SLIDE 1 During this week’s presentation, the anatomy and physiology of the lymphoid system will be introduced. The anatomy of the lymphoid system is designed to facilitate a successful immune response, as lymphoid organs are located at strategic points throughout the body to concentrate & trap antigens. The lymphatic system is designed so that lymph travels from around the body, picking up antigens and debris, and then circulates to & is concentrated into the secondary lymphoid organs. Multiple cell types present in these lymphoid organs are now strategically located so that they can rapidly communicate and mount a specific response to an antigen, if present in the lymph. Then, specific products of the immune response will leave the secondary lymphoid organs for travel back to the site of infection. It is a very cool process!

SLIDE 2 Objectives for Anatomy & Physiology of the immune system. These objectives will be tested in both the activity and quiz for this week, so especially focus on the topics mentioned on this slide as you move through the presentation.

SLIDE 3 The immune system is composed of a variety of cellular systems. These systems include encapsulated immune organs and diffuse aggregates of immune cells in the mucosal tissues known as MAIT.
SLIDE 4 The lymphatic system is extremely important in trapping & concentrating any foreign antigens, as the lymph drains into the lymph nodes. The diagram on this slide also details the lymph nodes in the body.

SLIDE 5 Lymph is the watery fluid that circulates throughout the lymphatic system, much as blood moves through the arteries and vessels of the circulatory system. This watery fluid is derived from blood, but leaks out of the circulatory vessels into the tissues of the body. The lymphatic system moves the lymph from the tissues and returns it to the circulation via the thoracic duct.

SLIDE 6 Lymphedema occurs when lymphatic fluid builds up in the soft tissues of the body, usually in arms or legs. This occurs if the lymphatic system is compromised, especially if lymph vessels become damaged or are missing. Lymph then cannot move freely through the system & fluid can build up to cause swelling in the affected arms or legs. There are 2 types of lymphedema, included inherited (congenital disease where you are born lacking lymph nodes and vessels) and secondary (resulting from an injury to your lymphatic system). Lymphedema is a debilitating progressive condition with no known cure.
SLIDE 7 In the primary lymphoid organs, the immune cells are undergoing development and do not produce an immune response in the primary organ. T cells undergo development in the thymus; and, B cells undergo development in the bone marrow. Mature lymphocytes leave the primary lymphoid organs in the blood or lymph and travel to the peripheral (secondary) lymphoid organs. T lymphocytes primarily patrol the body on the lookout for foreign antigens in the lymph & blood to mucosal & cutaneous tissues.

SLIDE 8 This slide identifies the primary and secondary lymphoid organs. Notice on the slide the location of the primary lymphoid organs. These organs include the blood marrow and the thymus. Also note the secondary lymphoid organs - Examples of these organs include the lymph nodes and the spleen. This diagram also shows the other major organs of the lymphoid system. Both tonsils and Peyer’s patches are small masses of lymphatic tissue, which serve to prevent infection in the body at areas where bacteria is abundant. There are Eve tonsils which form a "ring" around the throat that helps trap and remove any foreign pathogens entering the throat through breathing, eating, or drinking. Peyer’s patches are located in the small intestine and resemble tonsils, where macrophages prevent infection of the intestinal wall by destroying the bacteria present in the moist environment of the intestine.
SLIDE 9 Bone marrow is essential for the production of B lymphocytes and functions as a primary lymphoid organ. In addition, red blood cells, granulocytes, platelets, and monocytes are produced in the bone marrow. It is thought that under certain conditions, limited immune responses can also occur in the bone marrow. Mature B cells are transported by the circulating blood to secondary lymphoid organs, where they will encounter and respond to foreign antigens. Leukemias are cancers of the blood or bone marrow characterized by an abnormal proliferation of white blood cells (leukocytes). Cytokines released by the stromal reticular cells that surround the immature B cells assist in B-cell maturation. Comparable with T-cells, B lymphocytes also undergo negative and positive selection. Once a B-cell is producing surface immunoglobulin (meaning IgM), it is committed to one antigen-binding specificity (This is also known as 1 cell-1 Ab rule).

SLIDE 10 The thymus gradually enlarges during childhood but then begins to decrease after puberty. Zinc and thymic protein supplements may improve thymus function. The thymus contains 4 cell types: lymphoid, epithelial, macrophages, and other supporting cells. The thymus is necessary for T-cell production. The thymus involutes and experiences cortical atrophy (or shrinks) as a person ages. There is no lymphatic drainage into the thymus. This means that the thymus does not receive lymph or antigens; and, therefore, there is no immune response in the thymus. Maturation of thymocytes occurs during the migration from the thymic cortex to thymic medulla. The flow is from the outer to the inner part of the thymus. Any thymocytes which can recognize and respond to “self” antigen as “foreign” are eliminated. This is known as negative selection and is important in preventing autoimmunity. Many of these cells undergo apoptosis which is programmed cellular death.
**Slide 11**

This diagram shows the structure of the cortex and medulla of the thymus. Notice the different cells that are surrounding the developing thymocytes.

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**Slide 12**

In addition, thymocytes with an affinity for “self” major histocompatibility (MHC) recognition are selected for survival. This is known as positive selection. “Self” MHC recognition is necessary for antigen presentation and the resulting immune responses that occur as we’ll see later in the course. Most T cells do not make it out into the circulation - 90-95% of all thymocytes die in the thymus.

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**Slide 13**

This diagram indicates the bone marrow as the source of progenitor cells, which then migrate to the thymus (only T cells for maturation) and then to secondary lymphoid organs.
SLIDE 14 This slide shows a thymic lobule. Note the blood and lymphatic flow in the lobule.

SLIDE 15 The secondary lymphoid organs are the battle sites— they function to trap the foreign antigens & then the B cells & T cells work closely together to neutralize them.

SLIDE 16 The secondary lymphoid organs include both the lymph nodes and spleen which are encapsulated organs and the Mucosal Associated Lymphoid Tissue or MAIT which are nonencapsulated tissues. Each of these secondary lymphoid organs protects different parts of the body. For example, the lymph nodes filter the regional lymph flow. The spleen filters the blood; and the MAIT protects mucosal surfaces.
Slide 17

The spleen is an encapsulated organ that filters blood to remove antigens and old erythrocytes. It contains both red and white pulp (PALS). The white pulp is composed of the PALS (or periarteriolar lymphoid sheath), which contain T cells along with B cells that are embedded in follicles. In addition, the white pulp also has a marginal zone which contains antigen-presenting cells (or APC’s) (Examples of APCs include macrophages and dendritic cells). As for the red pulp, it is responsible for the removal of old erythrocytes; and, it also contains phagocytes. The next slides will show examples of the spleen and will illustrate the PALS.

Slide 18

The spleen is the major organ in the body where antibodies are synthesized and from which they are released into the circulation. This slide also shows the internal structure of the spleen. Note the sites of the red and white pulp.

Slide 19

This slide shows the exterior of the spleen and the blood supply for the spleen. The spleen is vulnerable to injury; particularly if it is enlarged due to any underlying disorder (infectious mononucleosis is the most common). Risk often increases with contact sports, bleeding disorders such as hemophilia, and illness that causes spleen enlargement (mono). A splenectomy (surgical removal of the spleen) is recommended, as the body can cope without it. A person might be more susceptible to infections after the operation and their blood may also contain odd-shaped red blood cells. Immunizations are recommended to prevent infection, especially the pneumococcal vaccine.
SLIDE 20 This slide shows both the white and red pulp of the spleen. Note the different divisions of the white pulp. The sections of white pulp are arranged around a central arteriole to form the PALS. T-cells primarily surround the central arteriole. The B-cells in the PALS may be found in aggregates of unstimulated B-cells or in aggregates of stimulated B-cells. These aggregates of stimulated B-cells in the PALS are known as germinal centers. These germinal centers contain memory B-cells. Approximately 50% of spleen cells are B lymphocytes, and 30-40% T cells.

SLIDE 21 Lymph nodes occur at strategic points in the body. They function to filter lymph from numerous sites including subcutaneous, visceral and mucosal areas. Principal groupings of lymph nodes are based in the armpits, neck, chest, abdomen, pelvis, and groin. The neck, armpits, and groin lymph node clusters are especially important because they are located where the head, arms, and legs (the extremities) meet the main part of the body (the trunk). Most injuries to the skin occur in the extremities, and this helps keep pathogens from reaching the vital organs.

SLIDE 22 The interior of the lymph node contains a cortex, a palacortex, and a medulla. The cortex is composed of follicles and germinal centers which contain B-cells. In contrast, the palacortex contains T-cells and antigen-presenting cells (APCs); and the medulla contains macrophages and plasma cells. Plasma cells are mature B-cells and are involved in antibody production. The lymphocytes normally exit the lymph nodes via the high endothelial venules (HEV). The HEV is composed of cuboidal endothelial cells, which are activated endothelial cells. This activation of the normally inactive endothelial cells can be produced by such cytokines as interferon gamma, interleukin-1 and tumor necrosis factor (TNF). These activated endothelial cells then express “addressins” that direct lymphocytes toward specific tissues. HEV may also develop in areas of chronic inflammation where normally HEV is not present. HEV at chronically inflamed sites direct lymphocytes to the areas of inflammation.
| Slide 23 | **Lymph Nodes**

Two directions of lymphatic flow:
- **Afferent** (contains Ag) lymphatics
  - into node, contains “bad” stuff
- **Efferent** (contains T cells & Ab) lymphatics
  - out of node, contains “good” stuff to circulate

SLIDE 23 The basic structure of the lymph node is composed of afferent and efferent lymphatic vessels. The afferent vessels enter the node and carry antigen to the immune cells in the node. In contrast, the efferent vessels leave the node and carry T-cells and antibodies to rest of the body. |

| Slide 24 | **Lymph Node**

SLIDE 24 This slide provides a detailed view of the organization of a lymph node. Notice the germinal centers and primary follicle in the palacortex. Do you remember what cells are primarily found in the germinal centers and primary follicle? |

| Slide 25 | **Lymph Node**

SLIDE 25 This slide shows the organization of a lymph node. Notice its detailed view of the post-capillary venule. In the node, the “trapped“ antigen interacts with macrophages, B cells, and T cells to bring about an antigen specific immune response (adaptive immunity). Lymph, antibodies, and T cells leave the node via the efferent lymphatic vessel & into the circulation. |
**Slide 26**

This slide shows the production of lymph. The heart pumps blood out to the body. As the blood moves through the arteries and arterioles, some of the fluid portion leaks from the post-capillary venules into the areas around tissues. This is interstitial fluid that assists in providing oxygen and nutrients to the cells. This fluid collects in the lymphatic vessels and is processed by the lymph nodes. The lymph drains into the thoracic duct and empties into the subclavian vein from where the fluid again reaches the heart.

<table>
<thead>
<tr>
<th>Blood in Capillary Fluid from post-capillary venule</th>
<th>Intestinal Fluid O₂, nutrients Ag in tissues</th>
<th>Lymph Collected in Lymphatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Arteries &amp; Arterioles</td>
<td>Lymph Node, Filtration Removal of Ag, Release of Abs and cells</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>L. Subclavian Vein to Blood</td>
<td></td>
</tr>
<tr>
<td>Lymph into Thoracic Duct</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Slide 27**

This slide shows the time frames for fluid circulation through the lymphoid organs throughout the body. It may take several hours for lymphatic fluid to make a complete circuit of the body. This slide also shows the lymphatic system circulation and its connections with the primary and secondary lymphoid organs.

**Slide 28**

Historically, plague has also been called the Black Death as the bacteria cause swelling, inflammation & necrosis of tissue, especially in lymph nodes called buboes (or Bubonic plague). It also earned the name due to the high mortality or death late when a person became ill with the disease. The blackened areas in photos are usually closest to a flea bite (inoculation site of bacteria), and show how lymph nodes drain & collect the bacteria from the extremities & become most affected (especially nodes in groin from bites on legs, or neck from bites on arms). There are various forms of plague, all caused by the bacteria Yersinia pestis. Bubonic plague is historically the most common. Symptoms of the 3 types of plague (source: CDC):

- **Bubonic plague**: historically the most common. Symptoms of the 3 types of plague (source: CDC):
  - Bubonic plague: enlarged, tender lymph nodes, fever, chills and prostration
  - Septicemic plague: fever, chills, prostration, abdominal pain, shock and bleeding into skin and other organs
  - Pneumonic plague: fever, chills, cough and difficulty breathing; rapid shock and death if not treated early.
PLAQUE & PUBLIC HEALTH

- Ancient disease that has caused 3 major pandemics (in the 6th, 14th, and 19th centuries), unlikely that it will ever be eradicated
- Each year, 1000 to 3000 cases occur worldwide
- Recent identification of multi-drug resistant strains (& its bioweapon potential) have kept plaque as a serious threat to public health

FEAR OF AN EPIDEMIC: Plaque outbreak in India reported in Newsweek, 1996

SLIDE 29 In the United States, 1 to 40 cases are typically reported each year, as the bacteria has established enzootic foci in wild rodents in the southwestern states.

LYMPHATIC FILARIASIS

- Parasitic filarial worms Wuchereria bancrofti and Brugia malayi cause Lymphatic Filariasis
- Infects over 120 million people in 80 countries
- Severe cases called ELEPHANTIASIS
- Worms live in lymphatic system and cause repeated attacks of inflammation
- Fluid collects and causes swelling in the arms, legs, breasts of females, scrotum of males
- Lymph vessels become dilated, thickened, fibrosed
- Fluid collects and causes swelling in the arms, legs, breasts of females, scrotum of males
- Constant inflammation causes permanent damage to lymphatics
- Lymphatic damage leads also to thickened skin & bacterial or fungal superinfections

SLIDE 30 Lymphatic filariasis is an important cause of permanent and long-term disability in tropical and subtropical countries, where it is endemic and transmitted by mosquitoes. The parasitic filarial worms are often transmitted to people when they are children, and overtime, lymphatic damage occurs as the worms make their home in the lymphatic system. In the most severe form, lymphatic filariasis leads to elephantiasis, which is a crippling condition where limbs or other parts of the body are grotesquely swollen. Patients often hide this disease due to these deformities, and because of significant social stigmas about people with elephantiasis. This disease can also have important economic impacts on a community with endemic disease because many patients that have this disease are unable to work. Endemic LF communities may have as many as 10% of women (with swollen limbs) and 50% of men (with mutilating genital disease) impacted by this disease. The good news is that treatment is available for the disease, and mass treatment programs hope to eventually eradicate the disease. GlaxoSmithKline & Merck have donated millions of doses of DEC & Mectizan drugs for use in these programs, which lower the parasite burden when given just once a year. In the late 1990s, programs in China & Tanzania added DEC to table salt to help eradicate the infection. Watch the videos listed on this slide, which showcases public health programs that aim to eradicate the disease by 2020!
### Slide 31
**Epstein-Barr Virus: Infectious Mono**
- EBV is a herpesvirus & one of the most common human viruses
- Up to 95% of adults in the US have been infected (usually as children or adolescents)
- Symptoms of infectious mono include fever, sore throat, and swollen lymph glands & usually resolve within 1-2 months.
- Virus remains dormant in the body for life
- No antiviral drugs or vaccines are available

### Slide 32
**Mucosal Lymphoid Tissue: MALT**
- Non-encapsulated tissue in mucosa of respiratory, gastrointestinal & genitourinary tract; makes up > 50% of the lymphoid tissue
- Protect mucosal surfaces; specialized functions (secretory IgA)
- Nodules containing germinal centers
- Mucosal lymphocytes; LPL & IEL (T memory cells), PC
- Local circulation of cells; homing molecules
- Tonsils, Peyer’s patches, etc.

### Slide 33
**Stress & Immunity**
- Stress can have a significant impact on immune response
- Short-term stressors boost immune system
  - “Fight or Flight” response prompts immune system to ready itself for possible attack (infectious)
  - Examples: public speaking or mental math challenges in a lab, or those in the real world such as academic tests
- Chronic stressors suppress immune system
  - Shifts immune system from adaptive changes of “fight or flight” to negative changes at both cellular level & overall function
  - Decrease nearly all measures of immune system function
  - Examples: injury leading to permanent disability, caring for spouse with dementia, refugee forced from native country by war
  - Elderly or those already ill more susceptible to stress-related changes

### Additional Information
**SLIDE 31** Epstein Barr virus is found in saliva and mucus. Usually it is passed from one person to another through kissing, although it may rarely be transmitted in other ways, such as coughing. Symptoms usually develop 4 to 7 weeks after exposure to the virus. Generally, a person only gets mono once. Sometimes serious complications occur, including the spleen enlarging and even rupturing.

**SLIDE 32** Mucosal lymphoid associated tissue (or MAIT) is non-encapsulated tissue that is found in the mucosa of respiratory, gastrointestinal and genitourinary tracts. MAIT makes up greater than 50% of the lymphoid tissue in the body. Familiar examples of MAIT may include the tonsils and Peyer’s patches. MAIT provides protection to mucosal surfaces and has specialized functions including the release of secretory IgA. Structurally, MAIT has solitary or aggregated nodules which contain germinal centers. There is only local circulation of cells in the MAIT; and, the cells contain homing molecules. MAIT also includes mucosal lymphocytes, lamina propria lymphocytes (LPL) and intraepithelial lymphocytes (IEL) (T memory cells).

**SLIDE 33** Hundreds of studies conducted during the last 50 years have shown the significant impact of stress on the immune system. These immune impacts stem from psychological and physiological signals that occur throughout the body in times of stress. The stress hormones of the fight or flight response either rev up the body for a quick response or tell it to slow down, and also signal the immune system to prepare for battle. For example, stress hormones in the body, such as adrenaline and cortisol released during stress, appear to increase suppressor T-cells, decrease helper T-cells, and decrease functioning of phagocytes and lymphocytes.
(we will learn more about these specific cell types next week). The impact of stress on health has also been shown in AIDS patients, where it has been shown to shorten the time between HIV infection and first symptoms of full-blown AIDS. Stress likely has a greater impact in these cases, as T cells are already compromised. The discussion board during this block will ask you to further research the relationship between stress & immunity. Please include personal stressors in your life that may contribute to less than optimal health (especially during exams, right?!) and how you cope with stress.

**Slide 34**

In Summary

- Primary vs. secondary lymphoid organs
- Know specific anatomic structures of the spleen, lymph node, and thymus
- Understand the function of each organ
- Recognize the close relationship between structure & function necessary of enhancement of immune response

**SLIDE 34 What you need to know . . .**

**Slide 35**

Self-Test Questions: Anatomy

- Name the 2 primary lymphoid organs. How do they function?
- Name the secondary lymphoid organs. How do they function?
- Where are T cells located in the spleen?
- Where are B cells located in the lymph nodes?
- What is an afferent lymph?

**SLIDE 35 Self-test questions for Anatomy & Physiology of the Immune System.**