I TOLD YOU I WAS SICK

B. P. ROBERTS

MAY 17, 1929

JUNE 18, 1979
• Check this out.

• What kind of pathogens are out there lurking?

• Any other cells you might want to get rid of?
Let’s dissect this…

<table>
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<th>Nonspecific defense mechanisms</th>
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<td>• Secretions of skin and mucous membranes</td>
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Newer terms:

• **Innate immunity** to pathogens is what you are born with and includes the nonspecific mechanisms.
  • ***Inverts also share much of these defenses.

**Acquired immunity** includes the specific mechanisms and is found only in vertebrates.
Here is what we share with inverts (and the AP folks want you to know this!!)

- Barrier defenses, like arthropod exoskeletons.
- Toll receptors on immune response cells.
  - Immune cells secrete proteins that bind to molecules that pathogens make but the organism doesn’t (non-self).
  - These then bind to Toll receptor proteins on the surface of immune response cells, triggering a signal transduction pathway causing those cells to release antimicrobial proteins. Let’s watch.
- Neat article about the Plague, toll receptors and evolution.
1. The skin and mucous membrane provide first-line barriers to infection

- Integument is your friend, both inside and out.
- AP objective - Vertebrate immune systems have nonspecific and nonheritable defense mechanisms against pathogens.
Integumentary chemistry!!

In humans, for example, secretions from sebaceous and sweat glands give the skin a pH ranging from 3 to 5, which is acidic and salty enough to prevent colonization by many microbes.

Saliva, tears, and mucous secretions bathe the exposed epithelium and contain antimicrobial proteins.

One of these, the enzyme lysozyme, digests the cell walls of many bacteria, destroying them.

So, let’s engineer some goats....
• Do you have a mucociliatory escalator? I do.

• Those cells that line the respiratory tubes have cilia that beat in synch to move a layer of mucous up and out, taking with it any particulates that you breath in and get stuck to the mucous, preventing them from getting to the gas exchange membranes of alveoli.
• Stomach acid (what kind?) kills most pathogens in your lunch.

• One exception, the hepatitis A virus, can survive gastric acidity and gains access to the body via the digestive tract.
2. What if the intruders get past the gates?

- Phagocytes to the rescue!! What kind of cells are these?
- Phagocyte function is coupled with an effective inflammatory response and also with certain antimicrobial proteins, like interferons and complement.
The phagocytic cells called neutrophils constitute about 60%-70% of all white blood cells (leukocytes).
• Then there are the BIG eaters.
  • **Macrophages**: large, long-lived phagocytes.
  • What are those “feet” called?
• This shouldn’t surprise you…

• Some bacteria have outer capsules to which a macrophage cannot attach.

• Others, like *Mycobacterium tuberculosis*, are readily engulfed but are resistant to lysosomal destruction and can even reproduce inside a macrophage.
• Some macrophages migrate throughout the body, while others reside permanently in certain tissues, including the lung, liver, kidney, connective tissue, brain, and especially in lymph nodes and the spleen. Here is one in the inner ear.

• So they are not just found in the blood.
New discovery links brain and immune. Newly discovered lymphatic vessels extend into the Meninges, the membranes that cover the brain. A T-cell signal molecule, Interferon gamma, has also been shown to affect social behavior, which helps spread disease. Applications of this knowledge may help treat diseases like MS and Alzheimer’s.
- Microorganisms, microbial fragments, and foreign molecules that enter the blood encounter macrophages when they become trapped in the netlike architecture of the spleen.
• Natural killer (NK) cells do not attack microorganisms directly but destroy virus-infected body cells and cells that have turned cancerous because these two types of cells have stopped producing a surface protein called a class I MHC molecule.

• NK cells mount an attack on the cell’s membrane, lysing the cell.
How about that inflammatory response.
Fig. 43.5
• Ever take an anti-histamine? Here’s why…

• Histamine is released by circulating leukocytes called **basophils** and by **mast cells** in connective tissue.

• Histamine triggers both dilation and increased permeability of nearby capillaries, giving you a runny nose and eyes.

• Leukocytes and damaged tissue cells also discharge **prostaglandins** and other substances that promote blood flow to the site of injury.
• Neutrophils arrive at the point of assault, followed by macrophages.

• The pus that accumulates at the site of some infections consists mostly of dead phagocytic cells and the fluid and proteins that leaked from capillaries during the inflammatory response.

• This pus is usually absorbed by the body within a few days. Mmmmm…..
• Severe tissue damage or infection may trigger a systemic (widespread) nonspecific response.

• Fever, another systemic response to infection, can be triggered by toxins from pathogens or by pyrogens released by certain leukocytes.

• How does that work, and why is it good for you to have a fever?

• Can there be too much of a good thing, though?
• Certain bacterial infections like MRSA can induce an overwhelming systemic inflammatory response leading to a condition known as **septic shock**.

• Characterized by high fever and low blood pressure, septic shock is the most common cause of death in U.S. critical care units.

• Clearly, while local inflammation is an essential step toward healing, widespread inflammation can be devastating.
A variety of proteins function in nonspecific defense either by attacking microbes directly or by impeding their reproduction.

- In addition to lysozyme, other antimicrobial agents include about 20 serum proteins, known collectively as the **complement system**.
  - These carry out a cascade of steps that lead to lysis of microbes.
  - Some complement components work with chemokines to attract phagocytic cells to sites of infection.
Here’s a 2016 update involving another kind of protein and Alzheimer’s


- Beta amyloid, the plaque causing protein involved in causing Alzheimer’s, apparently traps microbes that have escaped the blood brain barrier and “cages” them for macrophage disposal. Could they also trap gluten breakdown fragments?
Another set of proteins that provide nonspecific defenses (albeit only against viruses) are the interferons, which are secreted by virus-infected cells.

While they do not seem to benefit the infected cell, these proteins diffuse to neighboring cells and induce them to produce other chemicals that inhibit viral reproduction.

So antibiotics work only against bacteria, and interferons only against viruses.
To summarize the nonspecific defense systems, the first line of defense, the skin and mucous membranes, prevents most microbes from entering the body by providing a mechanical barrier, like walls, doors and windows do for your house.

The second line of defense uses phagocytes, natural killer cells, inflammation, and antimicrobial proteins to defend against microbes that have managed to enter the body, like a shotgun, rotweilers and mace would in your house.

These two lines of defense are nonspecific in that they do not distinguish among pathogens.

They give an organism what is now called INNATE immunity.
Update: 2016 – the overlap you would expect between innate and acquired.

• Much evidence now shows that the cellular players in innate defenses – natural killers, macrophages and other phagocytes undergo epigenetic changes during infections that makes them show increased responsiveness to subsequent infections, which is now being referred to as “trained immunity” or “innate immune memory.”
Here’s a distinctly southern defense system:
While pathogens are under assault by phagocytic cells, the inflammatory response, and antimicrobial proteins, they inevitably encounter lymphocytes, the key cells of the immune system - the body’s third line of defense.

Lymphocytes are WBC’s that eliminate specific invaders.

- This includes pathogens, transplanted cells, and even cancer cells, which they detect as foreign.

2.D.4.b.1. Describe the two types of specific responses in the Mammalian immune system

2.D.4.b.2. In the cell-mediated response, what is the role of cytotoxic T cells?

2.D.4.b.3. In the humoral response, what is the role of B cells?

2.D.4.b.4. Explain how antigens and antibodies work together.

2.D.4.b.6. How does a second exposure to an antigen differ from the primary exposure?
1. Lymphocytes provide the specificity and diversity of the immune system

- The vertebrate body is populated by two main types of lymphocytes: B lymphocytes (B cells) and T lymphocytes (T cells).
  - Both types circulate throughout the blood and lymph and are concentrated in the spleen, lymph nodes, and other lymphatic tissue.
  - One difference is reflected by their name.
A foreign molecule that elicits a specific response by lymphocytes is called an antigen.

Antigens include molecules belonging to viruses, bacteria, fungi, protozoa, parasitic worms, and nonpathogens like pollen and transplanted tissue.
• One way that an antigen elicits an immune response is by activating B cells to secrete proteins called antibodies.

• Each antigen has a particular molecular shape and stimulates certain B cells to secrete antibodies that interact specifically with it.
• B and T cells recognize specific antigens through their plasma membrane-bound antigen receptors.

• A single T or B lymphocyte bears about 100,000 receptors for antigen, all with exactly the same specificity.
• How can there be so many different cells with different receptors?

• Not those jumping genes again…

• Follow the events…
Fig. 43.6
• In this process of **clonal selection**, each antigen, by binding to specific receptors selectively, activates a tiny fraction of cells from the body’s diverse pool of lymphocytes.

• This relatively small number of selected cells gives rise to clones of thousands of cells, all specific for and dedicated to eliminating only that antigen.
3. Lymphocyte development gives rise to an immune system that distinguishes self from nonself

- Lymphocytes, like all blood cells, originate from pluripotent stem cells in the bone marrow or liver of a developing fetus.
Early lymphocytes are all alike, but they later develop into T cells or B cells, depending on where they continue their maturation.
• While B cells and T cells are maturing in the bone marrow and thymus, their antigen receptors are tested for potential self-reactivity.

• For the most part, lymphocytes bearing receptors specific for molecules already present in the body are rendered nonfunctional or destroyed by apoptosis, leaving only lymphocytes that react to foreign molecules.

• This capacity to distinguish self from nonself continues to develop as the cells migrate to lymphatic organs.

• Thus, the body normally has no mature lymphocytes that react against self components, but failures of self-tolerance can lead to autoimmune diseases, like arthritis, in which lymphocytes attack cells in your joints.
There are two main types of T cells, and each responds to antigens held by molecules on the cell surface called MCH (major histocompatibility complex) molecules.

- Cytotoxic T cells (\(T_C\))
- Helper T cells (\(T_H\))
- Check out the difference…
3.D.2.a. Using an example from below, explain how cells communicate by cell-to-cell contact.

1. Immune cells interact by cell-cell contact, antigen-presenting cells (APCs), helper T-cells and cytotoxic T-cells.

2. Plasmodesmata between plant cells that allow material like auxin to be transported from cell to cell.
• Class II MHC molecules are made by only a few cell types, chiefly macrophages, B cells, and dendritic cells.

• These cells, called antigen-presenting cells (APCs) in this context, ingest bacteria and viruses and then destroy them.
**Dendritic cells** (DCs) are immune cells forming part of the mammalian immune system. Their main function is to process antigen material and present it on the surface to other cells of the immune system. That is, dendritic cells function as antigen-presenting cells. They act as messengers between the innate and acquired immunity.

Dendritic cells are present in tissues in contact with the external environment, such as the skin (where there is a specialized dendritic cell type called Langerhans cells) and the inner lining of the nose, lungs, stomach and intestines. They can also be found in an immature state in the blood. Once activated, they migrate to the lymph nodes where they interact with T cells and B cells to initiate and shape the acquired immune response. Immature dendritic cells are also called **veiled cells**, as they possess large cytoplasmic 'veils' rather than dendrites.
Immature dendritic cells constantly sample the surrounding environment for pathogens such as viruses and bacteria. This is done through pattern recognition receptors (PRRs) such as the toll-like receptors (TLRs). Once they have come into contact with a presentable antigen, they become activated into mature dendritic cells and begin to migrate to the lymph node. Immature dendritic cells phagocytize pathogens and degrade their proteins into small pieces and upon maturation present those fragments at their cell surface using MHC molecules. Then the dendritic cell travels through the blood stream to the spleen or through the lymphatic system to a lymph node. Here they act as antigen-presenting cells: they activate helper T-cells and cytotoxic T-cells as well as B-cells by presenting them with antigens derived from the pathogen. Every helper T-cell is specific to one particular antigen. Only professional antigen-presenting cells (macrophages, B lymphocytes, and dendritic cells) are able to activate a resting helper T-cell when the matching antigen is presented.

However, macrophages and B cells can only activate memory T cells whereas dendritic cells can activate both memory and naive T cells, and are the most potent of all the antigen-presenting cells.
The immune system can mount two types of responses to antigens: a humoral response and a cell-mediated response.
Humoral (antibody-mediated) immune response

Free antigens directly activate B cell
B cell Stimulates Helper T cell
Helper T cell Stimulates Memory helper T cell
Memory helper T cell Stimulates Antigen (2nd exposure)
Antigen (2nd exposure) Stimulates Memory T cells
Memory T cells Secrete Antibodies
Plasma cells
Antibodies

Defend against extracellular pathogens by binding to antigens and making the pathogens easier targets for phagocytes and complement.

Cell-mediated immune response

Antigen (1st exposure) Engulfed by Macrophage (APC)
Macrophage (APC) Stimulates Cytotoxic T cell
Cytotoxic T cell
Cytotoxic T cell Gives rise to Active cytotoxic T cells
Active cytotoxic T cells

Antigens displayed by infected cells activate

Defend against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells.

Fig. 43.10
1. Helper T lymphocytes function in both humoral and cell-mediated immunity:

- Helper T cells can trigger both responses.
  - See animation 43.1.1 por favor. 2 min. Show for sure
(1) An APC engulfs a pathogen and transports a fragment of it (antigen) to the cell surface via a class II MHC molecule. See what happens next…
Fig. 43.11

1. Bacterium
2. APC (macrophage)
3. T-cell receptor
4. CD4
5. Interleukin-1
6. Interleukin-2 and other cytokines
7. T\(_H\) cell
8. T\(_C\) cell
9. B cell
10. Class II MHC molecule
11. Antigen fragment

Cell-mediated immunity (attack on infected cells)
Humoral immunity (secretion of antibodies by plasma cells)
3.D.2.a. Using an example from below, explain how cells communicate by cell-to-cell contact.

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2. Plasmodesmata between plant cells that allow material like auxin to be transported from cell to cell.
Just in case you thought this was too simple, take a peek at

- This 4:30 or here (same video)
- See how much of this you can recognize.
- See how much we all have to learn😊.
2. In the cell-mediated response, cytotoxic T cells counter intracellular pathogens: a closer look

- Antigen-activated cytotoxic T lymphocytes kill cancer cells and cells infected by viruses and other intracellular pathogens.
- This is mediated through class I MHC molecules.
  - Let’s analyze the diagrams and videos…
  - First the live version, no details. 1:00
  - Now here Animation 43.1.2 1:00
  - Watch here first (last actually) for high level stuff! 2:30
• If the cell contains a replicating virus, class I MHC molecules expose foreign proteins that are synthesized in infected or abnormal cells to cytotoxic T cells.
• The activated cytotoxic T cell differentiates into an active killer, which kills its target cell - the antigen-presenting cell - primarily by releasing **perforin**.
  • This protein forms pores into the target cell, which swells and eventually lyses.
• The death of the infected cell not only deprives the pathogen of a place to reproduce, but it also exposes it to circulating antibodies, which mark it for disposal.
• Once activated, the $T_C$ cells kills other cells infected with the same pathogen.
• In the same way, $T_C$ cells defend against malignant tumors.

• Because tumor cells carry distinctive molecules not found on normal cells, they are identified as foreign by the immune system.

• The body also has a backup defense in the form of natural killer cells, part of the nonspecific defenses, which lyse virus-infected and cancer cells.
More than you need to know, but this is called the MISSING SELF HYPOTHESIS
For NK cells to defend the body against viruses and other pathogens, they require mechanisms that enable the determination of whether a cell is infected or not. The exact mechanisms remain the subject of current investigation, but recognition of an "altered self" state is thought to be involved. To control their cytotoxic activity, NK cells possess two types of surface receptors: activating receptors and inhibitory receptors, including killer-cell immunoglobulin-like receptors. Most of these receptors are not unique to NK cells and can be present in some T cell subsets, as well. These inhibitory receptors recognize MHC class I alleles, which could explain why NK cells preferentially kill cells that possess low levels of MHC class I molecules. This mode of NK cell target interaction is known as "missing-self recognition", a term coined by Klas Kärre and co-workers in the late 90s. MHC class I molecules are the main mechanism by which cells display viral or tumor antigens to cytotoxic T cells. A common evolutionary adaptation to this is seen in both intracellular microbes and tumors: the chronic down-regulation of MHC I molecules, which makes affected cells invisible to T cells, allowing them to evade T cell-mediated immunity. NK cells apparently evolved as an evolutionary response to this adaptation (the loss of the MHC eliminates CD4/CD8 action, so another immune cell evolved to fulfill the function).[9]
Difference between cytotoxic T’s and Natural Killer cells

- Induction of apoptosis
- Cytolytic T cell
  - MHC I inhibitory receptor
  - Natural killer cell

- MHC class I molecule
- Intracellular pathogen

- Normal MHC Class I expression

- MHC Class I downregulation by pathogen: "Missing Self"
If cancer cells do not cause inflammation, they will also be regarded as self and will not induce a T cell response. A number of cytokines are produced by NKs, including tumor necrosis factor α (TNFα), IFNγ, and interleukin (IL-10). TNFα and IL-10 act as proinflammatory and immunosuppressors, respectively. The activation of NK cells and subsequent production of cytolytic effector cells impacts macrophages, dendritic cells, and neutrophils, which subsequently enables antigen-specific T and B cell responses. Instead of acting via antigen-specific receptors, lysis of tumor cells by NK cells is mediated by alternative receptors, including NKG2D, NKp44, NKp46, NKp30, and DNAM. NKG2D is a disulfide-linked homodimer which recognizes a number of ligands, including ULBP and MICA, which are typically expressed on tumor cells.
3. In the humoral response, B cells make antibodies against extracellular pathogens: *a closer look*

- The humoral immune response is initiated when B cells bearing antigen receptors are selected by binding with specific antigens.
- B cells then have the ability to engulf some pathogen/antigen and present them with MHC II’s to Helper T’s, the binding of the two then activating the B cells to a MUCH greater degree than when the B cells only encounter the antigen.
- This is how Helper T’s activate the right B cell.
• Antigens that elicit a humoral immune response are typically the protein and polysaccharide surface components of microbes, incompatible transplanted tissues, or incompatible transfused cells.

• In addition, for some humans, the proteins of foreign substances such as pollen or bee venom acts as antigens that induce an allergic, or hypersensitive humoral response.

• See animation 43.1.4 1:45
• Antibodies constitute a group of globular serum proteins called immunoglobins (Igs).

• A typical antibody molecule has two identical antigen-binding sites specific for the epitope that provokes its production.

• What is an epitope, you ask…
• An antibody interacts with a small, accessible portion of the antigen called an epitope or antigenic determinant.

• A single antigen such as a bacterial surface protein usually has several effective epitopes, each capable of inducing the production of a specific antibody.
• At the two tips of the Y-shaped antibody molecule are the variable regions (V) of the heavy chains and light chains.

• A heavy-chain V region and a light-chain V region together form the unique contours of an antibody’s antigen-binding site.

• Multiple noncovalent bonds form between the antigen-binding site and its epitope.
Fig. 43.15

(a) Basic structure of an antibody molecule

(b) Close-up view of an antigen-binding site with bound antigen
• Analyze this graph to see differences and similarities between the primary and secondary immune responses.
Check out this young man…

• If any of you who are not paying attention right now are instead doing something like what young Jack was doing in his bio class – keep right on doing it.

• [http://www.youtube.com/watch?v=Nq4x8C6Dcf8&feature=youtu.be](http://www.youtube.com/watch?v=Nq4x8C6Dcf8&feature=youtu.be)
1. Immunity can be achieved naturally or artificially

- Immunity conferred by recovering from an infectious disease such as chicken pox is called **active immunity** because it depends on the response of the infected person’s own immune system.

- Active immunity can be acquired naturally, as above, or artificially by **immunization**, also known as **vaccination**.

- In the 1500’s in India a crude vaccination against smallpox was accomplished with pus from sores. Benjamin Jesty, 1774, used cowpox pus to vaccinate his family against smallpox, then in 1798, watch the story of [the first one](#). 8:06

- Vaccines include inactivated toxins, killed microbes, parts of microbes, and viable but weakened microbes.
Unfortunately, not all infectious agents are easily managed by vaccination, and there are dangers such as the risk of being infected by the vaccine as well as side effects such as are suspected with vaccines causing autism. This however, has been shown to NOT BE TRUE!!!! Watch here 12:30

Here’s a link with more detail if we have time. Map http://www.iflscience.com/health-and-medicine/one-map-sums-damage-caused-anti-vaccination-movement


Here’s a history of this vaccine mess. No audio, just data.

Another new study about measles vaccine (handout).
Antibodies can be transferred from one individual to another, providing **passive immunity**.

- This occurs naturally when IgG antibodies of a pregnant woman cross the placenta to her fetus.

- In addition, IgA antibodies are passed from mother to nursing infant in breast milk, especially in early secretions called colostrum.

- Passive immunity persists as long as these antibodies last, a few weeks to a few months.

  - This protects the infant from infections until the baby’s own immune system has matured.
Passive immunity can be transferred artificially by injecting antibodies from an animal that is already immune to a disease into another animal.

- This confers short-term, but immediate protection against that disease.

- For example, a person bitten by a rabid animal may be injected with antibodies against rabies virus because rabies may progress rapidly, and the response to an active immunization could take too long to save the life of the victim.

- Actually, most people infected with rabies virus are given both passive immunizations (the immediate fight) and active immunizations (longer term defense).
Please Be safe.
Do not stand, sit, climb or lean on zoo fences.
If you fall, animals could eat you and that might make them sick.
Thank you.
Let’s revisit Gluten for a good lesson in how complicated things can be….

- https://www.youtube.com/watch?v=3VAQ5pC7w_A

- This features an experiment into possible causes of problems people have after eating wheat products.

- Gluten or FODMAPS. Or….

- 6 min.
In addition to attacking pathogens, the immune system will also attack cells from other individuals.

For example, a skin graft from one person to a nonidentical individual will look healthy for a day or two, but it will then be destroyed by immune responses.

Interestingly, a pregnant woman does not reject the fetus as a foreign body, as apparently, the structure of the placenta is the key to this acceptance.
• ABO blood groups are all about antigens on the surface of RBC’s.
• A person with type A blood already has antibodies to the B antigen, even if the person has never been exposed to type B blood.
  • These antibodies arise in response to bacteria (normal flora) that have epitopes very similar to blood group antigens.
  • Thus, an individual with type A blood does not make antibodies to A-like bacterial epitopes - these are considered self - but that person does make antibodies to B-like bacterial epitopes.
  • If a person with type A blood receives a transfusion of type B blood, the preexisting anti-B antibodies will induce an immediate and devastating transfusion reaction.
Another blood group antigen, the **Rh factor**, can cause mother-fetus problems because antibodies produced to it are IgG.

- This situation arises when a mother that is Rh-negative (lacks the Rh factor) has a fetus that is Rh-positive, having inherited the factor from the father.
- If small amounts of fetal blood cross the placenta as may happen late in pregnancy or during delivery, the mother mounts a T-dependent humoral response against the Rh factor.
- The danger occurs in subsequent Rh-positive pregnancies, when the mother’s Rh-specific memory B cells produce IgG antibodies that can cross the placenta and destroy the red blood cells of the fetus.
• To prevent this, the mother is injected with anti-Rh antibodies after delivering her first Rh positive baby.

• She is, in effect, passively immunized (artificially) to eliminate the Rh antigen before her own immune system responds and generates immunological memory against the Rh factor, endangering her future Rh-positive babies.
The major histocompatibility complex (MHC) is responsible for stimulating the rejection of tissue grafts and organ transplants.

- Because MHC creates a unique protein fingerprint for each individual, foreign MHC molecules are antigenic, inducing immune responses against the donated tissue or organ.

- To minimize rejection, attempts are made to match MHC of tissue donor and recipient as closely as possible.

  - In the absence of identical twins, siblings usually provide the closest tissue-type match.
In addition to MHC matching, various medicines are necessary to suppress the immune response to the transplant.

- Cyclosporin was one of the first.

- However, this strategy leaves the recipient more susceptible to infection and cancer during the course of treatment.

- More selective drugs, which suppress helper T cell activation without crippling nonspecific defense or T-independent humoral responses, have greatly improved the success of organ transplants.
• In bone marrow transplants, it is the graft itself, rather than the host, that is the source of potential immune rejection.

• Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological diseases.

• Prior to the transplant, the recipient is typically treated with irradiation to eliminate the recipient’s immune system, leaving little chance of graft rejection.

• However, the donated marrow, containing lymphocytes, may react against the recipient, producing graft versus host reaction, unless well matched.
• Allergies are hypersensitive (exaggerated) responses to certain environmental antigens, called allergens.

• One hypothesis to explain the origin of allergies is that they are evolutionary remnants of the immune system’s response to parasitic worms.

• The humoral mechanism that combats worms is similar to the allergic response that causes such disorders as hay fever and allergic asthma.
• The most common allergies involve antibodies of the IgE class, which can attach to Mast cells.

• Later, when pollen grains enter the body, they attach to the antigen-binding sites of mast cell-associated IgE, cross-linking adjacent antibody molecules.
• This event triggers the mast cell to *degranulate* - that is, to release histamines and other inflammatory agents from vesicles called granules.

Fig. 43.18
• High levels of histamines cause dilation and increased permeability of small blood vessels.

• These inflammatory events lead to typical allergy symptoms: sneezing, runny nose, tearing eyes, and smooth muscle contractions that can result in breathing difficulty.

• Antihistamines diminish allergy symptoms by blocking receptors for histamine.
Sometimes, an acute allergic response can result in **anaphylactic shock**, a life threatening reaction to injected or ingested allergens.

- Anaphylactic shock results when widespread mast cell degranulation triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure.
  - Death may occur within minutes.

- Triggers of anaphylactic shock in susceptible individuals include bee venom, penicillin, or foods such as peanuts or fish.

- Some hypersensitive individuals carry syringes with epinephrine, which counteracts this allergic response.
• Sometimes the immune system loses tolerance for self and turns against certain molecules of the body, causing one of many autoimmune diseases.

• In systemic lupus erythematosus (lupus), the immune system generates antibodies against all sorts of self molecules, including histamines.

  • Lupus is characterized by skin rashes, fever, arthritis, and kidney dysfunction.

• Rheumatoid arthritis leads to damage and painful inflammation of the cartilage and bone of joints.

• In insulin-dependent diabetes mellitus, the insulin-producing beta cells of the pancreas are the targets of autoimmune cell-mediated responses.
• *Multiple sclerosis (MS)* is the most common chronic neurological disease in developed countries,

• In MS, T cells reactive against myelin infiltrate the central nervous system and destroy the myelin of neurons.

• People with MS experience a number of serious neurological abnormalities.
4. AIDS is an immunodeficiency disease caused by a virus

- In 1981, increased rates of two rare diseases, Kaposi’s sarcoma, a cancer of the skin and blood vessels, and pneumonia caused by the protozoan *Pneumocystis carinii*, were the first signals to the medical community of a new threat to humans, later known as acquired immunodeficiency syndrome, or AIDS.

  - Both conditions were previously known to occur mainly in severely immunosuppressed individuals.

  - People with AIDS are susceptible to *opportunistic diseases*. 
In 1983, a retrovirus, now called human immunodeficiency virus (HIV), had been identified as the causative agent of AIDS.
• With the AIDS mortality close to 100%, HIV is the most lethal pathogen ever encountered.

• Molecular studies reveal that the virus probably evolved from another HIV-like virus in chimpanzees in central Africa and appeared in humans sometimes between 1915 and 1940.

• These first rare cases of infection and AIDS went unrecognized.
• There are two major strains of the virus, HIV-1 and HIV-2.
  • HIV-1 is the more widely distributed and more virulent.
• Both strains infect cells that bear CD4 molecules, especially helper T cells and class II MCH-bearing antigen-presenting cells, but also macrophages, some lymphocytes and some brain cells.
  • CD4 functions as the major receptor for the virus.
  • Here’s how it works  5 min.
• Once inside a cell, HIV RNA is reverse-transcribed, and the product DNA is integrated into the host genome. (Remember this is how retroviruses work)

• In this provirus form, the viral genome directs the production of new virus particles.
Let’s analyze this graph...
• The time required for an HIV infection to progress from severe helper T cell depletion to AIDS varies greatly, but it currently averages about ten years.

• During most of this time, the individual exhibits only moderate hints of illness, such as swollen lymph nodes and occasional fever.
• At this time, HIV infection cannot be cured, and the progression to AIDS cannot be prevented.

• New, expensive drug therapies can slow this progression.
  
  • These drugs slow viral replication by inhibiting DNA synthesis, reverse transcriptase, and protease.
    
    • Protease inhibitors prevents a key step in the synthesis of HIV proteins.
  
  • Combinations of these drugs decrease viral load and therefore allow the number of helper T cells to rise.

• Other drugs treat the myriad of opportunistic diseases as they develop. Good time for a video clip, eh? 2 min.
Transmission of HIV requires the transfer of body fluids containing infected cells, such as semen or blood, from person to person.

Unprotected sex (that is, without a condom) among male homosexuals and transmission via nonsterile needles (typically among intravenous drug users) account for most of the AIDS cases reported thus far in the United States and Europe.

However, transmission of HIV among heterosexuals is rapidly increasing as a result of unprotected sex with infected partners.

In Africa and Asia, transmission has been primarily by heterosexual sex, especially where there is a high incidence of genital lesions from other diseases.
• HIV is not transmitted by casual contact.

• So far, only one case of HIV transmission by kissing has been reported, and both individuals had bleeding gums.

• Transmission of HIV from mother to child can occur during fetal development or during nursing.

• HIV screening has virtually eliminated blood transfusions as a route of transmission in developed countries.
• The best approach for slowing the spread of HIV is to educate people about the practices that transmit the disease, such as using nonsterile needles and having sex without a condom.

• Although condoms do not completely eliminate the risk of transmitting HIV (or other similar transmitted viruses, such as the hepatitis B virus), they do reduce it.

• Any individual who has sex - vaginal, oral, or anal - with a partner who had unprotected sex with another person during the past three decades risks exposure to HIV. You effectively have sex with everyone your partner has.

• **Vaccine, someday??**
Now, if you have time,

- See this [new genetic engineering](#) involving HIV and leukemia. 3:40

- Navigate through this. It is a great combination of many things you have learned about genetics.

- [Here it is](#). Link to Lessons and Media, then Media.