

Leukocytosis and Leukopenia

Gary J. Kociba, DVM, PhD

Diplomate ACVP

Professor of Clinical Pathology

Department of Veterinary Biosciences

College of Veterinary Medicine

The Ohio State University

Columbus, Ohio 43210

KEY WORDS

- neutrophil kinetics
- leukocyte responses
- neutrophils
- leukocytes
- eosinophils
- monocytes
- basophils

GRANULOCYTE PRODUCTION AND KINETICS

Granulopoiesis follows the same pattern for neutrophils, eosinophils, and basophils, but neutrophils are the predominate granulocytic cell in the marrow. The proliferation, differentiation, and maturation steps from a myeloblast to a segmented granulocyte take about 6 days in dogs.¹ The neutrophils in the marrow compartment often are divided into two compartments for interpretive purposes: (1) the proliferating pool, which consists of myeloblasts, progranulocytes, and myelocytes, and (2) the maturation and storage pool, which contains the nondividing granulocytes including metamyelocytes, bands, and segmented cells. The pool of granulocytes in the marrow of a normal dog represents about a 5 day supply of neutrophils under steady-state conditions. Release from the marrow compartment favors the most differentiated cells. Therefore segmented neutrophils are preferentially released over bands or metamyelocytes; this is an advantage because segmented neutrophils are more effective at phagocytosis and killing of bacteria than are less mature cells. Granulopoiesis can be markedly increased during inflammatory diseases.

GENERAL RESPONSES OF NEUTROPHILS¹⁻³

The neutrophils in the blood either are in the axial blood flow (circulating pool) or are loosely associated with the walls of blood vessels (marginated pool). In normal dogs the marginated pool is about equal in size to the circulating pool, whereas in cats the marginated pool is two to three times larger than the

circulating pool. When blood samples are collected for hemograms, the circulating pool is the only granulocyte compartment that is directly sampled. Based on data from the circulating pool and knowledge of leukocyte responses and the disease processes, predictions are made about the likely changes in other granulocyte compartments. A schematic presentation of changes in these granulocyte compartments associated with physiologic leukocytosis and with inflammatory disease is presented in Figure 1. It is important to recognize that neutrophils spend only a short time in the bloodstream (half-life of about 7 hours). Neutrophils do not reenter the bloodstream from the tissues.

Neutrophilia

In inflammatory diseases, neutrophils are released from the bone marrow at an increased rate. As the release rate increases, band neutrophils also are released, creating a left shift. In general, the degree of left shift is proportional to the inflammatory stimulus. The total neutrophil count reflects a combination of factors including bone marrow reserves, the egress rate from the vascular compartment, the severity of the stimulus, and the size and distribution of the inflammatory lesions. A regenerative left shift refers to a leukocytosis with an increase in immature neutrophils and more segmented neutrophils than immature neutrophils. A degenerative left shift refers to a condition with a decreasing leukocyte count and a greater number of immature neutrophils than segmented neutrophils in the blood. Usually the leukocyte count is normal to subnormal in degenerative left shifts, reflecting a depletion of reserves of granulocytes in the marrow. In small animals the following general guidelines can be applied to interpretation of neutrophilic responses in animals with left shifts:

- Immature neutrophils <5%—Normal
- Immature neutrophils 5% to 25%—Inflammatory response
- Immature neutrophils 25% to 50%—Marked inflammation
- Immature neutrophils >50%—Guarded to poor prognosis

Stress Leukogram

Most animals develop a consistent set of changes in leukocytes under the influence of increased glucocorticoids of either exogenous or endogenous sources.

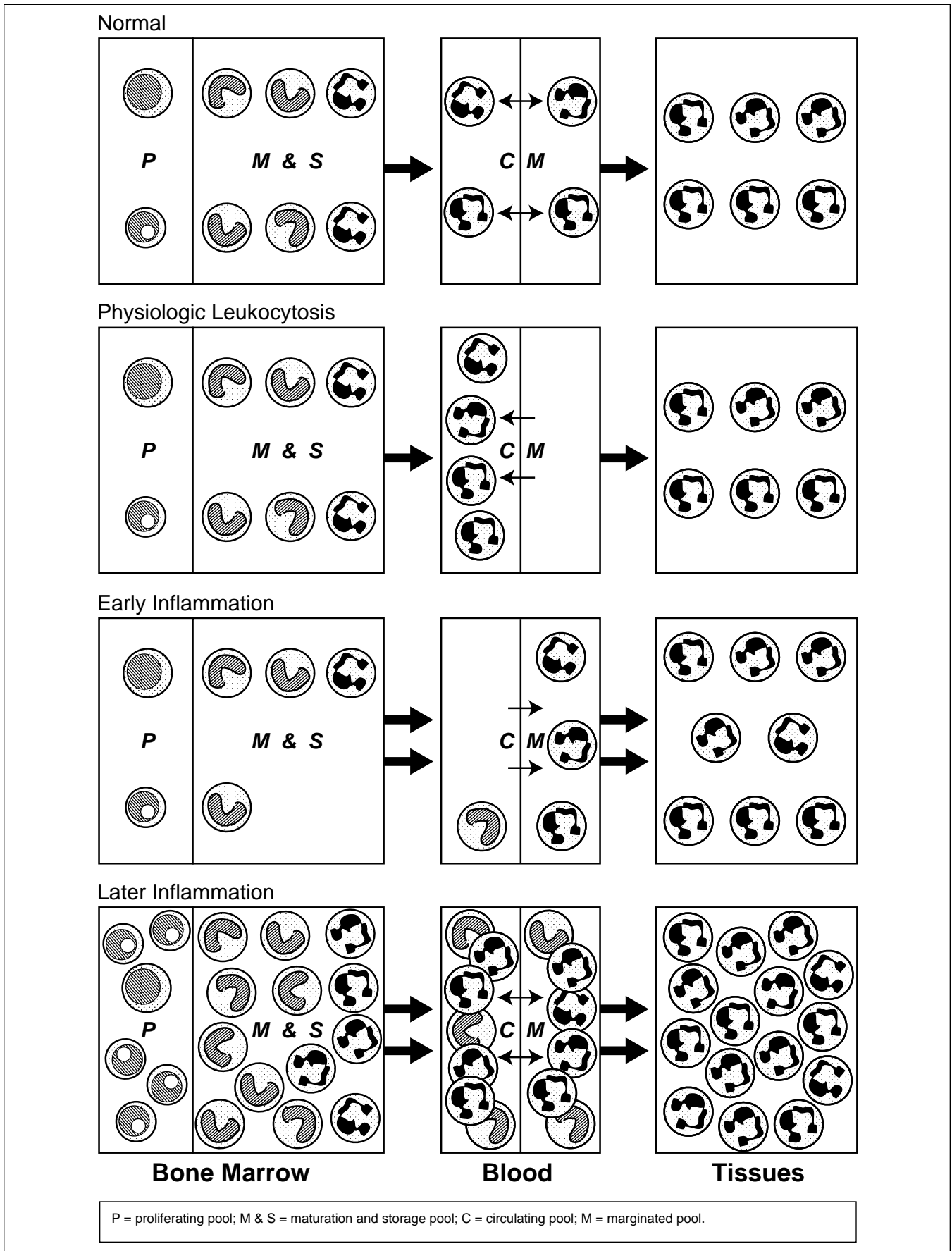


Figure 1. Representative responses of neutrophils.

The expected changes include a neutrophilia without a left shift, lymphopenia, and low or absent eosinophils. In dogs but usually not in cats, monocytosis also occurs under steroid influence. The neutrophilia is related to the release of neutrophils from the marrow with a prolongation of the circulation time. The neutrophilia does not impart greater resistance to infections because the cells have inhibited functions. Lymphopenia is related to steroid-induced apoptosis and redistribution of lymphocytes. The eosinopenia is related to decreased stimuli of release of eosinophils from the marrow.

It is important to note that steroid-induced lymphopenia and decreased eosinophils often are found in association with inflammatory responses, which results in the combination of neutrophilia with a left shift and monocytosis with lymphopenia and eosinopenia.

Morphologic Abnormalities in Neutrophils

Under conditions of enhanced neutrophil turnover rate, a number of morphologic abnormalities may occur in neutrophils. These include Döhle bodies, cytoplasmic vacuolation and basophilia, toxic granulation, and giant neutrophils. Most if not all of these changes reflect intense marrow stimulation and shortened maturation times in the marrow. Döhle bodies (pale blue-gray bodies in the cytoplasm) represent crystalline arrays of endoplasmic reticulum. They are more frequent and less significant in cats because they are seen in even some minor inflammatory responses. Cytoplasmic basophilia is seen in conditions with enhanced neutrophil turnover. The intense stimulation of granulopoiesis results in the release of cells with increased residual cytoplasmic RNA imparting the basophilia. Toxic granulation is relatively rare in small animals and represents retention of the blue-purple staining of primary granules formed in the progranulocyte stage. Giant forms of neutrophils are sometimes seen in the recovery stage of diseases that caused previous destruction of marrow precursors and represent cells that skipped a mitotic division. Overall, these morphologic abnormalities should be interpreted as evidence of enhanced neutrophil turnover rate, which usually correlates with severe inflammatory disease. A combination of these changes may suggest more severe disease.

Neutropenia

Neutrophils are decreased in the early stages of a variety of inflammatory diseases, but neutropenia usually is not recognized in this phase because it is a very transient change that occurs before animals are pre-

sented for evaluation. Neutropenias can be related to either increased egress from the blood in inflammatory disease, decreased production due to injury to marrow precursors, or increased destruction due to immune-mediated processes. In diseases with depletion of marrow reserves, a degenerative left shift is associated with the neutropenia and is a bad prognostic sign. Neutropenia is a part of the pancytopenia seen with parvovirus infection related to the destruction of granulocytic precursors in the marrow. If the dog or cat recovers from parvovirus infection, neutrophilia in the blood and granulocytic hyperplasia in the marrow develop within 1 week. In the recovery phase, a large left shift with release of atypical cells may be seen as the marrow is maximally stimulated to produce granulocytes. Neutrophilic precursors have a high replicative rate, which makes them susceptible to many cytotoxic anticancer agents. When neutrophil counts dip below 500/ μ l in the blood of animals on chemotherapy, consideration must be given to stopping treatment or lowering the dose until neutrophil numbers increase. If neutropenia is of unknown cause and persists for over 1 week, bone marrow biopsy is recommended to evaluate for aplastic anemia, leukemic infiltrates, or myeloproliferative diseases. Idiopathic neutropenias may be asymptomatic in some animals. If recurrent infections accompany the neutropenia, a careful search for causes is warranted. If none is found, the remote possibility of immune-mediated neutropenia should be considered. If a therapeutic trial with immunosuppressive doses of glucocorticoids is considered for an animal with neutropenia, it should be noted that steroid inhibition of leukocyte function may predispose to infectious diseases.

Lymphocytes

One distinct difference in lymphocyte kinetics is the fact that lymphocytes, especially T-lymphocytes, are recirculated. Changes in lymphocyte concentration in the blood may reflect variations in production, recirculation, or destruction. Cells with morphologic characteristics of lymphocytes include those with a wide variety of functions in the immune system.

Lymphocytosis may be associated with immune responses, especially those associated with chronic immune stimulation. The increases usually are modest, although marked increases occasionally occur in young animals. Reactive lymphocytes with deeply basophilic nongranular cytoplasm and larger nuclei with fine chromatin are commonly associated with immune-stimulating diseases. Blood parasites and other protozoan diseases may be associated with lymphocytosis. The increased lymphocytes appear to be sec-

ondary to the immune stimulation from the persistent organisms. Variable increases in small lymphocytes occur with chronic lymphocytic leukemia. Lymphocyte counts between 8,000 and 20,000/ μ l are difficult to interpret because tests for clonality of the population or specific markers are not widely available; retesting in a few weeks is warranted because reactive lymphocytosis related to immune stimulation frequently is transient. Lymphocyte concentrations in excess of 20,000/ μ l in which the small lymphocytes account for more than 90% are compatible with chronic lymphocytic leukemia.

Lymphopenia most frequently reflects apoptosis and redistribution of lymphocytes in response to increased concentrations of endogenous or exogenous glucocorticoids. In animals with a variety of diseases, this is a nonspecific change related to the stress response. Viruses such as distemper virus, parvovirus, or infectious canine hepatitis virus that infect lymphocytes may induce lymphopenia by direct injury of lymphopoietic cells.

Eosinophils

Eosinophilia usually develops in subacute or chronic diseases associated with increased degranulation of mast cells. The causes are diverse and include parasitic diseases, some allergies, and a variety of tissue injuries. The degree of eosinophilia appears to be related more to the individual responsiveness of an animal and the specific agent rather than to parasitic load or the degree of tissue injury. Eosinophilic responses in German shepherd dogs are often more dramatic than in other breeds.

Eosinopenia is difficult to define because most reference ranges for dogs and cats extend to zero. Most commonly, eosinopenia is used in the description of hemograms with no eosinophils as part of a stress leukogram. Corticosteroid hormones inhibit the release of histamine from mast cells, thereby decreasing the stimuli for release of eosinophils from the marrow. The number of eosinophils is decreased nonspecifically in many acute infections, reflecting corticosteroid and catecholamine effects.

Basophils

Basophils are present in very low numbers or are absent in the blood of normal dogs and cats. Basophil-

ia is most often seen in association with eosinophilia. Basophils appear to be important in the induction of immediate hypersensitivity reactions or responses to parasites or allergens. Basophilia also is sometimes associated with the presence of a mast cell tumor, although the connection between the two is not apparent. Basopenia is not a defined entity because many normal animals have no basophils.

Monocytes

Monocytes are important cells involved in the phagocytosis and killing of bacteria, viruses, fungi, and protozoa. In the tissues, monocytes differentiate into free or fixed macrophages of the mononuclear phagocyte system. They are important scavengers of damaged cells and particulate debris. Macrophages derived from monocytes also play important roles in immune responses, regulation of inflammation, and regulation of hematopoiesis. Monocytosis frequently is associated with chronic inflammatory diseases, but it should be recognized that monocytosis can occur within hours as an early change in the same diseases that cause neutrophilia.

PROGNOSTIC INDICATORS

A degenerative left shift characterized by a decreasing leukocyte count and a majority of immature neutrophils indicates depletion of marrow reserves and is a grave prognostic sign. Although less reliable, neutrophil counts greater than 100,000/ μ l in dogs or cats raise concern because they suggest severe inflammatory disease with prolonged stimulation of granulopoiesis resulting in granulocytic hyperplasia in the bone marrow.

In inflammatory diseases, a decreasing left shift indicates decreased stimuli for release of neutrophils from the marrow and is a positive sign. Rising lymphocyte and eosinophil counts in convalescence are good prognostic signs indicating decreasing steroid release from the adrenal glands.

REFERENCES

1. Jain NC: *Essentials of Veterinary Hematology*. Philadelphia, Lea & Febiger, 1993, pp 222–307.
2. Duncan JR, Prasse KW, Mahaffey EA: *Veterinary Laboratory Medicine*, ed 3. Ames, IA, Iowa State University, 1994, pp 37–62.
3. Meyer DT, Coles EH, Rich LJ: *Veterinary Laboratory Medicine: Interpretation and Diagnosis*. Philadelphia, WB Saunders, 1992, pp 27–41.