CELLS OF INFLAMMATION

INTRODUCTION

- **Inflammation** is characterized by several familiar signs, *redness*, *swelling*, *heat* and *pain*.
- These signs represent a response that is programmed into your tissue. This response is one of your body's principal defense reactions, designed to anticipate, intercept and destroy invading problem.
- Inflammation is best appreciated by understanding your body's functioning at the level of cells and tissues.
- Subsequent processes of tissue repair (healing) involve cell growth and division, cell movement and differentiation, and manufacture of extracellular material.

CARDINAL SIGNS OF INFLAMMATION

- The four cardinal signs of inflammation -- **the four "ORs"**
- **Rubor** -- redness.
- **Tumor** -- swelling (puffiness, edema).
- **Calor** -- heat.
- **Dolor** -- pain.
- (A fifth sign, ***loss of function***, is sometimes included in this list.)

PHYSIOLOGY OF

The four cardinal signs of inflammation are readily explained by the behavior of the underlying cells and tissues. The inflammatory response consists of several physiological processes, all of which are triggered by the release of pharmacologically active substances such as *histamine* and *heparin*. These triggers of acute inflammation are released by ***mast cells***, sensitive cells which are scattered throughout ordinary connective tissues and which react to tissue damage or other disturbance. *Chronic* inflammation is maintained by more complex interactions among several cell types.

The basic components of the inflammatory response are:

- Vasodilation
- Increased vascular permeability
- Emigration of white blood cells

Vasodilation

- *Increased vascular perfusion*.
- Relaxation of the smooth muscle which surrounds terminal arterioles results in increased blood flow into the connective tissue capillary bed.
- Increased tissue perfusion in turn causes redness (***rubor***), as more red blood cells pass through the tissue, and warmth (***calor***), as blood carries body heat from the body's core to cooler peripheral tissues.

Increased vascular permeability

- The endothelial lining of capillaries becomes more leaky, allowing more fluid (blood plasma) to exude into the connective tissue spaces.
- There is normally a balance between fluid leaving vascular spaces and fluid re-entering the system. Inflammation shifts this balance, causing accumulation of interstitial fluid.
- The fluid build-up which follows this permeability change is called **edema** and is visible as puffiness or swelling (***tumor***).

Emigration of leukocytes

Emigration of leukocytes**,** vasodilation and increased vascular perfusion are designed to prepare the way for the inflammatory infiltrate to enter the inflamed tissue.

•A combination of vasodilation with thickening of the blood (due to fluid leaking out of the vessels) causes a slowing of flow rate, which encourages leukocytes to stick to the sides of the vessels. This is called "margination" or "pavementing" (the white blood cells gather along the endothelium, like bricks paving a road).

•From here the leukocytes crawl between the endothelial cells and enter the inflamed connective tissue. Increased metabolic activity associated with leukocyte activity also generates heat (calor), contributing to local warmth.

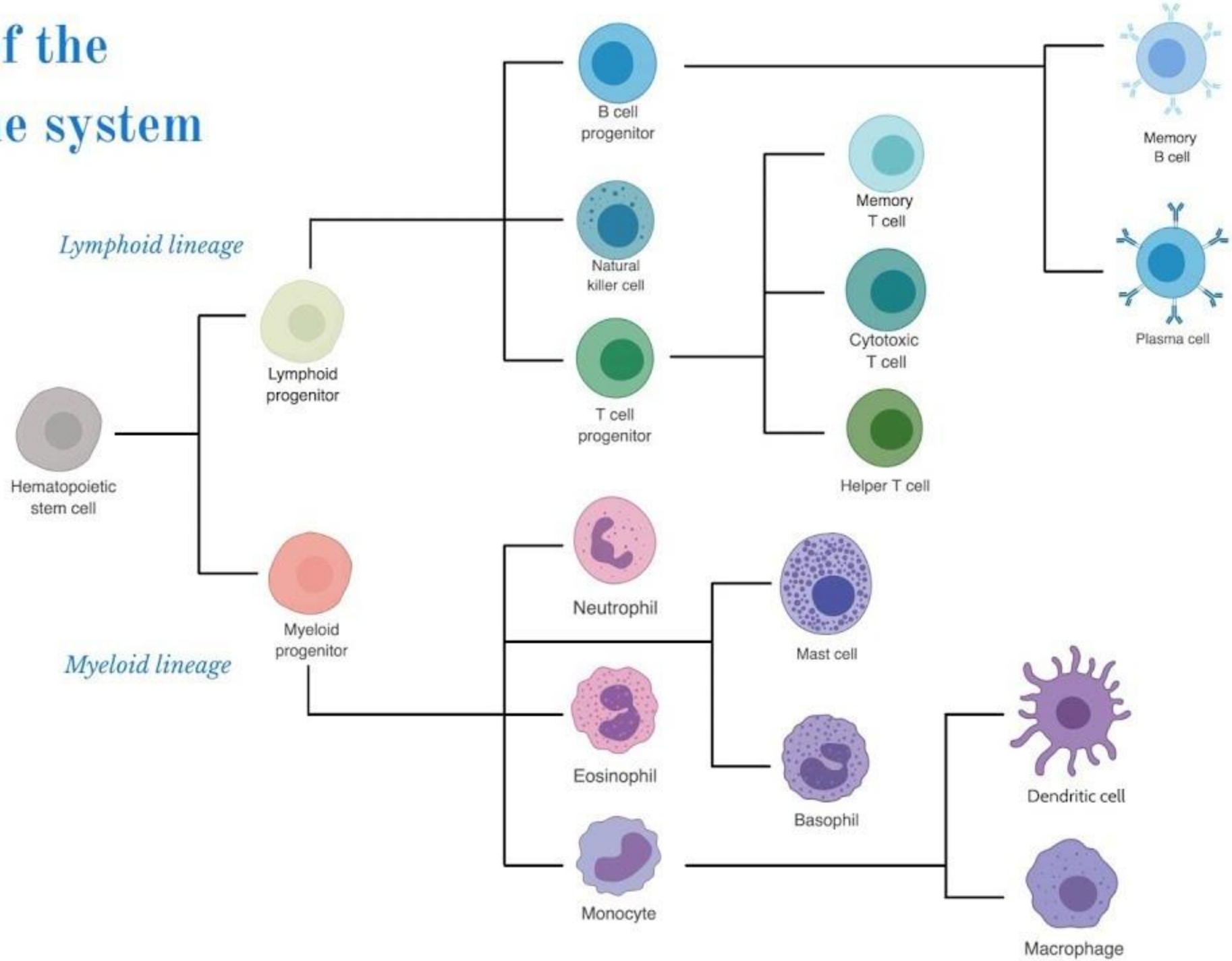
Pain and/or itching

- Pain and/or itching (dolor) is caused by direct action on nerve endings of the chemical agents released during inflammation.

CELLS OF INFLAMMATION

- Cells of the inflammation include
- Neutrophils,
- Lymphocytes and
- Monocytes.
- Immigration of these cells into peripheral tissues is one of the principal purposes for inflammation, bringing to a site of injury the immune-system cells which can combat infection and clean up damaged tissue.

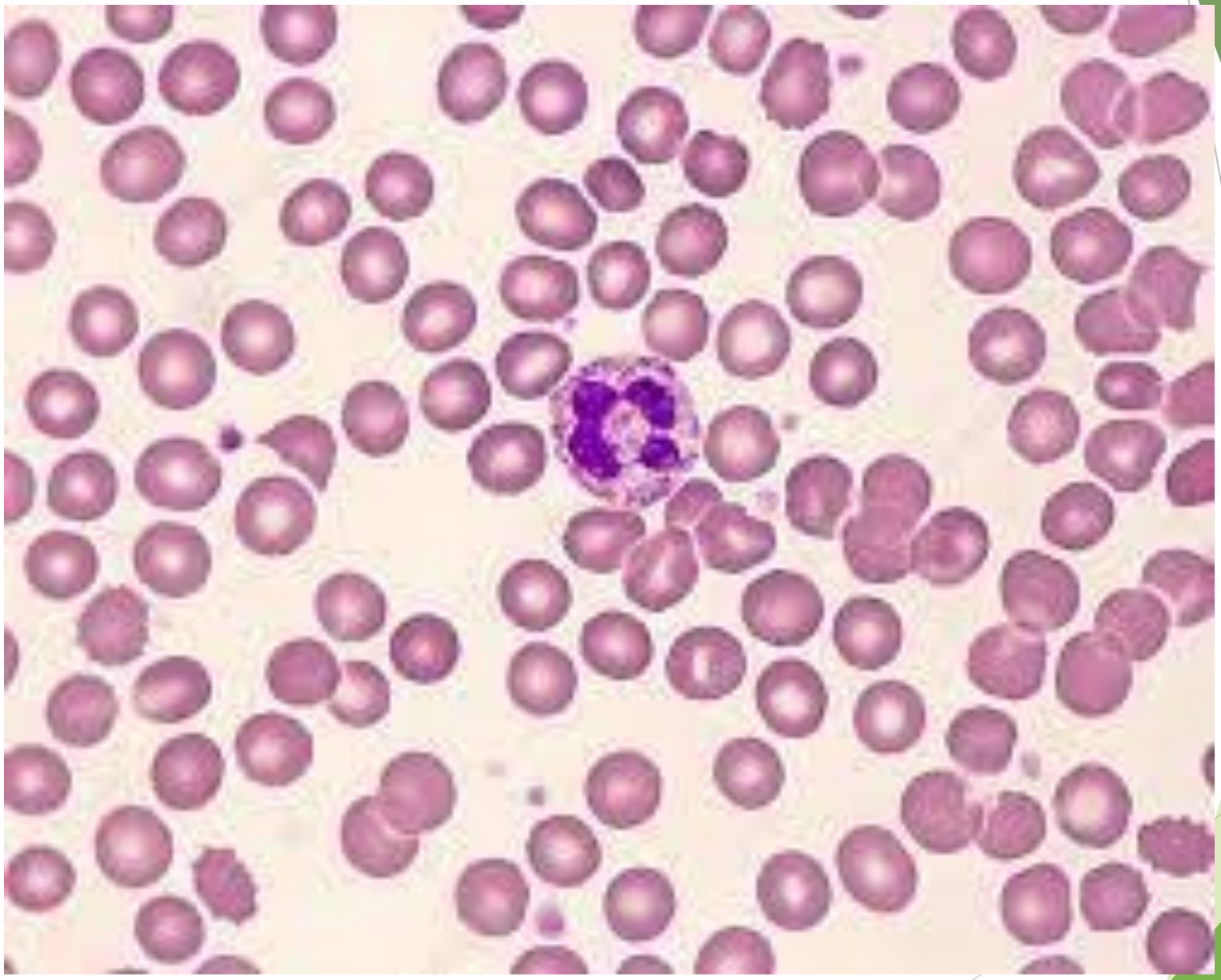
Cells of the immune system



Neutrophils

- Neutrophils are the first white blood cells to enter the tissue during acute inflammation
- They are the most numerous of the leukocytes, about 60% of the white blood cell count
- Neutrophils are anti-bacterial cells which lyse (break down) bacterial cells by releasing lysosomal enzymes.
- Neutrophils recognize bacteria as foreign by the antibody molecules which have attached to the bacterial surface. Antibody molecules (molecules which bind to one specific antigen or foreign substance which the body has previously encountered) are found in blood plasma and interstitial fluid.
- Neutrophils are about 12 μm in diameter in blood smear preparations (about twice the size of red blood cells), and are *polymorphonuclear* (meaning their nuclei have a variable shape with several lobes; neutrophils are also called *PMNs* or *polys*, short for polymorphonuclear neutrophilic leukocytes). The cytoplasm contains many lysosomal granules (vesicles storing lysosomal enzymes) whose specific staining properties give these cells their name. The granules are neutrophilic, meaning they do not show a special affinity for either acidic or basic stains, but are stained mildly by both.

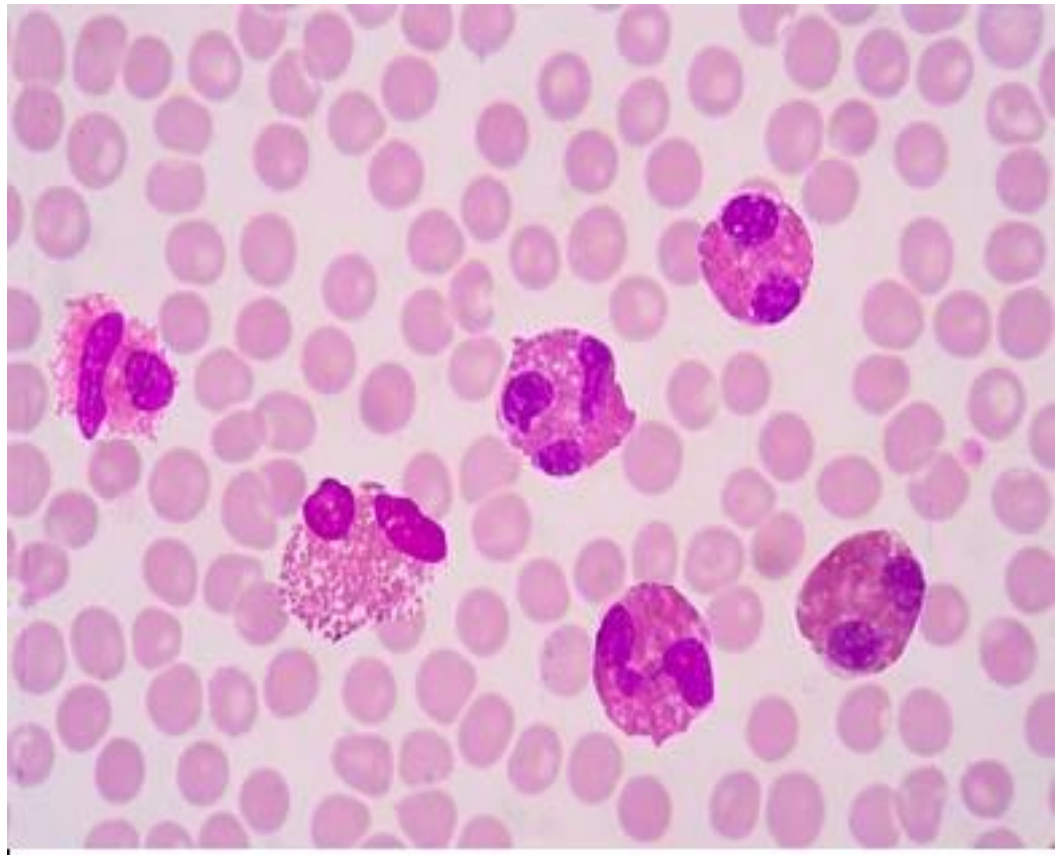
- This is in contrast to the specific granules of eosinophils, which stain red with eosin, and basophils, which stain with basic stains.
- Severe inflammation may increase the numbers of neutrophils in blood, resulting in neutrophilia
- Neutrophils are only occasionally seen in tissue sections outside blood (except, of course, in inflamed tissue).
- Here they may be most easily recognized by their lobed nuclei.
- One neutrophil nucleus might be mistaken for a cluster of very small nuclei, but each of the lobes is much smaller than any whole nucleus--only two or three µm across, much smaller than the nuclei of lymphocytes which are among the smallest of our cells.



Eosinophils

- Eosinophilic functions include: movement to inflamed areas, trapping substances, killing cells, anti-parasitic and bactericidal activity, participating in immediate allergic reactions, and modulating inflammatory responses.

- Eosinophils play roles within various diseases via the release of inflammatory mediators into tissue sites such as specific granule proteins, leukotrienes, radical oxygen species, and a variety of cytokines or chemokines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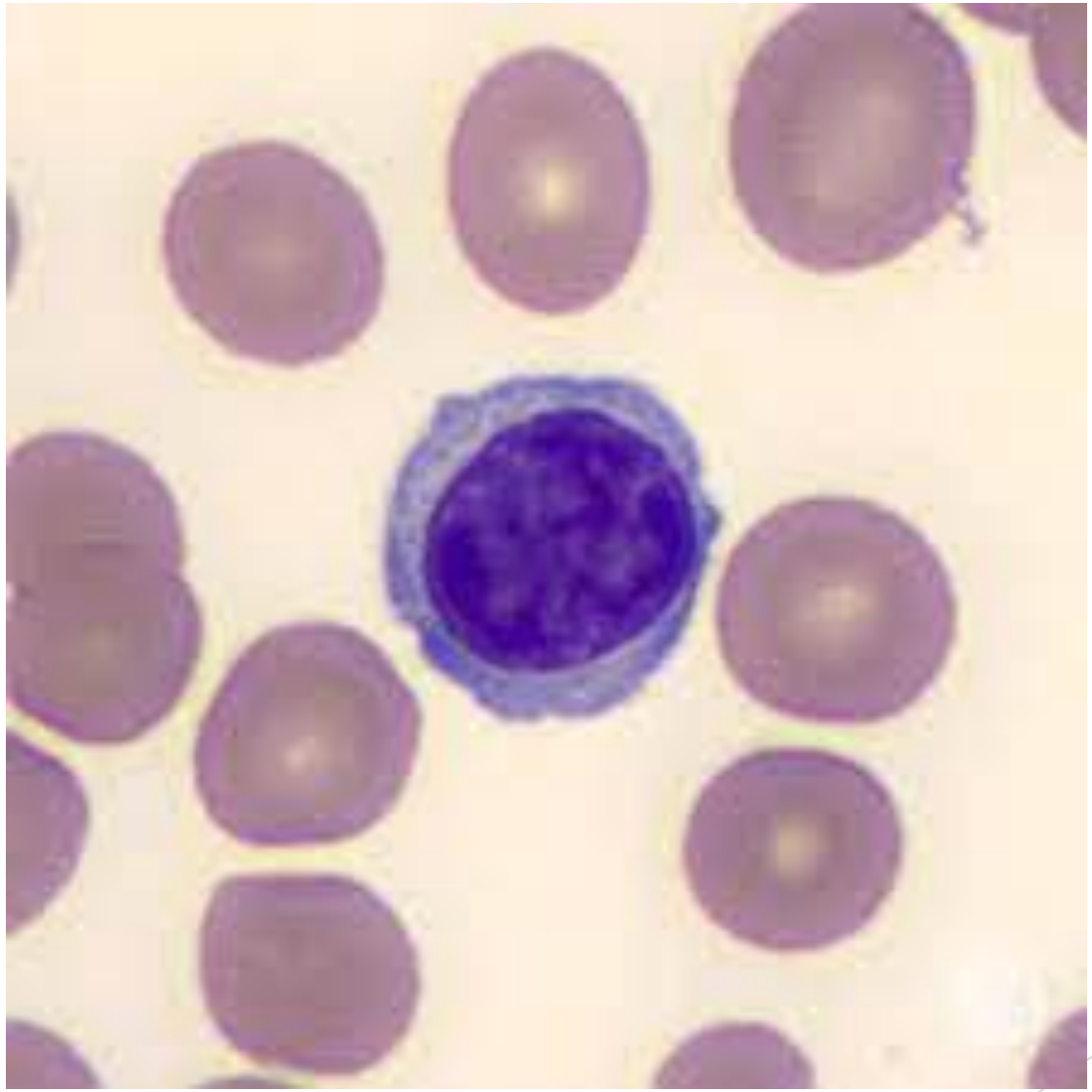
Lymphocytes

- Lymphocytes are small cells, 7-9 µm in diameter in blood smears, and are the second most common white blood cell type (about 30% of the WBCs).
- Each lymphocyte has a round heterochromatic (deeply staining) nucleus surrounded by a relatively thin rim of cytoplasm.
- Lymphocytes are most easily recognized in histological sections as small "naked" nuclei (the cytoplasm is usually inconspicuous) which occur here and there in most ordinary connective tissues.
- They are encountered most commonly near mucous membranes.
- Lymphocytes are found densely packed in lymphoid tissue, such as tonsils, spleen, and lymph nodes.

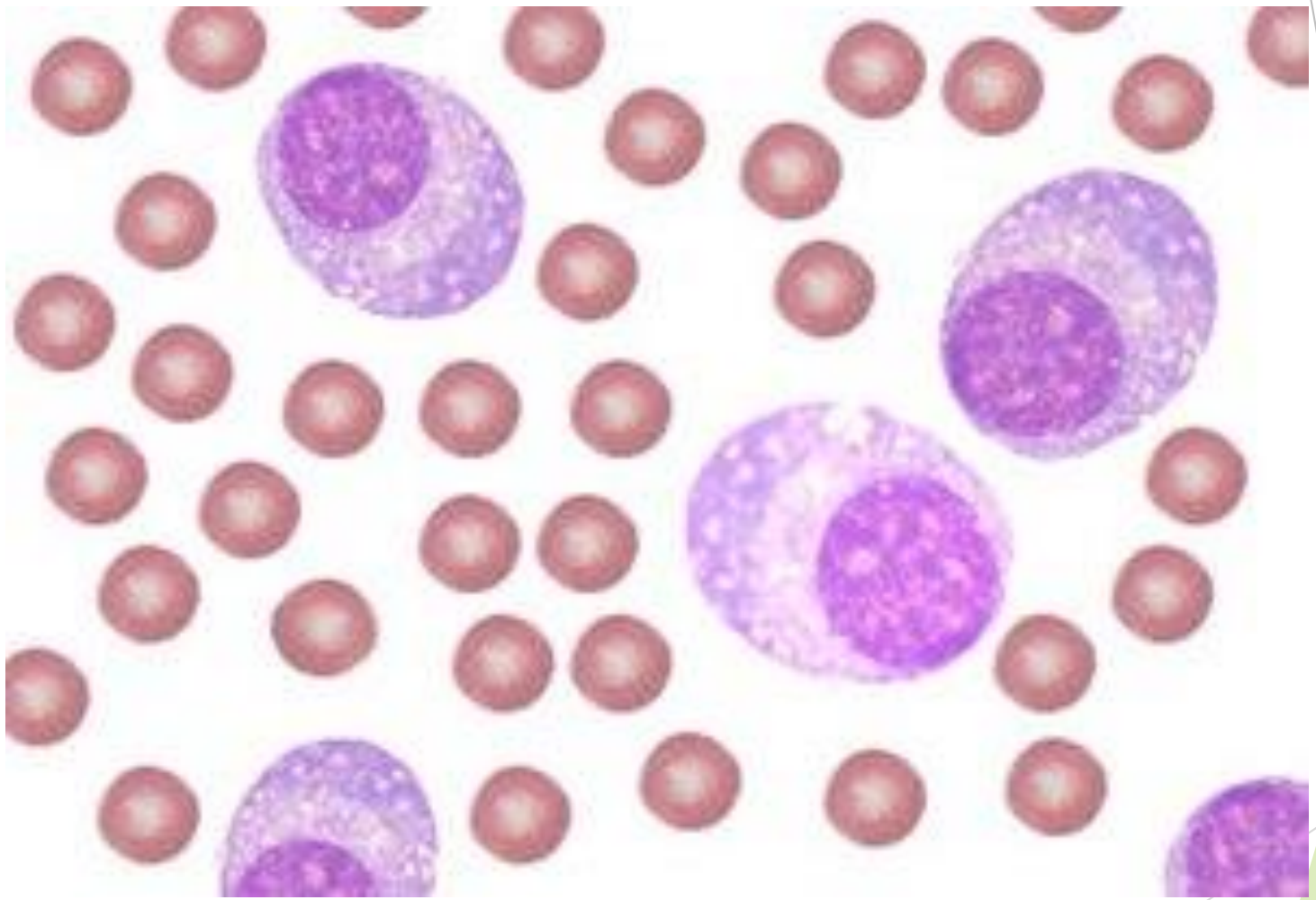
- Lymphocytes accumulate somewhat later during the inflammatory process.
- Their presence in large numbers indicates the continuing presence of antigen and thus may suggest an established infection.
- Lymphocytes produce a multitude of diverse antibody molecules (one specific type of antibody per lymphocyte) which provide the mechanism for chemical recognition of
- foreign materials (distinguishing between self and non-self) and so for mediating and regulating immune responses.
- Lymphocytes travel in the blood, but they routinely leave capillaries and wander through connective tissue.
- Therefore, lymphocytes may be normally encountered at any time in any location.
- They even enter epithelial tissue, crawling between the epithelial cells.

- They re enter circulation via lymphatic system channels .Lymph channels drain into lymph nodes, where dense aggregations of lymphocytes form **lymph nodules**.
- Each lymph nodule has a "germinal center", where activated lymphocytes proliferate.



Plasma cells

- **Plasma cells** are lymphocytes which are specialized for mass production and secretion of circulating antibodies.
- Plasma cells have more extensive cytoplasm filled with rough endoplasmic reticulum (for synthesizing protein, specifically antibody molecules).
- This cytoplasm is distinctly basophilic, a consequence of the large numbers of ribosomes associated with the rER, and typically forms a bulge on one side of the nucleus.
- The heterochromatin of plasma cells is typically clumped in a characteristic "spoke-wheel" arrangement which also aids plasma cell recognition.



T cell

- T cell, also called T lymphocyte, type of leukocyte that is an essential part of the immune system. T cells are one of two primary types of lymphocytes
- T cells play a critical role in autoimmune and inflammatory diseases and can act to drive or suppress immune responses , depending on their phenotype. CD4+ T cells polarize into different helper T cell subsets depending on the context of the conditions under which they are activated.
- T lymphocytes synthesize and export heparin-binding epidermal growth factor-like growth factor and basic fibroblast growth factor, mitogens for vascular cells and fibroblasts: differential production and release by CD4+ and CD8+ T cells.

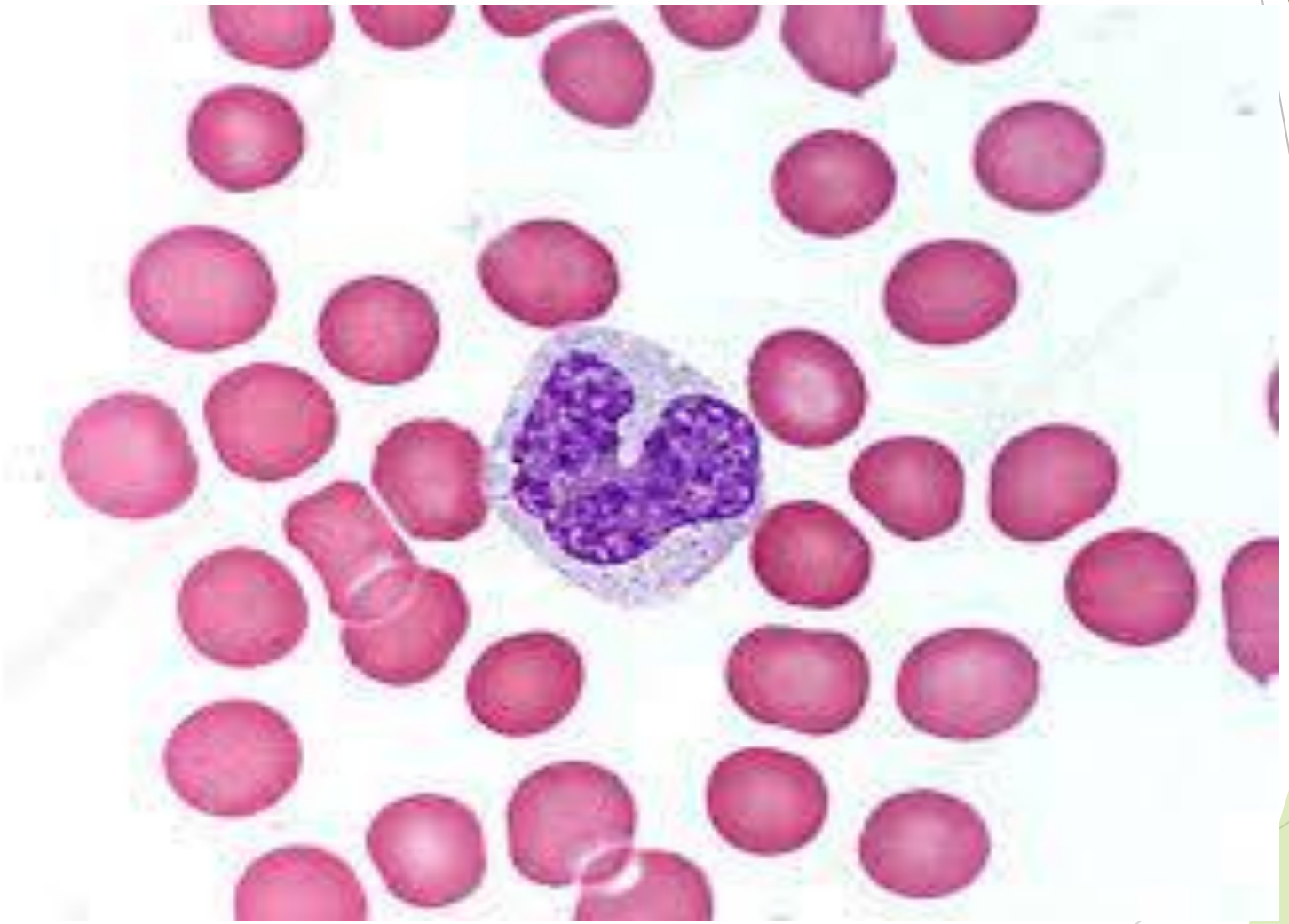
NK Cells

- NK cells were originally described as large granular lymphocytes with natural cytotoxicity against tumor cells.
- NK cells were later recognized as a separate lymphocyte lineage, with both cytotoxicity and cytokine-producing effector functions[1].
- The acquisition of cell cytotoxicity during evolution has been associated with the development of highly sophisticated and robust mechanisms that control the initiation of the cytolytic processes and avoid tissue damage.
- Besides cytotoxic activity, NK cells activation is accompanied by secretion of pro-inflammatory cytokines.
- Hence, NK cells have the potential to act both in driving inflammation and in restricting adaptive immune responses that may otherwise lead to excessive inflammation or even autoimmunity

Monocytes

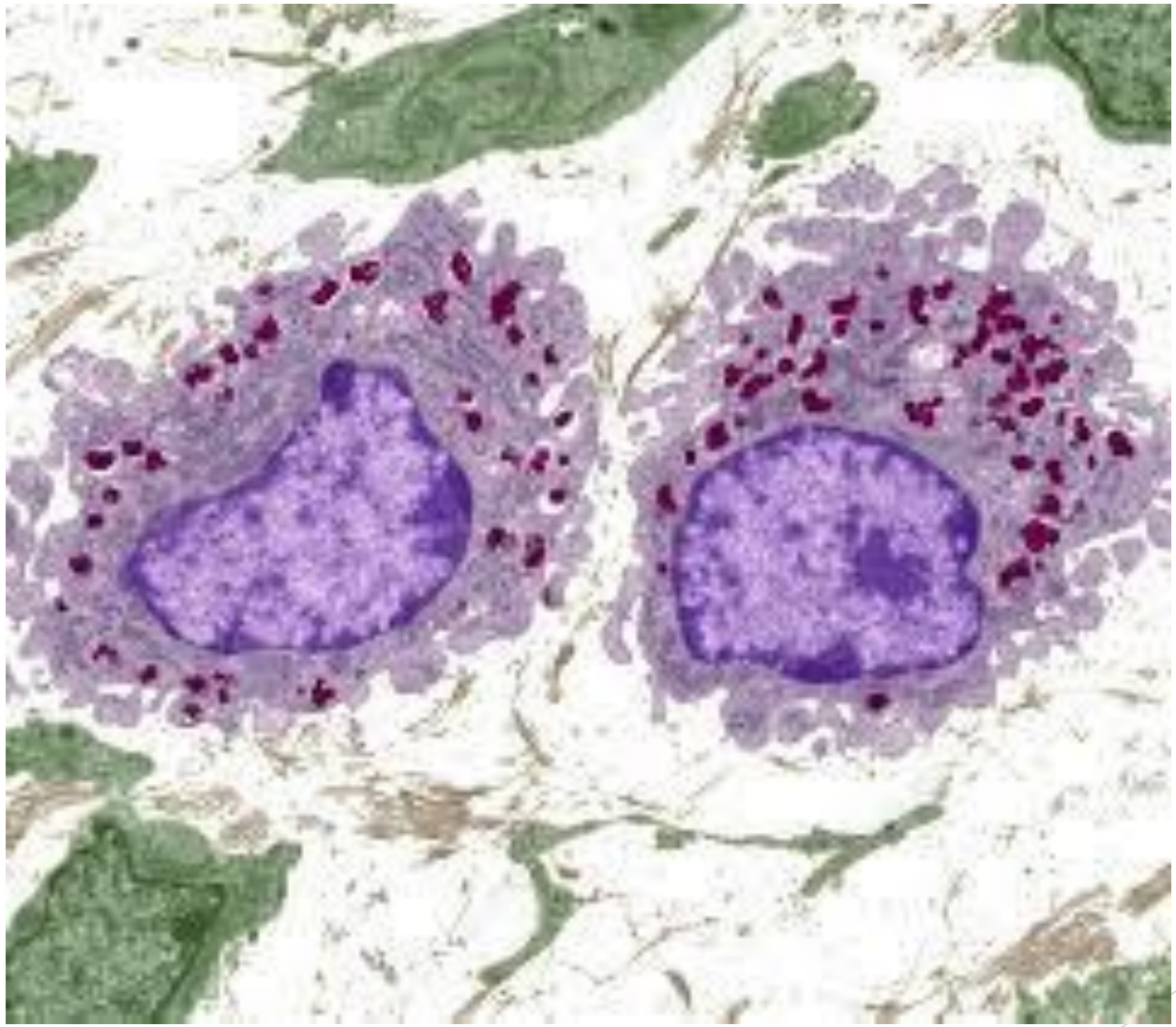
- **Monocytes** are phagocytic cells which circulate in the blood. An equivalent cell type, called the *macrophage*, is a resident cell in connective tissue.
- Monocytes/macrophages engulf and digest foreign microorganisms, dead or worn-out cells, and other tissue debris. They interact closely with lymphocytes to recognize and destroy foreign substances.
- Resident macrophages normally remain at rest (rather than circulating in and out of tissues like the lymphocytes).
- But the normal number of fixed macrophages is supplemented during inflammation by the influx of many monocytes from the blood.

- When faced with a target too big for one cell, a splinter for example, several macrophages may fuse together to form a single huge multinucleate mass called a "foreign body giant cell."
- Monocytes are the largest of the leukocytes, and constitute about 5% of the white blood cell population.
- In blood smears, monocyte nuclei are typically indented, with a kidney-bean shape. Tissue macrophages are diverse in appearance and not easily distinguished from the more common fibroblasts.
- Macrophages are generally larger, and may contain brown pigment granules which represent indigestible residue in tertiary lysosomes.
- In electron micrographs macrophages are generally recognized by the presence of numerous lysosomes of various sizes, including large heterophagic vesicles



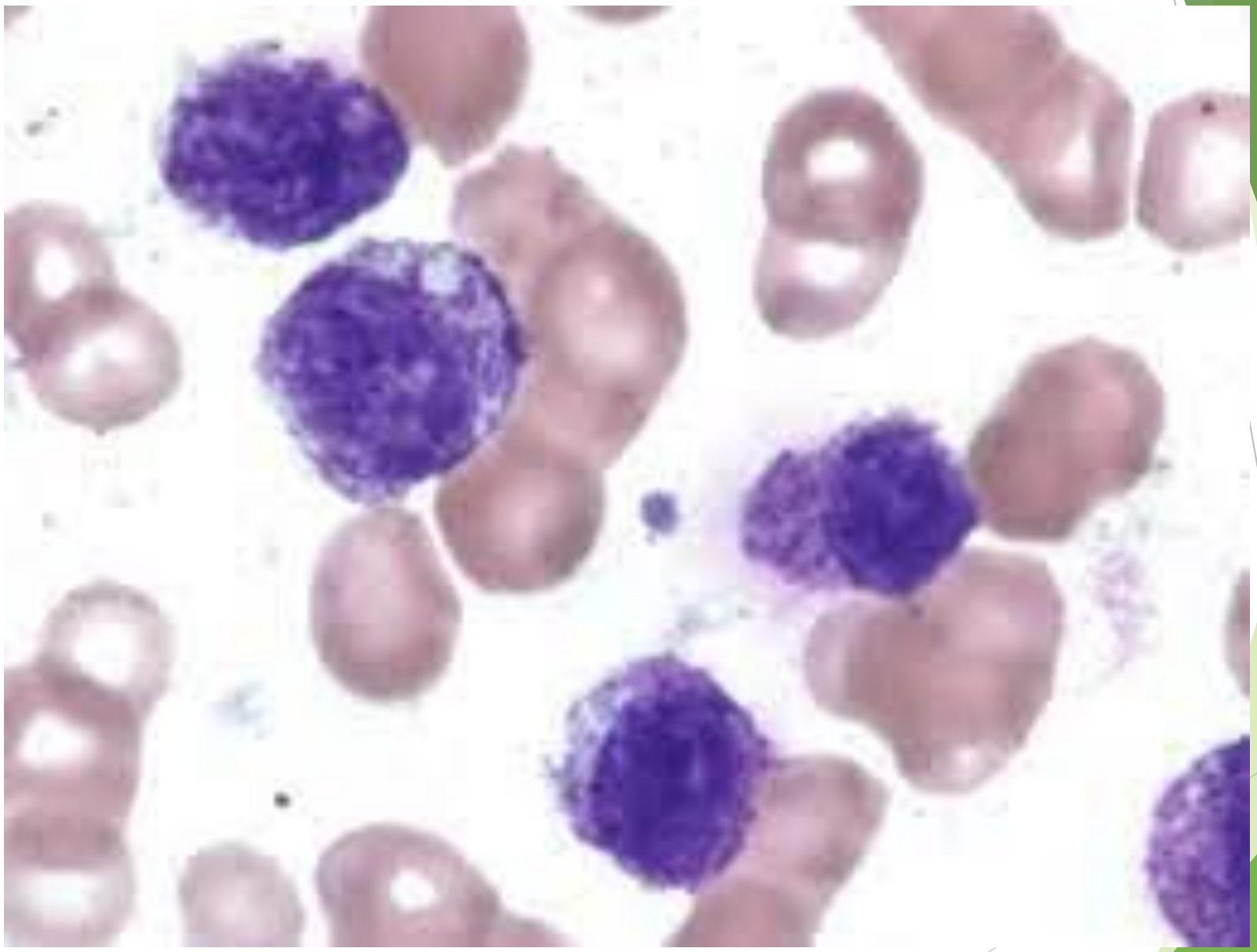
Macrophage

- The cytoplasm of a macrophage contains vacuoles and granules that are basophilic in nature .
- The nucleus is ovoid and measures about 6-12 µm in diameter.
- *Macrophages* engulf and process cell debris, pathogens, and cancer cells. They are involved in wound healing, tissue regeneration, and pro-inflammatory activities.



Mast Cells

- Mast cells are oval or irregularly shaped cells.
- Under light microscopy, a dense granular cytoplasm is seen, often obscuring the nucleus and other organelles.
- When it can be visualized, the nucleus is central, and the cell is mononuclear.
- Mast cells are found throughout the body in loose connective tissue.
- They can be activated to release a wide variety of inflammatory mediators, by many different antigens including allergens, pathogens and physiological mediators.
- They contain/release chemicals such as histamine, heparin, cytokines, and growth factors.



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