INTRODUCTION TO THE IMMUNE RESPONSE

Date: Monday, March 11th, 2013
8:30 AM
LH190

LEARNING GOALS

You will be able to identify the fundamental characteristics of both the innate and adaptive immune systems and begin to understand how they must work in concert to protect the host from infectious diseases.

Students who have never had immunology might benefit from reading **Chapter 57** in the **Review of Medical Microbiology and Immunology, 11e.** This is available through the Medical School library at:
http://www.accessmedicine.com/resourceTOC.aspx?resourceID=519

OBJECTIVES

You will be able to:

- Identify the cardinal characteristics of the innate immune response
- Identify the cardinal characteristics of the adaptive immune response
- Understand the relationship between the two systems
- Develop a general perspective on how the immune system responds to survival threats

BACKGROUND READING

Janeway 8th edition: 1-14; 17-25; 37-47(don't even look at Figure 2.2, page 39); 75-78; 85.
Do **NOT** memorize any Table or Figure in the textbook.

LECTURER

John A Robinson, MD

INTRODUCTION TO THE IMMUNE RESPONSE- A SYSTEM DESIGNED TO COUNTER THREATS TO SURVIVAL

I. The immune system is a highly integrated, complex system of cells and molecules with specialized roles for defense against infection.

A. **Who is the enemy**? **Pathogens** are organisms that cause disease. They can be grouped into four major classes- **Parasites**, **Fungi, Bacteria and Viruses**. **You will learn about all of them in detail next semester**. In general, most pathogens need a host (the patient) for some survival advantage so, in many instances, a type of accommodation is reached by which both the host and the pathogen survive to meet another day. Before the advent of antibiotics, host survival might be defined in days or weeks, but during that time the pathogen had usually exploited the living host as a base for proliferation and a launch pad for infecting another host (think lung infection, cough that generates an aerosol of new infectious particles in a crowded elevator).

B. In some cases however, the pathogen can be so lethal that the host can only survive by developing widespread genetic resistance in order to survive. Extreme examples of this can be found in nature- there is good evidence that eons ago an unknown virus almost succeeded in completely wiping out higher primates. The primates that survived appeared to have had a preexisting genetic mutation in an enzyme system, the absence of which prevented the virus from infecting their cells. Less dramatic examples are found today with HIV and presumably with Ebola virus and even avian influenza if either of them should ever break out into widespread epidemics.

C. Both the immune system and pathogens have evolved over time, reacting to each other's strategies by deploying new countermeasures that enhance survival. As threats became more numerous and complex, the immune system also became more complex, specialized and collaborative with the nervous and endocrine systems. The contemporary immune system is now recognized to be a **supersystem.**

II. The primary mission of the immune system is to resist infection.

A. Overview of the Immune System. The immune system in mammals can be broken down into 2 major subsystems**, the innate and the adaptive.**

1. Characteristics of an **innate** immune system are present in most, if not all, multicellular organisms and can be traced back to very ancient times. For example, plants, flies and humans share several innate system genes and receptors.

2. The innate system can be considered **"hardwired**" in that its responses are **encoded in the germ line.** It functions as a sentinel or danger sensing system that is capable of either physically obstructing pathogen entry into the host or directing the ultimate demise of an invader via a network of cells and defensive molecules. The **key advantage** of the innate system is that it can be activated almost instantaneously. The **shortcomings** of the innate system are its lack of the ability to precisely target pathogens, limit collateral damage, and effectively "remember" the encounter. Hence, an innate immune response, once activated, can be indiscriminate in destruction and also may not learn much from the encounter.

3. The **adaptive** immune system developed after the innate system in response to the ever-increasing complexity of infectious threats. In contemporary terms, the immune system had to be **upgraded.** The evolutionary upgrade retained the critical killing components of the innate system and **modified** some of its existing cells to provide critical transition functions for the new **Adaptive** system. The key **advantage** of this system is its memory and specificity. The key **disadvantage** is that it takes 7-10 days before it becomes fully operational.

4. In summary, the innate immune system delays the ability of a pathogen to infect the host, the adaptive immune system can eliminate the pathogen.

B. Initial barriers to infection. To successfully infect a human, a pathogen must breach surface or mucosal barriers. The first level of innate defense is characterized by physical obstructions and simple biochemical toxins.

1. Skin-can be characterized as a tough layer of epidermal cells that can react with local production of various chemicals (see chart below) and antimicrobial peptides called **defensins** in response to pathogens trying to breach the epidermis. Skin, under normal conditions, can rapidly repair itself. The simplest way to understand the importance of skin as an effective barrier is to take care of severely burned patients-they are basically helpless against invasive bacterial infections even in the presence of potent antibiotics.

2. Mucosa-developed as a **host/environmental interface capable of gas and nutrient transfer-** lacks the tough semi-permeable layer of skin epidermis and is more vulnerable to invasion. Its innate defensive strategies must be different and they range from mucus that can trap invaders, constantly beating cilia that eject particles from the lung to very low pH in gastric secretions, the vagina and urine. Tears and saliva are rich with hydrolytic enzymes to reduce bacterial populations. Mucosal-rich regions like gut and lung subsequently developed their own ***regional*** immune systems with specialized molecules not found in most other parts of the body (more on this later in the Course).

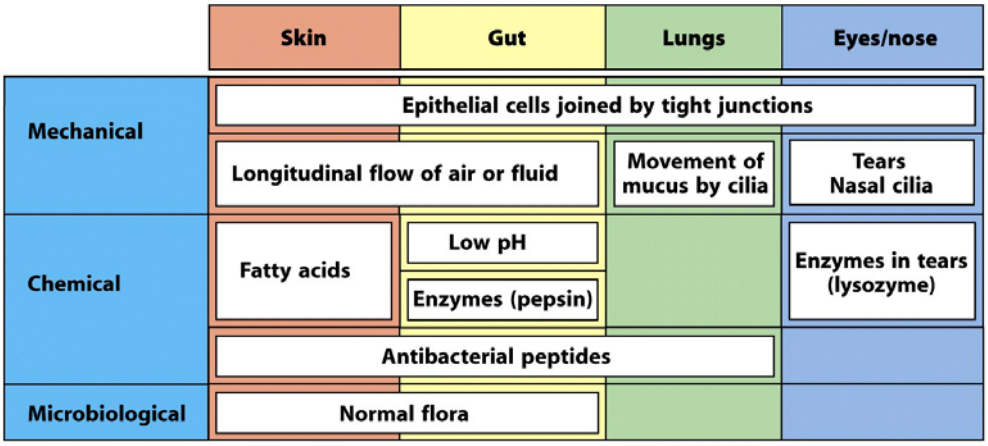


Figure 2-7 Immunobiology, 7ed. (© Garland Science 2008)

C. The second line of innate immune defense is a group of cells that provide initial protection against pathogens that have successfully breached physical barriers. These cells can be rapidly mobilized to sites of infection and have very effective killing mechanisms.

1. Activation of the Innate Immune System

a. The first requirement of a system designed to protect humans is that it must be able to **RECOGNIZE** danger.

i. To sense danger, innate immune cells need to be able to detect differences between themselves and a pathogen or a damaged cell. They do so by sensing molecular patterns unique to microbes and damaged cells and absent in normal cellular structures.

ii. The molecular danger patterns are called **pathogen-associated molecular patterns (PAMPs)** or, in the case of damaged cells, **damage**-associated molecular patterns **(DAMPS**) and the receptors on the innate cells that recognize both of them are called **PRR (pattern recognition receptors).** There are 3 known major families of PRR: TOLL-like receptors (TLR), retinoic acid inducible gene receptors (RLR) and nucleotide binding domain and leucine rich repeating receptors (NLR). ***Do not memorize their full***

descriptive names- from now on they should be known only by their acronym- and to make matters even easier, I will refer only to TLR but in a functional sense TLR means TLR, RLR & NLR.

b. Activation of a TLR is the "ON" switch for an innate immune response and the gateway to an immune response.

2. Once danger has been detected, innate immunity uses 2 general pathways to neutralize the threat.

a. One pathway utilizes **soluble proteins synthesized in the liver.**

i. **One family of these proteins** that circulate in the plasma can bind to mannose containing structural components of bacterial cell walls (mannose very rarely, if ever, is displayed on a human cell surface). The activation of the **mannose** (aka mannan) **binding receptor** facilitates the uptake of the bacterium into phagocytic cells. The mannose binding protein system is the **ancestral precursor of the antibody (immunoglobulin) systems** that are key components of the adaptive system.

ii. Another innate amplifying system is a complex series of serum proteins, most of which are synthesized in the liver, designated the **complement system.** You will learn much more about this innate defense mechanism later in the Course

b**.** The other pathway utilizes **immune effector cells** that you will learn how to recognize in the upcoming Dr Clancy lecture and an on-line histology tutorial.

3. The Cells of the Innate Immune System. The innate system has developed a large coterie of rapid response white blood cells called leukocytes that are derived from pluripotent stem cells in the bone marrow. A general characteristic of several groups of these cells is a cytoplasm rich in granules. These granules contain a rich blend of killer molecules and metabolic pathways that can generate low pH and oxidizing agents. Release of the granules to the extracellular environment will be highly lethal to pathogens but also to surrounding tissue. Most of these cells can be produced in prodigious quantities once the bone marrow is instructed to do so and can be then rapidly transported by peripheral blood to an area of infection. They do not have antigen specific receptors and do not remember their encounters with pathogens. **The origin, development and basic functions of leukocytes will be fully covered by Dr. Clancy in a subsequent lecture.**

4. Innate leucocyte highlights

a. Neutrophils are also termed **granulocytes** or **polymorphonuclear leukocytes (PMN).** This is the most common leukocyte in the peripheral blood and is the final arbiter in most inflammatory reactions.

b. Eosinophils are closely related to neutrophils but have specialized granules that were originally developed to drill holes in large parasites like worms. Over time they have become pathologic mediators of several types of allergic reactions. Eosinophils are relatively rare in peripheral blood under normal conditions but can increase rapidly in patients with parasites or allergic reactions.

c. Basophils and **Mast cells** are the least common leukocytes found in peripheral blood. These cells can act as antigen presenting cells and also have specialized granules and receptors that are important in specialized antibody reactions and parasite defense.

d. Monocyte/Macrophage (M/M). A vital cell for almost all types of immune functions and a pivotal cell in both the innate and adaptive immune systems. The monocyte is the circulating precursor to the tissue avid macrophage. This cell is highly adaptive and has very effective phagocytic ("to eat") and killing mechanisms. M/M can differentiate into 2 subsets with different functions.

e. Dendritic Cells (DC) are the sentinel cells of the immune system and the critical cell that activates the adaptive system. These bone marrow derived cells are present in all tissues and continuously sample the environment for danger. DCs are rich in TLR and activated by recognizing DAMPs and PAMPs **(much more to follow).**

5. Innate lymphoid cell highlights (ILC)

a. Natural Killer Cells (NK) are large granular lymphocytes that most likely developed in response to the debut of viruses in the scheme of things. Although they contain granules, they are usually called lymphocytes, not granulocytes. Like DC, NK cells constantly sample the cell surface of host cells looking for evidence of viral infection or mutations. NK cells recognize DAMPS & PAMPS and do not have antigen specific receptors. For a long time, it has been dogma that they are incapable of remembering pathogen encounters and had no regulatory functions. Both those dogmas now appear not to be true and this revelation emphasizes the blurring of the traditional lines between the adaptive and innate immune responses.

b. **γδ lymphocytes and NKT lymphocytes** can interface with both innate and adaptive immunity, are assigned to patrol certain anatomical sites and may represent a key evolutionary step in the development of the adaptive system

III. Cytokines are mandatory participants in immune responses.

A. Once activated, innate system cells facilitate rapid reactions to infections by "talking" to each other with small messenger peptides called **cytokines.**

B.What are cytokines?

C. Fundamental concepts of cytokines.

1. Most cytokines have two peptide chains encoded by separate genes. Homology studies strongly suggest "new" cytokine genes and the genes for their receptors have evolved from primordial hemo-proliferative growth factors and immunoglobulin gene clusters by duplication events. For example, fish and even worms, have some cytokines similar to those found in humans.

2. Evolutionary pressures have driven most cytokine systems to develop **families, pleiotropism and redundancy**. The overlapping of many of their biologic effects supports this concept.

3. Cytokines act at concentrations similar to endocrine hormones, are polypeptides with 70-190 amino acid composition, and usually are produced only after appropriate cell stimuli

4. Most cytokines can be expressed by a wide variety of immune and non-immune cells. Many cytokines have fundamental homeostatic housekeeping functions and cytokine production and receptor availibility are dependent on multiple genes

5. Cytokines are **the mediators** of cellular communications that provide the critical links in humoral (antibody-mediated) and cellular mediated immunity (CMI).

6. Antigen specific immune effector cells (lymphocytes) and their non-antigen specific counterparts such as monocytes and macrophages (M/M) and dendritic cells, **"talk" to each other via cytokine production, release and cytokine receptor display.**

IMMUNOCOMMUNICATION

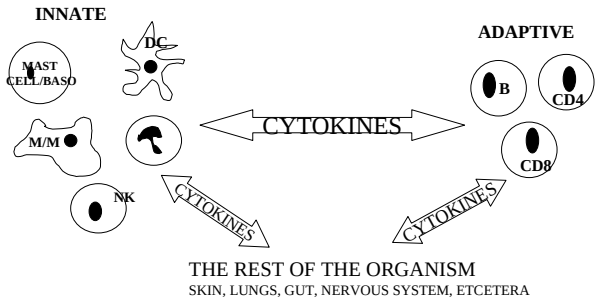


Figure by John A. Robinson, MD

7. Lymphocytes and macrophages produce multiple cytokines and use them to either dampen or accentuate the level of intensity of an immune response, i.e., regulate the response by altering not only cytokine production but also the **density and affinity** of their cytokine **receptors**.

8. Most cell-cytokine systems have **agonist/antagonist** (Yin/Yang) dynamics in order to prevent runaway immune reactions.

9. Cytokine effects can vary, often paradoxically, depending upon stage of activation and differentiation of their **target cells.**

10. Poorly regulated or deficient cytokines can be **pathologic.**

THE FIRST HOST DEFENSES

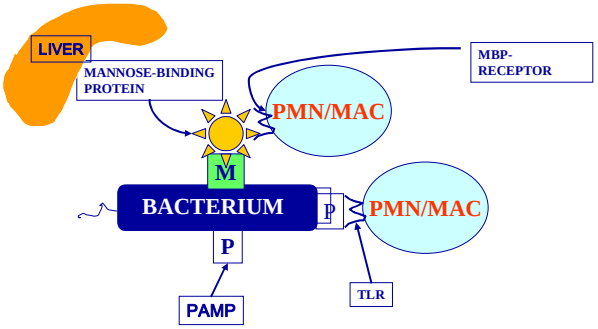


Figure by John A.Robinson, MD

IV. The Adaptive Immune System-also called Acquired Immunity (All the following are discussed in detail in subsequent lectures, this is a fundamental overview ONLY.)

A. An increasingly complex world forced parallel evolutionary changes in the way organisms react to threats. **The innate system is one that reacts to ancestral cues and is hard-wired in the sense that its recognition mechanisms are in the germ line.** Neutrophils and macrophages are recruited, activated and destroy rather indiscriminately.

B. About 450 million years ago, when recombinase genes rather abruptly appeared in early-jawed vertebrates (the so-called "big bang of immunology"), a higher level of defense evolved.

1. The **adaptive immune system** was born when the innate system was refined and provided with new capabilities that permitted immune cells to **specifically recognize an almost infinite number of antigens.**
2. **Antigens,** sometimes called immunogens, are usually foreign proteins/peptides that **stimulate immune responses**. **They can be viewed as a refinement of the PAMP concept.**
3. **Clonal expansion** of the immune cells **after** antigen recognition guarantees a highly efficient response.
4. **The adaptive system learns how NOT to react with self antigens (autoimmunity).**
5. **The adaptive system REMEMBERS the specific encounter.**

C. The innate system now not only provides the initial response to a pathogen while the adaptive response is gearing up by virtue of clonal expansion (usually 3-5 days) but also becomes **the gateway to and facilitator of the adaptive response and then is re-utilized as the final arbiter of the defensive reaction.**

D. In summary, the emergence of the adaptive immune system represents a quantum leap in immunologic efficiency.

E. Cells of the Adaptive System.

1. **Macrophages and especially dendritic cells** are given **new functions-** the uptake and processing of pathogens, intracellular transportation systems to take the processed portions back to their surface and display them as red flags proclaiming the presence of

infection. This alerts the adaptive system that an immune response needs to be initiated.

2. **The Small Lymphocyte is the orchestrator of the adaptive immune response.** It is highly likely that this cell evolved from ILC. The small lymphocyte has the ability to generate specific antigen receptors on its surface, communicate with other cells after it recognizes an antigen, proliferate in response to the antigen and then amplify a specific targeted lethal response by the production of specifically targeted killer cells or antibodies to the pathogen. The lymphocyte also remembers the encounter so that a **secondary,** specific reaction to the same pathogen will be much more rapid and efficient.

F. **Recognition and regulation mechanisms of the Adaptive System**.

1. Parallel to the development of **antigen presenting cells (APC)** such as dendritic cells, **lymphocytes** developed the genetic machinery to specifically recognize antigens being presented to them by APC.
2. **Adaptive Lymphocytes** further developed into two major specialized groups.

a. One group, **called B cells,** ultimately differentiate into **plasma cells** that produce highly specific protein **antibodies.** This specific immune reaction is called the **humoral immune response** and is a major defense against infections and toxins that thrive in extracellular fluids.

b.**T cells** are the other major group of lymphocytes**.** T cells orchestrate the immune response (**helper function**) and can also specifically target and kill cells when necessary (**cytotoxicity function).** The T cell arm of the adaptive response is called **cell-mediated immunity** and is particularly effective against infections that hide inside host cells. T cells also **regulate** the immune response in several different ways. and can turn on the host and cause disease.

G. **Effector Molecules of the Adaptive System**

1. Innate amplifying systems have been **adopted** by the adaptive system. A prime example is the **complement system**, a complex series of enzymes that act in cascade fashion to amplify an innate response. The adaptive system uses it to **amplify** the specific immune response generated by an specific antigen-antibody reaction
2. **B-lymphocytes** have developed the capacity to **clonally** proliferate after they recognize and bind a discrete antigen to specific antigen receptors on their surface. The specific binding of an antigen to its receptor induces B lymphocytes to differentiate into plasma cells. The latter are protein-producing factories that release **antibodies** into the plasma and extracellular

fluids. The antibodies have exquisite specificity for the antigen that stimulated their production and can induce a wide spectrum of protective biological effects after they encounter and bind to that antigen.

3. **Cytokines.** The "cell phones" and communicators of the innate immune system have been upgraded to regulate and fine- tune the adaptive response. You will learn their specifics in the context of the different types of immune responses discussed in future lectures.

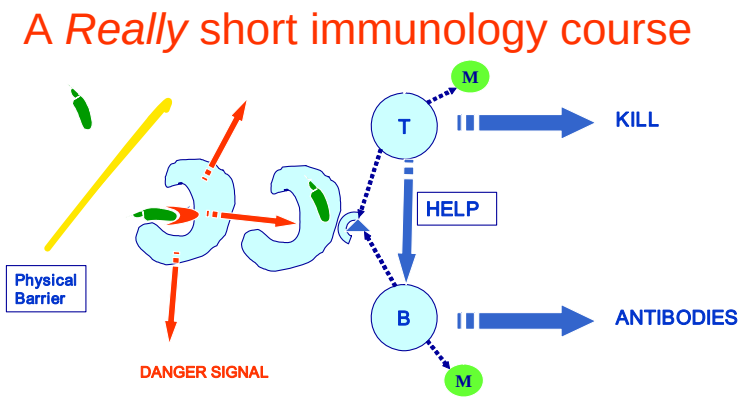


Figure by John A. Robinson, MD

Comparison of Innate and Adaptive Immunity

	Innate Immunity	Adaptive Immunity
Timing	Immediate response	Lag between exposure and response
Specificity	Effector cells are not antigen specific	Effector cells are antigen specific
Memory	No immunologic memory	Immunologic memory

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Expressed by all cells of a particular type (e.g. macrophages)	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogens	Yes	No
Interacts with a range of molecular structures of a given type	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal distribution	No	Yes
Able to discriminate between even closely related molecular structures	No	Yes

Figure 2-13 Immunobiology, 7ed. (© Garland Science 2008)

Study Questions:

1. Identify three major differences between the innate and the adaptive immune systems.
2. Identify a major mechanism that evolution has employed to counter infections.
3. Describe how pattern recognition by immune effector cells benefits the host.

WELCOME TO HOST DEFENSE

- This is the best course in the first year
- This is the most interesting course in the first year
- This is the most difficult course in the first year
- This is the most fun course in the first year
- I have heard that this class is all high achievers, so I am going to assume you are second years now and there is a lot of clinical information in the course

Host Defense

- The Textbook
- Lecture Notes and lectures-**ALWAYS TRUMP THE BOOK.** This is very important to remember at test time and during the test review.
- There is extensive redundancy in the course- with good reason
- For those of you who have never had immunology…some of you (probably 10% or more) will be very lost early on….do NOT panic..I promise you that it all comes together as the course progresses
- If it doesn't , I will help you with it but do NOT wait until after the first test!

Histology & Small Groups

If you view the movies, most of you will know the necessary histology. Histology will also be part of a small group. There will be questions on normal histology on the first test.

A third of the final is material taken from the small groups

If you understand the small groups you cannot fail the course

To understand the small groups you need to be there for the facilitated discussion

A master answer is posted at the end of each small group so that everyone gets the same information

Over the past 2 years, enough people decided to not go and just read the master answer. That unfortunately has led to a need for a sign in sheet for small group attendance.

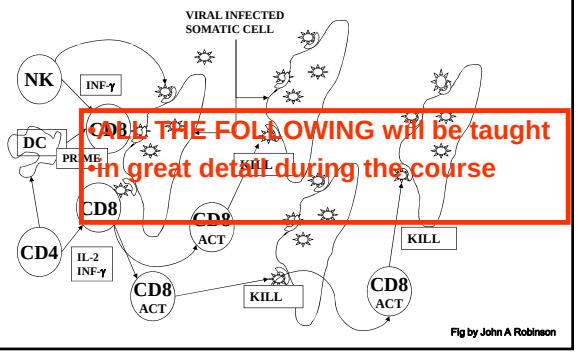
Tests

- There are only two (2) tests with approximate equal value.
- Testing is cumulative
- A word to the wise….be sure you don't do poorly on the first test…it is very difficult to catch up if you fail the first exam
- If you are not getting it: SEE ME SOONER RATHER THAN LATER!
- I am always around and can be paged or called(65335 or 68777-11118)

OK- let's get started:what is the immune system????

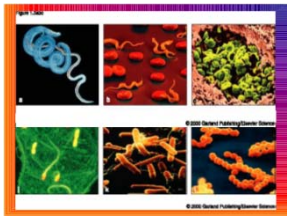
- **The immune system is a highly integrated, complex system of cells and molecules with specialized roles for host defense against infection**
- **The immune system is closely integrated with the nervous and the endocrine systems- making it a supersystem**

PART OF THE SUPERSYSTEM:BELIEVE IT OR NOT-YOU WILL UNDERSTAND THIS IN ABOUT 6 WEEKS



The Problem

– **Major classes are viruses, bacteria, fungi and parasites-all of which you will learn about in detail next semester**



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THE PROBLEM

- HOST- pathogens use the host for a survival/propagation advantage
- To ensure survival, the host employs genetic resistance,physical barriers and……..
- evolved an immune system to counter the creativity of pathogens
- as pathogens increased their complexity, the immune system responded by implementing a super system to ensure survival

Overview of the immune system

- 2 major subsystems
- Innate responses encoded in the germ line and are rapid responders
- Adaptive appeared later and added several improvements but a key disadvantage is that its response time is 7-10 days
- The innate system delays the ability of a pathogen to infect the host, the adaptive system can eliminate the pathogen
- The rest of the course concerns how that happens (and can fail at times)

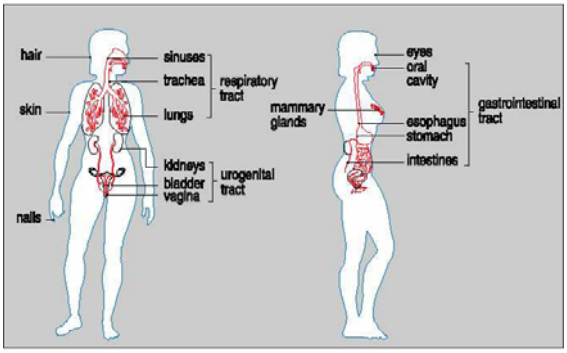
Fundamentals of the Innate system

- **THE FIRST DEFENSE LEVEL IS PHYSICAL AND CHEMICAL**
  - **For example: What defense do Clancy and the dogs have that I don't have?**

SURVIVAL STRATEGIES OF THE HOST

- **SKIN has physical toughness, local molecules called defensins that are toxic and rapid repair capability**
- **MUCOSA FOUND AT OTHER HOST-ENVIRONMENTAL INTERFACES is not as impermeable as skin and has developed cilia, secretions with hydrolytic enzymes and organized regional immune systems**
  - **tears and saliva have hydrolytic enzymes**
  - **gut has wide pH range**
  - **urine very low pH**

Figure 1.4



First line Innate Immunity defense mechanisms

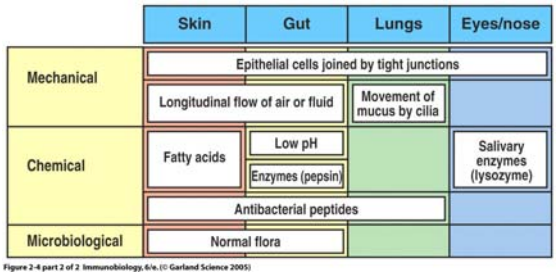


Figure 2-4 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

What is the innate immune system?

I tried but could not do better than this definition!

"The most evolutionarily ancient type of immunity exists in all living multi-cellular species. When exposed to to pathogens or cellular damage, cells of an organism's innate immune system activate responses that coordinate defense against the insult, and enhance the repair of tissue injury. There is a modern day cost associated with these responses, however, because innate mechanisms can damage normal tissue and organs……human life is a balance between dual threats of insufficient innate immune responses – which would allow pathogens to prevail- and over abundant innate immune responses –which would kill or impair directly"

Kevin J. Tracey. 2011.Science 332:673-674

THE INNATE IMMUNE SYSTEM

- Is the second level of defense after a physical barrier has been breached
- The Innate system:
  - Goes **WAY** back in time
  - IS "HARDWIRED" WITH **GERMLINE DERIVED** RECOGNITION MECHANISMS
  - IS CAPABLE OF RAPID RESPONSE
  - IS SOMEWHAT INDISCRIMINATE
  - IS HIGHLY DESTRUCTIVE
  - HAS **NO MEMORY** OF THE ENCOUNTER

Recognition molecules and Activation of the Innate System

- **The Innate immune system must be able to recognize danger**
- **Danger comes in two forms: cell damage or presence of a pathogen**

Recognition and activation of the Innate System

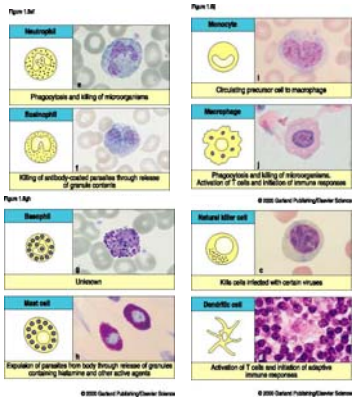
- **Innate immune cells detect danger by sensing molecular patterns unique to microbes or damaged cells.**
- **These patterns are called pathogen-associated molecular patterns (PAMPs) or damage -associated molecular patterns (DAMPS).**
- **Receptors for both are TOLL like receptors (TLR) on the innate cells**
- **When TLR recognize and bind PAMP or DAMP, a signaling mechanism activates phagocytic and killing mechanisms of the cell.**
- **TLRs are the gateway to the immune system and the ignition switch that turns it on**

Once danger is detected, how is it dealt with?

- **Innate Immunity devised 2 general pathways to neutralize a threat**
- **One arm utilizes circulating proteins, the other utilizes immune effector cells**

CELLS OF THE INNATE SYSTEM

- Called leucocytes and characterized by the ability to respond rapidly and in large numbers.
- As a rule, their cytoplasm contains granules that are loaded with killer/hydrolytic/oxidizing molecules that are released in response to a perceived threat.
- Release of these molecules prove lethal to many pathogens but unfortunately can't discriminate between them and underlying tissue.
- Two groups of leucocytes –neutrophils and macrophages-are efficient at phagocytosis



These two are really good at detecting PAMP/DAMPS

All these innate cells Will be discussed in Dr Clancy's lectures & referred to in specific contexts later

Be sure to check out the video on how to identify them that is available on the HD website

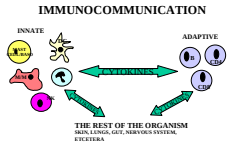
Danger Recognition MOLECULES OF THE INNATE SYSTEM

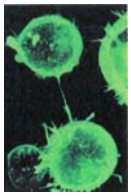
- The innate system utilizes soluble proteins synthesized by the liver that circulate in the vascular system and facilitate activation of immune reactions process during infection
- One family of proteins binds to mannose-containing structural components of bacterial cell walls (mannose very rarely, if ever, is displayed on human cell surfaces) and another group binds to pathogen associated molecular patterns (*pamps)* and expedites pathogen uptake by focusing the coated pathogens on specialized receptors on neutrophils and macrophages.
- The liver also produces another system of proteins that can activate effector cells and recruit them to sites of infection- this system forms the basis of our modern complement system (future lecture)

THE INNATE IMMUNE SYSTEM is an efficient communicator

- Innate cells also developed a crude communication system where they could not only tell each other a pathogen was present but could activate themselves and their neighbors
- these molecules are our ancestral cytokines and the cofounders of our modern adaptive immune system
- Thus the innate system serves as a critical first line of defense, provides fundamental components to our modern immune system and is used as the gateway and bridge between innate and adaptive immunity- our third and best line of host defense

Talking to one another

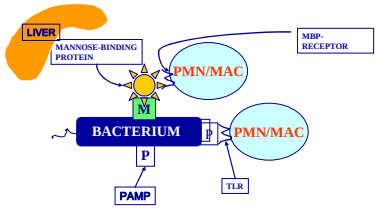




Cytokines are mandatory participants in immune responses

- Usually two chain peptides encoded by separate genes
- Almost all exhibit pleiotropism and redundancy
- Act at concentrations similar to hormones
- Many cytokines can be produced by a wide variety of cells
- They are the great communicators of the immune system
- Lymphocytes and macrophages use cytokines to regulate the intensity of an immune response
- Most cell/cytokine systems have agonist/antagonist (yin/yang) dynamics
- Cytokine actions can vary and are dependent upon the state of the target cell
- Abnormal cytokine responses are associated with serious clinical diseases

THE FIRST HOST DEFENSES



THE ADAPTIVE(ACQUIRED) IMMUNE SYSTEM

- The so called “Big Bang” of immunology
- Was born about 450 million years ago
- has four cardinal characteristics:
  - Recognizes antigens (pathogen components that stimulate immune responses) with very specific receptors
  - can distinguish precisely between self from non-self
  - can clonally expand antigen specific cells after their activation
  - can remember specific encounters (memory)

The strategy of the contemporary immune system

- The Innate system will now provide the initial response to a pathogen and function as the gateway to the adaptive response.
- The initial innate protective response protects the host while the adaptive system is gearing up for a very effective specific response

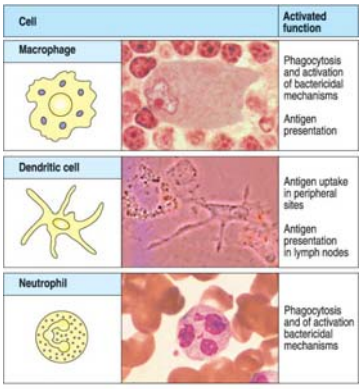


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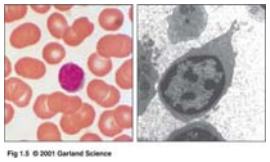
Fig 1.4 part 1 of 2 © 2001 Garland Science

CELLS OF THE ADAPTIVE SYSTEM

- THE LYMPHOCYTE IS THE ORCHESTRATOR OF THE ADAPTIVE IMMUNE RESPONSE
- Lymphocytes with different functions can be identified by markers on their cell surface. These are CDs (cluster of determination) and you will have to memorize a few of them



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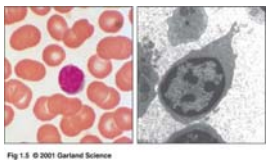
CELLS OF THE ADAPTIVE SYSTEM the small lymphocyte

- Has specific antigen receptors
- Communicates with other cells by cytokines and receptors
- Clonal proliferation
- Generates a response specific for the occasion



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SMALL LYMPHOCYTES

- **Differentiate into two major subgroups:**
  - **B cells differentiate into plasma cells that can produce highly specific antibodies that bind to pathogens and can destroy them by several mechanisms**
  - **T cells that have helper and killer functions. These cells also regulate the immune response by controlling cytokine production**

EFFECTOR **MOLECULES** OF THE ADAPTIVE SYSTEM

- **A highly complex network of cytokines- communicators, activators and regulators – can think of them as iCytokines**
- **innate immunity recognition molecules that evolved to recognize, activate and amplify immune responses**
  - **antibodies are prime example- can think of them as mannose recognizing upgrade**
  - **Complement system**

A *Really* short course

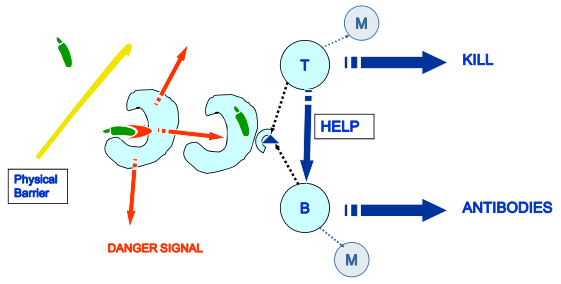

Fig by John A Robinson

Comparison of Innate and Adaptive Immunity

- Timing
  Innate: immediate
  Adaptive: Lag between exposure and response
- Specificity
  Innate: effector cells NOT antigen specific
  Adaptive: effector cells are antigen specific
- Memory
  Innate: None
  Adaptive: Present

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Expressed by all cells of a particular type (eg, macrophages)	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogen	Yes	No
Interacts with a range of molecular structures of a given type	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal distribution	No	Yes
Able to discriminate between even closely related molecular structures	No	Yes

Figure 2-10 Immunobiology, 6/e. (© Garland Science 2005)

Janeway, et. al.
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Christopher M. Wiethoff, Ph.D.

Innate Immunity

Date: Monday, March 11, 2013

Reading Assignment: Janeway 8th edition. Pages 1-13; 37-47.

Learning Goals and Objectives: You will be able to describe the cells and processes involved in innate immunity.

To attain the goals for this lecture you will be able to:

a. Define innate immunity.
b. Identify important receptors and molecules in the innate immune response.
c. List the types of leukocytes that participate in the innate immune response.
d. Describe the recognition mechanisms used by leukocytes to identify pathogens.
e. Describe the early sequence of events at a site of injury or microbial invasion.
f. Identify the key components of the inflammatory process.
g. Understand how the innate and the adaptive system interact to produce optimal immune responses

I. The innate immune system- continued and in more detail.

A. The innate system is our **non-adaptive** host defense against pathogens. The global defense strategies used by the innate system are highly conserved in germ lines throughout nature.

B. Key cells in the innate immune response.

1. **Phagocytes.** Leukocytes that recognize, ingest, and kill invading microbes are called phagocytes. There are two major types of phagocytes.

Macrophages
-are long-lived leukocytes.
-are widely distributed in normal tissues.
-are often the first cell to encounter a pathogen.
-represent the mature form of circulating monocytes.
-increase in number at sites of injury or infection.

Neutrophils
-are short-lived circulating leukocytes.
-are the most abundant type of white cell in the circulation.
-are rarely found in **normal** tissues.

-can be quickly recruited to sites of injury or infection.

2. Macrophages and neutrophils perform several functions that are critical to innate immunity.

a. **Phagocytosis**: The process by which particulate materials are engulfed by a cell and delivered to a digestive compartment within the cell is called phagocytosis. Professional phagocytes are found in large numbers in the peripheral circulation. Tissue bound phagocytes are found in most tissues, but are prominent in the lung, liver, spleen, and skin. Several types of receptors can mediate recognition of foreign particles.
b. Pathogen Associated Molecular Pattern (PAMP) Recognition: Germline encoded intracellular and cell surface PAMP recognition receptors (PRRs) present in macrophages and dendritic cells can recognize bacterial, viral and fungal components and initiate signals leading to the recruitment and direction of B and T-cells. These receptors include the Toll like receptors (TLRs), NOD-like receptors (NLRs), RIG-I helicase-like receptors (RLRs) and, C-type lectin receptors (CLRs).
c. In some circumstances, pathogens undergo **opsonization.** Opsonization is the coating of particles by molecules that enhance recognition by phagocytes.
d. Mediator Production: Upon activation by an appropriate stimulus, phagocytes, particularly macrophages, produce a large variety of cytokines and other soluble protein and lipid mediators that assist in clearance of pathogens. This can occur solely based on innate responses and can be greatly amplified by an adaptive response.

C. **Inflammation.** (You will spend a lot more time on this topic next semester in Mechanisms of Human Disease). Inflammation is a general term for the accumulation of fluid, plasma proteins and white blood cells that occurs in tissue subjected to injury, infectious agents, or immune responses. The initiation of inflammation is part of the innate immune response, and the inflammation that results from an innate response to a threat is termed acute inflammation.

. Inflammation is fundamentally protective.
. Is triggered when pro-inflammatory mediators are released from preformed stores or quickly produced in response to either a infectious or traumatic event.
. Is intended to destroy or wall off the offending agent.
. Is interwoven with tissue repair; as the inflammatory process resolves, tissue regeneration or scar formation occurs.
. Can be destructive, particularly if prolonged.

1. The inflammatory response includes three key events

a. Alteration in blood flow (*calor, rubor, dolor*)
Vasodilatation is an early response, and leads to increased blood flow. Increased

blood flow facilitates the movement of additional serum mediators and white cells into the area of insult.

b. Increased vascular permeability (*tumor*)
Endothelial cells contract, leading to widened intracellular junctions. This is an immediate response and occurs primarily in venules. Later, direct endothelial injury can also occur, causing cell necrosis and detachment. The result is increased vascular permeability and the leakage of serum components into the tissue space.

c. Infiltration of white blood cells into the affected area (tumor)
The time course for the movement of leukocytes into sites of inflammation can be within from hours after injury. The early inflammatory lesion is marked by a preponderance of neutrophils. Later, macrophages (derived from monocytes) predominate. Lymphocytes are generally the last cell type to arrive. In chronic inflammation, lymphocytes may eventually become the predominant cell type.

History for the day: The four cardinal signs of inflammation, Rubor, Dolor, Calor, and Tumor, were described in the first century AD.

II. What turns on the innate system?

The innate system has the ability to recognize danger by microbial pattern recognition. A key advantage of this system is that it can be **activated in minutes**. Understanding how pattern recognition shapes the subsequent nature of an immune response is the key to understanding an optimal immune response works and, even more importantly, understanding how an immune response can go wrong and cause disease.

A. Pattern recognition receptors (PRRs) on DC or macrophages activate an immune response. Eons ago, there was probably one type of PRR because there were simple threats to an organism. Over time, life got more complicated and new PRRs had to evolve or the organism didn't survive. The discovery of the critical role of PRRs in immune responses is also a great example of the need for basic research that, on the surface, appears to have nothing to do with anything in general- actually in this case, dorsal/ventral patterning in flies!

1. What are PRRs?

.a. PRRs are transmembrane (TLRs and CLRs) or soluble intracytoplasmic (NLRs and RLRs) receptors found on many different cell lineages but especially on dendritic cells,

macrophages and monocytes.

.b. They can bind to a wide array of bacterial, fungal, viral and parasitic molecular patterns. The patterns are called **Pathogen Associated Molecular Patterns (PAMPs)**

.c. There are at least 11 human TLRs, 22 NLRs, 3 RLRs and 15 CLRs (DON'T MEMORIZE). They have arisen in an evolutionary response to increasingly complex forms of life that pose a threat to humans.

.d. Typical PAMPs include mannose containing structures, lipids in complex microbial lipopolysaccharides and viral and bacterial nucleic acids.

.e. While some of these PAMPs are not present in eukaryotes possessing PRRs making them easily distinguished from "self", other PAMPs such as DNA are recognized by PRRs by virtue of their improper location (e.g. DNA is not normally found in the cytoplasm or lysosomes of healthy cells unless they are infected with DNA viruses or intracellular bacteria).

.PRRs confer a **limited** specificity to the innate response – nothing like the exquisite specificity of the adaptive response. However that you will learn about later.

.f. Natural selection has dictated that PRRs will recognize a specific PAMP and activate an immune response **best suited to eliminate the type of infecting organism that bears the PAMP**. A prime example is the TLR that specifically recognizes viral nucleic acids. Activation of this TLR will then initiate specific anti-viral responses by signaling for the production of specific antiviral mediators.

.g. In some cases multiple PRRs may recognize a pathogen and their integrated signal will lead to an appropriate response.

Example of PAMP recognition: TLRs

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Innate immune recognition by Toll-like receptors

Toll-like receptor	Ligand
TLR-1:TLR-2 heterodimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI (*T. cruzi*) Zymosan (yeast)
TLR-2:TLR-6 heterodimer	
TLR-3	dsRNA
TLR-4 dimer (plus MD-2 and CD14)	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)
TLR-5	Flagellin
TLR-7	ssRNA
TLR-8	G-rich oligonucleotides
TLR-9	Unmethylated CpG DNA

Figure 2-16 Immunobiology, 7ed. (© Garland Science 2008)

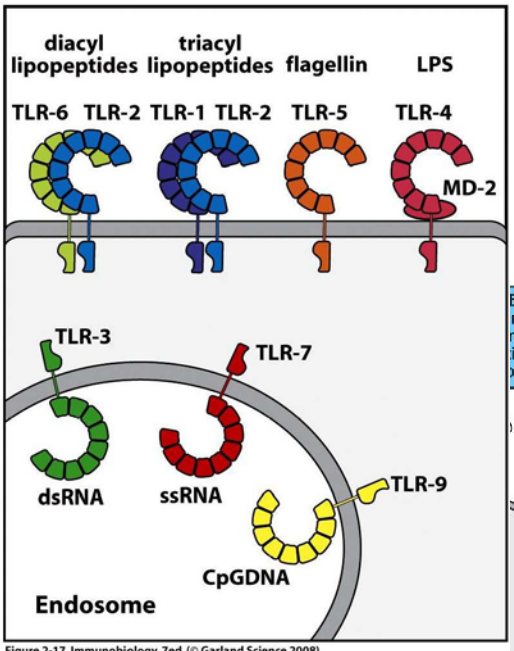


Figure 2-17 Immunobiology, 7ed. (© Garland Science 2008)

Figure 6-21 Immunobiology, 6/e. (© Garland Science 2005)

DO NOT MEMORIZE THE ABOVE TABLE/FIGURE!!!!.

2. What happens when a PRR is activated?

.a. Common characteristics of TLR activation are downstream signaling pathways in phagocytes/DC (see above figure). The final common path for pro-inflammatory activation is NF-κB. Activation of transcription factor NF-κB activates genes encoding pro-inflammatory cytokines. You will learn much more about these later

.b. On many occasions, PRR activation on a phagocyte (macrophage or neutrophil) is all that is required to resolve a simple threat by phagocytosis and intracellular destruction of foreign particles and "simple" bacteria.

3. What happens when the TLR is missing or incorrectly activated?

a. By the end of the course you will be able to answer this question and predict what type of pathology might ensue when there are either too many copies of TLR present or the TLR is mutated or missing.

III. Critical cells in the innate immune response that interface with the adaptive system.

These cells are not only responsible for initiating and maintaining an innate immune response but also provide the transition to an adaptive immune response and determine its character, intensity and type.

A. Dendritic cells. In many ways, DC are the most important cell in the immune system. DC are key sentinel cells that act as the gateway to the adaptive response. DC determine what type of adaptive response will occur.

1. Characteristics of Dendritic cells:

.a. Roam freely throughout most, if not all, tissues and organs.
.b. Display multiple types of PRR
.c. Phagocytize pathogens (antigens)
.d. Become effective antigen presenting cells
.e. Direct the type of adaptive response based on PRR activation and/or interaction with other innate cells, especially NK and γδ lymphocytes
.f. Can secrete different cytokines that also shape the character of the adaptive response by influencing lymphocyte differentiation and maturation.

B. Natural Killer Cells.

.a. A small proportion of lymphocytes circulating in the blood are called natural killer (NK) cells because they are can directly kill specific target cells, including virally infected cells and some cancer cells.

.**b.** Natural killer cells are derived from lymphoid progenitors.

.**c.** The specificity of the receptors that NK cells use to recognize targets is not diversified like T and B cells. Because NK cells are pre-programmed to respond to their targets, and do not diversify in response to antigens, they are often considered a part of the innate immune response.

.d. NK continuously sample the environment by looking for cells with altered self expression, such as virally infected cells and some cancer cells.

.e. There is increasing evidence that there are critical interactions between activated DC and NK cells that are critical for determining the type of adaptive response.

C. Restricted subsets of lymphocytes. Several minor subsets of lymphocytes express only a limited diversity of receptors, and are thus termed innate-like lymphocytes. The functions of these subsets are not well understood yet. But they may have strong influences on DC maturation.

.**a. NKT cells**. NKT cells are not NK cells, but are instead a subset of T cells and very likely represent a transitional cell during evolution of the system. NKT cells carry a TCR that is restricted to **glycolipid (instead of peptide) antigens**. The function of NKT cells is probably to provide immediate help for the adaptive immune system, as they produce cytokines that can influence both cell-mediated and antibody-mediated responses.

.**b.** $\gamma\delta$ **lymphocytes** may have been the first step in the evolution of lymphocytes to specialized subsets of the adaptive response. They recognize small molecule phosphoantigens which are metabolic intermediates in lipid biosynthesis in bacterial but not in mammals under normal circumstances. They serve unique functions at host-environmental interfaces and care found in large numbers in the respiratory and gastrointestinal submucosa (more on these later in the course)

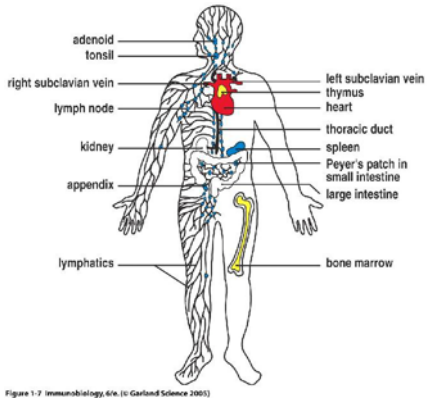
IV. Functional geography of the Innate and Adaptive immune system.

A. The architecture of the immune system is similar to a network.

1. **Primary Lymphoid Tissue**: The bone marrow is our major source of almost all effector cells, the thymus is a gland in which a major group of lymphocytes learn how to distinguish self from non-self. (full lecture later)

2. Secondary lymphoid tissue: Lymph nodes function as regional processing, manufacturing and distribution centers for specific resistance to infection. The spleen acts in similar fashion but also specializes in responding to blood-borne pathogens and is a major antibody production and immune effector cell center (full lecture later).

3.Regional/Specialized lymphoid tissue: Submucosal lymphoid tissue is organized to respond to respiratory and gastrointestinal threats. The liver is a major immunologic scavenger site (later lecture).



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A. The very short geographic course on innate immunity is that it will activated wherever there is a breach of defense and will be characterized by recruitment of inflammatory cells

B. The very short anatomic/geographic course on adaptive immunology is then:

1. Antigens (immune stimulatory molecules) derived from pathogens are either delivered to the Lymph Node/Spleen system by dendritic cells or via the blood.
2. Once there, the antigens activate the adaptive system of B and T cells residing in the lymphoid tissue
3. The adaptive response culminates in activated T cells and antibodies
4. The activated T cells and antibodies exit the Node/Spleen and migrate to area of infection and eliminate the infection.

V. THE BEAUTY OF IT ALL –or what the rest of the Course covers ……..

. A major difference between the Innate and Adaptive immune systems is that the innate system has a relatively simplistic way of identifying microorganisms by sensing foreign sugars and DNA but the adaptive system recognizes microbial peptide derivatives by virtue of specific cell receptors on lymphocytes.

. The innate system has no specific memory of a response whereas the adaptive system does.

. Lymphocytes in the adaptive system can marshall large populations of antigen specific cells by clonal expansion after they recognize "their" antigen but there is no such parallel in the innate system.

. The innate system modified its danger sensing mechanisms to include ways of showing the adaptive system what the precise cause of danger was. The adaptive system in parallel developed ways to specifically attack the pathogen after being alerted to it by the innate system to and uses components of the innate system as the end solution to the threat.

. The 2 systems have joined forces to provide the host with a coordinated, highly efficient, focused response to external threats characterized by **cellular immunity,** a process during which host effector cells are induced to kill pathogens directly, and

humoral immunity, a process that utilizes the production of antigen specific antibody immunoglobulins to neutralize or target pathogens for elimination.

Below is a simplified cartoon view of innate and adaptive immunity. The Course builds on this and by the end you will understand and appreciate the Supersystem.

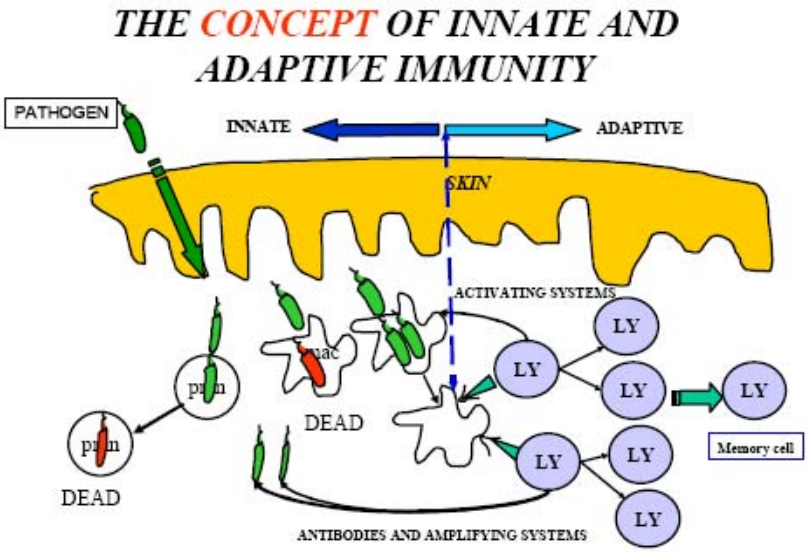


Figure by John A. Robinson, MD

Sample study questions:

1. What are the key differences and commonalities of the 2 key phagocytic cells in the innate system?
2. How can toll receptors control the type of immune response?
3. Which innate cells are critical links to the adaptive system and what type of link do they provide?

Cells and Structure of the Immune System

Date: Friday, March 15th, 2013
9:30 AM
LH190

LEARNING GOALS

You will be able to describe the location, structure and general function of the bone marrow, thymus, lymph nodes, spleen and mucosal associated lymphoid associated lymphoid tissue.

OBJECTIVES

To attain the goal of this lecture you will be able to:

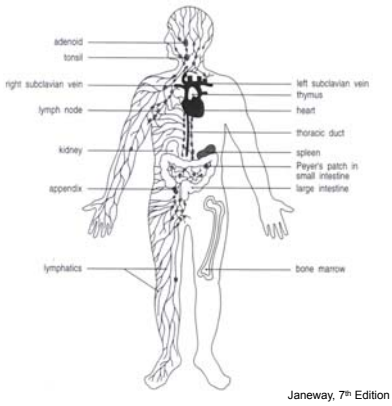
- Describe the growth factor control of erythropoiesis, thrombopoiesis, granulopoiesis, monocytopoiesis, dendritic cell development, and lymphopoiesis.
- Describe the hematopoietic niche and its importance.
- State the difference between central (primary) versus peripheral lymphoid organs.
- Describe the development, structure and general function of the thymus.
- Diagram the path taken by lymph versus blood as they flow through lymph nodes. Understand the similarities and differences between T and B cell circulation as well as location within the lymph node.
- Describe the structure and function of the spleen. Understand the difference and function of the white and red pulp.
- Compare and contrast the path taken by T and B cells as they circulate through lymph nodes and spleen.
- Describe the different classes of lymphoid tissue associated with the gastrointestinal tract (GALT).

LECTURER

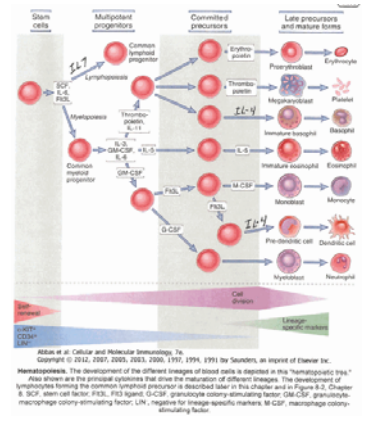
John Clancy, PhD

Cells and Structure of the Immune System

John Clancy, Jr., Ph.D.



Janeway, 7th Edition



Abbas et al. Cellular and Molecular Immunology, 7e.
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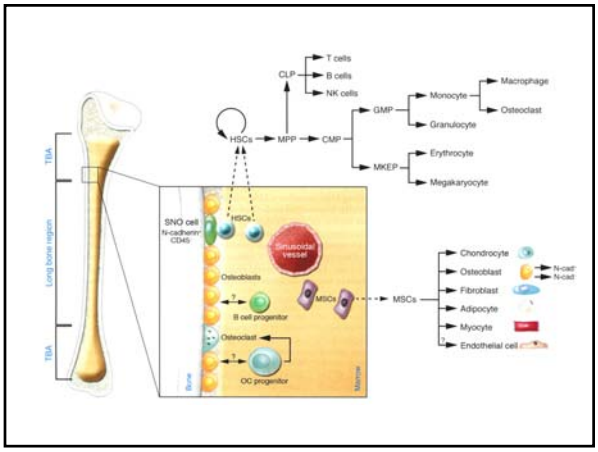
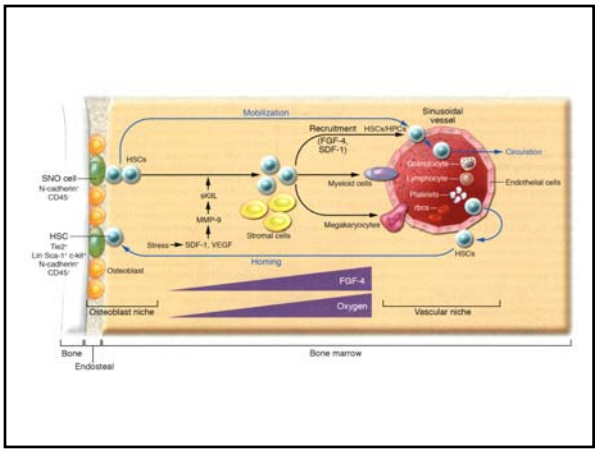
Hematopoiesis. The development of the different lineages of blood cells is depicted in this "hematopoietic tree." Also shown are the principal cytokines that drive the maturation of different lineages. The development of lymphocytes forming the common lymphoid precursor is described later in this chapter and in Figure 8-2, Chapter 8. SCF, stem cell factor; Flt3L, Flt3 ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; LIN-, negative for lineage-specific markers; M-CSF, macrophage colony-stimulating factor.

Note: Multipotent Hematopoietic Stem Cells (MHSC) sit in a niche of either

osteoblasts or sinusoidal **endothelial** cells. Also require stromal cells (to release growth factors) as they differentiate.





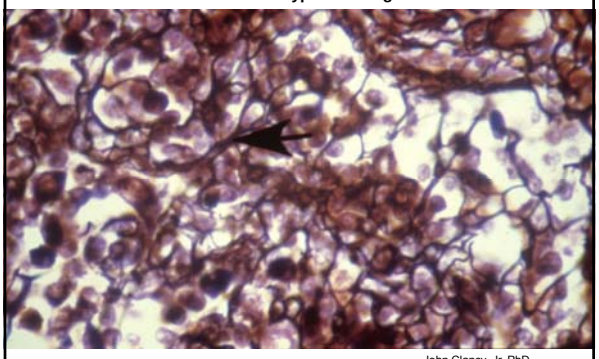
I. Central Versus Peripheral Lymphoid Organs (Fig. 1.7)

- ***1°*** or Central: Bone Marrow, Thymus
- ***2°*** or Peripheral: Lymph nodes, Spleen, Tonsils, Peyer's Patches, Appendix
- ***3°*** Where immune responses occur outside lymphoid organs, E.g. Pannus in an arthritic joint.

- ***Stroma***: Reticular cells and fibers (**Type III Collagen**) except thymus.
- ***Parenchyma***: Lymphocytes, macrophages, dendritic cells, NK cells (spleen)

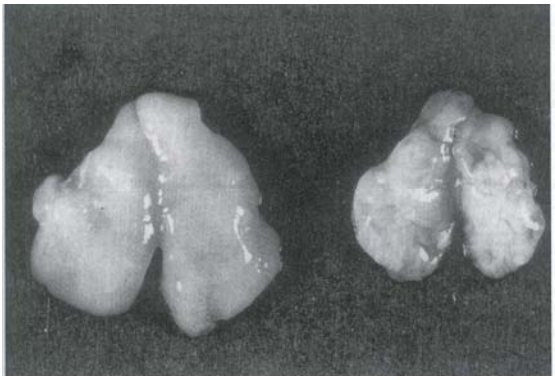
Lymph Node

Silver Stain: → Type III Collagen



John Clancy, Jr. PhD

Young and Old Thymus

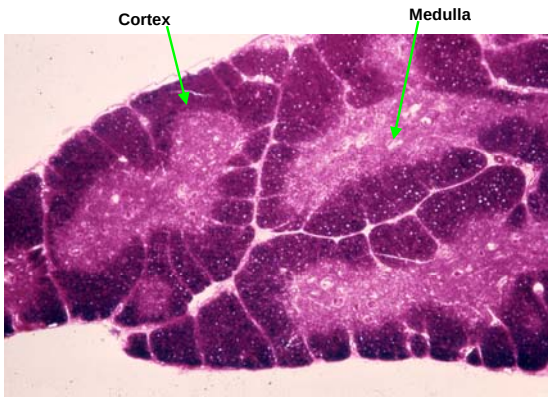


John Clancy, Jr., PhD

II. Thymus: Encapsulated with Epithelial stroma (Figs. 7.15 and 7.21)

- ***Origin***: Ventral part of 3rd pharyngeal pouch and third branchial cleft. Endoderm and underlying mesoderm origin. Two lobes.
- ***Capsule*** of Fibroblasts that form trabeculae or septa which separate the cortex into lobules. Each lobule connected to a central running confluent medulla.

Young Thymus



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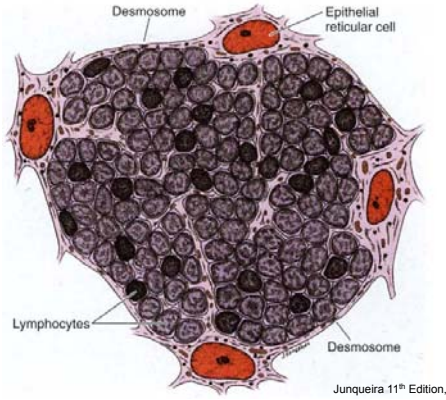
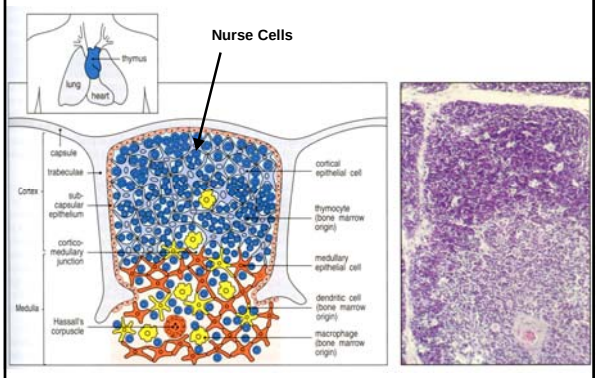
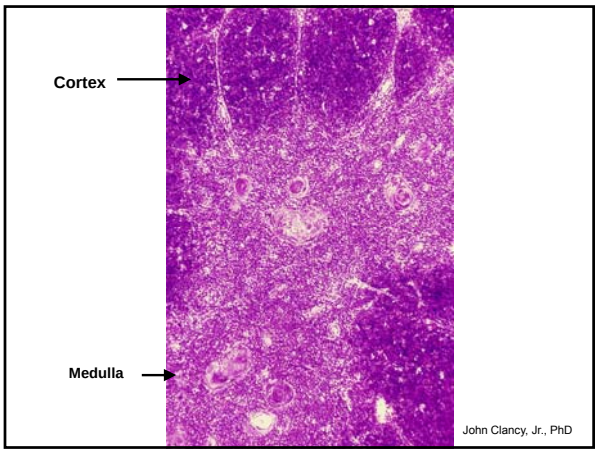


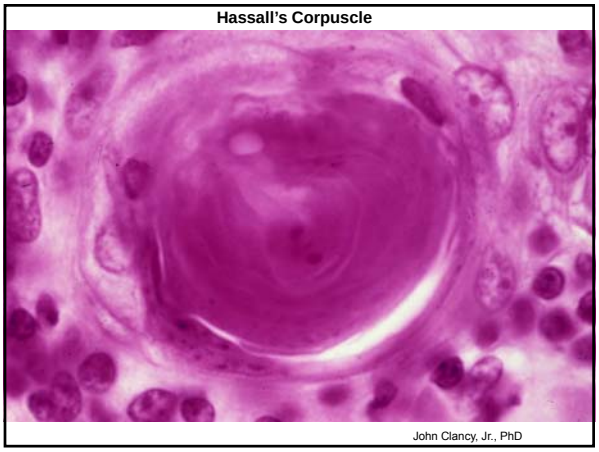
Junqueira 11th Edition, Fig 14-16

- ***Stroma*** of ***Epithelial Reticular Cells*** which secrete ***IL-7*** and contain tonofilaments .



Janeway 7th Edition



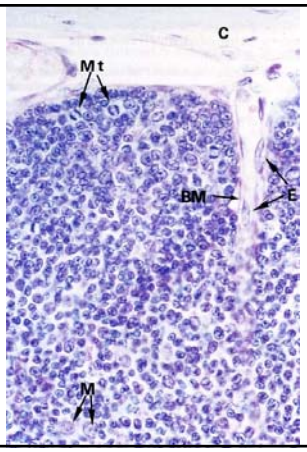


- Parenchyma: Thymocytes
  - Origin: pro-T from marrow: $CD3^-,4^-,8^-$ which localize in the subcapsular cortex, where they are surrounded by IL-7 secreting nurse cells

- cortex contains 80-90% of all thymocytes.
  - Superficial (subcapsular): 5% of all thymocytes which are mainly large blasts: $CD3^-,4^-,8^-$ cells proliferate for 1 week

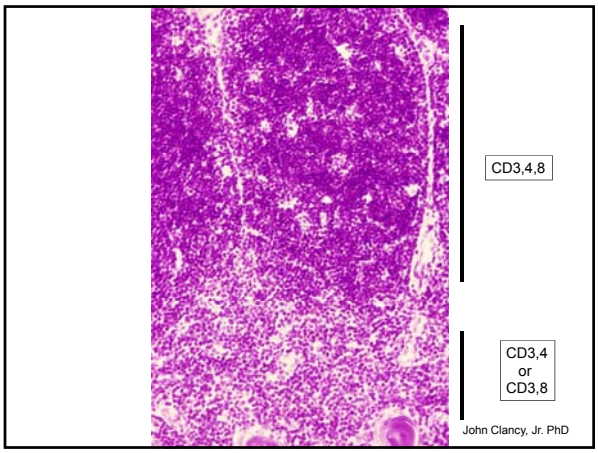
Mt: Mitosis

C: Capsule

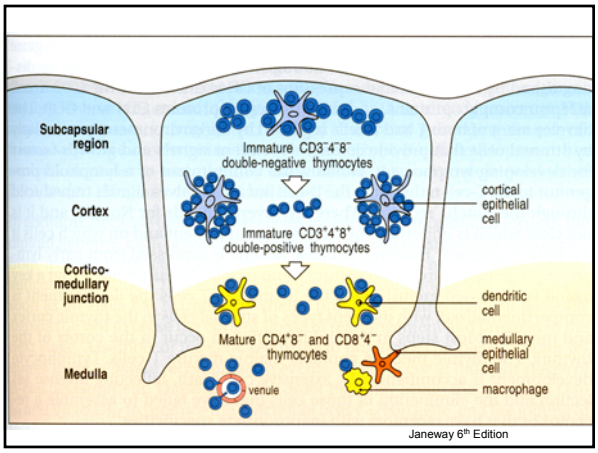


Wheater's 5th Ed. Fig 11.6

- Mid-Cortex to Cortico-Medullary junction: $CD3^+4^+8^+$ mature for 2 weeks.
  - + **and then** – **selection** eliminate unnecessary or potentially autoreactive cells via apoptosis as no inflammation. This is a selection process where thymocytes must recognize self MHC antigens but not **too** well.



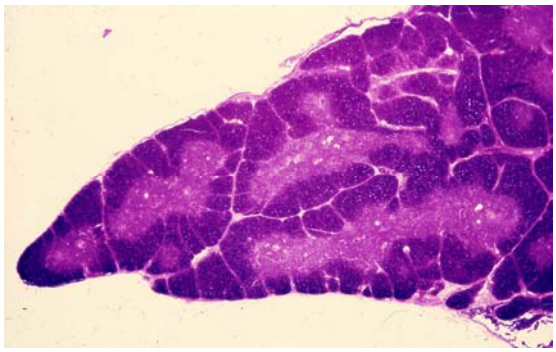
- Medulla: 10% of all thymocytes: $CD3^+4^+$ or $CD3^+8^+$ mature cells which exit to peripheral lymphoid organs.



- Proliferation
  - **>any other lymphoid organ** but under endogenous control as not antigen driven.
  - **<4%** of all thymocytes produced after three weeks **leave** for periphery as CD3+4+ or CD3+8+ lymphocytes. Most cells die via apoptosis. **Twice** as many **CD3+4+** survive than CD3+8+.

- Young vs. Old: The thymus is well developed at birth but looses much of its parenchyma as we age. A **decrease** in **cellularity** is particularly evident **after puberty**. Nevertheless, recent evidence indicates that **even older thymuses** are **functional**.

Young Thymus



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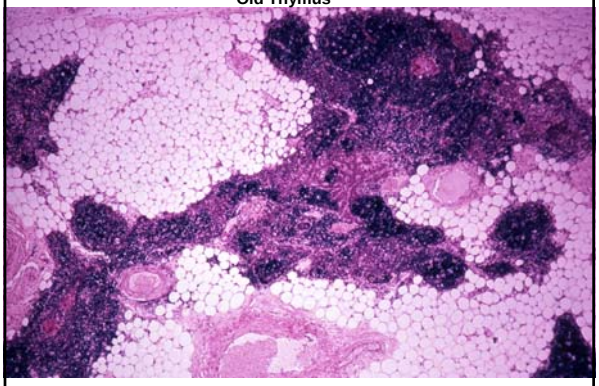
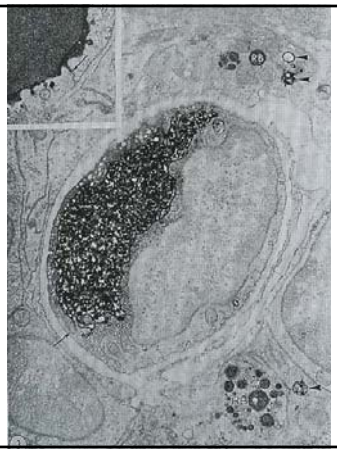
Old Thymus



John Clancy Jr., PhD

- Weakly permeable protective environment in the thymus such that **most circulating antigens** are excluded from developing immature cortical cells. Blood-thymus barrier.



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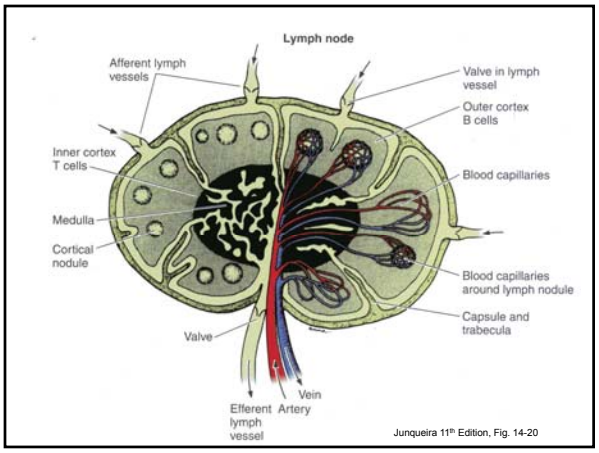
III. Lymph node: Encapsulated with Type I collagen with reticular cell and fiber (Type III Collagen) stroma attached.

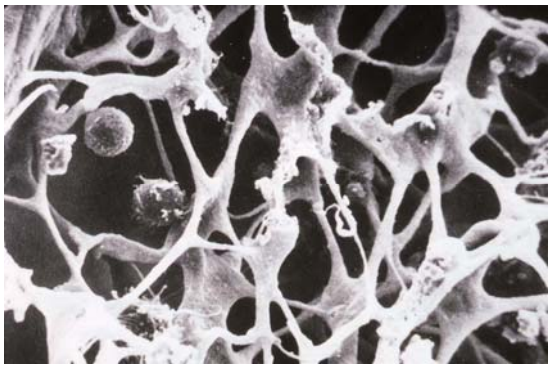


Junqueira 11th Edition, Fig. 14-20

- **Trabecula** extended from capsule and separate cortex into **superficial outer** cortex with **follicles** and an **inner paracortex** or **deep cortex**. An inner **medulla** leads to a **hilus** where **blood vessels** and the **efferent lymphatic** is **found**.

- **Parenchyma** made up of **lymphocytes** in the superficial outer cortex with follicles and an inner paracortex or deep cortex. An inner medulla leads to a hilus where blood vessels and the efferent lymphatic is found.

Reticular Stroma



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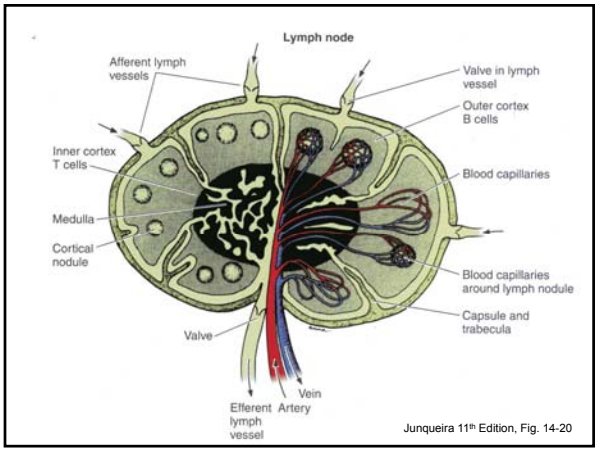
- **Reticular stroma** creates **lymph sinuses** which are called **subcapsular**, **trabecular** and **medullary**.



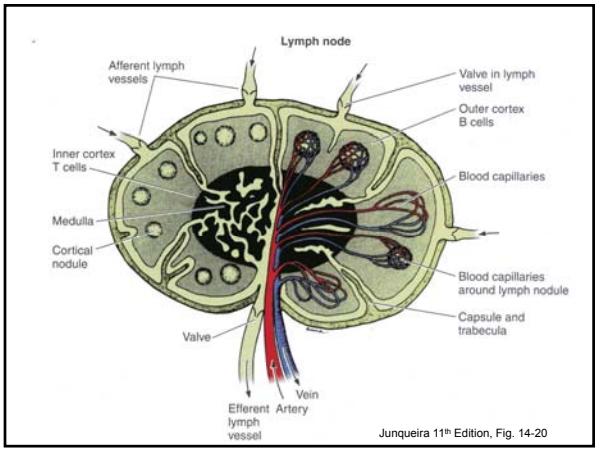
Junqueira 11th Edition, Fig. 14-20

- Lymph circulation (Fig. 14-20).
  - **Afferent lymphatics** receive lymphatic vessels from the periphery. Have valves directed to the subcapsular sinus.

- **Subcapsular → Trabecular → Medullary** Sinuses → **Efferent Lymphatic → Thoracic Duct**. Sinus made up of stellate reticular cells and fibers. Macrophages extensively attach.

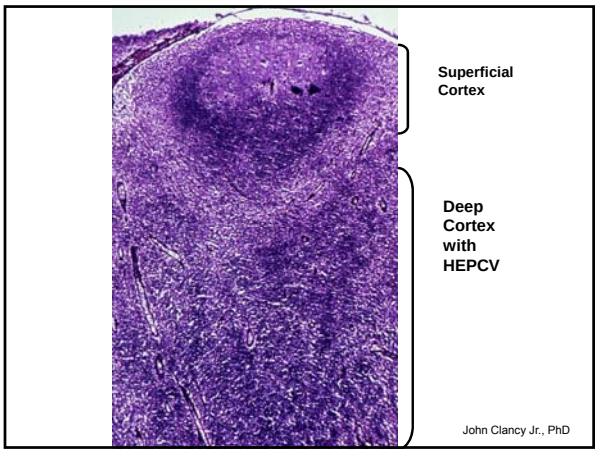
  Which contains:

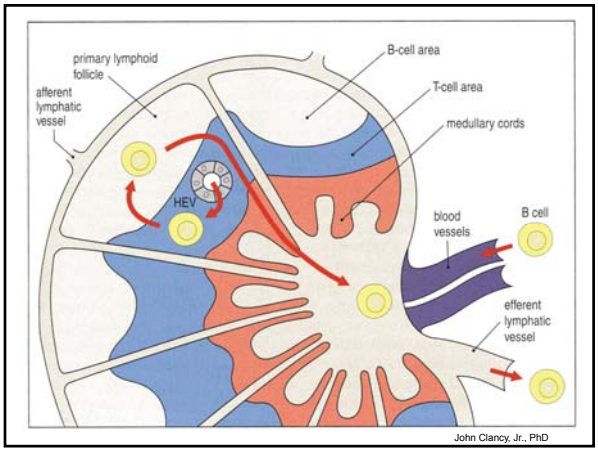
  - Lymphocytes (B & T)
  - Lymphoblasts (B & T)
  - Macrophages



Junqueira 11th Edition, Fig. 14-20

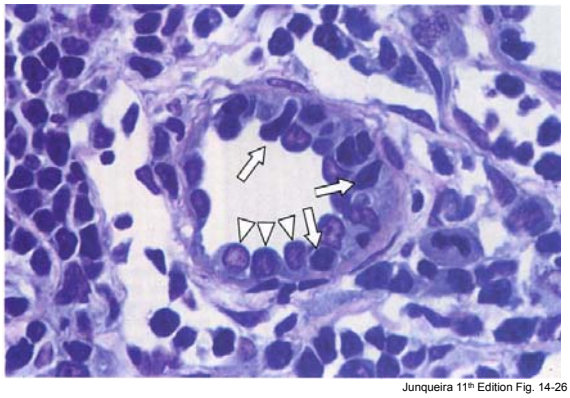
- Blood Circulation
  - Hilar artery → Cortical nodule capillaries → Deep Cortical Post – Capillary venules with a high endothelium (**HEPCV**) → Hilar vein.





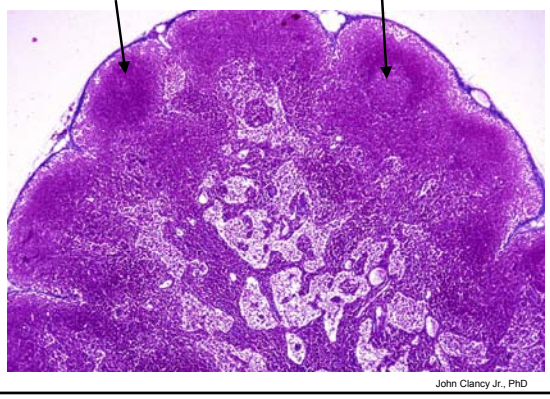
- It is through the HEPCVs that the main players of the **Adaptive Immune System** (T and B cells) gain entrance into the lymph node from the circulation.

HEPCV



Junqueira 11th Edition Fig. 14-26

- Cortex
  - Superficial
    - **1° nodule** (follicle): **B cells** mainly



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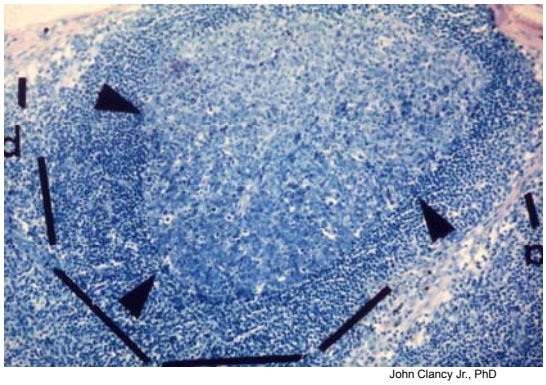
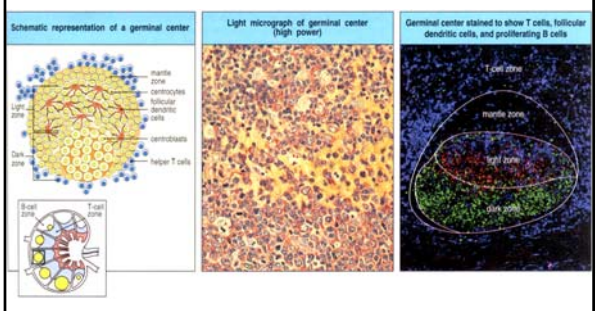
2° Nodule with Germinal Center within Arrowheads



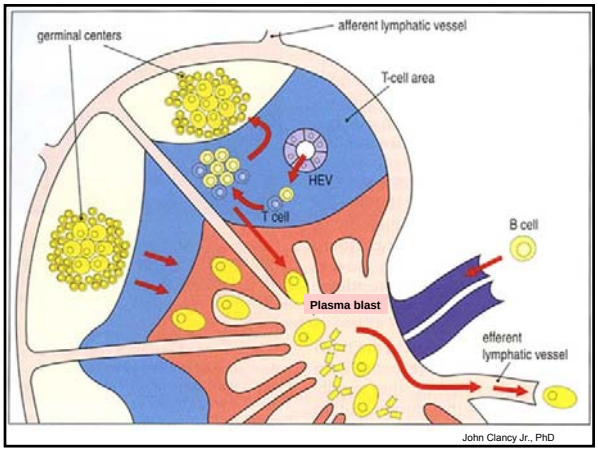
John Clancy Jr., PhD

- **2° nodule** with **germinal center** are the sites where B cells mature with the help of $CD4^+$ T cells into either Plasmablasts or Memory Cells (Fig. 1.8, 9.12)
  - Macrophages
  - Follicular Dendritic Cell which retain antigen for long periods
  - Small and Large Lymphocytes (1°B, some T)
  - Peripheral corona (mantle) surrounds 2° nodule and is a migration zone.

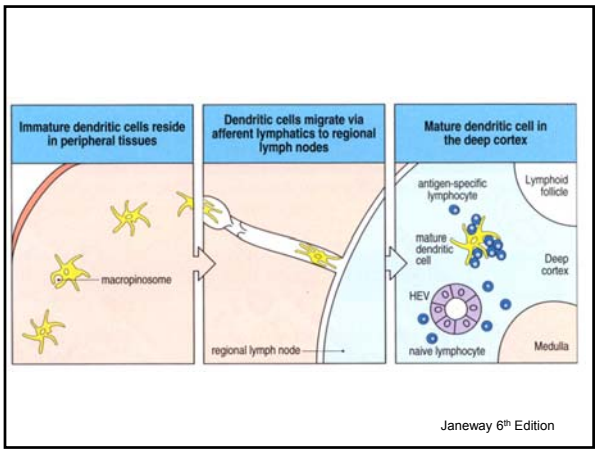


Janeway 6th Edition

- Migration and Differentiation of some B blasts into the **Medullary** Cords to become **Plasma Cells** (**short lived**). **Long-lived plasmablasts** leave via the efferent lymphatics and go to the bone marrow.
- **Follicular Mantle**: **Memory Cells** and some **non-reactive B cells**.

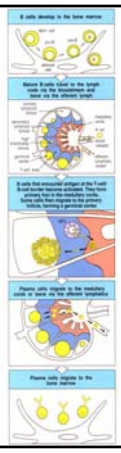


- **Inner or paracortex or deep cortex**
  - Diffuse cells: **1° T**, some **B**
  - ***Langerhans Cell*** (Immature Dendritic Cell) originates in the marrow and localize in the epidermis of the skin. It brings processed antigen into the node from periphery via afferent lymphatics and becomes a mature antigen presenting cell called an ***Interdigitating Dendritic Cell***. It presents antigen to T cell (Fig. 1.9)
  - High endothelial post-capillary venule (HEPCVs) function as the gate of entry of T and B cells from the circulation into the lymph node.

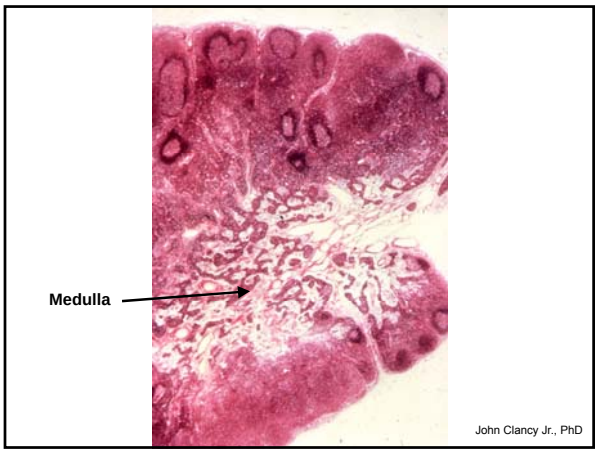


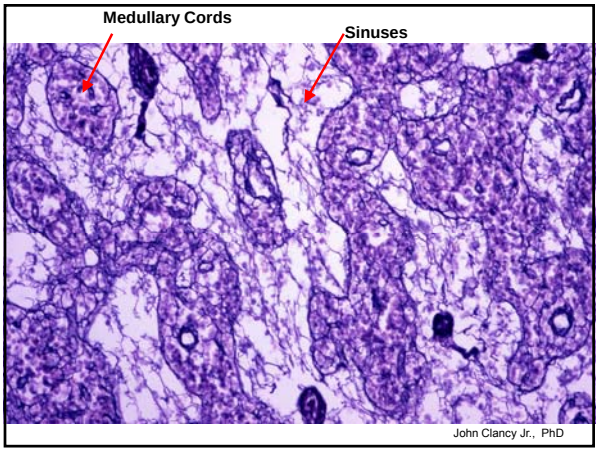
Janeway 6th Edition

- Medulla (Figs. 4.17, 9.9)
  - Cords
    - Contains Plasmablasts and plasma cells which live 10-20 days; long lived Plasmablasts enter the efferent lymph and go to bone marrow. Plasmablasts that will differentiate into IgA producing plasma cells go to the lamina propria of the gut.
  - Medullary Sinuses drain into the efferent lymphatics.



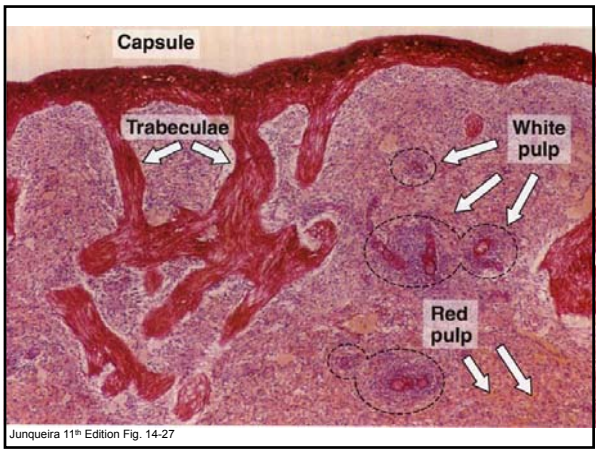
Janeway 7th Edition



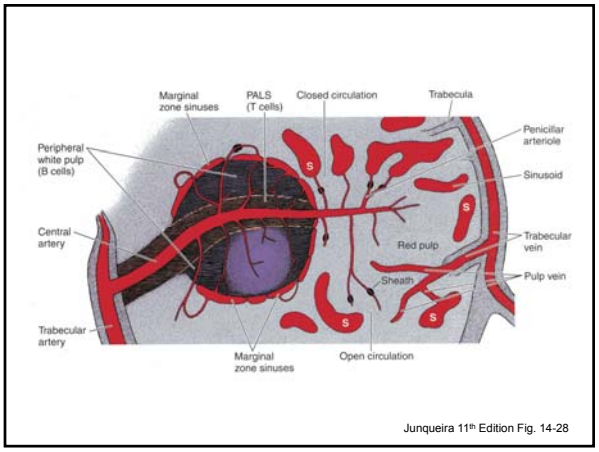


IV. Spleen: Encapsulated with Reticular Stroma

- Connective tissue trabecula extend from capsule and ensheath splenic blood vessels forming Trabecular Arteries and Veins. Reticular fiber network attached to capsule and trabeculae forming a framework or stroma.

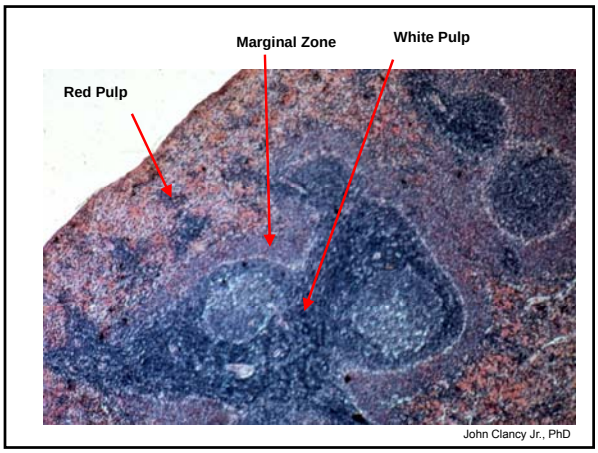


Junqueira 11th Edition Fig. 14-27

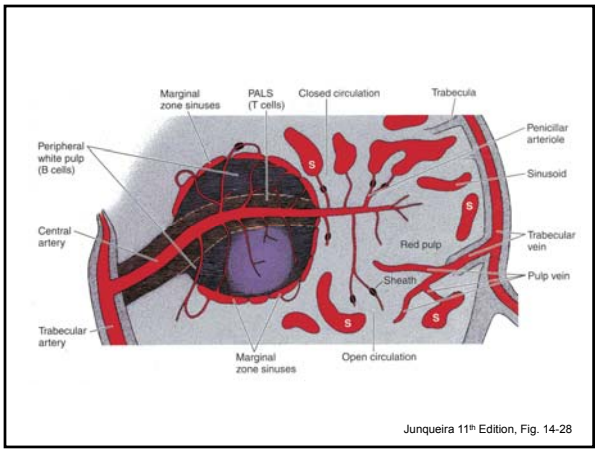


Junqueira 11th Edition Fig. 14-28

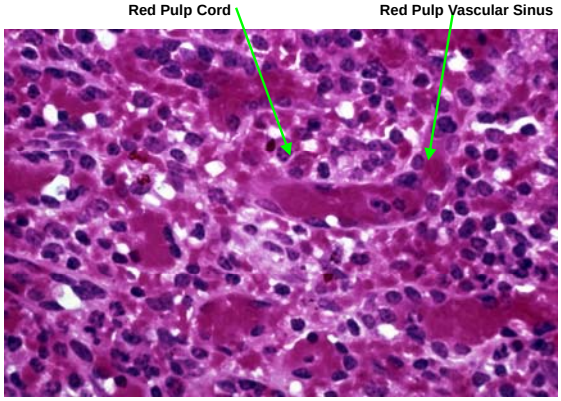
- ***White pulp*** (Fig. 14-28) is lymphoid tissue
  - Splenic nodules 1° and 2° nodules like lymph node.
  - Central artery comes from trabecular artery.
  - Periarteriolar lymphoid sheath (**PALS**): **1°T cells** ensheathing central artery.



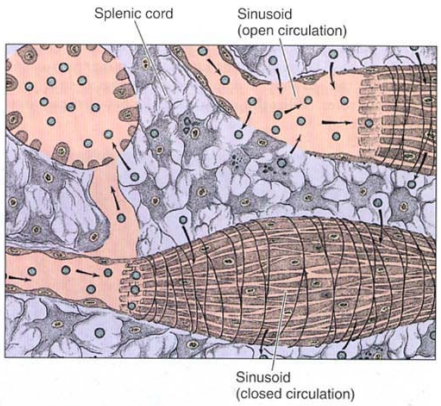
- ***Marginal zone*** contains **memory B cells**, **T independent B cells** (polysaccharides of bacterial cell walls), and macrophages. Separates white and red pulp.
  - **Marginal zone blood sinuses** are found at the periphery of the nodules and receive T and B cells from small branches of the central artery.



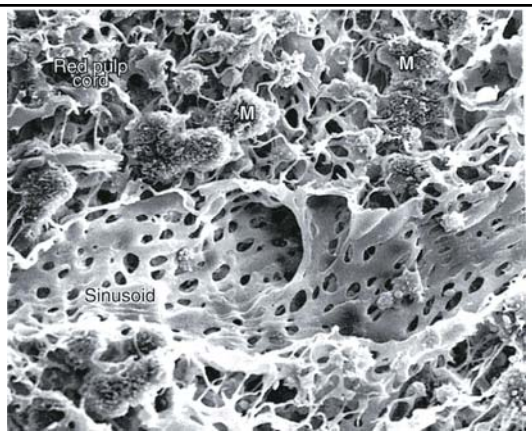
- **Red pulp** (RP)
  - **Cords of Bilroth** (RP cords) which can extend from the white pulp:
    - Contain Hematopoietic tissue and Plasma Cells and are separated by blood sinusoids



- Sinusoids are lined by endothelial cells with holes (2-3 um wide) in them and an incomplete (discontinuous) basal lamina as in the bone marrow. **Many macrophages attached**.



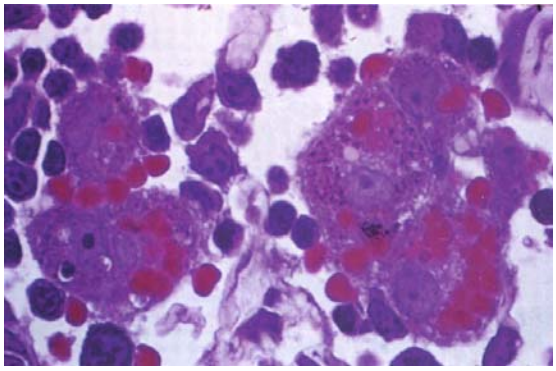
Junqueira Fig. 14-34



Junqueira Fig. 14-33

- Old RBCs lose surface sialic acid exposing surface galactose which are phagocytosed by sinusoid adhering macrophages.
- Hemopoietic in second trimester and some disease states.

Red Pulp Macrophages

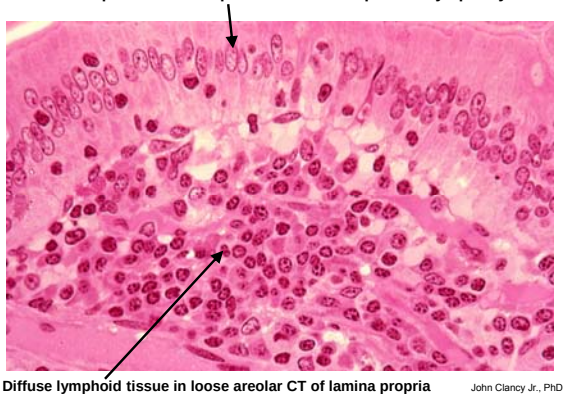


Junqueira Fig. 14-35

V. Gastrointestinal Tract

- **Epithelial lining** contains **CD3+8**+$\alpha\beta$ and **CD3+**$\gamma\delta$ cells to monitor luminal antigens.

Simple Columnar epithelia with intraepithelial lymphocytes

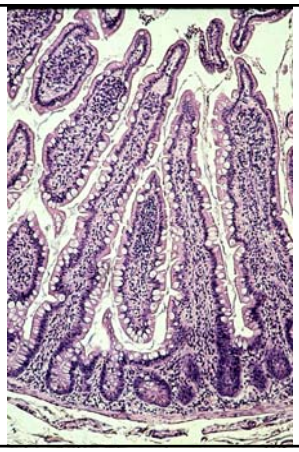


Diffuse lymphoid tissue in loose areolar CT of lamina propria

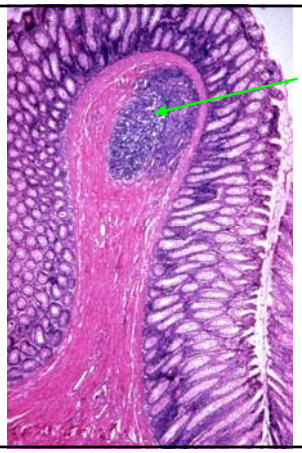
John Clancy Jr., PhD

- **Diffuse**, in lamina propria just underneath the epithelia lining throughout the GI tract.

Diffuse lymphoid tissue in LP of villi



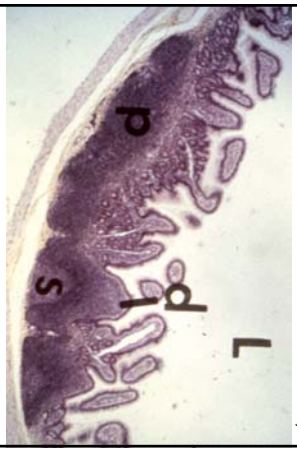
John Clancy Jr., PhD



John Clancy Jr., PhD

- 1° nodule: **IgA** producing B cells.
- 2° nodule with germinal center
  - 1° B cells, some T cells as well as same cells found in lymph node and spleen germinal centers
- T Cells ($\alpha\beta$, $CD3^+$)

P = Peyer's Patch (PP)
d= Dome



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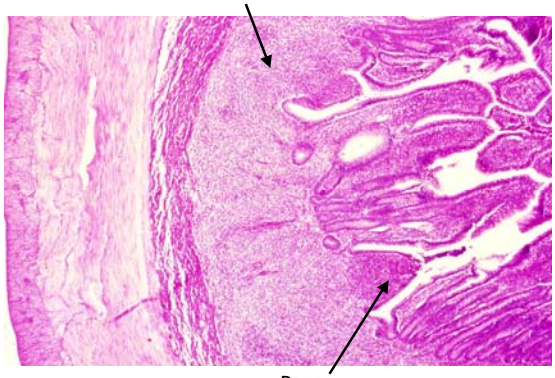
Submucosa of PP



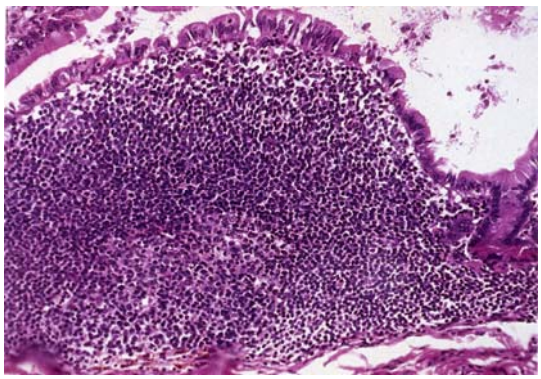
Dome

John Clancy Jr., PhD

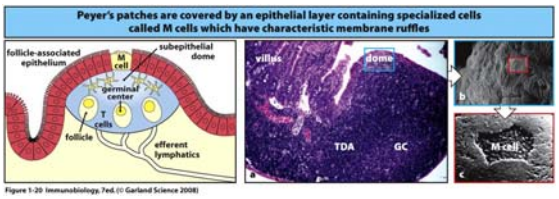
- **Partially encapsulated** and covered by epithelium. Present in lamina propria and submucosa of certain areas of GI tract.
  - **Peyer's Patches** (**Ileum**) (Fig. 1.20, 10.19 and 14-40)
    - **Villi** and **Domes** which overlie lymphoid tissue

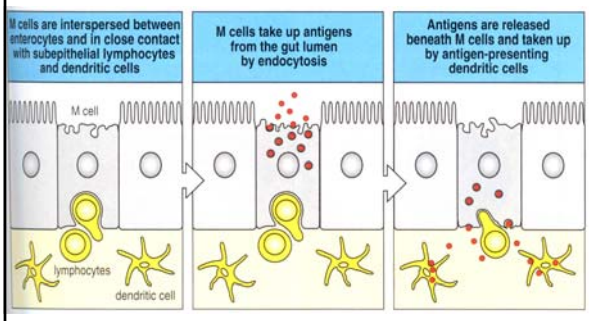
- Domes are covered by **M cells**: **Epithelial** cells which become **antigen transporting**. They are derived from surface lining epithelium and require B cells for their development. Also found in the lung.

Dome



Wheater's 6th Edition, Fig 11.17

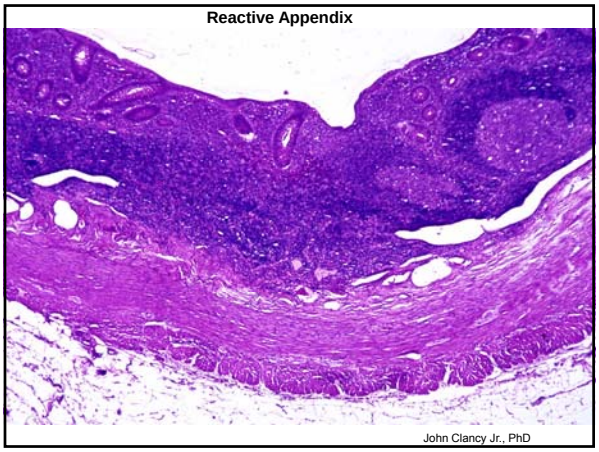




Janeway 6th Edition

- Appendix at the beginning of the large intestine.
  - No villi but lamina propria and submucosal lymphoid tissue .

Reactive Appendix



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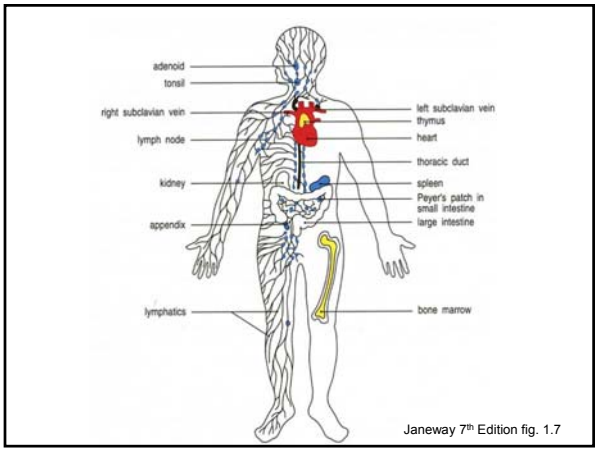
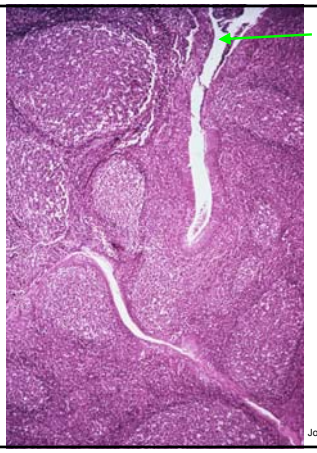


Janeway 7th Edition fig. 1.7

Palatine Tonsil

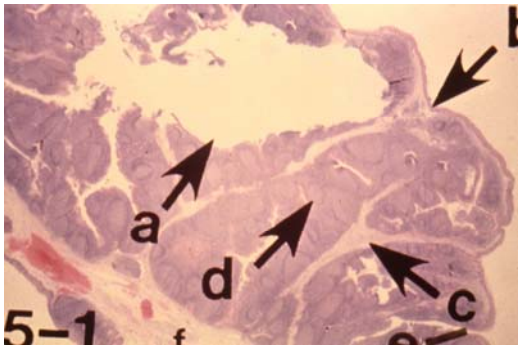


Crypt

John Clancy Jr., PhD

Palatine Tonsil

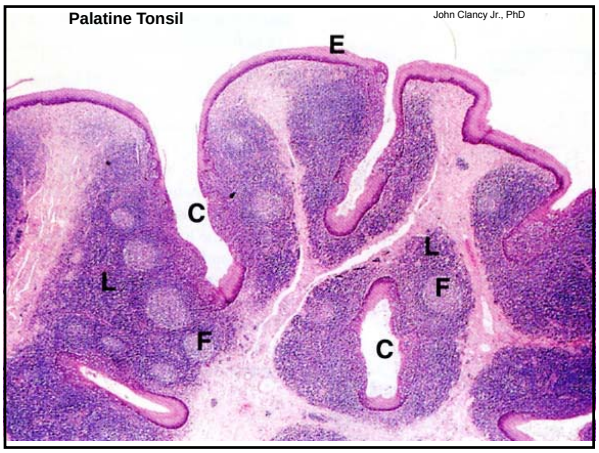
a = cyst **c = crypt**



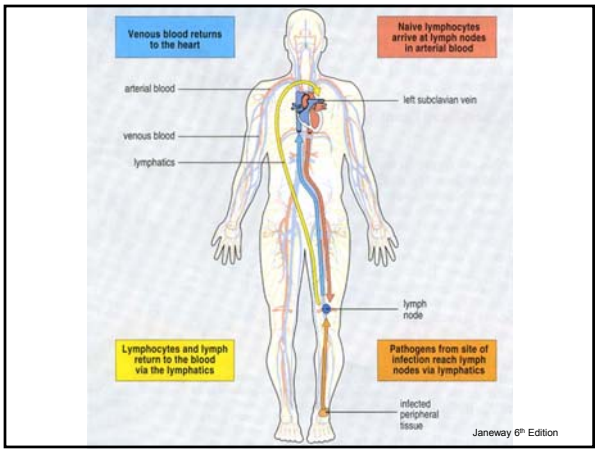
John Clancy Jr., PhD

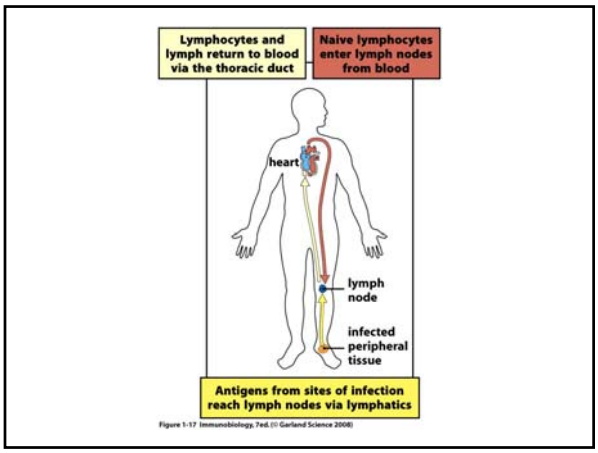
- Tonsils
  - Palatine: lined by stratified squamous nonkeratinizing epithelium. Between palatoglossal and palatopharyngeal folds.
    - Many (10-12) deep crypts
    - Capsule underneath
    - Skeletal muscle deep to capsule

- Pharyngeal (Adenoids): pseudostratified ciliated columnar with some stratified squamous; no crypts but shallow **pleats**. Roof of nasal pharynx.
- Lingual: stratified squamous, single crypt.



- **Mucosal Associated Lymphoid Tissue** (MALT) is found under all epithelial linings of mucosa (respiratory, gut, urinary, etc.)
  - **Gut Associated Lymphoid Tissue** (GALT) is thus only a part of the MALT system





- Lymphocytes circulate from the blood into various tissues and lymphoid organs and back to the blood continuously. 5 x 10^{11} leave the circulation to enter the spleen and return into the blood per day.

- Lymphocytes leave the blood thru HEV in lymph nodes and Peyer's Patches. They eventually enter efferent lymphatics and the thoracic duct system which joins the left subclavian and internal jugular veins. O.3 X 10^{11} return to the blood from the lymph per day.

- Lymphocytes enter the white pulp of the spleen from the marginal zone blood sinuses. They eventually find their way into the red pulp blood sinuses and leave via the splenic vein.