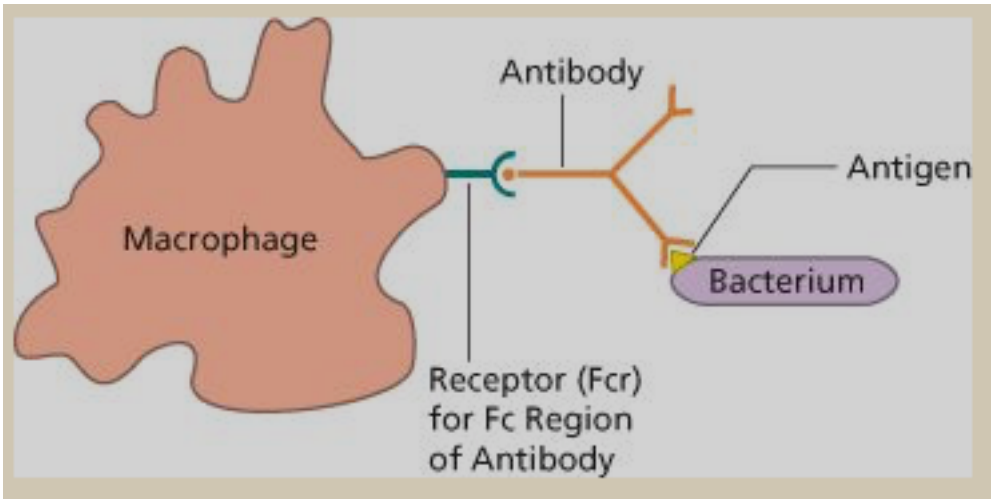
What Antibodies Do

Interestingly, although antibodies are very important in the defense against invaders, they really don't kill anything. Their job is to plant the "kiss of death" on an invader – to tag it for destruction. If you go to a fancy wedding, you'll usually pass through a receiving line before you are allowed to enjoy the champagne and cake. Of course, one of the functions of this receiving line is to introduce everyone to the bride and groom. But the other function is to be sure no outsiders are admitted to the celebration. As you pass through the line, you will be screened by someone who is familiar with all the invited guests. If she finds that you don't belong there, she will call the bouncer and have you removed. She doesn't do it herself – certainly not. Her role is to identify undesirables, not to show them to the door. And it's the same with antibodies: they identify invaders, and let other players do the dirty work.



In developed countries, the invaders we encounter most frequently are bacteria and viruses. Antibodies can bind to both types of invaders and tag them for destruction. Immunologists like to say that antibodies can "opsonize" these invaders. This term comes from a German word that means "to prepare for eating." I like to equate opsonize with "decorate," because I picture these bacteria and viruses with antibodies hanging all over them, decorating their surfaces. Anyway, when antibodies opsonize bacteria or viruses, they do so by binding to the invader with their Fab regions, leaving their Fc tails available to bind to Fc receptors on the surface of cells such as macrophages. Using this strategy, antibodies can form a bridge between the invader and the phagocyte (e.g., a macrophage), bringing the invader in close, and preparing it for eating (phagocytosis). In fact, it's even better than this. When a phagocyte's Fc receptors bind to antibodies that are opsonizing an invader, the appetite of the phagocyte increases, making it even more phagocytic. Macrophages have proteins on their surface that can bind directly to many common invaders.

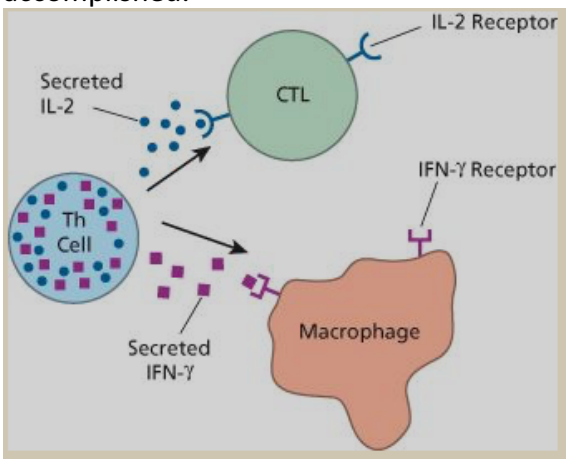
However, the ability of antibodies to form a bridge between a macrophage and an invader allows a macrophage to increase its catalog of enemies to include any invader to which an antibody can bind, common or uncommon. In effect, antibodies focus a macrophage's attention on invaders, some of which (the uncommon ones) a macrophage would otherwise ignore. During a viral attack, antibodies can do something else that is very important. Viruses enter our

cells by binding to certain receptor molecules on a cell's surface. Of course these receptors are not placed there for the convenience of the virus. They are normal receptors, like the Fc receptor, that have quite legitimate functions, but which the virus has learned to use to its own advantage. Once it has bound to these receptors and entered a cell, a virus then uses the cell's machinery to make many copies of itself. These newly made viruses burst out of the cell, sometimes killing it, and go on to infect neighboring cells. Now for the neat part: antibodies can actually bind to a virus while it is still outside of a cell, and can keep the virus either from entering the cell or from replicating once it has entered. Antibodies with these properties are called "neutralizing" antibodies. For example, some neutralizing antibodies can prevent a virus from "docking" on the surface of a cell by binding to the part of the virus that normally would plug into the cellular receptor. When this happens, the virus is "hung out to dry," opsonized and ready to be eaten by phagocytes!

T CELLS

Although antibodies can tag viruses for phagocytic ingestion, and can help keep viruses from infecting cells, there is a flaw in the antibody defense against viruses: once a virus gets into a cell, antibodies can't get to it, so the virus is safe to make thousands of copies of itself. Mother Nature recognized this problem, and to deal with it, she invented the famous "killer T cell," another member of the adaptive immune system team. The importance of T cells is suggested by the fact that an adult human has about 300 billion of them. T cells are very similar to B cells in appearance. In fact, even under an ordinary microscope, an immunologist can't tell them apart. Like B cells, T cells are produced in the bone marrow, and on their surface they display antibody-like molecules called T cell receptors (TCRs). Like the B cell's receptors (the antibody molecules attached to its surface), TCRs also are made by a mix-and-match, modular design strategy. As a result, TCRs are about as diverse as BCRs. T cells also obey the principle of clonal selection: when a T cell's receptors bind to their cognate antigen, the T cell proliferates to build up a clone of T cells with the same specificity. This proliferation stage takes about a week to complete, so like the antibody response, the T cell response is slow and specific. Although they are similar in many ways, there are also important differences between B cells and T cells. Whereas B cells mature in the bone marrow, T cells mature in the thymus (that's why they're called "T" cells). Further, although B cells make antibodies that can recognize any organic molecule, T cells specialize in recognizing protein antigens. In addition, a B cell can export (secrete) its receptors in the form of antibodies, but a T cell's receptors remain tightly glued to its surface. Perhaps most importantly, a B cell can recognize an antigen "by itself," whereas a T cell, like an old English gentleman, will only recognize an antigen if it is "properly presented" by another cell. I'll explain what this means in a bit. There are actually three main types of T cells: killer T cells (frequently called cytotoxic lymphocytes – CTLs for short), helper T cells, and regulatory T cells. The killer T cell is a potent weapon that can destroy virus-infected cells. Indeed, by recognizing and killing virus-infected cells, the killer T cell solves the "hiding virus" problem – the flaw I mentioned in the antibody defense against viruses. The way the killer T cell does this is by making contact with its target cell and then triggering it to commit suicide! This "assisted suicide" is a great way to deal with viruses that have infected cells, because when a virus-infected cell dies, the viruses within the cell die also. The second type of T cell is the helper T cell (Th cell). As you will see, this cell serves as the quarterback of the immune system

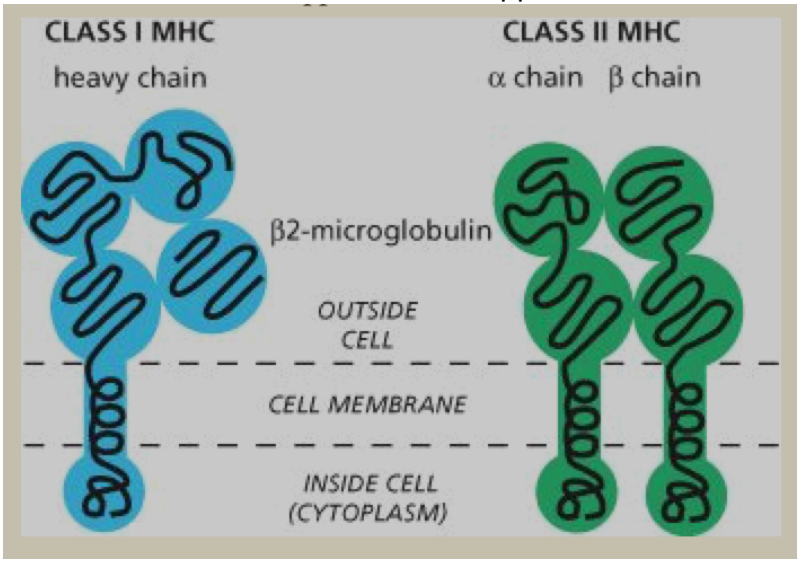
team. It directs the action by secreting protein molecules called cytokines that have dramatic B cells mature in the bone marrow, T cells mature in the thymus (that's why they're called "T" cells). Further, although B cells make antibodies that can recognize any organic molecule, T cells specialize in recognizing protein antigens. In addition, a B cell can export (secrete) its receptors in the form of antibodies, but a T cell's receptors remain tightly glued to its surface. Perhaps most importantly, a B cell can recognize an antigen "by itself," whereas a T cell, like an old English gentleman, will only recognize an antigen if it is "properly presented" by another cell. I'll explain what this means in a bit. There are actually three main types of T cells: killer T cells (frequently called cytotoxic lymphocytes – CTLs for short), helper T cells, and regulatory T cells. The killer T cell is a potent weapon that can destroy virus-infected cells. Indeed, by recognizing and killing virus-infected cells, the killer T cell solves the "hiding virus" problem – the flaw I mentioned in the antibody defense against viruses. The way the killer T cell does this is by making contact with its target cell and then triggering it to commit suicide! This "assisted suicide" is a great way to deal with viruses that have infected cells, because when a virus-infected cell dies, the viruses within the cell die also. The second type of T cell is the helper T cell (Th cell). As you will see, this cell serves as the quarterback of the immune system team. It directs the action by secreting protein molecules called cytokines that have dramatic effects on other immune system cells. These cytokines have names like interleukin 2 (IL-2) and interferon gamma (IFN-γ), and we will discuss what they do in later lectures. For now, it is only important to realize that helper T cells are basically cytokine factories. The third type of T cell, the regulatory T cell, is still somewhat mysterious. The role of regulatory T cells is to help keep the immune system from overreacting. However, in some cases, it is not clear how this is accomplished.



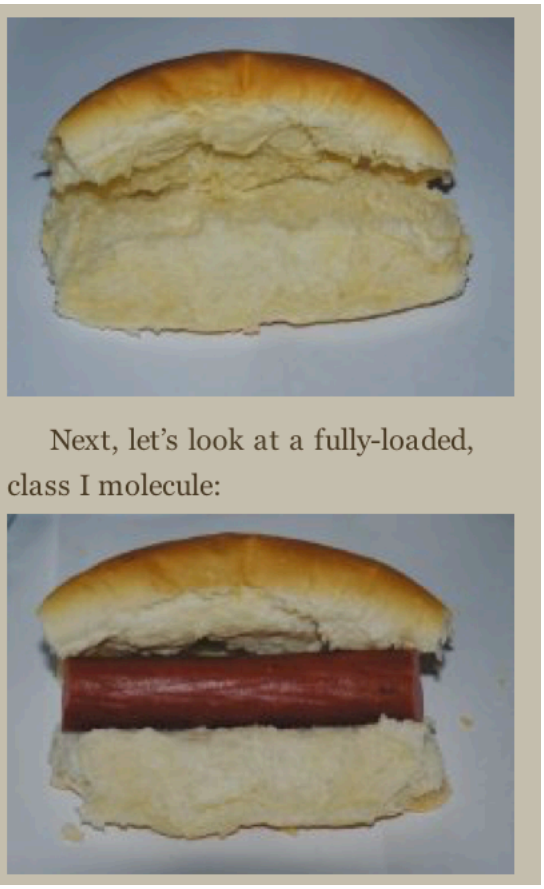
Antigen Presentation

One thing I need to clear up is exactly how antigen is presented to T cells. It turns out that special proteins called major histocompatibility complex proteins (MHC for short) actually do the "presenting," and that T cells use their receptors to "view" this presented antigen. As you may know, "histo" means tissue, and these major histocompatibility proteins, in addition to being presentation molecules, also are involved in the rejection of transplanted organs. In fact, when you hear that someone is waiting for a "matched" kidney, it's the MHC molecules of the donor and the recipient that the transplant surgeon is trying to match.

There are two types of MHC molecules, called class I and class II. Class I MHC molecules are found in varying amounts on the surface of most cells in the body, and they function as "billboards" that inform killer T cells about what is going on inside these cells. For example, when a human cell is infected by a virus, fragments of viral proteins (called peptides) are loaded onto class I MHC molecules, and transported to the surface of the infected cell. By inspecting these protein fragments displayed by class I MHC molecules, killer T cells can use their receptors to "look into" the cell to determine that it has been infected and that it should be destroyed. Class II MHC molecules also function as billboards, but this display is intended for the enlightenment of helper T cells. Only certain cells in the body make class II MHC molecules, and these are called antigen presenting cells (APCs for short). Macrophages, for example, are excellent antigen presenting cells. During a bacterial infection, a macrophage will "eat" bacteria, and will load fragments of ingested bacterial proteins onto class II MHC molecules for display on the surface of the macrophage. By using their T cell receptors, helper T cells can scan the macrophage's class II MHC billboards for news of the bacterial infection. So class I MHC molecules alert killer T cells when something isn't right inside a cell, and class II MHC molecules displayed on APCs inform helper T cells that problems exist outside of cells. Although a class I MHC molecule is made up of one long chain (the heavy chain) plus a short chain (β2-microglobulin), and a class II MHC molecule has two long chains (α and β), you'll notice that these molecules are rather similar in appearance.



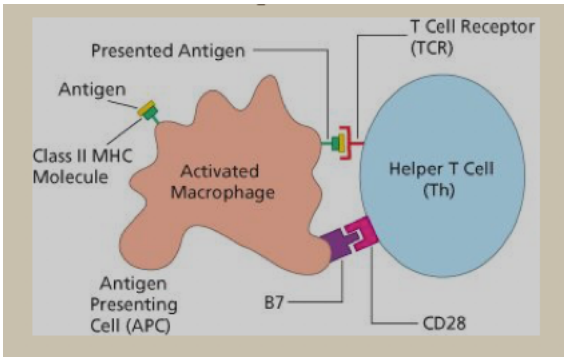
I know it's hard to visualize the real shapes of molecules from drawings like this, so I thought I'd show you a few pictures that may make this more real. Here's what an empty MHC molecule might look like from the viewpoint of the T cell receptor. Right away you see the groove into which the protein fragment would fit.



I can tell it's a class I MHC molecule because the peptide is contained nicely within the groove. It turns out that the ends of the groove of a class I molecule are closed, so a protein fragment must be about nine amino acids in length to fit in properly. Class II MHC molecules are slightly different:

Here you see that the peptide overflows the groove. This works fine for class II, because the ends of the groove are open, so protein fragments as large as about 20 amino acids fit nicely. So MHC molecules resemble buns, and the protein fragments they present resemble wieners. And if you imagine that the cells in our bodies have hot dogs on their surfaces, you won't be far wrong about antigen presentation. That's certainly the way I picture it! Activation of the

Adaptive Immune System Because B and T cells are such potent weapons, Mother Nature put into place the requirement that cells of the adaptive immune system must be activated before they can function. Collectively, B and T cells are called lymphocytes, and how they are activated is one of the key issues in immunology. To introduce this concept, I will sketch how helper T cells are activated. The first step in the activation of a helper T cell is recognition of its cognate antigen (e.g., a fragment of a bacterial protein) displayed by class II MHC molecules on the surface of an antigen presenting cell. But seeing its cognate antigen on that billboard isn't enough – a second signal or "key" is also required for activation. This second signal is non-specific (it's the same for any antigen), and it involves a protein (B7 in this drawing) on the surface of an antigen presenting cell that plugs into its receptor (CD28 in this drawing) on the surface of the helper T cell.

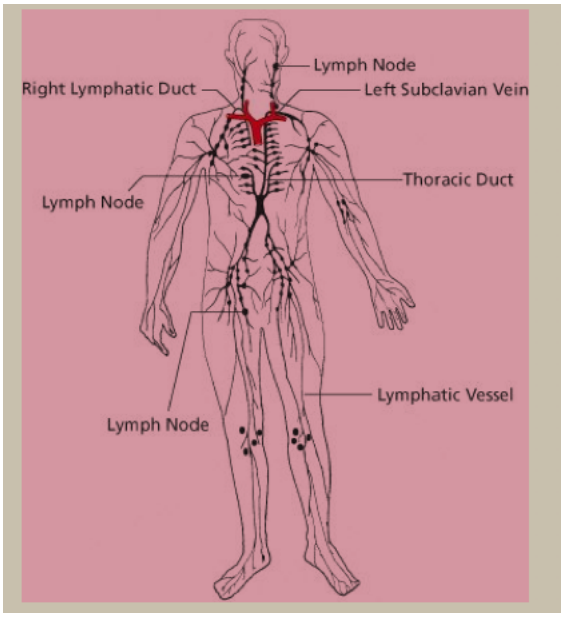


You see an example of this kind of two-key system when you visit your safe deposit box. You bring with you a key that is specific for your box – it won't fit any other. The bank teller provides a second, non-specific key that will fit all the boxes. Only when both keys are inserted into the locks on your box can it be opened. Your specific key alone won't do it, and the teller's non-specific key alone won't either. You need both. Now, why do you suppose helper T cells and other cells of the adaptive immune system require two keys for activation? For safety, of course – just like your bank box. These cells are powerful weapons that must only be activated at the appropriate time and place. Once a helper T cell has been activated by this two-key system, it proliferates to build up a clone composed of many helper T cells whose receptors recognize the same antigen. These helper cells then mature into cells that can produce the cytokines needed to direct the activities of the immune system. B cells and killer T cells also require two-key systems for their activation, and we'll talk about them in another lecture.

The Secondary Lymphoid Organs

If you've been thinking about how the adaptive immune system might get turned on during an attack, you've probably begun to wonder whether this could ever happen. After all, there are probably only about 10 000 T cells that will have TCRs specific for a given invader, and for these T cells to be activated, they must come in contact with an antigen presenting cell that also has "seen" the invader. Given that these T cells and APCs are spread all over the body, it would not seem very likely that this would happen before an invasion got completely out of hand. Fortunately, to make this system work with reasonable probability, Mother Nature invented the "secondary lymphoid organs," the best known of which is the lymph node. You may not be

familiar with the lymphatic system, so I'd better say a few words about it. In your home, you have two plumbing systems. The first supplies the water that comes out of your faucets. This is a pressurized system, with the pressure being provided by a pump. In addition, you also have another plumbing system that includes the drains in your sinks, showers, and toilets. This second system is not under pressure – the water just flows down the drain and out into the sewer. The two systems are connected in the sense that eventually the waste-water is recycled and used again. The plumbing in a human is very much like this. We have a pressurized system (the cardiovascular system) in which blood is pumped around the body by the heart. Everybody knows about this one. But we also have another plumbing system: the lymphatic system. This system is not under pressure, and it drains the fluid (lymph) that leaks out of our blood vessels into our tissues. Without this system, our tissues would fill up with fluid and we'd look like the Pillsbury Doughboy. Fortunately, lymph is collected from the tissues of our lower body into lymphatic vessels, and is transported by these vessels, under the influence of muscular contraction, through a series of one-way valves to the upper torso. This lymph, plus lymph from the left side of the upper torso, is collected into the thoracic duct and emptied into the left subclavian vein to be recycled back into the blood. Likewise, lymph from the right side of the upper body is collected into the right lymphatic duct and is emptied into the right subclavian vein. From this diagram, you can see that as the lymph winds its way back to be reunited with the blood, it passes through a series of way stations – the lymph nodes.



There are thousands of lymph nodes that range in size from very small to almost as big as a Brussels sprout. Invaders like bacteria and viruses are carried by the lymph to nearby nodes, and antigen presenting cells that have picked up foreign antigens in the tissues travel to lymph nodes to present their cargo. Meanwhile, B cells and T cells circulate from node to node, looking for the antigens for which they are "fated." So lymph nodes really function as "dating bars" – places where T cells, B cells, APCs, and antigen all gather for the purposes of communication and activation. By bringing these cells and antigens together within the small volume of a lymph node, Mother Nature increases the probability that they will interact to

efficiently activate the adaptive immune system. Immunological Memory After B and T cells have been activated, have proliferated to build up clones of cells with identical antigen specificities, and have vanquished the enemy, most of them die off. This is a good idea, because we wouldn't want our immune systems to fill up with old B and T cells.

On the other hand, it would be nice if some of these experienced B and T cells would stick around, just in case we are exposed to the same invaders again. That way, the adaptive immune system wouldn't have to start from scratch. And that's just the way it works. These "leftover" B and T cells are called memory cells, and in addition to being more numerous than the original, inexperienced B and T cells, memory cells are easier to activate. As a result of this immunological memory, the adaptive system usually can spring into action so quickly during a second attack that you never even experience any symptoms.

Tolerance of Self

As I mentioned earlier, B cell receptors and T cell receptors are so diverse that they should be able to recognize any potential invader. This raises a problem, however, because if the receptors are this diverse, many of them are certain to recognize our own "self" molecules (e.g., the molecules that make up our cells, or proteins like insulin that circulate in our blood). If this were to happen, our adaptive immune system might attack our own bodies, and we could die from autoimmune disease. Fortunately, Mother Nature has devised ways to educate B cells and T cells to discriminate between ourselves and dangerous invaders. Although the mechanisms involved in teaching B and T cells to be tolerant of our self antigens still are not completely understood, the education which B and T cells receive is sufficiently rigorous that autoimmune disease is relatively rare.

A COMPARISON OF THE INNATE AND ADAPTIVE IMMUNE SYSTEMS

Now that you have met some of the main players, I want to emphasize the differences between the innate and adaptive immune system "teams." Understanding how they differ is crucial to understanding how the immune system works. Imagine that you are in the middle of town and someone steals your shoes. You look around for a store where you can buy another pair, and the first store you see is called Charlie's Custom Shoes. This store has shoes of every style, color, and size, and the salesperson is able to fit you in exactly the shoes you need. However, when it comes time to pay, you are told that you must wait a week or two to get your shoes – they will have to be custom-made for you, and that will take a while. But you need shoes right now! You are barefoot, and you must have something to put on your feet until those custom shoes arrive. So they send you across the street to Freddie's Fast Fit – a store that only carries a few styles and sizes. Freddie's wouldn't be able to fit Shaquille O'Neal, but this store does stock shoes in the common sizes that fit most people – so you can get a pair right away to tide you over until your custom shoes are made for you. This is very similar to the way the innate and adaptive immune systems work. The players of the innate system (like the macrophage) are already in place, and are ready to defend against relatively small quantities of the invaders we are likely to meet on a day-to-day basis. In many instances, the innate system is so effective and so fast that the adaptive immune system never even kicks in. In other cases, the innate system

may be insufficient to deal with the invasion, and the adaptive system will need to be mobilized. This takes a while, however, because the B and T cells of the adaptive system must be custom-made through the process of clonal selection and proliferation. Meanwhile, the innate immune system must do its best to hold the invaders at bay.

THE INNATE SYSTEM RULES!

Until fairly recently, immunologists thought that the only function of the innate system was to provide a rapid defense which would deal with invaders while the adaptive immune system was getting cranked up. However, it is now clear that the innate system does much more than that. The adaptive immune system's antigen receptors (BCRs and TCRs) are so diverse that they can probably recognize any protein molecule in the universe. However, the adaptive system is clueless as to which of these molecules is dangerous and which is not. So how does the adaptive system distinguish friend from foe? The answer is that it relies on the judgment of the innate system. In contrast to the antigen receptors of the adaptive immune system, which are totally "unfocused," the receptors of the innate system are precisely tuned to detect the presence of the common pathogens (disease-causing agents) we encounter in daily life – viruses, bacteria, fungi, and parasites. In addition, the innate system has receptors that can detect when "uncommon" pathogens kill human cells. Consequently, it is the innate system which is responsible for sensing danger and for activating the adaptive immune system. In a real sense, the innate system gives "permission" to the adaptive system to respond to an invasion. But it's even better than that, because the innate system does more than just turn the adaptive system on. The innate system actually integrates all the information it collects about an invader, and formulates a plan of action. This "game plan," which the innate system delivers to the adaptive immune system, tells which weapons to mobilize (e.g., B cells or killer T cells) and exactly where in the body these weapons should be deployed. So if we think of the helper T cell as the quarterback of the adaptive immune system team, we should consider the innate immune system to be the "coach" – for it is the innate system which "scouts" the opponents, designs the game plan, and sends in the plays for the quarterback to call. EPILOGUE We have come to the end of our turbo overview of the immune system, and by now you should have a rough idea of how the system works. In the next nine lectures, we will focus more sharply on the individual players of the innate and adaptive system teams, paying special attention to how and where these players interact with each other to make the system function efficiently.