Leukocyte Response in the Dog and Cat

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INTRODUCTION

The total and differential leukocyte counts are the tests used in monitoring the leukocyte numbers and proportions in large vessel peripheral blood. Knowledge of leukocyte origin, function, and transitory presence in the peripheral blood is imperative when evaluating change in white blood cell and differential counts. Proper interpretation of these changes will aid in revealing the true nature of the physiological or pathological state of the animal.

THE NEUTROPHIL

The neutrophil originates from the stem cell in bone marrow. The stages in the development of the neutrophil which are capable of mitotic division include the myeloblast, progranulocyte, and myelocyte. Neutrophilic characteristics can be differentiated at the myelocyte stage. The remaining non-mitotic stages, the metamyelocyte, band and segmented neutrophil make up the bone marrow reserve pool. This pool opens into the circulation during periods of increased tissue demand for neutrophils. Release from the bone marrow is an orderly process according to the age of the developing neutrophils, with the oldest cells being released first. The time they spend in the circulation is of varying length, but the half-life in the normal individual is between 6–7 hours. Movement of neutrophils into tissue is a normal and constant process and is random with respect to age of the cells. In other words, any age neutrophil can move into the tissue at anytime.

The neutrophil functions in injured tissue, and the transitory presence of neutrophils in the blood should be viewed as a means of transportation of neutrophils from the bone marrow to the tissue in which they function. Neutrophils function in the defense of the body against particulate material through the process of phagocytosis. The neutrophils ability to marginate along the walls of small vessels, respond to chemotactic stimuli, and migrate into tissue is vital to its function.

The total blood neutrophil pool consists of cells in a circulating pool and a marginal pool. Neutrophils in the circulating pool are those encountered in a total and differential leukocyte count, whereas, those in the marginal pool comprise an additional number of cells in the blood circulation. The neutrophils in the marginal pool are found lining the vascular system and sequestered in collapsed capillary beds.

Under the influence of an inflammatory disease, the tissue demand for neutrophils will be observed by changes in the white blood cell and differential counts. The total number of neutrophils summoned by the tissue will reflect the intensity of the disease, and the types of neutrophils responding to the tissue demand will indicate the severity of the disease. It is important to remember that there are certain non-inflammatory diseases and physiological processes which also cause changes in the neutrophil numbers and types.
THE EOSINOPHIL

The eosinophil has the same stem cell as the neutrophil and can likewise be differentiated at the myelocyte stage. Eosinophils serve an antihistaminic function and are attracted to tissue into which histamine has been released. Following insult to tissue and the release of histamine, the eosinophil migrates from the blood into the tissue, and the effect on white blood cell and differential counts will be a reduction in eosinophils. If histamine release should be great enough to spill into the blood, the eosinophils in the bone marrow will be attracted into the circulation. Subsequently, there will be an increase in the number of circulating eosinophils. Diseases involving tissues high in histamine will usually cause an increase in the number of circulating eosinophils.

THE LYMPHOCYTE

The lymphocyte originates from lymphoid tissue, primarily lymph nodes, spleen, thymus and scattered lymphocytic foci. Lymphocytes are capable of producing antibodies, thereby accounting for their gamma globulin rich cytoplasm. Unlike the neutrophil, which perishes in tissue, the lymphocyte recirculates between lymph, blood and tissue so that the lifetime of lymphocytes is many times longer than that of neutrophils. The number of lymphocytes in the blood reflects the number in the tissue as well as the activity and state of the lymphoid tissue in general.

SIGNIFICANCE OF BLOOD VALUE CHANGES—NEUTROPHIL

Physiological neutrophilic leukocytosis is a condition characterized by a rise in circulating neutrophils, without the associated tissue demand for neutrophils. Any stressful condition, excitement, exercise, acute illness, trauma or shock, can precipitate physiological leukocytosis. With the onset of stress the pituitary-adrenal axis is stimulated, the resultant effect being the release of corticosteroid from the adrenal gland. Corticosteroids cause marginated cells to circulate, impede the random loss of neutrophils from the blood to tissue and impair the function of the neutrophil. The functional impairment occurs because of stabilization of lysozymal membranes. Therefore, with respect to the total and differential leukocyte count, corticosteroids produce a neutrophilic leukocytosis.

Physiological leukocytosis is more easily elicited in the cat than in the dog. Strange surroundings can cause a leukocyte count increase of about 2000 cells above the normal range, with the typical picture being one of neutrophilia with a left shift. However, in a diseased cat, physiological leukocytosis is less apt to occur. It is felt that illness alone can alter the cat's attitude toward strange surroundings, thus minimizing excitement and stress which precipitates the physiological leukocytosis. Physiologic neutrophilia is also observed with exogenous corticosteroids and in hyperadrenal-corticism.

The effect of corticosteroids on leukocyte counts is illustrated in Figure 1.

Non-infectious diseases exhibit a neutrophilia resulting from the demand of the tissue for neutrophilic phagocytic function due to aseptic cellular damage. Pyrogenic irritation to tissue caused by breakdown products of hemoglobin, as seen in hemolytic anemias such as autoimmune hemolytic anemia (AIHA), creates a tissue demand for neutrophils. Other examples of non-infectious neutrophilia are secondary necrosis in malignant neoplasia and cellular damage due to the toxic end products of uremia. The stimulating factor for the neutrophil response is the tissue demand for the phagocytic function of the neutrophil.

Non-viral infectious diseases caused by
bacteria, fungi and other tissue parasites cause injury to tissue and set in motion the mechanism leading to neutrophilic demand. Experimentally it has been shown that early in an infectious process the movement of neutrophils into the tissue is very rapid and that the time interval spent in the blood is shortened. This fact coupled with the less than maximum efflux of neutrophils from the bone marrow would result in numbers of neutrophils slightly above or below the normal values. As the course of the infection proceeds, the bone marrow releases cells at a higher rate, resulting in neutrophilic leukocytosis and a left shift. Then, as the infection stabilizes, the tissue demand for neutrophils is less acute and they remain in the blood for a longer period of time before moving into the tissue. The result is that once past the early acute part of the infectious process, the neutrophil count in the blood will be higher than initially in the infection. As the infectious process moves toward convalescence, there is less need for neutrophils in the tissue and bone marrow release declines. The neutrophil count will then decrease toward normal. An example would be the marked neutrophilia observed with localization and pus formation due to a bacterial infection. Before encapsulation the tissue demand is great, but with encapsulation completed, the count will tend to fall.
If the infectious process progresses to a long chronic suppurative disease, a neutrophilic response occurs, which is illustrated in Figure 2.

The areas of chief diagnostic dilemma are those on each side of the peak of neutrophilic response. Both exhibit a neutrophilia with a left shift, but it is difficult to tell that the area to the right of the peak is actually tending toward bone marrow exhaustion, and in time will become a shift to the right. In this situation, one must rely on knowledge of the longevity of the disease.

The effect of bacterial endotoxins from gram negative organisms is one of an initial neutropenia. Neutrophils in the circulating pool become sequestered in the marginal pool adding to an endotoxic shock syndrome. Eight to 12 hours following initial insult the neutrophils redistribute and the bone marrow also responds leading to a neutrophilia. In overwhelming septicemic conditions there is usually no leukocytosis and often a degenerative left shift. This results from the inability of the bone marrow to put forth a large number of mature cells, and the rapid utilization of the cells in the septicemia.

Of special interest in the feline species as reported by Schalm, is that a significant number of adult cats with a history of infectious or suppurative disease exhibit a neutropenia with a degenerative left shift. The morphological appearance of the neutrophils is abnormal. Studies have shown that the cause is probably an interference in the maturation of the neutrophil. Arrest of maturation of the cytoplasm, indicated by increased basophilia, and continued growth of the nucleus yields cells with bizarre nuclear patterns. With less severe interference of maturation of the cytoplasm, the cells appear as large band forms with foamy cytoplasm. Still less maturation interference results in large angular blush bodies in the cytoplasm, Doehle Bodies. These phenomena are referred to as toxic granulopoiesis and toxic granulation respectively and are indicative of toxemia. Similar toxic changes in the canine neutrophil produce cells with a "moth-eaten," vacuolated cytoplasm. Other than those variations cited, feline responses are similar to those of canine.

Viral diseases characteristically exhibit a neutropenia and consequently a leukopenia. The neutropenia occurs during the viremic stage of the disease. With the exception of feline panleukopenia, the mechanism of the neutropenia is unknown. In panleukopenia, the neutropenia is due to the insult of the virus on the granulopoietic tissue, and its subsequent mitotic depression. In a viral disease such as canine distemper, neutropenia occurs during the viremic stage, but with the recovery of the granulopoietic tissue and the stimulation by secondary bacterial invaders, the neutrophil response parallels that of non-viral infectious disease.

Except for certain physiological processes, the neutrophil response monitored by total and differential WBC counts is a manifestation of the tissue demand for the need of the neutrophilic function. The total number of neutrophils responding is an indication of the intensity of the process, and the type of neutrophilic shift points to the severity and longevity of the process.

**SIGNIFICANCE OF BLOOD VALUE CHANGES—EOSINOPHIL**

Eosinopenia occurs in a majority of stressful disease states. The eosinophil has an antihistaminic function and responds to the presence of histamine in the tissue and blood. Corticosteroids, whether endogenously secreted in stress or exogenously administered, also have an antihistaminic effect. Therefore, the antihistaminic effect of the corticosteroid which removes the histamine stimulus for the eosinophil, plus the short life of an eosinophil in the blood, explains the eosinopenia observed in stressful situations. If histamine levels in the blood are greater than the corticosteroid can neutralize, the stimulus for drawing eosinophils from the bone marrow exists and an eosinophilia develops. Tissue such as skin, subcutaneous tissue, pleura, lungs, mesentery, scrotum, uterus, thymus and liver are high in histamine content, and cell damage in these tissues...
results in the release of large quantities of histamine into the tissues and circulation, which in turn causes local and circulating eosinophilia.

The presence of an eosinophilia during a stressful situation is a grave prognostic sign. It indicates that more histamine is being released from damaged tissue than the endogenous corticosteroid can neutralize. It also indicates that the body defenses are not being successful in localizing the condition and that additional tissue insult is occurring. The release of histamine in allergic reactions and sensitization reactions to parasitic proteins commonly results in an eosinophilia, however only those parasitisms with prolonged parasite-tissue contact will produce this reaction.

**SIGNIFICANCE OF BLOOD VALUE CHANGES—LYMPHOCYTE**

Circulating lymphocyte numbers in stressful diseases decline, (figure 1). This reflects the state of generalized lymphoid depletion of tissues in disease. The cause of the decrease in lymphocyte numbers is the presence of corticosteroid, endogenous or exogenous, which causes lysis of the lymphocyte and subsequent release of its gamma globulin rich cytoplasm into the circulation. The effect of the corticosteroid on the lymphoid tissue is characterized by depletion and mitotic inhibition. With the passage of the stressful condition the effect of the corticosteroid is decreased and lymphoid activity resumes, followed by a rise in the lymphocyte numbers. Stress caused by any severe disease which is not overcome by body defenses will result in a continued corticosteroid secretion and a prolonged period of lymphopenia. This persistent lymphopenia is a poor prognostic sign.

In a situation of prolonged stress and pituitary-adrenal stimulation, adrenal insufficiency may develop. The decrease in lympholytic corticosteroid would allow a rise in activity of lymphoid tissue and the lymphocyte count would begin to rise. The rise in lymphocyte numbers in a clinically stressed animal is a good indication of adrenal insufficiency and is viewed as a poor prognostic sign. An increasing lymphocyte count in an animal which does not appear clinically stressed is indicative of a condition moving to chronicity or the state of convalescence.

An absolute increase in circulating lymphocyte numbers is uncommon. Only in lymphosarcoma and hypoadrenal corticism will an absolute increase occur. In the dog with lymphosarcoma there is usually no increase in cell numbers or presence of leukemic cells until terminally. In the lymphosarcoma cat, two thirds of the cases are leukemic with high numbers of lymphocytes, or the numbers are normal in a severely stressed cat which should have reduced numbers.

**SUMMARY**

The use of white blood cell and differential counts should be viewed as an adjunct to history, clinical signs and other diagnostic procedures. Rarely are they diagnostic in themselves. A knowledge of leukocyte origin, function and movement in the body is mandatory for maximum utilization of total and differential leukocyte counts in diagnostic and prognostic logic.

**REFERENCES**