Biological Foundations for Public Health

An overview of the understanding of the biological basis to health problems

Infectious Agents

Learning Objectives

1. Explain the major differences between prokaryotic and eukaryotic cells
2. List major types of infectious agents and be able to distinguish between living and non-living
3. Explain key differences among bacteria, fungi, protozoa, and prions
4. Describe how bacteria and viruses reproduce
5. List and describe the four general patterns of viral infection
6. Define 'prion' and discuss the role of prions in the epidemic of bovine spongiform encephalopathy (BSE) in the UK
7. Discuss the role of prions in Creutzfeldt-Jakob Disease (CJD)
8. Discuss how the British BSE epidemic in cattle caused disease in humans

The 5 Kingdoms

Every species can be categorized as a plant, animal, bacteria, fungi, or protozoa. While natural selection implies competition among and within species there is a strong interdependence among species. For example, most bacteria are non-pathogenic and live in and outside our bodies and provide many benefits, such as preventing pathogenic species from gaining a foothold.

Bacteria

Healthy internal tissues are free of microorganisms but skin & mucus membranes in our gastrointestinal tract, respiratory tract, and genito-urinary tract are in contact with organisms in the environment and become colonized with many bacterial species. These bacteria are referred to as "normal flora". The normal flora for a human consists of more than 200 species of bacteria, which depend on a variety of factors.

BACTERIUM	Skin	Eyes	Nose	Pharynx	Mouth	Colon	Lower urethra	Vagina
Staphylococcus epidermidis	++	+	++	++	++	+	++	++
*Staphylococcus aureus**	+	+/-	+	+	+	++	+/-	+
Streptococcus salivarius				++	++			
*Enterococcus faecalis**				+/-	+	++	+	+
*Streptococcus pneumoniae**		+/-	+/-	+	+			+/-
*Streptococcus pyogenes**	+/-	+/-		+	+	+/-		+/-
*Neisseria meningitidis**			+	++	+			+
*Escherichia coli**		+/-	+/-	+/-	+	++	+	+
Proteus sp.		+/-	+	+	+	+	+	+
*Pseudomonas aeruginosa**				+/-	+/-	+	+/-	
*Haemophilus influenzae**		+/-	+	+	+			
Lactobacillus sp.				+	++	++		++
*Clostridium sp.**					+/-	++		

The above chart shows several common bacterium and where they are commonly found on the human body. (+/--) denotes they may or may not be present (++) means they are most always.

These normal flora provide a variety of benifits which include:

- Prevent colonization by pathogens by competing for attachments & netrients
- Some synthesize vitamins that are absorbed as nutrients by the host (e.g. K & B12)
- Some produce substances that inhibit pathogenic species
- Simulate production of cross reactive antibodies. Since normal flora behave as antigens in an animal, they induce low levels of antibodies that cross react with similar antigens on pathogens, preventing infection
- With the help of fungi, bacteria play a vital role in breaking down dead organisms

Some data suggests the inappropriate use of antibiotics and avoidance of microbes through disinfecting ourselves and our environment may have adverse effects on health. Over-disinfection in children may increase risk of autoimmune disease, obesity and asthma.

Bacteria as Pathogens

While only 5% of bacterial species are pathogenic, bacteria have historically been the cause of a disproportionate amount of human disease and death. Among those born in the UK in the 1800s, it is estimated that 70% died before the age of 25 and a large proportion of deaths were due to bacterial infections. Unsurpisingly, the burden of disease then still fell most heavily on the poor. However, during the 19th century the emergence of "the sanitary idea" in the UK and US made efforts to provide better water, waste disposal, nutrition, and all around better working conditions that was rewarded with a remarkable reduction in disease and death rate.

Prokaryotes Vs Eukaryotes

The bacteria are the oldest and simplest living organisms and all of the bacteria are "prokaryotes" meaning they do not have a true membrane-bound nucleus as eukaryotes do.

Prokaryotes

- Simpler than eukaryote cells
- Have a cell membrane and cell wall, and may have a gummy exterior capsule that enables bacteria to attach to surfaces and resit drying out
- May have a pili; a pilus is a hairlike projection from the cell membrane that aids in attachment
- May have a special sex pilus which forms a tube like bridge between two prokaryotes to enable transfer of plasmids (extrachomosomal genes)
- Tend to have a single chromosome composed of DNA, sometimes referred to as "nucleoid" because there is no nuclear membrane surrounding it. There are also ribosomes that are free-floating within the cytoplasm.
- May have simple whip-like flagella that enables them to be motile in fluid environment

Fungi

- Fungi are plant-like are were once classified as plants, but lack chlorophyll and differ in other ways so are now classified in a separate kingdom
- Fungi are structurally different from plants, and are not truly multi-cellular
- Fungi are sometimes mutualistic, living with other species and growing with symbiotic relationship on rocks & trees.
- They can provide food, nutrients and yeasts enable the fermentation of sugar to alcohol
- Sometimes they provide a source of antibiotics, in 1928 Sir Alexander Fleming observed colonies of bacterium could be destroyed from the mold pennicillum notatum
- Fungi are saprophytes that decompose dead organic matter by growing into a substrate and absorbing nutrients from it
- Parasitic fungi often feed on living organisms without killing them (e.g. ringworm & athletes foot)
- Fungi are generally composed of branching filaments (hyphae) that sometimes form a large interlacing mass called a "mycelium"
- The hyphae have cross walls, but are perforated allowing free passage of nuclei and cytoplasm
- There are three main types of fungi; Mold, Mushrooms and Yeast

Fungal Infections

Fungi can act as pathogens, causing a number of diseases in plants and animals. Because mushrooms are more genetically similar to animals than other organisms they are often very difficult to treat.

Mycotic (fungal) infections pose an increasing threat to public health for several reasons. The scientific and medical staff of the Mycotic Diseases Branch is involved with prevention and control among three broad categories of fungal infections:

1. Opportunistic Infections such as cyrptoococcosis and aspergillosis are increasingly problematic due to the rise in number of people with weakened immune systems
2. Hospital associated infections such as candidemia are leading cause of bloodstream infections in the US. Changes in healthcare practices can provide opportunities for new and drug-resistant fungi to emerge in hospital settings
3. Community-aquired infections such as Valley fever, blastomycosis, and histoplasmosis are caused by fungi that are abundant in the environment. Climate change may effect their growth

Protozoa

Protozoa are single-celled eukaryotes that ingest food (algae and bacteria) by phagocytosis and generally move via pseudopods (flowing extensions of the plasma membrane) or a whip-like flagella. Most are too small to be seen with the naked eye. They reproduce by fission.

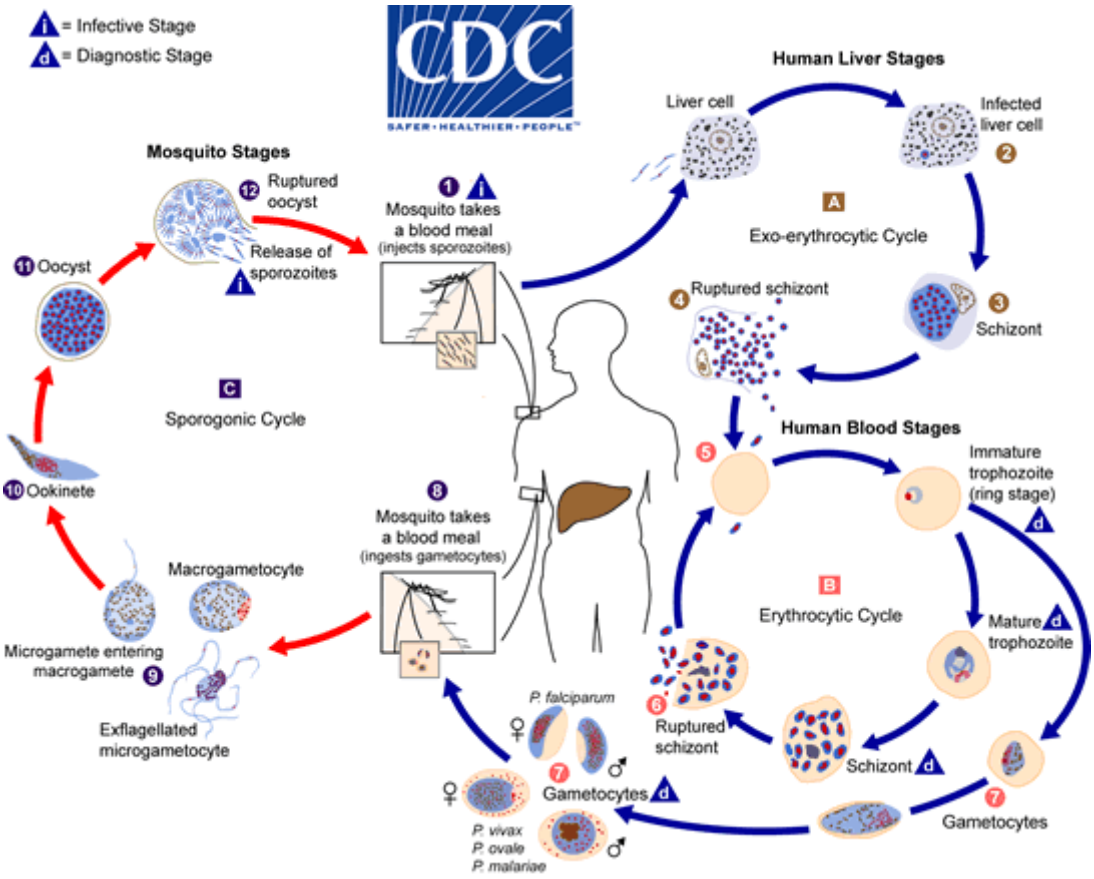
- **Phagocytosis** is the process of by which a single cell engulfs and ingests particles or other cells to form a phagosome or food vacuole, which is a membrane-bound spericale vacuole that forms by pinching off from the cell membrane. The phagosome can fuse with a lysosome, which is another membrane-bound vacuole that contains digestive enzymes, to form a phagolysosome, which digests the engulfed material. The product can be used for energy or synthesis of other compounds and unused debris can be ejected via exocytosis.
- **Binary Fission** is a form of asexual reproduction and cell division used by all prokaryotes and some organelles within eukaryotes.

Animal-Like Protista

There are a number of protozoa that inhabit the gastrointestinal tract of humans. Most are harmless or cause only mild problems, but others cause serious disease. Many protozoa infections are transmitted via the fecal-oral route, while others are transmitted via insect vectors (e.g. malaria) or STD. Some have fairly complex lifecycle that may include a cyst stage to remain dormant in the environment for a period of time until a new host is acquired.

Malaria Life Cycle

Malaria is caused by infection with one of several species of protozoa called Plasmodium. The lifecycle is complex but note there is no animal reservoir. It is transmitted from human to human by mosquitoes, so it may be possible to eradicate.



Plant-Like Protozoa

Ex. Karenia vrevis algae blooms are red algae formed as a result of nutrient pollution.

Animal-Related Infections

Helminths are large multicellular organisms that are generally visible to the naked eye in their adult stages. Like protozoa they can be either free-living or parasitic in nature. Ex. tapeworks, hookworms. Most of these infections occur in warm cllimates and effect poor communities, with more than 1.5 billion infections a year (1 in 4 people). These spread through the soil and can be carried through feces.

Anthropods are blood sucking parasites that refer to organisms that attach or burrow into the skin for relatively long periods of time (ticks, fleas, mites, etc). Antropods are important in causing diseases in their own right but are even more important as vectors or transmitters.

Non-Living Infectious Agents

Scientists generally agree that there are 5 requisite characteristics of living organisms:

1. Have one or more cells with DNA
2. Are capable of reproducing, growing and developing
3. They are capable of capturing & using energy & raw materials
4. They are able to sense & respond to the environment
5. They are capable of evolving over generations

There are two agents of disease which do not fit into these categories: Viruses and Prions.

Viruses

Viruses are assembles of organic molecules that consist of some short strands of RNA or DNA encapsulated within a protein shell. In a sense, they represent a primitive assembly of organix molecules that resemble living cells yet do not meet the characteristics and complexity needed to be truly living organisms. All viruses are parasitic because they need a living host cell in order to replicate.

Once a virus binds to a living cell they can use a host's cellular energy and machinery (ribsomomes) to replicate its genetic material and its proteins to self-assemble new virus particles. These can lie dormant or can cause the host cell to rupture and release particles to infect other host cells.

Viruses can infect all kinds of living cells, including bacteria, and almost all viruses are pathogenic. When a virus infects a host cell they can cause disease through several mechanisms:

- Weakening a cell's membrane or lysosomal membranes leading to lysis of cell
- Triggering the body's immune system to attack and destroy virus-infected cells
- Provoking such a strong response from the immune system that the response itself damages or kills the host
- Weakening immune function (e.g. HIV)
- Synthesizing viral proteins that interfere with host cell function (e.g. HPV)

DNA Viruses

Viruses that contain short strands of DNA (herpes, varicella, human papilloma virus) attach to specific human cells via proteins on their surface. The cell membrane then engulfs the virus giving it access to the cell's interior where it uses the host cell enzymes to replicate its DNA, transcribe the DNA to make messenger RNA, and then translate the messenger RNA into viral proteins. The replicated DNA and viral proteins are then assembled into complete viral particles and the new viruses are released from the host cell. In some cases, virus-derived enzymes destroy the host cell membranes, killing the cell and releasing new virus particles. Other times, the new virus particles exit the cell by a budding process, weakening but not destroying the cell.

RNA Viruses

Some viruses contain RNA in their core, such as influenza infection. The protein on the exterior of the shell binds to a protein on the host cell, triggering the host cell to internalize the virus. The

virus then sheds its protein coat and releases RNA into the cell. The viral RNA is used a messenger RNA to produce viral proteins. In this process, the host cell's ribosomes, amino acids, and ATP are used to create new viral proteins. Once there is a critical mass of new viral proteins and RNA, they self-assemnble to form new viral particles that are released from the host cell by budding off or rupturing. and infect additional cells.

Other RNA viruses called retroviruses use an enzyme called reverse transcriptase to copy the RNA genome into DNA. The DNA then integrates itself into the host cell genome. These viruses frequently exhibit long latent periods in which their genomes are faithfully copied and distributed to progeny cells each time the cell divides. The HIV virus is a familiar example or retrovirus.

Patterns of Viral Infection

Acute Viral - The virus begins to replicate and kills cells. Over a couple of days either the immune system defeats the infection and symptoms disappear or the host dies. (Influenza, smallpox, SARS)

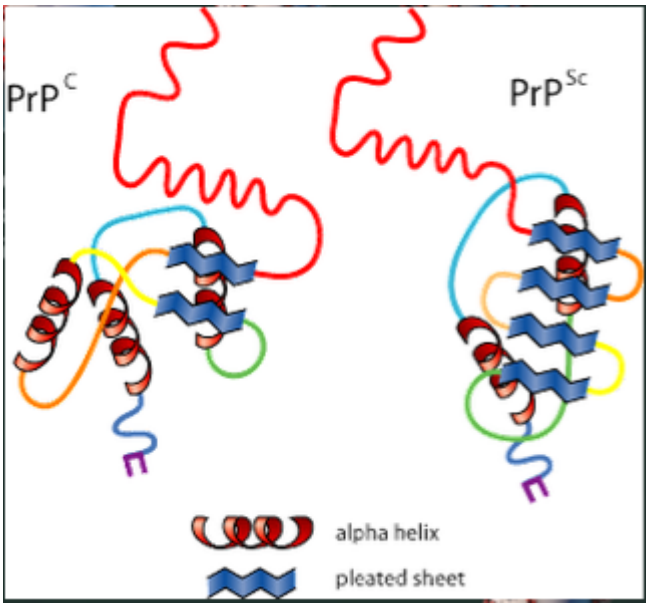
Chronic Viral - The viral load increase quickly after initial infection and the remains sustained for a prolonged period, although the host is asymptomatic. (Hepatitis B or C)

Latent Viral - Virus remains dormant within certian cells, and can periodically reativate. (Shingles due to chicken pox)

Prions

"Protein Infection Particle" or Prion diseases have been with us for some time but only came to attention of the general public during the 1970's. Prion proteins are normally found in all mammalian brains but it is believed that altered forms of these proteins fold abnormally as a result of mutations that cause the proteins to fold into abnormal shapes that prevent them from being broken down by normal remodeling processes.

In 1997 Stanley Prusiner was awarded a Nobel Prize for his hypothesis that a mutant prion is an abnormally folded prion protein (PrPSc) that is resistant to heat & sterilization and does not evoke an immune system response. The protein is chemically the same but folds differently. The abnormal protein contacts normal proteins in neural tissue and induces them to refold into an abnormal confirmation as well. refolded molecules induce the same change in still more proteins. The abnormal proteins resist degradation and accumulate in neural tissue causing damage.

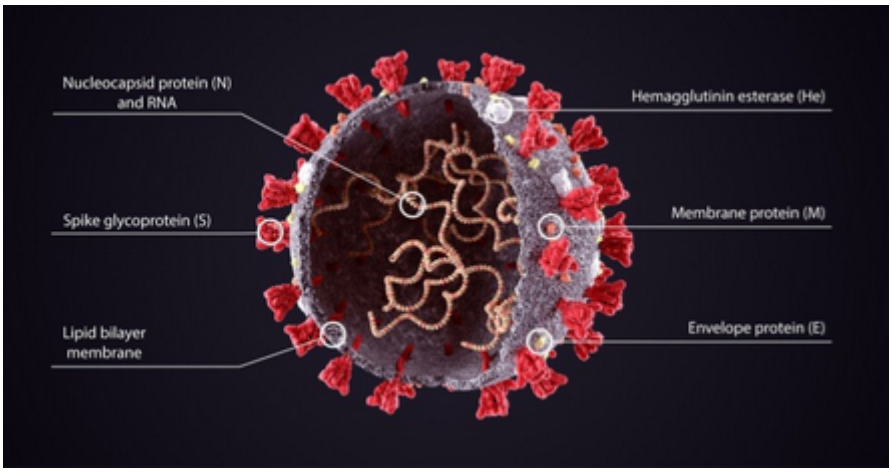


The above illustration represent a normal protein on the left (PrPc) and an abnormal on the right (PrPSc). The abnormally folded protein has segments folded into "beta sheets" (the segments with green arrows). These segments tend to stick together causing clumps of proteins that resist breakdown. Over time the clumps grow larger and destroy nerve cells in areas of accumulation leading to progressive neurological symptoms.

The Biology of a Pandemic

The COVID-19 pandemic which began in late 2019 has been truly devastating event that has caused not only widespread illness and death, but disruptions in virtually all human activities.

COVID-19 is the disease caused by the coronavirus SARS-CoV-2. The Coronaviruses are a large family of viruses that can infect mammals and birds causing diseases that range from mild colds to acute respiratory syndromes (hence SARS) and death. The term "coronavirus" comes from the spike proteins that radiate from the external envelop (corona=crown).

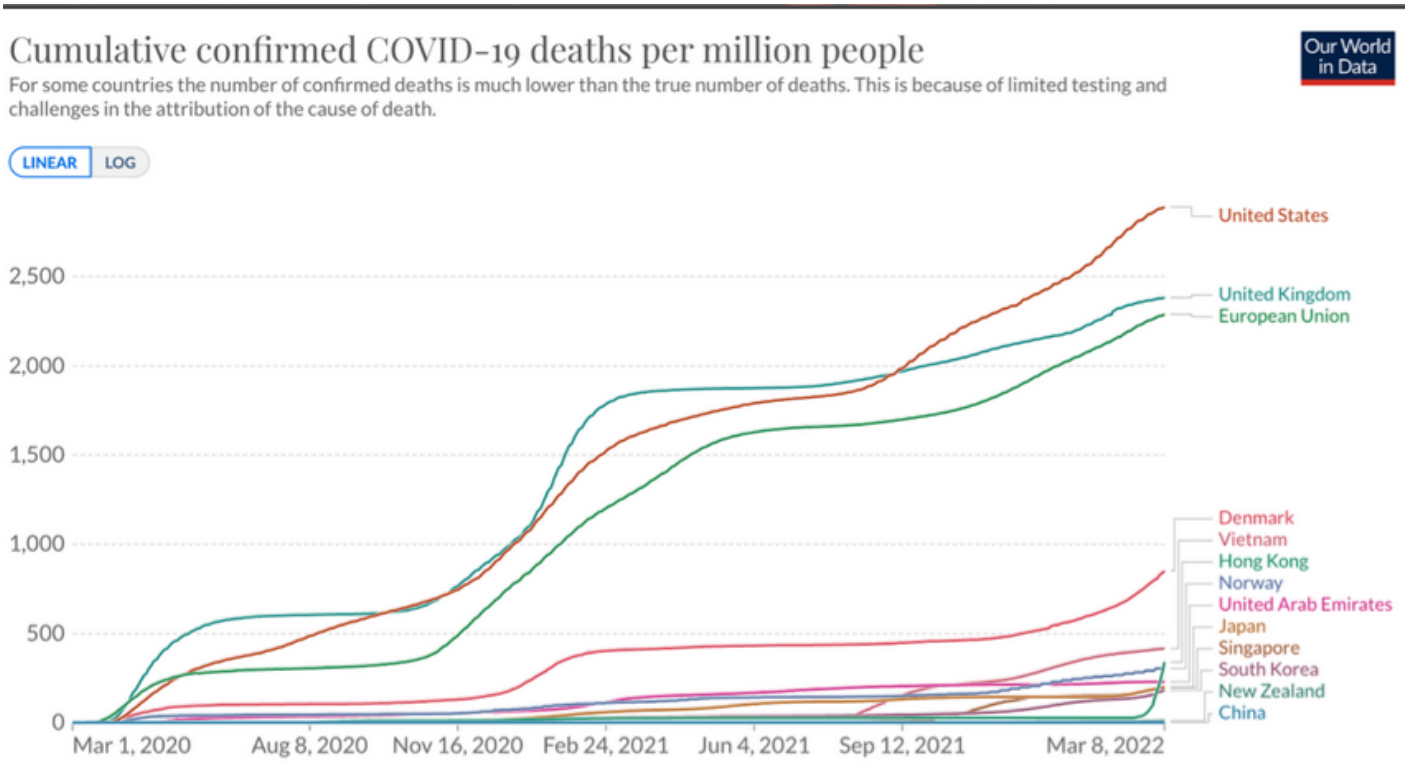


The envelope consists of spike proteins sticking out of a lipid shell that encloses the single RNA genome and some proteins.

The virus enters the body through the mouth or nose, and fuse with a specific proteins on the surface of a cell and inject their RNA genome into the cell. The cell's ribosomes translate the virus's RNA into proteins including RNA polumerase which transcribe the virus's RNA, making more RNA copies that are translated into proteins and more copies of the genome. Then the genome and proteins combine to make a new virus packaged into an envelope formed from the cells membranes. Newly formed cells travel to the cells surface and are released outside the cell, where they can infect other cells or leave the body in mucus and saliva droplets.

By the Numbers

Death Rate



The COVID-19 pandemic emerged in 2019 and as of April 2022 is estimated to have caused illness in 500 million people globally and killed more than 6 million. Note how widely the death rate varied from country to country and how the rate declines and surges due to mutations of the viral genome. The factors responsible for these variations are not completely understood, but several major factors have been identified.

Basic Reproductive Number (R0)

Viruses differ in their inherent contagiousness and and in the absence of any preventive measures the contagiousness of a virus or bacterium is estimated as a quantity called R0 ("R naught").

R0 is a measure of the average number of new cases caused by an infected person in a population with no immunity.

Ex. If R0=3 one infected person would infect 3 more people to become infected on average. Each of those 3 infect 3 more and etc, resulting in an exponential increase.

Disease	R_0
HIV/AIDS	2-5
Diphtheria	6-7
Influenza	2-3
Measles	12-18
Mumps	4-7
Pertussis	12-17
Polio	5-7
Rubella	5-7
Smallpox	6-7

At the beginning of the pandemic everyone was susceptible and early estimates of R0 were around 2.2-2.7; causing a rapid increase in cases.

The Effective Reproductive Number

The basic reproductive number was relevant at the beginning of the pandemic because no one was immune and no control measures had been instituted. However the reproductive number has changed over time, partly because people who were infected and have immunity for a while. In addition, the probability of transmission of a respiratory virus or bacterium may be influenced by other factors such as:

- Immune Status
- Frequency of contact with others
- Duration of contact
- Proximity of contact
- Ventilation
- Wearing an effective mask
- Hand Washing
- Climate and seasonal variation
- The duration of disease in infected persons
- COVID testing and contact tracing
- Isolation and Quarantine
- Availability and utilization of effective vaccine

Seasonal variation is beyond our control, but the other known factors provide opportunities for interventions that can reduce the effective reproductive number.

If the effective reproductive number remains greater than 1 an epidemic or pandemic will continue. If interventions reduce the effective reproductive number below 1 and keep it there it will eventually disappear.

In absence of any intervention, diseases like COVID-19 can spread rapidly in a susceptible population.

The US and most of Europe experienced much higher morbidity and mortality rates compared to countries such as China, Japan, South Korea, and New Zealand which adopted rigorous social distancing measures. These measures prevented the early exposure surge and when relaxed the rates of infection rebounded.

Vaccines and Heard Immunity

Social distancing is effective in delaying new cases and preventing the surges that overwhelm the healthcare system, but the most effective measure for driving the effective reproductive number down and ending an epidemic or pandemic is to vaccinate a sufficiently large proportion of the population to achieve "heard immunity".

If this can be achieved, the opportunities for transmission to susceptible people become diminished to the point that propagation of the virus cannot be sustained. When this is achieved, even susceptible persons enjoy a significant degree of protection.

The fraction of a population that must be immune (by being vaccinated or by recovering from infection) to achieve heard immunity can be estimated by [1 - (1/R0)]

Ex. For a typical strain of influenza A with R0 = 2.5, it would be desirable to vaccinate at least 1 - 1/2.5 = .6 or 60% of the population. Since R0 for COVID was in this range early in the pandemic, this was the goal that many articulated when vaccines began development.

Highly effective vaccines against COVID-19 became available in Dec 2020. Many people were eager to get it at first, but after a while vaccinations slowed due to vaccine hesitancy. As of April 2022, only ~66% of the US was fully vaccinated. This would have been sufficient if the R0 was still 2.4 but unfortunately mutations produced more transmissible strains such as the Delta strain with R0=5.08, and Omicron with 8.2. Achieving herd immunity against Omicron would theoretically require a vaccination rate of 88%.

Testing, Case Investigation and Contact Tracing

Many people infected with SARS-CoV-2 have minimal or no symptoms but can still transmit the disease to others.

In addition to promoting vaccination, another important strategy is abundant testing to identify symptomatic and asymptomatic cases in order to isolate them until they are no longer effective.

Also, contacts of infected people should be traced and counseled regarding quarantine and what steps to take if symptoms develop.

Viral Mutations

When viruses replicate, random mutations occur occasionally. These may increase or decrease the transmissiblity or adverse effects of the virus, or have no effect. The more a virus replicates, the more likely that strains with altered properties occur. One consequence of not controlling the pandemic quickly is that viral replication continued at a staggering rate that is increased the probability of generating more transmissible strains.

COVID-19 Accentuates Inequities

Health equity means equal distribution and access to health resources for all people. It is strongly influenced by social determinants of health such as neighborhood, health care, work conditions, income, wealth, and education.

The CDC notes some racial and ethnic groups have been disproportionately effected by COVID-19 due to longstanding disparities in these determinants. Many politicians are noting that black people have more underlying medical conditions but they're not explaining why. They blame the choices made by black people or poverty or obesity - but never racism.

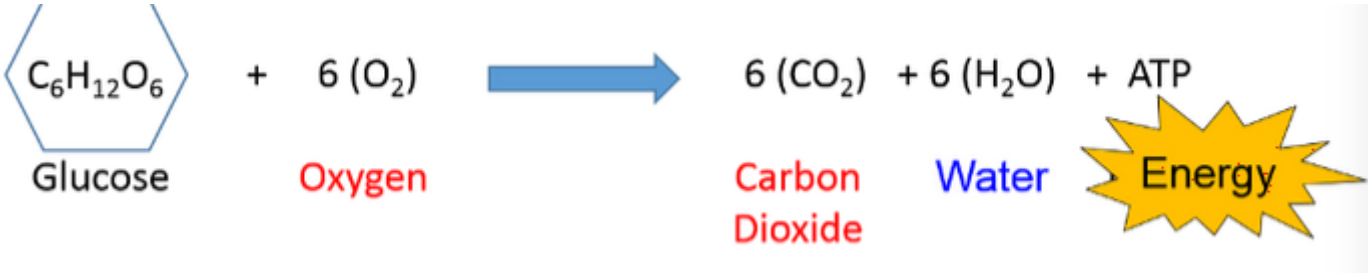
Communities of color are often redlined into housing with crowded neighborhoods with less access to public transportation, nutritious food and quality health care. These groups are also less likely to have health insurance and access to care. In addition, they disproportionately work in "essential" non-remote work settings such as health care, factories, food production, sales and public transportation. These workers generally also have lower incomes, less wealth, less paid sick leave, and more debt.

Medical and public health institutions have repeatedly violated the trust of communities of color through historic injustices including mistreatment and racism within public health and healthcare, leading to a well-earned skepticism of new interventions such as the COVID-19 vaccines. It was initially assumed people of color were accessing vaccines less but as of April 2022 this trend has changed, some communities of color have high vaccination rates than their white neighbors.

The life expectancy declined in all income groups during the pandemic but the poorest 20% which already had the lowest life expectancy had the greatest decrease.

Respiratory Health

All animals need oxygen to metabolize nutrients to generate cellular energy.



The above equation illustrates how nutrients (glucose) are converted to cellular energy in the form of adenosine triphosphate (ATP). Note carbon dioxide is produced as a by-product of metabolism.

The lungs are the interface between our blood stream and the external environment and the site where O2 is taken up and CO2 leaves the bloodstream to be expelled into the environment. The intimacy of this interface between our internal and external environment with the need to exchange air has a major impact on health for several reasons:

- Continual exposure of the respiratory tract to air from the environment provides an important portal for entry of viruses and bacteria that can cause infection.
- Disease processes that impede the mechanisms of ventilation (e.g. asthma and emphysema) can cause severe illness or death; these processes can also be triggered or exacerbated by substances in the air we breath.
- Air is a variable and complex mixture of many substances including particulate matter and chemicals that can have a detrimental effect on lung function; moreover many of these chemicals can be absorbed into the blood and cause a wide range of health problems.

Learning Outcomes

1. Describe the function of alveoli with respect to exchange of oxygen and carbon dioxide
2. Describe the role of hemoglobin in oxygen transport and the adverse effects of CO
3. Explain how the occurrence and severity of chronic obstructive pulmonary disease (COPD) and asthma relates to environmental factors and be able to give examples of factors known to trigger asthma attacks
4. List the six criteria air pollutants and discuss the impact of air pollution on health
5. Discuss the impact of environmental tobacco smoke on health

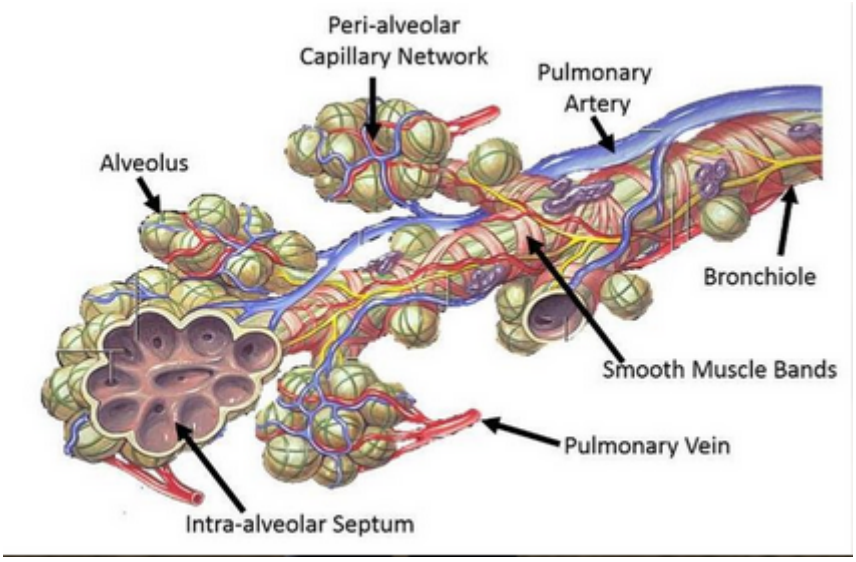
The Respiratory Tract

Inspired air enters through the nose or mouth, passes through the pharynx (throat) and larynx (voice box) and then enters the tracheo-bronchial tree. The trachea bifurcates into the rate and main stem bronchi which branch again and again into increasingly smaller conduits called bronchioles.

Respiration continually brings air from the environment in contact with the delicate cells in our lungs to provide oxygen and to expel carbon dioxide. The air must be warmed, moistened and filtered for the lungs. When harmful contaminants are carried in the air there are several mechanisms to mitigate the effects of these contaminants.

Nasal hairs and mucus can trap dust and other particulate matter, and goblet and ciliated cells work in tandem to remove particulate matter. Goblet cells create a mucus layer on the lining of the surface that protects the cells and traps dust and other foreign material while ciliated cells have hair-like projections that move rhythmically and sweep the mucus and particulate matter upwards where it can be swallowed or expectorated.

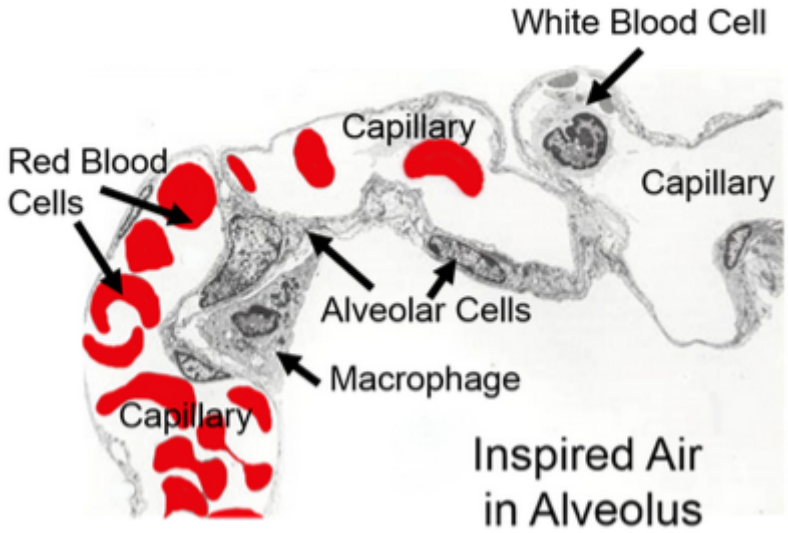
Supplying Oxygen and Expelling CO2



The above figure shows a bronchiole terminating in several clusters of bronchiole. The bronchiole has a vacular supply of oxygenated blood (in blue) and nervous enervation (nerves in yellow) and the bronchiole is wrapped by smooth muscle cells that can contract or relax in response to physiologic conditions.

Contraction of smooth muscle narrows the airways, and relaxation increases their diameter. Abnormally severe contraction of this smooth muscle is of central importance to asthmatic attacks.

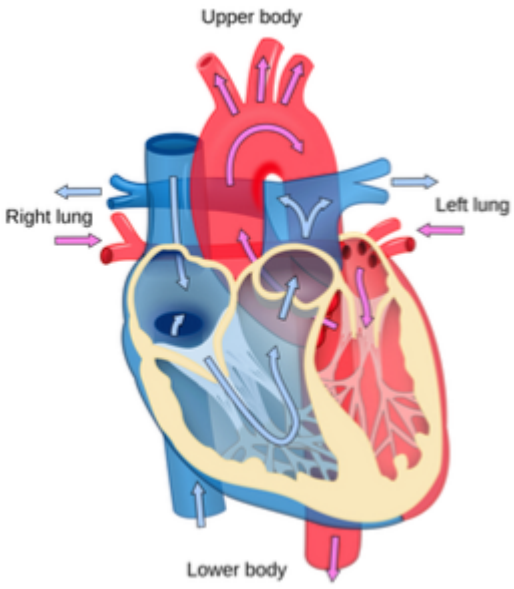
Eventually, the terminal bronchioles open into thousands of alvelo - delicate grape-like clusters of air sacs where gas exhange occurs. There are several types of alveolar cells: type 1, type 2, and macrophages.



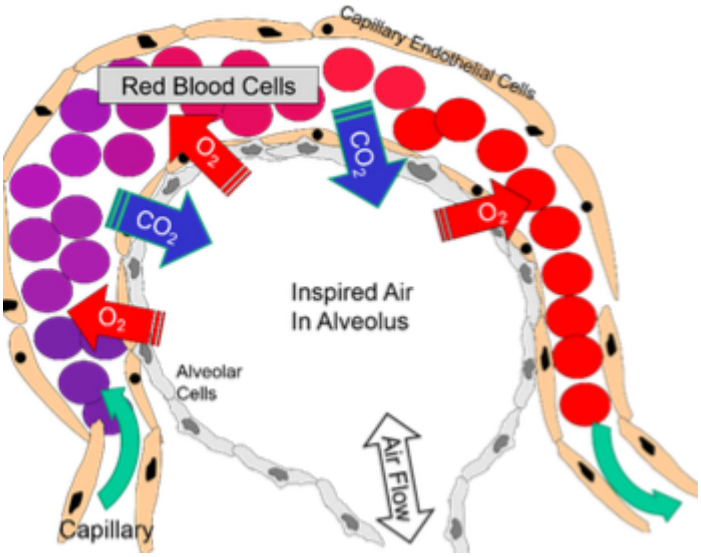
The above image focuses on the details in a single alveolus. Note the capillaries surrounding the alveolar cells are in very inimate contact, which facilitates the exchange of oxygen and carbon dioxide between the air in the alveolus and blood in the capillary.

The alveolus is lined with alveolar cells; type 1 are for exchange of O and CO2, while type 2 can divide to give rise to new type 1 cells and also synthesize and secrete a substance called surfactant which reduces surface tension in the alveolus and prevents collapse during expiration.

Within the alveolus there are also macrophages (also called "dust cells") - phagocytic cells that engulf particulate matter then migrate up the bronchioles where the ciliated cells sweep them up into the pharynx where they are swallowed or expelled.



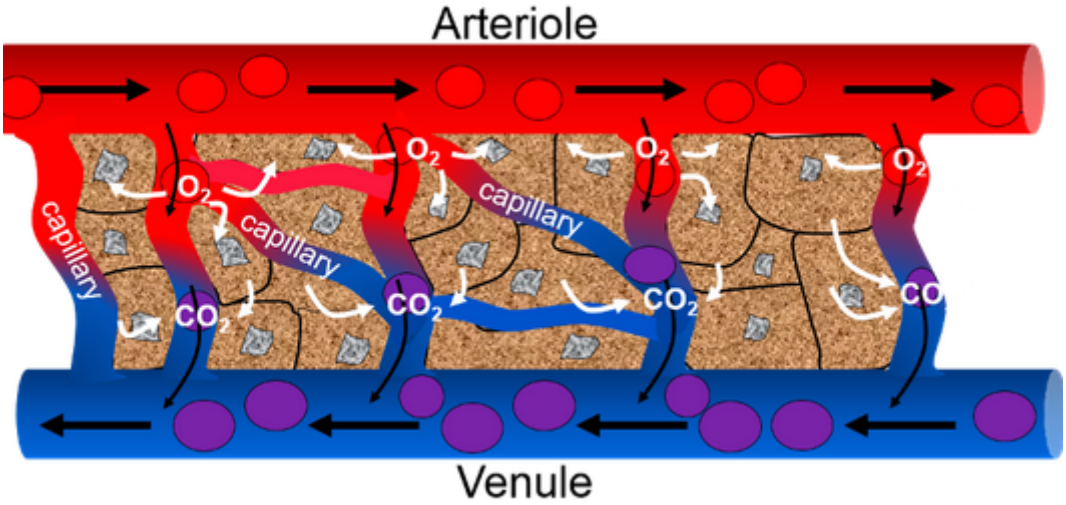
The graphic above illustrates that blood returning to the heart is de-oxygenated (in blue) and returns to the right atrium of the heart and then the right ventricle. When the heart contracts blood in the right ventricle is pumped to the lungs where it enters capillary vessels that circulate around the alveoli where gas exchange takes place. As blood circulates around the alveoli it becomes re-oxygenated and CO2 moved from the pulmonary arterial blood into the alveolus to be exhaled. Blood returning to the left atrium of the heart then to the left ventricle is fully oxygenated and when the heart contracts it is pumped into the aorta to be distributed throughout the body via the arterial system.



Blood returning from the peripheral tissues has a relatively low concentration of oxygen but is rich in CO2 as a result of cellular metabolism. As a result, the oxygen readily diffuses from the alveolus across the alveolar cells and into the capillary where it binds to the hemoglobin in red blood cells. Conversely, CO2 diffuses from the capillary blood into the air in the alveolus which is exhaled.

Cellular Gas Exchange

Cells use oxygen to metabolize, or create cellular energy from glucose or fatty acids. Arteries branch into arterioles which eventually branch into capillaries.



The image above shows an arteriole branching into smaller capillaries which supply nutrients and red blood cells to metabolizing cells. Capillaries are often so thin that often red blood cells can only pass one at a time.

Smoking

Tobacco smoke is a complex mix of toxic and carcinogenic chemicals and particulate matter. Emission levels of 98 components in mainstream smoke constitute a human inhalation risk with potential to contribute to many adverse effects.

Below is a list of some of the known effects:

- Cancer of the bladder, blood, cervix. colon, esophagus, kidney, larynx, liver, oropharynx , pancreas, stomach, trachea, bronchus, or lung
- Generates free radicals that damage tissue membranes
- Increases blood pressure and clotting
- Promotes atherosclerosis
- Causes 2 to 4 fold increased risk of coronary heart disease; Including stroke and peripheral vascular disease
- 12 fold increased risk of COPD
- Heavy smokers have a 20 fold risk for lung cancer
- Many maternal/fetal effects
- Nicotine and free radicals kill osteoblasts - bone-making cells
- Older people who smoke experience significant bone loss
- Smoker's bones take longer to heal and may experience more complications during healing
- Second hand smoke puts non-smokers at risk

Since carbon monoxide from smoke binds to hemoglobin in red blood cells, effecting delivery of oxygen and causing platelets to become stuck together causing blood clots, thus every organ is effected by smoking. In addition, nicotine and CO can damage the inner lining of arteries. In coronary heart disease plaques can reduce or block flow of blood to the heart, causing chest pain. In more serious cases when the heart muscle is starved of oxygen for too long an area of the heart may die, causing a heart attack.

Smoking is the leading preventable cause of death in the US. More than 480,000 deaths per year can be attributed to cigarette smoking. Smoking causes 90% of lung cancer deaths. While COPD is more common in men, more women die from COPD annually. More women die from lung cancer each year than breast cancer. About 50-80% of all deaths from COPD caused by smoking.

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a global health problem that effects millions of people. COPD is one of the top 10 causes of death worldwide and the direct cost of treating it in the

US alone is ~$30 Billion per year.

Symptoms

- Shortness of breath
- Wheezing
- Chest tightness
- Difficulty with routine activities
- Weight loss
- Fatigue

COPD actually represents a spectrum of disease ranging from destruction of the alveoli and thickening of the terminal airways and impaired airflow (emphysema) to the thickening of the airways with chronic inflammation and repeated bouts of infection (chronic bronchitis). The hallmark of COPD is reduced airflow, which occurs as a result of one or more of the following:

- Loss of elastic recoil in the alveoli due to excessive breakdown of the protein elastin
- Destruction of the walls between the alveoli as a result of excessive action of enzymes called "proteases"
- Thickening of the walls of the airways due to inflammation
- Excessive secretion of mucus, which can clog airways.

While smoking is the leading cause of COPD, it can also be caused by genetic or environmental factors. Respiratory infections such as influenza do not cause COPD, but can make it much worse.

Asthma

Asthma is a common, chronic syndrome characterized by intermittent episodes of symptoms which can be severe and life-threatening. The clinical episodes are triggered by antigens, viruses, exercise, or inhalation or irritating substances. Any of these stimuli can trigger a hyperactive allergic response which produces:

- Inflammation of the respiratory tract
- Bronchoconstriction
- Hypersecretion of mucus

These can cause varying degrees of airflow obstruction causing shortness of breath, wheezing, coughing, tightness in chest, and some times sever "air hunger" panic. Some episodes resolve spontaneously, while others require medical treatment.

The CDC estimates nearly 20 million Americans have asthma, and it is more common in children than adults, more common in women than men, and more common in black people than white people. The mortality from asthma rose in the 1980's, but then plateaued and declined since 1999 due to improved treatment.

Why do some people have seasonal allergies?

Seasonal allergies are a hyper-sensitive immune response to something that's not actually harmful. Pollen or some allergen finds it's way into the mucus membrane and the immune system attacks it. When the white blood cell attaches to the allergen it releases a chemical which simulates nerve cells and cause blood vessels and the mucus membrane to swell and leak fluid; itchiness, sneezing, congestion, etc. An allergy can even bring on full anaphylaxis.

Asthma Triggers

- Allergens (pollen, dust, molds, animal dander, bugs, etc)
- Tobacco smoke
- Exercise/activity (especially in cold air), as well as laughing, crying, or hyperventilating
- Cold air, wind, rain, and sudden changes
- Medications
- Air pollutants and irritants
- Sinusitis - respiratory tract infections including the flu and common cold
- Sulfities (preservatives added to some perishable foods)
- Emotional Stress

Environmental Remediation for Asthma

The medical management of asthma and treatment of acute attacks has improved substantially, but the prevalence of asthma continues to rise in urban settings in industrialized countries. There is some evidence that interventions to reduce trigger exposures are effective, but the literature indicates that allergen reduction is difficult to achieve and the effectiveness is not as great as expected.

Air Pollution

Air pollutants are the particles, vapors, and contaminants not found in pure air. These primarily come as a result of burning hydrocarbon fuels and releasing by-products into the atmosphere. Pollutants can be naturally occurring or the result of human activity (anthropgenic).

The energy humans require for energy is mostly derived by combustion. Combustion involves oxygen combining with hydrocarbons (gas, oil, propane, natural gas, wood, etc) to produce energy. The by-products are CO2 and CO, water vapor, smoke, and ash. CO tends to be formed when there is insufficient oxtgen for the hydrocarbon to burn completely.

Combustion of hydrocarbon fuels also produces "particulates" some of which are visible as smoke. These can pose treats to health and the environment. Nitrogen is the most abundant gas in the air we breathe, and it to combines with oxygen during combustion to form a series of compounds called nitrogen oxides, sometimes referred to as NOx. Sulfur dioxide SO2 is also formed at combustion of surfer-containing fuels such as coal. Other pollutants can also be released by combustion, coal also contain concentrations of mercury which gets turned into vapor and returns

to our waterways driving concern about mercury in the ocean. Polycylic aromatic hydrocarbons (PAH) represents a large family of molecules can also be produced when dirty fuel is burned, which cause tumors and birth defects.

DNA, Heredity and Drug Resistance

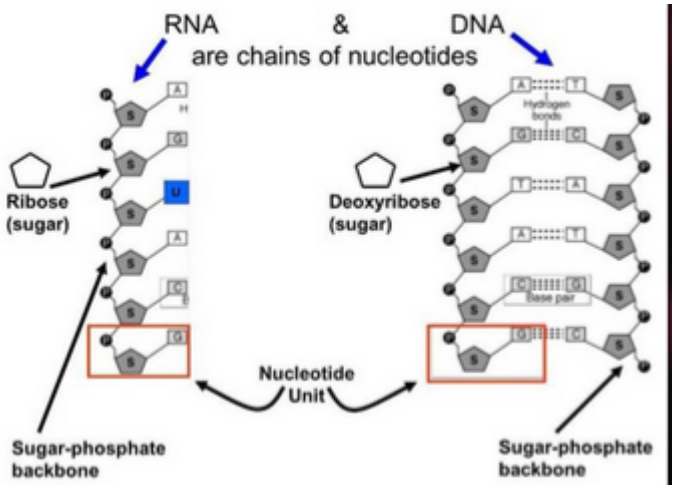
Chromosomes are molecules of DNA that provide the essential genetic code for all living organisms, and it is the code that directs the synthesis of proteins that define each organism's structure and function. Genetic factors contribute to causation of many diseases, such as breast cancer and heart disease. Understanding genetics also enables one to understand the major threats to health as a result of the development of drug resistance.

Learning Outcomes

1. Explain how DNA encodes genetic information and the role of messenger RNA and transfer RNA
2. Explain how DNA directs protein synthesis and roles of DNA and proteins in regulating cell function
3. Demonstrate how to predict the possible genotypes that could occur in an offspring provided one knows the genotype of both parents
4. Explain what a mutation is and give examples of how it might occur

DNA

Deoxyribonucleic acid (DNA) is an extremely long polymer made from units called nucleotides.

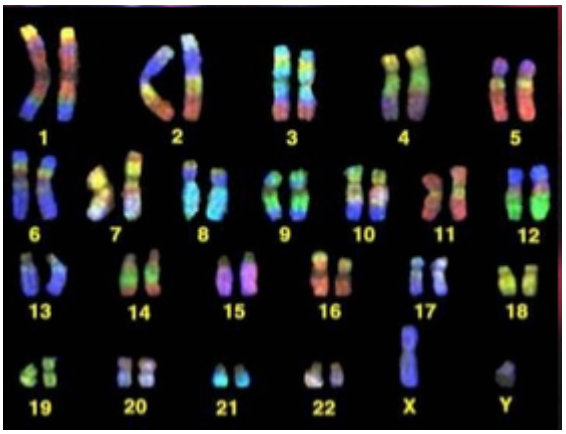


The backbone of each molecule is composed of alternating sugars (the pentagon with "S") and each sugar is also covalently bonded with one of the following nucleotide bases:

- Adenine (A)
- Thymine (T)
- Cystosine (C)
- Guanine (G)
- Uracil (U)

DNA and RNA differ in several ways:

- DNA is double stranded, while RNA is single stranded (though RNA forms loops by hydrogen-bonding to itself)
- DNA contains the sugar deoxyribose while RNA has the sugar ribose
- RNA contains the base uracil in place of thymine



The illustration above shows the 46 chromosomes that contain the human genome. There are 22 homologous pairs and 2 sex chromosomes in humans. Sex chromosomes are XX in females and XY in males. The XY chromosomes are physically different from one another in that the Y chromosome is much shorter, only containing about 9 gene loci that match those on the X chromosome. This means that, except for the sex chromosome, each gene has one chromosome is inherited from one's mother and one from the father. Each chromosome is a single molecule of DNA.

Since Y chromosomes are much shorter than those on the X chromosome, almost all of the alleles on a male's single X chromosome are expressed since there is no alternative dominant allele to mask them. This results in a distinct inheritance patter for traits that are encoded on the X chromosome. For example, color-blindness is a defective allele always carried on the X chromosome.

With the exception of red blood cells (which lost their nucleus) each cell in the human body has all 46 chromosomes, so there are about 3 billion base pairs. The single chromosome of a bacterium is located diffusely in the cytoplasm, but chromosomes of higher species are contained with a membrane-bound nucleus. If we were to take the physical human chromosome and stretch it out, it would be about 5 centimeters, or all 46 would be about 2 meters laid end to end.

One of the helical strands of DNA is the coding strand. The coding strand of a chromosome has thousands of genes along its length (segments which contain genetic code for specific cellular proteins).

Genes and Inheritance

Each chromosome contains thousands of genes. This takes up up only 3-5% of our DNA, while the rest of DNA is considered "non-coding areas." Altogether 23 pairs of chromosomes carry the code for 20k-25k genes. Most genes are transcribed into "messenger RNAs" (mRNA) that provide a template that is used to translate the code into specific proteins. About 100 genes are transcribed into "ribosomal RNAs" and "transfer RNAs" that also play a vital role in the synthesis of proteins.

The sequence of bases in DNA can be though of as "letters" that provide the basis for all genetic code for proteins synthesized by our bodies, which provide the basis of structure of all our cells, enzymes and our traits and characteristics. The production of cellular proteins requires two major processes: transcription followed by translation.

Transcription and Translation

Transcription occurs in eukaryotic cells within the nucleus where DNA is used as a template to create mRNA with the help of RNA Polymerase. The initial transcript has coding segments (exons) and alternating non-coding segments (introns).

Splicing happens in 3 stages: Initiation, elongation, and termination. During initiation the polymerase binds to the promoter region of the template, the DNA "unwinds" and opens. During elongation the polymerase links complimentary bases to the new RNA molecule until it reaches the termination part of the gene and the polymerase and mRNA strand dissociate from DNA.

Before the mRNA leaves the nucleus the inrons are removed from the transcript by a process called RNA splicing. Extra nucleotides are then added to the ends of the transcript; these non-coding "caps" and "tails" protect the mRNA from attack by cellular enzymes and aid in recognition by ribosomes. Helper proteins assemble at these caps and form a splicing machine, or splicisome. It brings exons close together and cuts the intron loop off before disassembling. Then in translation, which occurs in the cytoplasm of the cell at the ribosomes, the information in mRNA is used to create a polypeptide.

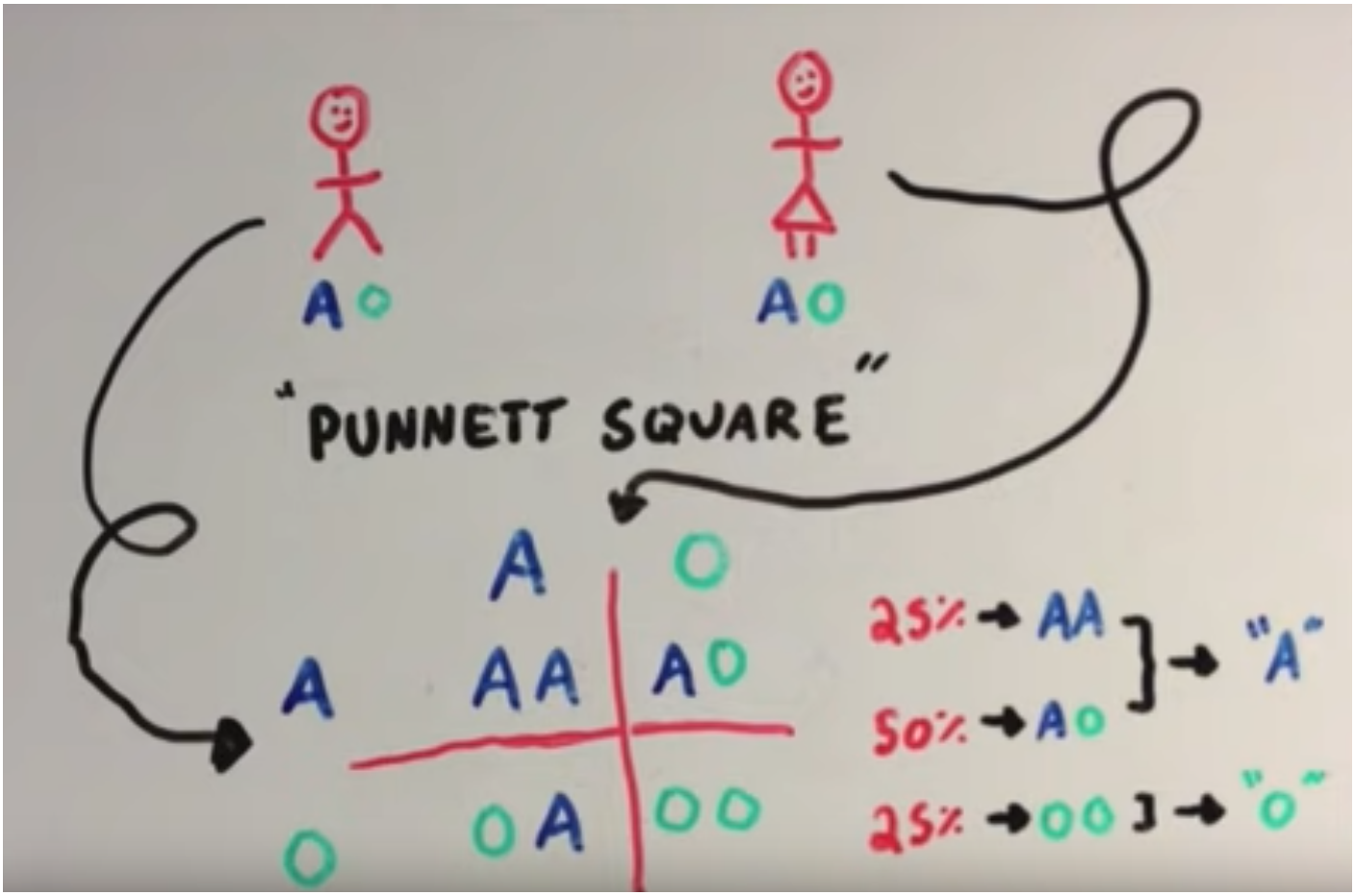
Alleles

The sequence of bases in the human genome is remarkably similar from person to person, but over hundreds of years of evolution mutations have been introduced to the human gene pool. Some are fatal, while others are passed down between generations, and they provide the basis for many variations in phenotype that make us all special. Over time, mutations have created variants of genes that are responsible for differences in the color of our hair, eyes, skin, how fast we can run, height, etc. Mutations introduce gene variants that encode for slightly different proteins, which in

turn influence all aspects of our phenotype. Note though, that an individual's phenotype is not solely the result of their genome, and could be a result of interaction with their environment.

Mutations have introduced gene variants that encode for slightly different proteins, influencing all aspects of our physical characteristics (phenotype). When mutations create variants of a particular gene the alternative gene forms are referred to as alleles. Some genes have a few alleles, while others have many.

Recall also that chromosomes come in pairs with the same gene in both members of a given pair. The two genes together can be referred to as the genotype. Genes are either dominant or recessive, and dominant genes are chosen. Also, different genotypes can create the same phenotype and blending a phenotype can occur with 2 dominant traits. Punnett squares are used to determine gene dominance.



There is an allele that contains genetic code for blood type. In the above A is the dominant trait and O is a regressive trait. A person can have 2 alleles for the same blood type, which is called homozygous, and they would have that blood type. Alternatively, a person could have an A and an O blood type allele, called heterozygous, and the dominant allele would win.

Dominant vs Recessive Inheritance Patterns

Some diseases are inherited, and the pattern of appearance within a family tree will depend on whether the faulty allele is dominant or recessive compared to the normal allele.

For example, the allele for Huntington's disease is dominant. If a man with a heterozygous Huntington's disease gene (Hh) has children with a woman with no Huntington's Disease gene (hh). Their children will have a 50% chance of having the disease. When diseases have dominant alleles it will occur quite frequently in the family tree.

In comparison, cystic fibrosis is caused by a recessive allele, meaning that individuals who are heterozygous for the gene (Cc) will not manifest signs or symptoms. As a result the cystic fibrosis allele can be passed along a family tree with only sporadic appearance of the disease.

Binary Fission

Prokaryotes reproduce by the relatively simple process of binary fission. The single chromosome replicates and each copy attaches to a different location on the cell membrane. The cell membrane then begins to invigilate and eventually separates into two genetically identical bacteria. A similar process is used to replicate mitochondria within eukaryotic cells, but the overall process is more complicated in eukaryotes.

Mitosis

Mitosis is the process by which eukaryotic cells replicate by dividing into two genetically identical cells. It is the process by which new cells are formed in the embryo and after birth, and mitosis also replaces cells that have died or shed. In humans some cells retain the capacity to divide throughout life. Benign and malignant tumors also grow through mitosis.

Meiosis

Meiosis is the specialized process by which gametes (sperm and eggs) are produced for sexual reproduction in the ovaries and testes. Each gamete has 23 chromosomes and joins with the other gamete to create a mixture of genetic information from both parents.

Meiosis produces sperm and eggs with novel mixtures of the original parental chromosomes due to:

Random Assortment - Separation of homologous pairs of maternal and paternal chromosomes results in each gamete randomly getting some maternal chromosomes and some paternal. Random assortment of 23 pairs of chromosomes can produce > 8 million possible combinations.

Crossing Over - After maternal and paternal chromosomes match up as homologous pairs they exchange sections of DNA, this further shuffles the genetic deck.

Epigenetics

Our genome is established when fertilization takes place, and the code remains unchanged throughout our life except for certain mutations that may occur in individual cells.

We now know that many external factors (epigenetics) can affect the timing of the gene expression, the degree expression, and the eventual phenotype that is expressed. These external

factors can produce small modifications to DNA, such as addition or removal acetyl or methyl groups to DNA, or to the histones that control the wrapping and packing of DNA. Attachment of methyl groups appears to reduce transcription or even shut it off. attachment of acetyl groups to histones turns genes on or off.

These biological changes to the genome is known as 'epigenetic factors', changes above the level of the genome. In essence, the DNA in our cells provide the code for making functional proteins, and the epigenetic factors act as switches to turn genes on and off.

Certain genes that predispose an individual to being lean, however the individual might still become fat due to overeating.

Mutations and Drug Resistance

All humans have the same set of genes and the sequence of our base pairs in remarkably similar. However this doesn't mean we have all the same nucleotide sequence in our genome. If this were the case, then all humans would be clones having exactly the same genetic code. While DNA replication is remarkably precise, errors occasionally occur and produce changes in the base sequence.

Mutations are random changes in the sequence of base pairs in DNA and metagens are factors that cause mutations (chemicals or radiation). Mutagens result four patterns of alteration in the base sequence:

- Replacement (substitution) of a single base pair
- Addition of one or more base pairs
- Deletion of one or more base pairs
- Relocation of a segment of base pairs

Addition or deletion of pairs can be substantially disruptive, since mRNA transcript is read in 3 letter codons a shift could throw off the entire sequence.

Mutations can result in:

- Inconsequential changes which do not alter protein product
- Small changes that alter the protein product to some degree
- Small changes that alter phenotype markedly
- Very large changes in base sequence that arise from insertion or deletion of a base pair, or relocation of a segment of nucleotides.

The term ""anti-microbial" is a generall term that encompasses drugs, chemicals, or other substances that kill or slow the growth of microbes. These include:

- Anti-bacterials (antibiotics)

- Anti-virals
- Anti-fungals
- Anti parasitics

Alexander Fleming is widely credited with the discovery of penicillin in 1928, though there are earlier reports of mold killing bacteria. Penicillin became widely used, and with it resistant strains of bacteria emerged. At first these problems were dismissed but by the 1980s it had become a clear problem. Exposure to antibiotics kill susceptible bacteria, but the resistant strains spread their genes. Bacteria can also spread the strand of DNA which contains antibiotic resistance to other bacteria.

To avoid antibiotic resistant bacteria we can focus preventing infection, and appropriate use of antibiotics.

Cancer

The oldest description of cancer were written in Egypt as early as 3000 BC as part of an ancient Egyptian textbook on surgery.

The word "cancer" comes from the Greek work carcinos, which means crab. Hippocrates used this term to describe the disease because the projections of a cancer invading nearby tissues. During the 16th century, when the theory of bodily humors prevailed, it was believed cancer was caused by excess black bile buildup; But this was discarded early when no black bile was found. After invention of the microscope, evidence accumulated that cancer was the result of uncontrolled cell division but the cause was still unknown.

Learning Objectives

1. Describe the distinguishing features of a cancer
2. Discuss the mechanism by which cancers evolve
3. Explain what is meant by "metastasis" and the mechanisms by which it occurs
4. Explain the difference between the "grade" and the "stage" of a cancer
5. Discuss risk factors for cancer and strategies for prevention
6. Define the following terms:
    - Cell differentiation
    - Benign tumor
    - Malignant tumor
    - Dysplasia
    - Carcinogen
    - Proto-oncogene and onogene
    - Tumor-suppessor gene (anti-oncogene)
    - Apoptosis

Cancer Biology

Cancer is the result of a long process that begins when one of the cells in organs or tissue becomes damaged or altered in a way that causes it to break free from normal controls that allow cells to work in harmony. Cancer cells with divide via mitosis even if they do not receive the appropriate signals. This can lead to a mass of cells, or a tumor.

The nucleus of a cell contains the genetic information, within the chromosomes. Certain genes make products that lead cells to reproduce. The genes responsible for making cells divide are called **proto-oncogenes.** Changes in normal genes lead to the production of proto-oncogenes,

making cells divide faster. There are also genes that stop the division of cells, known as **tumor-suppressor genes** (AKA anti-oncogenes). We have two of these genes (one from each parent), so if one tumor-suppressor gene is damaged, usually the other is able to stop the cell from behaving abnormally.

The process by which tumors cause the body to provide the cell with nutrients is call **angiogenesis.** The tumor sends out messages that say "feed me" and the nearby blood vessels send over new extensions that deliver food and oxygen. The blood vessels also act as a passageway for movement of tumor cells. The movement of tumor cells to other parts of the body is called **metastatis.** 90% of cancer deaths occur when the tumor spreads to different parts of the body.

One way the development of cancer is prevented is the death of defective cells. If the body is unable to replace or repair the damaged, stressed, or worn-out cells it commits cellular suicide, or **apoptosis.** This leads to the breakdown and death of the cell. It is estimated over 50 billion cells undergo apoptosis each day in adults, and is carefully regulated through complex mechanisms. Cancer cells lose this critical capability and lead to buildup of abnormal cells. Cancer cells can also develop resistance to drug or chemotherapy treatment in the same way bacteria might.

Cell Differentiation

A major difference between cells in a growing embryo and those in an adult is that most of an adult's are differentiated (they have become specialized in structure and function). Muscle cells are elongated and contain an abundance of contractile proteins, whereas pancreas cells are specialized for secretion of digestive enzymes.

The cells in the earliest stages of an embryo are totipotent, meaning they have the capacity to divide and give rise to any of the specialized cells in the body. In contrast, in an adult the replacement if shed or worn out cells takes place by division of somatic stem cells (also called adult stem cells), which are not fully differentiated but can give rise to only a limited array of cells.

For example, stem cells in the bone marrow (hematopoetic steam cells) and divide and give rise to progenitor cells that can differentiate into cellular elements of blood and immune system, including red blood cells, lymphocytes, platelets and more. Bone marrow stromal stem cells (mesenchymal stem cells or skelatal stem cells) can generate bone, cartilage and fat cells.

When stem cells are called upon to generate a particular type of cell, they undergo asymmetric cell division in which one of the child cells has a finite capacity for cell division and begins to differentiate and the other sibling cell remains a stem cell with unlimited proliferative ability.

New cells are born through the division of an existing cell into two through mitosis. The need for new cells continues through our entire life, but is greatest in early life. A fertilized egg divides into two cells, which splits to 4, 8, 16, 32, 64, etc... In a fully grown adult the rate of cell proliferation is much less, and under normal circumstances only takes place when signals indicate cells need to be replaced.

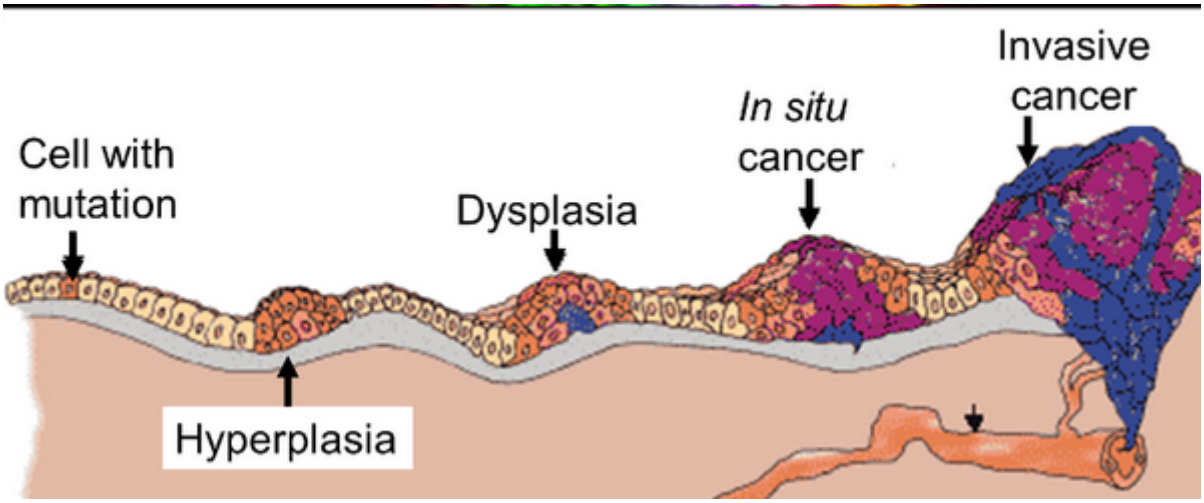
Cell differentiation is not completely understood, but involves the activation or inactivation of certain genes in response to the cell's interaction with neighboring cells and with its extracellular matrix (ECM). Receptors on the cell will bind to specific molecular elements in the ECM and this binding activates the intracellular signal transduction pathways that turn certain genes on or off. As a result some genes can be expressed in a given cell, and others cannot. Some cells, like sketelal and muscle cells, become terminally differentiated meaning their ability to proliferate is permanently lost, though they can continue to perform their functions.

Ex. of Normal Cell Division: The outer layer of skin (eipdermis) is about 12 cells thick. Cells in its lowermost basal layer divide just fast enough to replinish shed cells. Division of a basal cell produces one cell that remains in the basal layer and retains the capacity to divide. The other migrates out of the basal layer and loses the capacity to divide, thus the number of dividing cells in the basal layer stays roughly the same.

Ex. of Abnormal Cell Division: The transition to skin cancer begins when the normal balance between cell division and cell loss is disrupted. Basal cells divide faster than needed leading to an increasing number of dividing cells. This creates a growing mass of a tissue called a "tumor" or "neoplasm". The organization of the tissue gradually becomes more disrupted.

Benign Tumors (skin moles, lipomas) are abnormal growths that are no longer under normal regulation, but grow slowly, resemble normal cells,and still have surface recognition proteins that bind them together and keep them from invading or metastasizing.

Evolution of a Cancer



Atrophy: Reduction in cell mess

Hypertrophy: Enlargement of cell size

Hyperplasia is an increase in the number of cells in a tissue with normal cell morphology and normal cell to cell interaction

Dysplasia is a pre-cancerous state characterized by increased cell proliferation with high abnormal and variable appearance to the cells. Cell to cell interactions are diminished, and the architecture of the tissue is less organized. Dysplasia is potentially reversible and doesn't always progress to cancer, but indicates a pre-cancerous state with high probability of evolving to cancer and considered "per-malignant".

Carcinoma "in situ" literally means cancer in place. These cells have transitioned to being cancerous. In situ cancer may remain contained indefinitely, but additional mutations may occur that enable it to invade neighboring tissue and shed cells into the blood or lymph.

Metastatis is the movement or spreading of cancer cells from one tissue to another and their prolideraation at the new site. Cancer cells usually spread through the bloodstream or lymphatic system. The tumor mass can also spread locally, compress other structures and damage surrounding tissues.

Characteristics of Cancer Cells:

- Self-sufficiency in growth signals; an autonomous drive to proliferate - pathological mitosis - by virtue of the activation of oncogenes such as ras or myc.
- Insensitivity to growth-inhibitory signals; they inactivate tumor suppressors.
- Evasion of programmed cell death (apoptosis); suppression and inactivation of genes and pathways that normally enable cells to die.

Cancer Risk Factors

Radiation

Non-ionizing - low frequency, long wavelength energy which is not energetic enough too penetrate deeply or create free radicals.It only penetrates single-celled organisms and the superfical cell layers of multicellular organisms. However, it can damage DNA in superfical cells and cause mutations. UV rays from the sun and tanning salons accounts for 50-90% of all skin cancers. Ex. radio signals, microwaves, power lines, heat lamps, etc.

Ionizing - Proton, neutrons, x-rays, and gamma rays have highly energetic wavelengths enabling them to deeply penetrate tissues. Lead shields block this form of radiation. DNA can be damaged by a direct hit, but it more often indirectly damages DNA by stripping away electrons when they strike a molecule, thereby creating a highly reactive free radical. The resulting free radical can damage other molecules by stealing electrons or breaking phosphate bonds in DNA, thus giving it a cumulative mutagenic effect. Ex. Nuclear fallout, radioactive chemicals, Radon, etc.

Chemicals

A chemical carcinogen is any discrete chemical compound which has been shown to cause cancer. These can enter the body through absorption, ingestion, or inhalation. Some of these include

formaldehyde, chloroform, asbestos, and arsenic. Tabaco smoke contains over 60 carcinogens.

Heterocyclic amines (HCAs) & Polycyclic Armoatic Hydrocarbons (PAHs) are a family of carcinogenic chemicals formed in cooking muscles meats (beef, pork, fowl and fish). Eggs and tofu are not associated. HCAs form when amino acids and creatine (a chemical found in muscles) react at high cooking temperatures.

Viruses

Viruses are estimated to cause 15-20% of all cancers. The host's genetic susceptibility, mutations, exposure and immune system deficiencies are also factors. Oncoviruses (cancer-causing viruses) include Epstein-Barr virus, hep B and C, HPV, and herpes. AIDs also indirectly increases risk of cancer due to impared immune function.

Consumption and Heredity

High BMI is associated with increased risk of colon, breast, kidney, esophagus, stomach, pancreas, gallbladder and liver cancer. Fat tissues produce excess amounts of estrogen, high levels are associated with some cancers. Obese people often have increased levels of insulin in their blood, which may promote the development of certain tumors. Fat cells may have a direct or indirect effect on tumor growth regulators.

Alcohol intake is associated with an increased risk of cancer of the mouth esophagus, pharynx, colon, and liver.

Most cancers are sporatic, and have to hereditary predisposition. However, there are some which can be hereditary such as Retinoblastoma, breast cancer, and colon cancer.

Heart Health

Atherosclerotic disease is a global health problem. Cardiovascular disease is the number 1 cause of death worldwide, claiming 12 billion lives annually in developing countries. In the US heart disease claims about 800,000 deaths per year. It is estimated 80% of deaths from cardiovascular disease worldwide occur in low-income and middle income countries. The high mortality is partly due to lack of access to care in many areas, but the problem will not be solved by better medical care.

Atherosclerotic is a complex process by which arteries become progressively narrowed, impairing the supply of oxygen. Impaired blood flow can result in ischemia and cause angina or intermittent claudication. Plaques can also rupture, triggering acute formation of a clot and abrupt loss of blood supply to tissues, resulting in an infarction.

Eventually, progression of atherosclerosis *generally* can manifest itself in three ways:

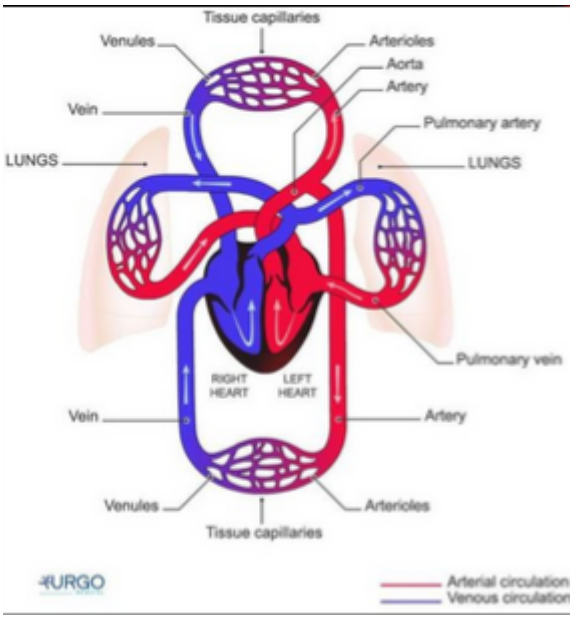
- Coronary artery disease
- Cerebrovascular disease
- Peripheral artery disease

Learning Outcomes

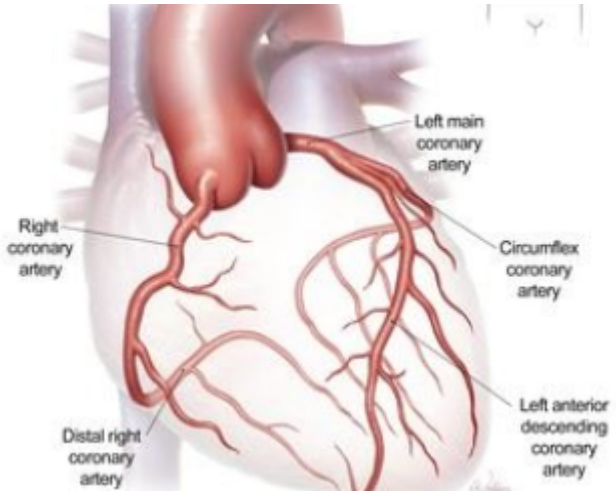
1. Define atherosclerosis and describe the basic mechanism by which it develops, including response to injury theory
2. Compare and contrast the terms ischemia and infarction
3. Explain the mechanisms by which poorly controlled diabetes and hypertension contribute to heart disease
4. Discuss the risk factors for atherosclerotic cardiovascular disease

The Cardiovascular System

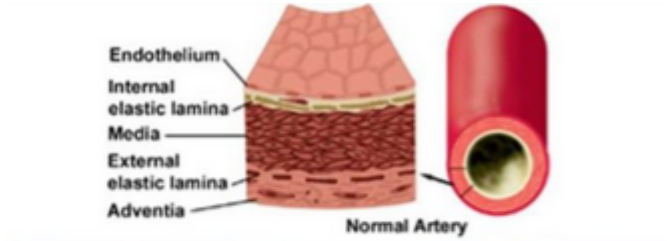
The primary function of the heart and blood vessels is to transport oxygen, nutrients, and byproducts of metabolism. Oxygen and nutrient-rich blood is delivered to tissues via the arterial system which branches into smaller and smaller blood vessels; from arteries to arterioles to capillaries (where most exchange occurs).

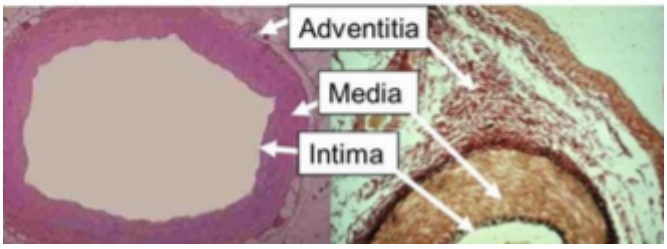


The heart is a discrete organ which has 4 chambers (in humans). Two chambers on the right side (right atrium and right ventricle) receive blood returning from the periphery and send it too the lungs for re-oxygenation. Blood then returns on the left side via pulmonary veins. After entering the left atrium blood enters the left ventricle and is pumped back into the aortic arch for distribution to the body.



Note also that the heart requires a continuous supply of oxygen an nutrients, just like any other tissue. The heart receives its blood supply from coronary arteries which arise from the root of the aorta.





All blood vessels (arteries and veins) have 3 primary layers: Intima, media, and adventitia. Normally, the walls of an artery are smooth to allow unobstructed blood flow. The innermost layer. intima, is lined with indothelial cells which are in direct contact with blood.

Atherosclerosis

The endothelial cells that line blood vessels provide a semi-permeable barrier that regulates exchange between blood and tissues. Endothelial cells also regulate a number of less obvious processes. They provide a unique surface that generally allows the cellular elements of blood to flow without adhering too the vessel lining unless something has perturbed the cells. When perturbation occurs, these cells secrete cytokines that trigger and maintain an inflammatory response. Endothelial cells also regulate constriction and relaxation of vessels by releasing vasodilatory molecules and vasoconstrictive molecules.

Atherosclerosis occurs when plaque builds up in the arteries. Enough can eventually lead to a heart attack or stroke. Atherosclerosis can be asymptomatic in its early stages but become serious as blood supply becomes compromised. It starts with damage to the artery wall, then calcium and blood cells begin to build on the damaged wall. Chemical reactions occur with LDL Cholesterol triggering inflammation and cells release a chemical SOS signal and white blood cells begin to eat the cholesterol, which cause the cells to turn to foam and turn to plaque.

Risk Factors

There is a direct link between risk of cardiovascular disease and concentration of cholesterol in the blood. Cholesterol is a waxy, fat-like substance that's found in all the cells in your body. Your body needs some cholesterol to make hormones, vitamin D, and substances that help you digest foods. LDL is the "bad" cholesterol that sticks to your arteries. Satins are currently the most powerful cholesterol lowering drugs, inhibiting the synthesis of cholesterol in the liver. HDL is the "good" cholesterol; Blood levels of HDL are inversely related to risk of coronary artery disease.

Obesity is associated with some cancers, Type II diabetes, hypertension, and heart disease. BMI is usually used to measure fatness, but can be inaccurate because it does not take into account muscular development or fat distribution. "Central adiposity" is fat deposition in the torso (the "apple-shaped" person) which is more indicative or cardiovascular risk.

Type 1 and 2 diabetes are risk factors for CAD. People with diabetes cannot produce insulin, which circulates in the blood and binds to insulin receptors on the muscles and fat cells triggering insertion of specialized glucose transporters to facilitate the entry of glucose from the blood to the cell.

Other factors:

- Smoking - smoking is really bad mmmkay
- Alcohol consumption - almost all studies have concluded that moderate alcohol consumption is associated with 20-40% lower incidence of CAD, compared with non-drinkers or heavy-drinkers. However, there could be an unknown confounding variable.
- Gender differences - Women tend to develop heart disease about 10 years after men
- Aspirin and Vitamins - A study in the 1900's suggested there may be a 30% risk reduction of myocardial infarction by taking aspirin.