Overview White Blood Cells

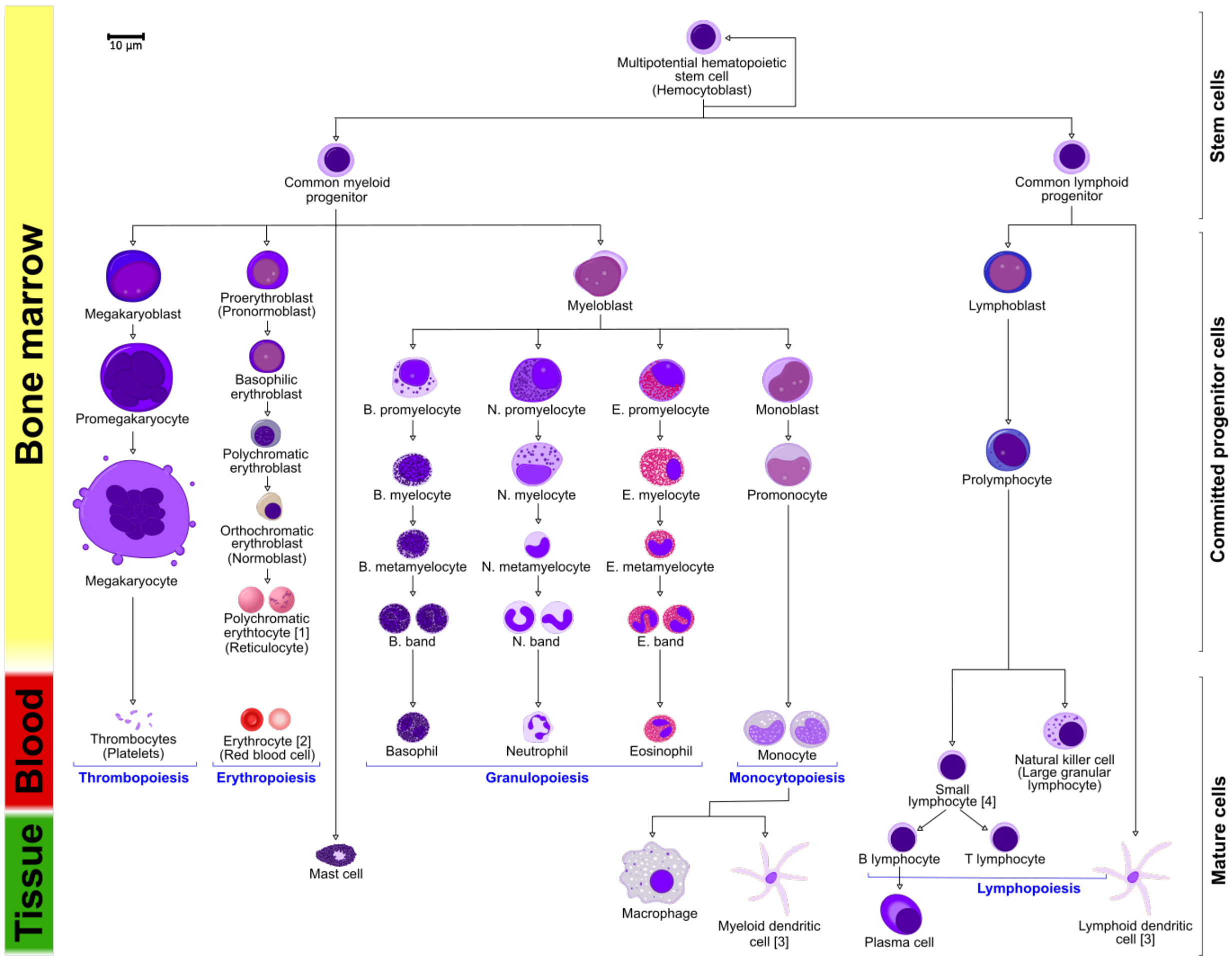

Figure 1 Hematopoiesis (human) diagram A. Rad, Rexx S, Mikael Häggström and birdy and Mikael Häggström, M.D.

Leukocytes/White Blood Cells

The primary purpose of white blood cells is to defend us against harmful cells that invade our body.

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There are three basic types of blood cells:

- The red blood cells (erythrocytes) carry oxygen from the lungs to all the tissues of the body.
- The platelets (thrombocytes) are essential for the clotting of the blood.
- The white blood cells (leukocytes) are in charge of the body's defense against infections. There are three main types of white blood cells: granulocytes, monocytes, and lymphocytes.

NEUTROPHILS

Neutrophils are the most abundant of all granulocytes accounting for about 50% - 60% of the total white blood cells in our blood. The neutrophils are the first to respond to harmful bacteria and fungi that invade our body. The neutrophil is so named because unlike other granulocytes the granules contained within the neutrophil do not stain when dye is applied.

Figure 2 Mature Neutrophil

Mature neutrophils have a very large nucleus with several segmented lobes. These mature cells are called "segs". Neutrophils not fully developed are called "bands" due to the elongated appearance of the nucleus within these cells but the bands are fully functional Neutrophils with more than five lobes are called hypersegmented neutrophils.

Presence of many bands within our blood usually indicates the presence of a major bacterial or fungal infection somewhere in our body. The presence of many hypersegmented neutrophils is most commonly related to someone having a folate or B12 deficiency. Reduced numbers of mature neutrophils within our blood is indicative of neutropenia. Manual differential studies may sometimes be ordered if the level of neutrophils is moderately to severely low. The manual differential count is done by a technician who first creates a blood slide and then counts the number of white blood cells seen on the slide. Lab reports may also include the morphology of the blood cells, this refers to the appearance of the cells (size, shape, structure, color). These studies would reveal premature release of immature cells into the blood stream from the bone marrow.

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Neutrophil Life Cycle

Less than half of the mature neutrophils may enter the blood stream. Most are engulfed while still in the bone marrow. When harmful bacteria and fungi are present in our body more neutrophils are released from the bone marrow into the blood stream to protect us from infection.

Once released, the neutrophil only circulates in the blood stream for a few short hours. The marrow releases premature and mature neutrophils into the blood stream. Only mature cells travel into our tissue. These mature neutrophils loosely adhere to the endothelium (blood vessel walls) through a process called rolling. Through this rolling process the neutrophil is pushed along the blood vessel wall by the blood, ready at any time to respond to infection within our body tissues.

The neutrophil only fights infection within our body tissues. It does not fight harmful bacterial and fungal infections while in the blood stream. When in the tissue, the neutrophil may live one to two days. When fighting infection its lifespan is quite brief.

Neutrophils may also be called polys, segs, segmented neutrophils, or granulocytes. Bands may be called Stabs, seg bands, or segmented bands. The absolute neutrophil count (ANC) is the total of neutrophils and bands added together.

The Call to Fight

Not all bacteria and fungi are harmful to our body. In fact, our body needs good bacteria and fungi to stay healthy. However some are very harmful. Fortunately, these harmful bacteria and fungi carry markers on the cell surface to differentiate friend from foe. A chemical signal alerts the neutrophil to the presence of a harmful invader in our body. The neutrophil has a surface receptor that allows it to recognize markers that are common to invading bacteria and fungi as well as distress signals sent by phagocytes (monocytes and macrophages, cells that engulf and cleans up dead or harmful cells). Through this process the neutrophil is activated into attack mode.

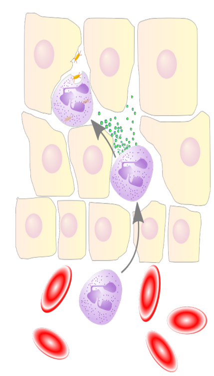

Figure 3 Nuetrophil extravasation, Dr. Mario Schubert, Heidelberg, Germany

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Moving to the Site of Infection

The process that creates the chemical signals leaves a trail throughout our body leading the neutrophil to the site of infection. The chemicals released by macrophages engaged in fighting an invader make our blood vessels swell and become leaky. This is known as inflammation and causes us to experience discomfort and pain. A substance called selectin sticks out from the pores within our swollen blood vessels. The activated neutrophil flowing in the blood stream grabs hold of the selectin and begins rolling along the vessel wall. Gaps are formed from the leaky pores in our blood vessels. These gaps allow the neutrophil enough space to squeeze through the vessel wall. The neutrophil then enters the tissue that is under attack from the harmful invader.

Killing the Invader

The neutrophil fights infection by secreting molecules that are toxic to invading pathogens. The neutrophil engulfs (eats) invader cells. The engulfed harmful invaders enter a chamber within the neutrophil. This chamber fills with a substance that dissolves the harmful pathogen. This heroic little cell becomes exhausted after a few kills. Then too, the neutrophil must die.

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Programmed Cell Death/Apoptosis

A good and necessary process

Programmed cell death is called apoptosis. Ironically the neutrophil, intended to protect us from harm can also cause us harm. The neutrophil doesn't sleep. Relentlessly the neutrophil scurries around the good cells in a hide and seek pursuit of the predator intended to do us harm. In the apoptotic phase, the neutrophil membrane undergoes changes to alert macrophage cells to ingest neutrophils.

A dying cell undergoes changes in its form. Just as the neutrophil changes its form from a band" into its mature segmented form in early development it also changes form in its death. Distinct morphological characteristics of cell death are detected when observed under a microscope.

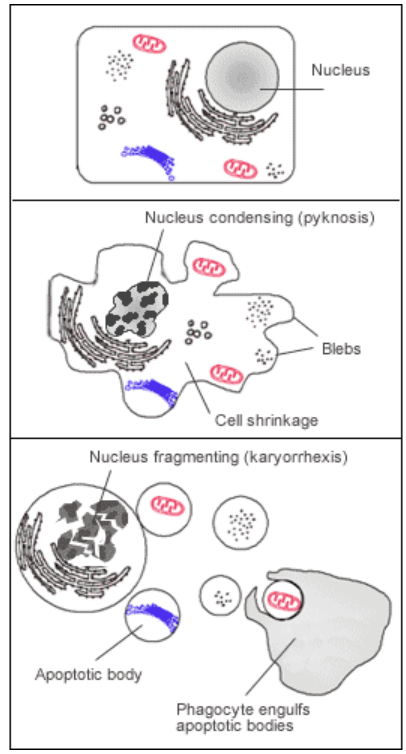

Figure 4 Apoptosis diagram by Emma Farmer

1. The cell shrinks
2. Organelles within the cell such as the mitochondria condense and cluster together
3. The nuclear envelope breaks into fragments
4. The cell membrane forms irregular buds or blebs
5. The cell breaks apart into smaller vesicle bodies known as apoptotic bodies
6. Apoptotic bodies are engulfed by macrophage cells

Upon its death the neutrophil releases its toxic cellular contents as the blebs break off into smaller fragments. This orderly cycle of cell death is called apoptosis. Clearing of the cell is called uptake. These events of cell death and cell clearance occur in our body every second of our life without notice. This process maintains homeostasis (balanced state of health) within our body. In times of good health cell death and uptake occurs without causing inflammation.

Improperly cleared, toxic contents within the cell are released within our body tissue. Even the neutrophil, a cell intended to protect us, can do us harm when its toxic

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contents are released into the body tissue. Damage of the tissue without response soon results in death (necrosis) of the tissue. So too, can necrosis arise when tissue is exposed to prolonged infection. Therefore, the signal sent to alert macrophages of the neutrophils death is as important in protecting our body as the signal the neutrophil receives when called to fight infection. In short, under normal conditions the macrophage receives the signal from the dying cell. As the neutrophil begins to break apart the macrophage is on the spot to clear its contents before the released toxins cause amage to our tissue.

Neutropenia

Neutropenia: An abnormally low number of neutrophils in the circulating bloodstream. When someone is neutropenic they are at greater risk to develop bacterial or fungal infections. There are three primary forms of neutropenia.

1. **Acute**: Sudden onset of neutropenia that may last for a period of hours or days
2. **Congenital**: The individual is born with a disease that causes neutropenia. This would be the case of those who have Barth syndrome.
3. **Acquired**: The individual acquires this symptom for a variety of reasons later in life.

Neutropenia is among one of the more difficult symptoms to detect in those who have Barth syndrome. Perhaps the reason may be attributed to affected males having an unpredictable pattern of neutropenia. In addition, many medications are known to contribute to neutropenia. In some cases neutropenia did not present until long after the initial symptom manifested among those diagnosed with BTHS. In some cases those diagnosed with BTHS have never been neutropenic. This symptom may occur in any of the following ways.

1. **Chronic**: Occurs for a greater period than three months
2. **Cyclic**: Occurs in a predictable timeframe
3. **Intermittent**: Occurs in no predictable timeframe

A reduced absolute neutrophil count (ANC) is revealed from a complete blood count (CBC) or a full blood count (FBC). The clinician may repeat the CBC to confirm neutropenia. The clinician may refer the patient to a hematologist for a more

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comprehensive evaluation to determine the cause and severity of neutropenia. A common evaluation will include CBCs three times a week for several weeks (four to six weeks is common). This information will determine if the ANC has a cyclic or variable pattern. The hematologist may suggest additional testing to rule out other potential risks in those who have been diagnosed with BTHS or to confirm a diagnosis of BTHS with neutropenia. Potential causes of neutropenia are as follows:

1. **Decreased Production of Neutrophils/Bone Marrow Failure**: The bone marrow fails to produce an adequate number or ratio of mature/immature neutrophils while in the bone marrow. Subsequently this reduces the number of cells in the blood stream available to respond to infection. This can be attributed to:
    a. Hereditary or genetic inheritance: Overall failure to make adequate numbers of cells caused by a defective gene resulting in neutropenia.
    b. Environmental exposure: This can be caused by agents such as radiation or other agents that are toxic to our body
    c. Nutritional deficiencies: Some of the more common nutritional factors that contribute to neutropenia are B_{12} or folate deficiencies
    d. Medications: Some medications, such as captopril and many others are known to contribute to neutropenia
    e. Infections: Some viruses are known to cause neutropenia

2. **Increased Destruction**: The neutrophil is killed too early
    a. Autoimmune: The neutrophil is mistaken as a harmful cell or a dying cells and subsequently it is killed too soon
    b. Early Clearance: The neutrophil sends a signal that it is ready to die before it should
    c. Neutrophil Injury: The neutrophil is damaged in some way by a substance such as chemotherapy or other factors that kills the cell

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A very low ANC imposes great risk to your health should you develop a bacterial or fungal infection. The lower the ANC the higher the risk of infection.

1. **Normal** level is when neutrophils fall between 1500 – 7000 per mm3 of blood
2. **Mild neutropenia** is when the neutrophil ANC is 1000 – 1500 per mm3 of blood.
3. **Moderate neutropenia** is when the neutrophil ANC is 500 – 1000 ANC per mm3 of blood.
4. **Severe neutropenia** is when the ANC falls below 500 per mm3

Depending upon the severity of neutropenia, frequency and clinical status of the patient a clinician may prescribe Granulocyte Colony-Stimulating Factor (G-CSF). This drug stimulates the bone marrow to increase production of neutrophils and prolongs the life of the cell.

When G-CSF is prescribed it is necessary for the patient to be carefully monitored. The clinician will monitor the patient through follow-up blood draws and possibly a bone marrow aspiration. Blood studies are necessary for the physician to titrate the G-CSF to determine the proper dosage and to monitor drug related risks that may arise. There is no "one size fits all" dose for G-CSF in patients who have BTHS. In fact, many patients have been reported to achieve a favorable response even when receiving a minor dose of G-CSF.

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RESOURCES

The Severe Chronic Neutropenia International Registry (SCNIR)
North Amercia Office
https://www.scnir-neutropenia.uw.edu/
European Office
Severe Chronic Neutropenia International Registry
https://severe-chronic-neutropenia.org/en
National Neutropenia Network
https://neutropenianet.org/
Neutropenia in Barth syndrome: characteristics, risks, and management
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6392059/
Barth Syndrome GCSF Dosing Guidelines SCNIR
https://cpb-us-e1.wpmucdn.com/sites.uw.edu/dist/6/5500/files/2020/02/Barth.Dosing.Flow_.Sheet_.pdf

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