THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
Review Article
January, 2026 Vol.6(1), 61-80

Neutrophil Kinetics & It's Toxic Changes: An Overview

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DOI:10.5281/ScienceWorld.18255247

Abstract

Neutrophils are key components of the innate immune system, serving as the first line of defense against rapidly multiplying pathogens. Upon recognizing exogenous signals from microbes (PAMPs) or endogenous signals from damaged cells (DAMPs) via pattern recognition receptors on sentinel cells, neutrophils are recruited to sites of infection through inflammatory cascades. Their antimicrobial actions include phagocytosis, degranulation, reactive oxygen species (ROS) production, cytokine secretion and the formation of neutrophil extracellular traps (NETs) to eliminate pathogens. Neutrophil production occurs primarily in the bone marrow, with extramedullary production under high demand. Their maturation, storage and trafficking through blood and tissues are tightly regulated, allowing rapid responses to inflammation. The magnitude and kinetics of neutrophil responses, including neutrophilia, neutropenia, left shift, and toxic changes, provide insight into disease severity and progression. Toxic changes, characterized by cytoplasmic basophilia, Döhle bodies, vacuolation, nuclear immaturity and toxic granulation, arise from accelerated maturation and reflect the intensity of inflammatory stimuli. Grading toxic neutrophils by number and severity aids in disease prognosis and guides clinical management. Recognition of congenital or acquired abnormalities, such as leukocyte adhesion deficiencies or Pelger-Huët anomaly, is important to avoid misinterpretation. Overall, evaluating neutrophil morphology and kinetics through blood smear and bone marrow analysis offers valuable diagnostic and prognostic information, particularly in emergency and critical care cases.

Keyword: Neutrophils, Innate immunity, Inflammation, Toxic change, Left shift, Phagocytosis, Neutrophil extracellular traps (NETs), Bone marrow, Leukogram, Disease prognosis

1.0 INTRODUCTION

Infectious microbes multiply very fast, so the body needs immediate, always-ready defences to recognize and destroy them before they cause harm. These rapid first-line defences are called the 'innate immune system', which is present in all multicellular organisms, including plants and animals. Inflammation is a key part of innate immunity that directs white blood cells and protective proteins to sites of infection or tissue damage, where they destroy invading microbes and help repair damaged tissue. (Tizard, 2013)

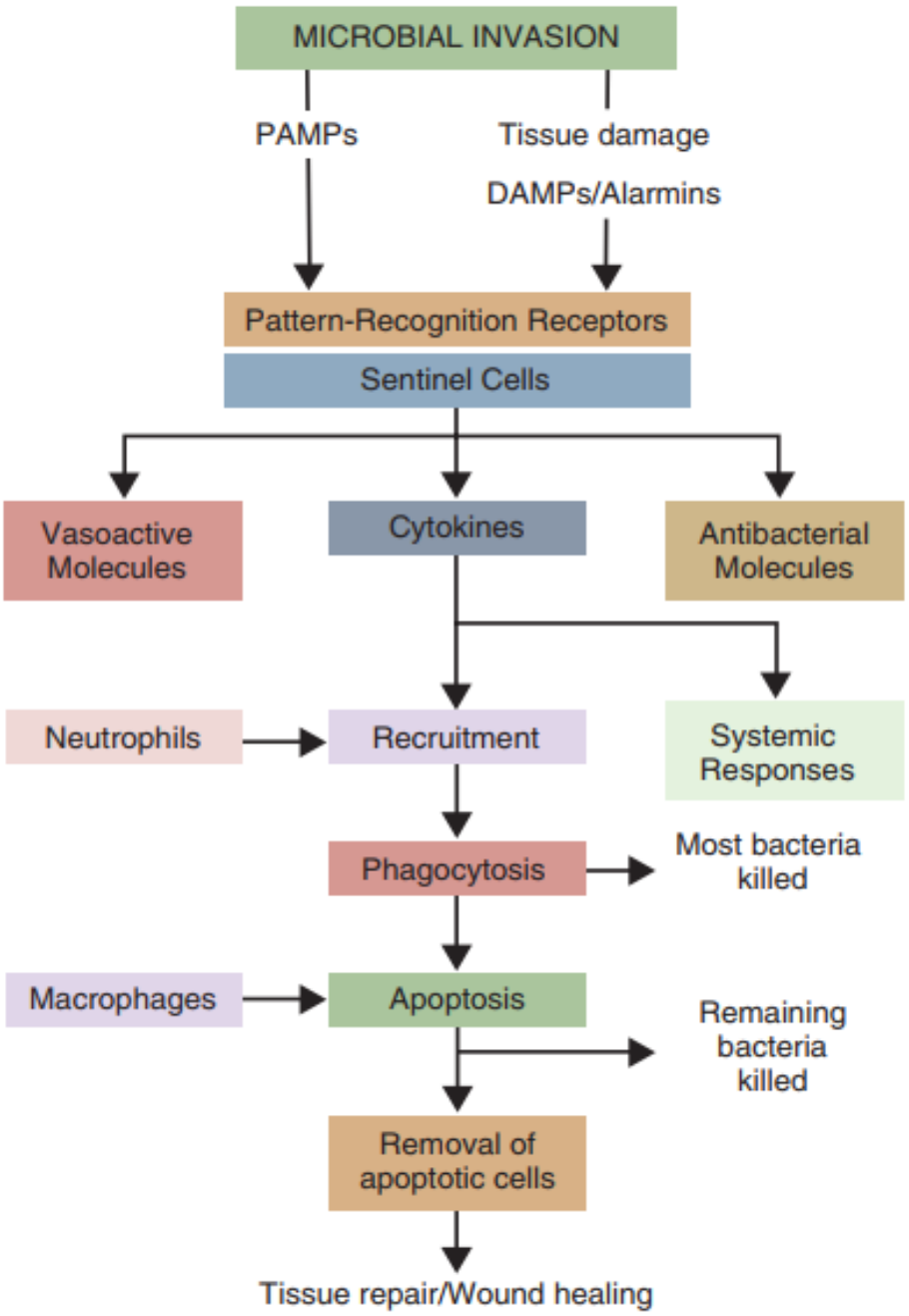

Figure-1 Overview of innate immune mechanisms

The innate immune system is activated when sentinel cells detect danger signals from microbes (PAMPs) or damaged cells (DAMPs) through pattern recognition receptors (PRRs),

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triggering an immune response. Sentinel cells (mainly macrophages, dendritic cells, and mast cells) detect invading microbes using PRRs and are concentrated near body surfaces, while other cells can also act as sentinels when needed (Tizard, 2013).

Functions of Neutrophils

Neutrophils eliminate pathogens through both intracellular and extracellular mechanisms. Following recruitment to sites of inflammation or infection, neutrophils phagocytose microorganisms and enclose them within phagosomes. Pathogen killing occurs through NADPH oxidase–dependent generation of reactive oxygen species (ROS) or via oxygen-independent antimicrobial proteins such as cathepsins, defensins, lactoferrin and lysozyme. These antimicrobial proteins are released either into phagosomes or into the extracellular environment through degranulation, allowing elimination of both intra- and extracellular pathogens. In addition, highly activated neutrophils can kill extracellular microorganisms by forming neutrophil extracellular traps (NETs) (Figure-2) (Kolaczkowska and Kubes, 2013).

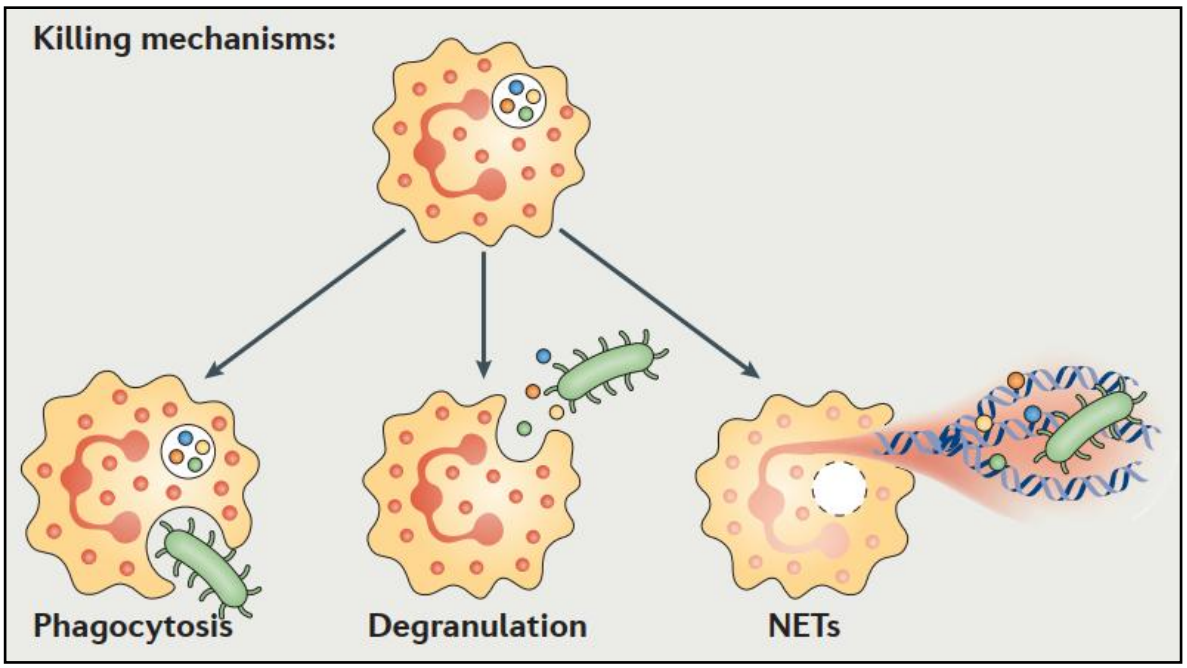

Figure-2 Killing mechanisms of neutrophils (Mayadas *et al*., 2014)

(I) Recruitment of neutrophils

Neutrophils are produced in the bone marrow and migrate to sites of tissue inflammation through the vasculature. Their exit from the bloodstream, mainly at postcapillary venules, follows a tightly regulated process known as neutrophil recruitment. This multistep adhesion cascade involves initial capture, rolling, firm adhesion with cell spreading, crawling along the endothelium and finally transmigration into the tissue (Figure-

3). These steps are mediated by sequential interactions between neutrophil receptors and ligands expressed on activated endothelial cells (Figure-4) (Mayadas *et al*., 2014).

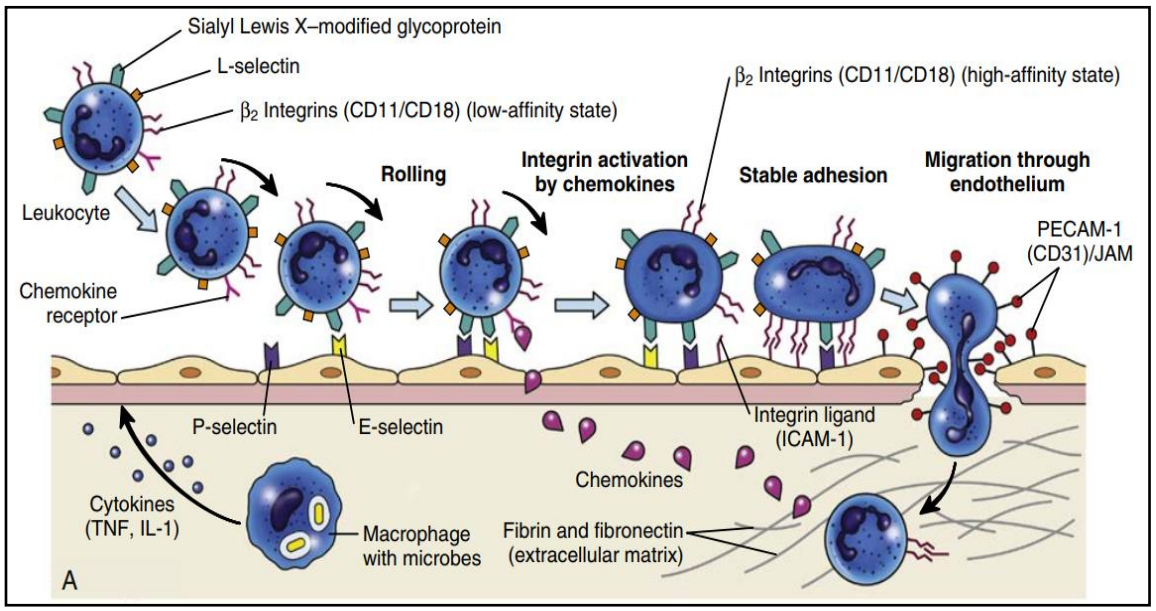

Figure-3 Neutrophils adhesions/recruitment cascade (Zachary, 2022)

Endothelial Molecule	Leukocyte Receptor	Major Role
P-selectin	Sialyl Lewis X PSGL-1	Rolling (neutrophils, monocytes, lymphocytes)
E-selectin	Sialyl Lewis X ESL-1, PSGL-1	Rolling, adhesion to activated endothelium (neutrophils, monocytes, T lymphocytes)
ICAM-1	CD11/CD18 (integrins) (LFA-1, Mac-1)	Adhesion, arrest, transmigration (all leukocytes)
PECAM-1	PECAM-1	Transendothelial cell migration
JAM A	JAM A, LFA-1	Transendothelial cell migration
JAM C	JAM B, Mac-1	Transendothelial cell migration

Figure-4 Endothelial cells/Neutrophils Adhesions molecule with their major roles

(II) Phagocytosis

Phagocytosis is the process by which particles larger than 5 µm are internalized into a membrane-bound vacuole called a phagosome. Neutrophils recognize microorganisms either directly via pathogen-associated molecular patterns (PAMPs) or indirectly through opsonin receptors. Opsonins, such as antibodies and complement components, enhance pathogen recognition and uptake. Phagocytosis triggers a respiratory burst leading to the generation of superoxide and secondary ROS, including hydrogen peroxide, hypochlorous acid, hydroxyl

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radicals, and chloramines. Concurrently, cytoplasmic granules fuse with phagosomes, delivering antimicrobial peptides and proteases that enhance microbial killing (Figure-5) (Rosales and Querol, 2018; Kobayashi *et al*., 2018).

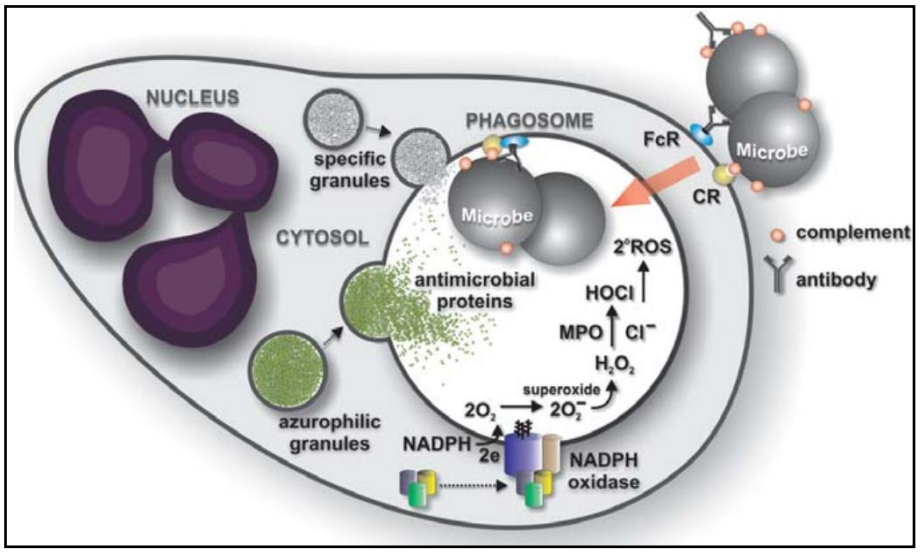

Figure-5 Neutrophil phagocytosis and activation of microbicidal system

NADPH oxidase and superoxide production:

In activated neutrophils, the NADPH oxidase complex assembles on the plasma or phagosomal membrane during phagocytosis. Cytosolic components translocate and associate with flavocytochrome b558, forming the active oxidase that transfers electrons from NADPH to molecular oxygen, generating superoxide. Superoxide rapidly dismutates to hydrogen peroxide and other potent microbicidal ROS (Kobayashi *et al*., 2018).

Myeloperoxidase-halide system:

The microbicidal activity of ROS is further enhanced by myeloperoxidase (MPO), a haemoprotein stored in azurophilic granules. MPO is delivered to phagosomes where it catalyzes the conversion of hydrogen peroxide and chloride ions into hypochlorous acid, a highly effective antimicrobial agent, constituting the MPO-halide system (Kobayashi *et al*., 2018).

(III) Degranulation

Degranulation involves the regulated exocytosis of neutrophil granules following receptor stimulation. Granules translocate to the phagosomal or plasma membrane, where they dock, fuse, and release their microbicidal contents (Figure-6). This process requires cytoskeletal rearrangement, increased intracellular Ca^{2+} levels and hydrolysis of ATP and GTP, ensuring controlled release of antimicrobial mediators (Lacy, 2006).

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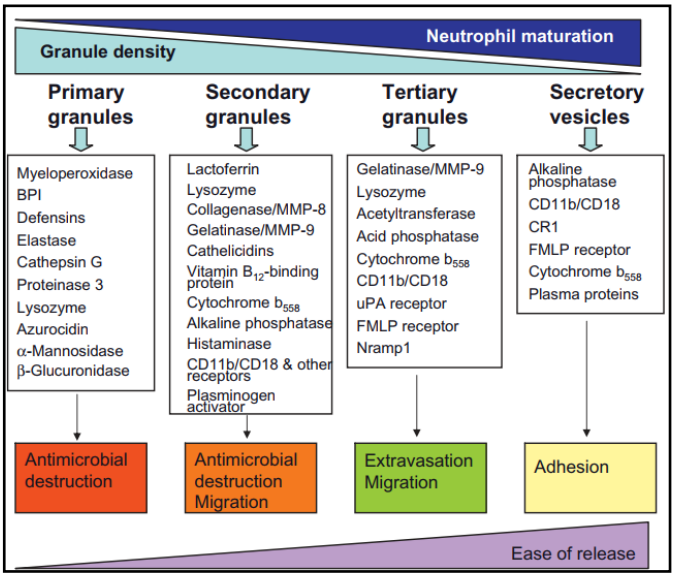

Figure-6 Neutrophil granules, contents and their functions (Weiss & Wardrop, 2011)

(IV) NETs (Neutrophil Extracellular Traps) formation

When pathogens are too large for phagocytosis or evade intracellular killing, neutrophils deploy NETs. NETs are extracellular networks of DNA decorated with histones and antimicrobial proteins that entrap and neutralize microbes. NET release occurs through NETosis, a distinct form of cell death characterized by loss of nuclear lobulation, chromatin decondensation, mixing of nuclear and granule contents, breakdown of intracellular membranes and eventual rupture of the plasma membrane, resulting in NET release into the extracellular space (Figure-7) (Burgener & Schroder, 2020).

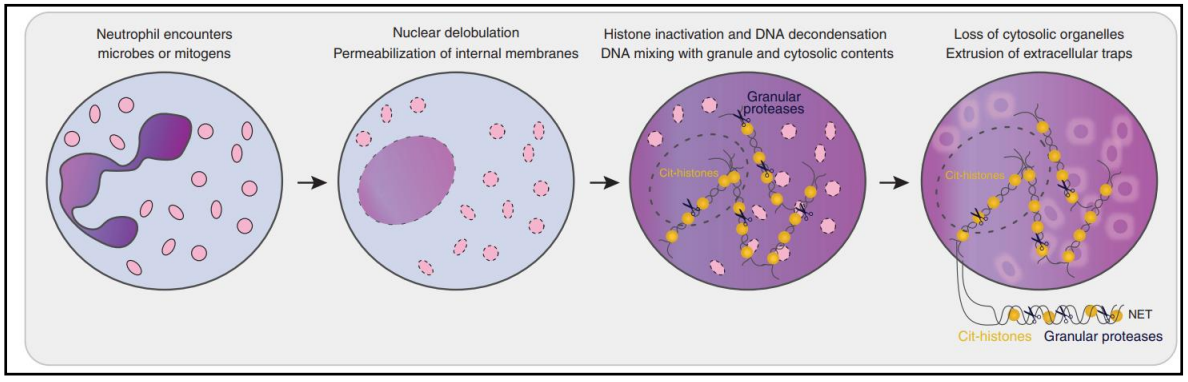

Figure-7 NETosis is a distinct cellular program in neutrophils (Burgener & Schroder, 2020)

2.0 NEUTROPHIL KINETICS

To interpret leukocyte patterns in disease, one must first learn the normal granulopoiesis, circulation of neutrophils in response to physiological/disease condition and characteristics of the leukogram as a basis for recognizing abnormal patterns.

Granulopoiesis:

Neutrophils are mainly produced in the active bone marrow of healthy adult animals. In young animals or during prolonged inflammatory conditions, they may also be produced

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outside the bone marrow, especially in the spleen and sometimes in the liver and lymph nodes (Thrall *et al.,* 2012).

A large portion of bone marrow activity is dedicated to producing neutrophils, which are made in huge numbers, circulate briefly in blood, then move into tissues and live only a few days. Although they form a major percentage of blood leukocytes (varying by species), most neutrophils are normally stored in organs. During bacterial infections, their numbers in the bloodstream can rise dramatically as stored cells are released (Tizard, 2013).

Neutrophils develop from common myeloid progenitor cells in the bone marrow (and spleen) through a shared pathway with other myeloid cells. Differentiation continues through the granulocyte–macrophage progenitor, after which cells commit to becoming granulocytes (neutrophils, eosinophils, basophils). Once committed, they undergo well-defined proliferative and maturation stages, which are important for interpreting bone marrow and blood changes during disease Production normally results in a progressive increase in the relative numbers of more mature stages, as indicated in Figure-9. This results from the combined events of proliferating early forms, which amplify both the number of cells and the progress toward more mature stages. In the process, each myeloblast may produce approximately 16 to 32 segmented neutrophils (Thrall *et al.,* 2012).

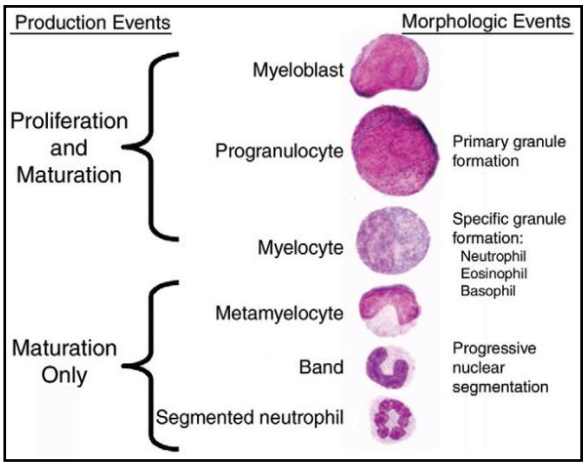

Figure-8 Stages of neutrophil maturation

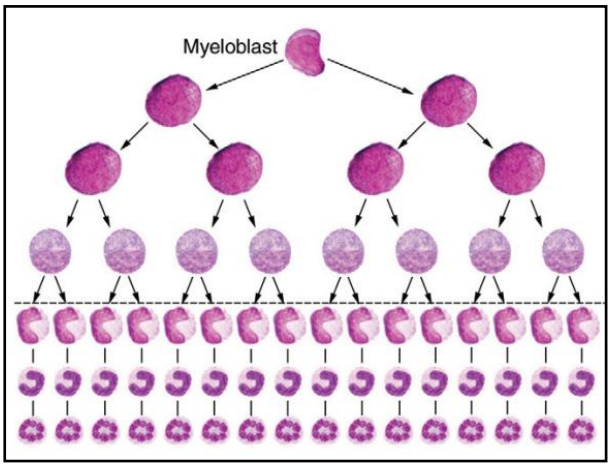

Figure-9 Orderly production of neutrophils (Thrall *et al.*, 2012)

Neutrophil production in bone marrow follows an orderly pattern, with few immature cells and many mature cells. This orderly process occurs both under normal conditions and when demand increases. In disease, disorderly production may occur, marked by excess immature cells and fewer mature forms. Neutrophils move through organized compartments: bone marrow, blood and tissues. In the bone marrow, they develop from stem cells, multiply in a proliferative pool and mature in a storage pool whose size varies by species (largest in dogs, smallest in ruminants). From there, neutrophils enter the blood, which consists of

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circulating and marginal pools, allowing movement between them. Finally, neutrophils migrate into tissues, where they carry out their main role in host defence (Thrall *et al.,* 2012).

Regulation:

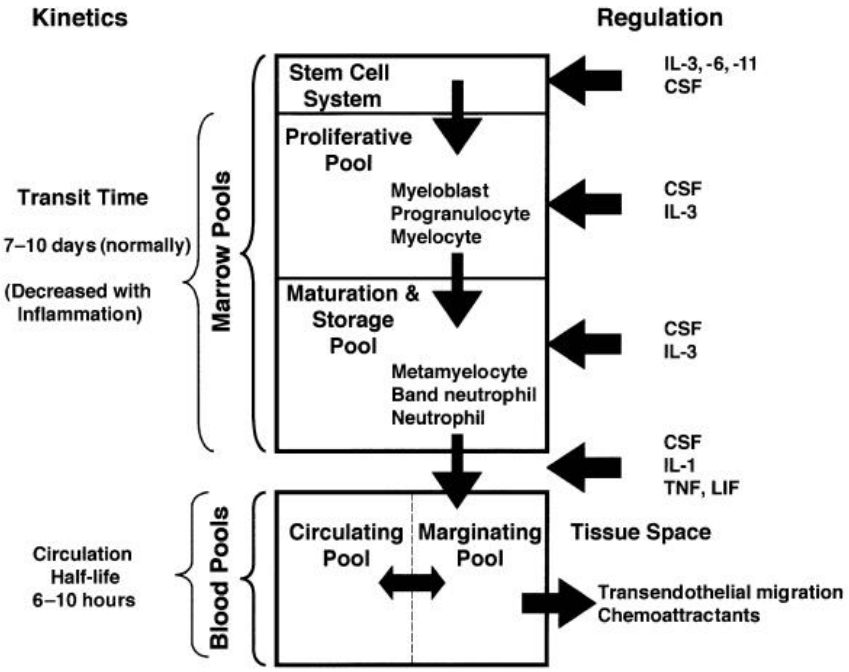

Figure-10 Bone-marrow neutrophils pool, blood neutrophils pools and it's regulation

Cytokines and growth factors regulate neutrophil production and release. Key factors include granulocyte-CSF and GM-CSF, mainly produced by mononuclear cells at inflammation sites, along with interleukins, TNF and IL-1, which speed neutrophil release from bone marrow. Normally, neutrophil production balances their movement into tissues, keeping blood levels stable. During inflammation, increased cytokines greatly boost neutrophil production, release and directed migration to the affected site. After inflammation resolves, neutrophil levels return to normal, likely through an unknown negative-feedback mechanism (Thrall *et al.,* 2012).

Neutrophil kinetics help interpret changes in the leukogram. Normally, neutrophils take about 7 days to mature in the bone marrow, but this can shorten to 2–3 days during inflammation. Once in the blood, they circulate for about 6–10 hours before entering tissues, renewing blood pools several times daily. Because of this rapid turnover, neutrophil counts in blood can change quickly and dramatically during disease.

Left shift: Left shift refers to an increased concentration of immature neutrophils in blood. This usually indicates band neutrophils but metamyelocytes and earlier forms may accompany increased bands. A left shift may occur with neutrophilia. A left shift also may occur with neutropenia; this indicates a more severe consumption of neutrophils by a more aggressive

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inflammatory lesion or an early repopulation of blood following a reversible stem cell injury. An orderly left shift suggests an inflammatory stimulus; in this case, the term orderly means that the concentration of each cell stage decreases with the degree of immaturity of the cell stage (Thrall *et al.,* 2012).

Right shift: Increased in number of hyper segmented neutrophils referred as right shift.

Leukemia: Presence of neoplastic cells in circulation is referred as leukemia.

Toxic changes in neutrophils/Toxic neutrophils: A set of disease or certain physiological conditions induced morphologic alterations in neutrophils called as toxic neutrophils.

The nature of the response is best understood by considering a modified neutrophil trafficking model (Figure-11). When inflammation is established, an orchestra of chemical mediators modulates many events. Vasodilation and chemotactic substances work to increase the egress of neutrophils from the local marginated pool into the inflammatory lesion. Cytokines released from local mononuclear cells (Figure-10) make their way to the bone marrow, where they increase the rate of release of maturing neutrophils and the rate of production by increasing stem-cell entry, proliferative events and maturation events. The net result is that the marrow response dramatically increases the delivery rate of neutrophils to blood. In summary, a complete cycle of consumption, production and release is activated, with the goal of delivering a supply of neutrophils to the inflammatory lesion until it resolves (Thrall *et al.,* 2012).

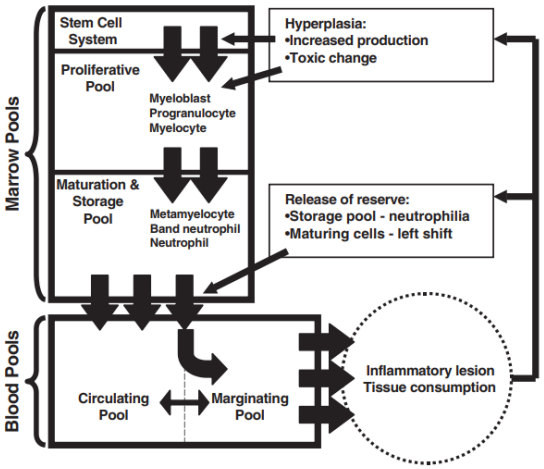

Figure-11 Modified neutrophil trafficking model in response to inflammation.

The pattern of neutrophil concentrations seen in blood may vary from severely decreased to markedly increased. It is helpful to think of the pattern being dependent on a balance between consumption by the lesion and production and release by the marrow. This balance may explain all neutrophil concentration patterns encountered during inflammation. In small animals, most inflammatory processes result in some degree of neutrophilia,

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indicating that marrow releases more cells to blood than are consumed at the site of inflammation. This is illustrated using the neutrophil trafficking model in Figure-12. Inflammatory patterns manifesting in neutrophilia may be regarded as mild to severe responses that are managing the lesion. The severity of the process predicted by the magnitude of the left shift and the presence of toxic change in neutrophils (Thrall *et al.,* 2012)

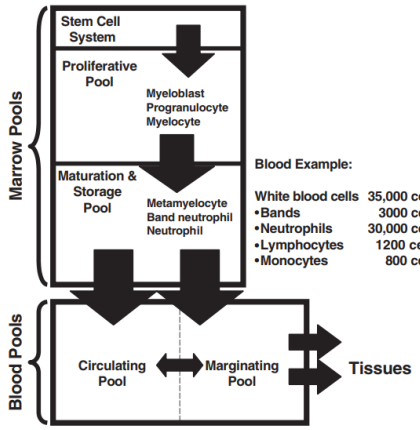

Figure-12 Modified neutrophil trafficking model illustrating used to illustrate a moderate inflammatory response.

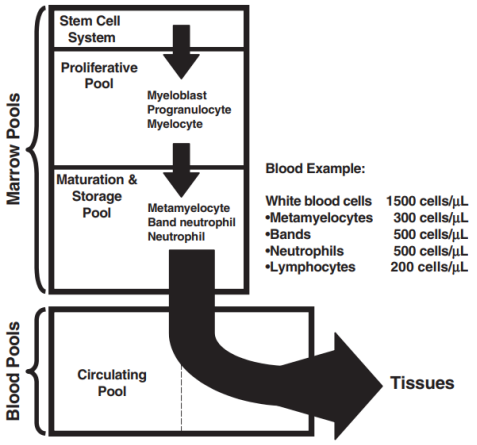

Figure-13 Modified neutrophil trafficking model used to illustrate a severe inflammatory response.

Very severe and typically acute inflammatory lesions, on the other hand, may consume neutrophils more rapidly than the neutrophils can be delivered to blood. When this occurs, neutropenia develops, as shown in the neutrophil trafficking model in Figure-13. In this case, a left shift is expected. At one or more time points, the concentration of bands and other left shift cells may be greater than that of segmented neutrophils. The balance between neutrophil consumption and delivery by bone marrow is affected by species differences, as outlined in Table 1. Species may vary in the amount of neutrophil reserve and in the proliferative capacity of the marrow. Dogs have the largest reserve and the greatest ability to produce neutrophils; cows and other ruminants form the other extreme. Cats and horses are somewhat intermediate in their capacities to deliver cells to blood (Thrall *et al.,* 2012).

Table-1 Comparative bone marrow contribution to neutrophil trafficking and relationship to ranges of neutrophilia seen with the inflammatory response in various species.

Species	Marrow Reserve	Regenerative capacity	Range of Neutrophilia (Neutrophils/µL)	Interpretation of Neutropenia During Acute Inflammation
Dog	Relatively High	Rapid	20,000-1,20,000	Very Severe lesions
Cat	Intermediate	Intermediate	20,000-60,000	Very Severe lesions
Horse	Intermediate	Intermediate	15,000-30,000	Probable Severe lesions
Cow	Relatively low	Slow	10,000-25,000	Usual findings, regardless of severity

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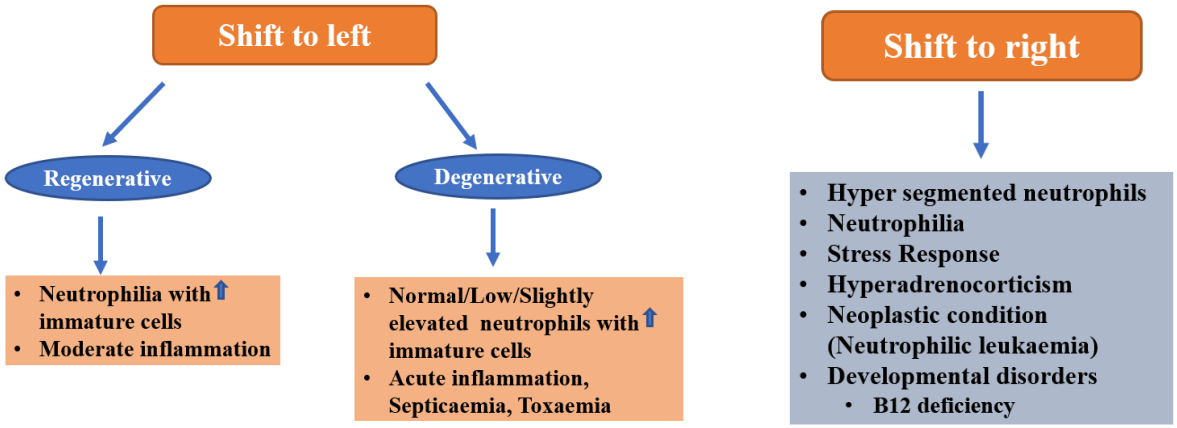
Species differences affect the degree of neutrophilia and how neutrophil counts reflect disease severity. For example, chronic inflammation can raise neutrophils up to about 120,000/µL in dogs but only around 25,000/µL in cows. Cats and horses will be intermediate, as indicated in Table-1. Neutropenia interpretation varies by species: in dogs, cats and horses, it signals severe inflammation and can be an emergency, while in cows, acute inflammation normally causes temporary neutropenia due to their low marrow reserve, followed by recovery with a left shift (Thrall *et al.,* 2012).



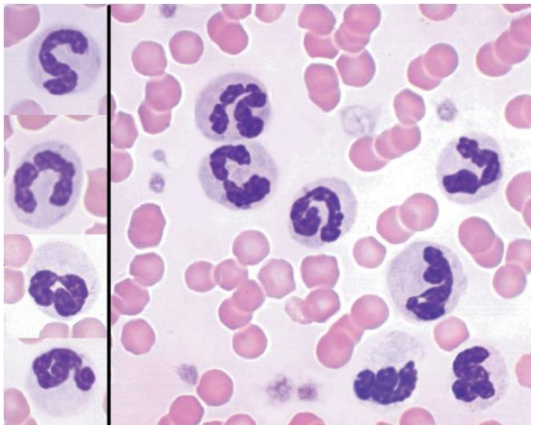


Figure-14 Segmented neutrophils illustrating variation in nuclear shape. Segmented neutrophils start with the horseshoe-shaped nucleus of the band cell.

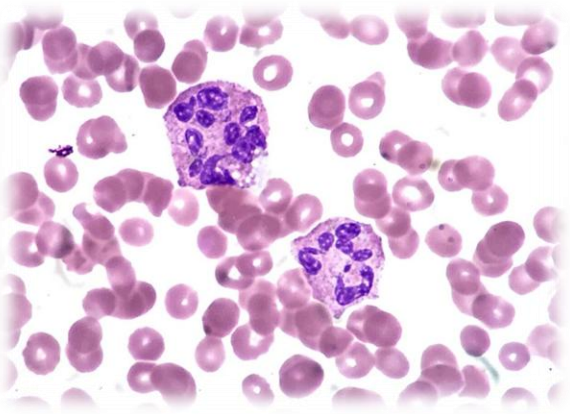


Figure-15 Hyper-segmented neutrophils indicative shift to right condition

Factors modulating the magnitude of neutrophilia in the inflammatory response:

The type of inflammation affects neutrophil balance. Acute lesions with high consumption, like cellulitis may cause mild neutrophilia or even neutropenia with a left shift. Chronic, walled-off lesions, like pyometra or abscesses, limit consumption, allowing marrow production to dominate, leading to very high neutrophil counts in dogs (up to 70,000–120,000/µL) (Thrall *et al.,* 2012).

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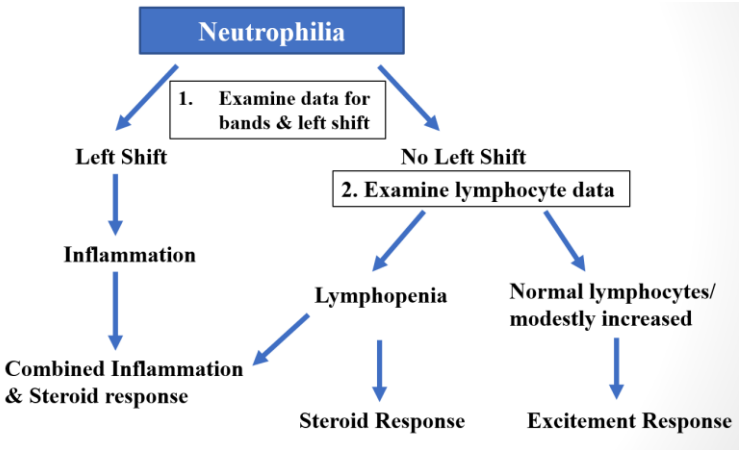
Excitement response: Epinephrine release:

The excitement response, triggered by epinephrine ("fight or flight"), increases blood flow and shifts leukocytes from the marginated to circulating pool. This doubles leukocyte counts, mainly neutrophils and lymphocytes, without a left shift. It is most notable in cats, with lymphocytosis up to ~20,000/µL (Thrall *et al.,* 2012).

Stress response: Corticosteroid release or administration:

Physiologic stress, driven by ACTH and cortisol release, occurs during illness, metabolic disturbances or pain. Common triggers include renal failure, diabetic ketoacidosis, dehydration, inflammatory diseases and trauma. In the leukogram, it typically causes lymphopenia due to steroid-induced lymphocyte apoptosis and altered recirculation. It also roughly doubles circulating neutrophils by reducing margination, which may lead to hypersegmentation. Other leukocyte changes can occur, reflecting the body's systemic response to stress and helping clinicians assess the severity and duration of the underlying condition (Thrall *et al.,* 2012).

Approach to neutrophilia



Neutropenia:

Neutropenia resulting from acute inflammatory consumption:

- Consumptive neutropenia shows a left shift and toxic changes, while immune-mediated neutropenia occurs when antibodies target neutrophils, destroying both circulating and maturing cells, often without an obvious inflammatory lesion. (Thrall *et al.,* 2012).

Neutropenia resulting from Stem Cell Injury (SCI):

- Stem cell injuries, which can be temporary or permanent, affect all marrow cell lines. Blood changes reflect injury duration: neutropenia appears first, followed by

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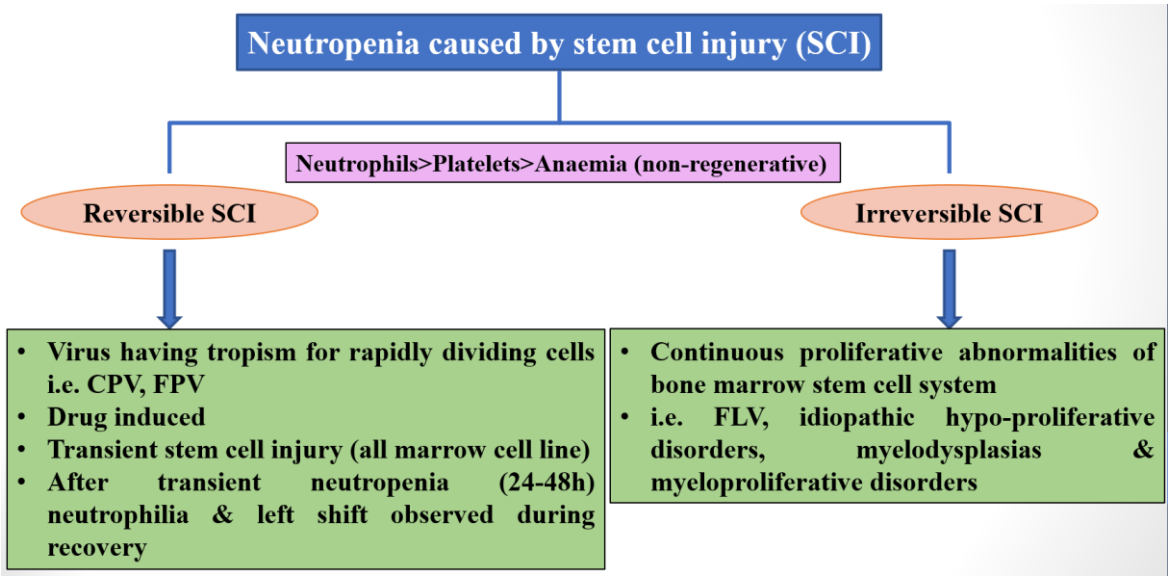
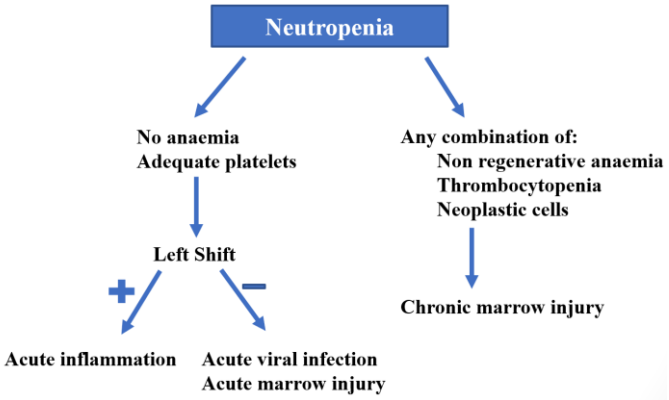
thrombocytopenia, and nonregenerative anemia occurs last due to longer erythrocyte lifespan. (Thrall *et al.,* 2012).

- Irreversible stem cell injury (See approach to neutropenia)
- Reversible stem cell injury (See approach to neutropenia)

Approach to neutropenia





Leukocyte	Dog	Cat	Horse	Cow	Sheep	Pig
Total WBC (cells/μL)	6000–17,000	5500–19,500	5500–12,500	4000–12,000	4000–12,000	11,000–22,000
Differential WBC:						
Band neutrophils (cells/μL)	0–300	0–300	0–100	0–100	0–100	0–800
Segmented neutrophils (cells/μL)	3000–11,500	2500–12,500	2700–6700	600–4000	700–6000	3200–10,000
Lymphocytes (cells/μL)	1000–5000	1500–7000	1500–5500	2500–7000	2000–9000	4500–13,000
Monocytes (cells/μL)	0–1200	0–800	0–800	0–800	0–800	200–2000
Eosinophils (cells/μL)	100–1200	0–1500	0–900	0–2400	0–1000	100–2000
Basophils (cells/μL)	Rare, 0–100	Rare, 0–100	0–200	0–200	0–300	0–400

Table-2 Reference intervals for absolute different leukocytes concentrations of common domestic animal species (Thrall *et al.*, 2012).

Certain morphological abnormalities of neutrophils may interfere with interpretation of neutrophil abnormalities in disease states as described below:

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1. Neutrophil degeneration (storage related artifacts)
2. Certain inherited abnormalities
    - Pelger-Huët anomaly (Figure-16,17)
    - Birman cat neutrophil granulation anomaly
    - Mucopolysaccharidoses (Figure-19)
    - Chédiak-higashi syndrome (Figure-18)
    - Bovine Leukocyte Adhesion Deficiency (BLAD)

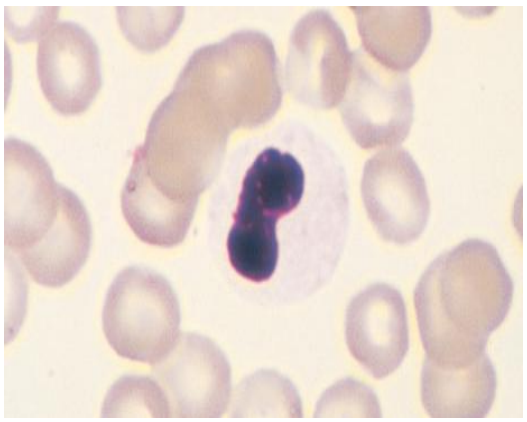

Figure-16 Pelger-Huët anomaly in Dog

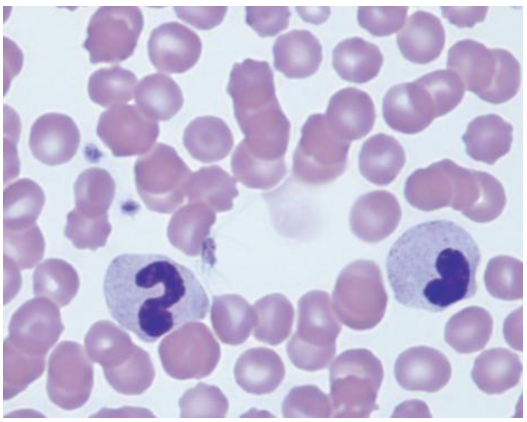

Figure-17 Pelger-Huet Anomaly, Cat

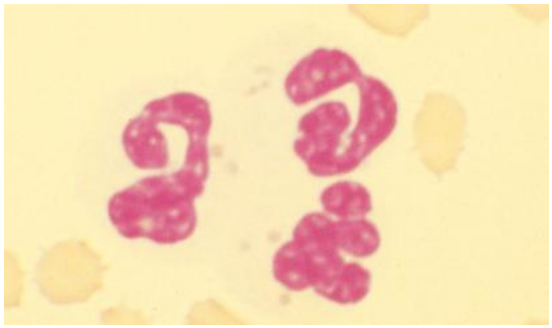

Figure-18 Chediak-higashi syndrome, Dog

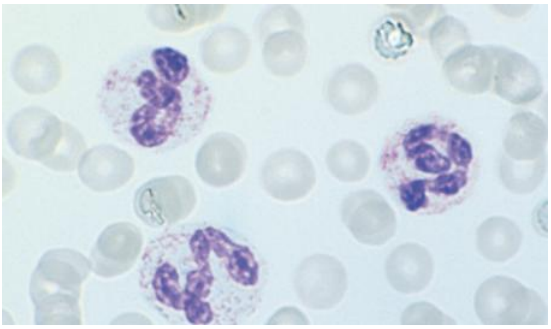

Figure-19 Cat with mucopolysaccharidosis

(Weiss & Wardrop, 2011)

3.0 TOXIC CHANGES IN NEUTROPHILS

"Toxic change" in neutrophils refers to morphologic abnormalities from accelerated bone marrow maturation, not direct bacterial toxicity. It occurs during intense neutrophil production, often due to inflammation, bone marrow recovery, or administration of hematopoietic cytokines like G-CSF. These changes can include cytoplasmic basophilia, vacuolation, and Döhle bodies, reflecting the shortened maturation time. Recognizing toxic change helps assess the severity of inflammation or bone marrow stress and can guide clinical decisions in both acute and chronic conditions (eclinpath,2023).

Most of the toxic changes reflect asynchrony of maturation between the nucleus and cytoplasm (Figure-20). During normal granulocyte maturation, the nucleus condenses and

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cytoplasmic RNA decreases, giving the cytoplasm a characteristic colour with hematologic stains. With accelerated maturation, cells may skip nuclear divisions, remain larger, and retain immature features such as abundant ribosomes, lighter chromatin, less visible granules, and frothy or vacuolated cytoplasm. These changes reflect the stress on the bone marrow to rapidly produce neutrophils and are commonly seen during severe inflammation, infection, or after administration of growth factors like G-CSF. Recognizing these features is important for assessing the severity and nature of the underlying condition (eclinpath,2023).

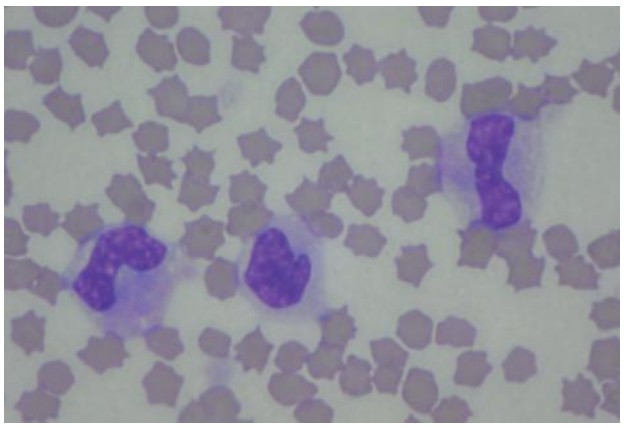
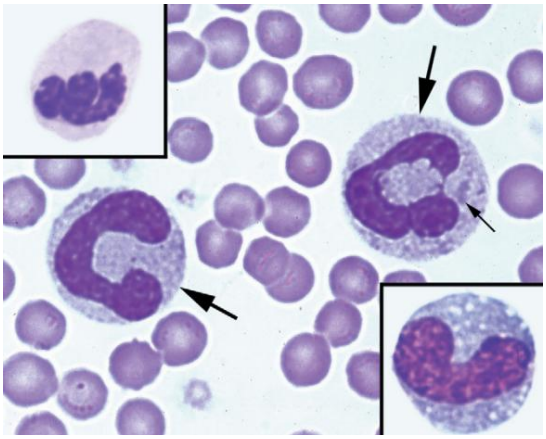


Figure-20 Equine toxic neutrophils, showing asynchrony of maturation between nucleus and cytoplasm with cytoplasmic basophilia and enlarged nucleus.



Figuure-21 Neutrophils with marked toxic change (arrows).

Toxic change usually accompanies a left shift in inflammatory leukograms, though either can occur alone. Rarely, non-inflammatory causes like marrow dysplasia or artifacts can cause toxic change. Severity of toxic change often reflects the intensity of the inflammatory stimulus (eclinpath,2023). There are certain features of toxic changes in neutrophils based on this feature we can characterize and determine level of toxic changes or magnitude of inflammatory response toxic neutrophils during blood smear examination as described below:

1. **Cytoplasmic basophilia:** A streaky diffuse irregular blue appearanceto the cytoplasm. It is due to the presence of polyribosomes and rough endoplasmic reticulum (Figure-20,21,22) (eclinpath ,2023).

2. **Döhle bodies:** Döhle bodies are pale blue cytoplasmic aggregates of rough endoplasmic reticulum and often indicate early toxic change. However, small numbers can appear in healthy cats or due to storage artifacts, so their presence alone doesn't always signify toxic change (Figure-21).

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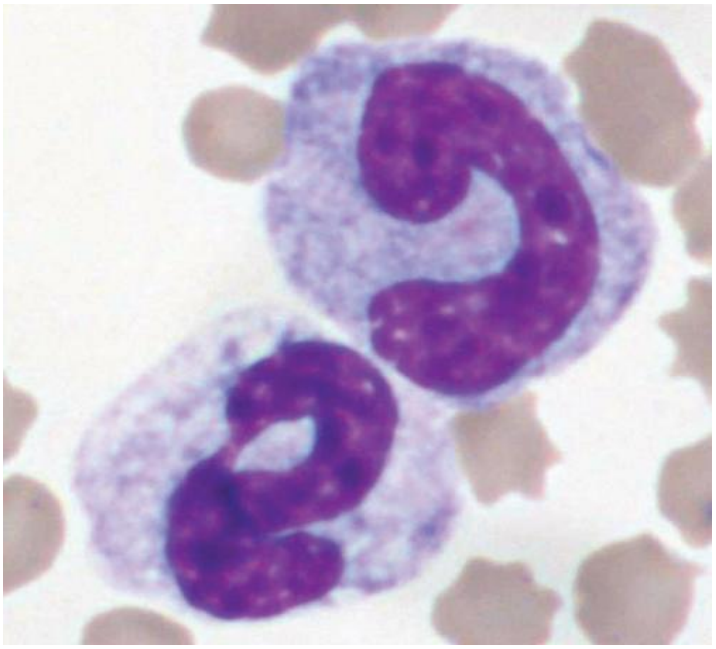

Figure-22 Toxic neutrophils from a cat with pyothorax. The dark blue (not neutral-colored) neutrophil cytoplasm indicates moderate to severe (3+) toxic change. The lower cell has indistinct clearing (lighter colored areas), indicating toxic vacuolation. Both are bands even though the lower neutrophil has a distinct narrowing of the width of the nucleus (asynchronous maturation).

3. **Cytoplasmic vacuolation**: Cytoplasmic vacuoles give a frothy appearance from lysosome degranulation. Clear punctate vacuoles are usually storage artifacts, not toxic change. (Figure-21,22,24) (eclinpath ,2023).
4. **Nuclear immaturity:** The nuclear chromatin is lighter (finer) and less coarsely clumped than normal. This is the hardest and most subtle change to see (Figure-20,22) (eclinpath ,2023).
5. **Toxic granulation:** Toxic granulation appears as distinct red cytoplasmic granules in segmented and immature neutrophils due to staining of primary granules. (Figure-23,24). The colour of these granules can range from dark purplish blue (usually) to an almost red appearance (rarely). Toxic granules are azurophilic granules normally seen in early myeloid cells but rare in bands and segmented neutrophils. They contain peroxidases and hydrolases and are most commonly caused by infection, inflammation, or sepsis, though burns, trauma, cancer, pregnancy, uremia, and myeloid growth factors can also induce them. They are most noticeable in large animals and may signal renal failure when seen with disfigured red cells. Artifacts like prolonged staining or low pH can mimic toxic granules (eclinpath ,2023; Sood, 2007).

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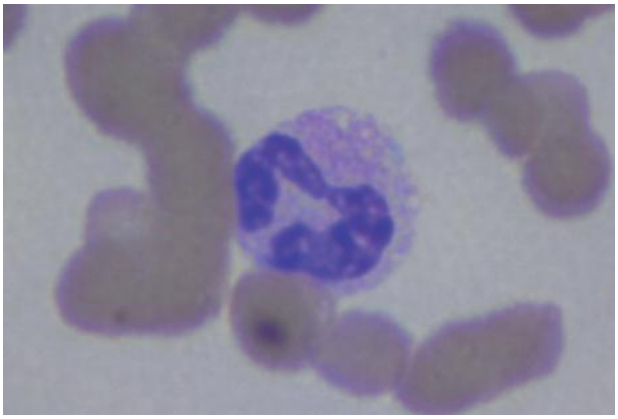

Figure-23 Equine band neutrophil showing toxic granulation.

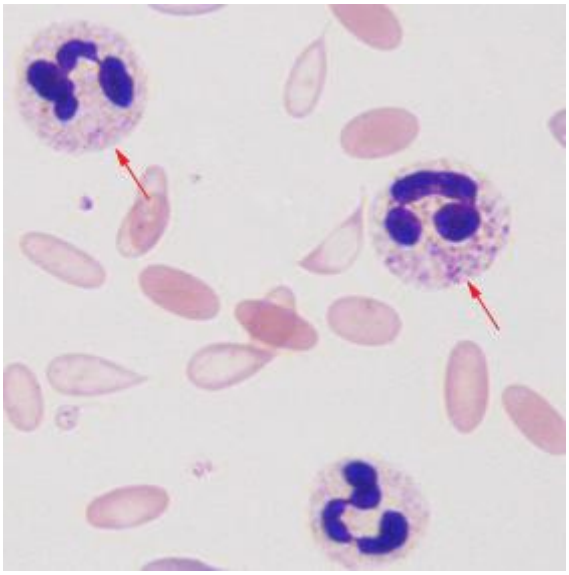

Figure-24 Alpaca blood, three segmented neutrophils are shown, all of which are toxic, demonstrating toxic granulation (upper two cells identified with the red arrows) and cytoplasmic vacuolation (all three cells).

4.0 Grading of toxic changes in neutrophils:

Toxic changes in neutrophils are graded by cytoplasmic and nuclear features, reporting both number affected and severity (mild, moderate, marked), which helps assess disease status and prognosis (Willard & Tvedten, 2011).

Table-4 Simple grading scheme for reporting appearance of toxic neutrophils:

Toxic+1	**Dohle bodies**
Toxic+2	**Dohle bodies with cytoplasmic basophilia**
Toxic+3	**Addition of large granule in cytoplasm**
Toxic+4	**Addition of vacuoles in cytoplasm**

(Willard & Tvedten, 2011)

Table-5 Grading of toxic granulation in neutrophils:

Grade	Morphology
0	Normal granulated neutrophils
1	Scattered granules in the cytoplasm with associated increase in stain intensity
2	Increased number of granules in the cytoplasm with associated increase in stain intensity
3	Numerous granules in the cytoplasm with intense blue black staining properties
4	Numerous coarse granules crowding the cytoplasm

(Tejeswini *et al*., 2012)

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Table-6 Grading of Döhle bodies in toxic neutrophils:

1-2 Döhle bodies/cell	**Mild severity**
3-4 Döhle bodies/cell	**Moderate severity**
>4 Döhle bodies/cell	**Marked severity**

(Segev *et al*., 2006)

Table-7 Criteria for grading toxic neutrophils within vacuoles:

Average number of vacuoles per Neutrophilic cell	Percent of Neutrophilic cells with cytoplasmic vacuoles	Grade
<1%	<5%	0
1 to 2	<5%	+/-
3 to 4	5 to 25%	1+
5 to 7	25.1 to 50%	2+
8 to 10	50.1 to 75%	3+
>10	>75%	4+

(Sood, 2017)

Complex grading of toxic changes in neutrophils:

Each individual type of toxic change was assigned 1 of 3 final grade scores of morphologic abnormalities: mild, moderate, or marked (scores 1, 2 and 3, respectively). The final grade of each type of toxic change was a combination of a quantitative assessment of the percentage of affected neutrophils (<10% = mild, 10–30% = moderate, >30% = marked) and a qualitative grade of the intensity of each of the individual toxic scores for each morphologic change.

Table-8 Grade of individual toxic changes in neutrophils[a] [a]Overall toxic score is the sum of all individual toxic grades (Segev *et al*., 2006)

MOPHOLOGIC CHANGE INTENSITY	Cells Affected With Change		
	<10%	10%-30%	>30%
Döhle bodies			
Mild	1	1	1
Moderate	1	1	2
Marked	2	2	3
Cytoplasmic basophilia			
Mild	1	1	2
Moderate	2	2	3
Marked	2	3	3
Cytoplasmic vacuolation			
Mild	1	1	2
Moderate	2	2	3
Marked	2	3	3
Giant toxic neutrophils	3	3	3

Mild overall neutrophil toxic change included a sum of scores of **1–6**. **Moderate** toxic change included a total score of **7–12**, whereas a total score **>12** was classified as **marked** toxic change

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Serial inflammatory leukogram findings and the interpretation for determining prognosis:

For an interpretation all you to need 3 things,

1. Number of absolute neutrophil counts with regards to species
2. Magnitude of left shift
3. Severity of toxic changes in neutrophils with regards to number of cells affected

Leukogram findings	Favourable prognostic sign	Unfavourable prognostic sign
Neutropenia	Increase in absolute neutrophil count	Continued neutropenia Development of grater left shift Development of toxic changes
Regenerative left shift	Decrease or lack of band cells Normal neutrophils count	Continued left shift along with neutropenia
Degenerative left shift	Increase in segmented neutrophils Decrease or lack of band neutrophils	Continued degenerative left shift
Toxic changes	Resolution of toxic changes Mature neutrophils are toxic & band cells are normal	Continued toxic changes Bands are toxic & matures are normal
Concurrent lymphopenia	Increase in absolute lymphocyte count	Continued lymphopenia

6.0 Conclusions:

Neutrophils are the major arm of innate immune response and soldier cells of the body. Through various cytotoxic mechanisms neutrophils kills the microbes and helpful to resolving the disease condition. In response to disease/inflammatory/physiological condition, there is alteration in kinetics occurs which will helpful for interpretation of leukogram. Development of acquired morphological abnormalities like toxic changes in neutrophils occurs depends on severity of disease conditions. Interpretation of toxic changes will be helpful for determining the disease status. Resolution of toxic change in neutrophils after appropriate treatment of the underlying disease is a favorable prognostic indicator in animals. The simple blood smear examination is very useful when severity of disease condition is unknown, especially in emergency medicine.

7.0 Future prospects:

More studies of clinical relevance to toxic changes and association with disease conditions in multiple species is required and standardization of toxic grading for a neutrophil in different species is also required.

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