Host Defenses

Introduction

Hans Selye said, “The body exists in a milieu of antagonistic environmental forces that are constantly attacking and threatening its integrity.” In the same vein, Francis Meehan gave us, “Men are at war with each other because each man is at war with himself.”

Being interested in disease, it is only natural that we should be concerned with how our body fends off infection. The multifaceted immune system is our answer to these attacks from our external foes.

The human immune system is a truly amazing constellation of responses to assaults from outside the body. It has many facets, a number of which can change to optimize the response to these unwanted intrusions. The system is remarkably effective—most of the time. This chapter will give you a brief outline of some of the processes involved. In particular, we will look at the three layers of defense: primary barriers, secondary barriers and innate immunity, and the final barrier consisting of cellular and humoral immunity.

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<td>Unbroken skin</td>
<td>Phagocytic white blood cells</td>
<td>T cells</td>
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<td>Mucus membranes and their secretions</td>
<td>Natural killer cells</td>
<td>B cells and antibodies</td>
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<td>Inflammation and fever</td>
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<td>Antimicrobial substances</td>
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First Line of Defense: Surface Barriers to Infection

The easiest way to prevent infection is to prevent the entry of the pathogen into the host organism. Our bodies have a host of impediments to unauthorized entry by foreign bodies.

1. The first and, arguably, most important barrier is the skin. The skin cannot be penetrated by most microorganisms, unless it already has been breached, such as a nick, scratch, or cut. Pores and hair follicles may afford some microbes points of entry.

2. Mechanical methods of removal: Pathogens are expelled from the respiratory tract by ciliary action as the tiny hairs lining the trachea move in an upward motion, pushing the mucus covering the lining of airways to the lungs upward toward the pharynx. Coughing and sneezing abruptly eject both living and nonliving things from the respiratory system. The flushing action of blinking, shedding tears, expectoration, and urination also force out pathogens, as does the sloughing off of skin.

3. Sticky mucus in the respiratory and gastrointestinal tracts traps many microorganisms. This mucus coating is also one way to prevent pathogens from attaching to host cells.

4. Acid pH (< 7.0) of skin secretions inhibits bacterial growth. Hair follicles secrete sebum that contains lactic acid and fatty acids, both of which inhibit the growth of some pathogenic bacteria and fungi. Areas of the skin not covered with hair, such as the palms and soles of the feet, are most susceptible to fungal infections. Think athlete’s foot. Vaginal secretions are also slightly acidic (after the onset of menarche).

5. Chemical approaches: Saliva, tears, nasal secretions, and perspiration contain lysozyme, an enzyme that destroys Gram-positive bacterial cell walls causing cell lysis, and lactoferrin, which binds so tightly to iron that it can cause microbial iron deficiency and death. Spermine and zinc in semen destroy some pathogens. Lactoperoxidase is a powerful enzyme found in mother’s milk.

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1 This action is called the mucociliary escalator.
6. The stomach is a formidable obstacle insofar as its mucosa secretes hydrochloric acid (0.9 < pH < 3.0, very acidic, more so than car battery acid and more like pure lemon juice) and protein-digesting enzymes that kill many pathogens. The stomach can even destroy some drugs and chemicals. Anything that has made it past the stomach must then encounter the alkaline environment of the small intestine. It starts out only slightly alkaline in the duodenum, but then progresses to an alkaline pH of nearly 13, virtually the same as lye.

Our Allies: Normal Flora
The body has even gone so far as to have formed alliances with certain mercenary alien species to better prevent infection. It offers these creatures symbiotic relationships that range from mutualism to commensalism.

Normal flora are the microbes, mostly bacteria, that live in and on the body with, usually, no harmful effects to us. There are about 400 different species that we play host to. The numbers and the proportions of each species vary from individual to individual. We have about $10^{13}$ (ten trillion) cells in our bodies and $10^{14}$ (one hundred trillion) bacteria, most of which live in the large intestine. There are $10^6$–$10^8$ microbes per cm$^2$ on the skin (Staphylococcus aureus, Staph. epidermidis, diphertheroids, streptococci, Candida, etc.). Various bacteria live in the nose and mouth. Lactobacilli live in the stomach and small intestine. The ileum or lower part of the small intestine has about $10^4$ bacteria per gram of its contents; the large bowel, which acts as a long and convoluted fermentation vessel, has $10^{11}$ per gram or about 40% of the fecal mass. 95–99% of these bacteria are anaerobes (An anaerobe is a microorganism that can live without oxygen, while an aerobe requires oxygen).

These inhabitants of our gut contribute significantly to our well-being. Germfree mice, with no intestinal bacteria, require about 30% more calories to maintain their weight than their intestinally infested comrades. When our dietary intake is low in vitamins K and B, various bacteria can synthesize them for us. Clearly our relation with these bacteria is one of mutualism, at best, and commensalism, at worst.

Even more abundant in our gut than the more commonly known Escherichia coli are Bacteriodes thetaiotaomicron. This species has been shown to enhance blood vessel growth in the intestines. Measurements have also shown that they exert some form of control over the intestine’s manufacture of basic sugars. This is an exemplary form of mutualism—likely one without which our lives would be much poorer.

Most previous research of the normal flora has relied exclusively on fecal samples. A recent study used mucosal samples and found an astonishing 13,000 prokaryotic ribosomal RNA gene sequences, far more than ever before. Fully 60% of the sequences were from “completely novel” organisms and “80% of the sequences came from species that have yet to be cultivated.”

They are of two types of internal bacteria: transient and resident. Resident intestinal flora attach themselves to the lining of the intestines and colonize the gut, whereas transient flora spend a relatively short time in the intestinal tract. Contrary to popular belief, the bacteria commonly used in the US in the manufacture of yogurt, Lactobacillus acidopholus and Streptococcus thermophilus, are only transient and do not colonize the colon. Nevertheless, yogurt can temporarily relieve some of the intestinal discomfort associated with prolonged antibiotic therapy.

The urogenital tract is lightly colonized by various bacteria and diphertheroids. After puberty, the vagina is colonized by the species Lactobacillus aerophilus that ferments glycogen to maintain a protective acid pH. If the vagina becomes too acidic, the normal flora living there are killed and susceptibility to infection increases markedly.

Normal flora fill almost all of the available ecological niches in the body and produce bacteriocidins, defensins, cationic proteins, and lactoferrin, all of which work to destroy other bacteria that compete for their niche in the body.

The resident bacteria can become problematic when they invade spaces in which they were not meant to be or when they overgrow their niche. As examples: (a) staphylococcus living on the skin can gain entry to the body through small cuts/nicks or burns. (b) Some antibiotics, in particular clindamycin, kill a large proportion of the friendly bacteria in our intestinal tract. This can cause an overgrowth of the considerably less friendly species Clostridium difficile, which results in pseudomembranous colitis, a rather painful condition wherein the inner lining of the intestine cracks and bleeds. Some forms of diarrhea and candidal vaginitis are also associated with an inadequate population of normal flora.

Normal flora are not the same in all people. In fact, they are environmentally determined (remember: Host-Agent-Environment). The residents of a tropical gut are not the same as those in an arctic gut. When NASA sent the first astronauts to the moon, they left in fairly sterile condition, i.e., with almost no intestinal bacteria. Upon return, their bodies were repopulated within about six weeks and the bacterial proportions depended on where they spent their six weeks of R&R. Very likely the bacterial population mix for human carnivores is different from that of vegans.
Immune Transport Systems of the Body

We have two main completely internal immune transport fluid systems: blood and lymph. The blood and lymph systems are intertwined throughout the body and they are responsible for transporting the agents responsible for the defense of the host.

The Blood System

The 5 liters of blood of a 70 kg (154 lb) person constitute about 7% of the body’s total weight. The blood flows out from the left-side of the heart into arteries, arterioles, and capillaries, and returns to the right-side of the heart through venules and then to veins.

Blood is composed of 52–62% liquid plasma and 38–48% cells. The plasma is mostly water (91.5%) and acts as a solvent for transporting other materials (7% protein and 1.5% other compounds). Blood is slightly alkaline (pH = 7.40 ± .05) and a tad heavier (density = 1.057 ± .009) than water, whose density is 1.000.

All blood cells are manufactured by stem cells, which live mainly in the bone marrow, via a process called hematopoiesis.

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2 The protein consists of albumins (54%), globulins (38%), fibrinogen (7%), and assorted other stuff (1%)
3 Arterial blood has a pH of 7.45 and venous blood 7.35. Blood pH outside the range of 6.8 to 7.8 is almost always fatal.
The stem cells produce hemocytoblasts that differentiate into the precursors for all the different types of blood cells. There are three types of blood cells: erythrocytes (red blood cells\(^4\) or RBCs), leukocytes (white blood cells or WBCs), and thrombocytes (platelets).

The leukocytes are further subdivided into granulocytes (containing large granules in the cytoplasm) and agranulocytes (without granules). The granulocytes consist of neutrophils (55–70%), eosinophils (1–3%), and basophils (0.5–1.0%). The agranulocytes are lymphocytes (consisting of B cells and T cells) and monocytes. Lymphocytes circulate in the blood and lymph systems, and make their homes in the lymphoid organs.

There are 5000–10,000 WBCs per mm\(^3\) and they live 5–9 days. About 2,400,000 RBCs are produced each second and each lives for about 120 days\(^5\). A healthy male has about 5 million RBCs per mm\(^3\), whereas females have a tad fewer than 5 million.

Some of the blood, but not red blood cells (RBCs), is pushed through the capillaries into the interstitial fluid.

Cardiac output is the volume of blood pumped out of either the right or left ventricle each minute. For an average resting adult, cardiac output is 3.0 liters per minute per square meter of surface area. Body surface area ranges from 1.4 m\(^2\) for a 5 foot tall person weighing 100 lbs to 2.3 m\(^2\) for a 6 footer weighing 240 lbs. That means that a particular red blood cell makes a round trip through your system in around one minute.

### Normal Adult Blood Cell Counts

<table>
<thead>
<tr>
<th>Blood Cell Type</th>
<th>Count (×10(^6)/mm(^3))</th>
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<tbody>
<tr>
<td>Red Blood Cells</td>
<td>5.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>2.5</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>7.3</td>
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- Neutrophil: 50–70%
- Lymphocyte: 20–40%
- Monocyte: 1–6%
- Eosinophil: 1–3%
- Basophil: <1%

**Aside:** The proteins on the surface of RBCs are responsible for the usual ABO blood grouping, among other things. The grouping is characterized by the presence or absence of A and/or B antigens. Blood type AB means both antigens are present and type O means both antigens are absent. Type A blood has A antigens and type B blood has B antigens. The proportion of blood types varies considerably by population groups as shown below.

### Percentage of Each Blood Type

<table>
<thead>
<tr>
<th>Population</th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
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<tr>
<td>U.S. (mean value)</td>
<td>46</td>
<td>40</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>African American</td>
<td>49</td>
<td>27</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Caucasian</td>
<td>45</td>
<td>40</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Japanese American</td>
<td>31</td>
<td>39</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Native North American</td>
<td>79</td>
<td>16</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Native South American</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
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In the ABO blood typing system, when an A antigen is present, the body produces an anti-B antibody, and similarly for a B antigen the body produces an anti-A antibody. The blood of someone of type AB, has both A and B antigens; hence it produces **neither** antibody. Thus the AB person can be transfused with any type of

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\(^4\) A typical red blood cell is about 6000 to 8000 nanometers across, which is more than a hundred times the size of a small virus.

\(^5\) They migrate to the spleen to die. Once there, that organ scavenges usable proteins from their carcasses. The original form of recycling?
blood, since there is no antibody to attack foreign RBCs. A person of blood type O has neither antigen and does have both antibodies and cannot receive A, B, or AB type blood, but they can donate blood for use by anybody. If someone with blood type A received blood of type B or AB, the body’s anti-B antibodies would attack the new blood cells causing agglutination (clumping) and/or hemolysis (bursting of blood cells). This would cause massive tissue damage and organ failure; death would be imminent.

The Lymph System

Lymph is an alkaline (pH > 7.0) fluid that is usually clear, transparent, and colorless. It flows in the lymphatic vessels and bathes tissues and organs. There are no RBCs in lymph and it has a lower protein content than blood. Like blood, lymph is slightly heavier (density = 1.019 ± 0.003) than water.

The lymph flows from the interstitial fluid through lymphatic vessels up to either the thoracic duct or right lymph duct, which terminate in the subclavian veins, where lymph is mixed into the blood. (The right lymph duct drains the right sides of the thorax, neck, and head, whereas the thoracic duct drains the rest of the body.) Lymph carries lipids and lipid-soluble vitamins (A, D, E, and K) absorbed from the gastrointestinal (GI) tract. Since there is no active pump in the lymph system, there is no pressure produced. Instead, the fluid moves by the contraction and relaxation of the skeletal muscles. The lymphatic vessels, like veins, have one-way valves that prevent backflow. Additionally, along these vessels there are small bean-shaped lymph nodes that serve as filters of the lymphatic fluid. It is in the lymph nodes where antigen is usually, but not always, presented to the immune system. These nodes serve as filters on the fluid highways of the body.

The human lymphoid system consists of the following:

- **primary organs**: bone marrow (in the hollow, but not empty, centers of bones) and the thymus gland (located behind the breastbone above the heart), and
secondary organs at or near possible portals of entry for pathogens: adenoids, tonsils, spleen (located at the upper left of the abdomen), lymph nodes (along the lymphatic vessels with concentrations in the neck, armpits, abdomen, and groin), Peyer’s patches (within the small intestine), and the appendix.

Second Line of Defense: Nonspecific Cellular Defenses

The nonspecific defensive system is what we are born with and it is innate; all foreign substances are attacked pretty much equally, whether they are new invaders or have invaded the body previously. The system kicks into action fairly rapidly, but it is not very flexible. It is genetically based and we pass it on to our offspring. It varies from species to species.

A phagocyte is a cell that attracts (by chemotaxis), adheres to, engulfs, and ingests foreign bodies. There are three types of phagocytes: macrophages, neutrophils, and eosinophils.

Promonocytes are made in the bone marrow, after which they are released into the blood and called circulating monocytes, which eventually mature into macrophages (meaning “big eaters”, see below).

Some macrophages are relatively immobile and concentrated in specific tissue or organs, such as the lungs, liver (Kupffer cells), lining of the lymph nodes and spleen, brain microglia, kidneys (mesoangial cells), and joints (synovial A cells). They are long-lived, depend on mitochondria for energy, and are best at attacking dead cells and pathogens capable of living within cells. Each macrophage is capable of consuming up to ten cells per day. The right-hand picture below shows a macrophage engulfing a bacterium.
In addition to fixed macrophages, there are wandering macrophages. The fixed macrophages adhere to the inner linings of blood and lymph vessels and various organs and can only move by slowly rolling along the surface after being struck by other blood cells. Wandering macrophages are free to move throughout the blood and lymph systems.

Once a macrophage phagocytizes a cell, it places some of that cell’s proteins, called **epitopes**, on its surface—much like a fighter plane displaying its hits. All cells that display parts of the proteins (called **peptides**) of antigens are called **antigen presenting cells** (APCs). The chemical MHC-II is present only in the cell membranes of APCs that are processing antigens. These surface markers serve as an alarm to other immune cells, which then infer the form of the invader. Furthermore, a phagocytizing macrophage secretes a hormone-like chemical called interleukin-1 (IL-1) that triggers a sequence of reactions that can raise the body’s temperature and cause a fever. These reactions can cause the muscles to release amino acids, enhance protein production in the liver, increase phagocytosis, increase production of the viral fighting substances called interferons, and increase production of T- and B-cells.

The sequence of cellular damage, cellular response, and raising the body temperature is collectively referred to as the **inflammatory process**. The diagram below summarizes the steps in this process, which ultimately leads to either disease resolution, scarring, chronic infection, or the infection overwhelms the body’s defenses. When antigen presenting cells are stimulated by either inflammatory factors or microbial products they begin to generate unstable chemicals that modify the peptides displayed by the APCs. These changes increase the likelihood that the antigen will be attacked in the third line of defense.

The following diagram shows the sequence of events that occur once the inflammatory process is triggered.
Wandering macrophages can even leave the blood and lymph vessels to go to an infection site where they destroy dead tissue and pathogens. Emigration by squeezing through the capillary walls to the tissue is called diapedesis. The presence of histamines at the infection site attracts the cells to their source.
Natural killer cells are major players in the process of immune reconnaissance. They move in the blood and lymph searching for cancer cells and virus-infected body cells. They are large granular lymphocytes that attach to the glycoproteins (combinations of carbohydrates and proteins) on the surfaces of infected cells and kill them by ejecting a chemical, called a **perforin**, which punctures their cell membranes and causes them to lyse (without damaging the NK cells).

Polymorphonuclear neutrophils, called polys for short, are phagocytes that have no mitochondria and get their energy from stored glycogen. They are nondividing, short-lived (half-life of 6–8 hours, 1–4 day lifespan), and have a segmented nucleus. They constitute 50–75% of all leukocytes. The neutrophils provide the major defense against pyogenic (pus-forming) bacteria and are the first on the scene, within about 90 minutes, to fight infection. They are followed by the wandering macrophages about three to four hours later.

Eosinophils are attracted to cells coated with a protein called complement C3B, where they release cytokines (major basic protein (MBP), cationic protein, perforins, and oxygen metabolites), which work together to burn holes in cells and helminths (worms). About 1–3% of the WBCs are eosinophils. Their lifespan is about 8–12 days. Both neutrophils and eosinophils are types of phagocytes called microphages. Once phagocytes do their job, they die and their “corpses,” pockets of damaged tissue, and fluid form pus.

Recently even platelets have been shown to participate in the innate immune response. They indirectly take part in killing microbes and they produce a surface protein that enhances the third line of defense, the adaptive immune response.

The **complement system** is a major triggered enzyme plasma system. It coats microbes with molecules that make them more susceptible to engulfment by phagocytes. It also causes lysis of body cells or pathogens. Vascular permeability mediators increase the permeability of the capillaries (anaphylaxis) to allow more plasma and complement fluid to flow out of the capillaries to the site of infection. They also attract neutrophils and phagocytes to foreign bodies where they encourage neutrophils to adhere to the walls of capillaries (by a process called **margination**) from which they can squeeze through in a matter of minutes to arrive at a damaged area.

**Dendritic cells** are covered with a maze of membranous processes that look like gossamer webs. Those that have been processed and matured are highly efficient antigen presenting cells. They bind tightly to T cells, forming a so-called immunological synapse across which signaling chemicals flow. Maturation of these cells is triggered by the presence of a substance called CD154, which is present on the surface of platelets.

Dendritic cells also use lysosomes to break down antigens and display the pieces on their surfaces. These cells come in four basic types: Langerhans’ cells, interstitial dendritic cells, interdigitating dendritic cells, and circulating dendritic cells. Our major concern will be **Langerhans’ cells**, which are found in the epidermis and mucous membranes, especially in the anal, vaginal, and oral cavities. These cells make a point of attracting antigen and efficiently presenting it to T helper cells for their activation.

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6 This accounts, in part, for the transmission of HIV via sexual contact.
Each of the cells in the innate immune system bind to antigen using **pattern-recognition receptors**. These receptors are encoded in the germ line of each person. Over the course of human development these receptors for pathogen-associated molecular patterns have evolved via natural selection to be specific to certain characteristics of broad classes of infectious organisms. There are several hundred of these receptors and they recognize patterns of bacterial lipopolysaccharide, peptidoglycan, bacterial DNA, dsRNA, and other substances. They are set to target viruses, both Gram-negative and Gram-positive bacteria, mycoplasmas, etc.

**Third Line of Defense: Adaptive or Acquired Immunity**

An **antigen** is any substance that is capable of eliciting the production of antibodies, anything from a virus to a bacterium to a worm to a sliver. (The word antigen comes from **antibody generating**.)

The adaptive immune system has a series of dual natures, the most important of which is **self/non-self recognition** also called **tolerance**. The others are:

- general/specific immunity,
- natural/adaptive = innate/acquired immunity,
- cell-mediated/humoral immunity,
- active/passive immunity, and
- primary/secondary immunity.

All of these categories have significant overlap with each other.

**Self/non-self recognition** is achieved by having every cell display a marker based on the Major Histocompatibility Complex (MHC). There are two major types of MHC: Classes I and II. Almost every nucleated cell not displaying an MHC-I marker is treated as non-self and attacked. The process is so effective that undigested proteins are often treated as antigens.

The adaptive immune system is **antigen-specific** (it recognizes and acts against particular antigens), **systemic** (not confined to the initial infection site, but works throughout the body), and has **memory** (recognizes and mounts an even stronger attack to the same antigen the next time it appears).

Sometimes the self/non-self recognition process breaks down and the immune system attacks self-cells. This is the case of **autoimmune diseases** like multiple sclerosis, systemic lupus erythematosus, diabetes, and some forms of arthritis. There are also times when the immune response to innocuous substances is inappropriate. This is the case of allergies and the simple substance that elicits the excessive response is called an **allergen**.

Lymphocytes come in two major types: **B cells** and **T cells**. The peripheral blood contains 20–50% of the circulating lymphocytes; the rest move in the lymph system. Roughly 80% of them are T cells, 15% B cells, and the remainder are null or undifferentiated cells. Lymphocytes constitute 20–40% of the body’s WBCs. Their total mass is about the same as that of the brain or liver. (Heavy stuff!)

Near each portal of entry there are lymph nodes where lymphocytes congregate and prepare to do battle with any incoming pathogens.

**B cells** are produced in the **stem cells** of the bone marrow; they produce antibody and oversee humoral immunity. **T cells** are nonantibody-producing lymphocytes which are also produced in the bone marrow but sensitized in the **thymus** and constitute the basis of cell-mediated immunity.
Parts of the immune system are changeable and can adapt to better attack the invading antigen. There are two fundamental adaptive mechanisms: cell-mediated immunity and humoral immunity.

**Cell-mediated immunity**

Macrophages engulf antigens, process them internally, then display parts of them on their surfaces together with some of their own proteins. These, and other antigen-presenting cells, sensitize the T cells to recognize these antigens.

All cells are coated with various proteins. The coatings are classified by CD numbers. CD stands for cluster of differentiation\(^7\) and there are more than one hundred and sixty clusters, each of which is a different molecule that may be present on a cell’s outer surface. CD8+ is read “CD8 positive.” That means that the cell has the protein CD8 on its surface.

Each T and B cell has about \(10^5 = 100,000\) molecules on its surface. B cells are coated with CD21, CD35, CD40, and CD45 in addition to other non-CD molecules. T cells have CD2, CD3, CD4, CD8, CD28, CD45R, and other non-CD molecules on their surfaces\(^8\).

The large number of molecules on the surfaces of lymphocytes allows huge variability in the forms of the receptors. They are produced with random variations in the configurations on their surfaces. There are \(10^{18}\) (a million, million, million) possible structurally different receptors. Essentially, an antigen may find a near-perfect fit with a very small number of lymphocytes—perhaps as few as one.

T cells are primed in the thymus, where they undergo two selection processes. The first, positive selection weeds out only those T cells with the correct set of receptors that can recognize the MHC molecules responsible for self-recognition. Then a negative selection process begins whereby T cells that can recognize MHC molecules complexed with foreign peptides are allowed to pass out of the thymus. Once primed, the T cell is ready to go to work.

**Cytotoxic** or **killer T cells** (CD8+) do their work by releasing lymphotoxins and perforins, which cause cell lysis. **Helper T cells** (CD4+) serve as managers, directing the immune response. They secrete chemicals called

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7 These are groups of proteins present on WBCs and they are used for the purpose of differentiating between types of cells.

8 T cells that express CD95 are primed for CD95- or CD3-mediated cell death. This is important in HIV-1 infection.
lymphokines that stimulate cytotoxic T cells and B cells to grow and divide, attract neutrophils, and enhance the ability of macrophages to engulf and destroy microbes. Suppressor T cells inhibit the production of cytotoxic T cells once they are unneeded, lest they cause more damage than necessary. Memory T cells develop from about 5% of killer T cells and are programmed to recognize and respond to a pathogen that has invaded, been repelled, and later returned for another attack. Mouse models indicate that memory cells do not develop adequately during a chronic viral infection.

Newborns have much higher CD4+ and CD8+ T cell counts than adults. Their counts peak at 3 weeks and again at 6 months of age. Then they decline slowly until they reach normal adult levels at about 6 years of age. Before age 9, CD4+ counts are higher among girls than boys and higher among children of pallor than children of color. This pattern is also true for the total numbers of lymphocytes.

Humoral immunity

An immunocompetent but as yet immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors and there is a T helper cell nearby (to release a lymphokine). This sensitizes or primes the B cell and it undergoes clonal selection, which means it reproduces asexually by mitosis. Most of the family of clones become plasma cells. These cells, after an initial lag, produce highly specific antibodies at a rate of as many as 2000 molecules per second for four to five days. The other B cells become long-lived memory cells.

Humoral immunity

Antibodies, also called immunoglobulins or Igs\(^9\), constitute the gamma globulin part of the blood proteins. They are soluble proteins secreted by the plasma offspring (clones) of primed B cells. The antibodies inactivate antigens by, (a) complement fixation (proteins attach to antigen surface and cause holes to form, i.e., cell lysis), (b) neutralization (binding to specific sites to prevent attachment—this is the same as taking their parking space so they have no place to go), (c) agglutination (clumping together which inactivates them), (d) precipitation (forcing insolubility and settling out of solution).

\(^9\) They have molecular weights of 150–900 megaDaltons, which means they are very heavy.
Constituents of gamma globulin are: IgG-76%, IgA-15%, IgM-8%, IgD-1%, and IgE-0.002%. IgG has antiviral, antitoxin, and antibacterial properties; it is the only antibody that can cross the placental barrier to the fetus and it is responsible for the 3- to 6-month-long immune protection of newborns that is conferred by the mother; it also activates complement and binds to macrophages. During breast feeding, maternal IgA provides protection for the newborn's intestinal tract and can decrease the incidence of diarrheal infections. IgA is the predominant antibody in most body secretions, e.g., saliva, nasal and respiratory secretions, and breast milk; it protects most mucus membranes. IgM is prominent in the primary immune response and it activates complement. IgD is found on B cells and is required for their maturation. IgE binds to mast cells and basophils, is involved in parasitic infections, and is responsible for responses, such as allergies, hypersensitivity, and diseases like arthritis, multiple sclerosis, and systemic lupus erythematosus.

Notice the many degrees of flexibility of the IgG antibody molecule. This freedom of movement allows it to more easily conform to the nooks and crannies on an antigen. The upper part or Fab (antigen binding) portion of the antibody molecule (physically and not necessarily chemically) attaches to specific amino acids on the antigen. Thus antibody recognizes the epitope and not the entire antigen. The Fc region is responsible for effector functions, i.e., the end to which immune cells can attach.

Lest you think that these are the only types of antibody produced, you should realize that the B cells can produce as many as $10^{14}$ conformationally different forms.

The process by which T cells and B cells interact with antigens is summarized in the diagram below.
All of these mechanisms hinge on the attachment of antigen and cell receptors. Since there are many, many receptor shapes available, WBCs seek to optimize the degree of confluence between the two receptors. This attests to the specificity of the interaction. Nevertheless, cells can bind to receptors whose fit is less than optimal when required. This is referred to as cross-reactivity. Cross-reactivity has its limits. There are many receptors to which virions cannot possibly bind. As an example, very few viruses can bind directly to external skin cells.

The design of vaccines hinges on the specificity and cross-reactivity of these bonds. The more specific the bond, the more effective and long-lived the vaccine. The smallpox vaccine, which is made from the vaccinia virus—not the cowpox virus—is an excellent match for the smallpox receptors. Hence, that vaccine is nearly 100% effective and provides immunity for at least 20 years. The vaccine efficacy for polio is 90% in the US and between 60% and 80% in developing countries. The efficacy for the current measles vaccine is about 95%.

To-date, vaccines for cholera have had a relatively poor fit, so they have had low efficacy, do not protect against all forms of the disease, and protect for less than a year. Influenza vaccines have a very good fit, but most vaccines...
are only trivalent, meaning that protect against only three forms of the influenza virus. Since we know that type A influenza viruses undergo both antigenic drift and shift, these vaccines are rarely protective beyond one year.

One of the difficulties with designing a vaccine for HIV is its high rate of mutation, it changes much more frequently than the influenza virus.

The goal of all vaccines is to promote a mild primary immune reaction—so that when the organism is again exposed to the antigen, a much stronger immune response will be elicited because of the presence of memory T and B cells. Any immune response subsequent to the initial infection by an antigen is called a **secondary immune response** and it has

- a. a shorter lag time,
- b. more rapid buildup,
- c. a higher overall level of response,
- d. a more specific or better “fit” to the invading antigen,
- e. utilizes IgG instead of the large, heavy multipurpose antibody IgM.

![Graph showing primary and secondary immune responses](image.png)

This is the reason that vaccines work as well as they do, i.e., they produce a mild primary response and the antigen then encounters a strong secondary response.

Of course, if you get a case of chickenpox and recover completely, it is very unlikely that you will be infected by that virus again. This is an example of a naturally acquired immunity.

**Summary**

Immunity can be either **natural** or **artificial** (also called **induced**), **innate** or **acquired** (also called **adaptive**), and either **active** or **passive**.

- Active natural (contact with infection): develops slowly, is long term, and antigen specific.
- Active artificial (immunization): develops slowly, lasts for several years, and is specific to the antigen for which the immunization was given.
- Passive natural (transplacental = mother to child): develops immediately, is temporary, and affects all antigens to which the mother has immunity.
- Passive artificial (injection of gamma globulin): develops immediately, is temporary, and affects all antigens to which the donor has immunity.

Graphically, this can be further subdivided as shown below.
Specific Resistance
- Responds to threats on an individualized basis

Acquired Immunity
- Produced by prior exposure or antibody production

Innate Immunity
- Genetically determined
- Prior exposure or antibody production necessary

Active Immunity
- Produced by antibodies that develop in response to antigens

Passive Immunity
- Transfer of antibodies from someone else

Induced Active Immunity
- Administration of antigen

Natural Passive Immunity
- Transfer of maternal antibodies

Induced Passive Immunity
- Administration of antibodies

Naturally Acquired Immunity
- Develops after exposure to antigens