

# INTRODUCTION TO THE IMMUNE RESPONSE

**Date:** March 7, 2011

Lecture Hall, 190

## 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.

## 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: 1-13; 711-720; 39-40; 46-57;. Do **NOT** memorize any Table or Figure in the textbook. Some students in past years class felt that Junquiera, pp 254-262 was helpful to them.

## LECTURER

John A Robinson, MD

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

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### **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 the 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.

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**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 **shortcoming** of the innate system is its lack of the ability to precisely target pathogens and “remember” the encounter. Hence, an innate immune response, once activated, can be indiscriminate in destruction and also doesn’t learn anything from it. .
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.

**B.** 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).

	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH Enzymes (pepsin)		Enzymes in tears (lysozyme)
	Antibacterial peptides			
	Normal flora			
Microbiological				

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. 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. **The origin, development and basic functions of leukocytes will be fully covered by Dr. Clancy in subsequent lectures and labs.**

## 2. Innate cell highlights

1.  
2. **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.

3.  
4. **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 large parasites or allergic reactions.

5.  
6. **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.

7.  
8. **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.

9.  
10. **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 activated by recognizing pathogen structures (**much more to follow**).

11.  
12. **f. 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.

**g.  $\gamma\delta$  lymphocytes and NKT lymphocytes** can interface with both innate and adaptive immunity and may represent a key evolutionary step in the development of the adaptive system

## 2. Recognition Mechanisms 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. The innate immune system has evolved two pathways to recognize danger.

**b. One arm 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

**c. The other, parallel arm of the innate system utilizes immune effector cells** that you will learn how to recognize in Dr Clancy's lectures and an on-line histology tutorial.

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

ii. The danger patterns are called **pathogen-associated molecular patterns (PAMPs)** and the receptors on the innate cells that recognize 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.*

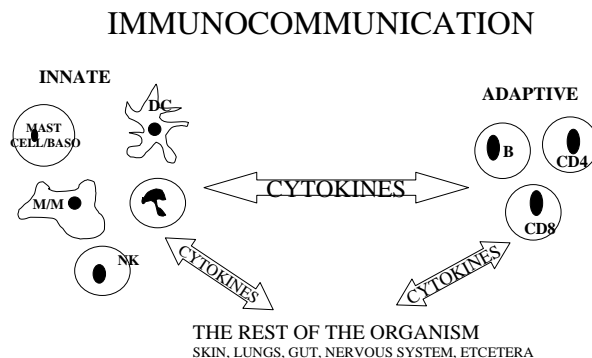
iii. **Activation of a TLR is the "ON" switch for an innate immune response and the gateway to an immune response.**

iv. Once activated, innate system cells facilitate rapid reactions to infections by “talking” to each other with small messenger peptides called **cytokines**. **What are cytokines?**

### III. Cytokines are mandatory participants in immune responses

#### A. 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 hemoproliferative 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 availability 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**.



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 cell**. Figure by John A. Robinson, MD
10. Poorly regulated or deficient cytokines can be **pathologic**.

## THE FIRST HOST DEFENSES

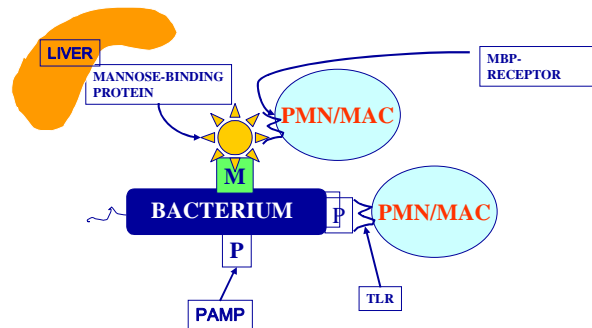


Figure by John A. Robinson, MD

### 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 recombinaase 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.** This cell 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. **Lymphocytes** further developed into two major specialized groups. 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. **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.

#### H. 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.

## A Really short immunology course

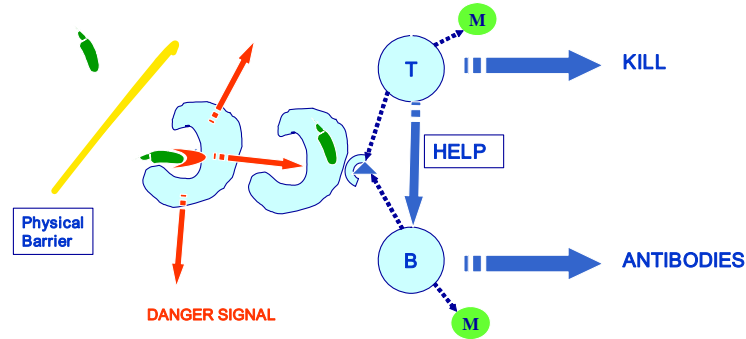


Figure by John A. Robinson, MD

### Comparison of Innate and Adaptive Immunity

	<b>Innate Immunity</b>	<b>Adaptive Immunity</b>
<b>Timing</b>	Immediate response	Lag between exposure and response
<b>Specificity</b>	Effector cells are <u>not</u> antigen specific	Effector cells are antigen specific
<b>Memory</b>	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

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## 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!

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## Small Groups

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.

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## 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
  - Last year about >30 did <70% on the first test and it was difficult for many of them to recover
- 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)

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## 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
- **A SYSTEM SO COMPLEX IT IS DESIGNATED A SUPERSYSTEM**

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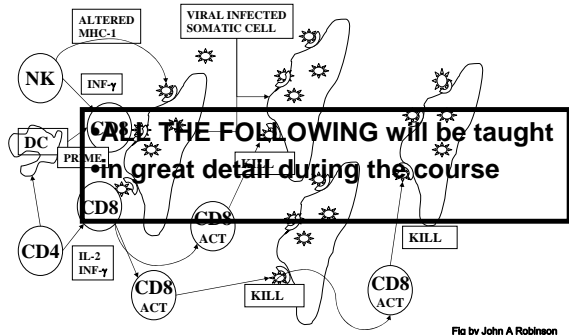
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PART OF THE SUPERSYSTEM:BELIEVE IT OR NOT-YOU WILL UNDERSTAND THIS IN ABOUT 6 WEEKS



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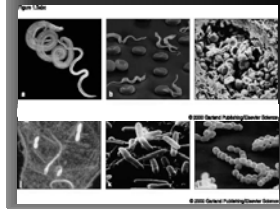
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## The Problem

– 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

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## SURVIVAL STRATEGIES OF THE HOST ARE BASED ON HOW TO RESIST INFECTION

- The primary role of the immune system is to resist infection.
- The immune system is subdivided into 2 major subsystems- the innate and the adaptive
- The Innate system goes way back in time and is "hardwired" in that its responses are encoded in the germ line
- The adaptive system appeared later as an evolutionary upgrade

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## 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?

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## 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

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## 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

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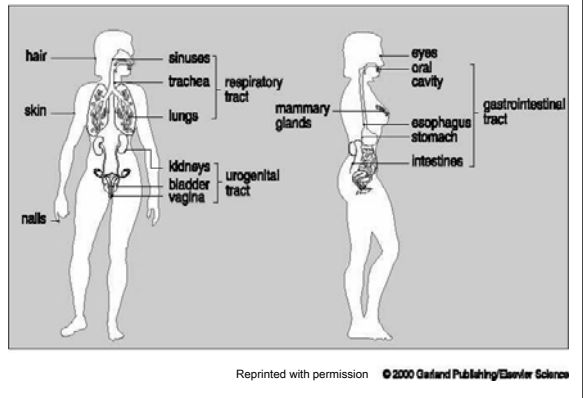
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Figure 1.4




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### First line Innate Immunity defense mechanisms

	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	
Chemical	Fatty acids	Low pH Enzymes (pepsin)		Salivary enzymes (lysozyme)
	Antibacterial peptides			
	Normal flora			
Microbiological				

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

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### 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
- You will learn how to identify all the innate cells in an lab exercise shortly after this lecture

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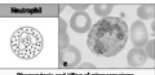
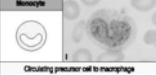
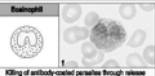
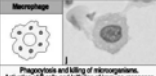
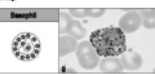
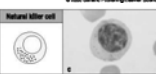

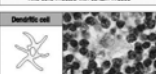
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<p><b>Figure 1.8a</b></p>  <p><b>Neutrophil</b></p> <p>Phagocytosis and killing of microorganisms</p>	<p><b>Figure 1.8b</b></p>  <p><b>Monocyte</b></p> <p>Circulating precursor cell to macrophage</p>	<p>All these innate cells Will be discussed in Dr Clancy's lectures &amp; referred to in specific contexts later</p> <p>Be sure to check out the video on how to identify them that is available on the HD website</p>
 <p><b>Basophil</b></p> <p>Killing of antibody-coated parasite through release of granule contents</p>	 <p><b>Macrophage</b></p> <p>Phagocytosis and killing of microorganisms. Activation of T cells and initiation of adaptive immune response</p>	
<p><b>Figure 1.8c</b></p>  <p><b>Basophil</b></p> <p>Urticaria</p>	<p><b>Figure 1.8d</b></p>  <p><b>Natural killer cell</b></p> <p>Kills cells infected with certain viruses</p>	
 <p><b>Mast cell</b></p> <p>Expulsion of parasites from body through release of granules containing histamine and other active agents</p>	 <p><b>Dendritic cell</b></p> <p>Activation of T cells and initiation of adaptive immune responses</p>	
<p><small>© 2008 Garland Publishing/Science Direct</small></p>		

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## Recognition molecules and Activation of the Innate System

- **The Innate immune system must be able to recognize danger**
- **Innate Immunity devised 2 general pathways to recognize a threat**
- **One arm utilizes circulating mediators, the other utilizes immune effector cells**

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## 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 entire lecture)

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## Danger recognition cells of the Innate System

- The Innate cellular system must also be able to recognize danger
- They do so by sensing molecular patterns unique to microbes and dendritic cells and macrophages are especially good at this.
- These patterns are called pathogen-associated molecular patterns (PAMPs) and their receptors are pathogen recognition receptors or TOLL like receptors (TLR) on the innate cells
- When TLR recognize and bind PAMP, 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

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## 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

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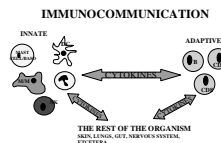
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## Talking to one another



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## 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

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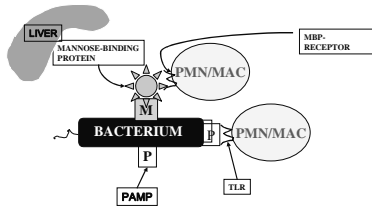
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## THE FIRST HOST DEFENSES




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## THE ADAPTIVE (ACQUIRED) IMMUNE SYSTEM

- **The Adaptive 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)

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## 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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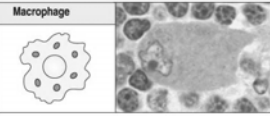


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Cell		Activated function
Macrophage		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell		Antigen uptake in peripheral sites Antigen presentation in lymph nodes
Neutrophil		Phagocytosis and of activation bactericidal mechanisms

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Fig 1.4 part 1 of 2 © 2001 Garland Science

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## 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 CD's (cluster of determination) and you will have to memorize a few of them

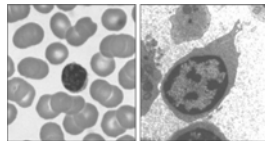


Fig 1.5 © 2001 Garland Science

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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

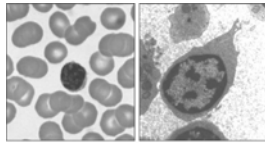


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**SMALL LYMPHOCYTES**

- **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

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**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

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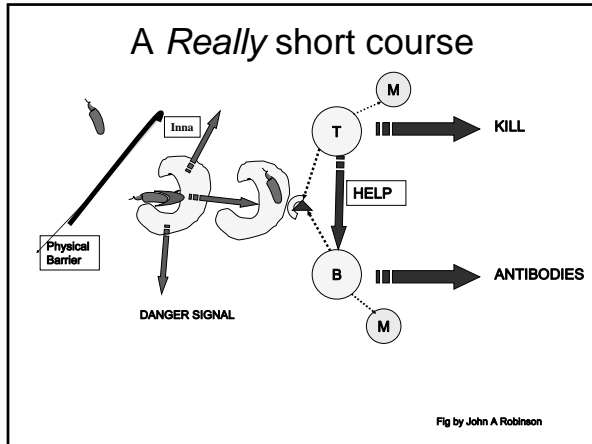
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### Comparison of Innate and Adaptive Immunity

- 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

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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. Reprinted with permission.

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# STEM CELLS AND BONE MARROW

Date: Monday, March 7, 2011  
9:30 – 10:30 AM

## LEARNING GOALS

You will be able to describe many of the properties of stem cells and recognize many of the various erythrocytic, granulocytic and monocytic precursors in photomicrographs or slides of bone marrow as well as some of the factors, which control their growth.

## OBJECTIVES

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

- Describe the structural and functional characteristics of stem cells and compare them with progenitor, precursor and mature circulating blood cells.
- Describe the phases of intrauterine hematopoiesis and the sites where each occurs.
- Describe the growth factor control of erythropoiesis, thrombopoiesis, granulopoiesis, monocytopoiesis, dendritic cell development, and lymphopoiesis.
- Identify many of the various members of the erythrocytic and granulocytic series in photomicrographs of slides of bone marrow. For each cell type, be able to name the cell type of the stage immediately proceeding and following. Also, which growth factor controls further development of a particular lineage?

## READING ASSIGNMENT AND REFERENCES

Junqueira, et al, **Basic Histology**, 11<sup>th</sup> Edition, Chapter 13.  
Wheater's **Functional Histology**, 5<sup>th</sup> Edition, Chapter 3, pp. 58-63.

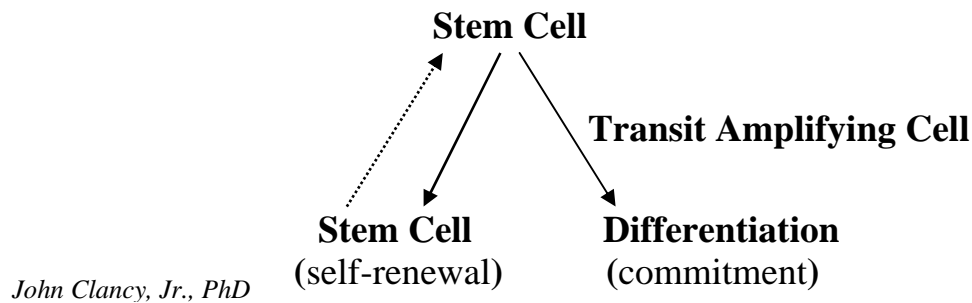
## LECTURER

John Clancy, Jr., Ph.D.



A. DEFINITIONS

- Stem Cells are generally considered to be a population of non-proliferating ( $G_0$  stage of cell cycle) epithelial or mesenchymal cells that can be **induced** to undergo constitutive proliferation in response to developmental or **injury/repair** signals.
- Progeny of stem cells are called **daughter** cells which are either exact copies of themselves (**self-renewal**) or are fated to begin **differentiation** into more lineage-restricted **progenitors** which could replace the entire complement of mature cells present within a **specific tissue** in which they reside (**commitment**). Thus, asymmetric cell division.
- Most stem cells sit in a protective **niche** within the tissue or organ they are found.
- Can undergo rapid cellular expansion in response to injury or specific disease states.

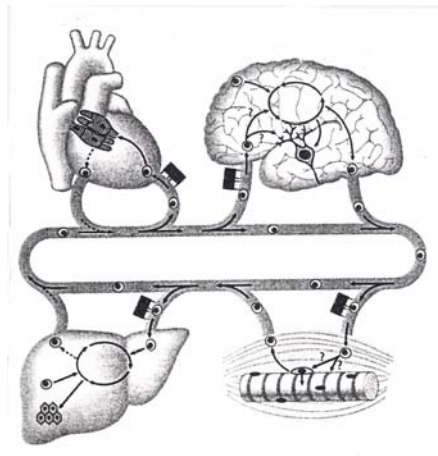


- **Pluripotent:** A defining feature of the most immature SC that allows them to give rise to **all the somatic cell types** of the organism. E.g. Neurons, muscle cells, etc. Analogous to **embryonic stem cells**. Are not **totipotent**, as can't recreate whole embryo.

Figure 1. Evolving Concepts of **Stem Cell Plasticity**  
Documented (solid arrows) and hypothesized (dashed

arrows) transitions in stem cell identity and differentiation are illustrated. In addition to **tissue-specific stem cells**, some stem cells may travel throughout the body via the

circulation. The scheme also suggests that cell fate decisions may not be irreversible. Flexibility is the hallmark of this depiction allowing for regeneration and changes in cell fate in response to need.



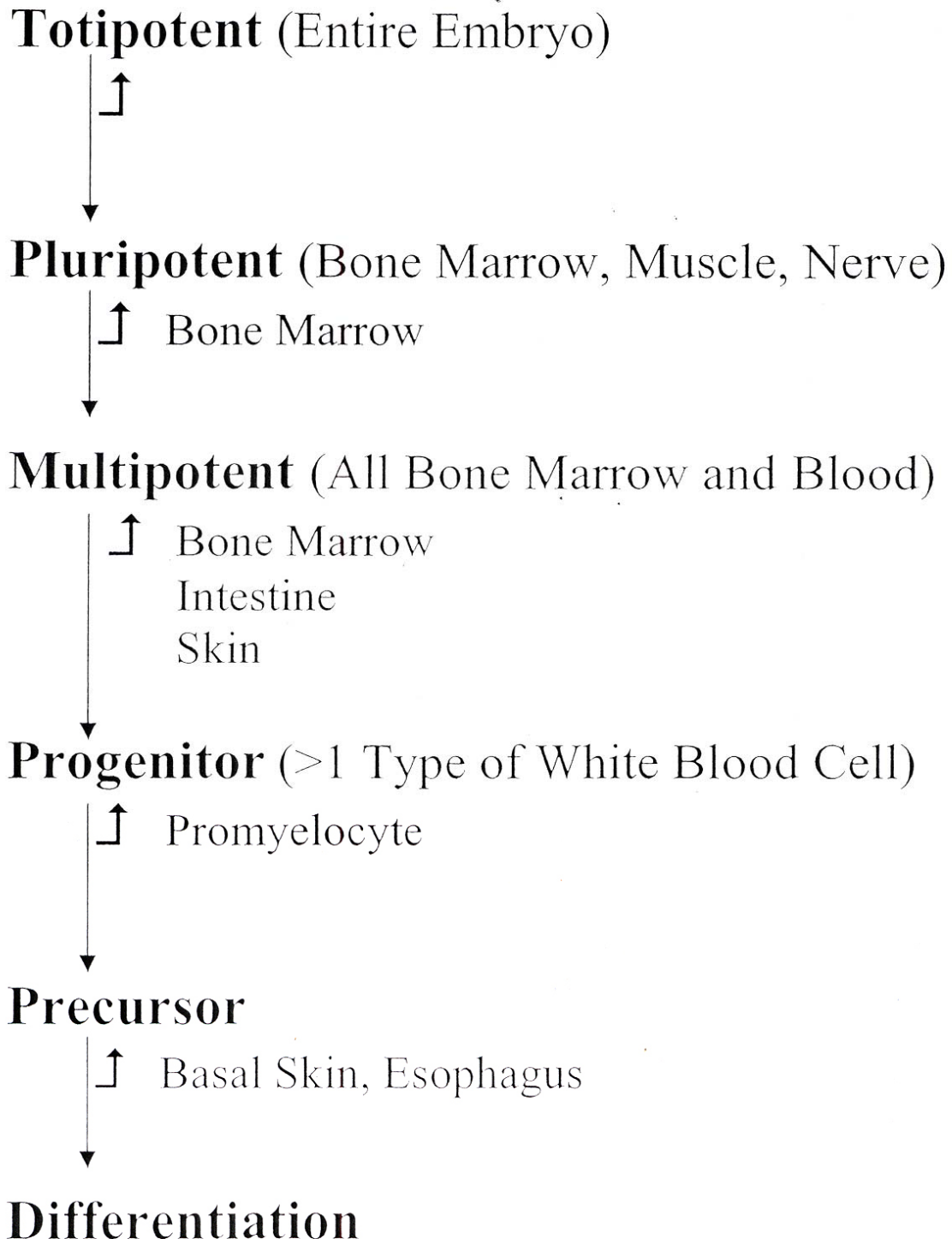
Bone Marrow

*John Clancy, Jr. PhD*

- **Multipotent:** A more restricted SC or primordial progenitor cell associated with the potential to give rise to all the cell types of the **tissue** or **organ** from which the cell is

derived. Thus, tissue specific. E.g. All **bone marrow** and blood cells (Hemopoietic SC); all cells lining the **intestine**.

## STEM CELLS



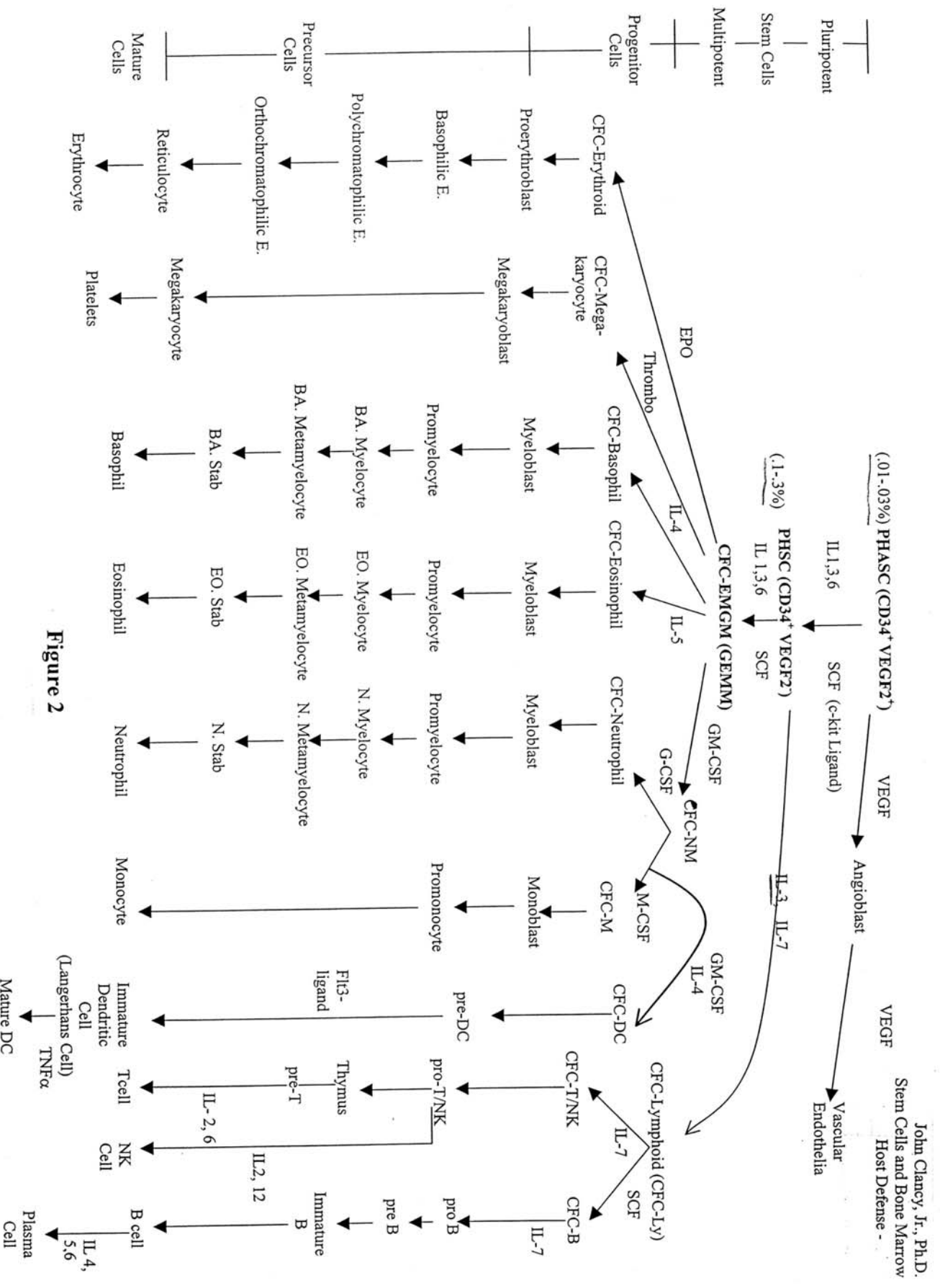
- **Progenitor:** The descendant of the multipotent tissue-specific SC. Possesses a more limited lineage potential compared to its parent. E.g. Cell that can give rise to **more than one** type of **white blood cell (promyelocyte)**.
- **Precursor (Lineage Restriction/Commitment):**  
Progressive loss of the potential of progenitor cells to give rise to multiple cell lineages. Culminates in the irreversible acquisition of cellular traits characteristic of a **single lineage** or **unipotentiality**. E.g. **Basal epidermal** cells of the **skin** or esophagus.
- **Differentiation:** Acquisition of genotypic and phenotypic characteristics of mature tissue-specific cell types. Depends upon the microenvironment (type and concentration of **growth factors** as well as **extracellular matrix interactions**).
- **Dedifferentiation:** Loss of phenotypic and genotypic characteristics of more mature progenitor or lineage-restricted cells coincident with a reversion to cellular characteristics of more immature cells. E.g. Mature cell reverts to an immature state.

## B. HEMATOANGIOGENESIS (Fig 2, Table 1)

- **Pluripotential SC** found in the “**blood islands**” of an embryo’s yolk sac at **2 weeks** of development. These cells are both Hematopoietic (Blood Making) and Angiogenic (sprouting of pre-existing blood vessels) or Vasculogenic (Blood vessel making) and are thus called Pluripotential Hemangiogenic Stem Cells (PHASC).
  - **CD34<sup>+</sup>** and Vascular Endothelial Growth Factor (**VEGF**) Receptor **2<sup>+</sup>** Cells which represent **0.01-0.03%** of all adult bone marrow (BM) cells and are called **adult BM stem cells**. (1/10,000). **CD34<sup>+</sup> VEGF2<sup>+</sup>(0.001% of adult blood cells)**.
  - **Angiopoietin-1 (VEGF)** makes them become **endothelial cells**. Interleukins (**IL 1, 3, 6**) and Stem Cell Factor (**SCF**) makes them become Pluripotential Hematopoietic Stem Cells (**PHSC**) which are **CD34<sup>+</sup> VEGF2<sup>-</sup>**. They represent **0.1-0.3%** of all adult marrow cells.
  - Further stimulation with **IL 1, 3, 6** and **SCF** makes the PHSC become **Erythroid/Myeloid Multipotential Cells**. These cells are called clinically Colony forming Cell Granulocytic Erythroid Megakaryocytic Monocytic (**CFC-GEMM**) because they have the potential to form colonies in vitro of any of these cell lines depending on what growth factors they are incubated with.
  - However, if the **PHSC** are incubated with **IL-7** they become Lymphoid Colony forming cells (**CFC-LY**).
  - Note: Also **Mesenchymal SC** (form bone, cartilage, tendon, adipose, muscle, neural cells) found in adult bone marrow.

**C. What makes multipotent CFC-GEMM and CFC-Ly become Progenitor, Precursor and Mature Cells? Answer: Specific cytokines or growth factors.**

- **Erythropoietin (EPO)** causes some CFC-GEMM to become CFC-Erythroid → Proerythroblast → **Erythrocyte**
- **Thrombopoietin (Thrombo)** causes some CFC-GEMM to become CFC-Megakaryocyte → Megakaryoblast → Megakaryocyte → **Platelets**
- **Interleukin-4 (IL-4)** causes some CFC-GEMM to become CFC-Basophil → Myeloblast → **Basophil**
- **IL-5** causes some CFC-GEMM to become CFC-Eosinophil → Myeloblast → **Eosinophil**
- **Granulocyte-Monocyte-Colony Stimulating Factor (GM-CSF)** causes some CFC-GEMM to become CFC-Neutrophil Monocyte (**CFC-NM**)
  - Granulocyte-CSF (**G-CSF**) causes CFC-NM to become CFC-Neutrophil → Myeloblast → **Neutrophil**
  - Monocyte-CSF (**M-CSF**) causes CFC-NM to become CFC-Monocyte → Monoblast → **Monocyte**
  - **GM-CSF, IL-4, Flt3-ligand** cause CFC-NM to become CFC-Dendritic Cell → **Immature Dendritic Cell (Langerhan's Cell of Skin)**.
  - **IL-7, 2, 6** causes CFC-Lymphoid to become CFC-T/NK → preT → Thymus → **T Cell**
  - **IL-7, 2, 12** causes CFC-Lymphoid to become CFC-T/NK → pre NK → **NK Cell** important in innate immunity.
  - **IL-7, SCF** causes CFC-Lymphoid to become **CFC-B** → pro B → pre B → immature B → mature B. **IL 4, 5, 6** helps an **activated B** cell mature into a **plasma cell**.



**Figure 2**

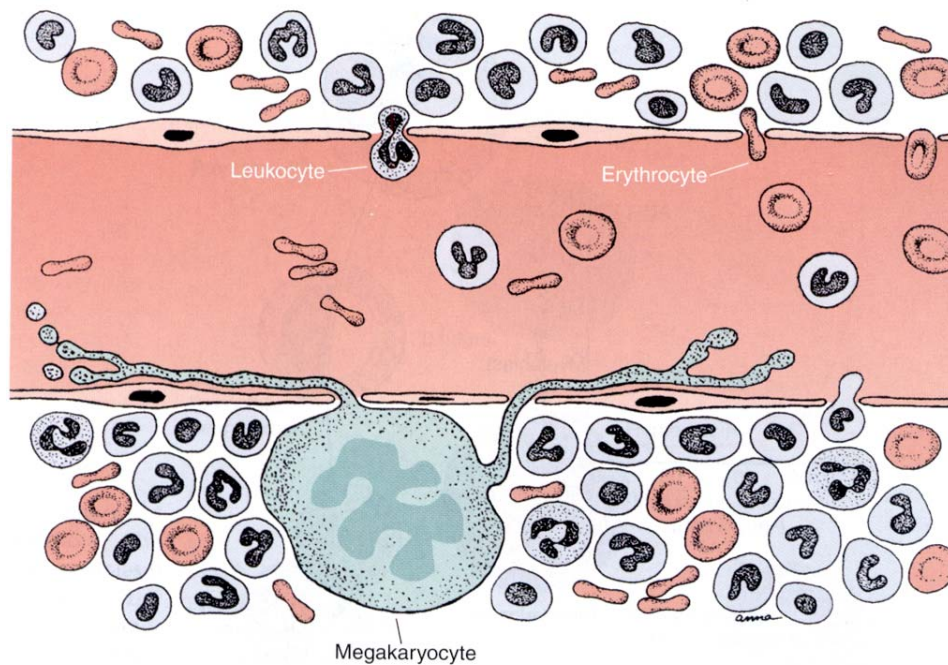
**Table 1. Hemopoietic Growth Factors**

<b>Factors</b>	<b>Principal Action</b>
Angiopoietin-1 (VEGF)	Promotes endothelial growth and development
Stem cell factor (SCF; c-Kit ligand)	Promotes hemopoiesis; critical for CFC-B development
GM-CSF	Promotes CFC-NM mitosis and differentiation; facilitates granulocyte activity; stimulates dendritic cell development
G-CSF	Promotes CFC-N mitosis and differentiation; facilitates neutrophil activity
M-CSF	Promotes CFC-M mitosis and differentiation; facilitates monocyte activity
Flt-3 Ligand	Promotes dendritic cell development
TNF $\alpha$	Stimulates immature dendritic cells to mature.
IL-1	In conjunction with IL-3 and IL-6, it promotes proliferation of PHSC, CFC-GEMM and CFC-Ly.
IL-2	Stimulates activated T- and B-cell mitosis; induces differentiation of NK cells
IL-3	In conjunction with IL-1 and IL-6, it promotes proliferation of PHSC, CFC-GEMM, and CFC-Ly as well as all unipotential precursors (except for LyB and LyT)
IL-4	Stimulates B-cell activation and development of mast cells and basophils Also stimulated dendritic cell development.
IL-5	Promotes CFC-Eo mitosis and activates eosinophils; Promotes B cell growth
IL-6	In conjunction with IL-1 and IL-3, it promotes proliferation of PHSC, and CFC-Ly; also facilitates B-cell differentiation into plasma cells.
IL-7	Promotes differentiation of CFC-Ly; enhances differentiation of CFC-T/NK cells and maturation of CFC-B to pro B cells.
IL-12	Stimulates NK cells development and function; enhances CTL function.
Erythropoietin	CFC-E development and differentiation
Thrombopoietin	Proliferation and differentiation of CFU-megakaryocyte and megakaryoblasts

CFC, colony-forming cell (Eo, eosinophil; G, granulocyte; GM, granulocyte-monocyte; Ly, lymphocyte); CSF, colony-stimulating factor (N-, Neutrophil; GM-, granulocyte-monocyte); M-, monocyte); IL, interleukin; NK, natural killer; PHSC, pluripotential hemopoietic stem cells. TNF $\alpha$ , tumor necrosis factor  $\alpha$ .

### C. BONE MARROW IS A SPECIALIZED CONNECTIVE TISSUE

- Red and Yellow Marrow with the Sternum, iliac crest as the primary sites for access. Also present in long bones, vertebral bodies, ribs, flat bones of cranium. 5% of total body weight.
- Contents:
  - Primitive blood cells in **Hematopoietic islands or cords: Red Marrow of developing blood cells and macrophages.**
  - **Fat cells: Yellow Marrow**
  - Stromal Cells (IL-7; SCF; GM-CSF; G-CSF; M-CSF; IL-1; IL-6). May be Mesenchymal SCs.
  - Type III collagen (Reticular tissue)
  - Sinusoids (discontinuous capillaries) – 45-80 um in diameter which drain into a central longitudinal → nutrient V.
  - Megakaryocytes (Polyploid:64N); Platelets (Fig 13-4)
  - Osteoclasts
  - Note: PHSC sit in a niche of either osteoblasts or sinusoidal endothelial cells.



**Figure 13-4, p. 242. Junqueira 11<sup>th</sup> Edition.** Drawing showing the passage of erythrocytes, leukocytes, and platelets across a sinusoid capillary in red bone marrow. Because erythrocytes (unlike leukocytes) do not have sufficient motility to cross the wall of the sinusoid, they are believed to enter the sinusoid by a pressure gradient that exists across its wall. Leukocytes, after the action of releasing substances, cross the wall of the sinusoid by their own activity. Megakaryocytes form thin processes that cross the wall of the sinusoid and fragment at their tips, liberating the platelets.

**D. HEMATOPOIESIS – Mesenchymal cells aggregate into Blood Islands in Yolk Sac (2 weeks) with the peripheral cells forming endothelial cells and the central cells erythroblasts→ Liver (6 weeks) → Spleen (14-15 weeks) → Bone Marrow (6 months) (Figs. 13-5, 13-6).**

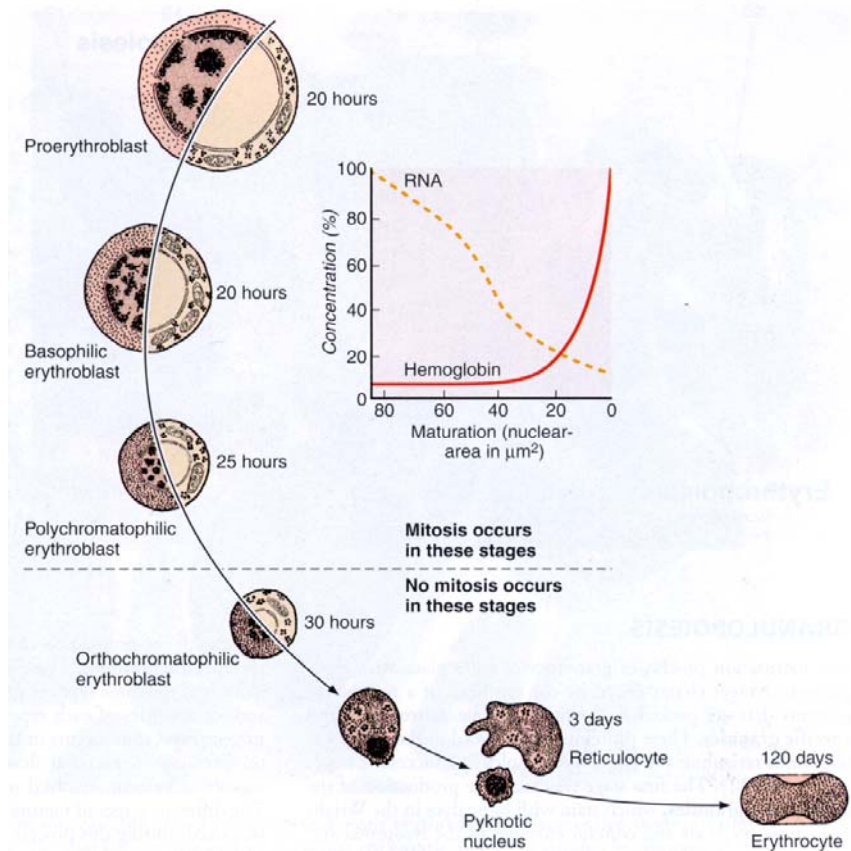


- **Erythropoiesis** - ↓size and basophilia (RNA); ↑eosinophilia, hemoglobin
  - $2.5 \times 10^{11}$  erythrocytes/day
  - CFU-E becomes a **Proerythroblast** (Pronormoblast): prominent nucleoli, basophilic cytoplasm
  - **Basophilic erythroblast**: denser nucleus, very basophilic cytoplasm
  - **Polychromatophilic erythroblast**: last cells in mitosis; hemoglobin synthesis, gray cytoplasm
  - **Orthochromatophilic erythroblast** or **Normoblast**: no mitosis, nucleus extruded, eosinophilia begins in cytoplasm.
  - **Reticulocytes**: polysomes, but no mitochondria in cytoplasm.
  - **Erythropoietin** is made in the kidney and very necessary for erythropoiesis
  - **Macrophages** form an erythroblastic island around developing erythrocytes, destroy aged erythrocytes and transfer ferritin, an iron-containing protein complex, to young erythroblasts. Macrophages also destroy the nuclei expelled by a normoblast via lysosomal DNAase-II and produce other growth factors that influence hematopoiesis.

Fig. 13-5, p. 253, Junqueira.



Figure 13-6. Summary of erythrocyte maturation. The stippled part of the cytoplasm (on the left) shows the continuous increase in hemoglobin concentration from proerythroblast to erythrocyte. There is also a gradual decrease in nuclear volume and an increase in chromatin condensation, followed by extrusion of a pyknotic nucleus. The times are the average life span of each cell type. In the graph, 100% represents the highest recorded concentrations of hemoglobin and RNA.



P. 244, 11E, Junqueira

Granulopoiesis - ↓ size and basophilia after the promyelocyte stage; ↑ granules and granule specificity; nuclear lobulation  
 (Fig. 13-5 and 13-11)

- CFC-N → Myeloblast: large cell (15um) with prominent nucleoli; looks like a proerythroblast
- Promyelocyte: 18-24 um with azurophilic granules (Reddish purple:lysosomal enzymes, myeloperoxidase). 500nm in diameter. Still some cytoplasmic basophilia.
- Myelocyte: specific granules for each granulocytic line
- Metamyelocyte: kidney shaped nucleus
- Band or Stab cell: in circulation, but more common with neutrophilic series.
- Segmented mature cell
- Growth Factors (Table 1)
  - GM-CSF; G-CSF; Interleukin-3 (IL-3); IL-5 (Eosinophils); IL-4 (Basophils)
- Neutrophils ( $8 \times 10^5/D$ ), Eosinophils ( $1.7 \times 10^5/D$ ), Basophils ( $6 \times 10^4/D$ ) are produced and released into the circulation.

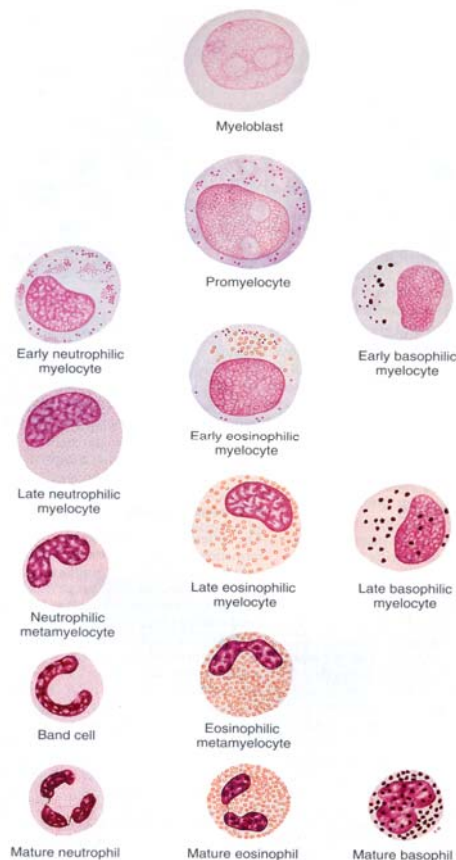


Figure 13-5, p. 243 Junqueira, 11<sup>th</sup> Edition. Stages in the development of erythrocytes and granulocytes

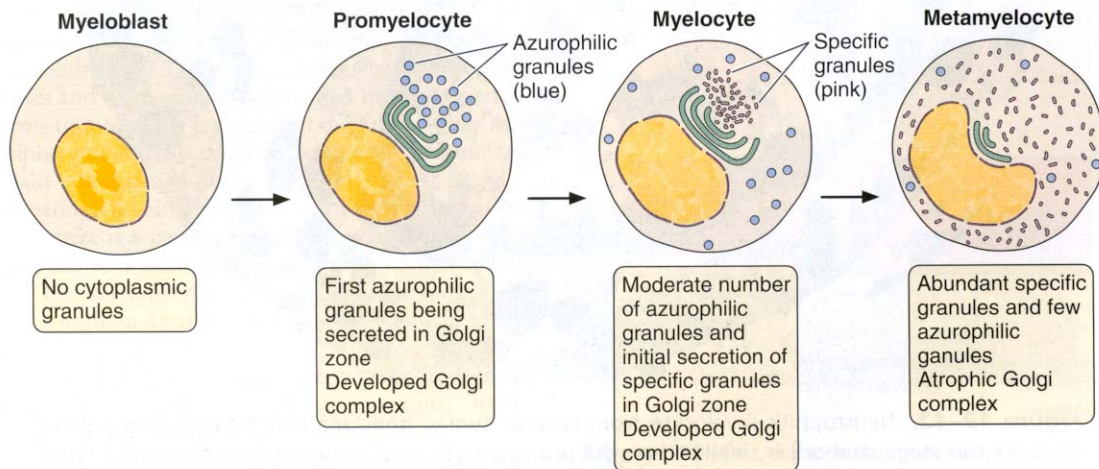


Figure 13-11, p 246. Junqueira, 11<sup>th</sup> Edition. Drawing illustrating the sequence of gene expression in the maturation of granulocytes. Azurophilic are blue; specific granules are pink.

- Lymphopoiesis → Lymphocytes
  - IL-7, 6, 2 (T cells) – Require thymic epithelial cells
  - IL-7, 2, 12 (NK cells) – Made in bone marrow and released into blood as functional cells.
  - IL 7, 4, 5, 6 (B cells) – Require bone marrow stromal cells
- Monocytopoiesis → Monocytes  
GM-CSF, M-CSF
- Dendritic Cell Development → Immature Dendritic Cells (Langerhans Cell) → Mature DC which is present in secondary lymphoid tissue and presents antigen to T cells for a cell-mediated immune response.
  - GM-CSF, IL-4, Flt3-ligand (Immature DC) → TNF $\alpha$  (Mature DC)

## STEM CELLS AND BONE MARROW

March 7, 2011  
Host Defense  
John Clancy, Ph.D.

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### A. DEFINITIONS

- Stem Cells are generally considered to be a population of non-proliferating ( $G_0$  stage of cell cycle) epithelial or mesenchymal cells that can be **induced** to undergo constitutive proliferation in response to **developmental** or **injury/repair** signals.

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- Progeny of stem cells are called **daughter** cells which are either exact copies of themselves (**self-renewal**) or are fated to begin **differentiation** into more lineage-restricted **progenitors** which could replace the entire complement of mature cells present within a **specific tissue** in which they reside (**commitment**). Thus, asymmetric cell division.

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Most stem cells sit in a protective **niche** within the tissue or organ they are found.  
e.g. bulge region → stratum basale of epidermis

hemopoietic stem cells found next to osteoblasts or sinusoidal endothelial cells.

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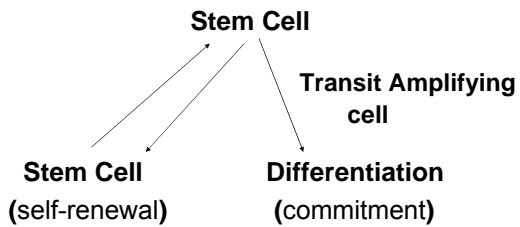
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- Can undergo rapid cellular expansion in response to injury or specific disease states.



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### Stem Cells

- Inducible proliferation
  - Development
  - Injury/Repair
- Self-Renewal or Differentiation
- Protective Niche

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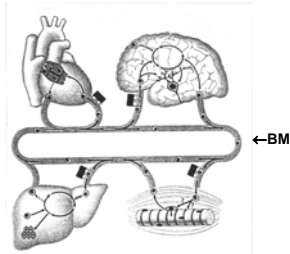
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• **Pluripotent:** A defining feature of the most immature SC that allows them to give rise to **all the somatic cell types** of the organism. E.g. Neurons, muscle cells, etc. Analogous to **embryonic stem cells**. Are not **totipotent**, as can't recreate whole embryo.



John Clancy, Jr, PhD

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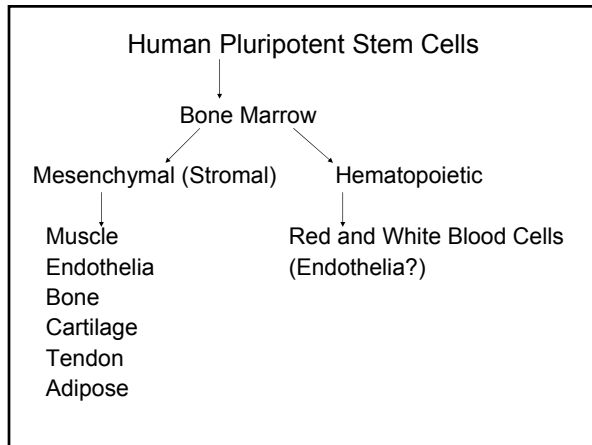
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• **Multipotent:** A more restricted SC or primordial progenitor cell associated with the potential to give rise to all the cell types of the **tissue** or **organ** from which the cell is derived. Thus, tissue specific. E.g. All **bone marrow** and blood cells (Hematopoietic SC); all cells lining the **intestine**.

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- **Progenitor:** The descendant of the multipotent tissue-specific SC. Possesses a more limited lineage potential compared to its parent. E.g. Cell that can give rise to **more than one type of white blood cell (promyelocyte)**.

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Progenitor

- > 1 type of WBC (e.g. promyelocyte)
- can proliferate extensively

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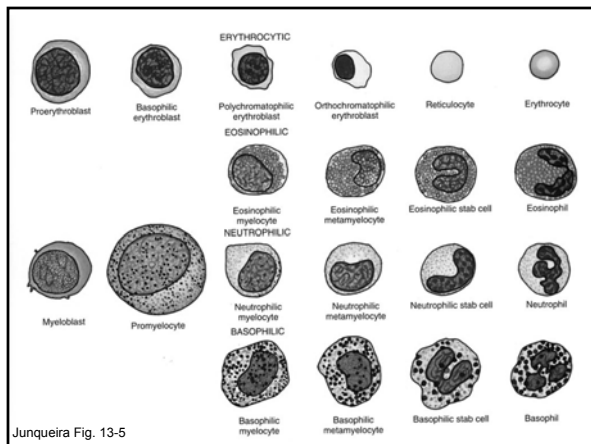
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- **Precursor (Lineage Restriction/Commitment):**

Progressive loss of the potential of progenitor cells to give rise to multiple cell lineages. Culminates in the irreversible acquisition of cellular traits characteristic of a **single lineage** or **unipotentiality**. E.g. **Basal epidermal** cells of the **skin** or **esophagus**.

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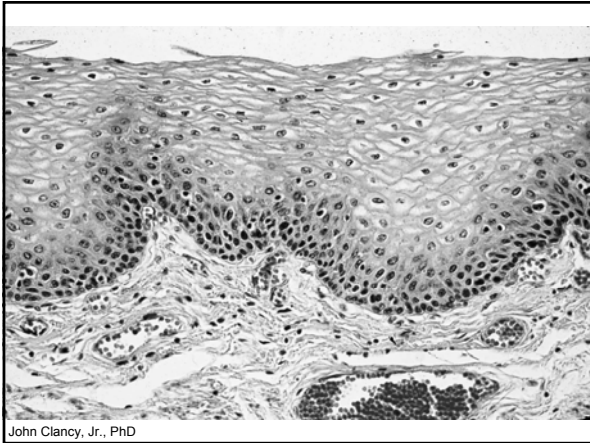
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- **Differentiation:** Acquisition of genotypic and phenotypic characteristics of mature tissue-specific cell types. Depends upon the microenvironment or **niche** (type and concentration of **growth factors** from cells of the niche as well as **extracellular matrix interactions**).

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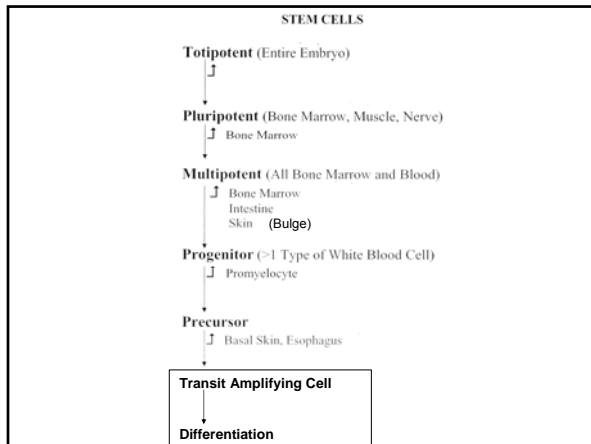
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- **Dedifferentiation:** Loss of phenotypic and genotypic characteristics of more mature progenitor or lineage-restricted cells coincident with a reversion to cellular characteristics of more immature cells. E.g. Mature cell reverts to an immature state.

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**B. HEMATOANGIOGENESIS (Fig 2, Table 1)**

- **Pluripotential SC** found in the “**blood islands**” of an embryo’s yolk sac at **2 weeks** of development. These cells are both Hematopoietic (Blood Making) and Angiogenic (sprouting of pre-existing blood vessels) or Vasculogenic (Blood vessel making) and are thus called Pluripotential Hemangiogenic Stem Cells (PHASC).

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## Pluripotent SC

- Blood islands yolk sac at 2 wks.
- Can make all tissue types
- First make red blood cells: Hematopoietic
- Then make blood vessels: Vasculogenic
- 0.01 – 0.03% adult bone marrow
- CD34<sup>+</sup> VEGF2<sup>+</sup>
- 0.001% of adult blood cells

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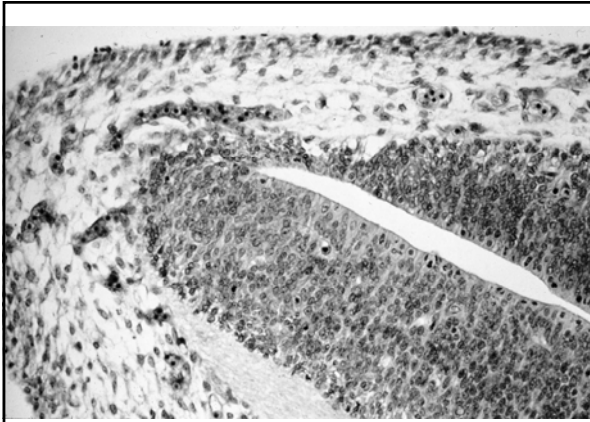
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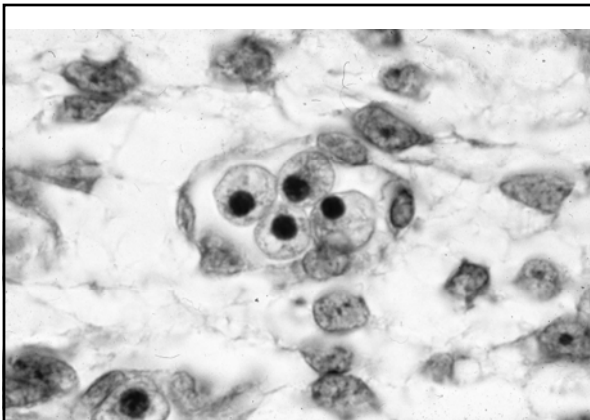
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- **CD34<sup>+</sup>** and Vascular Endothelial Growth Factor (**VEGF**) Receptor **2<sup>+</sup>** Cells which represent **0.01-0.03%** of all adult bone marrow (BM) cells and are called **adult BM stem cells**. (1/10,000). **CD34<sup>+</sup> VEGF2<sup>+</sup>** (0.001% of adult blood cells).

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- **Angiopoietin-1 (VEGF)** makes them become **endothelial cells**. Interleukins (**IL**) **1, 3, 6** and Stem Cell Factor (**SCF**) makes them become Pluripotential Hematopoietic Stem Cells (**PHSC**) which are **CD34<sup>+</sup> VEGF2<sup>-</sup>**. They represent **0.1-0.3%** of all adult marrow cells.

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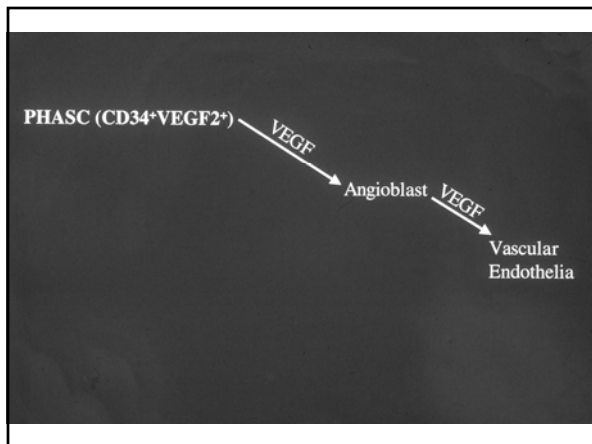
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- Angiopoietin-1 (VEGF) → endothelial  
IL. 1, 3, 6, SCF → multipotent, but  
called Pluripotent HSCS
  - CD34<sup>+</sup> VEGF2<sup>-</sup>
  - 0.1 – 0.3% adult bone marrow
  - 0.001 – 0.00.3% adult blood

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- Further stimulation with **IL 1, 3, 6** and **SCF** makes the PHSC become **Erythroid/Myeloid Multipotential Cells**. These cells are called clinically Colony forming Cell Granulocytic Erythroid Megakaryocytic Monocytic (**CFC-GEMM**) because they have the potential to form colonies in vitro of any of these cell lines depending on what growth factors they are incubated with.

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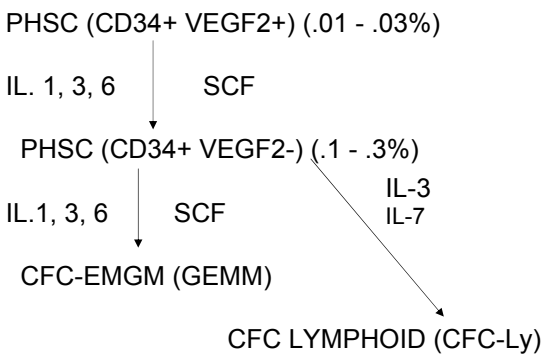
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- However, if the **PHSC** are incubated with **IL-7** they become Lymphoid Colony forming cells (**CFC-LY**).

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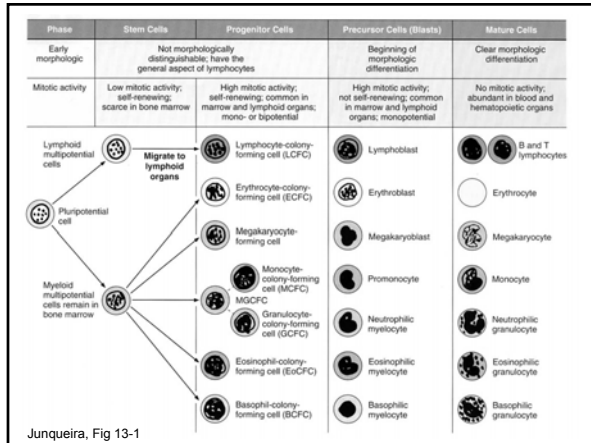
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- Note: Also, **Mesenchymal SC** form bone, cartilage, tendon, adipose, muscle, neural cells) found in adult bone marrow.

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C. What makes multipotent CFC-GEMM and CFC-Ly become Progenitor, Precursor and Mature Cells? Answer: Specific cytokines or growth factors.

- **Erythropoietin (EPO)** causes some CFC-GEMM to become CFC-Erythroid → Proerythroblast → **Erythrocyte**
- **Thrombopoietin (Thrombo)** causes some CFC-GEMM to become CFC-Megakaryocyte → Megakaryoblast → Megakaryocyte → Platelets

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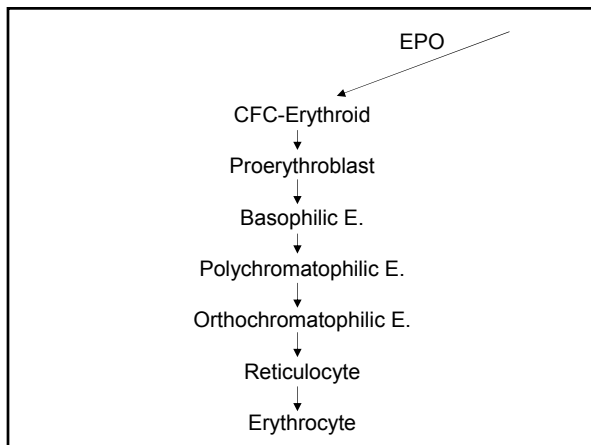
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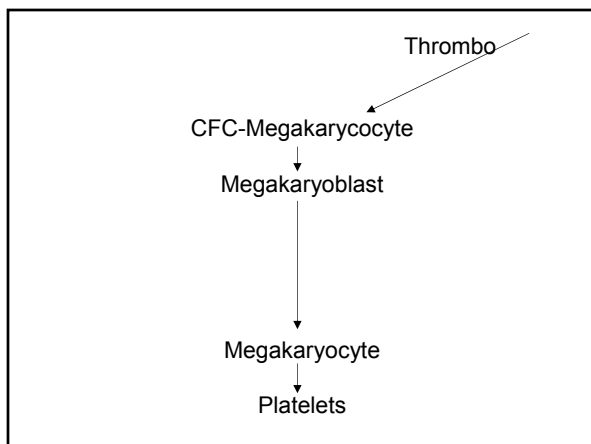
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- **Interleukin-4 (IL-4)** causes some CFC-GEMM to become CFC-Basophil → Myeloblast → **Basophil**

- **IL-5** causes some CFC-GEMM to become CFC-Eosinophil → Myeloblast → **Eosinophil**

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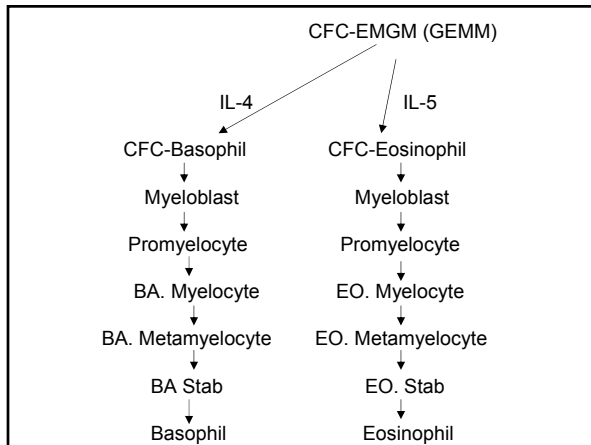
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- **Granulocyte-Monocyte-Colony Stimulating Factor (GM-CSF)** causes some CFC-GEMM to become CFC-Neutrophil Monocyte (**CFC-NM**)

- Granulocyte-CSF (**G-CSF**) causes CFC-NM to become CFC-Neutrophil → Myeloblast → **Neutrophil**

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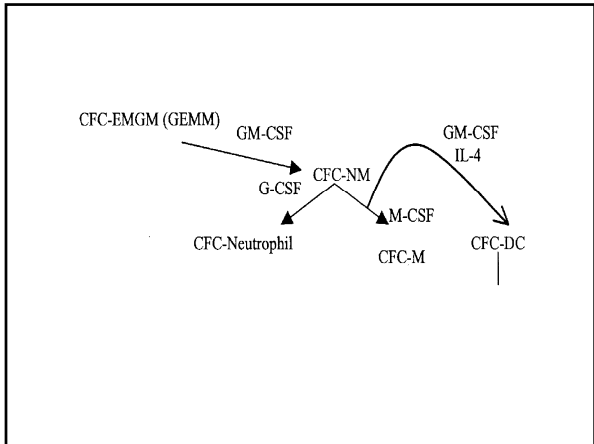
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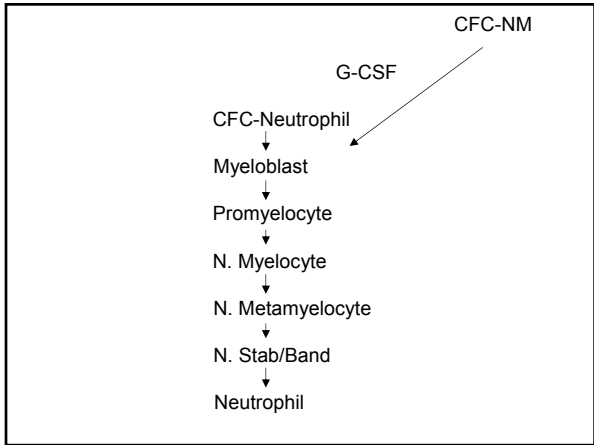
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• Monocyte-CSF (**M-CSF**) causes CFC-NM to become CFC-Monocyte → Monoblast → **Monocyte**

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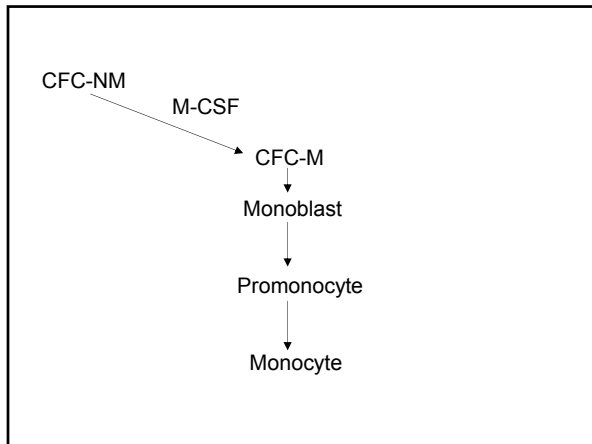
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• **GM-CSF, IL-4, Flt3-ligand** cause CFC-NM to become CFC-Dendritic Cell → **Immature Dendritic Cell (Langerhan's Cell of Skin)**.

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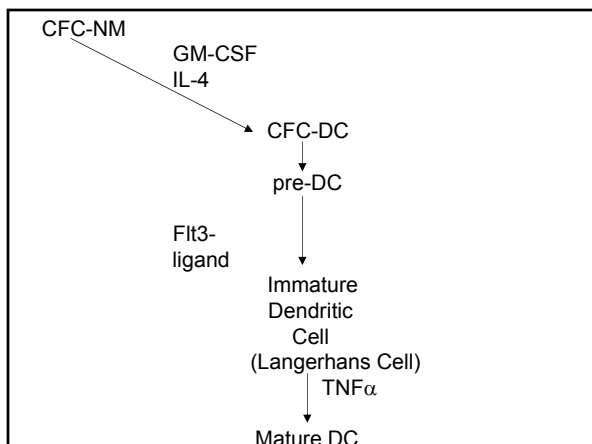
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- **IL-7, 2, 6** causes CFC-Lymphoid to become CFC-T/NK → preT → Thymus → T Cell

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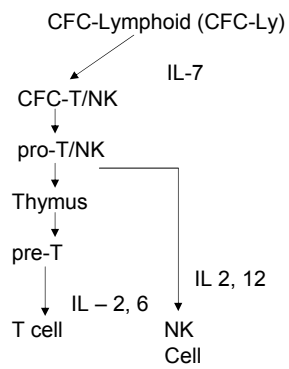
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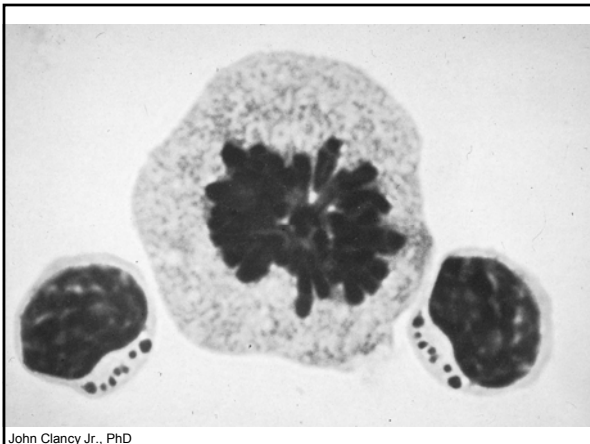
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- **IL-7, SCF** causes CFC-Lymphoid to become **CFC-B** → pro B → pre B → immature B → mature B. **IL 4, 5, 6** helps an **activated B** cell mature into a **plasma cell**.

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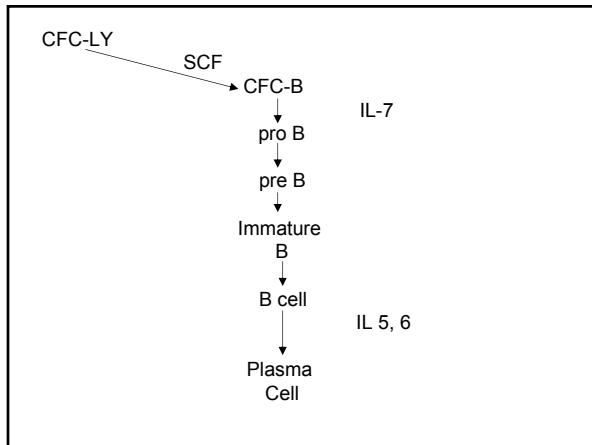
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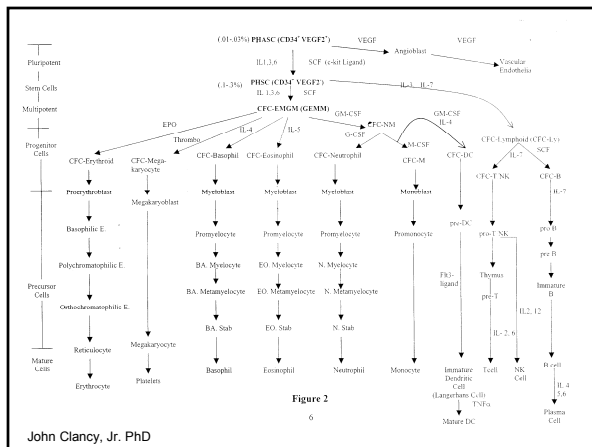
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Factors	Principal Action
Angiopoietin-1 (VEGF)	Promotes endothelial growth and development

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Factors	Principal Action
Stem cell factor (SCF; c-Kit Ligand)	Promotes hemopoiesis; critical for CFC-B development
GM-CSF	Promotes CFC-NM mitosis and differentiation; facilitates granulocyte activity; stimulates dendritic cell development
G-CSF	Promotes CFC-N mitosis and differentiation; facilitates neutrophil activity
M-CSF	Promotes CFC-M mitosis and differentiation; facilitates monocyte activity

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Factors	Principal Action
Flt-3 Ligand	Promotes dendritic cell development
TNF $\alpha$	Stimulates immature dendritic cells to mature.

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<b>Factors</b>	<b>Principal Action</b>
IL-1	In conjunction with IL-3 and IL-6, it promotes proliferation of PHSC, CFC-GEMM and CFC-Ly
IL-2	Stimulates activated T- and B-cell mitosis; induces differentiation of NK cells
IL-3	In conjunction with IL-1 and IL-6, it promotes proliferation of PHSC, CFC-GEMM, and CFC-Ly as well as all unipotential precursors (except for LyB and LyT)

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<b>Factors</b>	<b>Principal Action</b>
IL-4	Stimulates B-cell activation and development of mast cells and basophils. Also stimulates dendritic cell development
IL-5	Promotes CFC-Eo mitosis and activates eosinophils; promotes B cell growth
IL-6	In conjunction with IL-1 and IL-3, it promotes proliferation of PHSC, and CFC-Ly; also facilitates B-cell differentiation into plasma cells.

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<b>Factors</b>	<b>Principal Action</b>
IL-7	Promotes differentiation of CFC-Ly; enhances differentiation of CFC-T/NK cells and maturation of CFC-B to pro B cells
IL-12	Stimulates NK cells development and function; enhances CTL function

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Factors	Principal Action
Erythropoietin	CFC-E development and differentiation
Thrombopoietin	Proliferation and differentiation of CFU-megakaryocyte and megakaryoblasts

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**C. BONE MARROW IS A SPECIALIZED CONNECTIVE TISSUE**

- Red and Yellow Marrow with the Sternum, iliac crest as the primary sites for access. Also present in long bones, vertebral bodies, ribs, flat bones of cranium. 5% of total body weight.

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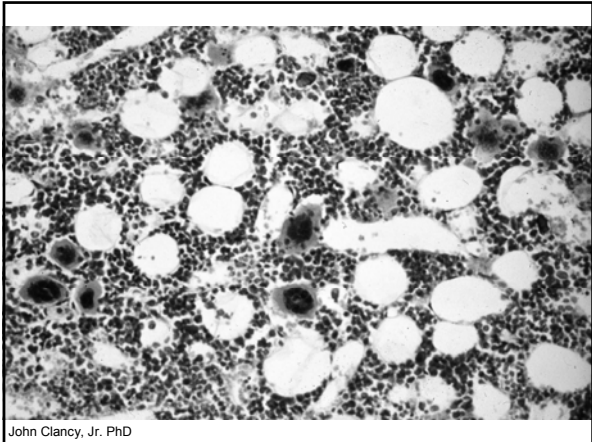
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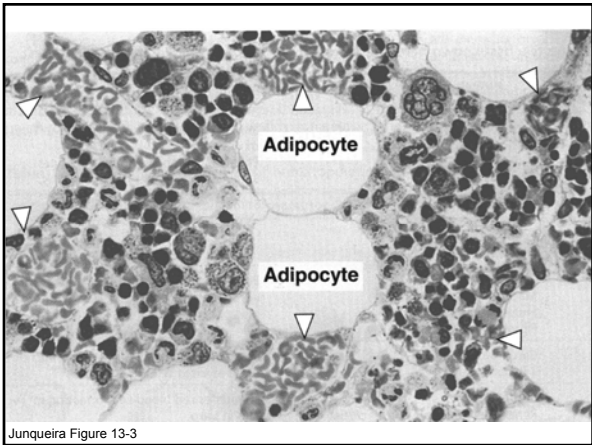
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- Contents:
  - Primitive blood cells in **Hematopoietic islands or cords: Red Marrow of developing blood cells and macrophages.**
  - **Fat cells: Yellow Marrow.**
  - Stromal Cells (IL-7; SCF; GM-CSF; M-CSF; 1; IL-6)

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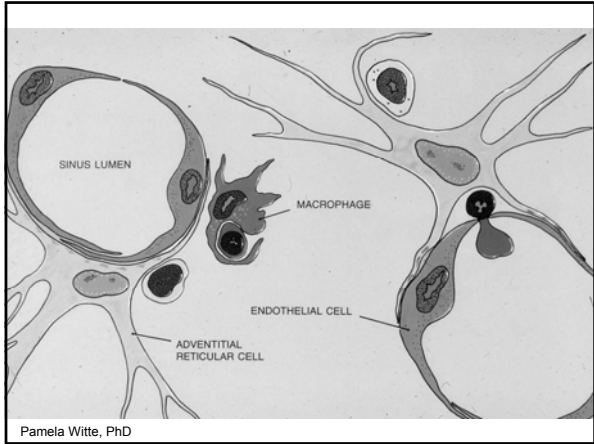
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Pamela Witte, PhD

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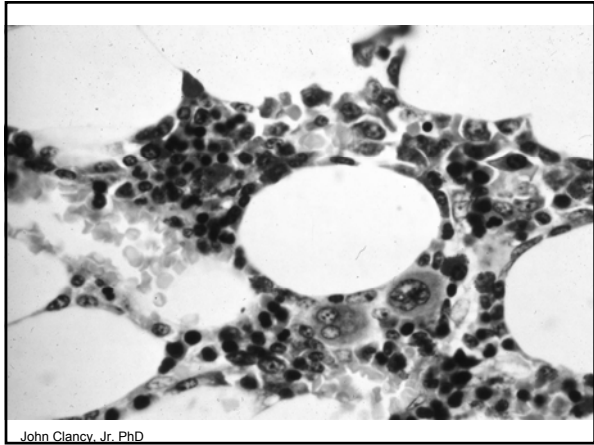
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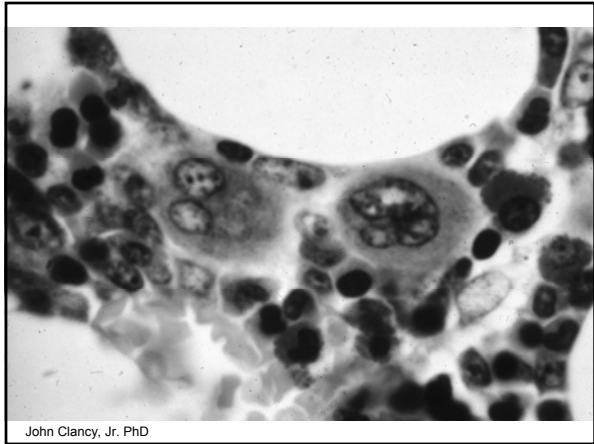
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- Type III collagen (Reticular tissue)
- Sinusoids (discontinuous capillaries) – 45-80 um in diameter which drain into a central longitudinal → nutrient V.
- Megakaryocytes (Polyploid:64N); Platelets (Fig. 13-4)
- Osteoclasts

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Note: PHSC sit in a **niche** of either **osteoblasts** or sinusoidal **endothelial** cells. Also require stromal cells as they differentiate.

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SC first gives rise to a committed transit amplifying cell which loses contact with the niche and enters the commitment stage.

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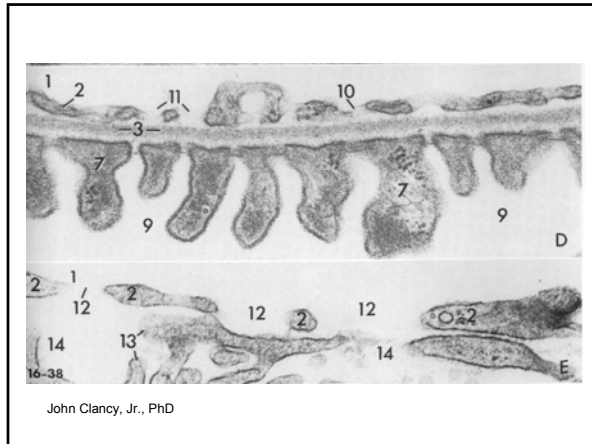
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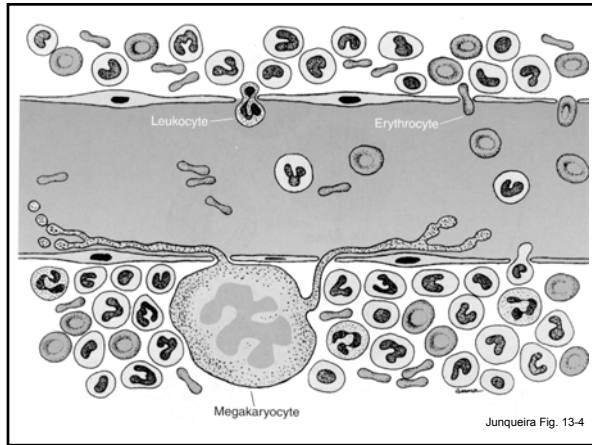
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Junqueira Fig. 13-4

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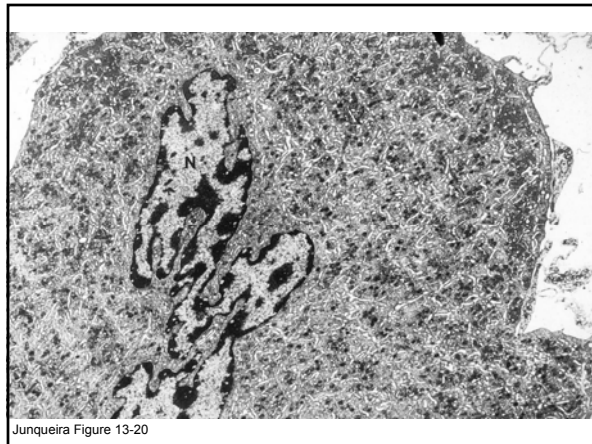
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Junqueira Figure 13-20

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Note: PHSC sit in a niche of either osteoblasts or sinusoidal endothelial cells.

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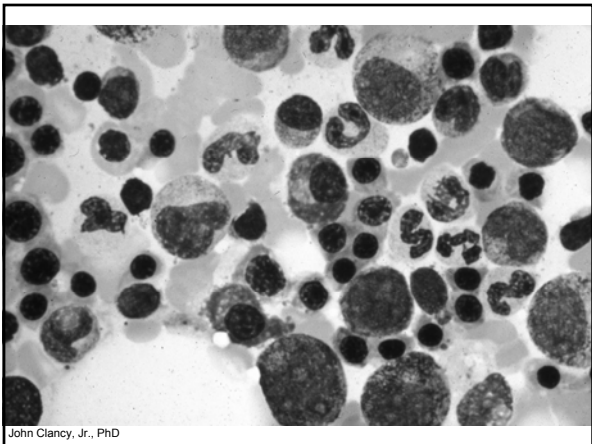
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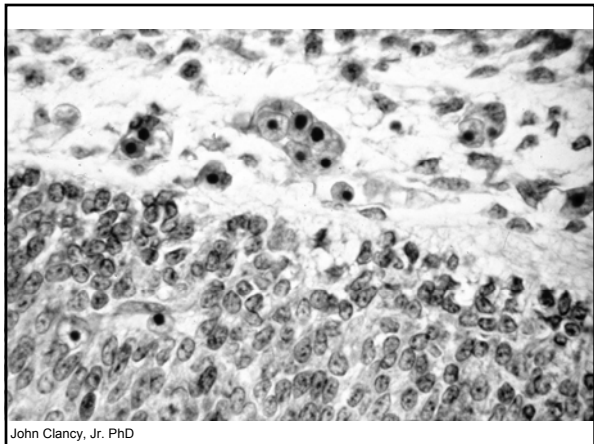
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**D. HEMATOPOIESIS** – Mesenchymal cells aggregate into Blood Islands in Yolk Sac (2 weeks) with the peripheral cells forming endothelial cells and the central cells erythroblasts → Spleen (14-15 weeks) → Bone Marrow (6 months) (Figs. 13-5, 13-6).

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- **Erythropoiesis** - ↓ size and basophilia (RNA); ↑ eosinophilia, hemoglobin
  - **$2.5 \times 10^{11}$  erythrocytes/day**
  - CFU-E becomes a **Proerythroblast** (Pronormoblast): prominent nucleoli, basophilic cytoplasm

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- **Basophilic erythroblast:** denser nucleus, very basophilic cytoplasm
- **Polychromatophilic erythroblast:** last cells in mitosis; hemoglobin synthesis, gray cytoplasm
- **Orthochromatophilic erythroblast or Normoblast:** no mitosis, nucleus extruded, eosinophilia begins in cytoplasm.
- **Reticulocytes:** polysomes, but no mitochondria in cytoplasm.

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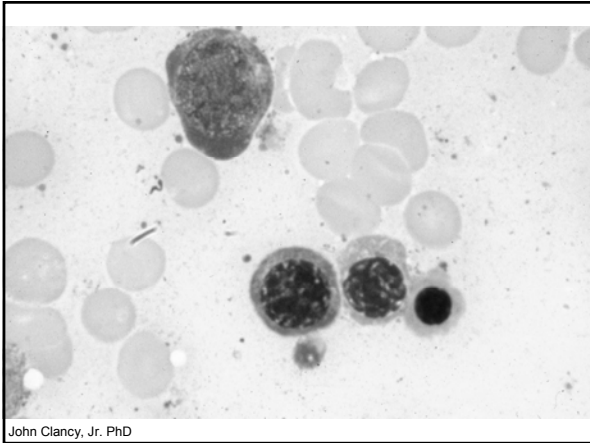
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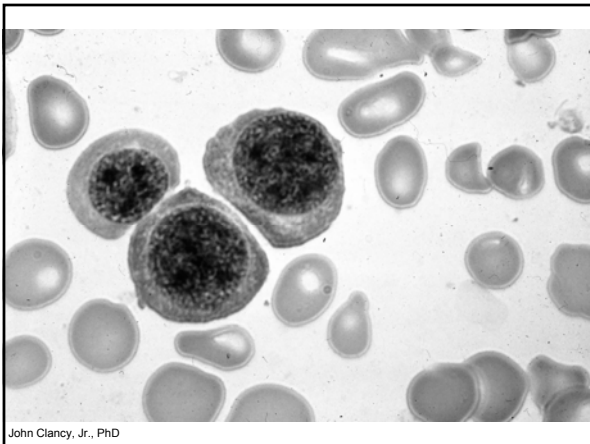
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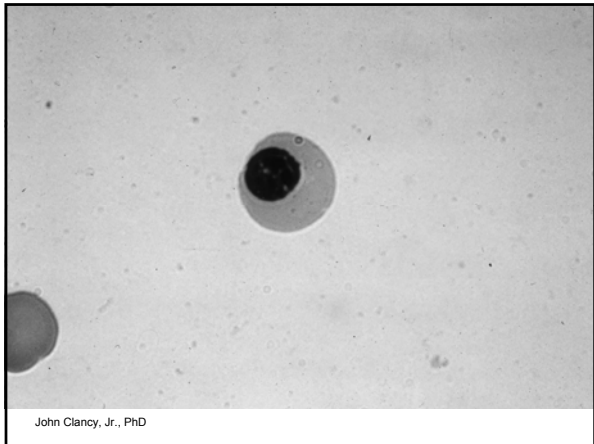
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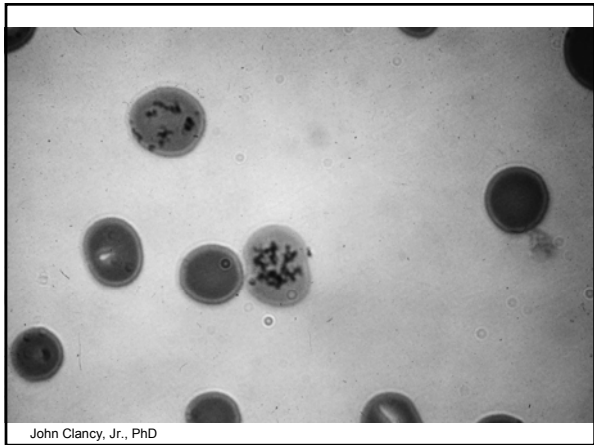
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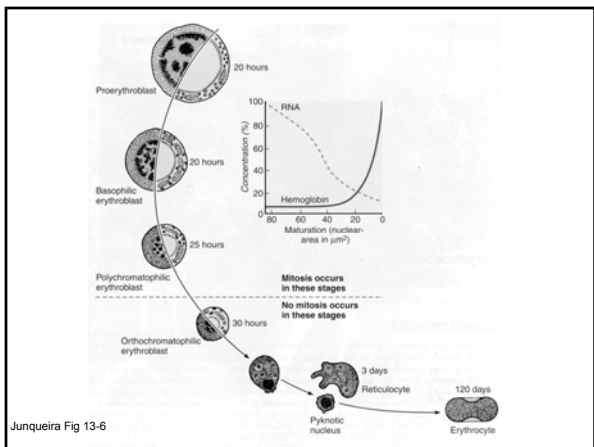
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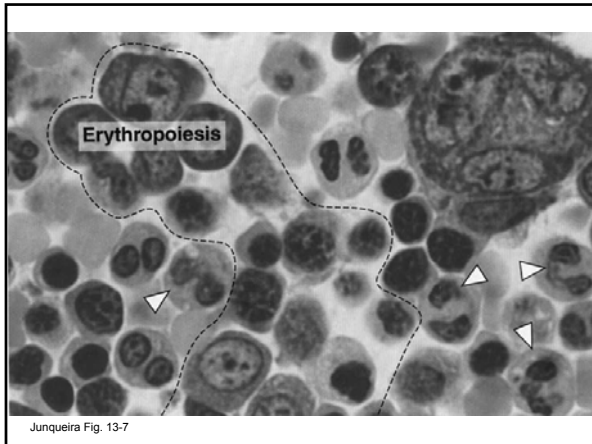
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- **Macrophages** form an erythroblastic island around developing erythrocytes, destroy aged erythrocytes and transfer ferritin, an iron-containing protein complex, to young erythroblasts. Macrophages also destroy the nuclei expelled by a normoblast via lysosomal DNAase-II and produce other growth factors that influence hematopoiesis.

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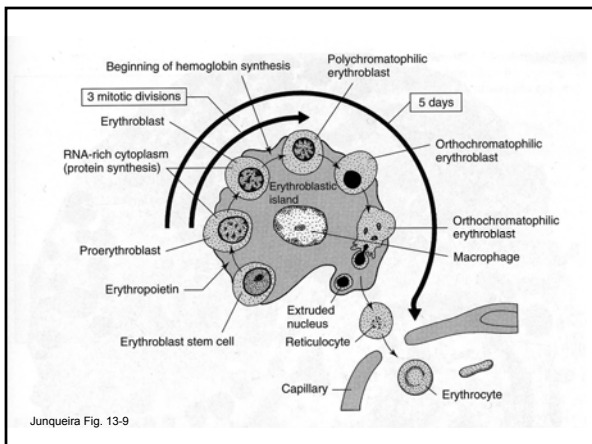
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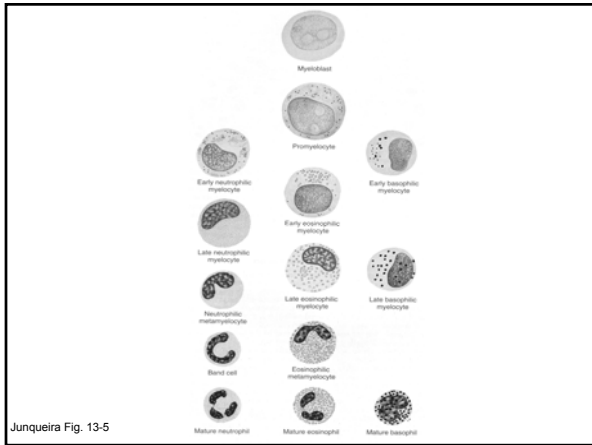
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Junqueira Fig. 13-5

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Granulopoiesis - ↓ size and basophilia after the promyelocyte stage; ↑ granules and granule specificity; nuclear lobulation (fig. 13-5 and 13-11)

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- CFC-N Myeloblast: large cell (15um) with prominent nucleoli; looks like a proerythroblast.

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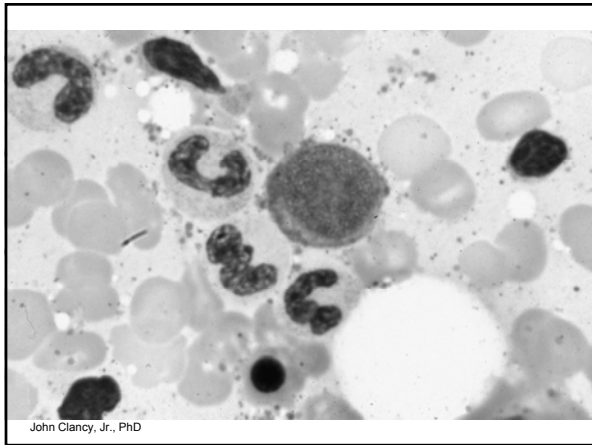
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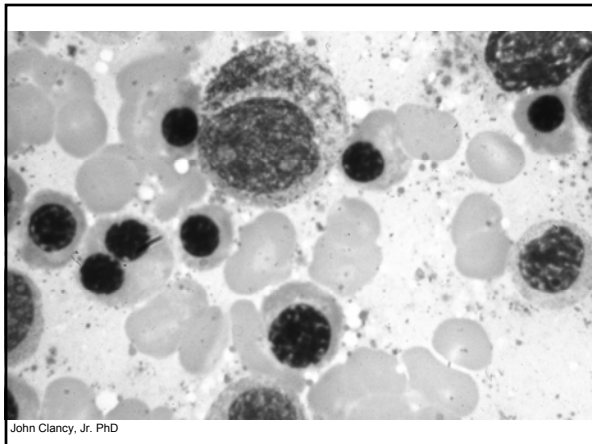
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- Promyelocyte: 18-24 um with azurophilic granules (Reddish purple: lysosomal enzymes, myeloperoxidase). 500nm in diameter. Still some cytoplasmic basophila.

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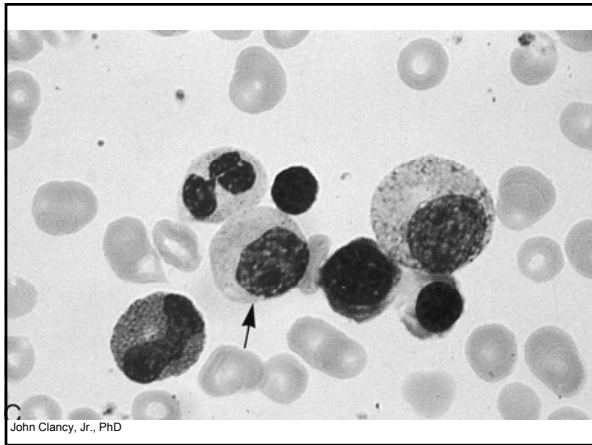
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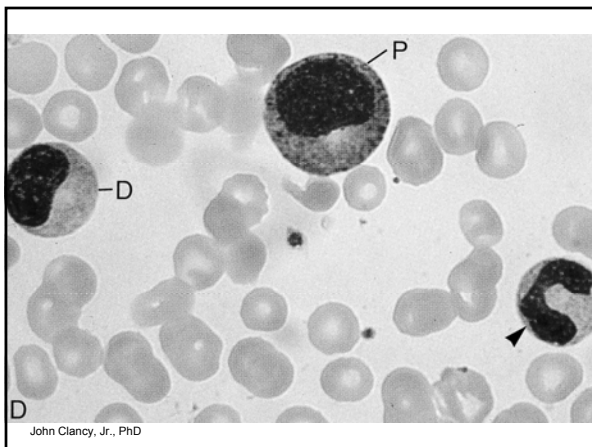
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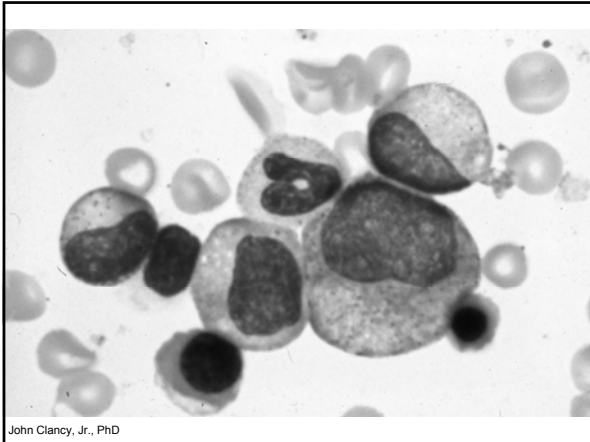
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- Myelocyte: specific granules for each granulocytic line
- Metamyelocyte: kidney shaped nucleus
- Band or Stab cell: in circulation, but more common with neutrophilic series.
- Segmented mature cell

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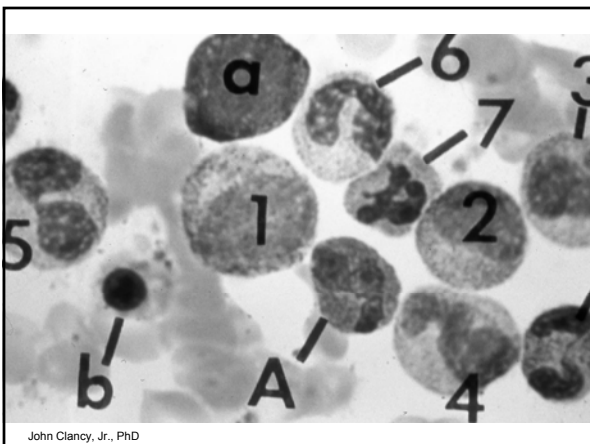
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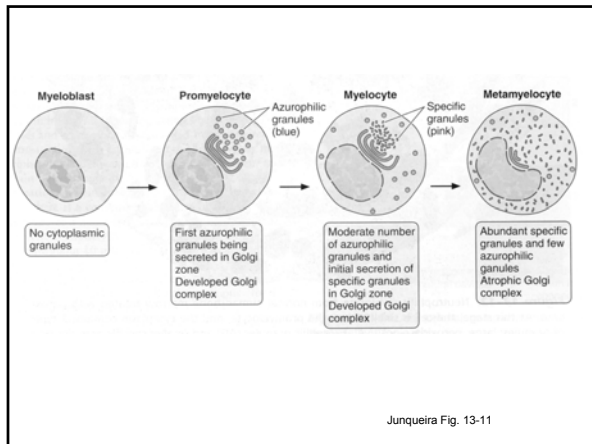
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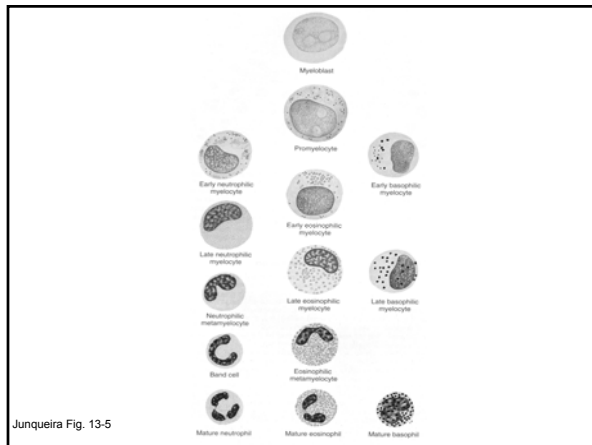
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- Growth Factors (Table 1)  
GM-CSF; G-CSF; Interleukin-3 (IL-3); IL-5 (Eosinophils); IL-4 (Basophils)
- Neutrophils ( $8 \times 10^5/D$ ), Eosinophils ( $1.7 \times 10^5/D$ ), Basophils ( $6 \times 10^4/D$ ) are produced and released into the circulation.

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- Lymphopoiesis → Lymphocytes
  - IL-7, 6, 2 (T cells) – Require thymic epithelial cells.
  - IL-7, 2, 12 (NK cells) – Made in bone marrow and released into blood as functional cells.
  - IL 7, 4, 5, 6 (B cells) – Require bone marrow stromal cells.

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Monocytopoiesis → Monocytes  
GM-CSF, M-CSF

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- Dendritic Cell Development → Immature Dendritic Cells (Langerhans Cell) → Mature DC which is present in secondary lymphoid tissue and presents antigen to T cells for a cell-mediated immune response.
  - GM-CSF, IL-4, Flt3-ligand → TNF $\alpha$   
(Mature DC)

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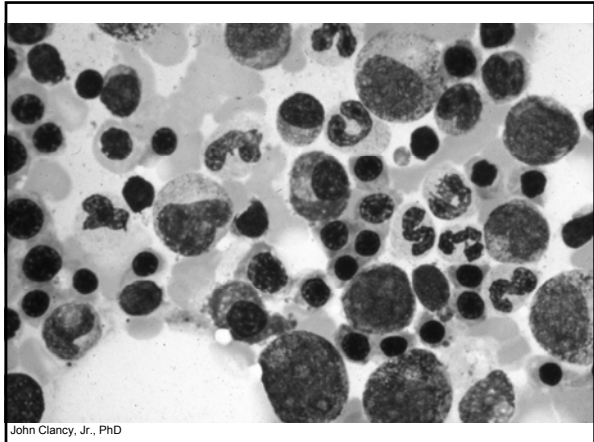
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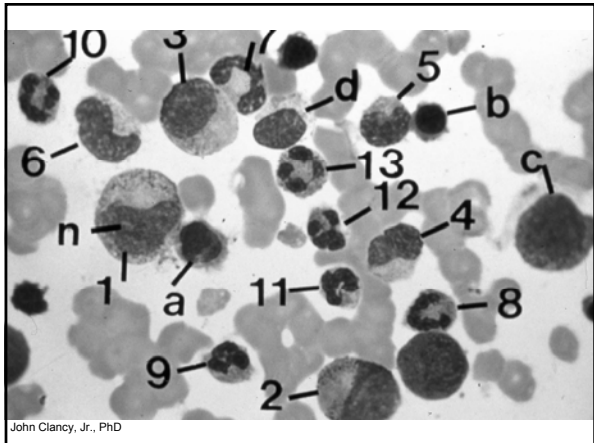
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## TISSUE AND ORGANS OF THE IMMUNE SYSTEM

Date: March 11, 2011 - 9:30 AM

### LEARNING GOALS

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

### OBJECTIVES

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

- State the difference between central (primary) versus peripheral lymphoid organs.
- Describe the development, structure and general function of the thymus.
- Draw the general sequence of events in CD4 and CD8 lymphocyte development from thymocytes. Understand where positive and negative selection occurs and its consequences. Describe where double negative, double positive, and single positive cells are found.
- Describe the structure and function of lymph nodes.
- 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.
- Describe the structure and function of the spleen.
- 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).

### READING ASSIGNMENTS

Junqueira, et al, **Basic Histology**, 11<sup>th</sup> Edition, Chapter 14.

Wheater's **Functional Histology**, 5<sup>th</sup> Edition, Chapter 11.

Janeway, et al, **Immunobiology**, 7<sup>th</sup> Edition, Chapters 1 (pp.3-13), 7 (pp.273-280), 8 (pp. 325-327), 9 (pp. 387-390).

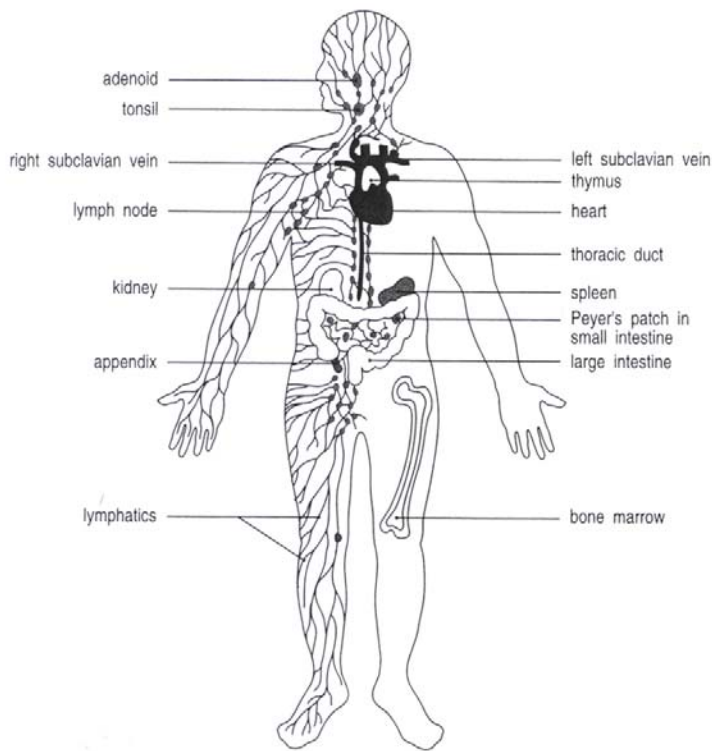
### LECTURER

John Clancy, Jr., Ph.D.



## I. CENTRAL VERSUS PERIPHERAL LYMPHOID ORGANS (Fig. 1.7)

- 1<sup>o</sup> or Central: Bone marrow, Thymus
- 2<sup>o</sup> or Peripheral: Lymph nodes, Spleen, Tonsils, Peyer's Patches, Appendix
- 3<sup>o</sup> : 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)

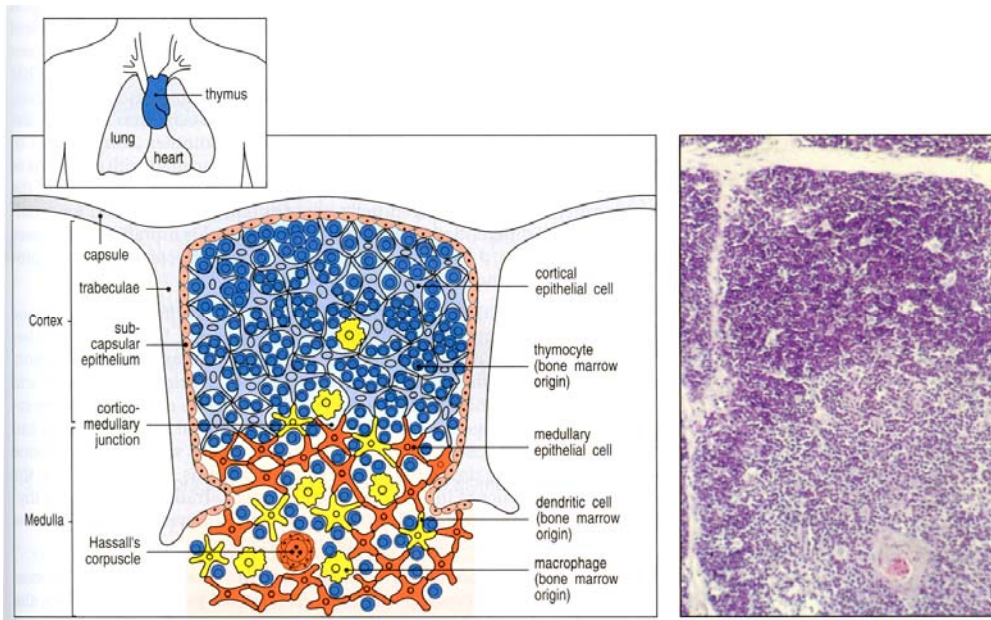


**Fig. 1.7 The distribution of lymphoid tissues in the body.** Lymphocytes arise from stem cells in bone marrow, and differentiate in the central lymphoid organs, B cells in bone marrow and T cells in the thymus. They migrate from these tissues and are carried in the bloodstream to the peripheral or secondary lymphoid organs, the lymph nodes, spleen, and lymphoid tissues associated with mucosa, like the gut-associated tonsils, Peyer's patches, and appendix. The peripheral lymphoid organs are the sites of lymphocyte activation by antigen, and lymphocytes recirculate between the blood and these organs until they encounter their specific antigen. T cells receive survival signals from dendritic cells (DCs) in the periphery, whereas the source of the survival signals for B cells is thought to be in the lymphoid follicles. Lymphatics drain extracellular fluid from the peripheral tissues, through the lymph nodes and into the thoracic duct, which empties into the left subclavian vein. This fluid, known as lymph, carries antigen taken up by DCs and macrophages to the lymph nodes and recirculating lymphocytes from the lymph nodes back into the blood. Lymphoid tissue is also associated with other mucosa such as the bronchial linings (not shown).

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## II. THYMUS: ENCAPSULATED WITH EPITHELIAL STROMA (Figs. 7.15 and 7.21)

- **Origin:** Ventral part of 3<sup>rd</sup> 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.
- **Stroma** of **Epithelial Reticular Cells** which secrete **IL-7** and contain tonofilaments.
  - Cortex:
    - Developing T cells:  $CD3^-4^-8^- \rightarrow \gamma:\delta^+$  (T cell receptor)  $CD3^+$  or  $\alpha:\beta$  (T cell receptor)  $CD3^+4^+8^+$ . CD3 is present on all T cells and acts in signal transduction.
    - Nurse cells (subcapsular epithelial cells); surround  $CD3^-4^-8^-$  cells and secrete IL-7.
    - Cortical Epithelial Cells which make contact with  $CD3^+4^+8^+$  cells and display self antigens.
  - Cortico-Medullary Junction
    - Dendritic cells (Bone Marrow Derived): make contact with  $CD3^+4^+8^+$ .
    - Macrophages make contact with  $CD3^+4^+8^+$ ; ingest apoptotic cells
  - Medulla:
    - **Hassall's Corpuscles** (Whorl-shaped Epithelial Cells): no known function but only found in the thymus. Increase with age.
    - Mature T cells:  $CD3^+4^+$  or  $CD3^+8^+$
- **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.
    - 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.



**Fig. 7.15 The cellular organization of the human thymus.** The thymus, which lies in the midline of the body, above the heart, is made up of several lobules, each of which contains discrete cortical (outer) and medullary (central) regions. As shown in the diagram, the cortex consists of immature thymocytes, branched cortical epithelial cells, with which the immature cortical thymocytes are closely associated, and scattered macrophages, which are involved in clearing apoptotic thymocytes. The medulla consists of mature thymocytes, and medullary epithelial cells, along with macrophages and dendritic cells of bone marrow origin. Hassall's corpuscles are probably also sites of cell destruction. The thymocytes in the outer cortical cell layer are proliferating immature T cells undergoing thymic selection. The photograph shows the equivalent section of a human thymus, stained with hematoxylin and eosin. The cortex is darkly staining; the medulla is lightly stained. The large body in the medulla is a Hassall's corpuscle. Photograph courtesy of C.J. Howe.

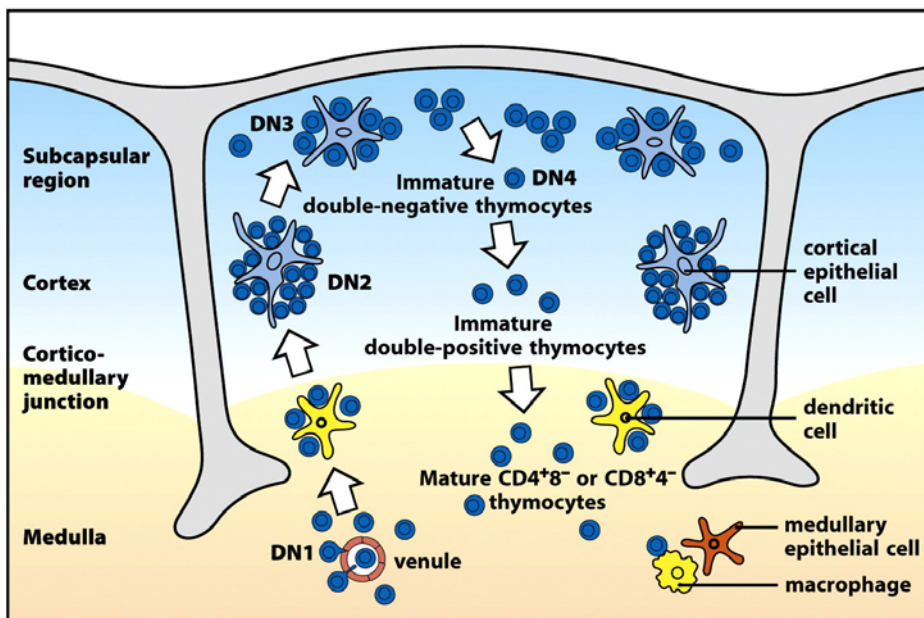


Figure 7-21 Immunobiology, 7ed. (© Garland Science 2008)

**Fig. 7.21 Thymocytes at different developmental stages are found in distinct parts of the thymus.** The earliest cells to enter the thymus are found in the subcapsular region of the cortex. As these cells proliferate and mature into double-positive thymocytes, they migrate deeper into the thymus cortex. Finally, the medulla contains only mature single-positive T cells, which eventually leave the thymus and enter the bloodstream.

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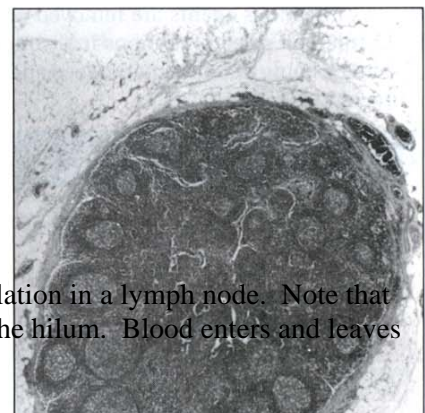
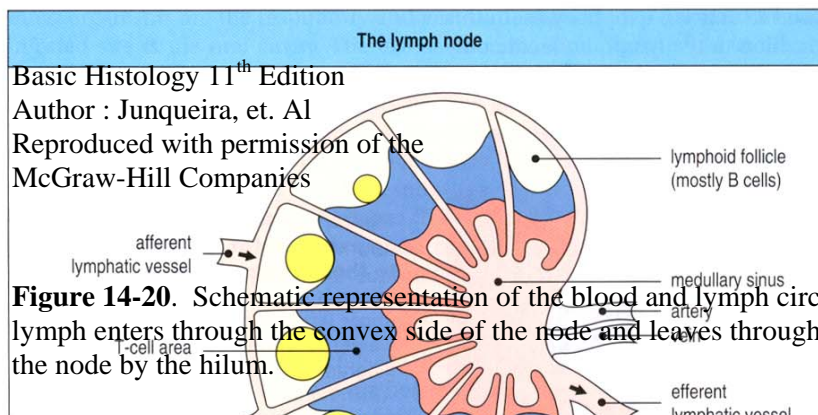
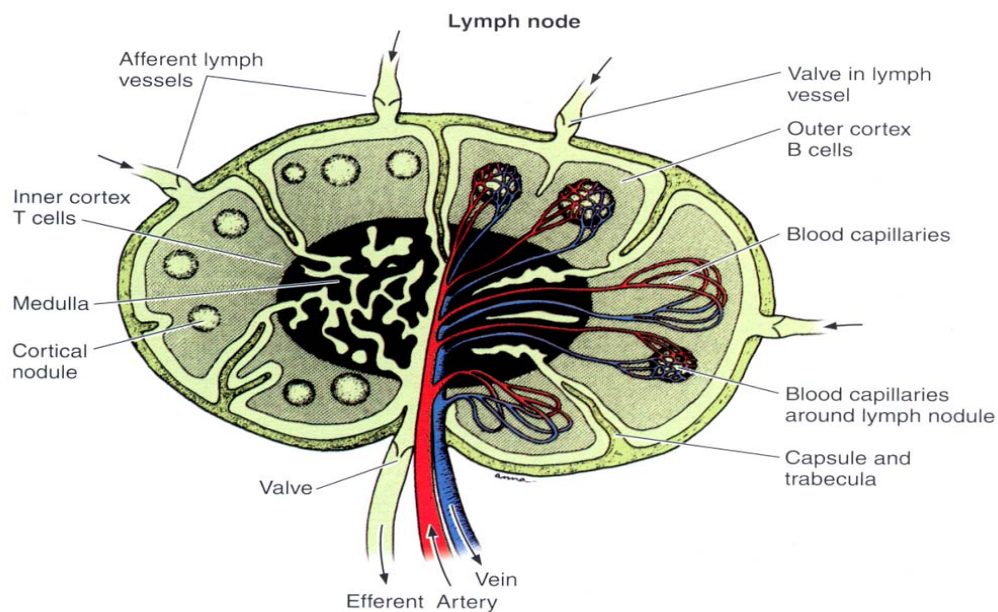
- Proliferation
  - **>any other lymphoid organ** but under endogenous control as not antigen driven.
  - **<4%** of all thymocytes produced after three weeks **leave** for periphery as CD3<sup>+</sup>4<sup>+</sup> or CD3<sup>+</sup>8<sup>+</sup> lymphocytes. Most cells die via apoptosis. **Twice** as many CD3<sup>+</sup>4<sup>+</sup> survive than CD3<sup>+</sup>8<sup>+</sup>.
- Thymosin or Thymopoietin hormone produced by thymic epithelial cells. This concept largely replaced by epithelial derived cytokines → **IL-7, IL-2 and IL-6** necessary for thymocyte development. Adrenocortico steroids decrease cortical T cell numbers.
- Young vs. Old: The thymus is well developed at birth but loses 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**.
- Weakly permeable protective environment in the thymus such that **most circulating antigens** are excluded from developing immature cortical cells. Blood-thymus barrier.
- **NK (CD56) cells** develop in the bone marrow and diverge early from the pro-T/NK pathway and are **not thymus dependent**.

**III. LYMPH NODE: ENCAPSULATED WITH TYPE I COLLAGEN WITH RETICULAR CELL AND FIBER (Type III Collagen) STROMA ATTACHED. (Figs. 14.20, 1.18, 4.17, 1.9, 9.9, 9.10)**

- **Trabecula** extend 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 follicles and homogeneous cortex which leads to medullary cords lined by medullary lymph sinuses.
- **Reticular stroma** creates **lymph sinuses** which are called **subcapsular, trabecular** and **medullary**.
- Lymph circulation (Fig 14-20).
  - **Afferent lymphatics** receive lymphatic vessels from the periphery. Have valves directed to the subscapular sinus.
  - **Subcapsular** → **Trabecular** → **Medullary Sinuses** → **Efferent Lymphatic** → **Thoracic Duct**. Sinuses made up of stellate reticular cells and fibers. Macrophages extensively attach.  
Which contains:
    - Lymphocytes (B & T)
    - Lymphoblasts (B & T)
    - Macrophages
- 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**

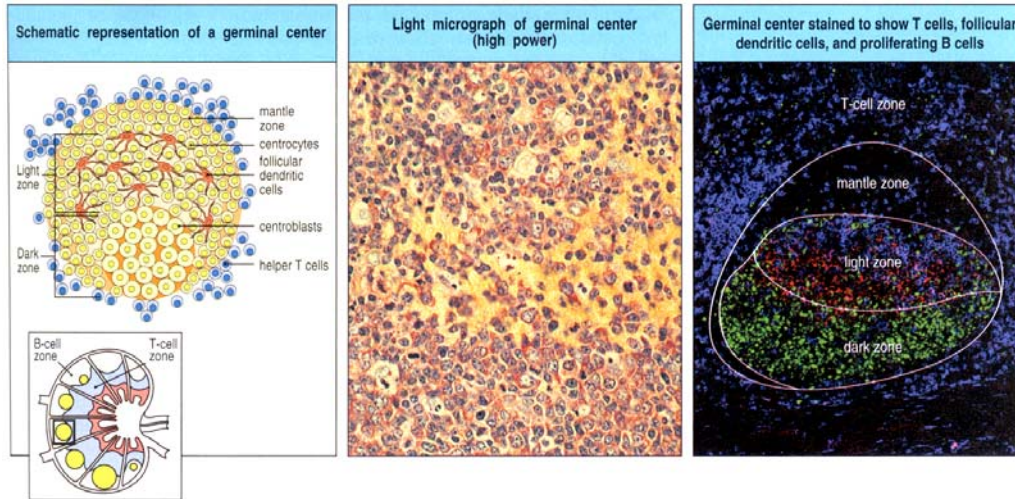
(T and B cells) gain entrance into the lymph node from the circulation.

- Cortex
  - Superficial
    - 1° nodule (follicle): B cells mainly
    - 2° nodule with **germinal center** are the sites where B cells mature with the help of CD4<sup>+</sup> T cells into either Plasmablasts or Memory Cells (Fig. 1.18, 9.10)
      - 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.

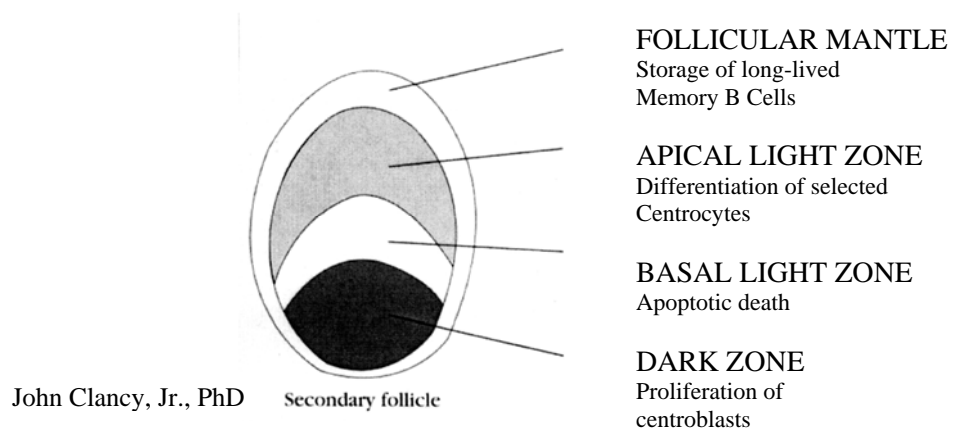


**Figure 14-20.** Schematic representation of the blood and lymph circulation in a lymph node. Note that lymph enters through the convex side of the node and leaves through the hilum. Blood enters and leaves the node by the hilum.

**Fig. 1.18 Organization of a lymph node.** As shown in the diagram on the left, a lymph node consists of an outermost cortex and an inner medulla. The cortex is composed of an outer cortex of B cells organized into lymphoid follicles and deep, or paracortical, areas made up mainly of T cells and dendritic cells. When an immune response is underway, some of the follicles contain central areas of intense B-cell proliferation called germinal centers and are known as secondary lymphoid follicles. These reactions are very dramatic, but eventually die out as senescent germinal centers. Lymph draining from the extracellular spaces of the body carries antigens in phagocytic dendritic cells and phagocytic macrophages from the tissues to the lymph node via the afferent lymphatics. Lymph leaves by the efferent lymphatics in the medulla. The medulla consists of strings of macrophages and antibody-secreting plasma cells known as the medullary cords. Naïve lymphocytes enter the node from the bloodstream through specialized postcapillary venules (not shown) and leave with

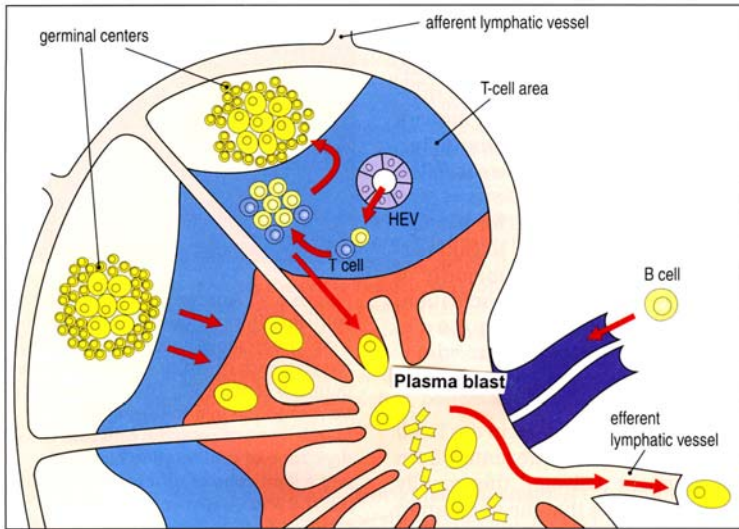


**Fig. 9-10 Germinal centers are formed when activated B cells enter lymphoid follicles.** The germinal center is a specialized microenvironment in which B-cell proliferation, somatic hypermutation, and selection for antigen binding all occur. Closely packed centroblasts from the so-called “dark zone” of the germinal center, as can be seen in the lower part of the photomicrograph in the center, which shows a high-power view of a section through a human tonsillar germinal center. The photomicrograph on the right shows a lower-power view of a tonsillar germinal center; B cells are found in the dark zone, light zone, and mantle zone. Proliferating cells are stained green for Ki67, an antigen expressed in nuclei of dividing cells, revealing the centroblasts in the dark zone. The dense network of follicular dendritic cells, stained red, mainly occupies the light zone. Cells in the light zone are also proliferating, though to a lesser degree in most germinal centers. Small recirculating B cells occupy the mantle zone at the edge of the B-cell follicle. Large masses of CD4 T cells, stained blue, can be seen in the T-cell zones, which separate the follicles. There are also significant numbers of T cells in the light zone of the germinal center; CD4 staining in the dark zone is mainly associated with CD4-positive phagocytes. Photographs courtesy of I. MacLennan.



- **Germinal Center Zonation:** activated B cells called Centroblasts or Centrocytes (Fig. 9.10)
  - **Dark Zone** at the base: **Centroblasts** (B blasts) without surface immunoglobulin (SIG). Hypermutation occurs to make more avid antibody.

- **Basal Light Zone: Centrocytes** (B cells) with SIG. Antigen-bearing **follicular dendritic cells** (FDCs). Centrocytes that bind antigen on FDCs survive, those that don't die by apoptosis.
- **Apical Light Zone: Differentiation** of surviving centrocytes to become B Blast (**Plasmablast**) or **Memory Cells**
- 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**. (Figure 4.17).
- **Follicular Mantle: Memory Cells** and some **non-reactive B cells**.
- **Inner or paracortex**
  - Diffuse cells: **1° T**, some B
  - **Langerhans Cell** (Immature Dendritic Cell) originates in the marrow and localizes 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 cells. (Fig 1.19)
  - High endothelial post-capillary venule (HEPCVs) function as the gate of entry of T and B cells from the circulation into the lymph node.
- 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.



activated by CD4 helper T cells in the T-cell areas

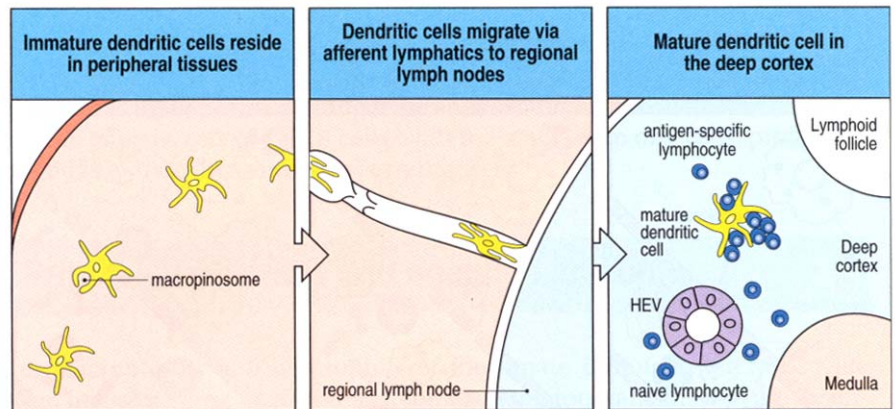
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**Figure 4.17 B cells encountering antigens in secondary lymphoid tissues form germinal centers and undergo differentiation to plasma cells.** A lymph node is illustrated here. A B cell entering the lymph node through a HEV encounters antigen in the lymph node cortex. Antigen was delivered in the afferent lymph that Drained from infected tissue. The B cell is

drained from infected tissue. The B cell is

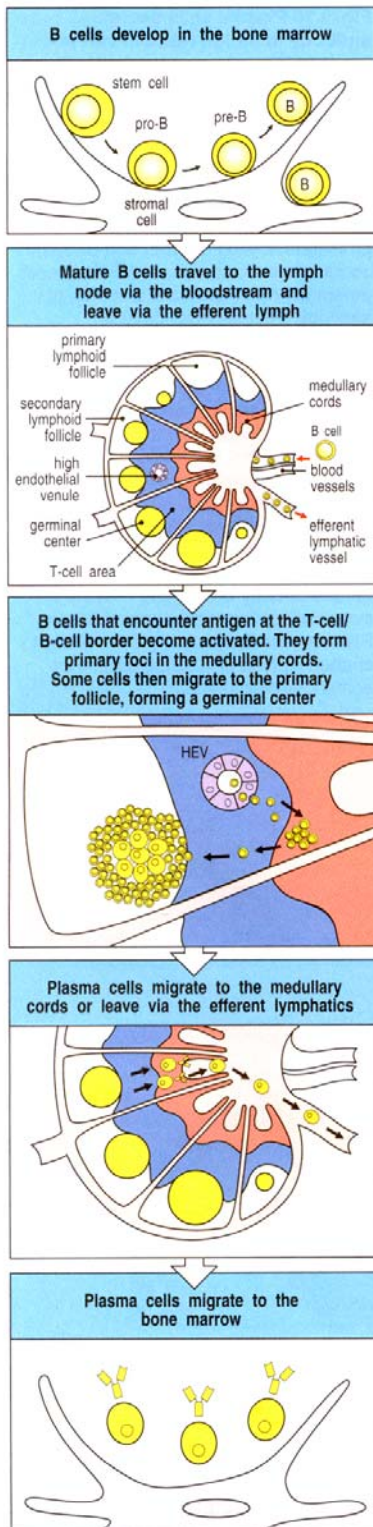
to form a primary focus of dividing cells. From this, some B cells migrate directly to the medullary cords secreting plasma cells. Other B cells migrate into a primary follicle to form a germinal center. B cells continue to divide and differentiate within the germinal center. Activated B cells migrate from the germinal center to the medulla of the lymph node or to the bone marrow to complete their differentiation into plasma cells.

**Fig. 1.9 Dendritic cells initiate adaptive immune responses.** Immature dendritic cells resident in a tissue take up pathogens and their antigens by macrophinocytosis and by receptor-mediated endocytosis. They are stimulated by recognition of the presence of pathogens to migrate through the lymphatics to regional lymph nodes, where they arrive as fully mature nonphagocytic dendritic cells that express both antigen and the necessary surface molecules to stimulate clonal expansion. In the lymph node, the mature dendritic cell encounters and activates antigen-specific naïve T lymphocytes, which enter the node from the blood through a specialized blood vessel known from its cuboidal endothelial cells as a high endothelial venule (HEV).



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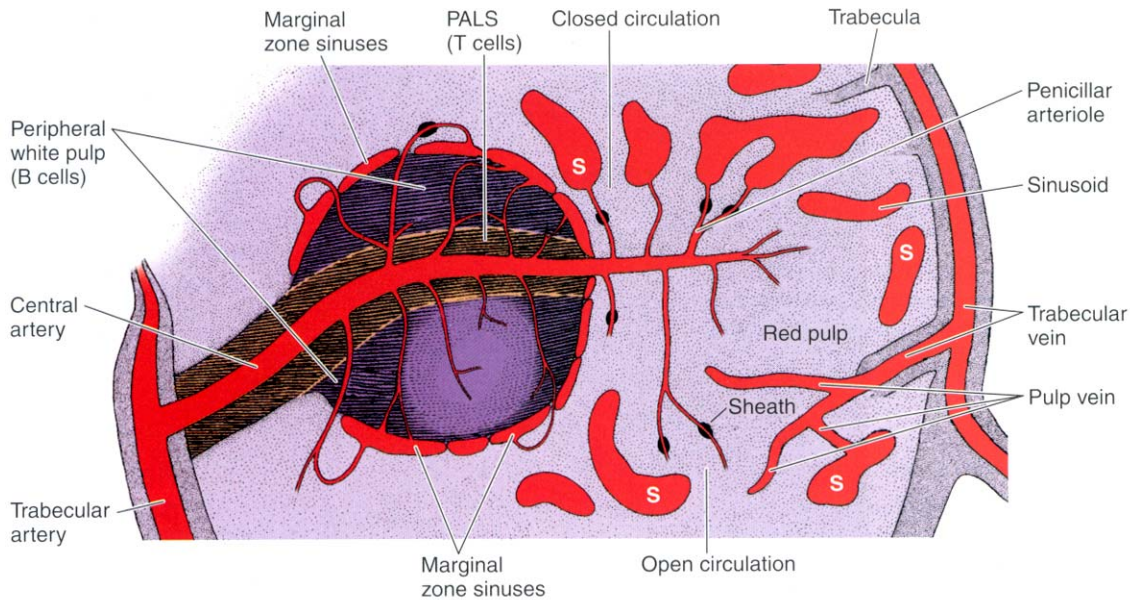


**Fig. 9.9 Activated B cells form germinal centers in lymphoid follicles.** Some B cells activated at the T-cell/B-cell border migrate to form a germinal center within a primary follicle. Germinal centers are sites of rapid B-cell proliferation and differentiation. Follicles in which germinal centers have formed are known as secondary follicles. Within the germinal center, B cells begin their differentiation into either Antibody-secreting plasma cells or memory B cells. Plasma cells leave the germinal center and migrate to the medullary cords or leave the lymph Node altogether via the efferent lymphatics and migrate to the bone marrow. Memory B cells continue to recirculate through the B-cell zones of secondary lymphoid tissue (not shown) and some may preferentially reside in the splenic marginal zone as described in Chapter 7.

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#### 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.
- **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 Billoth** (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.**
  - **Penicillar arteries** come from central arteries and may empty into sinusoids or RP cords.
- Open versus closed (continuous) circulation refers to whether penicillar arteries:
  - 1) **Open** → parenchyma of RP cords and then into sinusoids, or
  - 2) **Closed** → directly into sinusoids
- Old RBCs lose surface sialic acid exposing surface galactose which are phagocytosed by sinusoid adhering macrophages.
- Hemopoietic in second trimester and some disease states.



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**Figure14-28** Schematic view of the blood circulation of the spleen. Theories of open and close circulation are Represented. Splenic sinusines (S) are indicated. PALS, periarterial lymphatic sheath.

## V. GASTROINTESTINAL TRACT

- **Epithelial lining** contains **CD3+8+ $\alpha\beta$**  and **CD3+  $\gamma\delta$**  cells to monitor luminal antigens.
- **Diffuse**, in lamina propria just underneath the epithelia lining throughout the GI tract.
  - 1° nodule: **Ig A** 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<sup>+</sup>)
- **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.

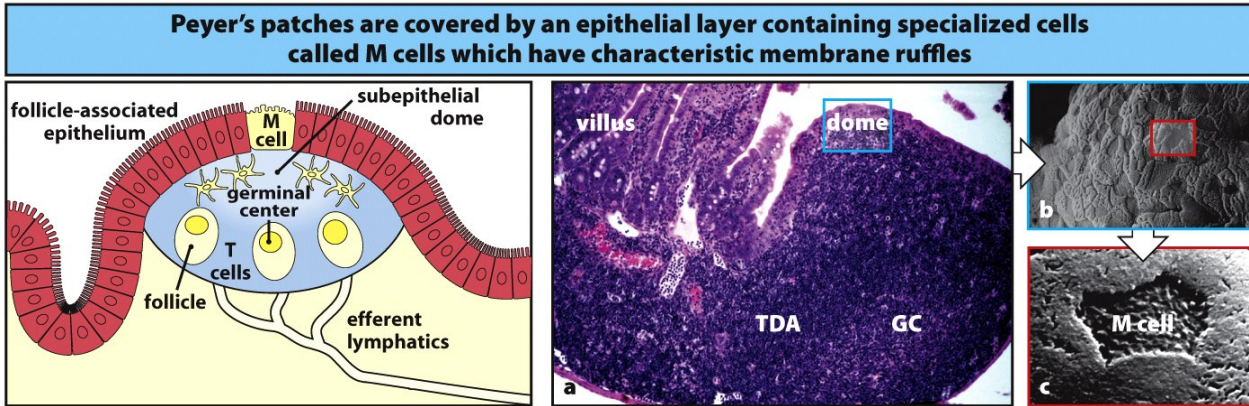
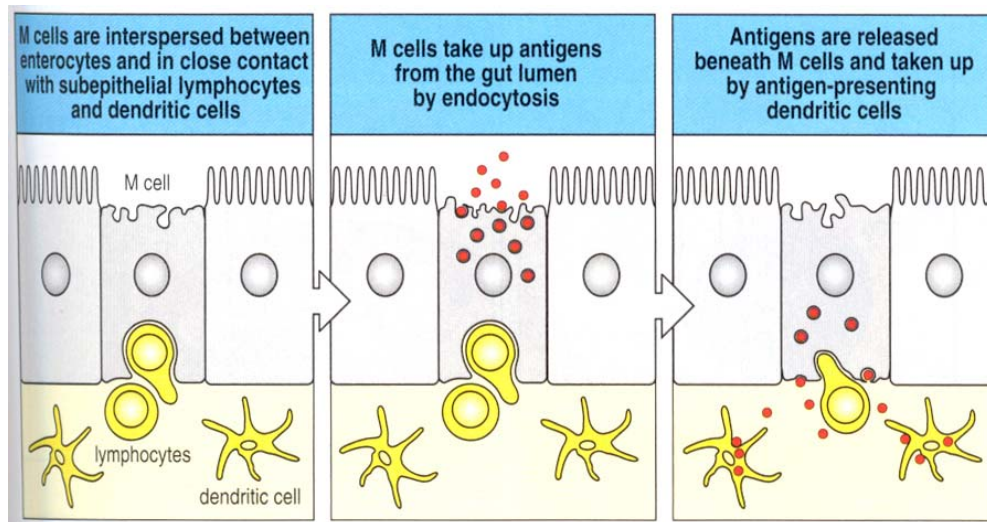


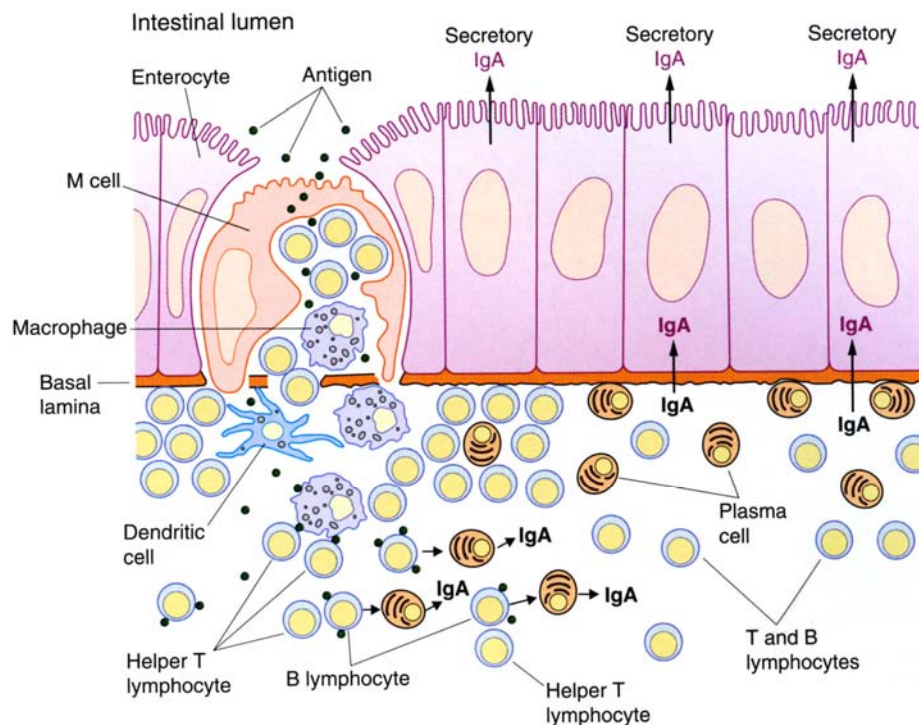
Figure 1-20 Immunobiology, 7ed. (© Garland Science 2008)

**Figure 1.20. A typical region of gut-associated lymphoid tissue.** A schematic diagram (left panel) and a light micrograph (right panel) of a typical region of gut-associated lymphoid tissue. M cells of the gut epithelial wall deliver pathogens from the luminal side of the gut mucosa to the lymphoid tissue within the gut wall. These areas are organized similarly to the lymph node and the white pulp of the spleen, with distinctive B- and T-cell zones, lymphoid follicles, and germinal centers. Photograph courtesy of N. Rooney. Janeway 6<sup>th</sup> Edition



**Fig. 10.19 M cells take up antigens from the lumen of the gut by endocytosis.** The cell membrane at the base of these cells is folded around lymphocytes and dendritic cells within the Peyer's patches. Antigens are transported through M cells by the process of transcytosis and delivered directly to antigen-presenting cells and lymphocytes of the mucosal immune system.

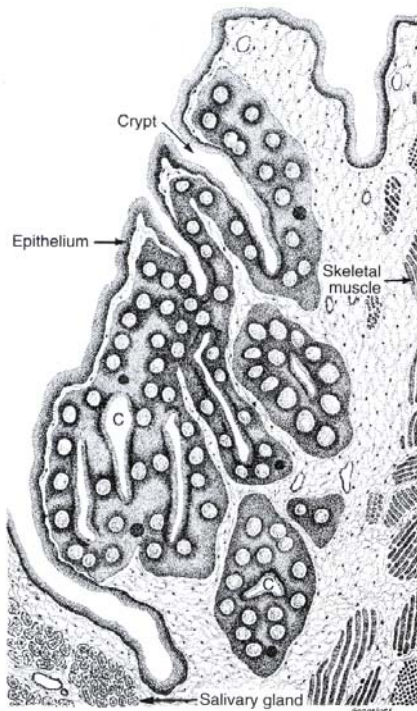
- **Intraepithelial** lymphocytes ( $CD3^+8^+ \alpha\beta$  and  $CD3^+\gamma\delta$ ) found here as well as all along the GI tract.
- Lymphoid nodules ( $1^0$  and  $2^0$ ) with B and T cells as in other lymphoid organs.
- **Internodular** (Interfollicular) tissue contain high endothelial venules and  $1^0$  T cells as in the paracortex of a lymph node and PALS of the spleen. **T** and **B** cells enter the Peyer's Patches here as HEVs found here.



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**Figure 14-11, p. 265** General view of the mucosa immunity in the intestine. Luminal antigens are captured by dome-shaped M cells present in the covering of Peyer's patches and transported to subjacent lymphocytes, macrophages, and dendritic cells. Macrophages and dendritic cells migrate to neighboring lymph nodes, where they stimulate B and T lymphocytes, which then enter the lymphatic circulation and later the blood circulation (lymph flows to the blood). The stimulated lymphocytes home in other tissues, including the mucosa lamina propria, where plasma cells produce considerable amounts of IgA. The lymphoid cells of the lamina propria of intestinal mucosa are a major antibody producer, because of their extension and close contact with antigens introduced into the digestive tract.

- Appendix at the beginning of the large intestine.
  - No villi but lamina propria and submucosal lymphoid tissue.
- Tonsils (Fig. 14-26)
  - Palatine: lined by stratified squamous nonkeratinizing epithelium. Between palatoglossal and palatopharyngeal folds.
    - Many (10-12) deep crypts (Fig. 14-26)
    - 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



Basic Histology 9<sup>th</sup> Edition  
Author: Junqueira, et Al  
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**Figure 14-26.** Palatine tonsil. Numerous lymphoid nodules can be seen near the stratified squamous epithelium of the oropharynx. The light areas in the lymphoid tissue are germinal centers. Note the sections through the epithelial crypt (C).

## VI. LYMPHOCYTE TRAFFIC (Fig. 1.16)

- Lymphocytes circulate from the blood into various tissues and lymphoid organs and back to the blood continuously.  $5 \times 10^{11}$  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.  $0.3 \times 10^{11}$  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.

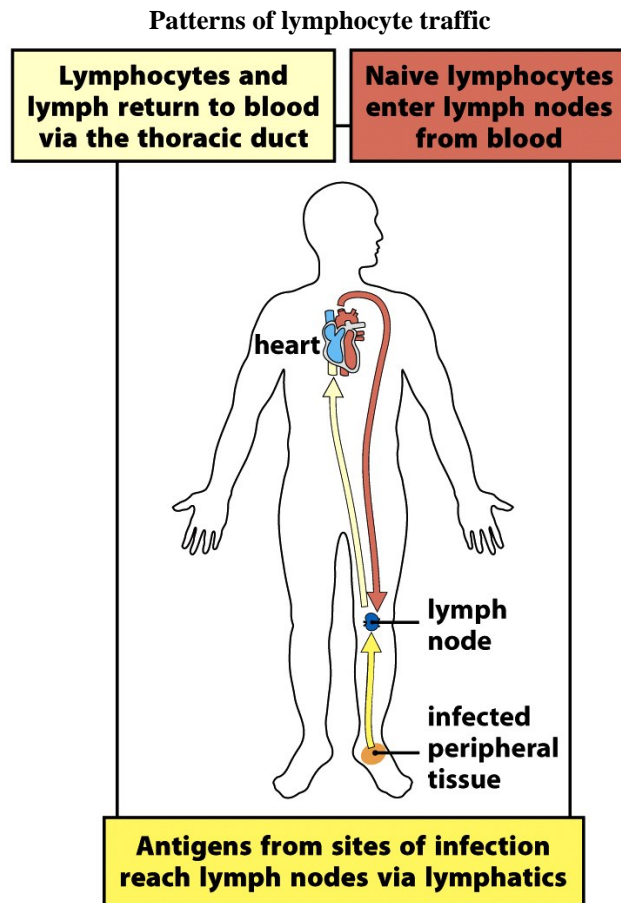


Figure 1-17 Immunobiology, 7ed. (© Garland Science 2008)

### Janeway 7<sup>th</sup> Edition

**Figure 1.17 Circulating lymphocytes meet lymph-borne pathogens in draining lymph nodes.** Lymphocytes leave the blood and enter lymph nodes, where they can be activated by pathogens draining in the afferent lymph from a site of infection. The circulation pertaining to a site of infection in the left foot is shown. When activated by pathogens, lymphocytes stay in the node to divide and differentiate into effector cells. If lymphocytes are not activated, they leave the node in the efferent lymph and are carried by the lymphatics to the thoracic duct, which empties into the blood at the left subclavian vein. Lymphocytes recirculate all the time, irrespective of infection. Every minute  $5 \times 10^6$  lymphocytes leave the blood and enter secondary lymphoid tissues.

## Innate Immunity

**Date:** Wednesday, March 17, 2010

**Reading Assignment:** Janeway 7<sup>th</sup> edition. Pages 1-13; 711-720; 39-40; 46-57.

**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?**

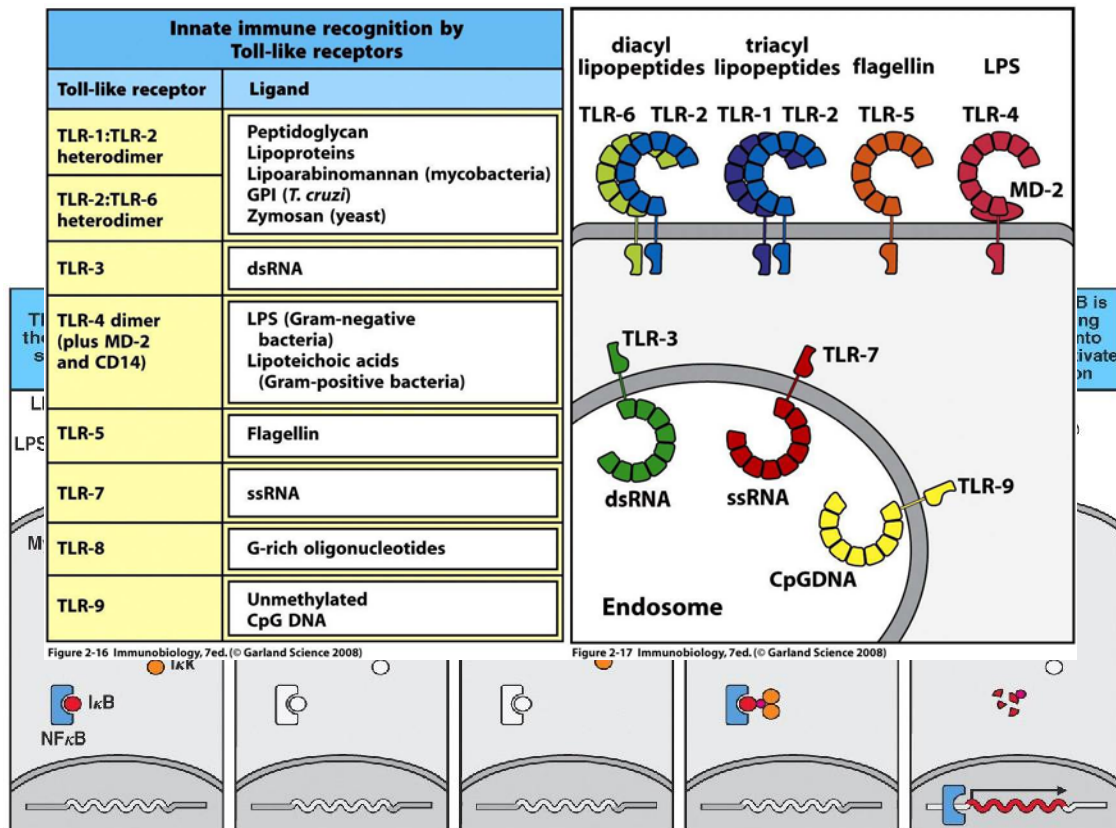
□.a. PRRs are transmembrane (TLRs and CLRs) or soluble intracytoplasmic (NLRs and RLRs) receptors found on many different cell lineages but especially on dendritic cells,

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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**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- $\kappa$ B. Activation of transcription factor NF- $\kappa$ B 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  $\gamma\delta$  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 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 are 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. **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. **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).

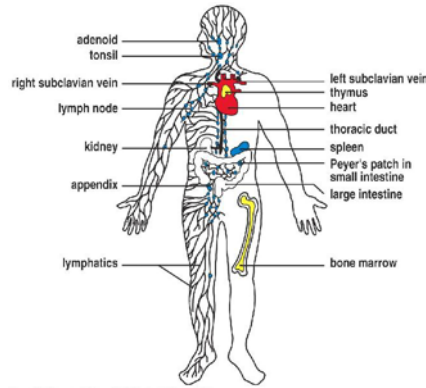


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

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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. 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. 2. Once there, the antigens activate the adaptive system of B and T cells residing in the lymphoid tissue
  3. 3. The adaptive response culminates in activated T cells and antibodies
  4. 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 marshal 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.

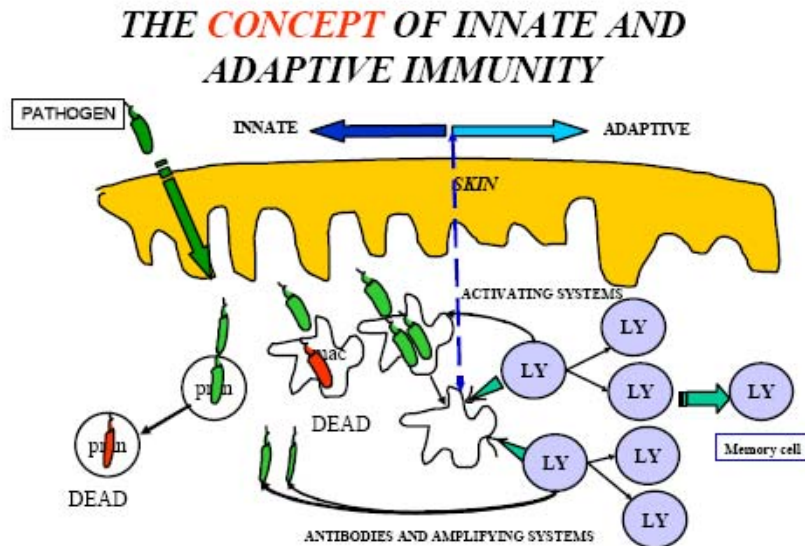


Figure by John A. Robinson, MD

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?