Blood Biochemistry
BCH 577

By

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Part II

- **Physiological Roles of Leukocyte Cells**

Cells in a normal peripheral blood smear and their physiological roles

Cell type	Function	Count (% of leuko-cytes)
Neutrophilic band granulocytes (band neutrophil)	Precursors of segmented cells that provide antibacterial immune response	0–4%
Neutrophilic segmented granulocyte (segmented neutrophil)	Phagocytosis of bacteria; migrate into tissue for this pur-pose	50–70%
Lymphocytes (B- and T-lymphocytes, morphologically indistin-guishable)	B-lymphocytes (20% of lymphocytes) mature and form plasma cells → antibody production. T-lymphocytes (70%): cyto-toxic defense against viruses, foreign antigens, and tumors.	20–50%
Monocytes	Phagocytosis of bacteria, pro-tozoa, fungi, foreign bodies. Transformation in target tissue	2–8%
Eosinophilic granulocytes	Immune defense against para-sites, immune regulation	1–4%
Basophilic granulocytes	Regulation of the response to local inflammatory processes	0–1%

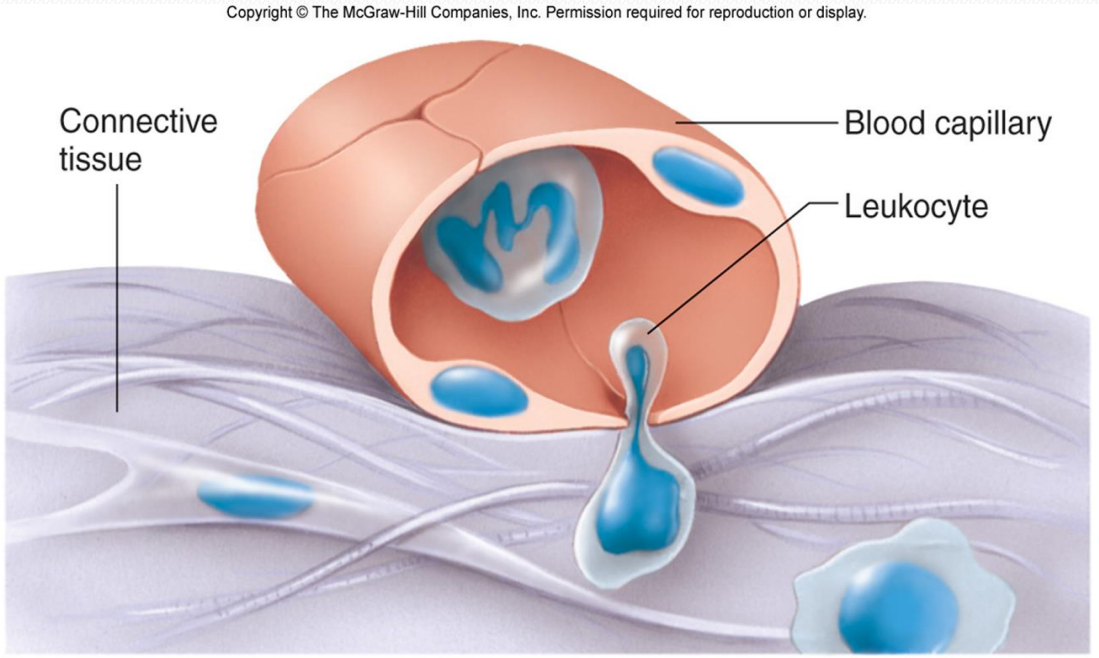
Neutrophils and Macrophages Defend Against Infections

- **The neutrophils and blood monocytes (tissue macrophages) attack and destroy bacteria, viruses, and other injurious agents.**
- **The mature neutrophils attack and destroy bacteria also in the circulating blood.**
- **The blood monocytes, (immature macrophage cells) have little ability to fight infectious agents in blood.**

- **However, once monocyte enter the tissues, they begin to swell (increasing their diameters as much as five fold to as great as 60 to 80 micrometers). These cells are now called macrophages, and they are extremely capable of fighting intratissue disease agents.**

White Blood Cells Enter the Tissue Spaces by Diapedesis:

Neutrophils and monocytes can squeeze through the pores of the blood capillaries by diapedesis.



White Blood Cells Move Through Tissue Spaces by Ameboid Motion:

Both neutrophils and macrophages can move through the tissues by ameboid motion. Some cells move at velocities as great as 40 mm/min, a distance as great as their own length each minute.

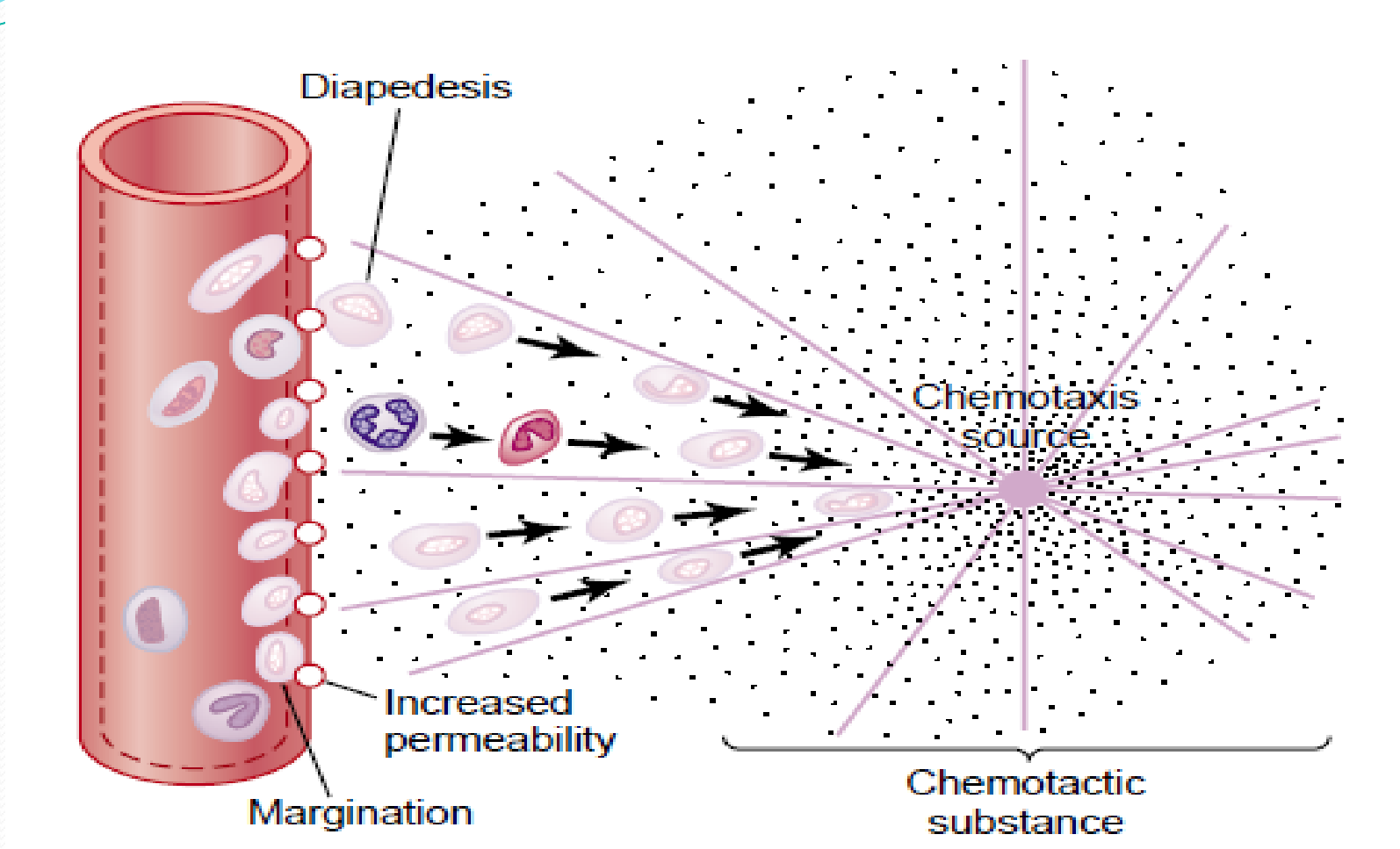
White Blood Cells Are Attracted to Inflamed Tissue Areas by Chemotaxis.

- **Many different chemical substances in the tissues cause both neutrophils and macrophages to move toward the source of the chemical (chemotaxis).**
- **When a tissue becomes inflamed, different products are formed that can cause chemotaxis toward the inflamed area. They include (1) some of the bacterial or viral toxins, (2) degenerative products of the inflamed tissues themselves,**

(3) several reaction products of the "complement complex" activated in inflamed tissues, and (4) several reaction products caused by plasma clotting in the inflamed area, as well as other substances.

- **chemotaxis depends on the concentration gradient of the chemotactic substance. The concentration is greatest near the source.**

- **Chemotaxis is effective up to 100 micrometers away from an inflamed tissue. Therefore, because almost no tissue area is more than 50 micrometers away from a capillary, the chemotactic signal can easily move groups of white cells from the capillaries into the inflamed area.**



Movement of neutrophils by diapedesis through capillary pores and by chemotaxis toward an area of tissue damage.

Phagocytosis:

- **The most important function of the neutrophils and macrophages is phagocytosis, which means cellular breakdown of the offending agent.**
- **Phagocytosis will occur depends especially on three selective procedures.**

First, most natural structures in the tissues have smooth surfaces, which resist phagocytosis. But if the surface is rough, the likelihood of phagocytosis is increased.

Second, most natural substances of the body have protective protein coats that repel the phagocytes. Conversely, most dead tissues and foreign particles have no protective coats, which makes them subject to phagocytosis.

Third, the immune system of the body develops antibodies against infectious agents such as bacteria.

The antibodies then adhere to the bacterial membranes and thereby make the bacteria especially susceptible to phagocytosis. To do this, the antibody molecule also combines with the C3 product of the complement cascade, which is an additional part of the immune system. The C3 molecules, in turn, attach to receptors on the phagocyte membrane, thus initiating phagocytosis. This selection and phagocytosis process is called opsonization.

Phagocytosis by Neutrophils.

- **The neutrophils entering the tissues are already mature cells that can immediately begin phagocytosis.**
- **The neutrophil first attaches itself to the particle and then projects pseudopodia in all directions around the particle.**
- **The pseudopodia meet one another on the opposite side and fuse. This creates an enclosed chamber that contains the phagocytized particle.**

- **Then the chamber invaginates to the inside of the cytoplasmic cavity and breaks away from the outer cell membrane to form a free-floating phagocytic vesicle (also called a phagosome) inside the cytoplasm.**
- **A single neutrophil can usually phagocytize 3 to 20 bacteria before the neutrophil itself becomes inactivated and dies.**

Phagocytosis by Macrophages.

- **Macrophages are the end stage product of monocytes that enter the tissues from the blood. When activated by the immune system they are much more powerful phagocytes than neutrophils, often capable of phagocytizing as many as 100 bacteria. They also have the ability to engulf much larger particles (malarial parasites)**
- **Neutrophils are not capable of phagocytizing particles much larger than bacteria.**

Once a foreign particle has been phagocytized, lysosomes and other cytoplasmic granules in the neutrophil or macrophage immediately come in contact with the phagocytic vesicle, and their membranes fuse, thereby dumping many digestive enzymes and bactericidal agents into the vesicle. Thus, the phagocytic vesicle now becomes a digestive vesicle, and digestion of the phagocytized particle begins immediately. Both neutrophils and macrophages contain an abundance of lysosomes filled with proteolytic enzymes especially geared for digesting bacteria and other foreign protein matter.

- **The lysosomes of macrophages (but not of neutrophils) also contain large amounts of lipases, which digest the thick lipid membranes possessed by some bacteria such as the tuberculosis bacillus.**
- **In addition to the digestion of ingested bacteria in phagosomes, neutrophils and macrophages contain bactericidal agents that kill most bacteria even when the lysosomal enzymes fail to digest them. This is especially important, because some bacteria have protective coats or other factors that prevent their destruction by digestive enzymes**

Inflammation: Role of Neutrophils and Macrophages

Inflammation

- **When tissue injury occurs, by bacteria, trauma, chemicals, heat, or any other factors, multiple substances are released by the injured tissues and cause secondary changes in the surrounding uninjured tissues. This entire tissue changes is called inflammation.**
- **Inflammation is characterized by:**

(1) vasodilation of the local blood vessels, with consequent excess local blood flow.

(2) increased permeability of the capillaries, allowing outflow of large quantities of fluid into the interstitial spaces.

(3) often clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries.

(4) migration of large numbers of granulocytes and monocytes into the tissue.

(5) swelling of the tissue cells.

Some of the many tissue products that cause these reactions are histamine, bradykinin, serotonin and prostaglandins.

“Walling-Off” Effect of Inflammation.

One of the first results of inflammation is to “wall off ” the area of injury from the remaining tissues. The tissue spaces and the lymphatics in the inflamed area are blocked by fibrinogen clots so that after a while, fluid barely flows through the spaces. This walling-off process delays the spread of bacteria or toxic products. The intensity of the inflammatory process is usually proportional to the degree of tissue injury.

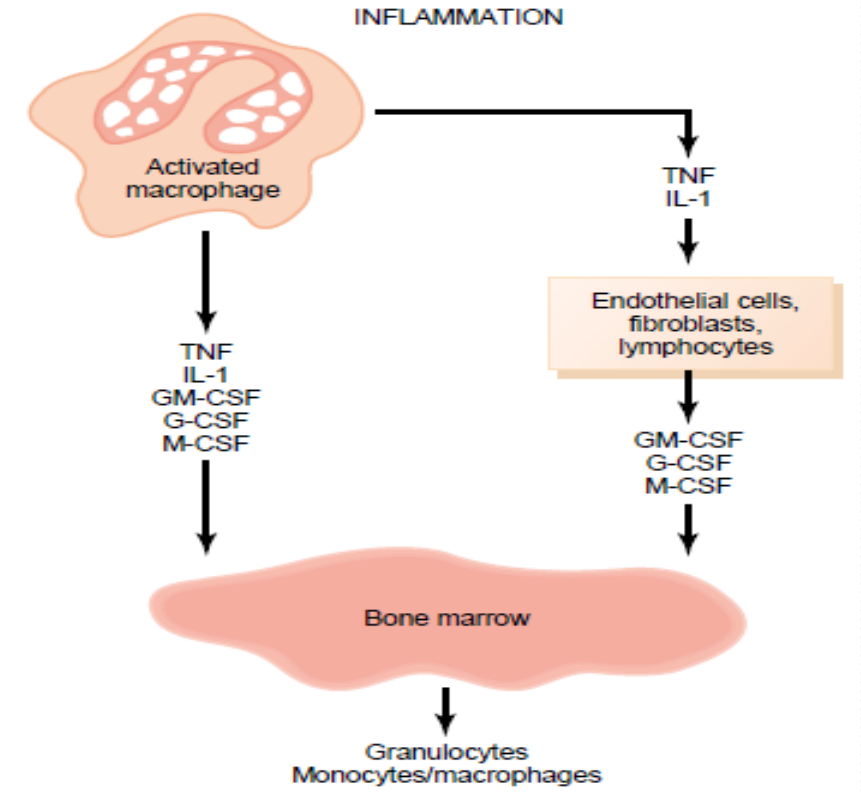
Macrophage and Neutrophil Responses During Inflammation

- **Within minutes after inflammation begins, the macrophages already present in the tissues, immediately begin their phagocytic actions.**
- **Next, many of the previously immobile macrophages break loose from their attachments and become mobile, forming the first line of defense against infection during the first hour.**
- **large numbers of neutrophils begin to invade the inflamed area from the blood.**

- **within a few hours after the onset of acute, severe inflammation, the number of neutrophils in the blood sometimes increases four fold to five fold (neutrophilia, which means an increase in the number of neutrophils in the blood). Neutrophilia is caused by products of inflammation that enter the blood stream, are transported to the bone marrow, and there act on the stored neutrophils of the bone marrow to mobilize these into the circulating blood. This makes even more neutrophils available to the inflamed tissue area.**

- **The number of monocytes in the circulating blood is low: also, the storage pool of monocytes in the bone marrow is much less than that of neutrophils. Therefore, the buildup of macrophages in the inflamed tissue area is much slower than that of neutrophils, requiring several days to become effective.**
- **After invading the inflamed tissue, monocytes are still immature cells, requiring 8 hours or more to swell to much larger sizes and develop tremendous quantities of lysosomes**

- **After several days or weeks, the macrophages finally come to dominate the phagocytic cells of the inflamed area because of greatly increased bone marrow production of new monocytes.**
- **The production of both granulocytes and monocytes by the bone marrow is increased by stimulation of the granulocytic and monocytic progenitor cells of the marrow.**



Control of bone marrow production of granulocytes and monocyte- macrophages in response to multiple growth factors released from activated macrophages in an inflamed tissue. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; IL-1, interleukin-1; M-CSF, monocyte colony-stimulating factor; TNF, tumor necrosis factor.

Formation of Pus

- **When neutrophils and macrophages engulf large numbers of bacteria and necrotic tissue, essentially all the neutrophils and many of the macrophages die.**
- **After several days, a cavity is often excavated in the inflamed tissues that contains varying portions of necrotic tissue, dead neutrophils, dead macrophages, and tissue fluid. This mixture is commonly known as pus.**

After the infection has been suppressed, the dead cells and necrotic tissue in the pus gradually autolyze over a period of days, and the end products are eventually absorbed into the surrounding tissues and lymph until most of the evidence of tissue damage is gone.

Eosinophils

- **Eosinophils are weak phagocytes, and they display chemotaxis.**
- **Eosinophils are often produced in large numbers in people with parasitic infections, and they migrate in large numbers into tissues diseased by parasites.**
- **Although most parasites are too large to be phagocytized by eosinophils, they attach to the parasites by way of special surface molecules and release substances that kill many of the parasites.**

For instance, one of the most widespread infections is schistosomiasis, the parasite can invade any part of the body. Eosinophils attach themselves to the juvenile forms of the parasite by (1) releasing hydrolytic enzymes from their granules (modified lysosomes); (2) releasing highly reactive forms of oxygen that are especially lethal to parasites; and (3) by releasing a highly larvacidal polypeptide called major basic protein.

Basophils

The basophils in the circulating blood are similar to the large tissue mast cells located immediately outside many of the capillaries in the body. Both mast cells and basophils liberate heparin into the blood, a substance that can prevent blood coagulation. The mast cells and basophils also release histamine, as well as smaller quantities of bradykinin and serotonin. Indeed, it is mainly the mast cells in inflamed tissues that release these substances during inflammation.

The mast cells and basophils play an exceedingly important role in some types of allergic reactions because the type of antibody that causes allergic reactions, the immunoglobulin E (IgE) type has a special propensity to become attached to mast cells and basophils. Then, when the specific antigen for the specific IgE antibody subsequently reacts with the antibody, the resulting attachment of antigen to antibody causes the mast cell or basophil to rupture and release exceedingly large quantities of histamine, bradykinin, serotonin, heparin, slow-reacting substance of anaphylaxis, and a number of lysosomal enzymes.

These cause local vascular and tissue reactions that cause many, if not most, of the allergic manifestations.