2023

Understanding Inflammation, Immunity, and Infection

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Chapter 1: Acute Inflammation

In ancient times, physicians pretty much got everything wrong about medicine. In fact, most of the treatments they came up with made matters worse. But they were right about one thing: that the body always responds the same way to injury or illness, with acute inflammation.

Redness, warmth, swelling, and pain characterize acute inflammation

This is something we know from insect bites, sunburns, cuts, scrapes, and sore throats. Why does our body react that way? Even though it usually hurts, acute inflammation is how our body prepares injured or infected tissue for healing. No inflammation—no healing.

Acute inflammation is also part of our immune system

There are three parts or "layers" of the immune system. First, there are protective barriers, like intact skin, and additional "surface" defenses to prevent microbes from "digging down" and "breaking into" our internal tissues and organs to establish infection.

Second, there is the immediately-acting innate immune system. Acute inflammation is part of the innate immune system. The third layer of the immune system is the adaptive immune system, which provides a slightly delayed, but powerful response, one in which specific immune weapons are created and unleashed against the specific invading microbe. Thus, acute inflammation has two major roles, immune defense and "clearing the way" for healing.

Tissue injury or infection triggers acute inflammation

Specific causes include: a) physical trauma; b) burns; c) frostbite; d) infection; e) toxic or irritating chemicals; f) allergies; g) autoimmune diseases; h) radiation; and i) electrical shocks; among others.

We have all been bitten by insects. In these situations, acute inflammation appears immediately. How does this happen? It begins with the response of mast cells to the injury caused by the insect's bite. Mast cells are located throughout the body. Most of them reside in the connective tissue beneath epithelial tissues, such as the dermis of the skin. But they underlie all epithelial tissues, including the linings of the oropharynx, respiratory tract, gastrointestinal tract, and genitourinary tract.

Mast cells "sound the alarm" in tissue injury or infection

Mast cells contain vesicles of "inflammatory mediators" that are released when anything damages the overlying epithelium or nearby cells. For example, when a bee stings us, there is damage due to the "hole" made by the stinger, as well as further damage by the bee venom. Both the physical injury and the injury caused by the venom trigger mast cells to "de-granulate"—that is, "spew out" their pre-packaged inflammatory mediators.

Inflammatory mediators are a subset of chemicals called cytokines. Cytokines are substances released by cells, especially cells of the immune system. These chemicals signal other cells to "do something." This is a major way that cells "act and work together." Inflammatory mediators are a subset of

cytokines that "bring about" and "coordinate" the inflammatory response. One of the major inflammatory mediators is histamine.

Histamine is released by mast cells and "launches" the acute inflammatory response

Histamine and other inflammatory mediators released by mast cells diffuse to nearby blood vessels where they cause them to dilate in diameter and become "leaky." When blood vessels in the dermis dilate in response to a bee sting, the redness of the blood is more visible in the overlying epidermis of the skin. And the greater blood flow to the skin can be appreciated as increased warmth.

The increased leakiness of blood vessels results in the movement of fluid from the bloodstream to the nearby interstitial tissue ("the space between cells"). As a result, swelling occurs, which can be easily appreciated after a bee sting.

The "tightness" of swollen tissue, in turn, stimulates pain-sensing nerve endings and sensory receptors (called nocioceptors). In addition, some of the mediators released by mast cells and damaged cells also trigger nocioceptors. This is experienced as pain.

Acute inflammation soon attracts white blood cells to kill bacteria

Say a person gets a splinter on the sole of a foot. The puncture of the skin will result in bleeding, which, in turn, will trigger hemostasis, which, in turn, will stop the bleeding by causing the blood to clot. Also at this time, as discussed above, mast cells will degranulate, and the area of the splinter wound will display the characteristics of acute inflammation, and cause the experience of pain.

Every time the skin is pierced, microbes, mostly bacteria, enter the depths of the wound. This is because we coexist with microbes both on our skin and within several internal areas including the nose, oropharynx, and gastrointestinal and genital tracts. In the case of a splinter in the foot--if bacteria could think and speak, they might say, "Look at that hole in the skin! Yay, a new place to live! A new place to expand my family! Let's go explore!"

And that's what bacteria from the skin do with every cut, scrape, or puncture. Surprisingly, while skin infections ensue occasionally, most "breaches" of the skin do not become infected. Why not? Because inflammatory mediators released by mast cells stimulate the endothelial cells of the blood vessels adjacent to the wound to "hold up signs" to attract circulating neutrophils. These "signs" are called adhesion molecules, and include such molecules as selectins and integrins.

Neutrophils are the blood's most plentiful type of white blood cell. In response to the expression of adhesion molecules and their attractive forces, neutrophils slow down and begin to roll along the endothelial surface. Ultimately, the neutrophils moving and "slither" between endothelial cells into the interstitial tissue adjacent to the wound. Neutrophils have motile abilities and "swim" through the tissue toward any and all bacteria that have invaded the wound.

Neutrophils are the first army to attack microbe invaders, macrophages come next

Neutrophils locate microbes by a "gps-like guided process" called chemotaxis. "Enticed" by chemotactic factors "shed" by bacteria and other sources, neutrophils seek and destroy these microbes by various mechanisms. They can secrete lytic enzymes and antimicrobial peptides, as well as "swallow" bacteria by phagocytosis. This process involves engulfing invading microbes within phagolysosomes, into which lethal microbe-toxins are delivered.

After about a day, inflammatory mediators signal the attraction of circulating monocytes to the endothelial surfaces adjacent to the wound. This time, it is monocytes that exit the bloodstream and become capable of secreting antimicrobial peptides and enzymes, as well as conduct phagocytosis. When monocytes leave the bloodstream they are called macrophages.

Neutrophils and macrophages both sterilize the wound and prepare it for healing

Not only do neutrophils and macrophages destroy invading microbes, but they also phagocytize dead tissue and other debris. When complete, the inflammatory process "winds down." This is directed by another set of mediators, which are termed anti-inflammatory mediators, another subset of cytokines. As inflammation dies down, macrophages and other cells begin to secrete yet another set of mediators or cytokines to begin healing and repair.

Acute inflammation can go wrong in two ways

Acute inflammation is "supposed to run its course" and be done--so that healing can begin. This does not happen always. In diseases such as asthma and inflammatory bowel disease, the initial acute inflammation continues on and on unless treatment is given. This is because the cause of inflammation "does not go away." In asthma, every day the person breathes in the causative allergens, the airways continue to respond by inflammation. And in inflammatory bowel disease—without treatment—the autoimmune attack of the bowel lining continues.

In summary, one of the ways acute inflammation "can go wrong" is by not resolving. When initial acute inflammation persists it is called chronic inflammation. Many diseases involve chronic inflammation. And much of medical treatment is an effort to "turn off" or "turn down" chronic inflammation.

Chronic inflammation is always bad

Why? In contrast to acute inflammation, in which healing and repair involve the production of a limited amount of fibrous or scar tissue, in chronic inflammation, excessive amounts are produced. In chronic viral hepatitis, for example, the chronic inflammation stimulates the deposition of large amounts of fibrous tissue. This tissue pierces and expands and extends throughout the liver, killing crucial hepatocytes, and distorting and blocking arterial flow, venous flow, and bile flow. This gradually destroys the liver's ability to function, which characterizes cirrhosis, a form of end-stage liver disease that can be fatal.

Acute inflammation can be too extreme

As discussed above, most of the time, acute inflammation is of limited severity. However, on occasion, it can be so extreme as to be potentially lethal. For example, in rare instances, a routine

medication can unpredictably result in an extensive allergic reaction involving most or all of the entire skin surface. This essentially causes the skin "to fall off." This unusual reaction is called toxic epidermal necrosis, and may require inpatient care in a burn unit.

In summary, while acute inflammation "is usually our friend"—and prepares damaged or infected tissue for healing, it can occasionally be destructive by its persistence or severity.

Total body inflammation is referred to as the systemic inflammatory response syndrome (SIRS)

So far, we have focused on localized inflammation. Can body-wide inflammation occur? Yes, but in medicine, the word systemic is used for "body-wide." Clues to the a body-wide inflammatory reaction include "non-localized" clinical manifestations such as fever, low blood pressure (hypotension), rapid heart rate (tachycardia), rapid respiratory rate (tachypnea), and changes within the blood stream, such as increased numbers of circulating white blood cells (leukocytosis).

The systemic inflammatory response syndrome is referred to by its acronym, SIRS (surz)

The triggers for SIRS are similar to those of localized inflammation: a) infection; b) allergies—in the form of anaphylaxis; c) trauma—in the form of extensive or "multiple trauma"; d) autoimmune reactions that are severe such as transfusion reactions or flare-ups of autoimmune diseases such as systemic lupus erythematosus ("lupus"); and e) major burns, among others.

In addition, localized inflammation that is severe enough can "spill over" to cause SIRS. Localized inflammation can be likened to a fire in the fireplace. But sometimes, this fire can spread and catch the house on fire. For example, many urinary tract infections are localized to the bladder and do not cause SIRS. On the other hand, a subset of bladder infections ("cystitis") are followed by the ascension of the causative microbe up one of the ureters, which, in turn, infects the kidney ("pyelonephritis"). A much more serious infection, pyelonephritis almost always triggers SIRS.

A patient with two or more out of four criteria are said to have SIRS

The four criteria are: a) heart rate (HR) > 90 beats/min; b) respiratory rate (RR) > 20 breaths per min; c) fever or hypothermia (> 38 F or < 36 F); d) leukocytosis or leukopenia (white blood cell count > 12,000 or < 4,000). Any patient with two or more have SIRS.

What leads to the body-wide or systemic manifestations of SIRS? Inflammatory mediators again. As previously discussed, inflammatory mediators are what leads to localized redness, warmth, swelling, and pain. It is the same or similar mediators—usually in high concentrations circulating though the bloodstream—that cause the manifestations of SIRS.

Chapter 2: Function of the Immune System

The purpose of the immune system is to defend the body against invasion by pathogenic microbes ("infection"). To accomplish this, the immune system must be able to recognize that the body's "perimeter" has been breached. One of the main way our immune system recognizes invasion is through the detection of unique cell-surface makers on microbes. For example, rhinovirus has "rhinovirus markers" and the causative agent of Strep throat has *Streptotococcus pyogenes* markers.

"Identity" markers are called antigens

Antigens not only exist on microbes, but also on our own body cells. The markers on our body cells are called self-antigens. On the other hand, the markers on microbes are called non-self-antigens (or foreign antigens). Our immune system is "trained" to be able to distinguish non-self-antigens from self-antigens.

The "discernment" between self- and non-self is essential to health

This allows our immune system to create immune weapons to attack microbial invaders, while, at the same time, refraining from making weapons against our own cells and tissues. Autoimmune diseases arise when our own immune system mistakenly attacks our cells and tissues. More about this will be discussed later.

Microbes are not the only source of non-self antigens encountered by the body

Many environmental proteins and other inanimate substances have foreign identity markers as well. These include pollen, pet dander (flakes of dead skin), bee sting venom, shellfish proteins, peanut proteins, and so on. But environmental proteins and other inanimate substances are NOT microbes, and they cannot ever infect our bodies.

Allergic diseases arise when our immune system attacks inanimate proteins and substances

Thus, allergic diseases are distinct from autoimmune diseases. In allergic diseases, the immune system attacks non-self molecules that we "eat" or "breathe in" or "touch our skin." But these molecules are not a part of our bodies. They are derived from the outside of our bodies. In autoimmune diseases, it is our own body cells and tissues that are attacked.

Both allergic and autoimmune diseases arise from errors committed by our immune system

But they are due to different errors. In allergic diseases, our immune system correctly identifies environmental or dietary molecules as foreign or non-self, but it incorrectly judges these molecules as threats to our bodies. In autoimmune diseases, our immune system incorrectly identifies our own cells and tissues as foreign or non-self AND incorrectly judges these essential components of our own bodies as threats. Before we discuss the details of allergic and autoimmune diseases, let us review the key functions of the healthy immune system.

The normal immune system has three parts or layers

The first component consists of anatomic surface barriers and related physiologic deterrents. Together, these are simply called "barriers."

Unbroken or intact skin is a robust barrier against infection

Intact skin blocks invasion by almost all viruses, bacteria, protozoans, fungi. Some superficial fungi can, however, infect the epidermis (like "athlete's feet); however, most of the deadly fungi that are capable of deep tissue and bloodstream infections cannot "breakthrough" intact skin.

Helminths or worms are exceptional as some can "burrow" through intact skin

In the U.S, fortunately, exposure to helminths is limited.

Mucus membranes are barriers, but are far less impenetrable than skin

Mucus membranes make use of antimicrobial peptides, like defensins and secretory IgA. Secretory IgA is one of five classes of antibodies that can bind to (and thereby inactivate or hinder) invading microbes. However, many pathogenic microbes can overcome this nonspecific immune system weapon.

Gastric acid creates a deadly milieu many ingested microbes

This is why we usually do not develop "food poisoning" every time we ingest contaminated foods like unwashed fruit. However, some microbes and microbial toxins can survive the low pH within the stomach.

The acidity of urine and vaginal secretions is also a barrier to some infections

However, the degree of acidity is much less than within the stomach.

The trachea and larger airways provide surprisingly good protection against infection

These large airways are "lined" with a ciliated pseudostratified columnar epithelium. Cilia are in constant motion "beating" upward. This continuously propels a mucus layer that overlies the epithelium. For example, when near a campfire, soot is often inhaled.

These particles "stick to" airway-lining mucus, which prevents them from penetrating more deeply into the lungs, and, in addition, moves them upward where they can be swallowed or spit out or coughed out. The same happens when pathogenic microbes enter these airways. In this way, many potential cases of pneumonia are prevented. It should be noted that the toxicity of tobacco smoke triggers ciliated stratified columnar cells to "morph" into squamous cells. This "metaplasia" is damaging because it impairs the function of the "mucociliary escalator."

The "microbiome" is an essential defense barrier against infection

What is the microbiome? It is a collection of viruses, bacteria, and fungi that live on, or in, the body. Each of us has an extensive microbiome. For example, there are about 10 microbial cells on and

within our body for every single body cell. The microbiome consists of a wide array of different microbial species and strains or variants of species.

Different people can have vastly different arrays of these microbes

In addition, there are differences among people in the quantities of various microbes. Why are there differences? This is not completely known, but some known or suspected factors include: a) genetics; b) immune system characteristics; c) age; d) general health status; e) diet; f) former diets; g) body weight; h) current and past antibiotic exposure; i) other medication exposures; j) smoking; k) alcohol; l) illicit drugs (exposure to substances); m) characteristics and health of family members; n) occupation; o) location; p) travel history; q) current and former infectious diseases; r) current and former diseases of all kinds, among others.

And individual's microbiome can decrease or increase susceptibility to infection

That is, there are microbiomes that are more healthy and those that are less so. Further, microbiomes can change many times or continuously through life.

Dysbiosis refers to the development of a less healthy microbiome

In the colons of healthy people, there are small numbers of pathogenic bacteria. These bacterial species, such as *Clostridioides difficile*—if "given the chance"—would replicate freely and cause infection of the colon, sometimes leading to life-threatening bloody diarrhea. However, a healthy microbiome—in ways we do not fully understand—"keeps these small numbers of trouble-making bacteria in check."

Unfortunately, when certain antibiotics are appropriately prescribed to treat infections outside of the bowels, these same antibiotics "kill off" some of the healthy microbiome. And in some cases, this change--this dysbiosis—can remove the inhibitory effect on resident *Clostridioides difficile* microbes so that they replicate and infect the colon.

Fecal transplantation can be used to improve a patient's microbiome

Amazingly, in *Clostridioides difficile* infections, transferring an array of normal microbiome bacteria from a healthy person into the colon of a patient with colitis is often curative. Whether improving the microbiome by fecal transplantation to cure or prevent other infectious or other diseases is an active area of research.

The second component or layer of the immune system is called the innate immune system

This layer of the immune system consists of four main immune system "weapons": a) acute inflammatory response, including phagocytosis; b) complement system of proteins; c) natural killer cells (NK cells); and d) interferons;

Acute inflammation has already been discussed in a prior chapter. The importance of this part of the innate immune system cannot be overstated. Think of all the times you have gotten a cut (laceration), scrape (abrasion), or insect bite (puncture wound). In these cases, skin bacteria, including some pathogenic species, are "allowed entry" into vulnerable deeper tissues.

However, it is uncommon for an infection to ensue. That is, it is uncommon for an infection to "take root" following most cuts, scrapes, or punctures of the skin. This is primarily due to the "swarming" of neutrophils, and later, monocyte-macrophages, which aggressively and effectively phagocytize the wound-contaminating bacteria.

Patients with insufficient neutrophils greatly weakens the innate immune response

This can occur, for example, in patients receiving cytotoxic chemotherapy. It can also occur when a cancer of white blood cells (called leukemia) develops within the bone marrow. In this situation, the excessive replication of abnormal ("leukemic") cells "crowds out" the production of normal white blood cells, including neutrophils.

Our bloodstream contains rapidly-acting microbe-fighting proteins

There are several dozen of these proteins, which together, make up the complement "cascade" or complement system. Some of these proteins will recognize and "stick to" microbes, for example, within the bloodstream.

"Opsonization" is the process whereby microbes are "marked for destruction."

As these "coated" bacteria circulate in the blood, and especially through the tortuous sinusoids of the spleen, macrophages recognize them as invaders. The macrophages are positioned along the lining of the sinusoids so that they can "swallow" and destroy them by phagocytosis. (phagocytosis).

In a different way, complement proteins can attach to virus particles in the blood—and in this way—render them incapable of invading body cells. This process is called "neutralization."

Complement proteins can "work together" to form a "membrane attack complex" (MAC)

This "assembly" of the following activated complement proteins--C5b, C6, C7, C8, and C9—attaches to the surface of a bacterium, for example, and actually "drills a hole" into it, killing it.
Some patients have genetic deficiencies of one or more complement components and as a result, are more susceptible to infection or death from infection. For example, those with deficiencies in any of the membrane attack complex proteins are at increased risk for infection and death from *Neisseria meningitides.*

Complement proteins, as well as other "weapons" of the innate immune system require a way to recognize invading microbes as threats to be destroyed. Fortunately, the molecular structures of most microbes have various "molecular patterns" that are recognized by the "pattern recognition receptors" (PRRs) of certain complement proteins and cells of the innate immune system.

The various molecular markers of microbes are called "pathogen-associated molecular patterns" (PAMPs) which are not present on body cells—only on microbes. These markers are general markers that are shared by many different microbes. This is in contrast to the very unique and specific markers that all microbes possess—specific markers (called antigens) that are used by the more powerful adaptive immune system (discussed below).

Natural killer (NK) cells are another weapon of the innate immune system

NK cells are a type of lymphocyte that can recognize when body cells are stressed or infected by intracellular microbes, such as viruses. Healthy body cells have major histocompatibility complex (MHC) class I molecules on their cell membranes. These markers prevent the "attack" by NK cells.

However, in body cells that lose these markers--stressed cells, damaged cells, malignant cells, and cells infected with intracellular microbes--NK cells recognize them and "connect to them."
Then the NK cell releases "perforins," which can "bore a hole" in an infected body cell. This is followed by the NK cell release of destructive enzymes called "granzymes"—which enter the hole and trigger cell death by apoptosis. The dying cell causes any intracellular microbes to perish as well.

Interferon proteins released by infected cells diffuse to nearby uninfected cells to protect them

This innate immune system weapon is counterintuitive. This is because the attacked body cell acts as if it has "given up" on saving itself, and instead "tries" to save other cells. When a body cell is infected by an intracellular microbe, like a virus, this triggers the production of interferon proteins, which enter nearby uninfected cells. Once inside healthy cells, interferon proteins trigger changes within these cells that "strengthen" or "harden" these cells against succumbing to infection themselves.

Released interferons also "strengthen" the virus-killing function of circulating NK cells. In fact, there is evidence that patients with deficiencies in interferon production –or inactivation of interferon by autoantibodies--have worse outcomes from Covid-19 infection.

The third part or layer of the immune system is the adaptive immune system

The word, "adaptive" refers to the fact that the corresponding immune system weapons are "adapted" or "specifically created" against the exact causative microbe. That is, adaptive immune system weapons are "perfectly shaped" to "seek and find" and "bind to and destroy" infecting microbes only—identified by their specific antigen markers.

Because these weapons are specifically created for the specific causative microbe, they are the most powerful immune system weapons.

Unfortunately, it takes a few days for these weapons to be "built" or "created."

This is because the antigen markers of an invading microbe must be captured and presented to the immune system—followed by the "mass production" of the specific adaptive weapons. Thus, some rapidly progressing infections can kill before these weapons are made.

There are two "arms" of the adaptive immune system

The humoral arm results in the production of the important weapon of antibodies, while the cellular arm results in the production of "cytotoxic T cells." The humoral arm relies of various B cells, plasma cells, antigen-presenting cells, soluble antibodies, and helper T cells, along with the cytokines that helper T cells release. The cellular arm relies on various T cells, including helper T cells and the cytokines that they release, antigen-presenting cells, such as dendritic cells, and cytotoxic T cells.

Helper T cells act like a "choreographer" or "stage director" of the immune response

Helper T cells--while not direct-weapons themselves, secrete various cytokines that signal various cells of both the innate and adaptive immune system to "ramp up" their capabilities and the strength of their weapons. That is, helper T cells cytokines "supercharge" other cells of the immune response.

In fact, without the participation of helper T cells, the entire immune system "falls apart." It is counterintuitive that the loss in helper T cell function alone prevents the "work" of so many immune system "effectors" or weapons. Without stimulation by helper T cells, all of the following are rendered less effective: a) phagocytosis by neutrophils and macrophages; b) replication of other classes of T cells, B cells, and plasma cells; c) production of antibodies by plasma cells; and d) cytotoxic T cell destruction of cells harboring intracellular microbes, to name a few.

The central role of helper T cells was seen vividly in the past in Acquired immunodeficiency syndrome (AIDS) due to infection by HIV. Ironically, the HIV virus selectively attaches to helper T cells, enters them, and destroys them (if not prevented by current antiretroviral treatment). Almost all of the many deaths from AIDS were due to the selective destruction of the essential "choreographer" or "coach" of the immune system, the helper T cell.

Dendritic cells that are "on the lookout" for invading microbes

Dendritic cells exist throughout the body at sites where microbes are likely to invade—for example, in the dermis of the skin and underlying the epithelia of the oropharynx, bronchial airways, alveoli, intestinal tract, urogenital tract, and elsewhere.

Dendritic cells are always "on the lookout" for microbes

When invasion by microbes occurs, nearby dendritic cells "swallow" or phagocytize them. In this process, they "collect" the microbe's unique markers or antigens. It is interesting that antigens can be broken down into smaller antigen fragments called "epitopes." These are also unique for each microbe.

Dendritic cells place digested microbe antigens and epitopes on their cells surface

This is why dendritic cells are called "antigen-presenting" cells or APCs. Dendritic cells are not the only cell type that can present antigens, but they are the most common one. Antigen-presenting cells

"advertise" or "reveal" the identity of the invading microbe to circulating T cells. The majority of both T and B lymphocytes circulate throughout the body within the bloodstream, lymphatic channels, and structures like lymph nodes and the spleen. In addition, some B and T lymphocytes reside in lymph nodes and the spleen.

There is a natural subset of circulating T cells that is a perfect match for any microbe's antigens

From very early life, a vast assortment of T cells is produced. In most ways, these T cells are identical in appearance and function. However, they are different with respect to one of their cell-surface receptors, the so-called T cell receptor. Although it may be hard to believe, by extensive and random genetically-programmed processes in early life, there are innumerable subsets of T lymphocytes, each with an unique T cell receptor.

For example, there is a natural subset of T cells with a T cell receptor that has a "perfect fit" for the antigen or epitope of the causative agent of influenza. Let us say a person develops influenza, what happens with respect to the immune response?

First, some invading influenza virus is phagocytized and digested by dendritic cells of the oropharynx. Influenza antigens and epitopes are then "presented" on the dendritic cell's surface to notify that the body has been invaded (and infected) with influenza virus. However, within the patient's body, for example, within the blood, lymph, and lymph nodes, there is a subset of T cells who have a receptor that is a match for the presented or displayed influenza virus antigen or epitopes.

The matching of a T cell's receptor with a microbe's antigen kick-starts the immune response

That is, it kick-starts the body's adaptive immune response. This is the part of the immune system that requires a few days to make powerful weapons against influenza virus--to continue our example.

T cells replicate wilding when a match occurs, creating a clone of T cells

This results in the creation of many millions of identical T cells. However, these T cells with "mature" into a few different types of T cell (but all retaining the "exact fit" for influenza virus antigens and epitopes—to continue our example)

Some become: a) helper T cells, that will stimulate and "supercharge" the cells of the entire immune system; memory T cells, which will "be ready" to form immune system weapons quickly in the future if the microbe is encountered again; c) cytotoxic T cells that are able to destroy invading microbes, especially those that "live" inside body cells, like influenza virus.

Antigen-presenting cells also engage matching B cells

When a specific subset of B cells recognizes a corresponding microbe's antigen or epitopes, these B cells replicate wildly, just as do corresponding T cells. Many of these B cells differentiate further (or "morph into") plasma cells.

Plasma cells function as antibody production "factories"

Antibodies are the powerful weapons of the humoral arm of the adaptive immune response. The most important characteristic of antibodies is that they recognize the causative invading microbe. That is, they are a weapon that was created—over 2-4 days—to bind tightly to the microbe's cell membrane or virion.

Antibodies opsonize microbes, but are even more powerful than complement proteins

Further, once antibodies attach to microbes, this often attracts complement to attach as well. In other words, the attack by both complement proteins and antibodies are synergistic. Antibodies are especially effective at neutralizing or triggering the destruction of extracellular pathogens, such as most bacteria.

Antibodies are not cells, but rather, an assemblage of polypeptides chains. There are five different classes: a) IgM; b) IgG; c) IgA; IgE; and IgD.

Specific IgM antibodies are the "first responders" to most infections

Thus, plasma cells first produce IgM antibodies against the infection's causative organism. Once produced, IgM antibody levels in the blood fall. Thus, the appearance of specific IgM in the blood can be used to diagnose an acute infection. For example, in the viral infection, hepatitis A, acute infection is diagnosed by the appearance of IgM in the blood.

Specific IgG antibodies are the second wave of antibodies produced by plasma cells

These antibodies also "attack" the invading microbe, however, in contrast to IgM, their levels persist in the blood for years. While detecting IgM against hepatitis A indicates "current" or "very recent" or "acute" hepatitis A, the finding of the corresponding IgG indicates only that the patient was once infected with hepatitis A.

For example, say in January of 2000, a patient develops acute hepatitis A. At that time, the IgM test will be positive, and soon afterward the IgG test will also be positive. But after a few months, the IgM test will be negative, while the IgG test will remain positive. And say the patient's blood is checked in January of 2010, the IgG test will still be positive.

The fact that it is still detectable in the blood indicates that there are plasma cells within the blood that are still producing IgG antibody against hepatitis A virus. This is why the patient cannot become re-infected with hepatitis A virus. That is, the patient is immune to hepatitis A by the continuing production of (low, but sufficient) levels of IgG antibody against the virus.

IgG antibodies are the only class of antibody that can cross the placental barrier

This provides some protection against neonatal infections in the first few months after birth. Further, IgG in breast milk can also be absorbed by the newborn's intestinal tract for a few months.

IgA antibodies are secreted by plasma cells at mucus membranes

For example, IgA antibodies are present in: a) tears; b) saliva; and c) the mucus of the: i) nasal cavity and sinuses; ii) oropharynx; iii) airways; iv) esophagus, stomach, and intestines; v) urinary tract; and vi) genital tract.

People with impaired production of antibodies are at increased risk of severe infections

This is especially true of pathogenic microbes that live and reside outside of body cells. Most bacteria, for example, reside within the blood and body fluids. This means that those with either genetic or acquired defects in the humoral arm of the adaptive immune system are more susceptible to bacterial infections and other extracellular infectious pathogens.

The main weapon of the cellular arm of the adaptive immune system is the cytotoxic T cell

Unlike antibodies, cytotoxic T cells to do "stick" to microbes. Also, unlike antibodies that are potent weapons against extracellular pathogens, cytotoxic T cells are most potent against microbes that "hide out" within body cells, such as viruses.

Cytotoxic T cells approach and bind to infected body cells. Once "in position," they release two types of molecules: a) perforins; and b) granzymes. Perforins "perforate" the infected cell's membrane, which provides a portal for destructive granzymes, which kill both the body cell and the contained microbe(s).

Those with impaired cellular immunity are susceptible to both extracellular and intracellular pathogens. However, intracellular microbes can be especially severe. Some of these include: a) a) viruses, especially those with latency, such as: i) cytomegalovirus (CMV); ii) herpes simplex virus (HSV); iii) and varicella zoster virus (VZV) ; b) intracellular bacteria, such as mycobacteria; and c) many fungi, such as *Pneumocystis jirovecii.*

Chapter 3: Immune System Dysfunction: Hypersensitivity Disorders

The purpose of the immune system is to defend the body against infection. To accomplish this, the immune system must be able to recognize that the body has been invaded. Thus—in early life—the immune system is "trained" or "educated" to detect invading microbes by their unique surface protein markers.

Unique surface protein markers on microbes are called antigens

For example, rhinovirus, a frequent cause of the common cold has "rhinovirus markers." And the causative bacterium that leads to Strep throat has *Streptococcus pyogenes* markers. These markers can be thought of as "identity markers." That is because they are used as "sign posts" to the body's immune system. These identity markers are formally called antigens.

Antigens are made of polypeptides, often large structures that have multiple, smaller areas that signal the identity of the specific microbe. These smaller areas are called "epitopes."

Microbe antigens are called "nonself" antigens—in contrast to "self" antigens of body cells

Nonself antigens are also known as "foreign" antigens. Self antigens exist on the surface of all body cells. For the immune system to function normally, it must be able to distinguish between nonself and self antigens.

The normal functioning immune system recognizes nonself antigens on microbe invaders—and produces weapons to attack and destroy them. On the other hand, the normal functioning immune system recognizes self antigens on body cells—and refrains from producing weapons to attack and destroy them.

When a patient's immune mistake mistakenly recognizes a self antigen as a nonself antigen, it produces weapons to attack and destroy the patient's own cells. This is the basis of a large array of "autoimmune" diseases."

Autoimmunity refers the attack of one's own body cells by the immune system

Because this "wrongful" or "misguided" attack on one's own body cells can be thought of as an over-reaction of the immune system, autoimmune diseases are also called "hypersensitivity" disorders. Autoimmune diseases differ from one another. However, the damage "inflicted" or sustained in autoimmune diseases is "brought about" or caused by one or more distinct hypersensitivity mechanisms.

There are four types of hypersensitivity, numbered I, II, III, and IV

While Types II, III, and IV hypersensitivity result in autoimmune diseases, Type I hypersensitivity causes allergic diseases. What is the difference?

In allergic diseases, the immune system attacks environmental substances

While the immune system appropriately recognizes nonself antigens of microbe invaders, there is absolutely no need for the immune system to recognize nonself environmental antigens. Because

when the immune system does so, it launches an needless attack on harmless substances like: a) pollens; b) pet dander; c) dust mites; d) cockroach proteins; e) shellfish; f) peanuts; g) tree nuts; h) hymenoptera venoms; i) latex; and j) like-saving medications, such as antibiotics.

Environmental antigens are not called nonself antigens, but rather, allergens

Allergens are not identity markers of microbes. Rather, they are simply protein components of inanimate (nonliving) substances such as foods, plants, medications, and "dead flakes of skin" of animals, for example.

There is no need for the immune system to recognize or attack allergens

Why does this occur? It is a "well-meaning" mistake. The immune system thinks it is attacking invading microbes. Yet, it is mistakenly attacking, for example, harmless pollen. There is no reason to attack pollen that is "breathed-in." If left alone, the pollen proteins will decompose and be removed from the airways by the upward-moving mucociliary escalator.

This is what happens when various pollens are inhaled by most people. Nothing bad happens because pollens, per se, are harmless. But in those with "allergic tendencies"--which is called "atopy"—the immune system "believes" pollens are not harmless proteins, but rather, invading microbes.

There is a large genetic component to allergic diseases

That is, affected individuals inherit an array of genetic polymorphisms at various genetic loci that predispose the immune system to "over-react" against harmless environmental substances. But allergies are not solely genetic, rather they are complex polygenic (or multifactorial) diseases. That is, in addition to a genetic predisposition, there must be one or more environmental exposures that are "co-responsible" for giving rise to allergic diseases. Further details of the pathophysiology of allergic disorders are beyond the scope of this book.

Common allergic diseases include childhood asthma, allergic rhinitis, and atopic dermatitis

In these conditions, initial childhood exposure—for example—of a certain pollen or several pollens—triggers the adaptive immune system to create weapons "against" one or more pollens.

The main immune weapon produced in allergic diseases is the IgE antibody

As you recall, IgE is one of the five classes of antibodies. Unlike IgM and IgG, which circulate through the blood and body fluids, IgE produced by B cell-derived plasma cells ultimately "stick to" the cell membranes of mast cells.

Let us say a child develops asthma from being allergic to tree pollen. By a week after initial exposure to tree pollen, the child's immune system will "pump out" IgE that is the "perfect match" to bind tree pollen. These IgE molecules will embed in mast cell membranes in a certain configuration.

That is, the longer, "constant" regions of the antibody will be stuck downward into the cell membrane, while the shorter, "variable" regions will extend upward out of the cell. It is the variable regions facing upward that have the perfect "fit" for tree pollen antigens or allergens.

When allergens—for example—are breathed in, they bind to, and activate mast cells

To return to our example, every time the child breathes in tree pollen, the protein antigens or allergens "seep downward" through the lining epithelium of the airways, which activate underlying mast cells.

From the study of acute inflammation, recall that when mast cells are activated, they "spew out" inflammatory mediators like histamine. These mediators cause all of the changes that occur within body tissues in inflammation.

However, we cannot appreciate any of the warmth like we can in the skin. And we can only see the redness via invasive procedures such as looking into the airways with a scope (bronchoscopy). And there is no pain per se, rather it causes symptoms such as chest tightness, coughing, wheezing, and sometimes, shortness of breath. And we can only see the airway swelling and leakage of fluid out of the blood vessels in the airway walls by bronchoscopy or imaging.

The inflammation in allergic diseases usually persists, causing chronic inflammation

Unlike the self-limiting acute inflammation of bee sting, allergies can continue indefinitely—unless the person ceases to be exposed to the allergen, or anti-allergic medications stop the inflammatory process.

Long-term immune system "warfare" against harmless allergens can be very damaging

This is why asthma, allergic rhinitis, and atopic dermatitis and other allergic diseases must be treated. For example, if asthma is not treated appropriately, the chronic inflammation over long periods of time can cause the airways to scarred and lead to severe symptoms.

Type II hypersensitivity causes a large subset of autoimmune diseases

In this type of hypersensitivity, self-directed (anti-self) antibodies "seek out" and bind to self- antigens on our own cells or tissues.

For example, in immune thrombocytopenic purpura (ITP), antibodies arise that attach to the patient's own platelets. In fact, they "swarm" on platelets as they flow through the bloodstream. This process "marks platelets for destruction." Recall that when antibodies recognize and stick to microbes, they are destroyed as they circulate through the spleen. This process ("opsonization")--which is so useful in fighting infections—is harmful when antibodies bind to body cells—or cell fragments--such as platelets.

Recall that blood flow slows greatly through the "obstacle course-like twists and turns" of the sinusoids in the spleen. This allows macrophages, which "line the outer margins" of sinusoids to phagocytize and "marked" microbes.

In ITP, splenic macrophages "swallow" (phagocytize) the patient's "antibody-marked" platelets

This is the major mechanism of the steep fall in platelet count (thrombocytopenia) in these patients. When the platelet count, which is normally more than 150,000, falls to less than 20,000, spontaneous bleeding occurs, especially into the skin. This results in tiny "freckle-like) petechiae and larger purpura. The color of these lesions includes brown, red, purple, and blue. Oozing from mucus membranes, such as within the nose, is also common, as is frank epistaxis ("nose bleeding").

Most cases of ITP, especially in children, are believed to occur in genetically susceptible people who acquire a minor viral infection, which triggers the formation of autoantibodies (of the IgG class) against the patient's own platelets.

Surprisingly, Type II hypersensitivity causes most cases of hypo- and hyperthyroidism

This is counterintuitive because one would guess that hypothyroidism and hyperthyroidism would begin with a problem within the thyroid. But this is not the case. Rather, its origin lies within the patient's genes and "rogue" immune response, in which antibodies are produced that recognize and bind to the patient's own thyroid cells.

Autoantibodies that bind to thyroid cells can block or stimulate thyroid hormone secretion

Autoantibodies "against" thyroid hormone secreting cells can impair thyroid hormone secretion (and cause hypothyroidism) by attacking, destroying, and/or blocking the function of these cells. This Type II hypersensitivity—mediated thyroid disease is sometimes called Hashimoto's thyroiditis.

Paradoxically, some patients develop a Type II hypersensitivity—mediated disorder in which the autoantibodies against the thyroid cells do not injure or kill them—rather--they stimulate them to over-secrete thyroid hormone!

In Grave's disease, autoantibodies against thyroid cells causes hyperthyroidism

How does this happen? By random chance—these antibodies have the "shape and fit" that allows them to mimic the normal pituitary hormone regularly stimulates thyroid cells to secrete thyroid hormone. The pituitary hormone that "drives" the thyroid is called "thyroid stimulating hormone" or TSH.

TSH circulates through the blood to the thyroid cells where it binds to TSH receptors on the thyroid cell membranes. This binding is what regulates how much thyroid hormone is secreted by the thyroid gland.

In Grave's disease the abnormal autoantibodies "slip right into the slots" of TSH receptors. In other words, it "fakes out" the thyroid cells. If thyroid cells could think and talk, they might say, "We better secrete a lot more thyroid hormone because our TSH receptors are being stimulated big time!"

Autoantibodies occur in Type III hypersensitivity--but they act indirectly rather than directly

As discussed above, in Type II hypersensitivity, autoantibodies directly bind to body cells and tissues. These autoantibodies are mistakenly "drawn to" or "attracted" to self-antigens that are fixed to cells (or fragments of cells in the case of the platelets in ITP).

Are there self-antigens that are not fixed to cells? Yes, these are referred to as "soluble antigens." Soluble antigens circulate through the bloodstream and other body fluids.

In Type III hypersensitivity, autoantibodies mistakenly bind to soluble self-antigens

When cells age and normally die, some of the internal component are released into the bloodstream. For unknown reasons, some of the leaked nuclear proteins and molecules have self-antigens that are occasionally mistaken for the nonself antigens of invading microbes.

Autoantibodies that bind soluble self-antigens create circulating immune complexes

That is, an immune complex consists of a soluble self-antigen-bearing portion of the patient's DNA or RNA bound to a "matching" autoantibody. Once this "meet up" occurs, the immune complex continues to circulate through the bloodstream and body fluids. If immune complexes only circulated around and around the body, type III hypersensitivity would be much less of a problem.

Circulating immune complexes often are attracted to certain capillary walls

For example, in systemic lupus erythematosus (SLE) or "lupus" many immune complexes are formed from autoantibodies bound to nuclear antigen-bearing DNA, RNA, and similar molecules. In most patients—sometime during their lives—these immune complexes will be attracted to glomerular capillary walls.

Whenever immune complexes bind to capillary walls, destructive inflammation occurs

This can partially or completely destroy the glomerular capillaries in both kidneys. Without prompt treatment, this so-called "glomerulonephritis" or "lupus nephritis" can lead to end-stage kidney disease, requiring dialysis (artificial "waste removal" of blood) or kidney transplantation.

But immune complexes often deposit in other capillary beds within the following tissues and organs: a) synovial membranes, leading to arthritis; b) dermis, leading to rashes; c) lining of the heart and lungs, leading to pericarditis and pleuritis (also called pleurisy); d) lungs, leading to pulmonary fibrosis; e) brain, leading to seizures or changes in cognition or personality; and many others, with corresponding multiorgan symptoms and dysfunction.

In Type IV hypersensitivity, the cellular arm of the adaptive immune system is involved

In contrast the role of autoantibodies in Type I, II, and III hypersensitivities, Type IV hypersensitivity makes use of a different immune system weapon, cytotoxic T cells.

In Type 1 diabetes, over a period of months or years, insulin-secreting pancreatic beta cells are gradually destroyed. When the number of viable beta cells falls to 10-20% of normal, there is insufficient production of insulin to "bring down" elevation of blood glucose.

What kills these beta cells. While autoantibodies are present in the blood of patients who "go on to" develop Type 1 diabetes, it appears that the death of beta cells is unrelated these circulating antibodies. Rather, it appears that cytoxic T cells mistakenly destroy beta cells—as if they were cells invaded by intracellular microbes.

While the exact pathophysiology of rheumatoid arthritis is unclear, it appears that cytotoxic T cells mistakenly attack and destroy synovial cells. Thus, it appears that a significant portion of joint destruction in this disease is initiated by autoimmune attack of the major weapon of the cellular arm of the adaptive immune system.

Chapter 4: Introduction to Infectious Diseases

Most microbes are helpful to both the planet and we humans. In fact, life on Earth would not be possible without them. What sets apart the relatively small subset of microbes that causes disease ("pathogens") from the many that make life possible?

Pathogenic microbes have "virulence factors" which harm the body of patients

Virulence factors of microbes are a "toolkit" that allows them to: a) "breach the barriers" to get inside our bodies; b) avoid or "outwit"—at least temporarily—the weapons of the innate and adaptive immune system; c) break into our cells or "take root" in our tissues, organs, or body fluids; d) replicated "wildly"; e) "inflict damage to our cells, tissues, organs or blood vessels; and f) oftentimes, spread and replicate wildly some more—still avoiding destruction by our immune system—at least temporarily.

"Attachment molecules" are a key virulence factor

If a microbe cannot "get up close and personal" to human cells and "stick there"—it will not be able to cause infection. For example, a bacterium that gets into the urethra will not cause infection if it can't "hold on to" cells of the urethral epithelium. If it cannot attach to the urethral lining—at least temporarily—it will be "flushed" out by the flow of urine down the urethra.

Urinary tract pathogens like *Escherichia coli* have so-called "adhesins" which "adhere" the bacteria to urinary tract epithelial cells. One of these in *E coli* are P fimbriae or pili.

Mobility (or "motility") is another important virulence factor for some microbes

Referring again to urinary tract infections, if microbes like *Escherichia coli* had no motility, they could not: a) move from the perianal area to the urethral orifice, b) enter the urethra; c) and "moved up" the urethra to infect the bladder (to cause "cystitis").

Toxins that form the structure of- or are released by microbes is a key virulence factor

Toxins are destructive molecules that damage cells and the barrier functions of epithelia and mucus membranes. This allows deeper invasion and spread. *E coli* toxins that perform this function are "alpha hemolysin" and "cytotoxic necrotizing factor type 1." Specific "strains" (or variants) of *E coli* with the greatest quantities of the most potent of these toxins are the ones that cause the most urinary tract infections and the most severe ones.

Even of the same species, most microbes exist as a "family" of strains or variants

Picture a family reunion. Everyone is biologically related so that their genetic endowments are similar in many ways, but also different in some ways. For example, even in a family where many have red hair, there are always some that do not have red hair. That is the way with most microbial species. There are some differences among individual members of the same "family" or species.

Some strains or variants of the same species of microbe are more pathogenic than others

It is assumed that genetic differences among strains leads to lesser or greater expression of virulence factors. Differences in "how sick patients became" with infection by different variants that caused Covid-19 illustrates this well. But this is true of many microbes.

There are hundreds of different virulence factors

For example, "protectins"—act to "protect" against destruction by immune system weapons like complement proteins. In *E coli*, outer membrane proteins known as " traT" and "Iss" block complement attachment to their cell bodies.

For microbes to spread via the bloodstream, they need to "break into the lumens" of blood vessels. *E coli* has "outer membrane protease T" which accomplishes this. This explains why some cases of *E coli* cystitis lead to life-threatening bloodstream infections and sepsis.

The production of "biofilms" is an interesting virulence factor of some bacteria

Used by several species of bacteria is the production of "biofilms." One way to think of a biofilm is a "group activity" of several individual bacteria. We always think of bacteria as acting alone and, of course, they have no brains or ability to think or plan ahead. But bacteria--by changing gene expression—can secrete extracellular matrix that "creates a fort or fortress" around a group of bacteria. This provides partial or sometimes complete protection not only against immune system weapon but also antibiotics. *E coli* strains that are adept at making biofilms express genes that lead to the production of the structural molecules cellulose and curli.

Related to microbe virulence factors is the concept of "tropism"

Tropism refers to the specific cells within a patient's body that can be infected by a specific microbe. Specific microbes can usually infect only a subset of patient cell types For example, *Streptococcus pyogenes* has great tropism for the oropharynx, *E coli* for the urinary tract, and *Streptococcus pneumoniae* for the lungs.

Microbes only have tropism for cells they can "attach to" and "break into or through"

Tropism across different species explains why most microbes that infect humans cannot infect animals, and why most microbes that infect animals cannot infect humans. For example, the bacterium, *Bordetella pertussis*, can easily infect people and cause whooping cough or pertussis. That is because this microbe has tropism for the human respiratory tract epithelium. But dogs cannot get pertussis because this microbe cannot "attach" to the respiratory tract epithelium of dogs. That is, it does not have tropism for canine cells.

People can't get canine "kennel cough" as the causal microbe has tropism only for dogs

Kennel cough is caused not by *Bordetella pertussis*, but rather, by *Bordetella bronchiseptica*, which does have tropism for the respiratory tract epithelium of dogs.

Some microbes actually have tropism for animals and people, and can cause "zoonoses"

There are at least 200 zoonoses. Further, some of these are catastrophic when the "jump" from an animal species to humans. For example, the virus that causes Covid-19 "jumped" from bats to us.

Surprisingly, infection by zoonotic microbes can be mild or asymptomatic in animals but deadly in people. For example, there is no "bat-Covid 19" that sickens these small mammals. Similarly, while deer that carry *Borrelia burgdorferi* do not become ill, we can develop Lyme disease. And the "deer ticks" ("black-legged ticks" or *Ixodes scapularis*) that carry the bacterium do not become ill either. In contrast, some zoonotic microbes can be deadly for both animals and people, such as rabies virus.

Infection requires more than tropism of a pathogenic microbe

Does exposure to a pathogenic microbe always cause infection? No. While exposure to a pathogenic microbe is necessary for infection to occur—exposure is NOT sufficient to cause infection. The transmission of infection from one person to another requires a series of steps.

The "catching" of an infection requires a "chain of transmission"—a chain that is unbroken

Thus, whenever a patient does "catch" a "communicable (contagious infectious) illness," it means that the following six "links" of the chain were intact. That is there were no "breaks" in the chain, or "missing links" of the chain. On the other hand, the way to prevent or block the transmission of communicable diseases is to "break the chain" at one or more "links."

The six essential links or components of the chain of transmission:

a) Infectious agent (microbe)

- A pathogenic microbe that has tropism for human cells or tissues. That is, the microbe must have the ability to infect human cells or tissues. For example, as discussed above, people cannot get "kennel cough" because the responsible microbe does not have tropism for humans.

b) Reservoir:

- A "storehouse" or "permanent residence" that "houses" the microbe. It is essential that the microbe stays alive in the world, for example, before and after patients are infected. If the microbe was no longer "available" to be transmitted or "caught," then that infection would "die off."
- For example, the reason that there is a possibility of a dog bite causing rabies is not because millions of dogs in the US are infected with the virus. Rather, there are millions of raccoons, shunks, bats, and foxes who carry rabies virus. Thus, it is these animal species that keep rabies

virus "alive in the world" allowing dogs to occasionally become infected—which can sometimes lead to human infection. Thus, the reservoir for rabies are wild animals.
- Farm animals are also a reservoir for zoonotic infections like Salmonella infections. And the reservoir for many human infections are humans themselves—for example, hepatitis, "strep throat," the common cold, and so on.

c) Portal of exit:

- For a microbe to be transmitted from one person to another, or from an animal to a person (in zoonotic infections), there has to be a way for the microbe to exit the body of the infected person or animal. That is, if the causative microbe cannot leave the body of the infected person or animal then it can't infect anyone else.
- Thus, a portal of (microbe) exit is required.
- There are many portals from which an infectious microbe can leave the body of an infected person or animal: a) mouth or nose; b) skin; c) genital tract; d) urinary tract; e) gastrointestinal tract; and f) bloodstream, for example.

d) Means of transmission:

- There must be a pathway for the microbe to "travel" from the portal of exit of an infected person or animal to the next person or animal that is infected. These "pathways" are called "means of transmission" or "modes of transmission." There are more than ten of these, as will be discussed below.

e) Portal of entry:

- Once a pathway exists to "move" or "carry" a microbe from one person or animal to another, there has to be a site for it to enter the next person or animal. These, "portals of entry" are similar to portals of exit, and include the following: a) mouth and nose; b) conjunctiva of the eyes; c) skin, especially broken skin; d) genital tract; e) urinary tract; vi) gastrointestinal tract; and vii) bloodstream via "insect bites," surgical procedures, open wounds, or transfusions, for example.

f) Susceptible host:

- Even if a pathogenic microbe enters a person's body, infection may not result. This is because not every person is susceptible to infection by various microbes. To infect a person, the microbe must "take root" and replicate. But this is prevented from occurring because of the attack of the innate and/or adaptive immune systems. There are other reasons that an infection may fail to "take root" and make the patient sick. This topic will be discussed below.

Chapter 5: Modes of Infectious Disease Transmission

There are a wide variety of ways to acquire infections. One way to divide these up is as follows:

a) Direct contact:

Transmission by direct contact can occur in several ways. Direct skin-to-skin contact can spread "impetigo." This is a superficial skin infection caused by *Streptococcus pyogenes* or *Staphylococcal aureus.* In the past, spread of this infection from one athlete to involve whole a whole team of high school or college wrestlers was not uncommon.

Shaking hands can easily spread microbes from one person to another

While the common cold is often spread by respiratory droplets (see below), direct contact spread is also frequent. To understand this, say a man, Jim, has a cold. For days, Jim will have cold virus on his hands due to coughing, sneezing, and even breathing.

Say that Jim shakes hands with Cathy. This will transfer cold virus to her hands. We frequently touch our mouths, noses, and eyes. Thus, cold virus that originated in Jim's mouth and nose was "transferred" to Cathy's mouth and nose. This is another example of transmission by direct contact.

Mononucleosis ("mono") can be transmitted by the direct contact via "kissing"

Mono is a viral infection caused by Epstein-Barr virus. Mouth-to-mouth contact is another form of direct contact. While "mono" is sometimes called the kissing disease, many cases occur without kissing via respiratory droplets, as will be discussed below.

"Unprotected" sexual contact always involves direct contact

This is why the microbe, *Treponema pallidum*--which causes syphilis--can be transmitted so easily. The most common syphilitic lesion is the "chancre." This is a superficial cutaneous lesion usually on the penis, vulva, vaginal mucosa, or perineal skin. It can also be directly transmitted between the penis and mouth or vulva/vagina and mouth in oral sex.

There are several different sexually-transmitted infections (STI's)

Some, like syphilis, are transmitted by direct contact with physical lesions on the skin or mucus membranes. Others include "genital herpes," which is caused by herpes simplex virus (HSV), and "genital warts," caused by certain strains of human papilloma virus (HPV).

Some STI's are transmitted by direct contact with infected semen or vaginal secretions

These infections include: a) chlamydia; b) gonorrhea; c) human immunodeficiency virus (HIV); and d) hepatitis B.

Risk of transmission can vary by type of intercourse. Most of the pertinent research has been with HIV transmission. For example, the likelihood of infection of the male partner in insertive penile-vaginal intercourse is about half of that of the female partner. This is likely due to limited exposure of mucus membranes of the penis during intercourse compared to exposure of vaginal mucus membranes during intercourse.

On the other hand, the risk of infection with insertive penile-anal intercourse is higher than insertive penile-vaginal intercourse. The higher risk with anal intercourse is likely due to the fact that the rectal "lining" is a single-layer thick epithelium, and therefore, quite fragile. In contrast, vaginal lining consists of many layers of stratified squamous epithelium. The highest risk type of intercourse is receptive penile-anal intercourse in which penile motion can easily "tear" the rectal epithelium.

b) Indirect contact:

Recall the example discussed above about transmission of a cold via handshaking. This is classified as transmission by direct contact because the virus goes directly from Jim to Cathy. But what if Jim had not shaken hands with Cathy? Could Cathy still become infected by some sort of contact? Yes.

Transmission by indirect contact can involve an inanimate object

Say Jim sneezes on the keyboard of the computer at the lectern during his lecture from 8-9 a.m. Now say that Cathy gives her lecture in the same classroom from 10-11 a.m. She could still acquire the infection by touching the keyboard contaminated by Jim's sneezes an hour earlier.

When an inanimate object "relays" a microbe from one person to another, it is called a fomite

Fomites are important fomites are important in transmitting several infections. Consider a child, Bethany, in daycare, who begins to have diarrhea from viral gastroenteritis. Where will the virus-contaminated diarrhea, go, for example, if she is not potty trained? It will collect within her "pull-up" diaper.

However, her pull-up may leak, and further, she may scratch or reach into her diaper, contaminating her hand. Let's say she is playing with blocks when her hand is contaminated. It is obvious that the virus could "end up" on the surface of one or more blocks.

Say another child, Jake, picks up some of one of the contaminated blocks and puts part of the block in his mouth, causing him to develop gastroenteritis in a day or so. But this transmission of infection was not by direct contact between Bethany and Jake, but rather, by indirect contact—with an intermediate step or "relay" by the blocks (fomites).

c) Carried by respiratory droplets:

It is well known that when we sneeze on our hands, they become covered by a fine spray or mist. These thousands of "wet particles" are called respiratory droplets. We "spew out" respiratory droplets not only when we sneeze or cough, but when we sing, speak, laugh, and even "breathe out" or exhale. This is the major way cold viruses are spread—even though--as we have discussed above--

transmission by direct contact (for example, by handshake) and indirect contact (by fomites) also occur.

Respiratory droplets are "weighted down" by gravity and usually travel less than three feet

It is thought that respiratory droplets can uncommonly travel up to 6 feet. The distance is related to the mass of the droplets. The mass of individual droplets is related to the mass of water within the droplet. Very large droplets may only "travel through the air" a foot or two, while tiny droplets occasionally more than 3 feet.

Overall, respiratory droplets are 5 or more microns in size. These droplets are "generated" or "produced" in the respiratory tracts of patients with, for example, viruses that cause the common cold, such as rhinovirus and adenovirus. Other pathogens spread predominantly by respiratory droplets of 5 or more microns in size include: a) influenza virus; b) coronaviruses, including the causative agent of Covid-19); c) *Streptococcus pyogenes*; d) *Bordetella pertussis*; e) *Haemophilus influenza*, type B; f) *Neisseria meningitidis*; and g) *Mycoplasma pneumonia*, among others.

In contrast, there are a few respiratory tract infections--for reasons we don't understand—that generate or produce droplets that are both "super small" and "super light." These droplets are given a different name, "droplet nuclei." They are < 5 microns in size and have less water content. As a result, their "physical behavior" is different. That is, droplet nuclei are so light that instead of soon falling downward through the air—rather, they are carried by the air.

Feather-light droplet nuclei are not technically considered respiratory droplets

Transmission by droplet nuclei is called "airborne transmission." This is because these particles "float on air currents" and therefore, travel long distances—such as across a classroom. It is because of the great distance traveled that respiratory droplet transmission is called "airborne" rather than transmission by respiratory droplets. Airborne transmission is discussed separately below.

d) Carried by blood:

Some infections are said to be "bloodborne." This means that a pathogenic microbe residing in the blood of one person has been "transferred" or "transferred" into the blood of another person.

The three most common bloodborne infections are hepatitis B, hepatitis C, and HIV

How does the blood of one person enter the bloodstream of another? First, transfusions of contaminated blood has—in the past--transmitted all three of the above infections. Why? Before the mid-1980s, HIV virus was unknown, and even after it was discovered, it took a few years to develop a test to screen donated blood. The same with hepatitis C virus before the mid-1990s.

Injection drug use can easily transmit hepatitis B and/or C and/or HIV

Say one person infected with hepatitis C virus injects fentanyl into a vein. After injection, some hepatitis-C-virus-contaminated blood remains in the needle. When this person shares the needle and syringe, residual hepatitis C virus can be directly injected into the bloodstream of others.

Fortunately, many are immune to hepatitis B vaccination due to childhood vaccination. However, there are no vaccines for hepatitis C or HIV.

Another way that blood can "mix" between two people can occur during pregnancy

Transmission from mother to child is called "vertical transmission." Further, there is also "mixing of blood" during delivery. Finally, breast milk can transmit hepatitis B. However, perinatal transmission of hepatitis B can usually be prevented if maternal infection is addressed in prenatal care. Similarly, the risk of HIV transmission can also be greatly reduced. Hepatitis C is much less commonly transmitted vertically, but there are no specific preventive interventions for this.

Another possible mode of bloodborne transmission is by "needle stick." However, the likelihood of transmission is low.

Finally, semen and vaginal secretions can transmit bloodborne infections. In fact, sexual transmission of hepatitis B is a relatively common in the US.

e) "Carried" by water:

Infectious microbes can contaminate water. And we not only drink water, but bathe, shower, and wash with water. Also, we swim in pools, lakes, and oceans. Thus, there are many potential opportunities for waterborne disease transmission.

When an infectious microbe in water or food transmits infection, it is said that the water or food were "vehicles" of infection.

Feces is the major contaminant that "drives" waterborne infections

Feces can contaminate water in the US, but this is much more common in countries without modern public health infrastructural necessities such as water purification and waste disposal.

In some parts of the world, feces drains into nearby rivers, and the same rivers are used for drinking water. In our country, however, backpackers and other outdoorspeople who drink untreated stream or river water can develop infections such as giardiasis, a protozoan. Giardiasis can cause prolonged diarrhea and other symptoms.

Surprisingly, water can be contaminated by non-fecal microbes. For example, the bacterium, *Legionella pneumophilia* happily resides in the water of fountains, air conditioners, and even showers in hospitals. This microbe is often "aerosolized" (suspended in the air) and "breathed in" by people. This can cause severe and lethal pneumonia in some patients.

f) "Carried" by food:

Foodborne diseases are common. In fact, what is surprising is that they do not occur even more commonly. Microbes, especially bacteria, thrive in foods. How they get there? There are several ways.

First, meat sources are heavily contaminated during processing at "slaughter houses." For example, species of Salmonella normally live within the digestive tracts of many farm animals. Thus, when butchered, the "nice-looking" chicken breasts seen in the grocery store already harbor high quantities of the bacteria.

Adequate cooking destroys microbes, but "cross contamination" is common

Say someone is having baked chicken breasts and fruit salad for dinner. The cook prepares and cuts the chicken on a cutting board. This transfers some of the Salmonella to the cutting board. Then—if the cook cuts up the fruit for the fruit salad on the same cutting board—this can be easily transferred to the fruit, which will be consumed without cooking. Salmonella is a common cause of bacterial gastroenteritis.

Another way that food can become contaminated is via physical transfer of microbes by "food handlers." This has led to several hepatitis A outbreaks.

g) "Carried" by the air ("airborne transmission):

As discussed above, under "respiratory droplets," some infectious diseases are transmitted by tiny droplet nuclei that are "float on air like feathers or helium balloons." Fortunately, these diseases are in a minority: a) tuberculosis (mycobacterium); b) varicella (Varicella-zoster virus); c) measles virus; d) smallpox virus (before this was eradicated); and e) some coronaviruses (including the causative agent of Covid-19).

It is not completely understood why these infections generate tiny droplet nuclei rather than the more common larger respiratory droplets. In tuberculosis, it appears that the droplets are "more dry" and therefore have less mass and size. But regardless of why, these infections can spread easily because the infectious particles can travel such large distances. This is why tuberculosis and smallpox resulted in extensive and repeated plagues in the past.

The transmission of Covid-19 is complex

At the beginning of the pandemic, it was assumed that much of the transmission was via the larger, "typical" respiratory droplets. And evidence did bear this out—that MOST cases were transmitted this way. This is the reason that 6-feet of social distancing was partially effective.

As the pandemic continued, it was found that some patients became infected despite that they had not been within 6 feet or even 10 feet of any infected patients. Further, there were some documented examples of widespread infection of patients many feet away from a single infected source. This triggered extensive research into the physics of droplets and related basic science.

Those with respiratory tract infections generate or produce droplets of varying size

In other words, it is not as simple as we thought. Patients with respiratory tract infections produce an array or mixture of particles of varying size and weight. This make sense because almost everything in nature varies on bell-shaped curves.

While those with rhinovirus and other common respiratory infections, produce a preponderance of larger respiratory droplets, some produce a mixture of large and small (and other sizes in between). This appears to be the situation with the spread of Covid-19. Most of the droplets are on the larger end and do not travel more than 3 feet, but some are smaller ones that travel farther, and a minority are tiny droplet nuclei that are occasionally able to transmit infection "across a room."

h) "Carried" by insects:

Part of the human experience is to experience "bug bites." Fortunately, many insects do not bite, and of those that do bite, many do not transmit infection. But ticks and mosquitoes, for example, can transmit a myriad of infections, some of which are lethal. Ticks and mosquitoes and similar insects are classified as arthropods.

Insects that cause infection are known as vectors

The reason that ticks and mosquitoes bite us is because blood is their "food." All spread to humans is just a byproduct of this. Where do these insects acquire the microbes that they transmit to humans? By feeding on animals that harbored the microbe.

For example, small mammals such as mice, as well as larger ones, such as deer, are "reservoirs" for the causative agent of Lyme disease, *Borrelia burgdorferi.* Interestingly, animal reservoirs often do not become ill with the microbe that they harbor.

Similarly, insect vectors do not become ill either. When a blacklegged tick (*Ixodes scapularis*) feeds on an infected mouse, for example, it will live healthily until it feeds on a person.

Ticks must "feed" for a day or two to transmit *Borrelia burgdorferi*

This is because the tick is "sucking out" blood from the patient, while the microbe must move against the flow of blood. That is, *B burgdorferi* is not "injected" by ticks, rather, it must "struggle against the current" of the "blood meal" the tick is craving. Thus, it takes hours for sufficient numbers of the microbe to enter the bloodstream of the person.

Other tickborne diseases in the US include: a) babesiosis (protozoan); b) ehrlichiosis (bacteria); c) Rocky Mountain Spotted Fever (bacteria); and d) anaplasmosis (bacteria).

Mosquitoes can transmit infection when obtaining a blood meal from us

The most common species of mosquito in North America that can transmit West Nile virus is Culex pipiens. Again, the mosquito does not become ill. However, the reservoir for this virus is birds, and some of these birds do become ill and die.

Other mosquito-borne diseases in the US include: a) La Cross virus; b) Jamestown Canyon virus; c) Powassan virus; d) St. Louis Encephalitis virus; e) Eastern Equine Encephalitis virus; f) Dengue virus; and g) Malaria (protozoan).

Chapter 6: Clinical Characteristics and Manifestations of Infectious Diseases

Time Course of Communicable Diseases

When we are exposed to an infectious microbe, do we always get sick? No. Say we do get sick, will we get sick immediately? No. It may not "show up" for a few days or few weeks.

Each infection has a "time course"—an unique story—with beginning, middle, and end

In fact, each disease in each person has a time course or story. Some are short and happy, some are short and terrible, some are long and ultimately positive, and some are long and tragic.
The "ups and downs" over time--from disease onset until cure or death—is the time course of the disease.

Without treatment, the time course of a disease—plus outcomes—is its "natural history"

The natural history of an infection—or any disease—begins with the biological onset of disease. In infections, the biological onset is when the transmitted microbe first "takes root" in the patient. However, in an individual patient, we rarely know the biological onset. This is because there are no clinical manifestations at the biological onset. It "takes time" for symptoms to arise.

The interval between biological onset and clinical onset is the "incubation period"

Say a graduate student, Brian, has a cold due to rhinovirus. Sally is Brian's friend and they sit together in class. Monday morning Brian sneezes on Sally. Soon afterward, rhinovirus particles enter Sally's oropharynx and nasopharynx. Some of these viral particles "break into" Sally's nasal and oral epithelial cells—and begin to hijack the genetic material in those cells—to replicate more rhinovirus. This is the biological onset of disease.

How does Sally feel at that time, on Monday? She feels great! This is because it "takes some time" for the body's response to this microbial invasion to trigger a big enough "immune system attack" to trigger symptoms.

Most clinical manifestations of infections are due to immune system warfare

This warfare cannot "get going" until there has been sufficient: a) proliferation of microbes; and/or b) production of microbial toxins; and/or c) production of inflammatory mediators and cytokines from the response of the innate and adaptive immune systems.

It is only at that time--hours, days, or occasionally weeks or months after the biological onset—that the patient "gets sick" (the clinical onset). This period of time is called the incubation period—because up to that point, the microbe was "just incubating."

Incubation periods are commonly a day, a few days, or a week

Less than a day is very uncommon, and weeks or months are also uncommon, but the latter does occur in some infections. Recall that Sally had the biological onset of rhinovirus infection on Monday

morning, but she felt well until late Tuesday night when she noted a mildly scratchy throat and runny nose. In this case, the clinical onset of disease occurred 36 hours after biological onset. Thus, the incubation period was 36 hours.

Selected incubation periods include: a) common cold, like rhinovirus (1-4 days); b) Salmonella gastroenteritis (½-3 days); c) "strep throat" (2-5 days); d) Herpes simplex virus (5-8 days); e) pertussis (7-10 days); f) giardiasis (7-14 days); g) toxoplasmosis (5-23 days); h) varicella or chicken pox (13-17 days); i) tuberculosis (2-12 weeks); j) hepatitis A (15-40 days); k) mononucleosis (30-50 days); l) histoplasmosis (several weeks); and k) acquired immunodeficiency syndrome (AIDS) (1-10 years).

Infected patients can shed microbes during incubation and after clinical recovery

However, most communicable diseases transmission does occur when the source of the transmission is sick—when he or she is coughing and sneezing, and so on. This is because most of the "shedding" of the infectious microbe is "spewed out" when the patient is sick.

Yet--depending on the particular infection—some shedding occurs before the source patient becomes sick—before realization that he or see is sick--before the patient feels ill—usually during the end of the incubation period.

This explains the common situation when you got a cold but "no one around you was sick." In these cases, it is likely that a close contact was incubating a virus, or had recovered, but was still shedding some virus. Another potential explanation is that a close contact was beyond the incubation period--but still had no symptoms because some infections in some people at some times are asymptomatic.

The entire period of time that an infected patient can shed the microbe and transmit disease is called the "period of communicability." While in some infections the period of communicability is only during the time the patient is sick, it is not uncommon in other infections for this period to begin near the end of the incubation period and extend some days after the patient has recovered.

Infections Can Remain Localized Or Spread More Widely

Most infections begin locally

Common locations include: a) the lung ("pneumonia"); b) an area of the skin (for example, cellulitis or skin abscess); c) bladder ("cystitis"); d) surgical site (surgical site infection); e) a synovial joint ("septic arthritis"); f) a bone ("osteomyelitis"); g) an abdominal organ (for example, the appendix ["appendicitis] or gallbladder ["acute cholecystitis"]); and h) an organ of the genital tract (for example, the urethra ["urethritis"] or cervix ["mucopurulent cervicitis"].

Cystitis (bladder infection) is a common localized infection that occasionally spreads

Cystitis is a bacterial infection most commonly caused by *Escherichia coli*. This infection often remains localized; however, not always. *E coli* has robust virulence factors to ascend the urethra and "stick" and "bust through" urinary tract epithelium. Thus, it can use those same "abilities" to ascend

one or both ureters to infect one or both kidneys ("pyelonephritis"). This is an example of a localized infection spreading to a nearby organ or region.

Cystitis causes localized symptoms because the "warfare" against the microbe is local

Common local symptoms include painful urination (dysuria), urge to urinate frequently (urgency), among others. But when spread results to the kidney, it usually causes both localized symptoms (flank pain, for example), and systemic manifestations.

As infections spread and/or worsen, the tissue damage and inflammation caused by the microbe intensifies. In addition, the warfare against the microbe intensifies. This often results in the "spill over" of the microbe, the microbe's toxins, or the immune systems response into the "entire body."

Progression of—or spread of—infection often leads to systemic manifestations

What are systemic manifestations of infection (or inflammation without infection)? These include the standard four criteria of "systemic inflammatory response syndrome" or "SIRS."
These are: a) fever (or, rarely, hypothermia); b) tachycardia (heart rate > 90); c) tachypnea (respiratory rate > 20); and d) elevation of peripheral blood white blood cell count (called "leukocytosis" or "neutrophilia"), or, rarely, decrease in white blood cell count (called "leukopenia" or "neutropenia").

Other common systemic manifestations include: a) loss appetite; b) headache; c) muscle aches ("myalgias"); d) fatigue; e) weakness; f) lightheadedness; and g) alterations of mental status.

Systemic manifestations are due to components of the immune system and the microbe

The "big three" causes of systemic manifestations are: a) components of microbe structure; b) soluble toxins secreted by microbes; and c) inflammatory mediators and cytokines secreted by cells of the innate and adaptive immune systems.

The immune response "aspires" to "nip infections in the bud." But this certainly does not always occur. Let's return to our patient with *E coli* cystitis who then developed pyelonephritis. Say that some of this *E coli* enters the bloodstream. When a bacterium enters the bloodstream it is called "bacteremia."

Bacteremia exposes blood vessel walls and other tissues to toxins that are part of the microbe

For example, Gram-negative bacteria like *E coli* contain molecules of "endotoxin." Endotoxin can trigger fever, lower blood pressure, raise heart rate, and raise respiratory rate. Circulating Gram-positive bacteria, like *Staphylococcus aureus*, also have components that are toxic, such as peptidoglycan.

Microbes that do not enter the bloodstream can secrete toxins throughout the body

These are often called "exotoxins." These molecules are also toxic to blood vessel walls and other tissues--and can elicit the same systemic manifestations as circulating microbes do during

bacteremia—even "without ever having to leave" the localized area where the infection began and remains localized. Two well-known exotoxins are: a) Staphylococcal shock syndrome toxin-1; and b) Pseudomonas exotoxin A.

Most systemic manifestations of infections are due to inflammatory mediators and cytokines

As the infecting microbe "takes root" and replicates, it damages tissues and kills cells. This, itself, triggers acute inflammation, which results in the release and synthesis of a multitude of inflammatory mediators and cytokines. In addition, the attack of the microbe by the innate and adaptive immune systems also results in the release of several inflammatory mediators and cytokines.

These molecules circulate throughout the bloodstream and can trigger the systemic manifestations associated with all infections. Two major inflammatory mediators or cytokines are: a) tumor necrosis factor alpha; and b) interleukin-1.

Progression of infection not only can lead to systemic manifestations, but to sepsis

Sepsis is the result of an "exaggerated" or "dysregulated" bodily response to infection. This can be triggered when a localized infection spreads or progresses. In other words, when the innate and adaptive immune responses fail to contain or limit a localized infection.

Sepsis is a body-wide overreaction of the immune system that inflects widespread damage

This is "double-bad." First, the triggered immune defenses are "punishing" and destructive to normal tissues. Second, the "punishment" and destruction occur throughout the body. What immune defenses are responsible? The same factors that lead to systemic responses like fever, tachycardia, tachypnea, and alterations of the white blood cell count.

Microbial toxins and inflammatory cytokines can destroy tissues and organs

The first "victim" or target is the circulatory system, as discussed above under "systemic manifestations." In fact, a sepsis involves "malignant intravascular inflammation." The structure of some microbes can directly damage endothelium (in bacteremia). In addition, soluble toxins-- even if released from a localized infection--can circulate and cause the same widespread endothelial damage.

Cytokines attract and activate neutrophils which can "accidentally" damage endothelium

One of the "weapons" against circulating microbes is the release of "neutrophil extracellular traps" or NETs. These neutrophil-released "butterfly net-like" structures--made up of nuclear chromatin, DNA, and antimicrobial peptides--can "inflict" widespread endothelial injury.

Damaged endothelium results in vasodilation, and the tendency to form blood clots

Widespread vasodilation expands the "space" within the circulation (decreases peripheral vascular resistance) and lowers blood pressure. Recall that mean arterial pressure = cardiac output * peripheral vascular resistance, or MAP = CO * PVR.

This can lead to septic shock with hypoperfusion of vital organs, such as the lungs, liver, kidneys, and brain. This hypoperfusion is one of the main mechanisms of multiorgan failure.

Damaged or dysfunctional endothelium also leads to abnormal clot formation—especially within the smaller blood vessels to vital organs. This adds superimposed ischemia to baseline widespread hypoperfusion.

Disseminated intravascular coagulation (DIC) often complicates sepsis

This process involves such widespread intravascular clotting that coagulation factors and platelets are "used up" or depleted. This allows the opposite process: excessive hemorrhage.
DIC can be signaled by spontaneous bleeding into the skin (petechiae and purpura), and well as bleeding from mucus membranes and vascular catheter puncture wounds.

Why do some infections progress to sepsis while others do not

Recall that the purpose of the immune system response is to "contain" and "bring under control" any infectious process, so that repair and healing can follow. However, the "ideal" response to infection is the production of immune system "warfare" that is just strong enough to "beat" the microbial "enemy"—but not so "over-the-top-destructive" as to annihilate the "entire landscape" upon which the battle took place.

That is, what is needed is a "measured" response—a response that is quickly "called off" when the battle is won. This requires an "unfolding" of the immune response that is precisely regulated or "choreographed." This requires "orderly moment-by-moment "marching orders" given to various cells and tissues via pro-inflammatory and anti-inflammatory cytokines.

The problem with sepsis is that it is "easy for the immune response to overreact"

There are many known and unknown factors that can lead to his "non-orderly" and "non-measured" response. For example, microbes with aggressive virulence factors are more likely to trigger sepsis. Also, everyone's immune system are "programmed" uniquely based on genetic endowment. Thus, the immune response of some patients (hosts) to infection can be excessive for this reason. But there are probably many other factors that are currently unknown.

The immune response to infection is biphasic

That is, the initial response is to contain and neutralize the infection, but the second phase requires an orderly "shutting down" process of the initial "battle" response. The bodily response to trauma and surgery (without infection) is also biphasic.

So far, we have talked only about an initial response that is too excessive. Let's say that a patient develops an infection, and the initial immune response is "perfect"—not excessive. At this point, the ideal second phase response involves an "orderly" or "measured" reduction in the previously needed pro-inflammatory response.

The healthy second phase of immune system response to infection is one of "anti-inflammation"

This phase of the body's response is signaled by the appropriate rise in levels of anti-inflammatory cytokines. However, the anti-inflammatory phase can sometimes be too extreme—that is, the immune system weapons and defenses are "taken offline" too quickly and/or "turned down" too much.

When this occurs, infection that was stabilized during the first phase is now "turned loose." This can lead to a later progression of lethal sepsis.

Thus, the best outcomes from serious infections is when both the initial pro-inflammatory response is appropriate (but not excessive) and the later anti-inflammatory response is appropriate (but not insufficient). But because the body has no "willful" or "planful" ability to control these responses, sepsis remains a common cause of death.

Why Exposure to Any Infectious Agent Can Have Wildly Varying Outcomes

There are many reasons for this that are important to understand. Say that one student in a classroom of many students has a "bad cold" and is coughing and sneezing, and is not wearing a mask. Colds are transmitted by big, heavy respiratory droplets that usually travel only 3 feet horizontally. A minority may reach a foot or two more, but never more than 6 feet.

Say that the sick student ("source patient" or "patient zero") spends Monday in class. About 36-48 hours later, we find that of 20 other students, 11 "catch" the cold, but 9 do not. There is no mystery in those who caught the cold. But what about the other 9, who remain well.

The outcome of exposure with a microbe depends on both the microbe and the person (host)

That is, an infection is a "relationship" between a patient (host) and the microbe (agent). Just like microbes are different (different virulence factors and "abilities"), hosts are different. The important differences among hosts will be discussed below. However, there is a third "player" in the interaction between a microbe and a host—the environment. How environmental factors can influence the outcome of exposure to a microbe will also be discussed below.

Exposure to low quantities of microbe (low "inoculum size") may not result in infection

Depending on the "virulence" of the microbe—or particular "strain" or "variant" of the microbe—infection may not "take root." In our class of students, perhaps, 1 of the 9 did not get very close to the source patient and therefore only "took in" a tiny number of cold virus. And this low number was not sufficient to "break into" epithelial cells to replicate sufficient virus to "get the infection started." In other words, there was not a "critical mass" of microbes. Some microbes require only a small number of organisms to take root, whereas other microbes are like sperm, needing large numbers of organisms for "success" to occur.

Exposure will not infect a host if the host is immune

Of our 9 students who did not get sick, let's say 7 were immune. Say that 5 students had already been infected by and recovered from the rhinovirus strain shed by our source patient. And say that 2 had partial immunity due to prior infection with different-but-related strains of rhinovirus. In partial immunity, the immune system weapons developed for "rhinovirus" strain X also are "good enough fits" to also fight off the current "rhinovirus" strain Y. Often times, however, weapons for strain X may not be a good enough fit for strain Y. Thus, partial immunity is not something that can be counted on, and is "hit or miss."

Vaccination can prevent infection by making potential hosts immune before exposure

Vaccination triggers the body's adaptive immune system to create weapons against a pathogenic microbe in advance host exposure. A discussion of different types of vaccines is beyond the scope of scope of this book. However, suffice it to say that whatever is used to trigger the immune system to create weapons against the "real pathogen" is not the real pathogen. That is, some vaccines uses either "dead" or other "weakened" ("attenuated") forms of the pathogen. Some vaccines do not use any form of the microbe. For example, the immune response can be triggered to make weapons against only the toxins secreted by a particular pathogen. In the coronavirus that causes Covid-19 the microbe is not used at all, rather, messenger RNA.

Some vaccines are more effective than others

This is true for several reasons including those that do not depend on vaccination sources or processes, but rather, a poor immune system response in the person who is vaccinated (due to host factors).

Back to our classroom example, there are no current vaccines for rhinovirus, so this could not account for any students who did not become ill.

Host factors include genetic differences among people

No two people are the same genetically—except identical twins. However, twins have different gene expression due to epigenetic changes that accrue during life. Inherited immunodeficiency diseases obviously increase the likelihood of infection. Many of these are very serious and diagnosed in childhood.

More common than inherited immune deficiency diseases are polymorphisms that affect immune system function in subtle ways that we do not understand. Interestingly, there are some known polymorphisms that "program" the function of the complement system. Some of these lead to greater susceptibility to severe infection by *Neisseria meningitidis*.

In addition to genetic and immune factors, there are many other important host factors

These include: a) age; b) sex; c) overall health; d) prior diseases; e) immunosuppressant medications; f) chemotherapy; g) radiation therapy; h) nutritional status; i) marital status; j) sexual behavior, and other behaviors and habits; k) occupation; l) customs; and m) religion, among others.

Environmental factors also impact disease transmission

This is especially true in communicable disease outbreaks. For example, say a patient has an infection spread by respiratory droplets. Say that a person lives in a small, crowded residence with 12 other people. This environmental factor (crowding) would be a crucial factor in the spread of this infection.

Major environmental factors include: a) contamination of food; b) contamination of water; c) lack of public health infrastructure (water purification, waste disposal); d) socioeconomical status; e) housing; f) crowding; g) climate; h) weather; i) humidity; j) temperature; k) altitude; and l) presence of vector that can spread disease (ticks and mosquitoes, for example), among others.

In our classroom example, crowding in the classroom was an important environmental factor. To review, 9 students did not get sick. One student did not become infected due to low inoculum size, 5 were immune due to having already had the same strain of rhinovirus of the source patient, and 2 were partially immune to having already had other strains of rhinovirus.

This leaves 1 other student who did not get sick. Is it possible that this student did get infected with rhinovirus but had no symptoms? Yes.

<u>The same pathogen can cause infection that is mild, moderate, severe, lethal, or asymptomatic</u>

In our classroom, let's say the one remaining student who "did not get sick"--in reality--did get infected—but no symptoms developed. Why some infected patients do not develop symptoms is not well understood. It must be related to host factors, probably an array of particular characteristics. This must also be the explanation for the fact that some patients develop mild symptoms and some much more severe.

In our classroom example, 11 students became sick, but it is likely that it didn't "hit them" in the same way." For example, some would likely have symptoms lasting 3-4 days while one may have nagging symptoms for a week or 10 days. Another example, is that it is likely that some had no sore throat, a few had a transient sore throat, and perhaps one had significant pain with swallowing for a few days.

<u>Patients with acute Covid-19 ranged from asymptomatic to rapidly fatal</u>

Not all infections have such a great range in severity as Covid-19, but a large number do. Strep throat can be asymptomatic, mildly symptomatic, or moderately severe, but is not lethal. Mucopurulent cervicitis due to *Chlamydia trachomatis* is commonly asymptomatic but can present occasionally with pelvic inflammatory disease.

Interestingly, most non-infectious diseases can affect different patients differently. For example, some patients with lupus have very mild disease on one hand but fulminant disease on the other. In multiple sclerosis, a minority of patients are identified only on autopsy—apparently with no manifestations during life. On the other hand, some patients are rapidly disabled.

Chapter 7: Four Illustrative Examples of Infectious Diseases

Varicella-Zoster Virus (VZV) has the property ("power") of latency

Varicella-Zoster virus is a very contagious double-stranded DNA virus. Before a vaccine was developed--and given routinely to children beginning in 1995--VZV caused chickenpox in childhood in everyone.

Chickenpox is spread via both respiratory droplets and tiny droplet nuclei

That is, chickenpox is one of the few infections spread by airborne transmission. After an incubation period ~ 14-16 days, the onset of disease manifests with fever, sore throat, anorexia, and malaise. This is followed in a day or two by a characteristic rash. Before the vaccine era, most recovered, but more than 10,000 were hospitalized per year. Death rates in those times were about 1 per 100,000 in children < 14, 6 per 100,000 in those 15-19, and 21 per 100,000 in those older than 19. Vaccination has prevented almost all deaths.

VZV virus is one of 8 viruses in the human herpesvirus family

These are: a) herpes simplex virus, type 1; b) herpes simplex virus, type 2; c) varicella-zoster; d) Epstein-Barr virus; e) cytomegalovirus; f) human herpesvirus 6; g) human herpesvirus 7, and h) human herpesvirus 8 (also called Kaposi's sarcoma virus).

An important characteristic of all 8 human herpesviruses is that the immune system cannot "rid the body" of them—even in those with normal immune systems ("immunocompetent" patients). That is, the immune response "contains" the infection, but does not kill the virus. Unfortunately, this allows the microbes to remain in a "latent" state. What this means is that they have the potential to "reactivate" and make the person sick again.

Several other microbes have the property of latency

These include: a) *Mycobacterium tuberculosis;* b) so-called "atypical" mycobacteria; c) *Toxoplasmosis gondii* (protozoan)*;* d) *Cryptococcus neoformans* (fungus); e) other "deep" or systemic fungi, like *Pneumoncystis jirovecii;* and f) retroviruses like HIV virus.

Initial VZV infection (Chickenpox) results in immune containment

It appears that during primary VZV infection, virus enters free sensory nerve endings and travels "backward" up the sensory nerve ("retrograde") to its sensory ganglion. Then it remains in the latent state, as if "hibernating" without active virus replication. This "immune system containment" is provided weapons of the cellular arm of the adaptive immune system--cytotoxic T cells and cytokines from helper T cells.

If immune system containment "relaxes" or "weakens," reactivation can occur

This involves a "waking up" of the virus. That is, active VZV virus replication recurs. This is followed by the movement (transport) of new virus down the sensory axon ("anterograde"). This allows virus to infect the skin, resulting in the rash of "shingles" or herpes zoster. In addition, the sensory nerves themselves become inflamed.

The rash of zoster usually involves only a single or a few contiguous dermatomes

Zoster is almost always very painful. Moreover, pain often persists after the rash resolves—so called "postherpetic neuralgia." This persistent pain is due to the damage "inflicted" on the nerve by the reactivated infection.

Zoster pain is "neuropathic"

Neuropathic pain is described as burning, stabbing, shooting, "electric-shock-like," aching, and/or throbbing.

The most common sites of reactivation are within the sensory ganglia of the lumbar and thoracic regions. About 10% involve reactivation of sensory nerves to the head. This is especially problematic when the ophthalmic branch of the trigeminal nerve is involved. This can result in infection of the cornea (viral keratitis). In some cases, blindness from retinal necrosis can also occur.

Zoster can occur in young people, but predominantly in those > 50

This is not surprising because the robustness of the immune response decreases with age. This is referred to as "immunosenescence." Other reasons associated with a "dipping" of the strength of the immune system include: a) diseases that impair immune function, such as HIV infection and cancer; and b) immunosuppressive medications for autoimmune diseases, transplantation, and cancer.

Botulism is a disease due to a secreted, soluble exotoxin

Botulism is a paralytic illness caused by the neurotoxin produced by the Gram-positive rod-shaped bacterium *Clostridium botulinum*. That is, the illness commonly occurs without bacterial replication. This is because *C botulinum* can exist as spores.

A spore is a single-cell, non-reproductive form of some bacteria

Spores are amazingly hardy. They can withstand freezing, drying, and high temperatures, such as 212 F (100 C) for several hours. This "sets the stage" for foodborne botulism due to improperly canned food.
C botulinum is a common contaminant of fresh vegetables. Unless "out of the ordinary" measures are taken in a home canning situation--such as using a pressure cooker or heating at 120 C for 5 minutes—spores will survive and later secrete ingestible botulinum toxin.

Botulinum toxin is more deadly than cyanide

That is, a cyanide concentration of 10,000 mcg/kg is equaled by a botulinum toxin concentration of only 0.0003 mcg/kg. Botulinum toxin is a polypeptide neurotoxin that prevents acetylcholine release from motor nerve endings.

Botulinum toxin results in "descending" weakness or paralysis

Initially there is weakness of muscles innervated by cranial nerves, resulting in blurred vision, diplopia, ptosis, dysphagia, dysarthria, and facial weakness. Bilateral involvement is the rule. Weakness follows in the upper extremities and the thorax, followed by the lower extremities. Diaphragmatic paralysis and respiratory failure or respiratory arrest can follow. Interestingly, these patients are afebrile, which is a diagnostic clue.

Infant botulism is the most common type in the US

This is caused by ingestion of spores located from environmental sources including raw honey. In these cases, the infants ingest spores that germinate within the intestines where neurotoxin is secreted.

Staphylococcus aureus is a common and potentially lethal cause of a variety of infections

S aureus is a Gram-positive coccus that is ubiquitous in the environment. Further, more than 50% of healthy people harbor this microbe in the nares as well as on the skin, particularly in the axillae, anogenital area, and intertriginous areas (areas where skin overlaps).

S aureus is "safe" if "outside" of us, but deadly if "inside" of us

Unbroken skin is a formidable barrier against *S aureus* and most microbes. On the other hand, any breaks in the skin provide "inviting" portals for this ubiquitous microbe.

S aureus is one of the most common causes of skin and soft tissue infections

These include: a) impetigo (infection of epidermis); b) folliculitis (upper dermis within hair follicles); c) furuncles, carbuncles, and skin abscesses (lower dermis and deeper); d) cellulitis and erysipelas (lower dermis and subcutaneous tissue); and e) necrotizing soft tissue infections (facial layers and deeper tissues). Necrotizing soft tissue infections were sometimes called "necrotizing fasciitis" or "flesh-eating bacteria."

S aureus is pathogenic because of its many virulence factors

There are too many to mention; however, a few will be discussed. Once *S aureus* has "broken through our barriers and gets inside," it continues to spread. It can "drill" or "bore" through tissues by "dissolving away" normal tissues with enzymes such as hyaluronidase. This allows the microbe to spread rapidly through tissues, such as in cellulitis, skin abscesses, and necrotizing soft tissue infections.

S aureus secretes "leukocidins" that "drill holes in" and destroy neutrophils and macrophages

This allows the microbe to withstand immune system attack. In addition, S aureus contains structural proteins that "repel" and prevent binding by immunoglobulins. The most potent one is "surface protein A" or SpA. This blocks opsonization, as does the microbes secretion of a protein that blocks the attachment and activation of complement factors, "staphylococcal complement inhibitor" or SCIN.

S aureus invades lymph channels and the bloodstream to cause "metastatic" infection

In this way, the microbe can infect: a) bone, causing osteomyelitis; b) synovial joints, causing septic arthritis; c) heart valves, causing endocarditis, as well as d) sepsis, septic shock, and multiorgan failure.

Ability to form "biofilms" is a key virulence factor in endocarditis and prosthetic infections

Biofilm formation is a property of some bacteria to "change form" from "individual acting" microbes to a "collection or group" that "appears to work together" to accomplish the following: a) "stick to" or adhere (especially to) heart valve leaflets or prosthetic joint components or intravascular devices; and b) secrete amorphous connective tissue that "builds a fort" surrounding the collection of bacteria.

The great problem with biofilms is that they block both antibiotics and immune system weapons to eradicate the infection. Thus, this is why these infections are so difficult to treat and can result in severe complications, including death.

S aureus is the most common cause of surgical site infections

This follows from the fact that most of these infections arise from skin flora that entered the surgical wound at the time of surgery. And *S aureus* is common on the bodies of patients.

Lyme disease is a vectorborne infection that comes from animals ("zoonosis")

The bacterium that causes Lyme disease in most of the US is *Borrelia burdorferi*. This microbe lives within wild animal species such as mice and deer. This "spirochete" bacterium is spread among animal populations by the bites (feedings) of blacklegged ticks (*Ixodes dammini*).

This bacterium does not sicken mice or deer. They act as the reservoir for the zoonotic infection that affects people. Blood is the unusual normal food for ticks. That is why they bite or feed. Adult ticks mate and the female lays eggs that result in tiny larva. The larva have to feed and so attach to small animals. Because many small animals harbor *B burgdorferi* in their blood, the larva becomes infected.

After feeding, when the cold months come, the larva is dormant. In spring, the larva develop into "nymphs," which have 8 legs instead of only 6.

Nymphs commonly feed on bigger animals such as deer or people

During feeding for several hours, the microbe, which is stored in the tick's salivary glands, can diffuse into the patient's bloodstream against the flow of blood away from the patient's bloodstream. Because the movement of the microbe is against the flow of blood, removal of the tick before a day of feeding, usually prevents transmission.

Nymphs develop into adult ticks the following spring and can also bite people. However, most infections are believed to be caused by nymphs. Nymphs are very small and can be difficult to spot on the skin, or scalp.

The incubation period for Lyme disease is commonly 1-2 weeks

In more than 90% of patients, a rash occurs, which spreads outward from the puncture site made by the tick. The rash (erythema migrans) gradually expands radially over several days and can be up to 20 cm in diameter. Other manifestations in some patients include fatigue, headache, muscle aches (myalgias), neck stiffness, joint pain, and fever. This stage of infection is called primary or early localized Lyme disease.

If primary Lyme disease is not treated, the microbe will disseminate

However, even without treatment, the rash will resolve. But the microbe will "travel in the blood" throughout the body. This occurs weeks to months after the original tick bite. This stage can manifest as the appearance of multiple patches of erythema migrans, as well inflammation of cranial nerves and spinal nerves. This stage is called secondary Lyme disease or early disseminated Lyme disease. This stage can also manifest as heart block (of the conduction system). Sometimes Lyme disease is missed at the primary stage and only diagnosed at this time.

Late Lyme disease occasionally occurs

In patients not diagnosed earlier, infection can persist especially in one or a few large joints. Lyme disease is similar to syphilis. They are both caused by spirochete bacteria—and if not treated early, they can present as secondary or tertiary disease.