic varieties—*dominant* and *recessive*.
7) **Allele**—different varieties of a specific gene; think of them as different recipes for a similar product.
   a) **Dominant alleles**—are expressed even if the other allele is different.
   b) **Recessive alleles**—are *masked* by the presence of a dominant allele, and will only be expressed if a person is homozygous for that recessive allele.
8) **Anaplasia**—loss of differentiation, a characteristic of malignant neoplasms
   a) There are differing degrees of anaplasia—it’s not just you have it or you don’t.
9) **Anemia**—inadequate oxygen carrying capacity of blood, either from a shortage of red blood cells or functional hemoglobin within red blood cells
10) **Aneurysm**—literally, “without oxygen.” When used to describe bacteria this term refers to organisms that are unable to survive in the presence of oxygen.
   a) **Aneuploid**—possessing a non-ploidy number of chromosomes
11) **Angiogenesis**—the formation of and development of blood vessels
   a) Because cancers are so metabolically active they require large blood supplies. They produce substances like VEGF (*vascular endothelial growth factor*) so they can stimulate development of the new blood vessels they need to survive and grow
12) **Anorexia**—loss of appetite or inability to eat
13) **Apoptosis**—“cell suicide” or “programmed cell death.” As opposed to the human variety of suicide, apoptosis is a normal cellular function.

14) **Arachnodactyly**—abnormally long fingers & toes
   a) “arachno” – spider-like, long & skinny; “dactyly”—pertaining to digits

15) **Ashkenazi**—Jews of central or eastern European origin

16) **Asthenia**—weakness

17) **Atrial septum**—the wall between the upper two (right & left) chambers of the heart

18) **Atrophy**—wasting away; degeneration, decline, or decrease.
   i) “a”—not or without & “trophy”—feed

19) **Autocrine**—relating to the production of a substance by a cell that acts on the surface receptors of the same cell

20) **Autosomes**—the non-sex chromosomes: chromosome pairs 1 through 22.

21) **Benign**—not malignant; your age after you be eight

22) **Bilirubin**—a metabolic byproduct produced during the recycling of heme
   a) from **hemoglobin**—the iron-containing, oxygen carrying molecule in red blood cells RBCs

23) **Brain death**—the expected state of most teenagers. Don’t feel bad. I was one myself once. Centuries ago.

24) **Cachexia**—ill health with emaciation (severe weight loss)

25) **Café-au-lait**—brown skin color; literally means “coffee and cream”
   (1) Cancer grade doesn’t always matter much, but cancer stage always matters.

26) **Cancer grade**—a description of how closely a particular cancer’s cells resemble their cells of origin. More anaplastic cancers are higher grade—they don’t resemble their cells of origin.

27) **Cancer stage**—a description of how widely spread a cancer is at the time of diagnosis.

28) **Carcinogenesis**—the process by which cancers develop

29) **Carcinogen**—a cancer-causing agent

30) **Carcinoma**—a malignant neoplasm arising from epithelial tissue
   a) **Carcinoma in situ**—an early carcinoma that has not yet invaded or penetrated the basement membrane of epithelial tissue

31) **Cardiomyocyte**—heart muscle cells

32) **Carrier**—a person possessing an unexpressed, recessive trait; the bearer of a defective gene who is not affected but who can transmit the disease to offspring

33) **Caseous**—the word actually means “like cheese”
34) **Caspases**—any of a group of proteases that mediate apoptosis
35) **Cataract**—clouding of the lens of the eye
36) **Chorea**—any of several diseases of the nervous system resulting in jerky, involuntary muscle movements
37) **Clotting factors**—a number of plasma proteins necessary to stop bleeding (specifically, coagulation)
   i) I think somebody ran out of names, because the clotting factors are referred to by numbers.
   ii) I have considered doing this with my children. Think how handy this would be.
38) **Codominance**—expression of both heterozygous alleles
39) **Codon**—a triple of adjacent nucleotides in DNA/RNA that codes for a specific amino acid during protein synthesis
40) **Complete response**—response to cancer therapy that causes all discernible cancer cells to have been destroyed. A term often used nearly synonymously is remission.
41) **Congenital**—a condition present at birth
   a) Congenital disorders are not necessarily genetic. For instance, fetuses affected by certain infections (like rubella, cytomegalovirus, etc.) have congenital abnormalities that are not genetic in etiology.
42) **Conjugate**—to join together
43) **Consanguinity**—close relationship or connection
   a) In discussing genetics consanguinity refers to mating of closely related individuals—like marrying your sister, for instance. (Don’t do this, by the way. It is not only unsafe, it’s weird.)
44) **Crossing over**—the process by which homologous chromosomal pairs randomly exchange genetic material during meiosis
45) **Cyst**—a fluid-filled sac
46) **Cytology**—the microscopic study of cells, particularly in regards to disease
47) **Cytotoxic**—a substance that has a damaging (toxic) effect on certain cells
48) **Deafness**—eh? What did you say?
49) **Death**—there are definitely worse problems
50) **Deficit**—shortage, deficiency
51) **Deletion**—involves loss of a portion of a chromosome
52) **Denature**—to treat (a protein or the like) by chemical or physical means so as to alter its original state
   a) **Denatured proteins** have such an alteration in their structure so as to make them non-functional. (They lose their secondary and tertiary structure.)
   b) Think of what happens to an egg when you cook it. The proteins are denatured. Yum—denatured protein for breakfast...
53) Denervation—cut off the nerve supply
54) Differentiation—the development of specialized structure, organization, or function
55) Disuse—discontinuation of use
56) Duplication—a chromosome aberration in which a region of a chromosome is repeated
57) Dysplasia—abnormal cellular growth or development
58) Embryology—deals with the early stages of development, specifically week 2-8 after conception
   i) I do offer extra credit for those of you that remember your own conception.
59) Encapsulated—enclosed in a fibrous sheath or skin
60) Endothelium—the single-cell thick innermost lining of the heart and blood vessels.
61) Endotoxin—toxins liberated when some microorganisms die and disintegrate
62) Epicanthic fold—a redundant fold of upper medial eyelid skin
63) Epithelial tissues—line body surfaces, like the outside of the body, the lining of inner body cavities, etc.
   a) These tissues lie on a basement membrane.
64) Erythropoietin—a hormone produced by the kidneys that stimulates erythropoiesis (red blood cell production)
65) Exocrine—glands that secrete their products through ducts onto an epithelial surface; the counterpart of endocrine (ductless) glands that deliver their secretions (called hormones) into the bloodstream
66) Exotoxin—a soluble toxin secreted by some microorganisms
67) Expressed—a term used to denote the actual use of a particular allele
68) Expressivity—the degree to which a particular gene produces a given effect.
69) Fatigue—weariness
70) Feminization—development of female-like characteristics in a male
71) Fibrillin-I—the defective gene in Marfan syndrome found on chromosome #15
72) Fibroblast—a cellular factory that creates and secretes components of connective tissue
73) Fibrosis—formation of excessive fibrous tissue
74) Free radicles—also known as reactive oxygen species are atoms, molecules, or ions with unpaired electrons in their outer orbital shell. These particles are highly chemically reactive and may be involved in degenerative diseases and cancers.
75) **G-protein**—cell membrane proteins that are coupled to receptors on the surface of the cell. When the receptors bind to their ligand, the G-protein is what actually stimulates the intracellular response.

76) **Gangrene**—actually has a meaning much like “necrosis,” but “gangrene” is often used when not only the cellular death but also the decomposition and putrefaction that occurs after necrosis is included in the meaning.

77) **Gastroesophageal reflux**—regurgitation of stomach contents up into the esophagus.

78) **Gene therapy**—treatment to replace a missing or defective gene.

79) **Gene**—a stretch of DNA that contains the “recipe” or code for creation of a specific protein.

80) **Genotype**—our genetic make-up.

81) **Glial cells**—a class of cells that supports, nourishes, aids, or insulates neurons.
   i) “*glia*” – “glue”

82) **Glycogen**—the molecule used to store glucose, especially abundant in liver and skeletal muscle.

83) **Gynecomastia**—abnormal enlargement of the breast in a male.
   a) “*gyneco*” – female; “*mastia*”—breast.

84) **Haploid number** (*n* or *1n*)—the number of chromosomes in a gamete or germ cell (sperms cells & eggs). These cells are produced by meiosis.

85) **Hayflick limit**—the maximum (or so) number of cell divisions a cell can undergo before the telomeres become so short that apoptosis is initiated.

86) **Hepatocyte**—a liver cell.

87) **Heterozygous**—possessing different alleles of a specific gene on homologous chromosomes.

88) **Hexosaminidase A**—the missing enzyme in Tay Sachs disease, whose function is to break down intracellular lipids that need to be “recycled.”

89) **Homologous chromosomes**—pairs of chromosomes, each of which contain the same genes (alleles), but these genes are not necessarily identical (homozygous).

90) **Homozygous**—possessing identical genes on homologous chromosomes.

91) **Hydropic**—swelling and taking up fluid; *edematous*.

92) **Hyperplasia**—increase in cell number.
   a) “*hyper*”—over, above.

93) **Hypertrophy**—increase in size or mass.

94) **Hypotonia**—abnormally low muscle tone; limp or flaccid.
95) **Hypoxia**—inadequate oxygen levels
96) **Immunomodulate**—to modify the immune system
97) **Immunotherapy**—medical treatment using components of the immune system
98) **In situ**—in place or position, undisturbed.
99) **Inborn**—inherited; present at birth
100) **Infarction**—cell death due to loss of blood supply (or a ritual commonly performed around campfires at scout camp)
101) **Initiation**—to begin
102) **Integrase**—a retroviral enzyme that controls the insertion of retroviral genes into the host cell’s DNA
103) **Ischemia**—a local deficiency of blood supply
104) **Karyotype**—a description of the number and structure of chromosomes as seen under a light microscope
105) **Lactic acid (lactate)**—a byproduct of anaerobic cellular respiration
106) **Lethal**—deadly
107) **Leucopenia**—deficiency in white blood cell (leukocyte) numbers
108) **Ligand**—a molecule like a hormone, antibody, or drug that binds to a receptor
109) **Ligand**—any substance that binds to a receptor (like hormones, neurotransmitters, etc.)
110) **Lipase**—enzymes that digest (break down) fat
111) **Liquefaction**—to make liquid
112) **Lymph nodes**—filter lymph before it is returned to the blood stream
113) **Lymphatic**—pertaining to, containing, or conveying lymph
114) **Lymph**—excess plasma that leaves the blood stream, enters tissues, and is transported back to the blood stream through specialized **lymphatic vessels**
115) **Macroglossia**—an abnormally enlarged tongue
116) **Malaise**—generalized body weakness or discomfort
117) **Malignancy**—a cancer
118) **Malignant transformation**—the process by which normal healthy cells change into malignant cancer cells.
   a) **Malignant**—actually means tending to produce death (like the bubonic plague, for instance), however when used to describe neoplastic lesions the term means: characterized by uncontrolled growth, cancerous, invasive, able to metastasize
119) **Maternal**—pertaining to the mother
120) **Meiosis**—the process of cell division resulting in gamete production (spermatocytes & oocytes); these are 1n, germ, or haploid cells (see above for more details)
121) **Melanin**—a class of pigments found in all forms of animal life that accounts for the dark color of skin, hair, eyes, etc.
122) **Melanocytes**—pigment producing cells that arise from the neural crest
123) **Melanocyte**—a cell that produces pigment (*melanin*)
124) **Mendelian genes**—are genes that code for a single trait. The name comes from Gregor Mendel, the monk who we credit as the father of genetics
125) **Metabolism**—all the chemical reactions that occur in the body
126) **Metaplasia**—transformation of one type of tissue into another
127) **Metastasize**—distant spread of a tumor
128) **Microcephaly**—a small head
129) **Micrognathia**—an abnormally small or recessed chin
130) **Micrometastasis**—spread of cancer not visible with the naked eye
131) **Mitoses**—plural of mitosis; refers to cells viewed under a microscope that are actively dividing (undergoing mitosis)
132) **Mitosis**—cell division resulting in 2 genetically identical (clone) cells that are both 2n, somatic, or diploid cells
133) **Monosomy** ("mono" – “one”; “somy” – refers to the somatic or non-sex) chromosomes)—the circumstance in which one of the somatic chromosomes is missing
134) **Morphology**—shape
135) **Mucopolysaccharides**—are now called glycosaminoglycans, and are important components of many body tissues.
   a) I kind of like the name, myself. Talking about sugarcoated snot always cheers me up.
136) **Mucopolysaccharidosis**—one of several inherited diseases in which mucopolysaccharides accumulate in tissues. (This is a bad thing.)
137) **Mucous membranes**—line internal body surfaces that connect with the outside world, like in the digestive tract (mouth included), reproductive tract, urinary tract, & respiratory tract
138) **Mutation**—a permanent change in DNA structure
139) **Nearsighted**—impaired distance vision (but “near” vision is OK)
140) **Necrosis**—death of a circumscribed portion of a tissue or organ
141) **Neoadjuvant**—giving the adjuvant therapy first
142) **Neoplasia**—tumor development
   i) "neo" – “new”; “plasia”—“growth
   ii) **Neoplasm** refers to any tumorous growth
143) **Neural crest**—an area in the developing embryo arising next to the developing nervous system that gives rise to tissues including spinal and autonomic ganglia, connective tissue around the brain and spinal cord, melanocytes, and parts of the facial bones.
144) **neurofibroma**—usually benign tumors that arise from neural crest cells.
145) **Neutrophil**—a type of white blood cell
146) **Non mendelian**—genetic traits that don’t follow mendelian (dominant, recessive, etc.) rules
147) **Nutrient**—yum
148) **Nutrition**—donuts
149) **Oncogene**—a cancer-causing gene
150) **Opportunistic**—causing disease only under certain conditions, specifically when a patient’s immune function is depressed
151) **Organogenesis**—the origin and development of a body organ
152) **Organomegaly**—enlargement of an organ
153) **Pain**—physical suffering or distress
154) **Palpebral fissure**—the gap between the upper and lower eyelids
155) **Pancreas**—a mixed endocrine & exocrine gland in the abdomen.
   i) The exocrine component produces digestive enzymes while the endocrine component produces hormones like insulin & glucagon
156) **Paraneoplastic syndrome**—a clinical manifestation that cannot be explained by the presence of the cancer itself
157) **Partial response**—response to cancer therapy involving at least a 50% decrease in tumor size or volume
158) **Paternal**—pertaining to the father
159) **Pathological fracture**—a broken bone in a location where the bone is affected with another disease, often metastatic cancer
160) **Phagocytic**—cells able to participate in (literally) “cellular eating”—engulfing and digesting large particles
161) **Phenotype**—body appearance or structure
162) **Phenylalanine hydroxylase**—the missing enzyme in PKU
163) **Phenylketones**—the metabolites present in the urine of PKU patients that aren’t controlling their diet
164) **Phenylketonuria (PKU)**—an autosomal recessive disease with faulty phenylalanine (an amino acid) metabolism; these individuals have phenylketones accumulate in tissues & urine which damages the developing nervous system
165) **Plasma**—the liquid portion of blood. (It contains lots of protein, which is why you can sell your plasma.)
166) **Platelets or thrombocytes**—cellular fragments necessary for blood clotting (coagulation)
167) **Pleiomorphic**—variable in shape
   i) “pleo” – “many”, “morph” – “shape”
168) **Pleomorphism**—variability in size and/or shape; synonymous with polymorphism
169) **Ploidy number**—the number of chromosomes that a particular organism normally possesses.

170) **Polygenic traits**—are phenotypic manifestations resulting from the interactions between several different genes.

171) **Polygenic**—traits caused by interactions between multiple genes

172) **Polysomy**—(“poly” – “many”)—possessing more than two copies of a specific autosome

173) **Preinvasive**—prior to invasion of tissues

174) **Prenatal**—before birth

175) **Preneoplastic**—preceding the formation of a neoplasm (**tumor**) in the course of development

176) **Primary**—first

177) **Proenzyme**—an inactive form of an enzyme. Many enzymes are secreted in inactive form so they don’t damage tissue in the process of being secreted and so they can be activated when they become necessary.

178) **Prognosis**—the probable course and outcome of a disease

179) **Progression**—moving forward, becoming larger & more established

180) **Proliferation**—rapid, often excessive increase

181) **Promoter sequence**—segments of DNA located at the beginning of a gene that function to “tell” a cell to use (transcribe and translate) that particular gene

182) **Promotion**—to sustain, encourage

183) **Proteases**—enzymes that break down proteins

184) **Proto-oncogene**—a normal gene that regulates and controls cellular growth and division

185) **Pulmonary**—referring to the lungs

186) **Putrefy**—rot or decay with an offensive odor

187) **Radiopaque**—substances dense enough to not allow (much) X-rays through, thus appearing as white on X-ray films; the term means “opaque to X-rays”

188) **Recurrence**—the reappearance of a disease after a period of remission

189) **Reperfusion**—reestablishment of interrupted blood supply

190) **Retina**—the neural structure in the eyeball where the photoreceptors are located

191) **Retinoblastoma**—a cancer of the retina (the light-sensitive portion of the eye).

192) **Retrovirus**—a RNA virus that allows the reversal of transcription, thus RNA dictating the production of DNA

193) **Satiety**—the state of being satisfied; full
194) **Serous membrane**—a smooth membrane consisting of a thin layer of cells that secrete a serous (watery) fluid.
   a) Examples of these membranes include the peritoneal membrane (abdomen), the pleura membrane (lungs), and the pericardial membrane (heart)
195) **Sex chromosomes** comprise the 23rd pair of chromosomes: “X” is female, “Y” is male. Males are “XY” and females are “XX.”
196) **Sex-linked genes**—are genes located on sex chromosomes
   i) Genes on the X chromosome cause most sex-linked disorders because it is MUCH larger than the Y chromosome. These are recessive genes, so they affect males.
197) **Simian**—like an ape or monkey
198) **Slough**—pronounced “sluff,” means to shed or cast off
199) **Somatic cells**—all the non-reproductive cells; therefore somatic cells have twice as many chromosomes. They possess a **diploid (2n)** number of chromosomes—the full complement. (“Di” means “two.”)
200) **Spontaneous abortion**—natural (unaided) termination of a pregnancy; miscarriage
201) **Stature**—height
202) **Stem cell transplantation**—treatment to replace **stems cells** (cells capable of differentiation)
203) **Systemic**—affecting an entire body or body system
204) **Telomerase**—an enzyme commonly produced by cancers that allow cancer cells to **evade apoptosis**.
   i) Telomeres typically shorten each time a cell divides, and shortened telomeres are one very important signal for a cell to undergo apoptosis.
205) **Telomere**—the segment of DNA that occurs at each end of a chromosome
206) **Teratogen (or teratogenic agents)**—a drug or other substance capable of interfering with the development of a fetus; causing birth defects
   i) Teratogens present when a particular organ is developing (the **period of organogenesis**) may impair development of that organ.
207) **Teratology**—study of abnormal formations; “terato” —monstrous, “ology” – study of
208) **Thalidomide**—a drug formerly used as a sedative in Europe that caused severe abnormalities of limb development
209) **Thrombocytopenia**—a deficiency in platelet numbers
210) **Tongue**—a weapon used to insult other children on school playgrounds
211) **Transcription**—production of mRNA (messenger RNA) formed by “reading” a gene (a sequence of DNA)
212) **Translation**—using mRNA molecules as a template (think “recipe”) to synthesize a protein

213) **Translocation**—chromosomal rearrangement in which a segment of genetic material from one chromosome breaks away and becomes linked to a different, non-homozygous chromosome.
   a) Translocation occurs because of faulty crossing over.

214) **Tropism**—typical movement patterns of a particular organism
   i) Fish head towards water, plants grow towards light, cancers often metastasize to characteristic locations.

215) **Tubercle**—a small, firm, rounded nodule or swelling

216) **Tumor marker**—a substance produced by some cancers

217) **Tumor necrosis**—necrosis that may occur in rapidly growing neoplasms that out-grow their blood supply

218) **Tumor suppressor genes**—another class of genes that also inhibits cellular proliferation

219) **Tyrosinase**—the enzyme responsible for melanin production

220) **Tyrosine**—an amino acid needed for production of melanin

221) **Ubiquitous**—present everywhere

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