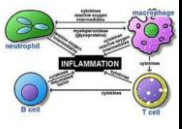
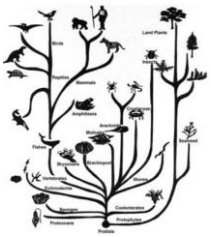
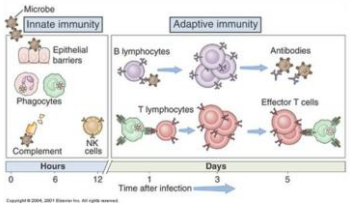
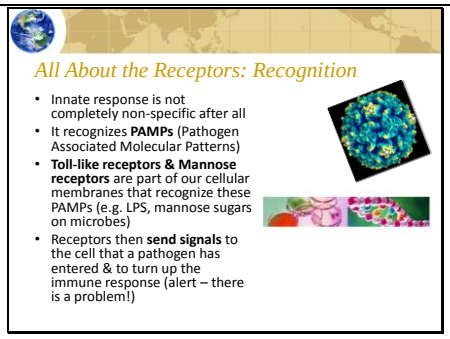
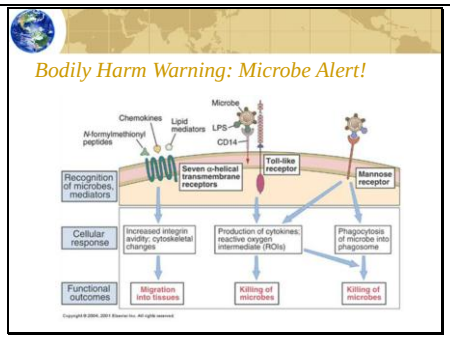
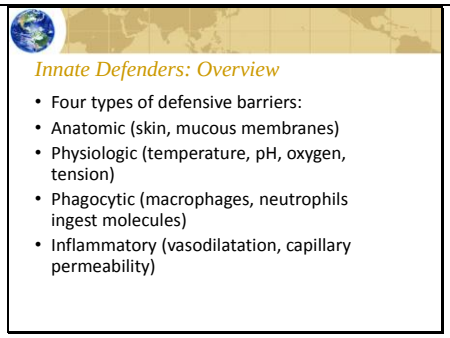
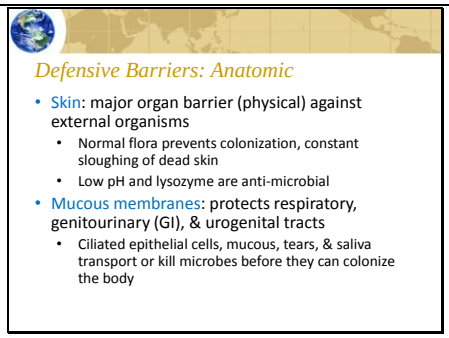
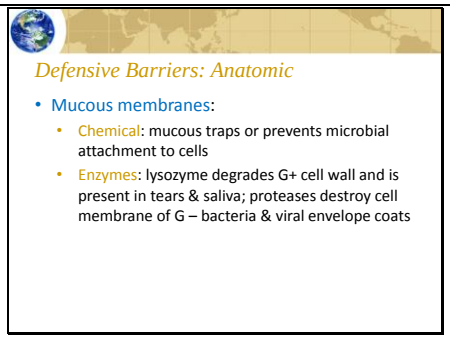
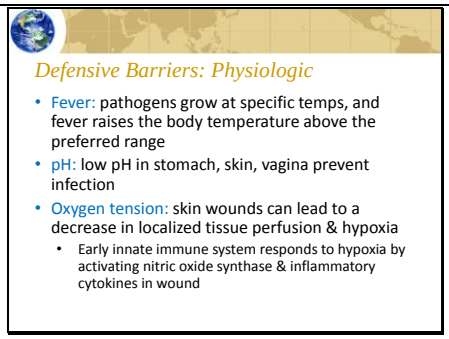
Slide 1	*Foundations of Public Health Immunology* Innate Immunity, Inflammation & Nutrition 	SLIDE 1 During this week's presentation, the innate immune system will be described. The innate system provides general resistance to disease, with several anatomic and physiologic barriers that prevent infection. The role of phagocytic cells and the inflammatory response will be highlighted. In addition, the impact of nutrition on the immune response will be described.
Slide 2	*Objectives* • Identify principles of innate immunity • Identify receptors and responses of innate cells to microbes (alert system) • Describe & identify examples of the 4 types of innate defensive barriers • Identify the cardinal signs of inflammation • Identify the differences between acute and chronic inflammation • Identify components of inflammation & how they enhance immunity • Understand role of nutrition in immune response & identify examples of nutrient deficiencies	SLIDE 2 Objectives for Innate Immunity. These objectives will be tested in both the weekly activities and Block 1 Quiz, so especially focus on the topics mentioned on this slide as you move through the presentation.

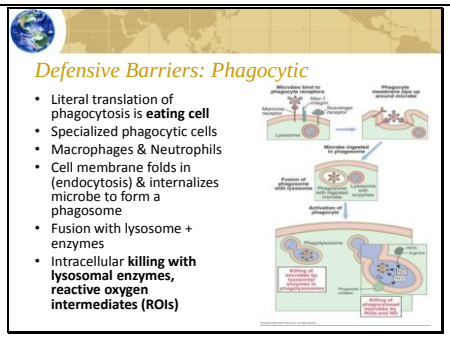
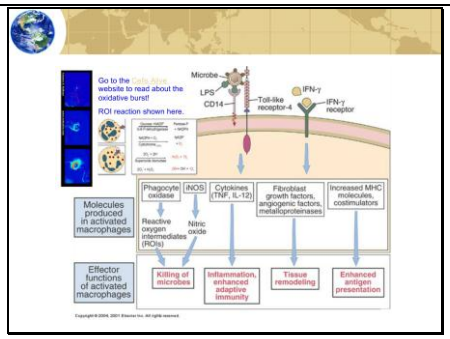
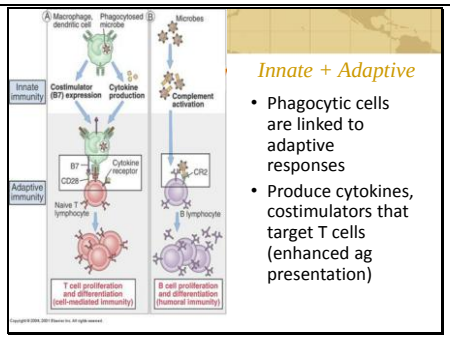
Slide 3	*Earliest Immune System*
	• Innate immunity refers to the basic resistance to disease that a species may possess
	• Phylogenetically ancient defense
	  • Invertebrates & vertebrates both have components of innate immunity (complement, receptors)
	  • Only vertebrates contain adaptive responses
	
	 
	Source: http://library.thinkquest.org/29178/treeoflife.htm
		SLIDE 3 Immunity is critical to the survival of a species, and all species needed to develop a way of combating disease in order to survive. The components of the innate immune system provide general resistance to disease and is evident in almost all species of life. Phylogenetically, components of the innate immune system have been shown to provide the earliest defense to disease (ancient defense). It is the dominant system found in primitive multicellular organisms, insects, and plants. Only vertebrates have further enhanced their immune systems with adaptive (specific) responses.

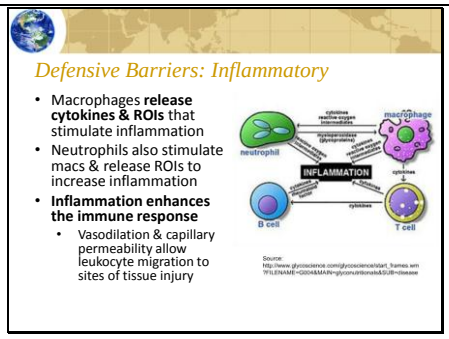
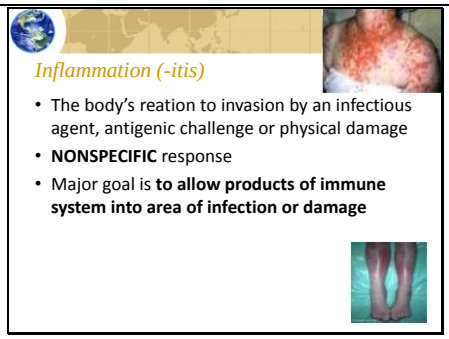
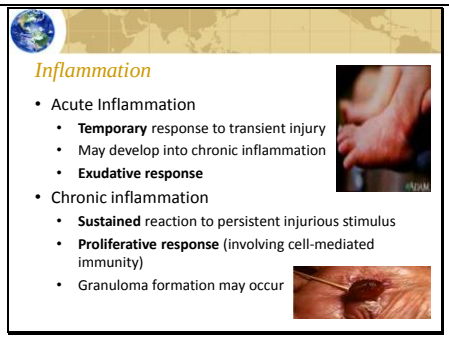
Slide 4	*Principles of Innate Immunity*
	• Also known as Natural or Native immunity
	• Provides general resistance to antigens
	• **Not specific** for any given pathogen or antigen
	  • Provides a **rapid** response to antigens
	• **No memory**
	  • Response does not improve with successive exposures to the same pathogen or antigen
		SLIDE 4 Innate immunity provides a general resistance to disease; however, this response is nonspecific. But, this does allow the response to be quite rapid and eliminate a wide variety of antigens before the adaptive immune system can respond. Additionally, innate immunity does not improve with repeated exposures to an antigen (or microorganism); and, it is considered as a "helper' for the adaptive immune system.

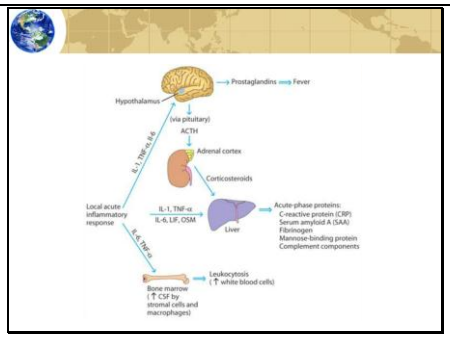
Slide 5	*Time is of the essence …*  	SLIDE 5 Innate immune responses often begin soon after infection, once epithelial barriers are breached. This rapid response occurs within hours of infection and can involve the complement system and multiple cell types to limit the spread of the infection. In contrast, the adaptive immune response takes several days to specifically fight an infection. It takes much longer to produce antigen specific antibodies and activated effector T cells to Fight the infection. Consequently, the innate immune response is critical in the early Fight against infection, as it attempts to neutralize the pathogen with a local inflammatory response at the site of infection. Later, these innate responses can draw the activated T cells and antibodies to the battle site.
Slide 6	*The Battle Begins* • A microbe enters the body … • How does the innate system **detect** it? • How does the innate system tell the rest of the body that there is a problem?	SLIDE 6 Once a microbe breaches the innate defense mechanisms or barriers, the battle begins. But, how does the innate immune system know that a microbe has entered? Especially as the pathogens don't announce themselves & often try to mask their entry into the body. The next slides will detail how the innate immune system first detects that a pathogen has entered the body and then how it communicates to the rest of the body that a pathogen has entered the premises.

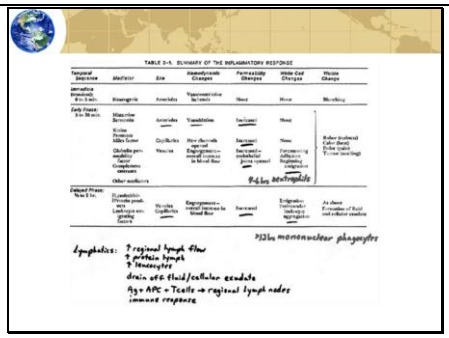
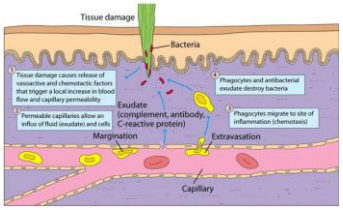
Slide 7		SLIDE 7 PAMPS are microbial factors that are rarely found in mammalian cells. Toll-like receptors are highly conserved throughout evolution- considered to be an early defense against pathogens. Toll is not a type of cookie, but is named for a Drosophila fly molecule that recognizes G+ and G- bacterial products. The innate response is not specific like the adaptive response because it recognizes only a pattern of microbial origin & will not remember it the next time the microbe enters the body. It will again recognize just the PAMP & start the whole process over, but will not specifically target the microbe with antibodies or activated T cells.
Slide 8		SLIDE 8 After the microbe binds to the receptors on the surface of a cell, it triggers a signaling cascade within the cell. This is how the Toll-like receptors communicate within the cell & to other cells that a microbe has entered the body. Cytokines and reactive oxygen intermediates are produced to kill the microbe, as well as stimulation of phagocytosis, and recruitment of additional immune cells to the area. Transmembrane receptors and other signals trigger cytoskeletal changes to occur that allow products of the immune response to move into the site of infection.
Slide 9		SLIDE 9 The body is protected by 4 types of defensive barriers, anatomic, physiologic, phagocytic, and inflammatory. These barriers form a continuous layer throughout the body that microbes must breach in order to gain entry & to establish infections.

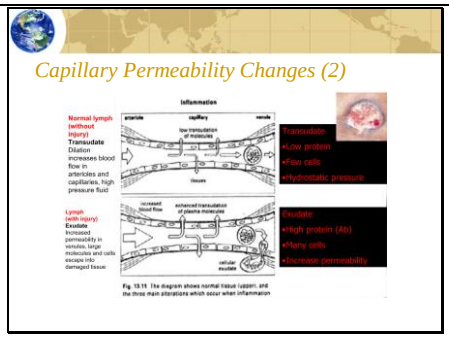
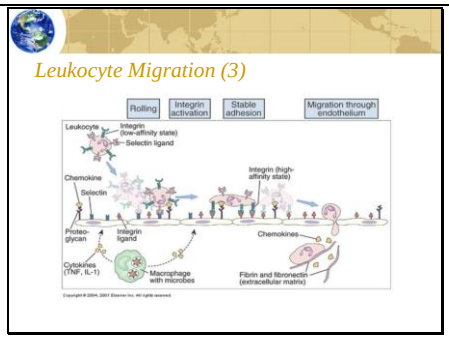
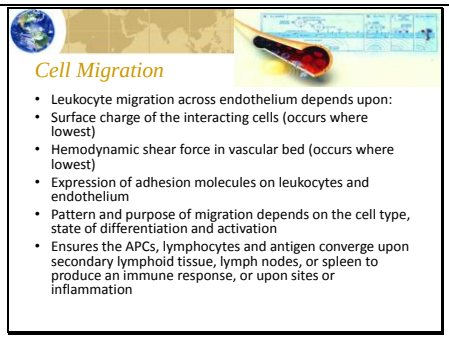
Slide 10		SLIDE 10 Anatomic barriers include the skin & mucous membranes that provide a continuous cover that must be breached to establish infection. In addition, mucous membranes are protected by cilia that continuously sweep particles in an upward motion away from the lower respiratory tract. Saliva, tears, and urine also mechanically expel microbes through a flushing action to protect the mouth, eyes, and urogenital tract.
Slide 11		SLIDE 11 Mucous and enzymes are important components that protect the epithelial lining. Lysosyme and proteases have microbicidal properties that can break down G+ & G- bacteria as well as viruses.
Slide 12		SLIDE 12 Fevers are part of the body's natural defense to pathogens by limiting their growth. For example, viruses grow best at "cooler' temps and a fever indicates that your immune system is in action. The highly acidic environment of the stomach is not conducive to bacterial growth. Normal bacterial flora of the vagina produces lactic acid, which serve to lower the pH and prevent infection. Lactobacillus acidophilus (L. acidophilus) is the most commonly used probiotic, or "friendly" bacteria. Yes, this is also found in yogurt! Disruption of this normal flora can result in yeast infections, urinary tract infections and may be caused by antibiotic use, poor hygiene, etc. Injuries to the skin or infections may result in a decline in normal tissue oxygen tension content (hypoxia). This leads to a decrease in localized tissue perfusion & may activate iNOS and inflammatory cytokines in the wound.

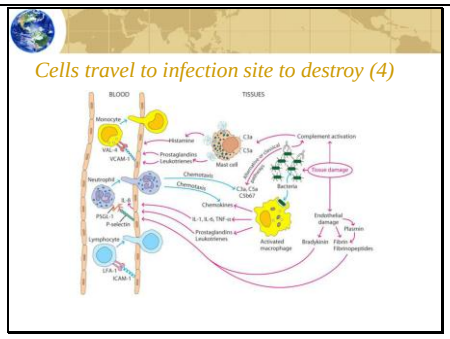
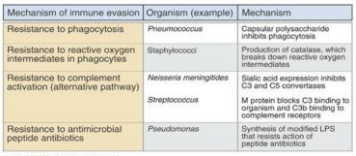
Slide 13		SLIDE 13 Phagocytes were extensively covered in the Cells portion of Week Three. Phagocytes are specialized cells that can internalize and kill microbes. Macrophages and neutrophils are 2 examples of innate immune cells that perform this function.
Slide 14		SLIDE 14 Activated macrophages are very important to the innate immune system. They increase inflammation in at the site of infection & enhance adaptive immune responses through a variety of cytokines that stimulate T cells, dendritic cells, etc (see Figure 2- 12 in the textbook). They also produce reactive oxygen intermediates (ROIs) and nitric oxide (NO) that create an oxidative burst to kill the microorganism intracellularly. Several growth factors are triggered by cytokine receptors that lead to tissue remodeling. And, macrophages are linked to the adaptive immune system through increased expression of MHC molecules that help communicate with T cells and enhance antigen presentation.
Slide 15		SLIDE 15 This figure also indicates the role that phagocytic cells have in the adaptive immune response.

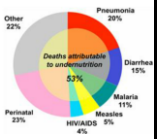
Slide 16		SLIDE 16 Inflammatory defensive barriers of innate immunity. Phagocytic cells communicate with each other through the release of cytokines and reactive oxygen intermediates that stimulate inflammation. The inflammatory response is important to the innate immune system it triggers the endothelial lining of circulatory vessels to become “leaky” and allows products of the immune response to reach the site of infection in the tissues.
Slide 17		SLIDE 17 The term inflammation comes from Latin word inflammare (to set on Ere). Inflammation is the body’s nonspecific reaction to invasion by an infectious agent, antigenic challenge or physical damage. The major goal of inflammation is to allow products of immune system into an area of infection or damage. Medical terminology often adds -itis to the end of a word to signify inflammation of a particular organ (e.g. carditis, inflammation of the heart).
Slide 18		SLIDE 18 Acute Inflammation is usually a temporary response to transient injury; however, it may develop into chronic inflammation. Acute inflammation produces an exudative response. In contrast, chronic inflammation is usually a sustained reaction to persistent injurious stimulus. Chronic inflammation produces a proliferative response. This proliferative response involves cell- mediated immunity; and, granulomas may eventually develop at the site of chronic inflammation.

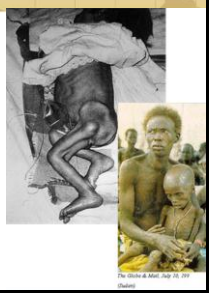
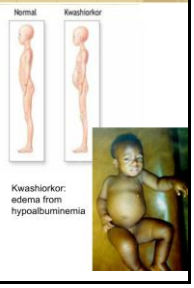
Slide 19		SLIDE 19 This diagram illustrates the systemic effects that can occur with the release of cytokines from an area of inflammation. These can trigger the hypothalamus to release prostaglandins that induce fever, as well as hormones to stimulate the release of acute phase proteins from the liver (such as complement) to enhance innate responses.
Slide 20		SLIDE 20 This slide lists the cardinal signs of inflammation. The Roman Comelius Celsus is credited with first identifying (in the 1st century AD) four cardinal signs of inflammation. In Latin, these signs are rubor et tumor cum calore et dolore (translation: redness and swelling with heat and pain). In 1871, Virchow added the 5th cardinal sign, functio laesa (or loss of function). Summary of Cardinal Signs of Inflammation English Latin Cause Heat Calor Vasodilation Redness Rubor Vasodilation Swelling Tumor Increased vascular permeability Increased granulation tissue Pain Dolor Physical and chemical stimulation of nociceptors Loss of function Functio laesa Pain Reflex muscle inhibition Disruption of tissue structure Fibroplasia and metaplasia Source: http:IIbjsm_bmjjouma|s.¢:omI¢:giI¢:ontentl fu||I38I3I248, What is "inflammation"? Are we ready to move beyond Celsus? A Scott, K M Khan, J L Cook and V Duronio

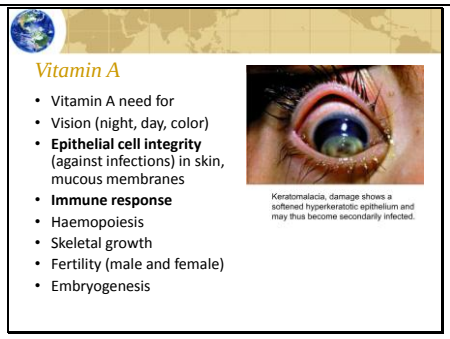
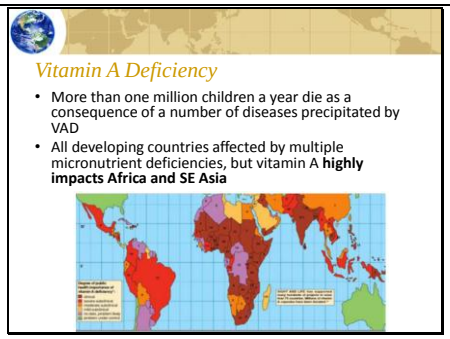
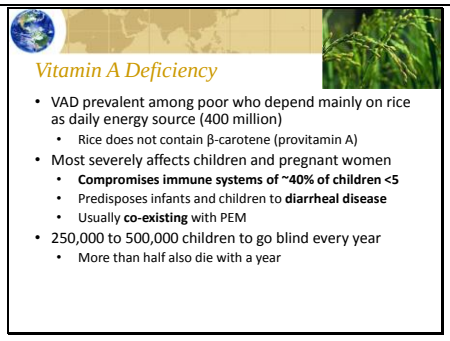
Slide 21		SLIDE 21 With acute inflammation after injury or infection, there are (1) Blood supply changes, (2) Capillary permeability changes, and (3) Leukocyte migration. This table summarizes the inflammatory response. Note the time flames, mediators (such as histamine & serotonin), hemodynamic changes, and visible changes that are occurring during the whole process of inflammation.
Slide 22	*Inflammatory Components* 1. Blood supply changes • Increases to bring cells and large molecules to area 2. Capillary permeability changes • Increases to allow exudation of serum protein 3. Leukocyte migration • Increase into affected area across venules	SLIDE 22 With acute inflammation, there are (1) Blood supply changes, (2) Capillary permeability changes, and (3) Leukocyte migration that allows products of immune system into an area of infection or damage.
Slide 23	 *Blood Supply Increase (1)*	SLIDE 23 This slide illustrates the 4 processes that occur after a splinter introduces bacteria into the skin. Number 1: Blood supply increases as tissue damage causes a release of vasoactive & chemotactic factors. Blood flow increases & creates a change in capillary permeability (this is what happens when you cut your skin & suddenly have blood pumping out everywhere!).

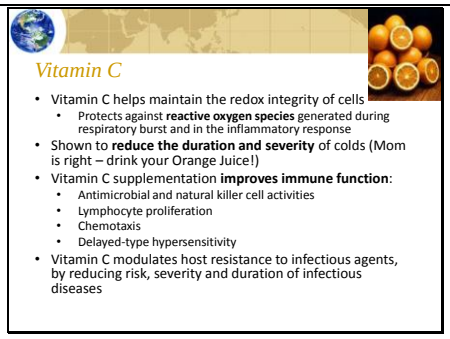
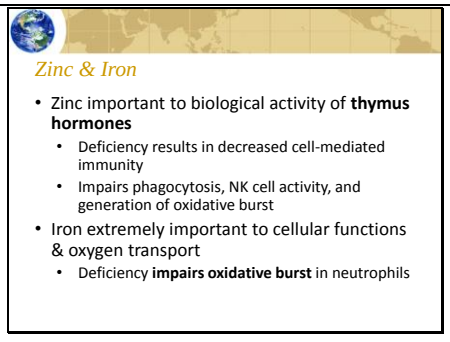
Slide 24		SLIDE 24 Number 2: Capillary permeability changes from the normal state of transudative (high hydrostatic pressure within the capillary, few cells, and low protein) to the injured state of exudative. In the exudative state, the hydrostatic pressure lowers to allow increased permeability so that many cells can squeeze between the endothelial cell lining to move out into the tissues. Exudates also have a high protein content, containing antibodies that can Fight the infection at the site of injury.
Slide 25		SLIDE 25 Number 3: It is not an easy process to slow the fast movement of cells through the blood vessels! An intricate process occurs during leukocyte migration as the cells of the endothelial lining express integrins that slow down the cells as they roll through the vessels. During adhesion, the cells stick to the integrins & crawl along the vessels until chemokines & chemotaxis directs them to migrate through the endothelium lining.
Slide 26		SLIDE 26 Cell migration is necessary to ensure that immune cells reach sites of inflammation and injury. Leukocyte migration across endothelium depends upon: (1) surface charge of the interacting cells (Migration occurs where the surface charge is lowest), (2) hemodynamic shear force in vascular bed (Migration occurs where the hemodynamic shear force is lowest), and (3) expression of adhesion molecules on leukocytes and endothelium.

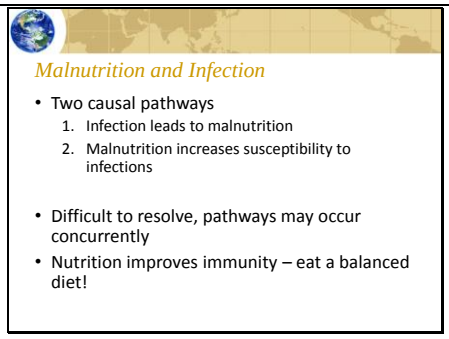
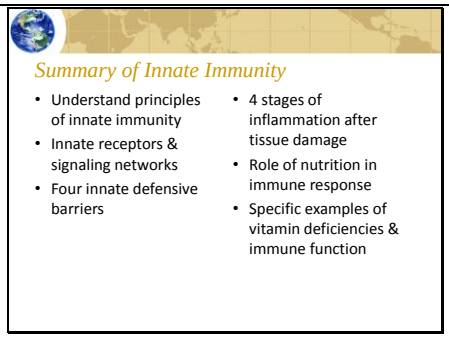
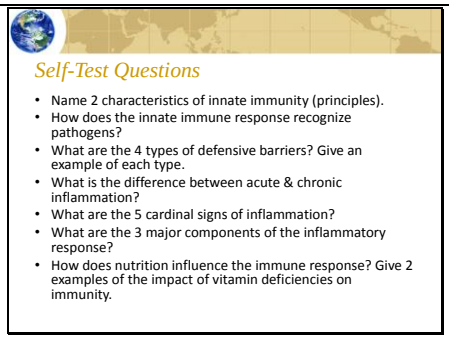
Slide 27		SLIDE 27 Number 4: Finally the cells have migrated out of the blood vessels & move by chemotaxis to the site of tissue damage or infection. At this point, the cells will kill the bacteria and then clean up the damage through phagocytosis.
Slide 28	*Microbial Evasion Strategies* • Some bacteria have developed ways to defeat innate immunity • Resist phagocytosis, ROIs to avoid death 	SLIDE 28 Microbes have developed evasion strategies to resist the innate immune response. One successful technique is the ability to after phagocytosis to prevent the oxidative burst or fusion of the phagolysosome. For example, Pneumococcus species of bacteria have an outer capsule that inhibits phagocytosis. Some Staphylococcus species produce catalase that breaks down the ROIs to prevent the oxidative burst.
Slide 29	*Role of Nutrition in Immunity* • Nutrition is a key element to a healthy immune system • Vitamin deficiencies have been shown to decrease immune function • And, lead to increased infections 	SLIDE 29 The remainder of this presentation will discuss the role of nutrition in immunity. Nutrient deficiencies can weaken several components of the immune response and lead to increased infections.

Slide 30	*Extremely Brief Review of HUMAN NUTRITION* • FOOD is a mixture of chemicals • NUTRIENTS are the essential chemicals in foods • 6 classes of nutrients found in food: • Carbohydrates 1) Lipids 2) Proteins 3) Vitamins 4) Minerals 5) Water 	SLIDE 30 A brief review of human nutrition, including the 6 classes of nutrients found in food.
Slide 31	*Macronutrients vs. Micronutrients* **Macro** • Nutrients such as **carbohydrates, fat, or proteins**, that are needed in relatively large amounts in the diets **Micro** • Nutrients such as a **vitamin or mineral** that is needed in relatively small amounts in the diet • Enables body to produce enzymes, hormones & other substances essential for proper growth and development • Vitamins A, C, D important to properly functioning immune system • Zinc & iron  Fruits and Veggies are important sources of nutrients, especially micronutrients. Photo by Peggy Greb, USDA Image Number K8666-1	SLIDE 31 Both macro & micro nutrients are extremely important to health. Macro nutrients are needed in large amounts in the diet and include carbs, fat, and protein. Micronutrients, on the other hand, are only needed in relatively small amounts in the diet. These nutrients are especially important to produce enzymes, hormones, and growth factors critical for proper growth & development. Vitamins & minerals have also been shown to be especially important to a properly functioning immune system.
Slide 32	*Malnutrition: The Silent Crisis* • Definition: Failure to achieve nutrient requirements which can **impair physical and/or mental health** • May result from consuming too little food or a shortage/imbalance of key nutrients • Several types: • Protein-energy malnutrition (PEM) • Kwashiorkor • Marasmus • Micronutrient deficiencies (Vitamins A, C, D) • Mineral deficiencies (Zinc, Iron)  	SLIDE 32 Malnutrition may result from not eating enough or from an imbalance of key nutrients. There are several types of malnutrition, but we will just concentrate on the ones that have been shown to impact immunity. These include protein-energy malnutrition (most significant contributor to immunodeficiency worldwide), which includes 2 subtypes, Kwashiorkor & Marasmus. Micronutrient deficiencies significantly impact the immune system and these include vitamins A, C, and D, as well as Zinc & Iron deficiencies. Deaths attributable to under nutrition are led by infectious diseases, including pneumonias, diarrhea, malaria, measles, and HIVIAIDS. The influence of malnutrition on the efficacy of the immune system is dramatically illustrated by these high death rates from infectious diseases in malnourished individuals.

Slide 33	*Protein-Energy Malnutrition (PEM)* • **Most widespread** form of malnutrition • Prevalent in Africa, Central & South America, East • Condition of infants and children • Develops after children are weaned from the breast • Micronutrient deficiencies linked to development of PEM • Widespread **atrophy of lymphoid tissues & 50%** reduction in circulating CD4+ T cells	SLIDE 33 Protein-energy malnutrition is the most widespread and serious form of malnutrition. This type of malnutrition results from too little animal protein in the diet. It often develops after children are weaned from breast milk when a second child is brn, and they lose the only source of complex proteins (amino acids) found in breast milk. PEM leads to serious impairment of cell-mediated immunity, as widespread atrophy of lymphoid tissues & reduction in circulating T cells occur.
Slide 34	*Marasmus* • A type of malnutrition resulting from **chronic protein-energy under nutrition** characterized by wasting of muscle and other body tissue • Physical term for **starvation** • Often occurs after child weaned from breast milk 	SLIDE 34 Marasmus is one type of PEM that leads to a wasting of muscle & other body tissue. In this type of malnutrition, children often look very old or skeletal as the skin tightens over the bones.
Slide 35	*Kwashiorkor* • Type of malnutrition that occurs primarily in **young children who have an infectious disease** • Diets supply marginal amounts of energy and very little protein (carbs ↑) • Common symptoms include poor growth, edema, apathy, weakness, & **susceptibility to infections** • Diarrhea & anemia compound problem 	SLIDE 35 Kwashiorkor is a type of malnutrition that occurs in children with infectious diseases, such as malaria. Their diets have very little protein, but are high in carbs, and vitamin deficiencies have been linked to the development of kwashiorkor. These children are especially vulnerable to infection.

Slide 36		SLIDE 36 Vitamin A is an important component of many physiologic processes in the body, including strengthening epithelial cells within the skin & mucous membranes. This micronutrient is especially integral to vision, skeletal growth, and the immune response.
Slide 37		SLIDE 37 Vitamin A deficiency is an underlying problem that weakens the immune system & leads to higher infections which kill more than 1 million children a year. Vitamin A deficiency is common in Africa and South East Asia.
Slide 38		SLIDE 38 Vitamin A deficiency is a serious disease that usually co-exists with protein energy malnutrition (PEM). Vitamin A deficiency has been shown to compromise the immune systems of 40% of children under 5 years old around the world & put them at a higher risk for diarrheal disease.

Slide 39		SLIDE 39 Vitamin C has always been linked to getting over a cold- much like eating an apple a day. This vitamin is extremely important to ameliorating the symptoms and shortening the duration of respiratory tract infections. It has also been proven to improve the outcome from pneumonia, diarrheal, and malarial infections, especially in children of low-income countries. Clinical trials of people given supplements of Vitamin C have shown improved immune function, including increased lymphocyte proliferation and antimicrobial and natural killer cell activities.
Slide 40		SLIDE 40 Vitamin D is needed to down regulate the immune response during inflammation (to prevent destruction of healthy tissues). When it is produced by macrophages, it instigates a negative feedback loop that Inhibits T cell proliferation & Th1 cytokine production. This helps slow the inflammatory response once the organism is contained to prevent T cell mediated damage to healthy tissues.
Slide 41		SLIDE 41 Minerals are also extremely important to a properly functioning immune system. Both zinc and iron contribute to oxidative burst that helps phagocytic cells kill internalized microbes. Zinc is also important to the activity of the thymus, where T cells mature. Consequently, a zinc deficiency results in cell-mediated immunity. Like Vitamin C, zinc also has been shown to improve the outcome of pneumonia, malaria, and diarrheal infections in children in developing countries.

Slide 42		SLIDE 42 Malnutrition greatly increases a person's susceptibility to infection. Unfortunately, infection often leads to malnutrition, through depletion of important nutrients, dehydration, and malaise that prevents a person from eating (HIV is one good example of how infection may impact nutritional status). These 2 pathways create a vicious cycle that is extremely difficult to break, especially in poor countries. The majority of the population in low-income economies around the world is malnourished. This is already a very serious global health challenge that is exacerbated by a high infectious disease burden in these countries (HIV, malaria, etc).
Slide 43		SLIDE 43 What you need to know . . .
Slide 44		SLIDE 44 Review questions.