GRANULOCYTES, polymorphonuclear leucocytes

- Characterized by GRANULES in their cytoplasm, as well as by their multilobular amorphous nuclei (hence polymorhonuclear)
- They typical granulocytes are
  - NEUTROPHILS
    - by far the most numerous
    - a neutrophil has a plasma half-life of only 6 hours
    - you produce about 100 billion every day
  - EOSINOPHILS
    - Very similar to neutrophils, in terms of short half-life and in the way they respond to insult, by migrating to the tissues via diapedesis
    - However, they are more selective for what they attack
    - IL-3, IL-5 and GM-CSF stimulate them the most
    - Most of them hang out in the intestinal tract and in the mucosa of the respiratory and genitourinary tracts
    - Their job is to destroy multicellular parasites
  - BASOPHILS
    - These also migrate into tissues, but they resemble mast cells more than neutrophils
    - Like mast cells they contain histamine in their granules
    - Activation of basophils requires IgE bound to antigen
    - Basophils and mast cells form the basis of type 1 hypersensitivity reactions

Neutrophil attack mechanisms
- inflammatory response triggered by the bacteria produces an inflammatory response
- the inflammatory response mediators stimulate the bone marrow to produce and release large numbers of neutrophils
- the neutrophils are attracted to the site of bacterial invasion by CHEMOTAXIS
- upon arriving to the area, local factors induce them to soften and ROLL along the endothelial lining of the inflamed capillaries before undergoing DIAPEDESIS
- Once at the site of injury, neutrophils phagocytose the offending bacteria; for this to take place, the bacteria must be opsonized (preferably by IgG but maybe also by complement components)
- The neutrophils also DEGRANULATE – both into the phagolysosomes, and into the interstitial fluid surrounding the neutrophil.
- The granules contain PROTEASES and antibacterial proteins called DEFENSINS

THE RESPIRATORY BURST
- When a neutrophil is activated, the cell membrane enzyme NADPH OXIDASE is activated
- This enzyme consumes a large amount of oxygen to produce O₂⁻
- O₂⁻ is a horribly toxic antibacterial agent

Contents of neutrophil granules
- MYELOPEROXIDASE: catalysis the conversion of Cl⁻, Br⁻ I⁻ and SCN⁻ to the corresponding acids
- DEFENSINS as mentioned before
- ELASTASE which degrades elastin
- METALLOPROTEINASES x 2 – dissolve collagen

MAST CELLS
- These live in the connective tissues which are most exposed to the outside environment; they are also full of histamine granules, much like basophils; and they are also triggered by the IgE-antigen complexes (in fact they are coated in the immunoglobulin E
- They defend against parasites, and release TNF-alpha to contribute to the non-specific immune response
MONOCYTES
- relatively long lived, circulate for about 72 hrs
- after they finish circulating they enter the peripheral tissues and become tissue macrophages
- the tissue macrophages may persist for up to 3 months, and do not reenter the circulation
- the monocyte lineage also contains Kupffer cells, alveolar macrophages and microglial cells
- when they attack bacteria, they do so in a manner similar to the neutrophils, but they release a larger range of substances, including more chemotactic factors, and prothrombotic factors

LYMPHOCYTES
- Formed in the bone marrow, mature in the thymus
- At a given time, only 2% of the lymphocytes are in the peripheral blood
- The rest are in lymphoid organs

CYTOKINES
- **IL-1**: Produced by macrophages; activates T-cells and macrophages, produces fever and septic shock
- **IL-2**: Produced by TH1 cells: Activates all lymphocytes, natural killer cells and macrophages;
- **IL-4**: produced by TH2 cells: stimulates IgE production, eg. in atopy
- **IL-5**: produced by TH2 cells; produces differentiation of eosinophils
- **IL-6**: produced by TH2 cells: stimulates the differentiation of B-cells, stimulates production of acute-phase proteins
- **IL-8**: produced by T-cells and macrophages: stimulates chemotaxis of neutrophils basophils and T-cells
- **IL-10**: produced by bone marrow stromal cells, stimulates production of acute-phase proteins
- **IL-12**: produced by macrophages and B-cells, stimulates TH1 cells and the production of interferon-gamma
- **TNF-alpha**: produced by just about all the cells, but mainly by the macrophages; it promotes inflammation in all its forms, is responsible for the systemic effects of septic shock, and is generally an unpleasant molecule
- **TNF-beta**: produced by TH1 cells and B-cells; also a nonspecific promoter of inflammation
- **GM-CSF**: produced by any non-PMNL inflammatory cells, and it stimulates the growth of granulocytes and monocytes in the bone marrow
- **Interferon-Alpha and Interferon-Beta**: produced by virus-infected cells, induces neighbouring cells to become resistant to the virus by a combination of effects, among which is a shutdown of protein synthesis
- **Interferon-Gamma**: produced by natural killer cells and TH1 cells – activates macrophages and TH2 cells; induces them to kill off phagocytosed bacteria in chronic granulomatous disease
- Cytokine receptors have no intracellular tyroine kinase activity, but they instead activate a free form of cytoplasmic tyrosine kinase.

COMPLEMENT
- 3 pathways:
  - CLASSIC PATHWAY: triggered by immune complexes
  - ALTERNATIVE PATHWAY triggered by contact with bacteria and fungi
  - LECTIN PATHWAY triggered when lectin binds the mannose groups on bacteria
- A series of 30 plasma proteins become activated in this way, causing a cascade of events which produces
  - Chemotaxis
  - Opsonization
  - Production of the Membrane Attack Complex (MAC) which perforates the bacterial cell and hereby causes its lysis
Innate immunity
- Neutrophils
- Macrophages
- Natural killer cells
- The key feature is that the response is not specific to antigens, and is the same for any sort of antigen be it fungus, bacteria or whatever

Acquired immunity
- Two components, HUMORAL and CELLULAR
  - HUMORAL immunity is a swarm of floating antibodies, specific to an antigen, produced by B-cells
  - CELLULAR immunity is a swarm of cytotoxic CD8 T-lymphocytes which recognize the antigen and destroy whatever is expressing it.
- The characteristic of this response is a sequence of initial exposure to a antigen, followed by clonal proliferation of the cells targeting that antigen, and a second exposure to that antigen which then triggers a massive immune response which is specific to it.

Development of the immune system
- T-lymphocytes mature in the thymus
- B-lymphocytes mature in the bone marrow

Antigen presentation and specific immune system activation
- All nucleated cells have MHC class 1 proteins
- Immune cells especially antigen-presenting cells, T-lymphocytes and B-cells have MHC class 2 proteins
- MHC class 1 molecules tend to present protein fragments from proteins synthesized by the cell itself
- MHC class 2 proteins present protein fragments from endocytosed and digested stuff
- The MHC-peptide complexes bind to receptors on T-cells;
- CD8 cytotoxic T-cells bind MHC class 1 proteins
- CD4 T-helper cells bind MHC class 2 proteins
- TH2 cells proliferate in response to IL-4, and TH1 cells proliferate in response to IL-12
- The cytokines produced by TH cells activate B cells, which undergo clonal proliferation and differentiate into MEMORY B-CELLS and PLASMA CELLS
- PLASMA CELLS then produce tons and tons of antigen-specific immunoglobulins

References: Ganong’s Review of Medical Physiology, Chapter 3