Overview of the Immune System

Physical Barriers: include epithelial, secretions, mucus, urine, proteolytic enzymes, low stomach pH and normal gut flora.

Central Sites	Peripheral Sites

▪ **Primary Lymphoid**
  ▪ Bone Marrow
  ▪ Thymus
▪ **Secondary Lymphoid**
  ▪ Spleen
  ▪ Lymph Nodes
  ▪ Mucosal/cutaneous associated lymphoid tissue
	▪ Skin
	▪ Liver
	▪ Gut
	▪ Heart
	▪ Brain
	▪ CNS
	▪ Muscle
	▪ Lungs

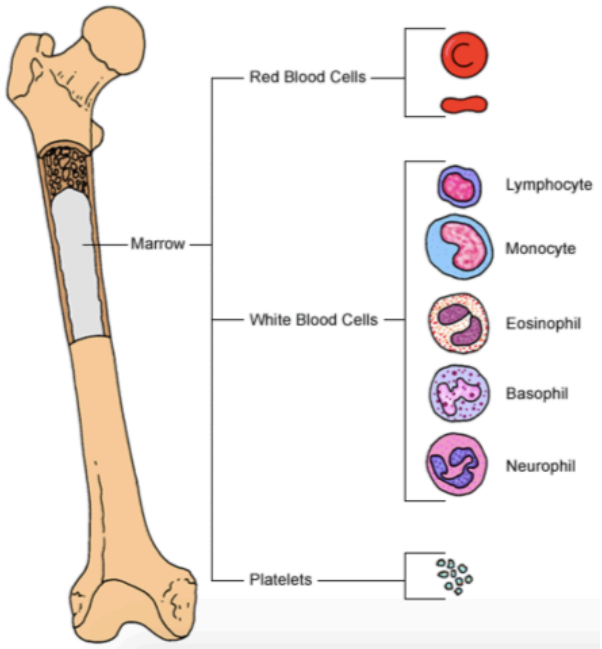
B Lymphocytes	▪ First discovered in the bursar of Fabricius ▪ Main function is to secrete antibodies! ▪ Derived from common lymphoid progenitors in BM ▪ Form part of the humoral response

T Lymphocytes	▪ Mature in the thymus
	▪ **CD4+ Helper T Cells**
	  ○ Surface expression of CD4 molecules
	  ○ Release cytokines or mediates via membrane bound molecules
	▪ **CD8 + Cytotoxic T lymphocytes**
	  ○ Characterized by surface expression of CD8 molecules
	  ○ Kill target cells in a highly specific way
	  ○ Get 'help' from CD4+ T cells
	  ○ Key role in viral infections and anti-tumour immunity

Autocrine: acting on the cell that produced the cytokine
Paracrine: acting on neighboring cells
Endocrine: acting on distant cells, or systemically

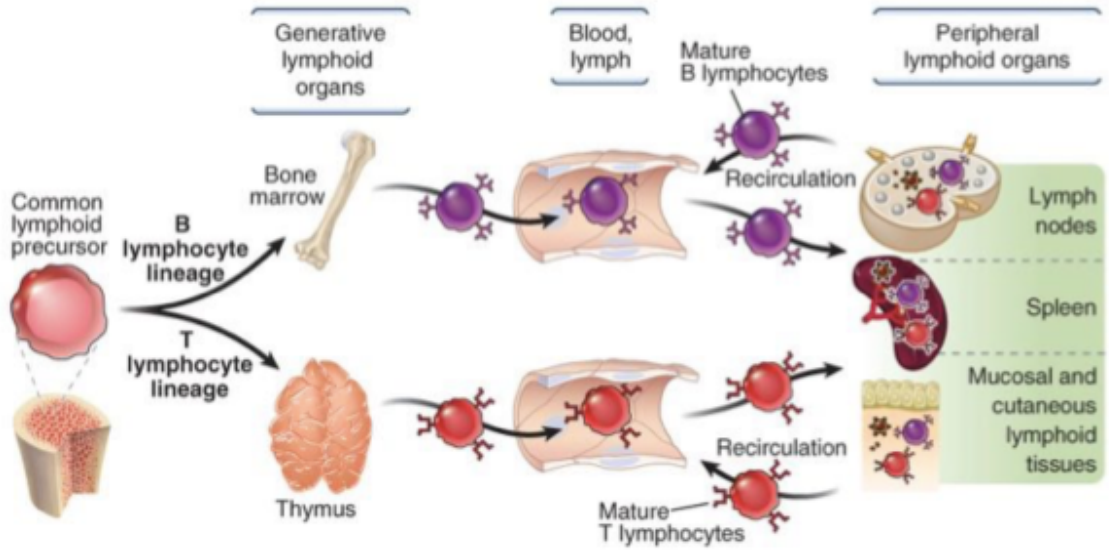
Immunity: defined as resistance to disease (specifically infectious disease)

Disease	Maximum number of cases (year)	Number of cases in 2014	Percent change
Diphtheria	206,939 (1921)	0	–100
Measles	894,134 (1941)	669	–99.93
Mumps	152,209 (1968)	737	–99.51
Pertussis	265,269 (1934)	10,631	–95.99
Polio (paralytic)	21,269 (1952)	0	–100
Rubella	57,686 (1969)	2	–99.99
Tetanus	1560 (1923)	8	–99.48
Hemophilus influenza type B	~20,000 (1984)	34	–99.83
Hepatitis B	26,611 (1985)	1,098	–95.87



Antigens: substances that induce immune response (they are immunogenic)
Epitope: the part of an antigen molecule to which an antibody attaches itself
Cytokines: can modulate inflammatory and immune reactions. Principal communicator!

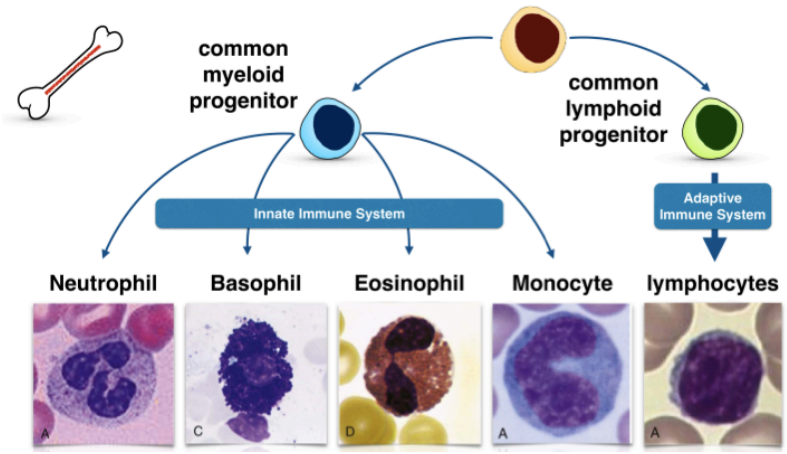
Immature Lymphocytes	Mature Lymphocytes
▪ Do not yet have antigen-specific receptors ▪ Unable to respond to foreign antigens ▪ Found in primary lymphoid tissues	▪ Have functional antigen-specific receptors ▪ Can respond to foreign antigens ▪ Found in secondary lymphoid tissues and in peripheral tissues



Principles of Innate Immunity

Characteristics of the Innate Immune System

- Early and fast
- Short-lived duration
- Repetitive response
- Interactive with cells of both innate and immune systems
- Non-reactive to host



Components of Innate Immunity

1. Epithelial barriers
2. Cells in circulation and tissues
    a. Phagocytes (neutrophils and macrophages)
    b. Exocytes (eosinophils, mast cells, basophils)
3. Molecules
    a. Cytokines (TNF, IL-1)
    b. Plasma proteins (complement, C-reactive protein, mannose binding lectin)

Phagocytes: scavengers that ingest microbes
Exocytes: release active mediates from granules

Pattern Recognition Receptors

- Expressed by epithelial, endothelial cell and Reside Immune Cells
- Recognise **PAMPs** (pathogen-associated molecular patterns) and **DAMPs** (damage-associated molecular patterns)
- Binding of PAMPs and DAMPs to PRRs triggers a cascade of events
  - Release of soluable mediators (e.g. cytokines)
  - Recruitment of innate immune cells (neutrophils, monocytes)

Toll-like Receptors

- Different TLRs are specific for different components of microbes
- Some TLRs are present on the cell surface (where they recognise products of extracellular microbes)
- Some TLRS present in endosomes (where they recognise ingested/phagocytosed microbes)
- **Result:** activation of transcription factors that stimulate expression of genes encoding cytokines, enzymes etc

PRR / PAMPs Binding – The Cascade of Events:

1. Release of histamine and inflammatory cytokines (**TNF, IL-1**)
2. Vasodilation (redness and swelling)
3. Expression of adhesion molecules (to attract neutrophils and monocytes - phagocytosis!)
4. Attracted cells adhere to endothelial cells *only at sites of inflammation*

Mast Cells

- Suggested that mast cells may regulate or suppress immune response
- **Function**: Important antibacterial functions. Kills bacteria by entrapping them in extracellular structures called 'traps'
- Important in the recruitment of inflammatory cells to sites of infection of danger (cytokines, TNF, histamine)
- **Location:** alongside blood vessels. Probe the lumen of blood vessels picking up antibodies (mainly IgE)

Neutrophils:

- Also called *polymorphonuclear leukocytes*
- Short lived!
- **Derivative**: common myeloid progenitors in bone marrow
- **Functions:**
  - Infiltrate inflamed peripheral sites
  - Potent antibacterial functions
  - Perform phagocytosis
  - Secrete cytokines (to promote further inflammation and recruitment)

CHEMOKINES

- Make migration possible!
- Different cells express different chemokine receptors (allows cell to response to different chemokines)

INTEGRIN

- On leukocyte surface. When activated, bind to ICAMs

SELECTIN

- Cell surface lectin that mediate the adhesion of leukocytes to endothelial cells

THE PROCESS OF CELL MIGRATION!

1. Tissue resident cells promote inflammation
2. TNF and IL-1 stimulate endothelial cells to rapidly express two adhesion molecules
   - **E-selection and P-selectin**
3. Circulating phagocytes express surface carbohydrates that bind *weakly* to the E-selectin and P-selectin
4. Cells spread out on endothelial surface of blood vessels
5. Firm adhesion is quickly followed by extravasation into the inflame tissue
6. Cells migration through endothelium
7. Once engulfed, the cell is activated