SYSTEMIC EFFECTS OF INFLAMMATION

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Learning Objectives:

- By the end of this lecture student should be able to;
- Enumerate systemic effects of inflammation
- Describe the systemic effects of inflammation in detail
- Understand the significance of these effects.

- Inflammation, even if localized, is associated with systemic reactions but mostly associated with systemic response.
- Systemic effects of inflammation are collectively called the acute-phase reaction or systemic inflammatory response syndrome (SIRS).
- The cytokines TNF, IL-1, and IL-6 are the most important mediators of the acute-phase reaction.

- Interferons also contribute.
- These cytokines are produced by leukocytes in response to bacterial products and other inflammatory stimuli.
- Often TNF induces the production of IL-1, which in turn stimulates the production of IL-6.
- TNF and IL-1 have similar biologic actions.
- IL-6 stimulates the synthesis of a number of plasma proteins in liver.

- Features of acute phase response are;

1. Fever
2. Lethargy (weakness)
3. Cachexia (weight loss)
4. Synthesis of acute phase proteins by liver
5. Leukocytosis
6. Other manifestations

1. **Fever** means elevation of body temperature, usually by 1° to 4°C.

- It is one of the most prominent manifestations of the acute-phase response.
- Fever is also called pyrexia
- Produced due to substances called pyrogens.

- They are usually breakdown products of microbial agents.
- Pyrogens stimulate prostaglandin (PG) synthesis in the brain.
- Pyrogens can be

a. Exogenous. Bacterial endotoxin (LPS), Teichioic and Lipoteichoic acids of gram +ve bacteria, and viral products
b. Endogenous. IL-1 and TNF

- Exogenous pyrogens stimulate leukocytes to release endogenous pyrogens which in turn increase the levels of cyclooxygenases that convert AA into prostaglandins.
- In brain, IL1 and TNF act on hypothalamic vascular and perivascular cells to cause production of PGs and especially of PGE2.

- PGE2 stimulates production of neurotransmitters which reset the temperature at a higher level.
- By reducing heat loss (vasoconstriction) and increased heat generation from brown fat and skeletal muscles.
- NSAIDs, including aspirin, reduce fever by inhibiting prostaglandin synthesis.
- It is assumed that elevated body temperature helps to remove microorganisms.

- It is the common mechanism found in amphibians.

2. The levels of **acute phase proteins** is increased 100 times in inflammation.

- Their levels inform us about ongoing inflammatory process.
- The most important ones are.

a. C-reactive protein (CRP).

b. Fibrinogen.

c. Serum amyloid A (SAA) protein.

- IL1 and TNF cause production of SAA.
- IL6 causes production of CRP and Fibrinogen.
- CRP and SAA, bind to microbial cell walls, and they may act as opsonins for complement.
- Also bind to chromatin and help removal of necrosed cells.

- Fibrinogen binds to erythrocytes and causes them to form stacks (rouleaux) that sediment more rapidly than individual erythrocytes (raised ESR in inflammation).
- So acute phase proteins have beneficial effects
- Prolonged production (in chronic inflammation) leads to diseases like secondary amyloidosis (SAA).

- Similarly raised levels of CRP associated with low grade inflammation.
- This low grade inflammation leads to atherosclerosis and IHD.
- Two other proteins produced in inflammation.
- Hepcidin
- Thrombopoietin

- Hepcidin decreases delivery of iron to RBC precursors in bone marrow.
- Over period of time leads to anemia of chronic diseases.
- Thrombopoietin is the major growth factor for megakaryocytes (platelet precursor).
- In inflammation, its production may lead to thrombocytosis.

4. **Cachexia** (weight loss)

5. **lethargy** (weakness), loss of appetite and somnolence is caused by TNF.

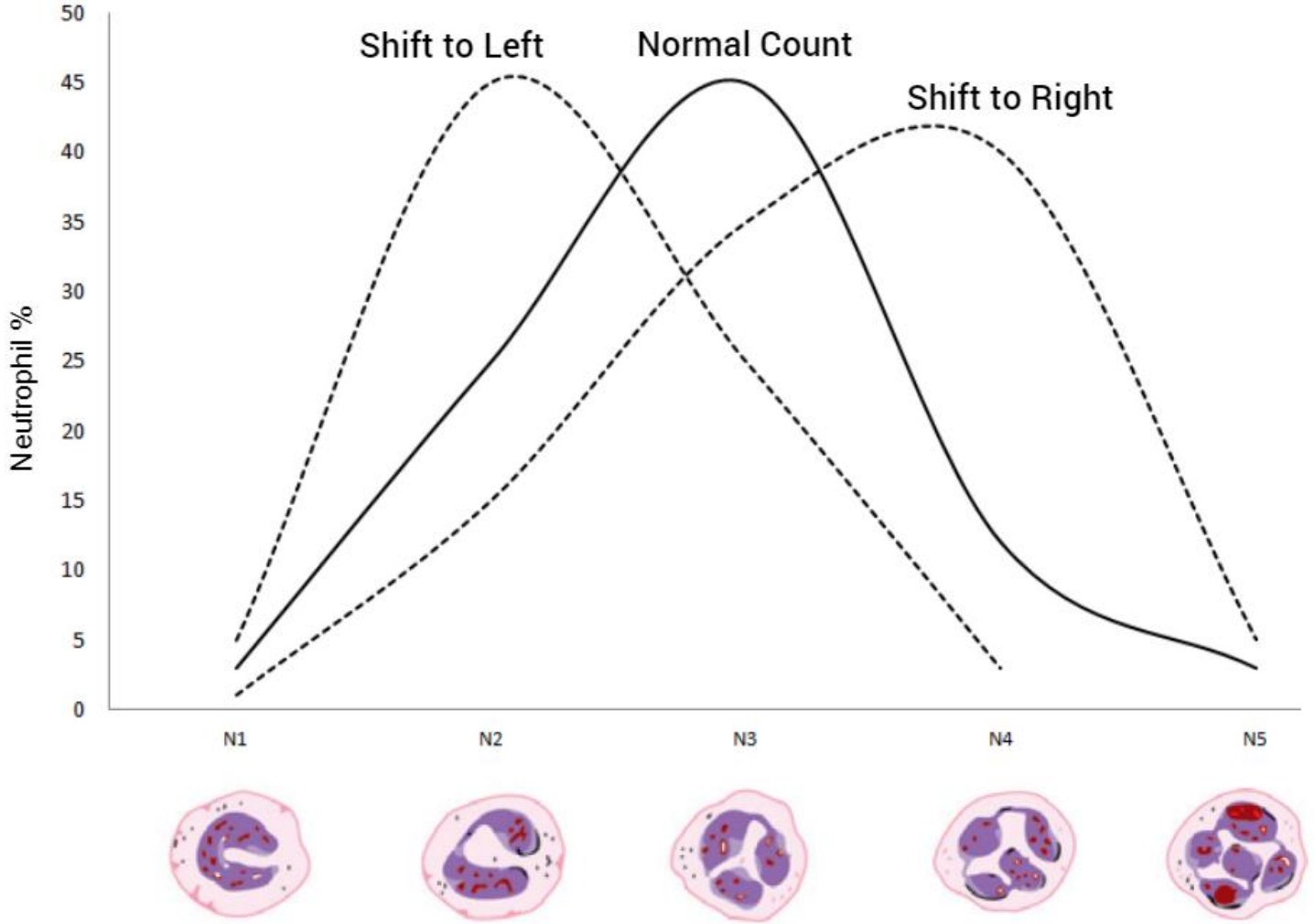
- TNF causes loss of appetite and it then causes weight loss and lethargy.

- TNF probably acts on brain cells to suppress appetite.

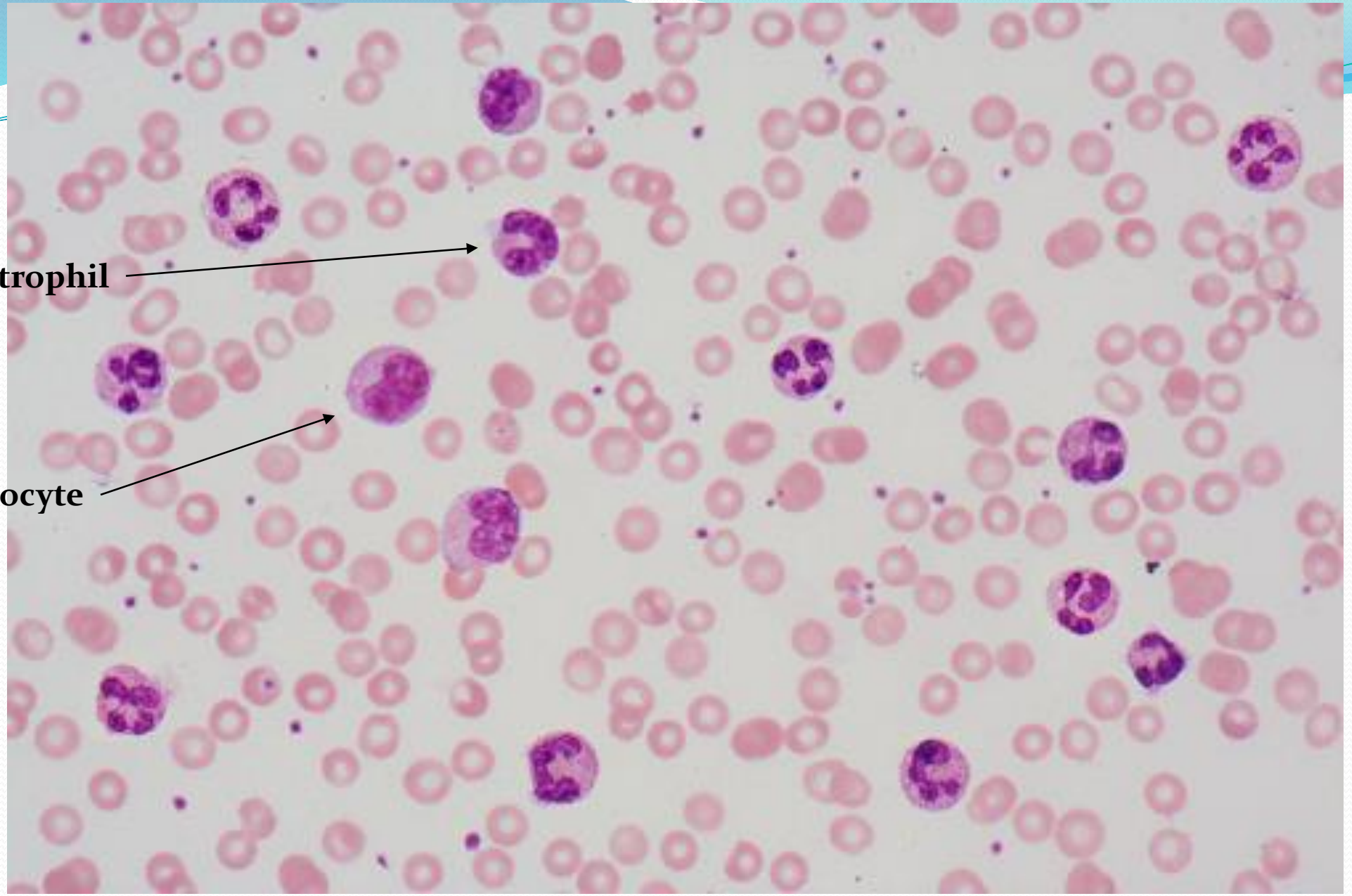
6. Leukocytosis is a common feature of inflammation especially in bacterial infections.

- IL1, TNF and others stimulate production of leukocytes from precursors in the bone marrow.
- Count may become 15000- 25000/mm^3.
- Sometimes rise to 40,000 -100,000/mm^3.
- Presence of high numbers of mature and immature leukocytes.

- It is called left shift.
- In old days immature forms used to be written and reported on left side of report.
- Joseph Arneth in 1920 in a publication used a graph showing left shift.
- Very high numbers of leukocytes with left shift is called leukemoid reaction.
- Leukemia like but not leukemia.

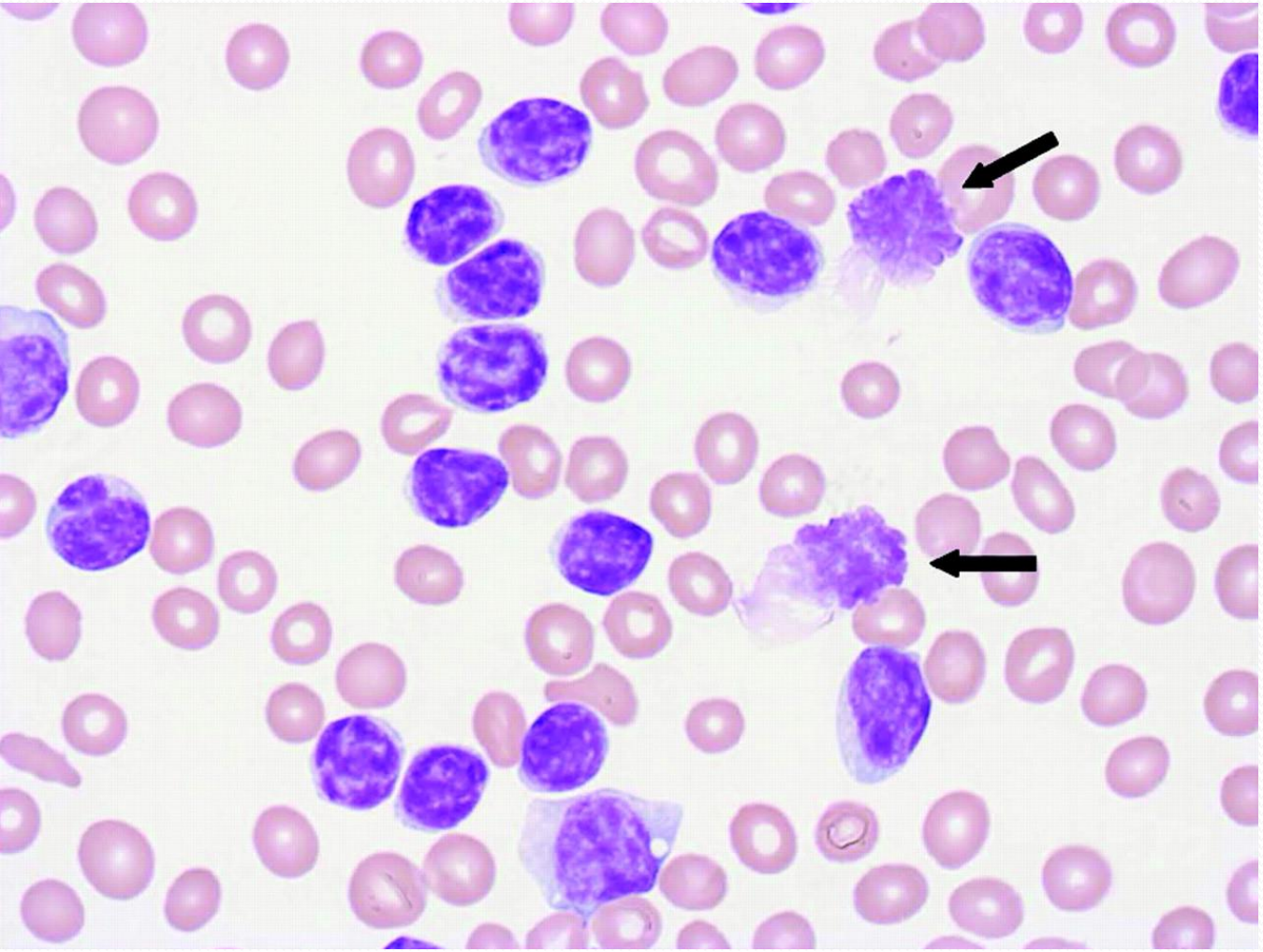


Arneth Count for Neutrophils

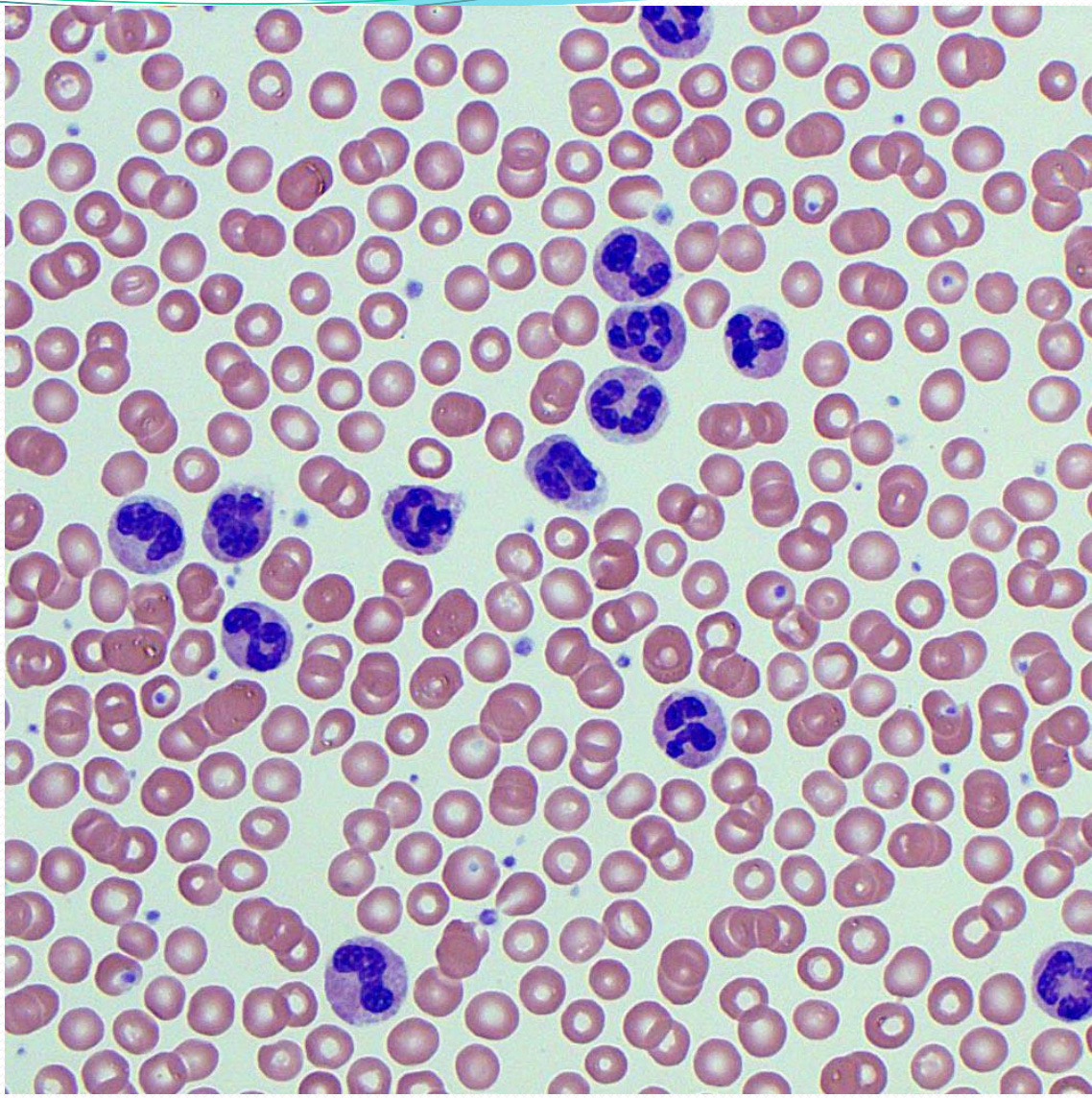


Leukemoid reaction

- Most bacterial infections induce an increase in neutrophil count called neutrophilia.
- Viral infections lead to lymphocytosis.
- Parasitic infestations cause Eosinophilia.
- Certain infections like typhoid fever and some viral infections associated with leukopenia (sequestration of leukocytes into interstitial tissues).



Lymphocytosis



Neutrophilia

6. Other manifestations include;

a. Increased heart rate

b. Increased blood pressure.

c. Decreased sweating due to redirection of blood from skin to deep tissues to minimize heat loss.

d. Rigors (shivering)

e. Chills (search for warmth)

- In severe bacterial infections (sepsis), large amounts of bacteria and their products in the blood stimulate the production of enormous quantities of TNF and IL-1.
- High levels of these cytokines cause different symptoms;
- Disseminated Intravascular Coagulation (DIC)
- Hypotension and shock
- Metabolic disturbances.

- This condition is called septic shock.
- A type of shock
- Caused by both gram –ve and gram +ve bacteria.

THANK YOU