A SURVEY OF FELINE ANEMIAS

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ABSTRACT

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By

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Thirty anemic cats which were patients at the Michigan State University Veterinary Clinical Center were surveyed. These animals varied in age from 10 weeks to 12 years, and several breeds were represented. The causes and pathogenesis of the anemias were studied utilizing a series of hematologic tests, blood chemistry determinations, urinalysis and fecal analyses, cytologic examinations, and histopathology.

The majority (73.3%) of animals studied were positive for the feline leukemia virus. Many of these animals had evidence of erythrocytic regeneration in peripheral blood, increased absolute reticulocyte numbers, and elevated reticulocyte indexes, but the anemias were usually progressive in nature and refractory to treatment. Necropsy results indicated that many of these animals had gross and microscopic lesions consistent with the feline leukemia complex, including both lymphosarcoma and the myeloproliferative disorders. Erythroid hypoplasia and neoplastic cell infiltration were common observations in bone marrows of these cats.

Other causes of anemia in these animals included autoimmune hemolytic anemia, chronic viral and bacterial infections, renal

disease, liver disease, hemobartonellosis, and the non-neoplastic anemias associated with the feline leukemia virus.

Only 4 of the 30 anemic cats recovered, which is characteristic of the poor prognosis associated with anemia in the cat.

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By

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INTRODUCTION AND OBJECTIVES

Anemia is a common phenomenon observed frequently in cats. The etiology and pathogenesis of anemia in the feline species often presents a diagnostic challenge. There is frequently an insidious course, and the routine diagnostic tests do not always identify the cause. As a result, many cases of feline anemia remain unexplained.

The objectives of this research project are the following:

1) To survey the causes of anemia in the feline species by studying 30 anemic cats which have been admitted to the MSU Veterinary Clinical Center.

2) To elucidate the pathogenesis of anemia and its severity utilizing the following tests: hematologic studies, blood chemistry determinations, urinalysis and fecal analyses, cytologic examinations, and necropsy and histopathology.

3) To classify the regenerative response to anemia in the cat in cases of anemias which are associated with the feline leukemia complex.

4) To correlate the results of the fluorescent antibody test for the feline leukemia virus with hematologic findings, necropsy results, and the Coombs test.

5) To acquire knowledge in the area of feline hematology.

REVIEW OF LITERATURE

Definition and Classification of Anemias

Anemia may be defined as a reduction below normal in the number of erythrocytes, hemoglobin concentration, or packed cell volume in circulating blood (Benjamin, 1961). In domestic animals, anemia is seldom a primary condition, but most often is a secondary response following or associated with disease conditions (Coles, 1974).

Anemias may be classified in several ways. The morphologic classification of anemia represents an estimation of alterations in size and hemoglobin concentration of individual erythrocytes, but has little reference to the precise cause of anemia (Coles, 1974). However, general conclusions as to the etiology of the anemia may be drawn by means of this classification system (Loeb, 1964; Medway et al., 1969). The macrocytic and microcytic anemias are clearly disorders of production; the normocytic comprise a large group of hematologic diseases which include bone marrow failure (Switzer, 1971a).

A physiologic classification of anemia may also be employed. Here, the anemias are divided into two general classes: regenerative vs. nonregenerative anemias (Tasker, 1966). The regenerative anemias are most commonly observed with hemorrhage or hemolysis (Schalm et al., 1975).

An etiologic classification of anemia can also be made. Four general categories may be considered: (1) blood loss, either acute

or chronic; (2) excessive destruction of red blood cells or shortened erythrocytic lifespan; (3) depression of bone marrow; and (4) nutritional deficiencies (Coles, 1974). However, a combination of factors may be involved in the development of anemia (Schalm et al., 1975).

Causes and Differential Diagnoses of Anemia in the Feline Species

Of all the domestic animals, cats suffer most often and most severely from anemia (Holzworth, 1956). There are many causes of anemia in this species which have been widely reported in the literature. The differential diagnosis of anemia in the cat may be difficult due to this variety of causes (Holzworth, 1956; Schalm et al., 1975).

Blood Loss

As in other species, blood loss is a cause of anemia in the cat (Medway et al., 1969). Hemorrhage may occur as a sequela to injuries, surgery, or bleeding tumors, but this is observed less frequently in cats than in dogs (Holzworth, 1956; Loeb, 1964; Gilmore and Holzworth, 1969). The packed cell volume will reach the low point 24 to 48 hours after acute hemorrhage, and it requires 3 to 4 days before the anemia appears regenerative. There may also be thrombocytosis and neutrophilic leukocytosis (Holzworth, 1956; Loeb, 1964; Schalm et al., 1975). Chronic hemorrhage may also lead to anemia, and may be caused by parasitic infestations, enteritis, ulcers, or neoplasms (Benjamin, 1961). Iron deficiency may develop as a result of chronic hemorrhage, and may be manifested as microcytic, hypochromic anemia (Davidsohn and Henry, 1969; Benjamin, 1961). Reduced plasma protein concentration usually accompanies chronic hemorrhage (Schalm, 1970).

Hemolysis and Decreased Lifespan of Erythrocytes

Anemias due to excessive destruction of red blood cells and decreased red cell lifespan also occur in the cat.

Hemobartonellosis. The most important anemia in the hemolytic category is caused by *Hemobartonella felis* (Flint and McKelvie, 1955; Holzworth, 1956; Schwartzman and Besch, 1958; Flint et al., 1959; Seamer and Douglas, 1959; Benjamin, 1961; Manusu, 1962; Gilmore and Holzworth, 1969; Switzer, 1971a,b; Norsworthy, 1976). Holzworth (1956) found 25% of 120 cases of feline anemia which gave positive results for *H. felis*. Schalm and Smith (1963) observed *H. felis* organisms in 20% of 60 cases of feline anemia. These authors also postulated that this organism may be associated with an even greater percentage of feline anemias due to the difficulty of making a specific diagnosis when the anemia is in the advanced stage. Loeb (1964) stated that *H. felis* may be associated with as many as 50% of the cases of feline anemia.

Hemobartonellosis often occurs in conjunction with other diseases (Flint et al., 1958; Seamer and Douglas, 1959; Manusu, 1962; Wilkinson, 1969; Switzer, 1971b; Schechter et al., 1973). Holzworth (1956) reported that in a study of 30 anemic cats with hemobartonellosis, only 40% appeared to be uncomplicated by other disorders. This is because any stress will activate, to a variable extent, the replication of *H. felis* (Flint et al., 1958; Wilkinson, 1969; Switzer, 1971b; Ott et al., 1974). Severe anemia from any cause is certainly a stress factor. It is thus not unusual to find a few organisms on circulating erythrocytes of a cat that is anemic because of feline

leukemia, infectious peritonitis, or other cause (Holzworth, 1956; Flint et al., 1958; Holzworth, 1960a; Ward et al., 1969; Theilen et al., 1970).

A study of feline leukemia and hemobartonellosis has been conducted by Priester and Hayes (1973). This study indicated that an association exists between the two diseases. Of 297 cats with feline infectious anemia, 6 developed leukemia. However, causality could not be implied because of short periods between diagnosis of the two conditions. Schalm et al. (1975) indicated that regeneration of young erythrocytes, which usually occurs with hemobartonellosis, may stimulate the replication of feline leukemia virus. Cotter et al. (1975) reported that hemobartonellosis occurred in only 13 of 134 cats with lymphosarcoma. Conversely, Ott et al. (1974) stated that most cats diagnosed as having feline infectious anemia would eventually die of lymphosarcoma.

Hemobartonella felis appears as either rod forms or as a single or clustered ring upon the surface of infected erythrocytes (Benjamin, 1961; Wilkinson, 1969; Glenn, 1970; Switzer, 1971b). The organisms are seen in immature as well as mature red blood cells in peripheral blood and bone marrow (Switzer, 1971b). Organisms have also been observed in plasma of parasitized animals (Wilkinson, 1969). Because of its cyclic reproduction, the organism may not always appear on a blood smear of an infected animal (Flint and McKelvie, 1955; Splitter et al., 1956; Schwartzman and Besch, 1958; Seamer and Douglas, 1959; Benjamin, 1961; Wilkinson, 1969; Switzer, 1971b). Blood smears may be negative or show sparse infection during the most acute stages of the disease (Splitter et al., 1956; Schalm and Smith, 1963). Therefore, several examinations over a period of several days may be

necessary to demonstrate the parasites (Wilkinson, 1969; Glenn, 1970). Recovery from the disease often leads to a carrier state, and relapses are common when the cat is subjected to stress (Splitter et al., 1956; Flint et al., 1958, 1959; Manusu, 1962; Wilkinson, 1969).

The degree of anemia may be mild or severe, and is usually macrocytic and hypochromic or normochromic (Flint and Moss, 1953; Splitter et al., 1956; Benjamin, 1961; Ott et al., 1974; Schalm et al., 1975). General signs of regeneration are usually observed and splenomegaly may occur (Holzworth, 1956; Switzer, 1971b). Icterus is irregularly seen (Holzworth, 1956; Schwartzman, 1958; Manusu, 1962). Normal or elevated white blood cell counts are frequently observed with a normal differential or neutrophilia (Flint and McKelvie, 1955; Benjamin, 1961; Ott et al., 1974; Holzworth, 1956). In uncomplicated hemobartonellosis, the bone marrow will usually show evidence of erythroid and myeloid hyperplasia, but in prolonged cases there may be evidence of depletion and exhaustion (Holzworth, 1956; Coles, 1974). The sedimentation rate has been reported to be increased (Benjamin, 1961).

Autoimmune reactions. Autoimmune reactions may also cause hemolytic anemia in the cat (Schalm et al., 1975). This is most often a condition which is secondary to some systemic disease, but it may be a primary disease of unknown etiology (Avolt et al., 1973). In veterinary medicine, the primary disease plays a minor role (Sodikoff and Custer, 1966).

Of all domestic animals, autoimmune hemolytic anemia (AIHA) has been most frequently reported in the dog (Lewis et al., 1963, 1965; Avolt et al., 1973; Schalm et al., 1975). However, reports have recently appeared in the literature of this syndrome in the feline

species (Sodikoff and Custer, 1965, 1966; Scott et al., 1973; Schalm et al., 1975). The anemia may be severe, with packed cell volumes as low as 10% being reported (Scott et al., 1973).

A positive Coombs reaction is indicative of AIHA (Coombs et al., 1945; Sodikoff and Custer, 1965, 1966; Goldwein, 1971; Scott et al., 1973; Schalm et al., 1975). However, a positive Coombs reaction is not always observed in cases of AIHA (Avolt et al., 1973; Scott et al., 1973; Rich, 1974). This is most likely due to relatively low concentration of gammaglobulin per cell. However, sufficient antibody is present to damage erythrocytes (Avolt et al., 1973; Scott et al., 1973). The Coombs test may also become negative as the patient recovers. This has been observed in both dogs and cats (Scott et al., 1973). In addition, corticosteroid therapy may affect the Coombs reaction (Schalm et al., 1975).

Positive Coombs reactions have also been reported in cats which are positive for feline leukemia virus. Scott et al. (1973) found 4 cats which were positive for feline leukemia virus among 7 cases of AIHA. These authors postulated that (1) the leukemia virus may alter host cells in some manner so as to make them antigenic; (2) the virus cross-reacts to some degree with normal host antigens; or (3) the virus causes synthesis of an abnormal autoantibody by altered immunocytes. These authors indicated that there is a high degree of correlation between virus, lymphoreticular disorders and AIHA in man.

In addition to a positive Coombs reaction, autoagglutination has been observed in cases of AIHA in man, cats and dogs (Sodikoff and Custer, 1965). However, the phenomenon is not uncommonly seen in cats not having AIHA (Scott et al., 1973). Schalm et al. (1975) reported that occurrence of irregular small clumps of erythrocytes on

blood smears or agglutination of polychromatophilic erythrocytes and rubricytes in bone marrow may indicate the presence of autoantibody.

Other manifestations of autoimmune disease include erythroid regeneration and indirect signs of hemolysis, but the latter is not always observed (Scott et al., 1973; Schalm et al., 1975). Thrombocytopenia has been observed in dogs with AIHA (Lewis et al., 1963, 1965; Avolt et al., 1973) and was observed in 27% of the cats with AIHA which were studied by Scott et al. (1973). Spherocytosis has been observed in man and dogs with AIHA (Davidsohn and Henry, 1969; Schalm et al., 1975). Spherocytosis was suspected in 18% of 11 cats with AIHA (Scott et al., 1973). Due to the lack of central pallor in the erythrocytes, it is more difficult to recognize spherocytes in the cat (Scott et al., 1973; Schalm et al., 1975). Schalm et al. (1975) reported an increase in osmotic fragility and erythrocyte sedimentation rate in cases of AIHA. Membranous glomerulonephritis has also been reported in cats with autoimmune disease (Anderson and Jarrett, 1971; Scott et al., 1973). Systemic lupus erythematosus has also been reported as a cause of hemolytic anemia in the cat (Heise et al., 1973).

Toxic agents. Toxic agents may cause hemolytic anemias in the cat and may progress to aplastic anemia. Causative agents include naphthalene and lead (Tasker, 1966; Switzer, 1971a). Drug-induced hemolytic anemias in the cat include those caused by methylene blue and other oxidant drugs (Fertman and Fertman, 1955; Schechter et al., 1973). Finco et al. (1975) reported hemolytic anemia associated with acetaminophen administration in cats, and Harvey and Kornick (1976) have reported phenazopyridine as another cause of hemolytic anemia

in the cat. Heinz bodies may be observed in association with these toxic anemias (Schechter et al., 1973; Harvey and Kornick, 1976). Heinz bodies are generally considered to be denatured hemoglobin produced through irreversible oxidation of hemoglobin. This may be caused by a variety of agents, most notably aromatic compounds possessing amino, nitro, or hydroxy groups (Schechter et al., 1973). Cats appear to be most susceptible to Heinz body anemias from oxidant drugs. This may be due to inherent differences in the metabolism of the normal cat erythrocyte (Schechter et al., 1973). Enzyme deficiencies, which may be associated with Heinz body anemias in man, did not appear to be a predisposing factor in the cat (Jandl, 1963; Necheles and Allen, 1969; Schechter et al., 1973).

However, variable numbers of Heinz bodies occur in normal cats (Schalm et al., 1975). Beritic (1965) has reported a wide range of incidence of Heinz bodies in cats (0.3-96.1%), but no correlation to age of the animal was found. This author also observed Heinz bodies in 93 of 94 randomly examined cats. Even when present in the majority of erythrocytes of normal cats, no hemolytic anemia has been evidenced, in contrast to humans (Beritic, 1965; Schechter et al., 1973). Heinz bodies in normal cats have also been referred to as Schmauch bodies or erythrocyte refractile bodies (Schechter et al., 1973; Schalm et al., 1975). Their regular occurrence may be due to the relative ease of formation of methemoglobin in the cat and may also be related to the unique structure of feline hemoglobins (Schechter et al., 1973; Schalm et al., 1975).

Other causes of hemolytic anemia. Hemolytic anemias are also associated with various bacterial infections, including leptospirosis,

streptococcal infections, and septicemias (Tasker, 1966; Switzer, 1971a). Hemolytic anemia also occurs in some leukemias, particularly lymphoid (Rosenthal et al., 1955; Holzworth, 1956; Troup et al., 1960; Goldwein, 1971). Hemolytic anemia may also occur in congestive splenomegaly, porphyria, and liver disease (Switzer, 1971a).

Anemias Associated with the Feline Leukemia Complex

Anemia is commonly associated with lymphosarcoma in the cat (Holzworth and Neilsen, 1955; Holzworth, 1956, 1960a; Gilmore et al., 1964; Zawidzka et al., 1964; Crighton, 1968b, 1969a; Gilmore and Holzworth, 1969, 1971; Medway et al., 1969; Owen, 1969; Theilen et al., 1970; Jarrett, 1971; Osborne et al., 1971; Love, 1972; Meincke et al., 1972; Cotter et al., 1973; Coles, 1974; Hardy, 1974; Cotter et al., 1975; Schalm et al., 1975). Anemia is also associated with other diseases in the feline leukemia complex (Holzworth, 1956, 1960b; Meier and Patterson, 1956; Holzworth and Meier, 1957; Squire, 1964; Reid and Marcus, 1966; Simon et al., 1967; Schalm, 1968; Gilmore and Holzworth, 1969; Medway et al., 1969; Herz et al., 1970; Hurvitz, 1970; Schalm and Theilen, 1970; Fraser et al., 1974; Hardy, 1974; Cotter et al., 1975).

Hematopoietic tumors are the most common malignancy in the cat, and the majority are of lymphoid origin (Schalm et al., 1975; Jarrett, 1971; Gilmore and Holzworth, 1971; Hardy, 1974). Dorn et al. (1968) found 438 histologically confirmed cases per million cats. The incidence was twice that in cattle and dogs, and 5 times that in humans. Meincke et al. (1972) indicated malignancies of blood-forming tissues in 10% of 1425 cases necropsied over a 12-year period. Ott et al. (1974) found lymphosarcoma in 1/3 of all diagnosed feline neoplasms. The mean annual incidence of lymphoreticular malignancies has been

reported by Meincke et al. (1972) to be 41.6/100,000 cats in the population at risk. Other authors reported a high incidence of lymphoreticular neoplasms in cats (Holzworth, 1960a; Gilmore et al., 1964; Crighton, 1969a,b; Schmidt and Langham, 1967; Engle and Brodey, 1969; Sabine et al., 1974; Hardy, 1974). The frequency and variety of forms of hematopoietic neoplasms are greater in the feline species than in other animals (Medway et al., 1969; Hardy, 1974; Schalm et al., 1975).

It is well documented that neoplastic diseases of the feline leukemia complex are associated with the feline leukemia virus (FeLV) (Jarrett et al., 1964, 1969, 1971; Kawakami et al., 1967; Rickard et al., 1967, 1969; Essex et al., 1973; Mackey et al., 1972; Hardy et al., 1974; Cotter, 1976). Anemias have also been observed with other diseases associated with FeLV, including feline infectious peritonitis, a panleukopenia-like syndrome, and a syndrome of nonregenerative anemia (Jarrett, 1971; Ward and Pederson, 1969; Hardy and O'Reilly, 1969; Colby and Low, 1970; Colgrove and Parker, 1971; Robison et al., 1971; Hardy et al., 1974).

An immunofluorescence test has been developed by Hardy et al. (1974) to detect the presence of FeLV in peripheral blood of cats. This test is not specific for neoplastic conditions (Hardy et al., 1974); however, a high percentage of cats with lymphosarcoma and myeloproliferative disorders are positive for the virus (Hardy et al., 1974; Wilkins, 1974; Schalm et al., 1975). Hardy (1974) reported 90% of lymphosarcoma cats and 95% of cats with myeloproliferative disorders to be FeLV+.

Lymphosarcoma. Classification of lymphosarcoma in the feline species includes the following forms: (1) alimentary, (2) thymic or mediastinal, (3) multicentric, and (4) unclassified (Jarrett, 1971; Schalm et al., 1975). Most authors found the alimentary form to be most common (Jarrett et al., 1966; Owen, 1969; Cotchin, 1956; Jarrett, 1971; Meincke et al., 1972). Conversely, Essex (1975) and Cotter et al. (1973) found the lymphocytic leukemic form without tumorous masses to be the most prevalent form in the Boston area. In addition, Takahashi et al. (1974) reported a higher incidence of the thymic form of lymphosarcoma in cats in Japan.

It has been stated that anemia is probably the most common clinical sign of generalized lymphosarcoma in the cat and is a progressive feature of nearly all feline leukemias (Holzworth, 1963; Jarrett, 1971; Gilmore and Holzworth, 1971; Coles, 1974; Ott et al., 1974; Schalm et al., 1975).

Anemia observed with lymphosarcoma is usually normochromic and normocytic, with few regenerative signs (Holzworth, 1963; Gilmore et al., 1964; Crighton, 1968a,b, 1969a; Medway et al., 1969; Hardy, 1974; Ott et al., 1974; Schalm et al., 1975). However, nucleated red blood cells may occur in peripheral blood in varying numbers, and may be out of proportion to the severity of the anemia or to the reticulocyte response (Holzworth, 1960a, 1963; Gilmore et al., 1964; Crighton, 1968a,b; Switzer, 1971a; Cotter et al., 1973; Coles, 1974; Davidsohn and Henry, 1969). Immature red blood cells may represent a response to hemolysis, a final effort of marrow that is fatally infiltrated by malignant cells, or occasionally may be attributable to blood-forming activity in the liver or spleen (Holzworth, 1960a). Some authors reported other regenerative signs such as polychromasia and

anisocytosis in response to anemia of lymphosarcoma (Holzworth, 1956; Benjamin, 1961; Gilmore et al., 1964; Loeb, 1964; Cotter et al., 1973). Cotter et al. (1973, 1975) reported that some cats may initially have increased reticulocyte counts, although it usually progresses to hypoplastic anemia. Aplastic anemia, particularly in cases of bone marrow invasion, may be observed with lymphosarcoma (Loeb, 1964; Medway et al., 1969; Switzer, 1971a).

The white blood cell picture may vary in lymphosarcoma, ranging from leukopenia to leukocytosis (Holzworth, 1956, 1960a, 1963; Benjamin, 1961; Gilmore et al., 1964; Crighton, 1968a; Osborne et al., 1971; Medway et al., 1969; Schalm et al., 1975). Most authors state that leukopenia occurs more frequently than leukocytosis (Holzworth, 1960a; Squire, 1964; Crighton, 1968b, 1969a,b; Gilmore and Holzworth, 1971; Switzer, 1971a; Cotter et al., 1975). Hardy (1974) reported absolute leukocytosis in 30% of observed lymphosarcoma cases and leukopenia in 10% of the cases. Crighton (1968a) reported leukocytosis in 28% of the cases and leukopenia in 12% of confirmed cases of lymphosarcoma. Holzworth (1960a) reported that leukopenias may be progressive in cases of hepatomegaly and splenomegaly.

Frank leukemias were uncommon, and most authors stated that this occurred in fewer than 25% of lymphosarcomas (Holzworth, 1960a, 1963; Crighton, 1968a,b, 1969a,b; Jarrett et al., 1966; Gilmore and Holzworth, 1969, 1971; Medway et al., 1969; Love, 1972; Wilkins, 1974; Schalm et al., 1975; Fraser et al., 1974; Schalm, 1976). However, Sabine et al. (1974) observed leukemia in 10 of 18 cases of spontaneous lymphosarcoma, and Cotter et al. (1973) and Essex (1975) reported a higher percentage of frank leukemias and lack of solid tumorous masses. The low incidence of frank leukemias may reflect the more

limited or localized form of lymphosarcoma which is usually reported in the cat (Holzworth, 1960a; Squire, 1964).

Leukemic changes may range from acute lymphoblastic forms to chronic lymphocytic leukemias (Holzworth, 1963; Gilmore et al., 1964; Benjamin, 1961; Coles, 1974). This may be related to the stage of disease, with lymphoblasts predominating in acute cases and small lymphocytes apparent in chronic stages (Holzworth, 1960a; Benjamin, 1961). Wilkins (1974) surveyed lymphocyte morphology in a number of cats and reported cytologic changes in peripheral blood consistently enough to use this as a diagnostic criterion for lymphosarcoma. Of 50 cats with lymphosarcoma, 46% had lymphocyte counts outside normal range, 10% had a lymphopenia, and 16% had a marked lymphocytosis. Lymphocytes were graded from I to V, and it was found that 74% of cats with lymphosarcoma had Grade IV and V lymphocytes (lymphoblasts) and 53% had Grade III lymphocytes in peripheral blood. In a group of 100 cats with other conditions, 14% had total lymphocyte counts outside the normal range. Sixty-six percent had Grade III lymphocytes, but Grade IV or V lymphocytes were not apparent. A high incidence of Grade III lymphocytes was found in panleukopenia, toxoplasmosis, chronic inflammatory diseases of the skin, urinary and gastrointestinal tracts, and fever of unknown origin. The reason for the appearance of Grade III lymphocytes may be that these diseases actively stimulate the immune system. Crighton (1968a) also reported the presence of atypical lymphocytes in conditions other than leukemia.

Absolute lymphocyte numbers may be out of the normal range in cases of lymphosarcoma (Holzworth, 1960a; Gilmore et al., 1964; Crighton, 1968a,b, 1969; Schalm, 1970; Anderson et al., 1971; Jarrett, 1971; Coles, 1974). Crighton (1969b) stated that leukopenia and

absolute lymphopenia were nearly twice as common as lymphocytosis. Schalm et al. (1975) reported a frank lymphopenia in 51% of 49 cats with lymphosarcoma. This was observed in spite of neoplastic involvement of lymphocytic tissue with tumor mass formation. Lymphoblasts and prolymphocytes were seen in variable numbers in 39% of 49 cats. Crighton (1968a) found lymphopenia in 38% of confirmed cases of lymphosarcoma, and lymphocytosis in 21%.

Lymphopenias associated with lymphosarcoma may be due to the depressive effect of FeLV on the immune system (Anderson et al., 1971; Perryman et al., 1972; Schalm et al., 1975). Anderson et al. (1971) observed atrophy of the thymus and other lymphoid tissues in kittens inoculated with FeLV which resulted in depression of cell-mediated immunity. This immunological deficiency may influence the pathogenesis of leukemia in surviving cats (Anderson et al., 1971). In addition, there is susceptibility to other infections due to this deficiency (Anderson et al., 1971; Mackey et al., 1972; Perryman et al., 1972).

Neutrophil counts were variable with lymphosarcoma. Crighton (1968a) found that nearly 50% of absolute neutrophil counts were abnormal in cases of lymphosarcoma, with 1/6 showing absolute neutropenia. Holzworth (1960a) found differential counts altered with neutrophilia in cases of lymphosarcoma.

Platelet numbers may be depressed in cases of lymphosarcoma, and enlarged and otherwise abnormal platelets may be observed (Holzworth, 1960a, 1963; Squire, 1964; Medway et al., 1969; Switzer, 1971a; Osborne et al., 1971). However, thrombocytopenia is rarely severe enough to produce clinical evidence of coagulation defect (Medway et al., 1969; Schalm, 1972).

The degree of bone marrow involvement is variable in cases of lymphosarcoma (Benjamin, 1961; Squire, 1964; Gilmore and Holzworth, 1971; Schalm et al., 1975). The presence of neoplastic cells in blood generally indicates bone marrow involvement (Holzworth, 1960a; Squire, 1964, 1975; Jarrett, 1971). Abnormal cells are not always observed in the peripheral blood in such cases (Holzworth, 1960a; Gilmore et al., 1964; Jarrett, 1971; Cotter et al., 1973; Schalm et al., 1975). Schalm et al. (1975) reported that 12 of 49 cats with lymphosarcoma had lymphocytic infiltration of the marrow, but lymphoblasts or prolymphocytes were observed in peripheral blood of only 7 of 12 animals. Cells of varying size, ranging from mature lymphocytes to lymphoblasts, were observed with neoplastic infiltration of the bone marrow. The normal number of lymphocytes in feline bone marrow has been reported by Gilmore and Holzworth (1971) and Schalm et al. (1975) to range from 5 to 15% small mature lymphocytes.

Smudge cells may also be observed in cases of lymphosarcoma, but are not thought to be indicative of leukemia (Crighton, 1968a, 1969b; Hardy, 1974). These may also be observed in blood films from cats with nonleukemic debilitating diseases (Crighton, 1968a,b, 1969b).

Crighton (1968a) reported an increased sedimentation rate in feline lymphosarcoma which correlated with the degree of anemia. Approximately 50% of animals with lymphosarcoma had sedimentation rates of 40 mm/hour or higher.

Schalm et al. (1975) reported total protein values and fibrinogen values of animals with lymphosarcoma to be within normal range.

Myeloproliferative disorders. Myeloproliferative disorders are also included in the feline leukemia complex, and classification of

these diseases is similar to that employed in man (Damashek, 1951), with inclusion of the following disorders: erythremic myelosis, granulocytic leukemia, polycythemia vera, erythroleukemia, megakaryocytic leukemia, reticuloendotheliosis, and myelofibrosis (Coles, 1974; Schalm et al., 1975). A combination of 2 or more of the different cell types may be observed (Schalm et al., 1975). The myeloproliferative disorders are reported less frequently than the lymphoid type (Holzworth, 1960b; Fraser et al., 1974; Medway et al., 1969). The most common myeloproliferative disorder in cats is granulocytic leukemia (Fraser et al., 1974).

Anemia associated with the myeloproliferative diseases is usually more severe than that observed with lymphosarcoma (Gilmore et al., 1964; Schalm and Theilen, 1970; Schalm, 1971). This anemia is generally progressive and refractory to treatment (Gilmore and Holzworth, 1969, 1971; Ward et al., 1969; Schalm and Theilen, 1970; Love, 1972; Coles, 1974; Fraser et al., 1974; Schalm et al., 1975). The packed cell volume has been reported to be in the range of 6 to 16% (Gilmore et al., 1964; Herz et al., 1970; Gilmore and Holzworth, 1971; Jarrett, 1971; Fraser et al., 1974; Giles et al., 1974; Schalm et al., 1975). There may be regenerative signs in peripheral blood, including anisocytosis, poikilocytosis, and polychromasia (Gilmore et al., 1964; Schwartz and Critchlow, 1952; Ward et al., 1969; Watson et al, 1969; Fraser et al., 1974). A reticulocyte response may or may not be present (Ward et al., 1969; Hurvitz, 1970; Jarrett, 1971; Cotter et al., 1975). In cases of erythremic myelosis and erythroleukemia the anemia is often macrocytic (Schwartz and Critchlow, 1952; Ward et al., 1969).

Small to moderate numbers of nucleated red blood cells have been reported in cases of myeloproliferative disorders (Holzworth, 1960b; Gilmore et al., 1964; Ward et al., 1969; Herz et al., 1970; Hurvitz, 1970; Schalm, 1971; Giles et al., 1974; Fraser et al., 1974; Watson et al., 1974). These may also be seen in variable numbers in areas of affected organs where undifferentiated cells are found (Ward et al., 1969). In cases of erythremic myelosis and erythroleukemia nucleated cells may be numerous, immature and large, and there may be disparity between the maturity of the nucleus and cytoplasm (Schalm, 1966; Sodikoff and Schalm, 1968). Also, binucleated cells may be observed (Ward et al., 1969; Gilmore and Holzworth, 1971; Watson et al., 1974; Schalm et al., 1975). In some cases, peripheral blood findings are less spectacular, with a few abnormal erythroid cells, or merely anemia with marked anisocytosis (Watson et al., 1974; Schalm, 1972).

Presence of abnormal erythroid precursors might suggest deficiencies of vitamin B_{12} and/or folates, but this association is rarely reported in the cat (Watson et al., 1974). In addition, cats with megaloblastoid hematologic changes have not responded to therapy with these vitamins (Ward et al., 1969; Zawidzka et al., 1964; Watson et al., 1974). However, Schalm (1972) reported a case of megaloblastic anemia in a kitten which did respond to treatment with vitamin B_{12}.

The total white blood cell count may also vary in myeloproliferative diseases, ranging from leukopenia to leukocytosis (Eyestone, 1951; Holzworth and Meier, 1957; Holzworth, 1960b; Squire, 1964; Sodikoff and Schalm, 1968; Reid and Marcus, 1966; Hurvitz, 1970; Fraser et al., 1974; Rich, 1974; Coles, 1974). Leukocytosis was

more frequently observed, particularly in cases of granulocytic leukemia (Squire, 1964; Gilmore and Holzworth, 1971; Coles, 1974).

Frank leukemias often occur in myeloproliferative disorders, although the number of neoplastic cells in peripheral blood is variable (Holzworth, 1960b; Gilmore et al., 1964; Gilmore and Holzworth, 1969, 1971; Ward et al., 1969; Jarrett, 1971; Fraser et al., 1974; Coles, 1974). These cells may be identified as immature granulocytes or erythrocytic cells, or they may be undifferentiated, as in reticuloendotheliosis (Ward et al., 1969; Herz et al., 1970; Jarrett, 1971; Fraser et al., 1974; Cotter et al., 1975; Schalm et al., 1975). Hurvitz (1970) reported ultrastructural evidence that the reticuloendothelial cells are primitive erythrocyte precursors. Michel et al. (1976) reported an increased number of giant and morphologically bizarre platelets in peripheral blood in a case which was classified as megakaryocytic myelosis.

The predominant neoplastic cell type may change during the course of the disease process (Zawidzka et al., 1964; Ward et al., 1969; Jarrett, 1971; Watson et al., 1974). This finding is similar to the DiGuglielmo syndrome in man, in which erythremic myelosis, erythroleukemia, and myeloblastic leukemia may all appear either sequentially or simultaneously (Damashek, 1969; Ward et al., 1969; Watson et al., 1974; Fraser et al., 1974; Schalm et al., 1975).

Many tissues, including liver, spleen, lymph nodes, and bone marrow, may be infiltrated with neoplastic cells in myeloproliferative disorders in addition to peripheral blood (Meier and Patterson, 1956; Holzworth, 1960b; Gilmore and Holzworth, 1969; Ward et al., 1969; Schalm and Theilen, 1970; Watson et al., 1974; Schalm et al., 1975). Hepatomegaly and splenomegaly are common findings due to this

cellular infiltration (Holzworth, 1960b; Gilmore and Holzworth, 1971; Love, 1972; Giles et al., 1974; Schalm et al., 1975). Other sites of cellular infiltration include the kidney, heart, mediastinum, and lung (Holzworth, 1960b; Squire, 1964; Watson et al., 1974). Extramedullary hematopoiesis has been frequently observed in the liver, spleen, and lymph nodes of affected animals (Herz et al., 1970; Hurvitz, 1970; Schalm and Theilen, 1970; Schalm et al., 1975). This is considered to be an expression of latent erythropoietic potentialities of various mesenchymal structures, but is inadequate to compensate for the severe myelophthisis (Meier and Patterson, 1956; Squire, 1964). Myeloid metaplasia may be observed in liver, spleen, and lymph nodes (Schalm and Theilen, 1970).

Bone marrow cytology often indicates maturation arrest of either erythrocytes or granulocytes, or both, with the presence of many undifferentiated cells (Holzworth, 1960b; Herz et al., 1970; Hurvitz, 1970; Medway et al., 1969; Giles et al., 1974; Watson et al., 1974; Coles, 1974; Schalm et al., 1975). Erythropoiesis may be active in surviving areas of blood-forming tissues despite anemia, but lacking in others (Holzworth, 1960b; Tasker, 1966; Coles, 1974; Watson et al., 1974). Holzworth (1960b) reported marrow in granulocytic leukemia to be extremely cellular with intense diffuse proliferation of myeloid forms, predominantly myeloblasts and promyelocytes. Schalm (1972) reported hypercellularity of marrow and maturation arrest at the myelocyte stage in cases of granulocytic leukemia. Fraser et al. (1974) stated that few erythrocyte precursors or mature granulocytes were seen in bone marrow in acute granulocytic leukemia. In cases of erythremic myelosis, Sodikoff and Schalm (1968) found almost no cells of the granulocytic series in bone marrow. The majority of cells

were undifferentiated, but clusters of cells were observed which had nuclear differentiation characteristics of prorubricytes and rubricytes, with an occasional cell having cytoplasmic characteristics of hemoglobin synthesis. In cases of reticuloendotheliosis, Gilmore and Holzworth (1969) reported a severe decrease in nucleated erythrocytes, a decrease in granulocytic cells, and 40% undifferentiated reticuloendothelial cells. Coles (1974) reported more than 15% undifferentiated cells in bone marrow in cases of reticuloendotheliosis. Michel et al. (1976) reported an abnormal proliferation of megakaryocytes in bone marrow of a cat with megakaryocytic myeloma.

M:E ratios were variable and were not quantitatively related to the leukocyte count or the degree of anemia (Gilmore and Holzworth, 1969; Medway et al., 1969; Coles, 1974; Schalm et al., 1975). Myelofibrosis of bone marrow was a sequela in cases of myeloproliferative disorders (Ward et al., 1969; Herz et al., 1970; Schalm and Theilen, 1970; Schalm et al., 1975).

Platelet numbers have been reportedly increased in peripheral blood in myeloproliferative disorders, but more frequently are reported to be decreased (Holzworth, 1960b; Benjamin, 1961; Schwartz and Critchlow, 1952; Ward et al., 1969; Fraser et al., 1974; Giles et al., 1974; Schalm et al., 1975). Giant forms were observed by Schalm et al. (1975). There may be increased or decreased numbers of megakaryocytes in the bone marrow (Coles, 1974).

C-type virus particles were found in tissues of animals affected with myeloproliferative disorders (Ward et al., 1969; Herz et al., 1970; Schalm and Theilen, 1970; Jarrett et al., 1971; Love, 1972; Hardy et al., 1974). Other authors indicated that the feline leukemia virus may be responsible for myeloproliferative diseases in

cats (Jarrett, 1971; Cotter et al., 1975; Cotter, 1976). Schalm and Theilen (1970) suggested that diseases which severely alter hematopoietic tissue may contribute to development of feline myeloproliferative disorders.

Icterus was observed with massive accumulation of neoplastic cells in liver sinusoids, which led to atrophy of the parenchyma (Holzworth, 1960b; Schalm et al., 1975). Icterus also occurred with extensive erythrophagocytosis in the spleen and lymph nodes (Schalm et al., 1975).

Giles et al. (1974) found an increased sedimentation rate of 50 mm/hour in a case of erythremic myelosis. Schalm et al. (1975) reported normal fibrinogen level in a cat with myeloproliferative disease.

Other forms of leukemia in the feline species. Other forms of leukemia were reported less frequently in the cat than lymphosarcoma or myeloproliferative disorders. These included eosinophilic, mast cell, reticulum cell myeloma, and multiple myeloma (Holzworth, 1960b; Simon et al., 1967; Silverman, 1971; Coles, 1974; Schalm et al., 1975; Meier and Gourley, 1957; Lucke, 1964; Gilmore and Holzworth, 1971; Holzworth and Meier, 1957; Farrow and Penny, 1971).

Anemias have been associated with the rarer forms of leukemia (Holzworth, 1960b; Squire, 1965; Simon et al., 1967; Schalm et al., 1975). Marked leukocytosis was observed in many of the reported cases of eosinophilic leukemia (Holzworth, 1960b; Simon et al., 1967; Silverman, 1971; Coles, 1974; Schalm et al., 1975). Schalm et al. (1975) reported one case in which the absolute eosinophil count exceeded 100,000/µl, and both hepatomegaly and splenomegaly were

observed. Simon et al. (1967) and Silverman (1973) reported a high relative eosinophil count with immature forms in peripheral blood, and a preponderance of eosinophils in bone marrow. Splenomegaly and widespread leukemic invasion by cells of the eosinophilic series were found at necropsy in these cases. Holzworth (1960b) reported severe neutrophilic leukocytosis with a left shift in cases of eosinophilic leukemia.

In cases of monocytic leukemia reported by Schalm et al. (1975) typical monocytes varied from 0 to 25% of the differential count, and unclassified large mononuclear cells varied between 1.0% and 39.5% in several hemograms. Monocytic blast forms were the predominant cell in bone marrow. In cases reported by Holzworth (1960b), there were primitive mononuclear cells in peripheral blood, liver, spleen, lymph nodes and bone marrow. Granulocytes were rare and did not mature past the band stage.

Mast cell leukemias were reported not to cause as severe an anemia as that observed with other leukemias in the cat (Meier and Gourley, 1957; Holzworth, 1960b; Gilmore and Holzworth, 1971; Schalm et al., 1975). This may be due to lack of extensive myelophthisis (Meier and Gourley, 1957). However, clusters of neoplastic mast cells were observed in bone marrow (Meier and Gourley, 1975; Lucke, 1964; Gilmore and Holzworth, 1971). Splenomegaly and hepatomegaly were reported due to infiltration with neoplastic cells (Meier and Gourley, 1957; Holzworth, 1960b; Lucke, 1964). There was slight but definite basophilia in peripheral blood, with leukocytosis (Holzworth, 1960b; Meier and Gourley, 1957).

A case of reticulum cell myeloma reported by Holzworth and Meier (1957) with anemia and mild jaundice had leukopenia, and

primitive binucleated white cells and erythroid cells were observed in peripheral blood. There was an increase in serum gammaglobulin, but Bence-Jones protein in the urine was negative. In a case of multiple myeloma reported by Farrow and Penny (1971) there was a normal white blood cell count, anemia, proteinuria, and plasma cells in peripheral blood and bone marrow.

Other Secondary Anemias

Secondary anemias may occur with a number of conditions. Anemia is commonly associated with infection in most species, including man (Cartwright et al., 1951; Holzworth, 1956; Schalm and Smith, 1963; Medway et al., 1969; Tasker, 1966; Davidsohn and Henry, 1969; Gilmore and Holzworth, 1969; Switzer, 1971a; Schalm et al., 1975). Holzworth (1956) indicated that in cats infection plays a far more significant role in producing profound anemia than in any other domestic animal. Among 120 anemic cats studied, infection played a principal role in approximately 50%. These infectious processes included panleukopenia during relapses, toxoplasmosis, and overwhelming bacterial infections. Localized infections such as abscessed and necrotic bite wounds, sinusitis, stomatitis, fibrinous pleuritis and peritonitis, tonsillitis, metritis, hemorrhagic enteritis, pancreatitis, and hepatitis also caused anemia. Chronic debilitating conditions may also cause anemia (Loeb, 1964; Gilmore and Holzworth, 1969). Pyothorax, commonly observed in cats, was not usually accompanied by severe anemia (Holzworth, 1956; Medway et al., 1969).

The typical blood picture is normochromic, normocytic anemia with few or no reticulocytes or other signs of regeneration (Holzworth, 1956; Schalm and Smith, 1963; Loeb, 1964; Davidsohn and Henry, 1969;

Medway et al., 1969; Switzer, 1971a; Coles, 1974). Occasionally, there is considerable variation in cell size, owing to the presence of numerous small cells deficient in pigment, a characteristic of iron deficiency which is believed to accompany metabolic disturbances resulting from infection (Holzworth, 1956). Infrequently there may be definite evidence of erythrocytic regeneration associated with infection (Holzworth, 1956; Gilmore and Holzworth, 1969). Bone marrow usually shows a decrease in erythrocytic precursors and a left shift in the myelocyte series with an elevated M:E ratio (Holzworth, 1956; Gilmore and Holzworth, 1969). A secondary form of autoimmune hemolytic anemia may be associated with infection (Goldwein, 1971).

In chronic infections, the white cell count is often elevated (Holzworth, 1956; Tasker, 1966; Gilmore and Holzworth, 1969; Medway et al., 1969; Switzer, 1971a). There may be monocytosis and the sedimentation rate may be increased (Switzer, 1971a). A severe infection of some duration may depress myeloid activity and leukopenia may be observed (Tasker, 1966; Gilmore and Holzworth, 1969; Medway et al., 1969). In man and other species, hypoferremia and hypercupremia have been reported in conjunction with chronic infection (Cartwright et al., 1946, 1951; Medway et al., 1969). Excretion of coproporphyrin I and III may increase, indicating some abnormality of hemoglobin synthesis associated with the chronic septic process (Schalm et al., 1975; Medway et al., 1969).

Nephritis and uremia may also cause anemia in the cat (Holzworth, 1956; Loeb, 1964; Switzer, 1971a; Medway et al., 1969). This anemia is also normochromic and normocytic with little evidence of regeneration (Davidsohn and Henry, 1969; Medway et al., 1969). Holzworth

(1956) observed 6 cats with kidney failure and found hemoglobin in the range of 5 to 8 gm/dl and no regenerative signs. The white cell counts were normal or slightly elevated, with a tendency to neutrophilia.

Chronic liver disease may also lead to anemia (Holzworth, 1956; Davidsohn and Henry, 1969; Medway et al., 1969; Switzer, 1971a). Holzworth (1956) reported cases of hepatitis in cats whose clinical signs simulated panleukopenia. High fever, initially moderate but slowly progressive anemia, and leukopenia were observed. Anemia associated with liver disease was generally normochromic and normocytic, with little evidence of regeneration (Medway et al., 1969; Switzer, 1971a). However, macrocytosis and a slight increase in reticulocytes were occasionally observed. Target cells were seen, especially in obstructive jaundice, and platelets were low-normal or decreased. Bone marrow may be slightly hypercellular (Davidsohn and Henry, 1969).

Neoplasia other than that of the hematopoietic system may cause anemia (Holzworth, 1956; Loeb, 1964; Medway et al., 1969; Gilmore and Holzworth, 1969; Switzer, 1971a). As in other forms of secondary anemia, there was little evidence of regeneration (Loeb, 1964; Medway et al., 1969).

Nutritional Anemias

Nutritional anemias are rare as a primary entity in the feline species, and were seen far less frequently than in man (Loeb, 1964; Gilmore and Holzworth, 1969; Schalm et al., 1975). Anemia of the macrocytic type, commonly associated with B_{12} and folic acid deficiency, was recognized by Holzworth (1956) in several patients

with gastrointestinal disorders, such as gastric fur ball, chronic pancreatic disease, and liver impairment. A few cases of suspected vitamin B_{12}-folic acid deficiency in the cat were observed by Schalm et al. (1975). Macrocytic anemias were associated with folic acid deficiency in cats on deficient diets to which sulfonamides had been added. In these animals, a single dose of 2 mg of folic acid was sufficient for recovery, but better results were obtained when B_{12} or liver extract was given concurrently. These animals also had leukopenia (Da Silva et al., 1955).

Iron deficiency may occur in kittens but occurs less commonly than in young animals of other species (Medway et al., 1969). Iron deficiency was uncommon as a primary syndrome in adult cats. In adults, the deficiency was usually related to a totally inadequate diet or exhaustion of the body's iron reserves by chronic blood loss (Loeb, 1964; Schalm et al., 1975). However, Holzworth (1956) reported that in a group of 120 anemic cats, iron deficiency did not develop from chronic blood loss due to parasitism except in heavy flea infestations. In this same group of animals, severe anemia occurred in several cats due to a fur ball lodged in the stomach which produced ulceration of the mucosa, and iron deficiency resulted from chronic blood loss and impaired nutrition. Even when parasitism and other blood loss were not present, iron deficiency was a factor if there was decreased protein intake or impaired absorption. The metabolic disturbances associated with severe local or systemic infections may have resulted in iron deficiency (Holzworth, 1956). Other mineral deficiencies which may cause anemia were rare in the cat (Schalm et al., 1975).

Aplastic Anemias

Aplastic anemias may result from a primary cause, or from exhaustion of marrow following chronic hemorrhage or hemolytic disease (Davidsohn and Henry, 1969; Medway et al., 1969; Loeb, 1964). Primary agents which produce aplastic anemia include ionizing radiation, certain drugs, including estrogens and chemotherapeutic agents, and toxic substances such as benzene compounds, arsenates, chlorinated hydrocarbons, sulfonamides, salts of heavy metals, streptomycin, and phenylbutazone (Holzworth, 1956; Coles, 1974; Schalm et al., 1975; Loeb, 1964; Switzer, 1971a). Holzworth (1956) reported 2 cases of lead poisoning in cats where there was a failure of erythrocytic regeneration and leukopenia.

Aplastic anemia may also occur due to depression of bone marrow produced by certain viruses. An example of this would be panleukopenia virus (Medway et al., 1969). Also included in this category might be nonregenerative anemias associated with feline leukemia virus (Hardy, 1974; Schalm et al., 1975). There are also idiopathic aplastic anemias (Davidsohn and Henry, 1969; Holzworth, 1956).

A normochromic, normocytic anemia is observed in aplastic anemias due to depression of erythrogenesis (Loeb, 1964; Coles, 1974). Immature erythrocytic forms are absent, and reticulocytes are reduced or absent. The anemia is progressive in course and, depending on etiology, may be accompanied by lymphopenia, granulocytopenia, thrombocytopenia, or pancytopenia (Loeb, 1964; Medway et al., 1969).

The bone marrow picture in aplastic anemia is that of relative lymphocytosis with 60 to 100% of nucleated cells being lymphocytes. There is also striking immaturity of erythrocytic and leukocytic

cells as a consequence of marked depression of marrow production of all cellular elements (Coles, 1974).

Other Causes of Anemia

Endocrine deficiencies (i.e., pituitary, thyroid) have been reported to cause anemias in some domestic animals, but these disorders are not well documented in cats (Schalm et al., 1975). Erythrocyte morphology in hypothyroidism was characteristic of a depression anemia (Schalm et al., 1975). Another reported cause of anemia in the cat was congenital porphyria (Tobias, 1964). In addition, Berman (1974) reported anemia in cats during late pregnancy.

Mechanisms of Anemia

Most anemias result from inadequate production of erythrocytes by bone marrow or excessive loss of these cells from blood due to hemorrhage or hemolysis (Tasker, 1966).

In hemobartonellosis, the hemolytic crisis is not caused primarily by direct intravascular hemolysis, but by invasion of erythrocytes by organisms, leading to phagocytosis by the spleen. This explains frequent lack of hemoglobinemia and hemoglobinuria in this condition (Loeb, 1964).

The production of autoantibodies, lysis of the cells, and sequestration of antibody-coated erythrocytes are the mechanisms of anemia in AIHA (Schalm et al., 1975). Autoantibodies may act by causing various disturbances by attachment to erythrocytes. These would include possible increase in osmotic and mechanical fragility of red cells, clumping of red cells which may obstruct narrow blood passages, spherocytosis, phagocytosis of erythrocytes, alteration in the role of the spleen removing modified erythrocytes, disturbance

of erythrocytic enzyme balance, and loss of potassium and entrance of sodium ions into red cells (Davidsohn and Henry, 1969). The development of autoantibodies in granulomatous and neoplastic diseases of animals has been suggested to contribute to anemia in these conditions (Medway et al., 1969). Toxic agents and certain bacterial agents produce anemia by direct lysis of red cells, often causing hemoglobinemia and hemoglobinuria (Schalm et al., 1975).

The anemias associated with lymphosarcoma and myeloproliferative disorders have been explained on the basis of a myelophthisic effect within marrow (Meier and Patterson, 1956; Holzworth, 1956; Troup et al., 1960; Benjamin, 1961; Reid and Marcus, 1966; Osborne et al., 1971; Schalm et al., 1975). However, this may not always explain the anemia, as the amount of erythropoietic tissue may be normal or increased (Rosenthal et al., 1955; Troup et al., 1960; Loeb, 1964; Davidsohn and Henry, 1969). The development of anemia may be due to varying combinations of (1) a decrease in erythropoiesis with normal or increased red blood cell destruction, or (2) a normal or increased erythropoiesis with increased red cell destruction or loss (Troup et al., 1960; Switzer, 1971a).

The decrease in erythropoiesis may be due to partial maturation, particularly in myeloproliferative disorders (Gilmore and Holzworth, 1971; Schalm, 1971). There may also be depression of erythropoiesis without infiltration of neoplastic cells in bone marrow (Owen, 1969; Troup et al., 1960; Jarrett, 1971; Gilmore and Holzworth, 1971). The feline leukemia virus has been shown to cause first an early anemia, but the mechanism involved is unclear. Animals with the early anemic phase of disease may have equivocal or no histologic

evidence of neoplasia (Theilen et al., 1970; Switzer, 1971a; Cotter et al., 1973).

In cases of human leukemia, morphologic abnormalities of red cells, including anisocytosis, poikilocytosis, and basophilic stippling, have been observed with hyporegenerative anemias and hypoplastic bone marrow. Leukopenias and thrombocytopenias have also been observed in these cases (Troup et al., 1960). Reticulocytosis has been observed in human patients with acute leukemia, and this is related to premature release of red cells from marrow, and does not indicate an increase in erythropoiesis (Troup et al., 1960).

There may also be a hemolytic component in cases of leukemia with a decrease in erythrocyte survival time (Rosenthal et al., 1955; Troup et al., 1960; Benjamin, 1961; Reid and Marcus, 1966; Osborne et al., 1971; Switzer, 1971a). This may be associated with tumorous infiltration of the spleen, or an enhancement of the destructive activities of the spleen (Holzworth, 1960a). In humans, cases have been reported with overt signs of hemolysis with regenerative signs in peripheral blood and a positive Coombs test. Autoimmune hemolytic anemia is a frequent complication of lymphocytic proliferative disease (Rosenthal et al., 1955; Troup et al., 1960). Owen (1969) reported that serum from dogs with lymphosarcoma has greatly increased hemolytic activity. Scott et al. (1973) found 4 cats which were positive for feline leukemia virus among 7 cases of AIHA.

With extensive kidney tumors, anemia is common concomitantly with uremia (Jarrett et al., 1966; Loeb, 1964; Ward et al., 1969; Osborne et al., 1971). Anemia is also present with jaundice and alterations in serum proteins when the liver is extensively involved with neoplasia (Holzworth, 1960a). Another contributing factor to

anemia may be interference with normal intake and assimilation of food (Loeb, 1964; Medway et al., 1969). Tumors of the alimentary tract are likely to be accompanied with some degree of anemia because little food is taken and tumor surfaces may be ulcerated (Holzworth, 1960a). There may also be deficient absorption or synthesis of one or more substances essential to erythropoiesis (Loeb, 1964).

Other secondary anemias may develop due to a number of mechanisms. In chronic infections, iron is diverted to tissues and is not available for hemoglobin synthesis, resulting in hypoferremia (Cartwright et al., 1946, 1951; Davidsohn and Henry, 1969; Medway et al., 1969). There is impaired reutilization of transferrin-bound iron and impaired conversion of protoporphyrin to heme (Switzer, 1971a). Oral or intravenous administration of iron does not increase iron levels in the serum (Cartwright et al., 1946, 1951; Davidsohn and Henry, 1969; Medway et al., 1969). There may also be decreased erythrocytic lifespan (Davidsohn and Henry, 1969; Switzer, 1971a).

The anemia resulting from nephritis and uremia has been explained as a toxic effect on bone marrow (Medway et al., 1969). There is also shortened survival of red cells and diminished production of erythropoietin, resulting in decreased stimulation to marrow (Davidsohn and Henry, 1969; Switzer, 1971a; Osborne et al., 1971). Normally levels of erythropoietin increase in plasma in response to tissue hypoxia (Davidsohn and Henry, 1969).

The anemia of chronic liver disease may be related to increased red cell destruction and relatively inadequate red cell production (Davidsohn and Henry, 1969). Hepatic disease may also produce moderate blood loss and be associated with either B_{12} or folic acid

deficiency (Switzer, 1971a). Impaired protein synthesis is another factor contributing to anemia (Switzer, 1971a).

Anemia associated with neoplasia other than that of the hematopoietic system may be related to bleeding and hemolysis rather than bone marrow invasion and failure (Switzer, 1971a). It is not certain whether malignancy may depress erythrocyte formation by some toxic action or whether this effect results solely from impaired function of organs involved (Holzworth, 1956).

Nutritional anemias result from lack of necessary substances for erythrogenesis (Schalm et al., 1975). In aplastic anemias, there may be pancytopenia in peripheral blood and complete absence of all types of cells in bone marrow. The development of aplastic anemias following hemorrhage or hemolysis is not clearly understood. The bone marrow hyperplasia observed in these conditions may terminate abruptly with resultant aplasia of marrow and progressive anemia (Medway et al., 1969).

Anemias due to endocrine deficiencies may result from inadequate stimulation of marrow (Davidsohn and Henry, 1969). The anemia of hypothyroidism may be due to reduced metabolic rate or possibly to a decrease in direct action of thyroxine upon erythropoiesis (Hollander et al., 1967).

MATERIALS AND METHODS

Animals

Thirty anemic cats which were patients in the MSU Veterinary Clinical Center were observed in this study. The ages of these animals ranged from 10 weeks to 12 years, and several breeds were represented. A complete history was obtained on each animal, and a complete physical examination was performed. A progress record was maintained on each animal.

Peripheral Blood Studies

Complete blood counts, successive where possible, were obtained on each animal. These included packed cell volume, hemoglobin, total red blood cell count, total white blood cell count, plasma protein determination, white blood cell differential count, and evaluation of the peripheral blood smear, including platelet numbers and morphology.

PCV, Plasma Protein, Total White and Red Cell Counts

The packed cell volume was obtained by the microhematocrit method (McInroy, 1954). The plasma protein value was obtained with the use of a refractometer.[a] The white blood cell counts were obtained in some cases by the hemacytometer method with the use of a

[a] T-S Meter, American Optical Co., Buffalo, NY.

white cell diluting pipette.[b] In the remaining cases, the white cell counts were obtained with an electronic Coulter counter.[c] The red blood cell counts were obtained in the earlier cases by the disposable pipette method[b] and in the remaining cases with an electronic Coulter counter.[c]

Hemoglobin

The hemoglobin values were obtained by the cyanmethemoglobin method (Hairline, 1958). The red cell indices (i.e., mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) were calculated by utilizing the packed cell volume, the hemoglobin level, and the total red blood cell count (Schalm et al., 1975).

Differential Count and Evaluation of Smear

The differential count was performed by making a blood smear, identifying 100 white blood cells, and calculating the percentage. In cases where the count exceeded 50,000/µl, 200 or 300 cells were counted. Conversely, when the count was less than 3,000/µl, it was often necessary to count fewer than 100 cells and calculate the percentage. The blood smear was evaluated for regenerative signs, such as polychromasia, anisocytosis, poikilocytosis, Howell-Jolly bodies, etc. These alterations were graded according to degree of response, but only significant changes were reported in the results. The smears were also carefully examined for the presence of blood parasites and

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[b] Unopette, Becton-Dickinson, Inc., Rutherford, NJ.

[c] Coulter Counter Model Z_{BI}, Coulter Electronics, Inc., Hialeah, FL.

abnormal cells. In addition, platelet numbers were evaluated, and an average of 5 to 10 platelets per oil immersion field was considered normal (Schalm et al., 1975). Platelets were also evaluated according to size and shape.

Reticulocyte Counts

Reticulocyte counts were performed utilizing the new methylene blue stain (Brecher, 1949). Type II and Type III aggregated reticulocytes as described by Schalm et al. (1975) were counted, and a percentage was calculated for 1,000 red cells counted. The new methylene blue-stained smears were also examined for the presence of Heinz bodies.

The reticulocyte index was calculated by multiplying the reticulocyte count by the ratio of the patient's hematocrit to the normal hematocrit of the cat (35%). When there was evidence of premature release of reticulocytes, the reticulocyte count was divided by 2 to correct for the additional day that these cells were in the peripheral blood (Davidsohn and Henry, 1969). The absolute reticulocyte counts were also calculated.

Osmotic Fragility

The osmotic fragility of erythrocytes was measured by placing a suspension of erythrocytes in varying strength solutions prepared from a 1% sodium chloride solution. The points at which initial and complete hemolysis occurred were noted (Coles, 1974). Controls utilizing normal cats were run concurrently with each patient sample.

Direct Coombs

The direct Coombs test (Coombs et al., 1945) was performed utilizing antiglobulin serum specific for the feline species.[d] After washing the cells, equal amounts of Coombs serum and a 3% red cell suspension were mixed, centrifuged, and observed for agglutination. This was repeated after a 15-minute incubation period at room temperature and at 37 C.

Fibrinogen Assay

The fibrinogen assay was performed by measuring the total protein value by the refractometer method[a] before and after incubation at 56 C for 3 minutes, centrifugation, and subtracting the results (Foster et al., 1959; Kaneko and Smith, 1967).

Sedimentation Rate

The sedimentation rate of erythrocytes was performed utilizing a large Wintrobe tube and allowing the sample to stand perfectly upright for 1 hour. The distance which the red cells had fallen during that time was measured in millimeters (Coles, 1974). Controls utilizing normal cats were run concurrently with each patient sample.

Fluorescent Antibody Test for the Feline Leukemia Virus

The fluorescent antibody test for the feline leukemia virus (Feleuk Test[R]) was performed by the National Veterinary Laboratory,

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[d]Feline Coombs serum prepared by Dr. Robert Bull, Departments of Human Medicine, Surgery, and Small Animal Surgery and Medicine, Michigan State University, East Lansing. Not available commercially.

Inc.[e] utilizing 3 unfixed blood smears from each anemic cat.

Blood Chemistries

The serum bilirubin level was measured on all cats by the modified Evelyn Mallory method (Mallory, 1937). Other blood chemistries were performed as indicated by the individual cases. The blood urea nitrogen levels were measured utilizing the Beckman BUN Analyzer.[f] The blood glucose levels were measured by the procedure outlined in Technical Bulletin #635, Sigma Chemical Company.[g] The serum glutamic pyruvic transaminase levels were measured utilizing the procedure outlined in Technical Bulletin #505, Sigma Chemical Company.[g] The serum creatinine levels were measured by the procedure outlined by Henry (1964). The serum amylase levels were measured utilizing the procedure outlined in Technical Bulletin #700, Sigma Chemical Company.[g] The serum lipase levels were measured utilizing the procedure outlined in Technical Bulletin #800, Sigma Chemical Company.[g]

Urinalyses and Fecal Analyses

A complete urinalysis was performed on each animal, and it was noted whether the sample was voided or collected by catheter. The color and character of the urine were evaluated by visual inspection. The specific gravity was measured with a refractometer.[a] The values for pH, ketones, glucose, protein, blood, bilirubin, and urobilinogen were assessed with a Multistix.[h] In cases with a positive protein

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[e]National Veterinary Laboratory, Inc., Franklin Lakes, NJ.

[f]Beckman BUN Analyzer, Beckman Instruments, Fullerton, CA.

[g]Sigma Chemical Company, St. Louis, MO.

[h]Ames Company, Division Miles Laboratories, Inc., Elkhart, IN.

test the Bumintest[g] was performed on the supernatant of the spun urine sample to better quantitate the amount of protein and to eliminate false positive reactions. The bilirubin level was also measured by the Ictotest.[g]

Ten milliliters of urine were centrifuged at 1000 rpm for 5 minutes to obtain a urine sediment. The sediment was stained with new methylene blue stain and the microscopic examination recorded. The urine sediment was evaluated for the numbers of white and red blood cells, epithelial cells, casts, bacteria, and crystals.

A fecal sample was examined for parasite ova by the flotation technique (Coles, 1974). An occult blood test was also performed on the feces, utilizing the Hematest.[g]

Cytologic Examinations

Bone marrow cytologies were performed in a few cases by aspirating the sample from the proximal portion of the femur or the iliac crest. Slide preparations were made, stained with new methylene blue and Wright's stains, and examined.

Cytologic examinations of thoracic and abdominal fluid were performed in those cases which indicated a possible thymic lymphosarcoma, pyothorax, or a feline infectious peritonitis. Lymph node aspirates were performed when indicated.

Smears or touch impressions were made of all samples. Cell counts were performed by the hemacytometer method (Schalm et al., 1975) and the total protein values and the specific gravity were measured with a refractometer[a] when possible. The slide preparations were stained with new methylene blue and Wright's stains, and examined.

Necropsy and Histopathology

Splenic and lymph node biopsies were obtained when indicated and tissues were fixed in 10% neutral formalin. The tissues were sectioned at 6 microns thickness and stained with hematoxylin and eosin or other special stains (Luna, 1968).

Many of the anemic cats died or were euthanatized, and were subsequently necropsied. Gross lesions were observed and appropriate tissues, including bone marrow, were taken for histopathologic examination. Tissues were fixed in 10% neutral formalin, and sectioned and stained as mentioned above. When indicated, tissues were cultured for the isolation of infectious agents.

RESULTS

Ages, Breeds and Sex of Affected Animals

The ages of these animals ranged from 10 weeks to 12 years; the mean age of the 30 cats was 4.2 $\pm$ 3.1 years. The majority were either younger than 3 years or older than 8 years of age. The mean ages for the FeLV+ and FeLV- cats are listed in Table 1. Table 2 includes the mean ages for the lymphosarcoma, myeloproliferative, and neoplastic groups.

Twenty-one cats were domestic felines, and 7 were Siamese. There was 1 Russian Blue and 1 Abyssinian. The distribution of cats among the sugbroups is listed in Tables 1 and 2.

Twenty-two cats were male and 8 were female. A higher number of anemic cats in all groups except the FeLV- group were intact males (Tables 1 and 2).

Etiologic Factors Associated with the Anemias

Table 3 is a summary of etiologic factors associated with the anemias, and the percentage distribution of these factors is listed in Table 4. The majority (73.3%) of cats were positive for FeLV. Of these 22 positive cases, 9 were confirmed at necropsy to have lymphosarcoma. Four had evidence of neoplasia in peripheral blood. Two additional cases had atypical lymphocytes in peripheral blood, but no necropsy was performed to confirm the diagnosis.

Table 1. Summary of ages, sex and breeds of 30 anemic cats with distribution between FeLV+ and FeLV- cats

	Age (yrs)	Sex (no. of animals)*				Breed (no.)*		
		M	MX	F	FX	D	S	O
30 animals	4.2 ± 3.1	14	8	3	5	21	7	2
22 FeLV+	4.0 ± 3.0	11	4	2	5	16	4	2
8 FeLV-	4.8 ± 3.5	3	4	1	0	5	3	0

*X = neutered, M = male, F = female, D = domestic, S = Siamese, O = other.

Table 2. Summary of ages, sex and breeds of 30 anemic cats with distribution between cats with lymphosarcoma, myeloproliferative disorders, and non-neoplastic conditions

	Age (yrs)	Sex (no. of animals)*				Breed (no.)*		
		M	MX	F	FX	D	S	O
30 animals	4.2 ± 3.1	14	8	3	5	21	7	2
11 lymphosarcoma	4.3 ± 3.0	7	2	1	1	7	3	1
5 myelproliferative disorder	4.6 ± 4.1	2	1	1	1	4	0	1
14 non-neoplastic	3.9 ± 3.0	5	5	1	3	10	4	0

*X = neutered, M = male, F = female, D = domestic, S = Siamese, O = other.

Table 3. Distribution of etiologic factors associated with anemia in 30 cats

Total feline leukemia virus positive		22	(73.3%)
FeLV+ - necropsied	17		
Lymphosarcoma	9		
Myeloproliferative disease	5		
Peritonitis (bacterial)	1		
Pleuritis and pericarditis	1		
Inconclusive	1		
FeLV+ - no necropsy	5		
Lymphosarcoma (peripheral blood)	2		
Neurologic symptoms	1		
Possible renal disease	1		
Inconclusive	1		
Total feline leukemia virus negative		8	(26.7%)
FeLV- - necropsied	4		
Chronic cellulitis - toxemia	1		
Renal failure	1		
Pyothorax (undetermined cause)	1		
Chronic liver disease	1		
FeLV- - improved	4		
Autoimmune hemolytic anemia	2		
Viral rhinotracheitis with secondary infection	1		
Chronic fungal infection, hemobartonellosis	1		

Table 4. Percentage distribution of etiologic factors associated with feline anemia

	Total	FeLV+	FeLV-
Lymphosarcoma	37.0%	50%	0.0%
Myeloproliferative disease	17.0%	24%	0.0%
Chronic infections	20.0%	9%	50.0%
AIHA	6.5%	0%	25.0%
Renal disease (not lymphosarcoma)	6.5%	3%	12.5%
Other	13.0%	14%	12.5%

Evidence was found of the myeloproliferative disease complex in 5 cases which were FeLV+. One was diagnosed as myelogenous leukemia, 3 had undifferentiated blast forms in bone marrow and/or peripheral blood, and 1 had evidence of myelofibrosis in bone marrow.

Three cases which were FeLV+ had no evidence of neoplasia in peripheral blood or at necropsy. Of these, 1 had what appeared to be bacterial peritonitis, 1 had a hypoplastic bone marrow and pleuritis, and 1 was inconclusive.

Three additional cases were FeLV+, but no necropsy was performed and no evidence of neoplasia was found in peripheral blood. One was showing neurologic signs, 1 had possible renal disease, and 1 had anemia and weight loss of undetermined cause.

Of 8 cats which were FeLV-, 2 were diagnosed as autoimmune hemolytic anemia. Four cats were suffering from a chronic infectious process. One had terminal renal failure, and 1 had chronic liver

disease with bile duct obstruction and fatty degeneration of the liver. Four FeLV- cats recovered.

Hematologic Data

Hematologic data of the 30 anemic cats are summarized in Table 5. Table 6 lists the data of the 22 FeLV+ animals, and Table 7 lists data of the 8 FeLV- animals. Table 8 is a summary of hematologic data of 11 cases of lymphosarcoma, and Table 9 lists data from those animals with myeloproliferative disease. Normal values for the cat as reported by Schalm et al. (1975) are listed in Table 10.

PCV, Hemoglobin, and Red Blood Cell Counts

The degree of anemia varied in the 30 animals. Means and ranges of packed cell volume (PCV), hemoglobin level, and red blood cell counts of the 30 animals (Table 5) were below normal values (Table 10).

The means for PCVs, hemoglobin levels, and red blood cell counts were lower for FeLV+ animals than FeLV- animals (Tables 6 and 7). In addition, means and ranges for these values were lower for 5 animals with myeloproliferative disease than 11 cats with lymphosarcoma (Tables 8 and 9).

Indices

Total mean values and ranges for the 30 cats (Table 5) would indicate an overall average of a normochromic and normocytic to slightly macrocytic anemia. The FeLV- group was closest to a normocytic response (Table 7), and the myeloproliferative group had the highest values for MCV (Table 9). Eight cats, 6 of which were FeLV+, had MCV values of 66 fl or higher, which would indicate a definite macrocytic response. Hemoglobin indices (MCH and MCHC) for all groups

Table 5. Ranges, means, and standard deviations in hematologic data of 30 anemic cats

	Range	Mean ± 1 SD
Erythrocytes (X 10^6/µl)	0.72 - 7.16	3.10 ± 1.02
Hemoglobin (g/dl)	1.4 - 11.0	5.9 ± 1.8
PCV (%)	5.0 - 34.0	17.7 ± 5.6
MCV (fl)	40.5 - 83.3	58.3 ± 8.2
MCH (pg)	12.1 - 37.5	19.7 ± 2.9
MCHC (g/dl)	26.7 - 41.0	34.0 ± 1.4
Plasma protein (g/dl)	5.0 - 8.8	6.9 ± 0.8
WBC/µl	900 - 36,700	9,360 ± 4,800
Neutrophils (total)	36 - 28,259	6,230 ± 4,790
Mature neutrophils	0 - 26,791	5,590 ± 4,420
Band neutrophils	0 - 6,860	630 ± 785
Lymphocytes	0 - 13,524	2,900 ± 2,720
Monocytes	0 - 1,360	90 ± 105
Eosinophils	0 - 3,060	200 ± 265
Basophils	0 - 1,360	10 ± 39
WBC (%)		
Neutrophils (total)	1.0 - 100.0	61.3 ± 40.0
Mature neutrophils	0.0 - 99.0	53.1 ± 29.0
Band neutrophils	0.0 - 70.0	8.2 ± 12.2
Lymphocytes	0.0 - 99.0	35.5 ± 29.7
Monocytes	0.0 - 18.0	1.1 ± 1.7
Eosinophils	0.0 - 28.0	1.9 ± 2.5
Basophils	0.0 - 5.0	0.1 ± 0.2

Table 6. Ranges, means, and standard deviations in hematologic data of 22 FeLV+ cats

	Range	Mean ± 1 SD
Erythrocytes (X 10^6/µl)	0.72 - 5.20	2.89 ± 0.91
Hemoglobin (g/dl)	2.0 - 11.0	5.8 ± 1.9
PCV (%)	5.0 - 34.0	17.3 ± 6.1
MCV (fl)	40.5 - 83.3	60.5 ± 6.7
MCH (pg)	14.9 - 37.5	20.5 ± 2.4
MCHC (g/dl)	27.6 - 41.0	34.1 ± 1.5
Plasma protein (g/dl)	5.4 - 8.7	6.8 ± 0.7
WBC/µl	900 - 21,700	8,085 ± 3,910
Neutrophils (total)	36 - 21,483	4,770 ± 3,920
Mature neutrophils	0 - 21,483	4,140 ± 3,440
Band neutrophils	0 - 6,860	630 ± 870
Lymphocytes	0 - 13,524	3,010 ± 2,980
Monocytes	0 - 1,360	90 ± 104
Eosinophils	0 - 3,060	190 ± 300
Basophils	0 - 1,360	10 ± 44
WBC (%)		
Neutrophils (total)	0.0 - 100.0	55.9 ± 31.8
Mature neutrophils	0.0 - 99.0	46.5 ± 28.6
Band neutrophils	0.0 - 70.0	9.4 ± 14.3
Lymphocytes	0.0 - 99.0	40.5 ± 31.6
Monocytes	0.0 - 18.0	1.2 ± 1.9
Eosinophils	0.0 - 28.0	2.3 ± 2.5
Basophils	0.0 - 5.0	0.1 ± 0.2

Table 7. Ranges, means, and standard deviations in hematologic data of 8 FeLV- cats

	Range	Mean ± 1 SD
Erythrocytes (X 10^6/µl)	0.90 - 7.16	3.69 ± 1.15
Hemoglobin (g/dl)	1.4 - 9.2	6.2 ± 1.3
PCV (%)	9.0 - 29.0	18.7 ± 4.3
MCV (fl)	31.5 - 78.1	52.2 ± 12.5
MCH (pg)	12.1 - 25.4	17.5 ± 3.1
MCHC (g/dl)	26.7 - 38.7	33.6 ± 0.8
Plasma protein (g/dl)	4.9 - 8.8	7.2 ± 1.0
WBC/µl	3,200 - 36,700	12,700 ± 5,564
Neutrophils (total)	1,404 - 28,259	10,000 ± 4,984
Mature neutrophils	952 - 26,791	9,400 ± 4,600
Band neutrophils	0 - 2,970	600 ± 537
Lymphocytes	0 - 8,466	2,480 ± 2,202
Monocytes	0 - 567	90 ± 113
Eosinophils	0 - 498	120 ± 109
Basophils	0 - 61	10 ± 23
WBC (%)		
Neutrophils (total)	23.0 - 99.0	76.1 ± 20.4
Mature neutrophils	14.0 - 95.0	71.2 ± 19.1
Band neutrophils	0.0 - 13.0	4.9 ± 2.2
Lymphocytes	0.0 - 73.0	21.9 ± 19.2
Monocytes	0.0 - 8.0	0.7 ± 0.9
Eosinophils	0.0 - 9.0	0.9 ± 1.2
Basophils	0.0 - 1.0	0.1 ± 0.2

Table 8. Ranges, means, and standard deviations in hematologic data of 11 cats with lymphosarcoma

	Range	Mean ± 1 SD
Erythrocytes (X 10^6/µl)	1.85 - 5.20	3.26 ± 0.65
Hemoglobin (g/dl)	3.5 - 11.0	6.5 ± 1.6
PCV (%)	10.0 - 32.0	19.4 ± 5.1
MCV (fl)	43.7 - 75.0	59.0 ± 7.2
MCH (pg)	15.4 - 25.7	19.9 ± 2.1
MCHC (g/dl)	30.1 - 36.4	33.9 ± 1.4
Plasma protein (g/dl)	5.4 - 8.3	6.6 ± 0.6
WBC/µl	900 - 21,700	9,100 ± 4,207
Neutrophils (total)	36 - 21,483	5,100 ± 4,711
Mature neutrophils	0 - 21,483	4,600 ± 4,572
Band neutrophils	0 - 6,439	500 ± 699
Lymphocytes	93 - 13,524	3,760 ± 3,941
Monocytes	0 - 890	120 ± 92
Eosinophils	0 - 429	100 ± 70
Basophils	0 - 143	20 ± 27
WBC (%)		
Neutrophils (total)	1.0 - 99.0	50.3 ± 33.9
Mature neutrophils	0.0 - 99.0	45.6 ± 31.1
Band neutrophils	0.0 - 47.0	4.6 ± 5.4
Lymphocytes	1.0 - 99.0	45.4 ± 33.1
Monocytes	0.0 - 18.0	1.9 ± 2.5
Eosinophils	0.0 - 17.0	2.0 ± 2.5
Basophils	0.0 - 5.0	0.1 ± 0.3

Table 9. Ranges, means, and standard deviations in hematologic data of 5 cats with myeloproliferative disorders

	Range	Mean ± 1 SD
Erythrocytes (X 10^6/µl)	0.72 - 4.84	2.40 ± 1.08
Hemoglobin (g/dl)	2.0 - 10.5	4.9 ± 2.3
PCV (%)	6.0 - 32.0	14.4 ± 7.3
MCV (fl)	40.5 - 83.3	63.9 ± 3.4
MCH (pg)	14.9 - 37.5	21.8 ± 1.8
MCHC (g/dl)	27.6 - 45.0	34.6 ± 1.2
Plasma protein (g/dl)	5.6 - 8.7	7.3 ± 0.4
WBC/µl	900 - 36,700	7,340 ± 4,484
Neutrophils (total)	36 - 28,259	3,190 ± 2,823
Mature neutrophils	0 - 26,791	2,680 ± 2,355
Band neutrophils	0 - 6,860	510 ± 516
Lymphocytes	0 - 13,524	3,300 ± 1,363
Monocytes	0 - 1,360	120 ± 152
Eosinophils	0 - 3,060	540 ± 495
Basophils	0 - 1,360	40 ± 87
WBC (%)		
Neutrophils (total)	9.0 - 100.0	50.4 ± 35.9
Mature neutrophils	3.0 - 77.0	32.6 ± 19.8
Band neutrophils	0.0 - 70.0	17.8 ± 24.2
Lymphocytes	0.0 - 90.0	44.8 ± 34.3
Monocytes	0.0 - 6.0	0.8 ± 0.8
Eosinophils	0.0 - 28.0	4.0 ± 4.2
Basophils	0.0 - 1.0	0.1 ± 0.1

Table 10. Means and ranges in hematologic data of normal cats as reported by Schalm et al. (1975)

	Range	Mean
Erythrocytes (X 10^6/µl)	5.0 - 10.0	7.5
Hemoglobin (g/dl)	8.0 - 15.0	12.0
PCV (%)	24.0 - 45.0	37.0
MCV (fl)	39.0 - 55.0	45.0
MCH (pg)	12.5 - 17.5	15.5
MCHC (g/dl)	30.0 - 36.0	33.2
Plasma protein (g/dl)	6.0 - 8.0	
WBC/µl	5,500 - 19,500	12,500
Neutrophils (mature)	2,500 - 12,500	7,500
Neutrophils (band)	0 - 300	100
Lymphocytes	1,500 - 7,000	4,000
Monocytes	0 - 850	350
Eosinophils	0 - 1,500	650
Basophils	rare	0
WBC (%)		
Neutrophils (mature)	35 - 75	59.0
Neutrophils (band)	0 - 3	0.5
Lymphocytes	20 - 55	32.0
Monocytes	1 - 4	3.0
Eosinophils	2 - 12	5.5
Basophils	rare	0.0

were within normal ranges or slightly higher, and therefore none could be classified as hypochromic.

Plasma Protein

Means and ranges for the 30 animals (Table 5) and all subgroups (Tables 6 through 9) were within normal limits (Table 10).

Total White Blood Cell Counts

Means and ranges of white cell counts for 29 cats (Table 5) and all subgroups (Tables 6 through 9) were within normal limits (Table 10). One cat had an extremely high white cell count, and was not included in the calculation of the mean.

The majority of animals had total white blood cell counts within normal range, but a higher percentage of FeLV- cats had leukocytosis, and none had leukopenia (Table 11). The FeLV+ group had the highest percentage of animals with leukopenia (Table 11).

Mature Neutrophils (Absolute)

Means and ranges of 29 cats (Table 5) and all subgroups (Tables 6 through 9) were within normal limits (Table 10).

The majority of cats had mature neutrophil counts within normal range, but a higher percentage of FeLV- animals had increased numbers of mature neutrophils, and none in this group had neutropenia (Table 11). Conversely, a higher percentage of the myeloproliferative and lymphosarcoma groups had depression in mature neutrophil numbers (Table 11).

Band Neutrophils (Absolute)

Means and ranges for the 29 animals and all subgroups were approximately the same, and all were elevated (Tables 5 through 9).

Table 11. Percent of anemic cats with normal, elevated, or decreased absolute numbers of total white blood cells, segmented neutrophils, and band neutrophils

	WBCs (total)*			Seg. Neut.*			Band Neut.*	
	↑	N	↓	↑	N	↓	N	↑
30 cats	10%	73%	17%	23%	63%	14%	40%	60%
22 FeLV+	5%	73%	22%	4%	65%	31%	50%	50%
8 FeLV-	25%	75%	0%	37%	63%	0%	12%	88%
11 lymphosarcoma	0%	82%	18%	0%	63%	37%	54%	46%
5 myeloproliferative disorder	20%	60%	20%	20%	40%	40%	40%	60%

*WBC = white blood cells, Seg. Neut. = segmented neutrophils, Band Neut. = band neutrophils, N = normal, ↑ = increased, ↓ = decreased.

The majority of animals had increased numbers of band neutrophils, and the FeLV- group had the highest percentage with band neutrophilia (Table 11).

Lymphocytes (Absolute)

Total mean and ranges for the 30 cats and all subgroups were approximately the same (Tables 5 through 9) and were within normal limits (Table 10). The FeLV- group had the highest percentage of animals with lymphopenia, and the lymphosarcoma group had the highest percentage with lymphocytosis (Table 12).

Monocytes, Eosinophils and Basophils (Absolute)

Monocyte, eosinophil, and basophil numbers were within normal range for all groups (Tables 5 through 10).

Table 12. Percent of anemic cats with normal, elevated, or decreased absolute numbers of lymphocytes

	Lymphocytes*		
	↑	N	↓
30 cats	7%	67%	26%
22 FeLV+	9%	68%	23%
8 FeLV-	0%	62%	38%
11 lymphosarcoma	18%	54%	28%
5 myeloproliferative disorder	0%	100%	0%

*N = normal, ↑ = increased, ↓ = decreased.

Relative Differential White Blood Cell Counts - Mature Neutrophils

The myeloproliferative animals were the only group which was out of normal range (Table 10), with a decreased percentage of mature neutrophils (Table 9). The FeLV- group had a higher percentage of segmented neutrophils when compared with the FeLV+ group (Tables 6 and 7).

Band Neutrophils

All groups had an increased percentage of band neutrophils, with the myeloproliferative group having the highest (Tables 5 through 9). The FeLV+ group had a higher percentage of band neutrophils than FeLV- negative animals (Tables 6 and 7).

Lymphocytes

All groups were within normal range (Tables 5 through 10). The FeLV- cats had a lower percentage of lymphocytes than FeLV+ animals (Tables 6 and 7).

Monocytes, Eosinophils, and Basophils

The relative number of monocytes, eosinophils, and basophils for all groups were within normal range (Tables 5 through 10).

Morphologic Alterations on Peripheral Blood Smears

Morphologic alterations which were noted on peripheral blood smears included the following: anisocytosis, poikilocytosis, polychromasia, nucleated red blood cells, Howell-Jolly bodies, basophilic stippling, toxic neutrophils and Döhle bodies, metamyelocytes, reactive lymphocytes, atypical cells, *Hemobartonella felis* organisms, Heinz bodies (new methylene blue stain), and smudge cells. The most frequent observations of regeneration were nucleated red blood cells, anisocytosis, and polychromasia (Table 13). A higher percentage of FeLV- animals had regenerative signs than FeLV+ animals. All regenerative signs except poikilocytosis were observed more frequently in the myeloproliferative group than in lymphosarcoma animals (Table 13).

Toxic neutrophils and Döhle bodies were observed in 73.3% of anemic cats (Table 13). All FeLV- animals had toxic cells, while these observations were less commonly observed in FeLV+ animals. Metamyelocytes were most frequently observed in the myeloproliferative group (Table 13).

A higher percentage of reactive lymphocytes was found in FeLV- than FeLV+ cats (Table 13). More than 1 atypical or undifferentiated cell was observed in peripheral blood of 36.7% of anemic cats, 50% of FeLV+ cats, 54.5% of lymphosarcoma animals, and 100% of myeloproliferative cats (Table 13). One atypical or undifferentiated cell was observed in 10% of anemic cats, 4% of FeLV+ animals, and 25% of FeLV- animals.

Table 13. Percent of morphologic alterations on peripheral blood smears of anemic cats

	Total	FeLV+	LY*	M*	FeLV-
Anisocytosis	50.0%	45.5%	45.5%	60.0%	62.5%
Poikilocytosis	23.3%	13.6%	18.2%	0.0%	50.0%
Polychromasia	40.0%	40.9%	36.4%	60.0%	37.5%
NRBCs	53.3%	50.0%	36.4%	60.0%	62.5%
Basophilic stippling	6.7%	9.1%	9.1%	20.0%	0.0%
Howell-Jolly bodies	33.3%	36.4%	27.3%	40.0%	25.0%
Toxic PMNs Döhle bodies	73.3%	63.6%	63.6%	40.0%	100.0%
Reactive lymphocytes	46.7%	31.8%	36.4%	0.0%	87.5%
Metamyelocytes	16.7%	13.6%	0.0%	40.0%	25.0%
H. felis	6.7%	4.5%	9.1%	0.0%	12.5%
Atypical cells	36.7%	50.0%	54.5%	100.0%	0.0%
Heinz bodies	6.7%	9.1%	9.1%	0.0%	0.0%
Smudge cells	13.3%	9.1%	9.1%	0.0%	25.0%

*LY = lymphosarcoma, M = myeloproliferative.

Hemobartonella felis organisms were observed on peripheral blood smears of 2 cats (Table 13). One animal had lymphosarcoma, and the other a chronic fungal infection.

Smudge cells and Heinz bodies were observed in a small percentage of animals (Table 13).

Platelets

The majority of animals studied had adequate or increased numbers of platelets (Table 14). All animals with consistent or progressive

Table 14. Percentage distribution of platelet numbers on peripheral smears of anemic cats

	Adequate	↑	Adequate then ↓	↓
30 anemic cats	36.7%	33.3%	13.3%	16.7%
FeLV+	36.4%	31.8%	18.2%	13.6%
FeLV-	62.5%	37.5%	0.0%	0.0%
Lymphosarcoma	27.3%	27.3%	27.3%	18.1%
Myeloproliferative	40.0%	40.0%	20.0%	0.0%

thrombocytopenia were FeLV+. The lymphosarcoma group had the highest percentage of animals with thrombocytopenia (Table 14). Thrombocytopenia was observed on peripheral smears of 2 FeLV- cats, but this was an inconsistent observation in the course of several hematologic evaluations.

Reticulocytes (Aggregate)

The 30 anemic cats had an average reticulocyte count of 3.7% (Table 15). The FeLV- group had the highest mean, while the lymphosarcoma group had the lowest (Table 15). The FeLV- animals had an average absolute number of reticulocytes which was approximately twice that of the FeLV+ group, and 3 to 4 times greater than the lymphosarcoma and myeloproliferative groups (Table 15). The reticulocyte index for the FeLV- group was greater than the normal value of 1, while all other groups had means lower than 1, with the myeloproliferative group being the lowest (Table 15). Considering the groups

Table 15. Summary of aggregate reticulocyte numbers in normal and anemic cats

	%	Absolute (X 10^3)	Index
Normal*	0.2 - 1.6	10.0 - 160.0	1.0
30 anemic cats	3.7 ± 3.7	115.0 ± 129.2	0.98 ± 1.12
FeLV+	3.3 ± 3.4	93.0 ± 106.6	0.84 ± 0.70
FeLV-	4.6 ± 4.4	173.0 ± 172.2	1.37 ± 1.43
Lymphosarcoma	2.0 ± 2.8	68.0 ± 99.2	0.60 ± 0.75
Myeloproliferative	2.7 ± 3.6	48.0 ± 59.3	0.44 ± 0.50

*Schalm et al. (1975).

individually, 31.8% of FeLV+ animals and 62.5% of FeLV- animals had increased absolute numbers of reticulocytes, and an increase in reticulocyte index. Twenty-seven and three-tenths percent of lymphosarcoma animals had an increase in the absolute number of reticulocytes, and

18.2% had an increased reticulocyte index. Twenty percent of the myeloproliferative group had an increase in both absolute reticulocyte numbers and reticulocyte index.

Osmotic Fragility

The mean for the 30 anemic cats was 0.72 for initial hemolysis and 0.56 for complete hemolysis. All subgroups were approximately the same (Table 16). Nine FeLV+ animals and 3 FeLV- animals had a moderate increase in osmotic fragility levels. Two FeLV- animals, both of which were Coombs positive, had a slight increase in osmotic fragility levels. One FeLV+ animal and 1 FeLV- cat had decreased osmotic fragility levels.

Table 16. Summary of osmotic fragility levels in 30 control and 30 anemic cats

	Initial	Complete
30 control cats	0.67 ± 0.05	0.50 ± 0.04
30 anemic cats	0.72 ± 0.04	0.56 ± 0.08
FeLV+	0.72 ± 0.04	0.56 ± 0.06
FeLV-	0.73 ± 0.05	0.56 ± 0.12
Lymphosarcoma	0.72 ± 0.05	0.55 ± 0.06
Myeloproliferative	0.73 ± 0.02	0.58 ± 0.04

Coombs Test

Only 2 animals were strongly positive for the direct Coombs test, and both were negative for the feline leukemia virus. One

animal was trace positive for the Coombs test, and also positive for the feline leukemia virus.

Fibrinogen

The 30 anemic cats averaged 3.4 g/l, and the FeLV+ cats had higher levels than FeLV- animals (Table 17). Approximately the same percentage of all groups had elevated levels of fibrinogen (Table 17). Six animals had values of 4.0 g/l or higher (5 FeLV+ and 1 FeLV-), and only 1 cat (FeLV+) had a markedly elevated level of fibrinogen (13 g/l).

Table 17. Summary of fibrinogen levels in 30 anemic cats

	Fibrinogen (g/l)	% Elevated
Normal*	0.5 - 3.0	
30 anemic cats	3.4 ± 2.1	46.7
FeLV+	3.5 ± 2.4	45.4
FeLV-	2.8 ± 1.0	50.0
Lymphosarcoma	3.8 ± 3.1	54.5
Myeloproliferative	3.7 ± 2.0	40.0

*Schalm et al. (1975).

Sedimentation Rate

Means for the 30 anemic cats and all subgroups were considerably higher than the control animals (Table 18). The myeloproliferative group had the highest values, which corresponded to the severity of

anemia. Only 5 animals, all of which were FeLV+, had sedimentation rates within the range of the control animals.

Table 18. Ranges, means, and standard deviations of sedimentation rates in 30 control and 30 anemic cats

	Range (mm)	Mean ± 1 SD (mm)
30 control cats	2.0 - 31.0	14.0 ± 8.6
30 anemic cats	20.0 - 87.0	53.2 ± 18.3
FeLV+	20.0 - 87.0	53.1 ± 19.5
FeLV-	32.0 - 68.0	53.6 ± 15.8
Lymphosarcoma	20.0 - 87.0	49.4 ± 22.2
Myeloproliferative	40.0 - 70.0	60.2 ± 16.0

Blood Chemistries

Serum Bilirubin

The means for all groups were higher than the normal level of serum bilirubin, with the FeLV- group being the highest (Table 19). Only 6 animals had bilirubin levels within normal range, and all were FeLV+. Four FeLV+ lymphosarcoma cats and 3 FeLV- animals had bilirubin values which were greater than 1.0 mg/dl, with an elevation of both direct and indirect fractions. One cat had a markedly elevated value (11.5 mg/dl), and this animal had chronic liver disease with bile duct obstruction. The 2 animals with AIHA did not have elevated levels of indirect bilirubin in their serums.

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Table 19. Means and standard deviations of total, direct, and indirect serum bilirubin levels in normal and 30 anemic cats

	Total (mg/dl)	Direct (mg/dl)	Indirect (mg/dl)
Normal*	0.15 - 0.20		
30 anemic cats	1.2 ± 2.2	0.8 ± 1.5	0.4 ± 0.8
FeLV+	0.9 ± 1.7	0.5 ± 0.7	0.4 ± 0.6
FeLV-	2.1 ± 1.9	1.4 ± 2.7	0.7 ± 1.2
Lymphosarcoma	1.4 ± 1.7	0.8 ± 0.9	0.6 ± 0.8
Myeloproliferative	0.5 ± 0.3	0.3 ± 0.2	0.2 ± 0.1

*Lopez Garcia et al. (1963).

Other Blood Chemistries

Blood urea nitrogen levels were measured on 12 animals. Eight cats had levels within the reported normal range of 20 to 30 mg/dl (Coles, 1974), 2 animals had moderate elevations (46 to 56 mg/dl), and these animals were both FeLV+. One FeLV+ and 1 FeLV- animal had marked elevations of BUN (103 to 158 mg/dl). The animals with markedly elevated BUNs also had significant elevation in creatinine levels (4.4 to 7.8 mg/dl). The serum creatinine levels are reported to be normally in the range of 1.0 to 2.0 mg/dl (Coles, 1974).

Blood glucose levels in the cat are normally in the range of 50 to 75 mg/dl (Kaneko, 1973). One anemic cat had a normal level of blood glucose, and 1 had an elevated level (189 mg/dl). This animal had other evidence of pancreatic disease.

Serum glutamic pyruvic transaminase (SGPT) levels were measured in 7 animals. The normal level of SGPT in the cat is reported to be

15.6 ± 9.9 IU/l (Cornelius and Kaneko, 1960). One FeLV- animal had a slight elevation in SGPT (74 IU/l), 2 FeLV+ animals had moderate elevations (220 to 270 IU/l), and 1 FeLV+ animal had a marked elevation of SGPT (1175 IU/l). Two of the latter also had elevations in serum bilirubin levels.

Amylase and lipase levels were measured on 1 animal suspected of having pancreatic problems. The amylase level was borderline and the lipase level was normal.

Urinalyses

A complete urinalysis was performed on all animals. The 2 animals with high BUN and creatinine levels had a specific gravity at the isosthenuric point. These animals also had proteinuria and moderate numbers of small round epithelial cells and granular casts in the urine sediment. Three other animals had low specific gravities near 1.012, and evidence of chronic interstitial nephritis was found in 1 cat at necropsy.

Only 1 cat (FeLV+) had a moderate amount of occult blood in the urine, and this animal also had significant numbers of red blood cells in the urine sediment. Two animals had a trace of bilirubin in the urine, and both of these had elevated levels of bilirubin in their serums. No other significant changes were noted in the urinalyses.

Fecal Determination

No parasite ova were found in these anemic cats. A trace of occult blood was found in 2 FeLV+ animals, and a 1+ occult blood was seen in 4 animals, 3 of which were FeLV+.

Bone Marrow Examination

Bone marrow cytologies were performed in 2 cases, and samples were examined at necropsy in 17 additional cases. The results of bone marrow examinations are summarized in Table 20. Five of 9 cases of lymphosarcoma which were necropsied and all cases of myeloproliferative disease had neoplastic involvement of bone marrow.

Cytologic Examinations

Thoracic fluid samples were examined in 3 cases. Evidence of lymphosarcoma was found in 1, 1 was a modified transudate with red blood cells, a few white blood cells, and an occasional macrophage, and 1 showed evidence of a pyogranulomatous pleuritis (Table 21). Peritoneal fluid was examined in 1 case, which was an inflammatory exudate. Cytologies were taken of superficial lesions in 2 cases. In 1 there was evidence of acute inflammation with foreign debris, and the other showed evidence of a mycotic granulomatous dermatitis. A lymph node aspirate was taken in 1 case which revealed a pleomorphic population of lymphocytes which was suggestive of lymphosarcoma (Table 21).

Biopsies

Lymph node biopsies were taken in 2 cats which were FeLV+. One was conclusive of lymphosarcoma, and 1 was inflammatory and necrotic, with no evidence of neoplasia. A splenic biopsy was also taken from the cat with lymphadenitis which revealed myeloid metaplasia but no evidence of neoplasia. A liver biopsy was taken in 1 FeLV- cat which revealed diffuse and extensive fatty degeneration. A biopsy of subcutaneous fat was taken in 1 FeLV+ cat in which steatitis was suspected,

Table 20. Summary of bone marrow examinations of 19 anemic cats

Case no.	Final diagnosis	FeLV	Bone marrow conclusions
1	lymphosarcoma	+	Mild erythroid hypoplasia, lymphoid neoplasia
2	lymphosarcoma	+	Elements in normal numbers
3	lymphosarcoma	+	Mild erythroid hypoplasia, lymphoid neoplasia
4	lymphosarcoma	+	Marked erythroid hypoplasia, small numbers of atypical lymphocytes
5	lymphosarcoma	+	Mild infiltration with lymphoblasts, mild erythroid hypoplasia
6	lymphosarcoma	+	Severe lymphoid neoplasia, normal elements displaced
7	lymphosarcoma	+	Elements in normal numbers
8	lymphosarcoma	+	Elements in normal numbers
9	lymphosarcoma	+	Slight erythroid hypoplasia, atrophy of bone marrow fat
12	myeloproliferative disease	+	Myelogenous neoplasia, marked erythroid hypoplasia
13	myeloproliferative disease	+	Predominance of undifferentiated blast forms, erythroid hypoplasia
14	myeloproliferative disease	+	Predominance of undifferentiated blast forms, marked erythroid hypoplasia
15	myeloproliferative disease	+	Stem cells present, but no maturation of erythrocytes - hypoplasia
16	myeloproliferative disease	+	Myelofibrosis replacing normal elements

Table 20 (continued)

Case no.	Final diagnosis	FeLV	Bone marrow conclusions
17	chronic peritonitis	+	Elements in normal numbers
18	pleuritis & pericarditis	+	Elements in normal numbers
19	inconclusive	+	R-E proliferation - not conclusive of neoplasia
25	pyothorax	-	Elements in normal numbers
26	chronic liver disease	-	Slight hyperplasia of erythroid elements

Table 21. Summary of cytologic examinations of 7 anemic cats

FeLV	Final diagnosis	Sample	Cytologic conclusions
+	lymphosarcoma	thoracic fluid	Lymphosarcoma
+	lymphosarcoma	lymph node aspirate	Suggestive of lymphosarcoma
+	lymphosarcoma	thoracic fluid	Modified transudate
+	chronic peritonitis	peritoneal fluid	Inflammatory exudate
-	chronic cellulitis, toxemia	left hock debridement	Acute inflammation with foreign debris
-	pyothorax	thoracic fluid	Pyogranulomatous pleuritis
-	chronic fungal infection, hemobartonellosis	dermal lesion	Mycotic granulomatous dermatitis

but no significant lesions were noted. Biopsies were taken in 2 cats with subcutaneous lesions and confirmed cytologic diagnoses.

Necropsy and Histopathology

Twenty-one of 30 animals were necropsied. Necropsy findings are summarized in Table 22. Of 9 cases of lymphosarcoma, 4 were of the alimentary form, 3 were thymic in origin, and 2 were multicentric.

Table 22. Summary of necropsy findings in 21 anemic cats

FeLV	Necropsy conclusions
+	Lymphosarcoma within mesenteric nodes, kidney, intestine, bone marrow; chronic interstitial nephritis
+	Lymphosarcoma within mesenteric nodes, ileum, spleen, kidneys
+	Thymic lymphosarcoma; also involvement of liver, kidneys, bone marrow
+	Lymphosarcoma within mesenteric nodes, liver, spleen, kidneys, bone marrow; chronic interstitial nephritis
+	Thymic lymphosarcoma; also involvement of liver, lymph nodes, spinal cord, bone marrow; myelomalacia of lumbar portion of cord
+	Lymphosarcoma within lymph nodes, spleen, bone marrow; chronic interstitial nephritis
+	Lymphosarcoma within lymph nodes, including mesenteric, liver, spleen
+	Thymic lymphosarcoma; no metastasis to other tissues
+	Lymphosarcoma within mesenteric nodes, kidney; chronic interstitial nephritis
+	Myeloproliferative disease; neoplastic myelogenous cells within bone marrow, liver, spleen; splenomegaly
+	Myeloproliferative disease; undifferentiated blast forms in bone marrow; no other evident lesions
+	Myeloproliferative disease; undifferentiated blast forms in bone marrow and spleen; splenomegaly
+	Myeloproliferative disease; stem cells in bone marrow, but otherwise hypoplastic marrow; pleuritis
+	Myeloproliferative disease; myelofibrosis of bone marrow; hyperplasia of R-E elements in spleen and liver
+	Chronic peritonitis, suggestive of bacterial; no evidence of neoplasia
+	Acute pleuritis and pericarditis; no evidence of neoplasia

Table 22 (continued)

FeLV	Necropsy conclusions
+	Inconclusive; large hairball in stomach; some hyperplasia of R-E elements, but not conclusive of neoplasia
-	Diffuse cellulitis of left hock; generalized toxemia; etiologic agent: *Pseudomonas* sp. or *Staphylococcus aureus*, or both
-	Chronic interstitial nephritis
-	Pyothorax (undetermined cause)
-	Fatty degeneration of liver; cholangitis

DISCUSSION

This survey supports the data that anemia in the cat is commonly associated with the feline leukemia virus (Cotter et al., 1975), as 73.3% of animals surveyed were positive for the virus. In addition, 72.7% of FeLV+ animals were suffering from the feline leukemia complex, which indicates a high degree of correlation between incidence of hematopoietic neoplasia and positive results in the FeLV test. The most common form of hematopoietic neoplasia observed was lymphosarcoma, as has been reported by several authors (Hardy, 1974; Ott et al., 1974; Dorn et al., 1975; Schalm et al., 1975), and all of these animals were FeLV+. The highest percentage of animals had the alimentary form of lymphosarcoma, with thymic and multicentric forms occurring less frequently. This would correlate with the incidence which is usually reported in the literature (Jarrett et al., 1966; Owen, 1969; Cotchin, 1956; Meincke et al., 1972).

A smaller percentage of animals had a form of myeloproliferative disease, and all were FeLV+. Six other FeLV+ animals had no evidence of neoplasia, but several were suffering from chronic infections which are also associated with FeLV due to immunosuppression (Anderson et al., 1971; Mackey et al., 1972; Perryman et al., 1972).

Several of the FeLV negative animals were also suffering from chronic infectious, which may be a cause of anemia in itself (Cartwright et al., 1951; Davidsohn and Henry, 1969; Schalm et al., 1975). The 20% incidence of anemias associated with chronic

infection was lower than the 50% incidence reported by Holzworth (1956). None of the FeLV- animals had evidence of neoplasia.

Other causes of anemia in the cat which were represented in this group of animals were hemobartonellosis, autoimmune hemolytic anemia, renal disease, and liver disease. The incidence of hemobartonellosis as a cause of anemia was less than is frequently reported (Schalm and Smith, 1963; Loeb, 1964; Holzworth, 1956), even though successive blood films were examined in all animals. This may be related to the cyclic nature of the organism (Wilkinson, 1969; Switzer, 1969b). Only 1 case of feline leukemia had hemobartonellosis concurrently, which is a lower incidence than is reported by some authors (Ott et al., 1974; Schalm et al., 1975). Anemias associated with acute blood loss, parasitism, toxic agents, nutritional deficiencies, neoplasia other than that of the hematopoietic system, or endocrine deficiencies were not observed in this study.

The anemias were most severe in the myeloproliferative disorders, as has been reported in the literature (Gilmore et al., 1964; Schalm and Theilen, 1970; Schalm, 1971). In addition, FeLV+ animals were more anemic than FeLV- animals.

Hemogram data of these cats indicated that many were suffering from nonregenerative anemias, which is usually reported to be the case in leukemias and chronic infections (Gilmore et al., 1964; Switzer, 1971a; Coles, 1974; Schalm et al., 1975). However, 8 animals did have a macrocytic response, and 6 were FeLV+. In addition, a significant percentage of animals had evidence of anisocytosis, polychromasia, nucleated red blood cells, and Howell-Jolly bodies observed on peripheral blood smears. Absolute numbers of reticulocytes and the reticulocyte index were increased in 31.8% of FeLV+ animals, and

62.5% of FeLV- animals. In addition, 27.3% of lymphosarcoma animals had an increase in the absolute number of reticulocytes, and 18.2% had an increase in the reticulocyte index. Twenty percent of the myeloproliferative animals had an increase in these two values. These observations would suggest a regenerative response in these animals, which is not often reported in cases of feline leukemias. However, many anemias became progressive and refractory to treatment in spite of some attempt at regeneration. This would agree with the observation of Cotter et al. (1973, 1975).

Absolute white blood cell values were quite variable in these animals, particularly in FeLV+ animals. In the lymphosarcoma cases, leukopenia was observed more frequently than leukocytosis. In addition, neutropenia was observed more frequently than neutrophilia, and lymphopenia was more frequent than lymphocytosis. In the myeloproliferative disorders, leukocytosis was observed as frequently as leukopenia, and a higher percentage of animals had neutropenia than neutrophilia. Also, thrombocytopenias were occasionally observed in FeLV+ animals, and not in FeLV- animals. These findings would be consistent with those most often reported in the literature (Holzworth, 1960a,b; Squire, 1964; Jarrett, 1971; Coles, 1974; Schalm et al., 1975), although some authors have noted other distributions of white blood cells in these conditions (Crighton, 1968a; Hardy, 1974; Wilkins, 1974). Thrombocytopenia has been reported in conjunction with autoimmune hemolytic anemia in the cat (Scott et al., 1973), but cats in this study with AIHA had normal numbers of platelets.

Heinz bodies were observed in a smaller percentage than is usually reported in cats (Beritic, 1965; Schechter et al., 1973 Schalm et al., 1975). Toxic neutrophils, Döhle bodies, and reactive

lymphocytes were seen in a high percentage of animals, which would be consistent with the reported incidence of these in sick cats (Schalm et al., 1975).

Significant numbers of lymphoblasts were observed in peripheral blood in 54.5% of lymphosarcoma animals, which is higher than the <25% incidence which is usually reported (Holzworth, 1960a; Schalm et al., 1975). However, this may be explained by the smaller number of animals surveyed (11) and the number which had involvement of bone marrow (50%). All of the cases of myeloproliferative disease had neoplastic cells in peripheral blood, which is consistent with reports in the literature (Holzworth, 1960b; Fraser et al., 1974; Coles, 1974; Schalm et al., 1975). A few animals had 1 atypical cell observed in peripheral blood, which is reported to occur in the cat in conditions other than hematopoietic neoplasia (Wilkins, 1974; Crighton, 1968a).

Approximately half of the confirmed cases of lymphosarcoma had infiltration of neoplastic cells within bone marrow, which is a higher percentage than is frequently reported in the literature (Holzworth, 1960a; Schalm et al., 1975). This percentage might have been even higher if bone marrow samples had been examined in 2 animals which had lymphoblasts in peripheral blood, but were not confirmed with necropsy and histopathology. This disparity from the reported incidence may also be related to the relatively small number of animals surveyed (11). All of the cases of myeloproliferative disease had neoplastic involvement of bone marrow, which usually occurs in these disorders (Holzworth, 1960b; Ward et al., 1969; Schalm et al., 1975). In addition to the infiltration of neoplastic cells, many bone marrows had evidence of erythroid hypoplasia.

The Coombs test was valuable in identifying 2 cases of autoimmune hemolytic anemia. It has been reported that animals which are positive for feline leukemia virus may be Coombs positive (Scott et al., 1973). This was observed in only 1 of 22 FeLV+ animals. In man, cases of AIHA have been reported in conjunction with lymphoreticular malignancies (Rosenthal et al., 19755; Troup et al., 1960). However, no confirmed cases of lymphosarcoma in this study were positive for the Coombs test.

The osmotic fragility, fibrinogen, and sedimentation rate tests were of questionable significance in these animals. Twelve animals did have increased osmotic fragilities, and 2 of these were cases of hemobartonellosis. The 2 cases of AIHA had only slight elevations in osmotic fragility. Schalm et al. (1975) reported increased osmotic fragility levels in these 2 conditions and concluded that increases in osmotic fragility may represent a shortened survival of red cells. The presence of young erythrocytes may be a cause of decreased osmotic fragility (Schalm et al., 1975), but the 2 animals with decreased levels did not have evidence of polychromasia in their peripheral smears or elevated reticulocyte counts.

The sedimentation rates were usually rapid and correlated with severity of anemia, which would correspond to the observations of Crighton (1968a). The fibrinogen level may be correlated with sedimentation rate (Schalm et al., 1975), and the animal in this study with the highest fibrinogen level also had the highest sedimentation rate. However, this animal was also severely anemic. Many animals had a slight elevation of fibrinogen, which may be related to inflammatory processes (Schalm et al., 1975).

The bilirubin levels were elevated in several of these animals. Neoplastic involvement of the liver was found in only 1 animal. Another with a marked elevation had chronic liver disease and bile obstruction. None of the animals had elevations of only the indirect fraction to indicate intravascular hemolysis.

The mechanism of anemia in these animals could not always be explained precisely but, in this group of animals, hemolysis did not seem to be a prevalent cause of anemia. Two cases were diagnosed as autoimmune hemolytic anemia, and *Hemobartonella felis* organisms were observed in 2 cases. Hemoglobinuria was observed in only 1 animal. Many animals did have regenerative signs in response to anemia, but these were dramatic in only a few cases.

Therefore, the most predominant cause of anemia in these cats was inadequate production of erythrocytes. Several leukemia cases had an infiltration of neoplastic cells within bone marrow and evidence of erythroid hypoplasia, and could therefore be explained as myelophthisis (Schalm et al., 1975). In addition, some cases of myeloproliferative disease had only partial maturation of erythrocytes and other cells in bone marrow, which would account for severe anemia. No overt signs of hemolysis were observed in any cases of the leukemia complex. Several of these animals did have neoplastic involvement of the kidneys and evidence of chronic interstitial nephritis, which would also contribute to anemia due to decreased levels of erythropoietin (Osborne et al., 1971).

It would have been helpful to have performed serum iron studies in these cases to further evaluate the mechanisms of anemia, particularly in cases of chronic infection. In addition, it would have been interesting to have evaluated calcium and phosphorus levels in serum

in these cats, particularly in cases of lymphosarcoma, to see if any cases might have had a hypercalcemia. Bone marrow examinations were performed on several animals, but a better evaluation could have been made if samples had been obtained on all animals.

Clearly, anemia in the cat is an important clinical entity. The prevalence of the feline leukemia virus is an important reason for the large number of anemic patients which are presented to the clinician. The use of laboratory parameters may aid in the diagnosis of these cases. Of particular importance would be serial peripheral blood studies, the immunofluorescence test for the feline leukemia virus, and bone marrow examinations.

Of the 30 animals in this study, only 4 cats recovered, which is characteristic of the poor prognosis associated with anemia in the cat.

SUMMARY

Thirty anemic cats which were patients at the Michigan State University Veterinary Clinical Center were surveyed. These animals varied in age from 10 weeks to 12 years, and several breeds were represented. The causes and pathogenesis of the anemias were studied utilizing a series of hematologic tests, blood chemistry determinations, urinalysis and fecal analyses, cytologic examinations, and histopathology.

The majority (73.3%) of animals studied were positive for the feline leukemia virus. Many of these animals had evidence of erythrocytic regeneration in peripheral blood, increases in absolute reticulocyte numbers, and elevated reticulocyte indexes, but the anemias were usually progressive in nature and refractory to treatment. Necropsy results indicated that many of these animals had gross and microscopic lesions consistent with the feline leukemia complex, including both lymphosarcoma and the myeloproliferative disorders. Erythroid hypoplasia and neoplastic cell infiltration were common observations in the bone marrows of these cats.

Other causes of anemia in these animals included autoimmune hemolytic anemia, chronic viral and bacterial infections, renal disease, liver disease, hemobartonellosis, and the non-neoplastic anemias associated with the feline leukemia virus.

Only 4 of the 30 anemic cats recovered, which is characteristic of the poor prognosis associated with anemia in the cat.

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