JANEWAY'S IMMUNOBIOLOGY, 9TH EDITION
CHAPTER 1: BASIC CONCEPTS IN IMMUNOLOGY

The origins of vertebrate immune cells

1.1 **Multiple choice:** In patients with lymphomas, the cancer cells invade the bone marrow and destroy the environment required for normal hematopoiesis. This leads to bone marrow failure, which disrupts the production of hematopoietic cell lineages. All of the following cell types would be affected by this EXCEPT:

A. Red blood cells
B. Macrophages
C. Lymphocytes
D. Endothelial cells
E. Granulocytes

Principles of innate immunity

1-1 Commensal organisms cause little host damage while pathogens damage host tissues by a variety of mechanisms

1.2 **True/False:** Our immune system efficiently kills all categories of microbes that attempt to colonize our bodies.

1.3 **Short answer:** Pathogenic organisms cause damage to the host by a variety of mechanisms, depending on the category of the pathogen and its mode of replication in the host. Give an example of two different types of pathogens that are unlikely to be dealt with by the same mechanism of immune protection.

1-2 Anatomic and chemical barriers are the first defense against pathogens

1.4 **Multiple choice:** The skin and bodily secretions provide the first line of defense against infection. One response in this category that is common during upper respiratory virus infections is:

A. Production of antibodies
B. Infiltration by white blood cells
C. Mucus production
D. Increased saliva production
E. Fever

1-3 The immune system is activated by inflammatory inducers that indicate the presence of pathogens or tissue damage

1.5 **Short answer:** A common mechanism by which sensor cells in the host detect micro-organisms relies on the production of unique microbial components not found in the host. Propose a strategy by which a clever microbe could evade this type of response.

1.6 **Multiple choice:** Adaptive immune responses are slow to develop, taking days to weeks after exposure to reach their peak. However, these responses are more specific than innate responses, and also generate immunological memory. These latter features, which provide enhanced protection upon re-infection with the same pathogen, are the basis of:

A. Vaccines
B. Antibiotics
C. Systemic shock
D. Complement activation
E. Phagocytosis

1-4 The myeloid lineage comprises most of the cells of the innate immune system

1.7 **True/False:** In the absence of an infection, most granulocytes (neutrophils, eosinophils, basophils) are found circulating in the blood, whereas other subsets of myeloid cells reside in tissues.

1.8 **Short answer:** Dendritic cells are phagocytic, but also capable of ingesting large amounts of extracellular fluid and its contents, a process known as macropinocytosis. What specialized function do dendritic cells have in immunity that might account for their need to perform macropinocytosis?

1-5 Sensor cells express pattern recognition receptors that provide an initial discrimination between self and nonself

1.9 **Multiple choice:** Some Pattern Recognition Receptors (PRRs) recognize nucleic acids, like RNA or DNA. Since our own cells contain human RNA and DNA, the activation of innate immune pathways by these PRRs must rely on additional criteria to discriminate self from nonself. Additional criteria include everything EXCEPT:

A. The subcellular location of the RNA
B. The presence of adenosine residues in viral RNA
C. The methylation state of the DNA
D. Unique structures found on viral RNA
E. The subcellular location of the DNA

1-6 Sensor cells induce an inflammatory response by producing mediators such as chemokines and cytokines

1.10 **Multiple choice:** When macrophages in a tissue encounter bacteria, they release cytokines that induce an inflammatory response. These cytokines act on other immune cells, to recruit them to the site of infection and to enhance their activities. In addition, these cytokines act on the endothelial cells of the blood vessel wall to:

A. Increase their permeability, allowing fluid and proteins to leak into the tissue
B. Solidify the tight junctions to prevent the bacteria from entering the blood
C. Proliferate, allowing the blood vessel to enlarge
D. Up-regulate microbicidal mechanisms, so they can kill bacteria
E. Secrete anti-microbial peptides

1.11 **Short answer:** A common characteristic of a site of infection, such as a pimple on the skin, is pus. What is responsible for the white color of pus?

1-7 Innate lymphocytes and natural killer cells are effector cells that share similarities with lymphoid lineages of the adaptive immune system

1.12 **True/False:** Innate lymphoid cells and NK cells are effector cells that respond rapidly after encountering a pathogen. Several different subsets of innate lymphoid cells exist, and each is specialized to respond to a category of pathogen (e.g., viruses, extracellular bacteria, helminthic parasites, etc). Innate lymphoid cells reside primarily in tissues such as the lungs, the lining of the gastrointestinal tract, and the skin, because these sites represent the major routes of entry of pathogens into the body.

Principles of adaptive immunity

1-8 The interaction of antigens with antigen receptors induces lymphocytes to acquire effector and memory activity

1.13 **Short answer:** Most B and T lymphocytes in the circulation appear as small, inactive cells, with little cytoplasm, few cytoplasmic organelles, and nuclei containing condensed inactive chromatin. Yet these cells comprise the adaptive immune response, without which individuals die in infancy. What is the explanation for this apparent dichotomy?

1.14 **Multiple choice:** Given the enormous heterogeneity of antigen receptors expressed on the populations of naive B and T lymphocytes, the adaptive immune response relies on a process whereby the rare lymphocyte that binds to the antigen is first induced to proliferate, before it can perform its effector function. For B cells, there is a clever mechanism that ensures that the specificity of the antibody secreted by the plasma cell will recognize the same pathogen that initially stimulated the B cell antigen receptor and induced B cell proliferation. This mechanism is:

A. The naive B cell expresses an array of different B cell antigen receptors, and randomly chooses which specificity of antibody to secrete as a plasma cell.
B. The naive B cell expresses a single specificity of B cell antigen receptor, and then up-regulates the expression of this receptor so it can bind tightly to the pathogen.
C. The plasma cell proliferates after it has finished secreting antibody to generate more plasma cells with specificity for the pathogen.
D. The plasma cell traps secreted antibody molecules in its extracellular matrix and uses these antibodies to bind to the pathogen.
E. The naive B cell expresses a membrane-bound form of the antibody as a receptor, and secretes that same antibody when it differentiates into a plasma cell.

1.15 **Multiple choice:** Unlike B lymphocytes, T lymphocytes do not generate a secreted form of their antigen receptor after they are activated and proliferate. This is because the effector functions of T cells are restricted to:

A. Responses important in protozoan infections, but not other types of infections

B. Interactions with large helminthic parasites, which cannot be phagocytosed
C. Interactions with other cells, such as virus-infected cells or other immune cells
D. Responses important in mucosal surfaces (e.g., the lung), where antibodies cannot go
E. Stimulating B cells and not any other types of cells

1-9 Antibodies and T-cell receptors are composed of constant and variable regions that provide distinct functions

1.16 **Short answer:** The antibody protein is often depicted as an uppercase letter Y, with the two variable regions (antigen-binding domains) pointing up, and the stem consisting of the Fc region (constant domain). An analogy has been made between an antibody protein and a guided missile, with one type of antibody domain functioning as the guidance system, and the other type of domain as the 'payload.' Which antibody domain serves as the guidance system, and which as the payload? Explain your answer.

1-10 Antibodies and T-cell receptors recognize antigens by fundamentally different mechanisms

1.17 **Multiple choice:** The antigen receptor on a T cell recognizes a degraded fragment of a protein (i.e., a peptide) bound to a specialized cell surface peptide-binding receptor called an MHC molecule. One key aspect of this system is that the peptides displayed on MHC molecules can be derived from intracellular proteins. This mode of antigen recognition is particularly important in allowing the adaptive immune response to detect infections by:
A. Large helminthic parasites in the gastrointestinal tract
B. Intracellular pathogens, such as viruses and some protozoa
C. Extracellular bacteria that colonize the lungs
D. Fungi that form hyphae in the bronchial airways
E. Fungal infections in the skin epithelium

1-11 Antigen-receptor genes are assembled by somatic gene rearrangements of incomplete receptor gene segments

1.18 **Short answer:** In the 1970s, immunologists discovered the genetic mechanism allowing a population of B cells to produce an enormous diversity of different antibodies. At the time, this discovery shocked the field of biology, as it called into question the 'immutable' nature of DNA, which was known to be the genetic material transmitted from generation to generation during the propagation of the species. Briefly describe this startling mechanism.

1-12 Lymphocytes activated by antigen give rise to clones of antigen-specific effector cells that mediate adaptive immunity

1.19 **True/False:** For cells of the innate immune system, each individual cell has multiple pattern recognition receptors, and can recognize many different pathogens. In contrast, cells of the adaptive immune system each express only a single antigen receptor, and have a single specificity for pathogen recognition.

1.20 **Multiple choice:** The clonal selection theory was first proposed in the 1950s, decades before the molecular details of B and T lymphocyte development and lymphocyte antigen recognition responses were elucidated. Nonetheless, Burnet, who proposed this theory, correctly inferred several key aspects of adaptive immune responses. One key postulate that Burnet proposed was that:

A. Cells of the innate immune system are distinct from those of the adaptive immune system.
B. Cells of the adaptive immune system are generated from a pluripotent hematopoietic stem cell that resides in the bone marrow.
C. B and T lymphocytes are closely related cells that have distinct properties from myeloid cells.
D. Circulating antibodies are generated by many different antibody-secreting cells, each of which expresses a single type of antibody on its surface as a receptor.
E. Antibodies binding to pathogens lead to efficient pathogen clearance by phagocytic cells.

1-13 Lymphocytes with self-reactive receptors are normally eliminated during development or are functionally inactivated

1.21 **Multiple choice:** The pattern recognition receptors on cells of the innate immune system are genetically encoded, meaning that their sequences and specificities are determined prior to the development of the individual. In contrast, the antigen receptors of B and T lymphocytes arise from a random rearrangement process that occurs differently in each lymphocyte as it develops. One potential problem entailed by the random process that generates lymphocyte antigen receptors is the possibility that:

A. Some antigen receptors might recognize the individuals on cells or antigens
B. Many lymphocytes might generate antigen receptors that don't recognize anything
C. Many lymphocytes might generate antigen receptors that recognize multiple different pathogens
D. Some antigen receptors might recognize foreign tissues and lead to graft rejection during organ transplantation
E. Some lymphocytes might not generate functional antigen receptor proteins

1-14 Lymphocytes mature in the bone marrow or the thymus and then congregate in lymphoid tissues throughout the body

1.22 **Multiple choice:** Secondary (or peripheral) lymphoid organs are sites for initiation of adaptive immune responses. Given the rarity of lymphocytes specific for any given antigen and the vast amount of body tissue that must be protected, the system of secondary lymphoid tissues is efficient because:

A. It concentrates antigens in centralized locations for rare lymphocytes to encounter
B. It provides the optimal environment for the rapid proliferation of lymphocytes
C. It traps the pathogens and antigens in a contained environment so they cannot spread to other tissues in the body

D. It helps the innate immune cells eliminate the infection by using lymphatic fluid to drain pathogens from the infected tissue
E. It filters the lymph fluid and removes pathogenic organisms before they can enter the bloodstream

1-15 Adaptive immune responses are initiated by antigen and antigen-presenting cells in secondary lymphoid tissues

1.23 Short answer: Dendritic cells, also called 'antigen-presenting-cells' are considered the bridge between the innate and the adaptive immune responses. Describe two key features of dendritic cells that are essential for them to provide this bridging function.

1-16 Lymphocytes encounter and respond to antigen in the peripheral lymphoid organs

1.24 Multiple choice: Lymph nodes function as meeting points between antigen-bearing dendritic cells arriving from the tissue and recirculating B and T lymphocytes. Whereas the dendritic cells coming from the tissue enter the lymph node via the afferent lymphatic vessels, the recirculating lymphocytes enter the lymph node:
A. Also from the lymph fluid draining the tissue
B. Directly from their primary lymphoid organ where they develop
C. From the blood by crossing the high endothelial venules
D. By being trapped in the lymphoid follicle by resident macrophages
E. By being carried there by dendritic cells

1.25 True/False: The spleen is a secondary lymphoid organ that performs several functions. In addition to its role as a site for initiating adaptive immune responses, the spleen is important in removing dead or damaged red blood cells from the circulation. Its immune function is important because blood-borne pathogens will not be transported to draining lymph nodes via the lymph fluid.

1.26 Multiple choice: An infant with recurrent bacterial and fungal infections is suspected to have an immunodeficiency disease. Within two days after exposure to a pathogen, the organisms have proliferated to dangerous levels requiring immediate systemic antibiotic treatment. It is unlikely that this infant has a defect in B or T lymphocyte responses to the infection because:
A. Bacteria and fungi do not require B cell or T cell responses for their clearance.
B. Bacteria and fungi are not efficiently transported to draining lymph nodes to initiate adaptive immune responses.
C. Systemic infections of bacteria and fungi are usually cleared by the spleen.
D. The defective immune response occurs too rapidly following infection to be due to a defect in B or T lymphocytes responses.
E. Adaptive immune responses require dendritic cells to take up and degrade pathogens.

1-17 Mucosal surfaces have specialized immune structures that orchestrate responses to environmental microbial encounters

1.27 **Multiple choice:** The mucosal tissues of the body have their own unique set of immune structures that function as sites for initiating adaptive immune responses. The necessity for mucosa-associated lymphoid tissues to have unique cell types (M cells) and structures is because:

A. The mucous layer lining mucosal surfaces makes it difficult for normal antigen-presenting cells to function.
B. The epithelial surfaces that line the gut, lungs, and nasal passages prevent antigen-presenting cells from accessing microbes and microbial products.
C. The epithelial cells found in mucosal tissues are distinct from those that provide barrier functions to the skin.
D. Mucosal sites, where most pathogens access the body, are exposed to vast numbers of diverse microbes.
E. Mucosal tissues lack innate sensor cells that can respond to PAMPs and provide short-term innate immune protection.

1-18 Lymphocytes activated by antigen proliferate in the peripheral lymphoid organs, generating effector cells and immunological memory

1.28 **Multiple choice:** The best evidence supporting the concept of immunological memory is:

A. The increased numbers of antigen receptors expressed by lymphocytes after primary exposure to an antigen
B. The increased levels of cytokines made by lymphocytes after primary exposure to an antigen
C. The increased rapidity and magnitude of the secondary response to the same antigen
D. The increased swelling of lymph nodes during the secondary response to the same antigen
E. The long lifespan of vertebrates, which would be impossible without immunological memory

1.29 **True/False:** One factor that contributes to the enhanced secondary response to an antigen is the increased number of antigen-specific lymphocytes present after the primary response; these are known as memory cells.

1.30 **Multiple choice:** Naive B and T lymphocytes are small, quiescent cells with little cytoplasm and low metabolic activity. Yet within hours after being activated following encounter with their antigen, these cells enlarge and up-regulate many biosynthetic and metabolic pathways. Approximately one day later, the cells begin dividing, and for several days they are the most rapidly dividing cells in the body, undergoing 2–4 rounds of cell division every day. In order to maintain this phenomenal rate of cell division, lymphoblasts must:

A. Use the large energy stores accumulated by them when they were naive quiescent cells prior to their activation
B. Engulf their neighboring small quiescent lymphocytes in order to take their lipids and proteins for raw material
C. Up-regulate synthesis of mRNA and proteins, some of which encode for glucose transporters and enzymes used for glycolysis

D. Phagocytose extracellular proteins and lipids and degrade them for energy production
E. Macropinocytose metabolites and sugars from the blood for use in glycolysis

The effector mechanisms of immunity

1-19 Innate immune responses can select from several effector modules to protect against different types of pathogens

1.31 **Short answer:** The effector activities important in eliminating infectious organisms from our bodies can be categorized into four different groups: cytotoxicity, intracellular immunity, mucosal and barrier immunity, and extracellular immunity. Briefly describe why the immune system requires four different effector modules for maximum protection.

1.32 **Multiple choice:** Several subsets of innate lymphoid cells (ILCs) have been identified that share their patterns of cytokine production with the known subsets of T cells. The combined activity of related ILC and T cell subsets is effective in eradicating pathogenic infections because:
A. ILCs cannot kill the pathogen, whereas the antigen-specific T cells can kill the pathogen.
B. The early response of ILCs that reside at the site of infection is followed by the later more robust response of pathogen-specific T cells that migrate to the site of infection.
C. The ILCs activate B cells to induce antibody responses whereas the T cells are able to directly eliminate the pathogen.
D. The ILCs are induced to migrate from the site of infection to the draining lymph nodes where they activate the antigen-specific T cells.
E. The ILCs are activated to secrete antimicrobial compounds which cause them to lyse, releasing RNA and DNA that act on T cells to stimulate T cell cytotoxic activities.

1-20 Antibodies protect against extracellular pathogens and their toxic products

1.33 **Multiple choice:** The majority of vaccines work by eliciting pathogen-specific antibodies that circulate in our bodies and protect us in the event that we are later exposed to that specific pathogen. For most viruses and bacterial toxins that we are vaccinated against, these pre-existing antibodies are protective because:
A. They neutralize the virus or toxin, preventing it from attaching to and entering our cells.
B. They bind to the virus or toxin and carry it to the liver where it can be degraded.
C. They bind to the virus or toxin and directly induce lysis.
D. They induce mucus production that helps flush the toxin or virus out of the body.
E. They bind to epithelial cells and induce the production of antimicrobial peptides.

1.34 **Multiple choice:** When complement proteins are covalently deposited onto the surface of a bacterium, this can sometimes lead to direct lysis of the bacterium. However, more commonly, the deposition of complement proteins onto the bacterial surface does not

directly harm the bacterium. Instead, these complement proteins aid in bacterial elimination by:

A. Recruiting antibodies to the bacterial surface, leading the antibody-dependent neutralization
B. Providing a mechanism for phagocytes to use their Fc receptors to recognize and ingest the bacterium
C. Cross-linking carbohydrate structures on the bacterial surface, thereby preventing the bacterium from replicating
D. Stimulating B lymphocytes to produce more antibodies against the bacterium
E. Providing a mechanism for phagocytes bearing complement receptors to recognize and ingest the bacterium

1-21 T cells orchestrate cell-mediated immunity and regulate B-cell responses to most antigens

1.35 **Short answer:** T cells expressing the co-receptor CD8 are generally cytotoxic cells, with an important function in eliminating virus infections that can occur in many different cell types and tissues. In contrast, CD4 T cells directly interact with a very restricted set of cells, such as dendritic cells, macrophages, and B cells. Describe one important mechanism that accounts for this division of labor between CD8 and CD4 T cells.

1.36 **True/False:** T_H1, T_H2, T_H17, and T follicular helper (T_{FH}) cells represent four different subsets of CD4 effector cells. Each of these subsets produces a distinct set of cytokines when stimulated, that in turn, act to mobilize distinct immune effector mechanisms. While T_H1, T_H2, and T_H17 cells recruit and activate innate immune cells, T_{FH} cells act to amplify the adaptive immune response.

1.37 **Multiple choice:** Individuals with defects in T cell development have a severe immunodeficiency disease called SCID (severe combined immunodeficiency disease). In these individuals, the absence of all T cells causes defects in both cell-mediated (T cell-based) and humoral (antibody-based) immune responses. The defect in antibody responses in SCID patients is due to:

A. The important role of T cells in regulating B cell development in the bone marrow
B. The inter-dependence of T cells and B cells for the normal development of secondary lymphoid organs.
C. The absence of phagocytic cells needed for antibody-dependent pathogen clearance in SCID patients
D. The poor survival of B cells in patients with defects in their T cells
E. The important role of T follicular helper cells in generating protective antibody responses

1-22 Inherited and acquired defects in the immune system result in increased susceptibility to infection

1.38 **Multiple choice:** Inherited immunodeficiency diseases result from a single gene defect in one component of the immune system. By identifying the class of microbial pathogens a given immunodeficient individual becomes susceptible to, studies of these diseases indicate:

A. Which type of antibiotics each patient should be given
B. The essential immune mechanism required for resistance to each category of pathogen
C. Whether the disease is a genetically inherited or an acquired form of immunodeficiency
D. Whether the immunodeficiency disease is likely to be transmitted to another individual
E. Whether the disease is likely to be life-threatening or not

1-23 Understanding adaptive immune responses is important for the control of allergies, autoimmune disease, and the rejection of transplanted organs

1.39 Short answer: The immune system evolved to protect us against infections from pathogenic microorganisms. However, immune responses can also cause, rather than prevent disease. Give two examples of situations in which an immune response causes a disease, whereas the absence of a response has no consequences.

1.40 Multiple choice: One surprising aspect of the immune system is that individuals make responses to human tissues from a different individual, causing serious problems for organ and tissue transplantation. The basis for this immune response is:
A. The extensive polymorphism of MHC genes in the human population
B. The fact that transplanted tissues often carry infectious microbes into the recipient
C. The fact that individuals may differ in their blood group antigens (i.e., their blood type)
D. The presence of many antigen-presenting-cells in the transplanted tissue
E. The presence of many B and T lymphocytes in the transplanted tissue

1-24 Vaccination is the most effective means of controlling infectious diseases

1.41 Multiple choice: Vaccination against many infectious diseases has provided enormous benefit in developed countries, leading to the virtual eradication of diseases such as polio, measles, smallpox, and others. However, efforts to create long-lasting vaccines against some viral infections, like Influenza and HIV, have not been successful to date because:
A. Viruses like HIV and Influenza undergo antigenic variation to evade previous immune responses.
B. Viruses like HIV and Influenza spread too rapidly in the population for a vaccine to be effective.
C. Viruses like HIV and Influenza have RNA, rather than DNA genomes, and are resistant to current vaccine strategies.
D. Viruses like HIV and Influenza infect via mucosal surfaces, a route that is not well protected by current vaccine strategies.
E. Viruses like HIV and Influenza are transmitted vertically (from mother to child) during fetal development, so babies are infected before they can be vaccinated.

1.42 **Synthesis question:** For each of the panels A–D in **Figure Q1.42**, identify the most likely component(s) of the immune response indicated by the red arrow, and briefly describe your reasoning.

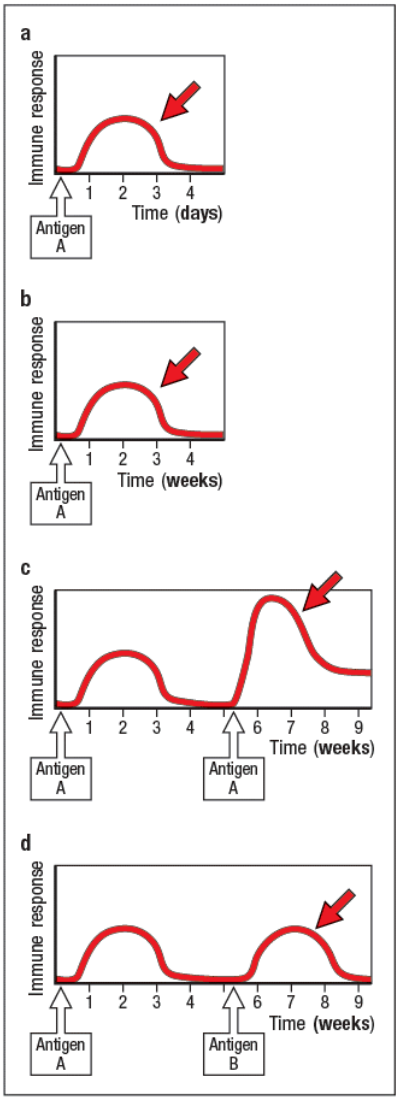

Figure Q1.42

1.43 **Synthesis question:** The immune system uses several types of effector modules to protect us against different categories of pathogens. Four major types of pathogens are shown in **Figure Q1.43**.

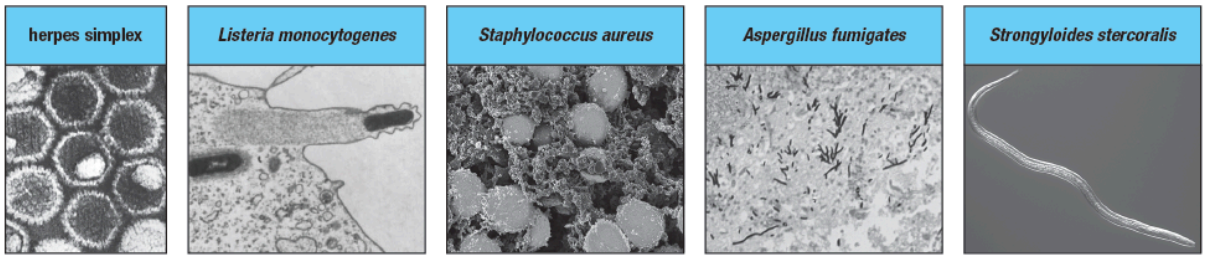

Figure Q1.43

a) Which of these categories might be effectively eliminated by innate immune responses that include antimicrobial peptides and phagocytic cells such as neutrophils and macrophages? Explain your answer.
b) Which of these categories of pathogenic organisms might be most effectively dealt with by antibodies, if the innate response is insufficient for their eradication?
c) Which of these categories of pathogenic organisms would require T lymphocyte responses for their elimination?

1.44 **Synthesis question:** One major difference between the innate and adaptive immune responses is in the mechanism by which pathogens are recognized. Innate immune cells use pattern recognition receptors (PRRs) to recognize conserved determinants shared by all the members of a category of pathogens, whereas adaptive immune cells (B and T lymphocytes) have highly specific antigen receptors.

a) Which of the patterns of receptor expression in **Figure Q1.44** represent innate immune cells?

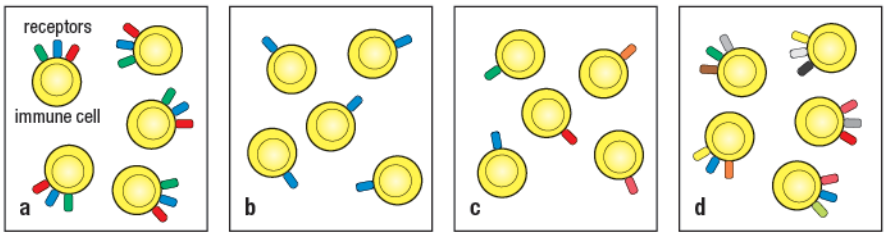

Figure Q1.44

b) Which of the patterns of receptor expression represent B and T lymphocytes?
c) Following an infection, how does the population of innate cells change? Starting with the cartoon representing your answer to part (a), draw the population present at one week post-infection.
d) Following infection, how does the population of B and T lymphocytes change? Starting with the cartoon representing your answer to part (b), draw the population present at one week post-infection.

ANSWERS

1.1: D.
Hematopoietic stem cells in the bone marrow give rise to all the blood cell lineages, including erythrocytes (red blood cells), myeloid cells (macrophages and granulocytes), and lymphocytes. Endothelial cells, which comprise the blood vessel walls, are not derived from hematopoietic stem cells.

1.2: False.
Not all microbes are pathogens, and our immune system does not attempt to eliminate all non-pathogenic microbes. Consequently, many body surfaces are colonized by large numbers of non-pathogenic microbes. These are called commensal micro-organisms, and they are found in places like the gastrointestinal tract, the skin, and the oral mucosa.

1.3: Pathogenic organisms that are very small (viruses, intracellular bacteria, single-cell parasites) will replicate inside host cells, and often induce cell lysis. Slightly larger pathogens are usually extracellular bacteria or fungi. These extracellular microbes cause damage by releasing toxins into the circulation. The largest pathogens are the helminthic parasites, which are too large to invade host cells. These organisms damage tissues by forming cysts that promote destructive responses in the tissues. In each case, the immune mechanisms required to eliminate the pathogen are different. Most notably, the mechanisms required to eliminate intracellular pathogens are different than those needed to eliminate extracellular pathogens.

1.4: C.
Based on common experience, students should know that mucus production is a common response to upper respiratory virus infection. Other responses may also occur, such as fever, production of antibodies, or infiltration of white blood cells, but these are not ‘bodily secretions.’ Increased saliva is not a symptom common to upper respiratory infections.

1.5: Sensor cells commonly recognize unique microbial components, such as bacterial lipopolysaccharide or other cell wall constituents. A clever microbe could evade this response by altering its membrane or cell wall components so that they are no longer recognized by the sensor cell receptors.

1.6: A.
Vaccines are designed to generate an adaptive immune response to a non-disease-causing form of a pathogen, or a pathogen product. Due to the specificity of this response, and the generation of immunological memory, vaccinated individuals make a substantially more robust response, and are often completed protected from infection, when exposed to the pathogen at a later time.

1.7: True.
Mast cells and macrophages are both cells of the myeloid lineage. These are tissue-resident cells that are poised to respond rapidly if an infectious microbe enters their tissue of residence.

1.8: Dendritic cells are essential in activating T lymphocytes. Therefore, it is important that dendritic cells acquire all possible categories of threats. While many intact microorganisms can

be taken up by phagocytosis, small toxins produced by pathogens are more efficiently ingested by macropinocytosis.

1.9: B.
The presence of adenosine residues would not discriminate between viral and host RNA, as both types contain these residues.

1.10: A.
The inflammatory response induced by macrophage-derived cytokines leads to the recruitment of cells, fluid, and soluble mediators into the tissue at the site of an infection. A key aspect of this response is the action of inflammatory cytokines on the blood vessel endothelial cells. These cells up-regulate adhesion molecules, allowing circulating white blood cells to stick to the blood vessel wall near the site of infection. In addition, the junctions between the endothelial cells loosen, allowing fluid and cells to leak out of the vessel into the tissue. In the fluid are soluble mediators, such as antimicrobial peptides, complement proteins, and antibodies.

1.11: White blood cells, primarily neutrophils.
Pus is an inflammatory response to a bacterial infection of the skin. The inflammatory response recruits neutrophils from the blood into the site of infection, along with some monocytes.

1.12: True.
Innate lymphoid cells are tissue-resident cells found primarily in the lung epithelium, the skin, and the intestinal epithelium. Since most pathogens enter the body through one of these sites, it is important to post innate immune cells in these locations where they will readily encounter a pathogen that has breached one of the body's barriers.

1.13: B and T lymphocytes are a heterogeneous population, comprised of cells that each express a unique antigen receptor. As a consequence, only a small number of B and T lymphocytes will respond to any particular pathogenic infection. The vast majority of the circulating cells will never encounter the pathogen that binds to their antigen receptor; hence these cells remain in a naive, inactive state.

1.14: E.
The B cell antigen receptor includes a membrane-bound form of the antibody protein, along with two transmembrane subunits that provide receptor signaling functions. When a given B cell binds to a pathogen using its B cell antigen receptor, the B cell is stimulated to proliferate and differentiate into a plasma cell. As a plasma cell, this B cell generates a secreted form of this same antibody protein by eliminating the transmembrane domains that anchor the antibody protein into the B cell membrane.

1.15: C.
The effector functions of T cells are all restricted to interactions with other host cells, and not with the pathogen directly. These effector functions include killing of cells infected with intracellular pathogens (cytotoxic T cells), activation of B cells and macrophages (helper T cells), and suppressing the activity of other lymphocytes (regulatory T cells).

1.16: The antibody variable domains form the antigen-binding sites on the protein, and these serve as the guidance system. The specificity of these domains determines where the antibody

protein binds, for instance, directly on a pathogen, or on a protein such as a toxin, or on a cell, etc. Antibody binding alone has limited effects. In order for antibodies to function in pathogen or toxin elimination, the antibody uses its Fc region, which functions as the 'payload.' This Fc region can be recognized by receptors on phagocytic cells, aiding in pathogen/toxin uptake, or it can promote complement activation on the pathogen. Without the 'payload,' antibody proteins would merely be binding molecules, with no other effector functions.

1.17: B.
Intracellular pathogens, such as viruses and some protozoa, cannot be eliminated by antibody-based mechanisms once they have begun replicating in host cells. In order to detect these intracellular pathogens, a system that surveils the intracellular status of host cells is needed. T cells fulfill this function by recognizing peptides on cell surface MHC receptors. The MHC receptors can pick up pathogen-derived peptides from within the infected cell and display them on the cell surface for T cells to 'see.'

1.18: Antibody diversity is generated when each developing B cell undergoes a DNA rearrangement process. This process involves the combination of small gene segments, encoded as separate elements in the genome, to form a complete coding sequence for the antibody protein. As a result of this process, the DNA of the B cell is irrevocably altered, and would no longer be able to transmit all the genetic information to the next generation.

1.19: True.
Cells of the innate immune system generally express multiple pattern recognition receptors. Each of these receptors recognizes a conserved feature of a class of pathogens. Therefore, a single innate immune cell can respond to a multitude of different pathogens. In contrast, the antigen receptor on B and T lymphocytes is clonally distributed; each single cell expresses only one version of this receptor, and has a single binding specificity.

1.20: D.
Clonal selection theory was original developed to explain the production of antibodies, as T lymphocytes were not known at that time. A key postulate of the theory was that the body contains a heterogeneous population of lymphocytes, each of which is programmed to produce a single type of antibody. Burnet proposed that each lymphocyte expressed a membrane-bound form of the antibody on its surface as a receptor. Following antigen binding, he proposed that this receptor would induce the proliferative expansion of that lymphocyte into a clone of cells. Each member of this clone of cells would express the identical antibody to the original cell, and all of them would then secrete this antibody.

1.21: A.
The random process that generates lymphocyte antigen receptors can create antigen receptors that are self-reactive. Many of these potentially self-reactive lymphocytes are eliminated during lymphocyte development, a process known as clonal deletion. Other self-reactive lymphocytes are functionally inactivated or inhibited from responding to their self-antigen. Altogether, these mechanisms ensure that the individual's lymphocytes remain tolerant to self.

1.22: A.
The system of secondary lymphoid organs is important in promoting interactions between rare antigen-specific lymphocytes and their antigens. Instead of requiring each naive lymphocyte to

traffic into every nook and cranny of the body, the pathogens and their products are brought to centralized locations and concentrated there. This allows the naive T and B lymphocytes to spend their time traveling from lymph node to lymph node looking for their antigen, making the encounters between lymphocytes and antigens much more efficient.

1.23: The most relevant features of dendritic cells in this context are:

1. Dendritic cells respond to infections using innate pattern recognition receptors (PRRs) that recognize PAMPs.
2. Once triggered by PRR stimulation, dendritic cells are induced to migrate from the infected tissue to the regional draining lymph node.
3. Following stimulation of the PRRs on a dendritic cell, dendritic cells up-regulate co-stimulatory molecules that are required to activate T lymphocytes.
4. Following pathogen uptake by the dendritic cell, the pathogen is degraded and peptides of the pathogen are displayed on the dendritic cell surface for recognition by the antigen receptors on T lymphocytes.

1.24: C.
Recirculating lymphocytes are in the blood, and are attracted by chemokines to enter the lymph node. They do this by binding to adhesion molecules and the chemokines posted at high endothelial venules, which are the regions of the blood vessel wall that are in the lymph node. The lymphocytes squeeze themselves through the blood vessel wall to leave the blood and enter the lymph node.

1.25: True.
The spleen is important for trapping blood-borne pathogens so they can be taken up and degraded by dendritic cells for presentation to T lymphocytes to initiate adaptive immune responses.

1.26: D.
The adaptive immune response, consisting of responses by B and T lymphocytes, takes approximately one week to become effective and participate in controlling an infection. The defect in this infant is in the very early innate response, which controls the infection during the first several days after exposure.

1.27: D.
Mucosal sites, such as the intestine, the reproductive tract, and the lungs are the locations in the body exposed to the greatest numbers and diversities of microbes. Most of those microbes are non-pathogenic, but a subset is capable of causing disease (i.e., is pathogenic). As a consequence, these mucosal sites have developed several unique mechanisms for immune protection. One of these is the presence of M cells that sample the antigens outside the epithelial barrier for surveillance by lymphocytes. Another is the presence of multiple subsets of tissue-resident lymphocytes that provide rapid responses to pathogens that breach the barrier.

1.28: C.
The most compelling evidence supporting the existence of immunological memory is the fact that the secondary response to an antigen is faster, of higher magnitude, and more effective than the response that occurs following an individual's first exposure to that antigen. This is the basis of vaccination.

1.29: True.
Several factors contribute to the enhanced secondary response to an antigen. One of these is the clonal expansion of antigen-specific lymphocytes that occurs during the primary response. While many of these cells die after the antigen is cleared, a subset of them remain as long-lived memory cells.

1.30: C.
Lymphoblasts up-regulate many biosynthetic and metabolic pathways to produce macromolecules and energy used for rapid cell division. Many of these processes require new mRNA and protein synthesis by the activated lymphocyte. For the purpose of energy production, lymphoblasts up-regulate glucose transporters and enzymes that are used in the glycolytic pathway.

1.31: Pathogenic microorganisms can be divided into groups based on their lifestyle in the host. Each of these lifestyles requires a different set of effector mechanisms for pathogen eradication. Cytotoxic activity is required to eliminate virus infections, which can take place in many different cell types in the body. Intracellular immunity is required for pathogens that have evolved to live inside phagocytes. Mucosal and barrier immunity is required for large parasites that generally enter the body through mucosal sites and cannot be engulfed by phagocytes. Extracellular immunity is required for most smaller extracellular pathogens that can be engulfed and eliminated by phagocytes.

1.32: B.
The ILCs are components of the innate response, as they respond rapidly following encounter with pathogens, and in most cases, these cells are resident in mucosal tissues. In contrast, T cells are slow to respond and are found recirculating through the blood and secondary lymphoid organs prior to their activation by specific antigen. The ILCs are thus positioned for rapid responses to pathogens that breach the barrier, and the cytokines they produce help control the infection, allowing time for the adaptive response to be initiated. The T cell response is more robust, owing to the clonal expansion of antigen-specific T cells, and these cells then migrate to the site of infection. Once there, the T cells produce cytokines that amplify the response started by the ILCs.

1.33: A.
Most vaccines against virus infections or bacterial toxins function by eliciting neutralizing antibodies. These antibodies bind to the virus or toxin immediately after entry (for the virus) or production by the bacteria (for the toxin) and prevent them from binding to and entering our cells.

1.34: E.
In most cases, the protective immune response elicited by a complement-tagged bacterium is the uptake and degradation of the bacterium by phagocytes expressing complement receptors. This includes both macrophages and neutrophils, both of which express complement receptors. In addition to aiding in bacterial engulfment, binding of the complement proteins on the bacterium to the complement receptors on the phagocyte can also enhance the production of microbicidal effector functions in the phagocyte.

1.35: CD8 T cells recognize antigenic peptides bound to MHC class I molecules, which are expressed on nearly all cells of the body. Therefore, any cell type that becomes virus-infected would be able to present viral peptides on MHC class I molecules for recognition by CD8 T cells. In contrast, CD4 T cells recognize antigenic peptides bound to MHC class II molecules. MHC class II proteins are expressed only on other cells of the immune system, such as dendritic cells, macrophages, and B cells. Due to the restricted expression of MHC class II proteins, CD4 T cells are restricted to interacting with these cells of the immune system.

1.36: True.
Most CD4 effector cells produce cytokines that act on innate immune cells, For instance, T_H1 cells activate macrophages, T_H2 cells recruit and activate mast cells, basophils, and eosinophils, and T_H17 cells recruit neutrophils. Unlike these subsets, T_{FH} cells function to promote B cell activation and antibody responses, and thus help amplify the adaptive immune response.

1.37: E.
T follicular helper cells are a subset of CD4 T cell that provide signals needed for B cell activation and the generation of protective antibody responses to most infections. In the absence of T cells, antibody responses are poor and generally not sufficient for pathogen clearance.

1.38: B.
The study of immunodeficiency diseases has been extremely informative about the essential mechanisms required for immune protection against different classes of pathogens. For instance, these studies have shown that individuals lacking B cells or antibodies are highly susceptible to extracellular bacterial infections, but have normal responses to most viral infections.

1.39: There are several cases in which immune responses can cause diseases, whereas their absence is a neutral event. One example is allergic responses to non-threatening antigens, such as food items, antibiotics, metal ions, or inhaled substances. Another example is autoimmune diseases, in which individuals make destructive immune responses to their own cells or tissues. Graft rejection in transplant patients is another possible example, although it doesn't quite fit the criterion of being 'an immune response that causes disease,' since in this case, the immune response is prevented 'the cure' rather than causing the disease.

1.40: A.
The major component of the graft rejection response is due to recognition of the 'foreign' MHC proteins on the graft by the recipient's T lymphocytes. This occurs because of the extensive polymorphism of MHC genes in the human population. As a result, two different individuals nearly always express different MHC molecules from each other. Since MHC molecules are efficiently recognized by T cells, the T cells in the recipient will respond to the donor's tissue and destroy it, just as if it were a pathogen.

1.41: A.
Viruses like HIV and influenza undergo rapid antigenic variation. Therefore, an immune response against one strain of the virus will not usually protect individuals from infection with a variant strain. Therefore, much of the current effort toward developing vaccines against these

viruses aims at targeting highly conserved regions of the virus, where an immune response would be broadly reactive to many viral variants.

1.42:

A. Innate immune response. The cells responding could be mast cells, dendritic cells, macrophages, or ILCs. The response initiates rapidly (<1 day) and lasts for 2–3 days, then disappears.
B. Primary adaptive immune response. Upon first exposure to antigen or pathogen, the response of B cells or T cells takes approximately 1 week to arise. It lasts for two weeks or so, then wanes.
C. Memory response of adaptive immune cells. Upon secondary exposure to the same antigen or pathogen, the response of B or T lymphocytes is more rapid than the primary response, and generates a response of greater magnitude than the primary response.
D. Primary adaptive immune response to a different antigen. Each time the immune system encounters an antigen/pathogen for the first time, a primary response is generated. This response will look similar each time. It is only when the same antigen/pathogen is encountered for a second time that a more rapid and more robust adaptive immune response is generated.

1.43:

a) Extracellular bacteria and fungi. These pathogenic microbes are often efficiently cleared by the innate immune response. The pathogens express PAMPs that stimulate PRR on innate cells in the infected tissue, such as macrophages and dendritic cells. These activated macrophages and dendritic cells induce an inflammatory response. The inflammatory response leads to the influx of fluid and phagocytic cells into the site of infection. The fluid contains some preexisting antibodies and complement proteins, that will ‘tag’ the microbes. The inflammatory response also recruits neutrophils and monocytes from the blood, which will phagocytose and destroy the bacteria or fungi. In many cases, this response is sufficient to eliminate the infection, without the necessity for an adaptive immune response.
b) Extracellular bacteria and fungi; helminthic parasites. These extracellular pathogens will elicit antibody responses, if they are able to avoid clearance by innate immune responses. Antibodies will coat the pathogens, leading to activation of innate immune cells that ultimately do the ‘dirty work’ of eliminating the pathogen. In the case of extracellular bacteria and fungi, the antibody-coated microbes are readily engulfed by phagocytic cells and destroyed. In the case of helminthic parasites, antibody-coated parasites will elicit activation of basophils and eosinophils that deposit toxic compounds onto the parasite surface.
c) Viruses; intracellular bacteria and protozoa. Microbes that replicate inside host cells cannot be eliminated by antibody-dependent mechanisms. Instead, T cells are required for eradicating these infections. In the case of viruses, cytotoxic T cells will recognize and kill virus-infected cells. In the case of intracellular bacteria and protozoa, these microbes generally infect and replicate in macrophages. Their elimination is dependent on CD4 T cells that will activate the infected macrophage to up-regulate multiple microbicidal mechanisms for killing the intracellular pathogen.

1.44:

a) A. Innate immune cells express multiple different receptors for recognizing PAMPs; however, all cells of the same innate subset express the same receptors.

b) C. B and T lymphocytes each express only a single specificity of antigen receptor; however, each B or T cell expresses a different receptor from the other cells of the same subset.

c) The population of innate cells is largely unchanged before and after infection.

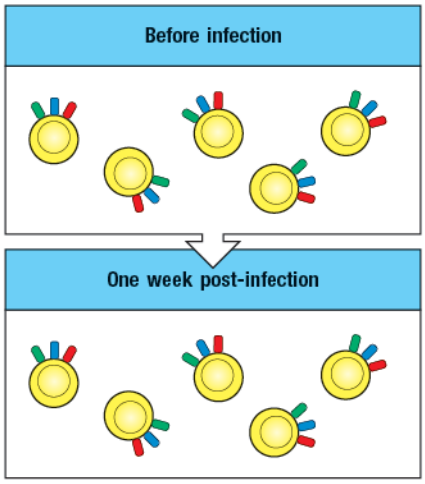

Figure A1.44C

d) The rare B or T lymphocyte with an antigen receptor specific for the pathogen undergoes clonal expansion. This population is therefore much more abundant after infection than before. All other lymphocytes remain unchanged.

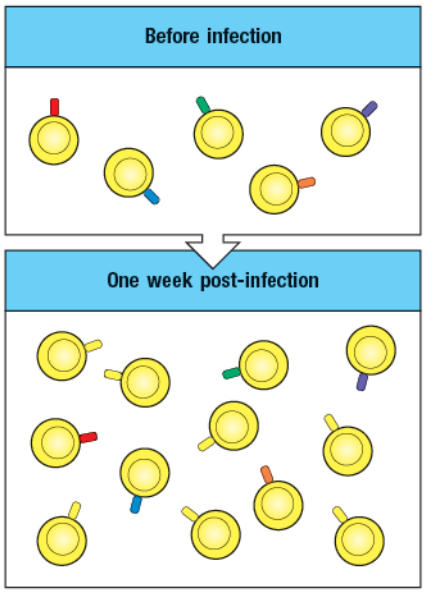

Figure A1.44D