

II. Neoplastic diseases of the haematopoietic and lymphoid tissues*

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Systemic lymphosarcomas are common in all species of domestic mammal. A binomial classification of these tumours, based on both the anatomical form (i.e., distribution of lesions) and the type of cytology, is proposed. Mast cell tumours also are common, especially in the dog. The categories of lymphoid neoplasms described are: lymphosarcoma, lymphoid leukaemia, nodular lymphoid hyperplasia, tumours of the immunoglobulin-forming cells, and thymoma. The myeloid neoplasms described are: myeloid leukaemia, erythro-leukaemia, acute erythraemia, polycythaemia vera, megakaryocytoid leukaemia, pan-myelosis, myelosclerosis, and monocytoid leukaemia. Mast cell tumours are divided into mastocytoma and malignant mastocytosis.

This classification incorporates the currently recognized neoplasms of the haematopoietic and lymphoid systems in six common domestic mammals. Confusion has arisen in the past because of differences in nomenclature at different times and in different countries. The quickened pace of interest in this area in recent years has led to the study of a much larger number of cases, to improved techniques, and to greater international cooperation. We have gathered cases from several countries and have studied the original material on which many of the publications of the last two decades are based. Most pathologists will no doubt agree with the categories although they might have used different names. As far as possible we have used the nomenclature in the WHO classification of tumours in man.

MAIN DIFFICULTIES IN CLASSIFICATION

It cannot be too strongly stressed that the accurate categorization of these neoplasms demands particularly good histological and cytological techniques. Many of the difficulties in the comparison of cases among laboratories are due to inadequate methods. Tissue sections should be prepared from fresh material; sections must be thin, as those more than 6 or

7 μm thick are in most cases useless. Blood and marrow smears must be well prepared on degreased slides and properly controlled staining procedures should be employed. Two major defects in assessing cytology have been obvious to us: first, if the concentration of anticoagulant, particularly EDTA, is wrong, then osmotic effects occur that markedly influence the nuclear: cytoplasmic ratio, the staining affinity of the cytoplasm, and the morphology of the nucleus; secondly, an intrinsic osmotic gradient occurs between the thickest and thinnest parts of a smear. This effect is easily seen on erythrocyte morphology. Assessment of nucleated cell morphology is best made only when the adjacent erythrocytes are of relatively normal shape and staining characteristics.

The main difficulties in nomenclature arise in two particular groups. These are the systemic lymphosarcomas and the myeloproliferative disorders. Together, these constitute the great majority of haematopoietic neoplasms in animals. The systemic lymphosarcomas are the most commonly diagnosed haematopoietic malignancies. They are clearly defined clinical and morbid anatomical entities. In cattle, the different types appear to have epidemiological significance in that the adult multicentric form is characteristic of the "enzootic leukosis" complex, whereas the calf multicentric and thymic forms are typical of the "sporadic" situation. Though it would appear that, among the experimentally induced lymphoid neoplasms, there is little overlap between different

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types in any one animal, this is not true of myeloid neoplasms. Myeloid leukaemia has been induced experimentally by virus inoculation in the cat and it has been shown to be associated with oncornavirus in several different types of naturally occurring case. There is considerable overlap between the various forms of myeloid neoplasia in individual cases and even within the same case over a period of time. However, since certain morphological criteria may be predominant at a given moment in the natural history of the disease, we have adhered generally to the current classification of the human diseases which probably reflects a set of similar temporal circumstances.

The cytological classification of the lymphoid tumours does not present any major difficulty. It is usual to find that one case shows only one of the standard patterns, but occasional cases show more than one. Since these are well-defined morbid anatomical and cytological categories, it would seem sensible to adopt a binary nomenclature for lymphoid neoplasia. This would help to reduce confusion, minimize description, and make results from different laboratories more easily comparable. The cytological type should preferably precede the morbid anatomical type in the case of the systematized lymphosarcomas—e.g., lymphoblastic alimentary and histiolympocytic multicentric. The correlation of morbid anatomical types with cytology is shown in Table 1 and the commonest morbid anatomical forms in the different species are given in Table 2.

It is difficult to apply the words "acute" and "chronic" to haematopoietic neoplasms in animals as is done in human medicine, where these terms indicate a fairly sharp division between diseases with different natural histories and may have diagnostic, prognostic, and therapeutic significance. Chronic leukaemia would appear to be rare in animals. On the other hand, the diseases corresponding to the acute blast cell leukaemias in man do not necessarily have a sudden onset or a short course in animals. Until more detailed clinical data become available, therefore, the terms "acute" and "chronic" should be avoided unless clearly justified.

It is now obvious that there are many analogies and similarities between human and animal neoplasms of this group; one major omission from this classification is Hodgkin's disease. Cases of this disease—or a condition resembling it—have been re-

Table 1. Correlation of anatomical form of lymphosarcoma with cytology

Anatomical form	Cytology
Multicentric	All cytological types are seen in this distribution.
Alimentary	The commonest is the lymphoblastic, but lymphocytic, histiocytic, and stem cell tumours also occur.
Thymic	Lymphoblasts are the most frequently seen cells, but tumours of small thymocytes also occur.
Leukaemia (true)	A range is seen, from lymphocytes to early blast or stem cells, even within one case. The commonest are polymorphocytes and lymphoblasts.

ported in animals, but none that we have been able to study has met the diagnostic criteria applied by specialists in the human disease.

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Table 2. Main anatomical forms of systemic lymphosarcomas in various domestic animals

Animal	Anatomical form
Ox	Multicentric, thymic, skin ^a
Dog	Multicentric, thymic, alimentary
Cat	Multicentric, thymic, alimentary
Pig ^b	Multicentric, thymic
Sheep ^b	Multicentric, thymic, skin
Horse ^b	Multicentric, alimentary

^a The rather rare skin form occurs in ruminants and is characterized by multiple subcutaneous and cutaneous nodules: an accompanying multicentric lymph node neoplasia may become clinically obvious only subsequent to the skin lesions.

^b At present, there are far fewer data available for these three species than for the first three.

HISTOLOGICAL CLASSIFICATION AND NOMENCLATURE OF NEOPLASTIC DISEASES OF THE HAEMATOPOIETIC AND LYMPHOID TISSUES

I. LYMPHOID NEOPLASMS

- A. LYMPHOSARCOMA (multicentric, alimentary, thymic, and other anatomical forms)
 1. Poorly differentiated
 2. Lymphoblastic
 3. Lymphocytic and prolymphocytic
 4. Histiocytic, histioblastic, and histio-lymphocytic
- B. LYMPHOID LEUKAEMIA
 1. Poorly differentiated
 2. Lymphoblastic
 3. Lymphocytic and prolymphocytic
- C. NODULAR LYMPHOID HYPERPLASIA OF THE CANINE SPLEEN
- D. TUMOURS OF THE IMMUNOGLOBULIN-FORMING CELLS
 1. Solitary plasmacytoma
 2. Myeloma
 3. Primary macroglobulinaemia (Waldenström)
- E. THYMOMA
 1. Predominantly epithelial
 2. Predominantly lymphocytic

II. MYELOID NEOPLASMS

- A. MYELOID LEUKAEMIA
 1. Poorly differentiated
 2. Well differentiated
 - (a) neutrophilic
 - (b) eosinophilic
- B. ERYTHROLEUKAEMIA
- C. ACUTE ERYTHRAEMIA (di Guglielmo)
- D. POLYCYTHAEMIA VERA
- E. MEGAKARYOCYTOID LEUKAEMIA
- F. PANMYELOSIS
- G. MYELOSCLEROSIS
- H. MYELOPROLIFERATIVE DISEASE, UNCLASSIFIED
- I. MONOCYTOID LEUKAEMIA

III. MAST CELL TUMOURS

- A. MASTOCYTOMA
 1. Well differentiated
 2. Poorly differentiated
- B. MALIGNANT MASTOCYTOSIS

DESCRIPTION OF TYPES

I. LYMPHOID NEOPLASMS

A. *Lymphosarcoma* (Plate IA-C, Fig. 1-5)

This is a malignancy of cells of the lymphoid series including the "histiocytic" lining cells of the sinuses. In domestic animals, the great majority can be categorized according to anatomical site as multicentric, alimentary, or thymic. The malignancy involves solid tissues, usually without an accompanying leukaemia, though the latter is found as an inconstant feature in approximately 20% of cases. Indeed, leukopenia is common and anaemia is often present. The lymphoid system is affected primarily; gross bone marrow involvement is variable. The malignant cells disseminate through the body *via* lymphatic pathways, i.e., in lymph nodes, the germinal follicles or paracortical areas are first affected; in the spleen, the white pulp is infiltrated; and in the liver the portal triads are invaded. At a later

stage, the architecture of these organs may become distorted and obscured by malignant cells, so that the pathways of spread are no longer apparent.

The principal features of the main *anatomical forms* of lymphosarcoma are as follows:

Multicentric. This is a disseminated neoplasm of the lymphoid organs in which there is usually bilateral and more or less symmetrical involvement of the lymph nodes; some regional groups may be more obviously affected than others. Involvement of the spleen is usual, but may range from a mere prominence of Malpighian bodies to a marked and diffuse splenomegaly. The other organs most commonly affected are the liver, kidneys, lungs, heart, gastrointestinal tract, and bone marrow.

Alimentary. The main lesions are in the gastrointestinal tract and in the nodes regional to it; as the process often appears to involve Peyer's patches,

this type is probably best regarded as a regional multicentric lymphoid neoplasm. Although the main tumour mass is usually in one site, it is not uncommon to find several Peyer's patches affected at some distance from the largest lesion. Neoplasms arise in the stomach, all parts of the small intestine, and the colon. The other organs most frequently infiltrated are the liver and kidneys. The spleen is involved in about a fifth of the cases and occasionally deposits are found in other organs.

Thymic. The main lesion is a large mass replacing the thoracic thymus. In some cases, the thymus is the only site affected but often there is spread to the mediastinal lymph nodes and other organs; if the animal lives long enough, the neoplasm may become widely disseminated.

Other anatomical forms. Only a fairly small number of cases do not belong to one or other of the three categories mentioned above. In the commonest of them, in the cat, the main lesion is in the kidney. Occasional lymphoma complexes are found, with the largest mass in one organ, giving the impression of a primary tumour with secondary deposits rather than a systemic neoplasia.

1. *Poorly differentiated.* The cells are round or oval, are large, and have round, open nuclei with a large prominent haloed nucleolus, the nuclei being of the "bird's-eye" type. The cytoplasm ranges from eosinophilic to mildly basophilic and may be irregular in outline.

2. *Lymphoblastic.* The neoplasm has a uniform population of typical lymphoblasts. The cells measure 12–15 μm , have a basophilic cytoplasm fairly closely surrounding the nucleus, and show a clearly defined cell membrane. The nuclei are large, show more roughly clumped chromatin than the previous type, and have prominent nucleoli.

3. *Lymphocytic and prolymphocytic.* Frequently there is a strong resemblance to normally differentiated cells. Irregularities of nuclear shape, such as indentations and lobulation, are fairly common.

4. *Histiocytic, histioblastic, and histiolympocytic.*^a The most obvious cells resemble closely the large lining cells of the cortical sinuses of the lymph node. They have a large oval nucleus, prominent nucleolus

or nucleoli, finely precipitated and reticulated chromatin, and fairly abundant eosinophilic cytoplasm, which may show evidence of phagocytosis. In the histioblastic form, the nuclei have sharp outlines and a large nucleolus. Binucleate cells are common. The cytoplasm is smaller in amount than in the histiocytic type.

The histiolympocytic lymphosarcoma is a mixed-cell type composed of histiocytes and lymphocytes with a range of differentiation. In field series it is of low incidence, but is fairly common in cases experimentally produced in cats, perhaps because it is usually a disease of very young animals.

B. *Lymphoid leukaemia* (Plate ID, Plate IIA, B, Fig. 6,7)

In this disease, malignant lymphoid cells are present in the blood and bone marrow. The cytological features are as described above under the headings "Poorly differentiated", "Lymphoblastic", and "Lymphocytic and prolymphocytic". The marrow may be almost entirely replaced and appears to be the site of origin of the disease. The leukaemic cells disseminate through haematopoietic pathways, i.e., in lymph nodes, the medullary cords and sinuses are mainly involved; in the spleen, the red pulp is invaded whereas the white is unaffected; and in the liver the leukaemic cells often permeate the sinusoids. Intravascular accumulations of leukaemic cells may be seen in other organs, where direct invasion can also occur. Solid tumours are not a feature. However, a leukaemic blood picture may supervene in cases of lymphosarcoma where the features already described distinguish this complex from true, primary, lymphatic leukaemia.

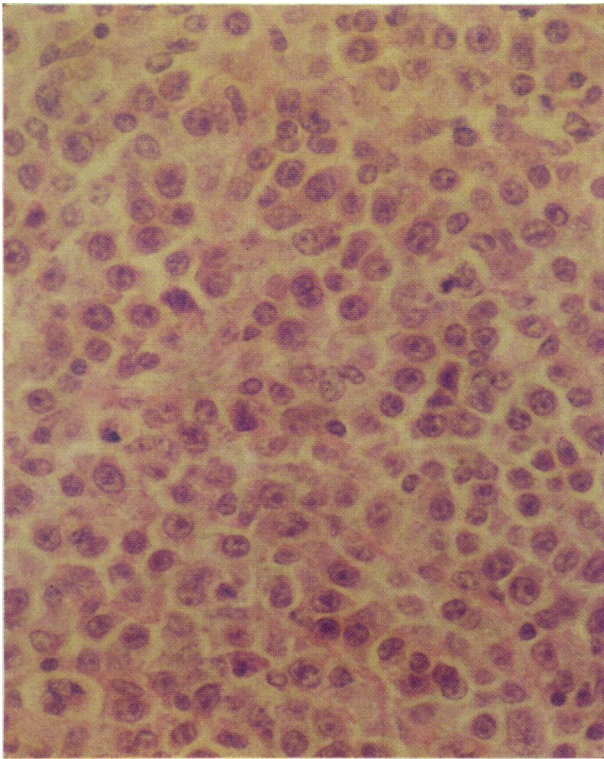
C. *Nodular lymphoid hyperplasia of the canine spleen*

The neoplastic nature of this lesion is disputed. It is sometimes called "benign lymphoma" and is common in old dogs. Individual nodules are usually less than 2 cm in diameter and project hemispherically from the surface. Histologically, they consist of large, irregular lymphoid nodules, separated by distended red pulp and having occasional areas of histiocytic proliferation.

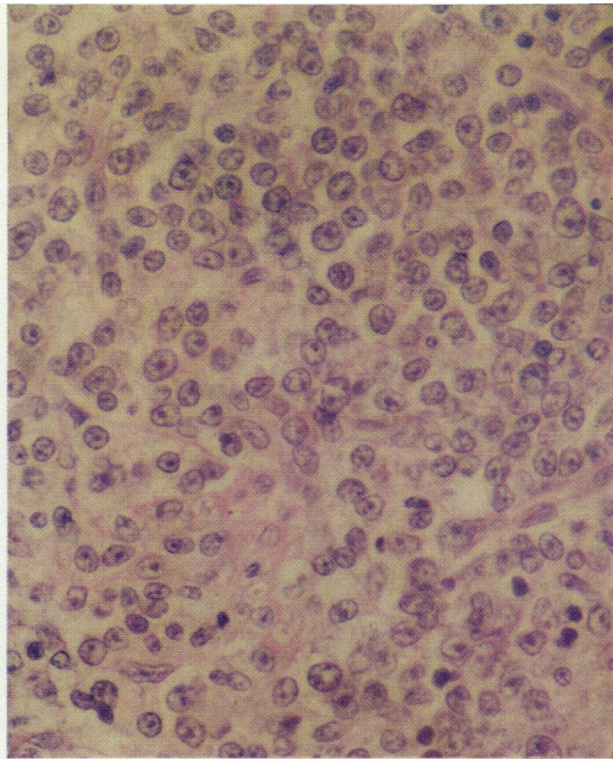
D. *Tumours of the immunoglobulin-forming cells*

1. *Solitary plasmacytoma.* In individual cases of this apparently benign, localized neoplasm, plasma cells may vary in their degree of differentiation. In well-differentiated tumours, the cells have the characteristic morphological features of normal plasma cells, with eccentric nuclei of oval shape and coarsely

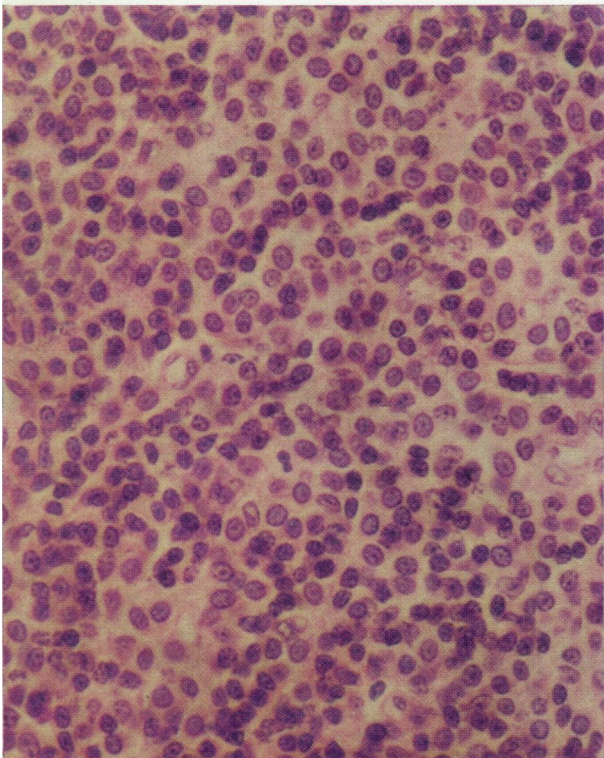
^a It may seem anomalous to include "histiocytic" neoplasms under lymphosarcoma. However, these have the same anatomical distribution as lymphosarcoma and the cell of origin is still unknown. In the cat, the various forms are all caused by the same virus. Formerly, these would have been classified as "reticulosarcoma" but it is now known that the sinus-lining cells are not reticulum cells.



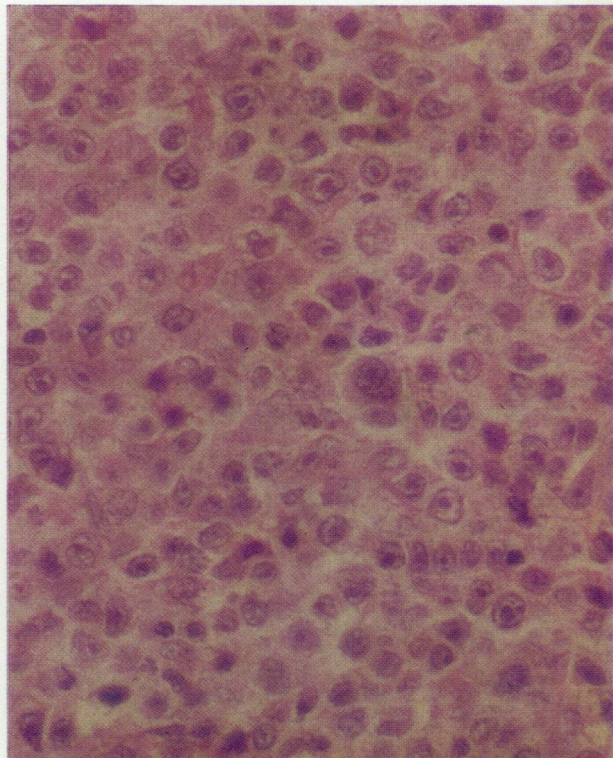
A. Lymphosarcoma, poorly differentiated (dog).



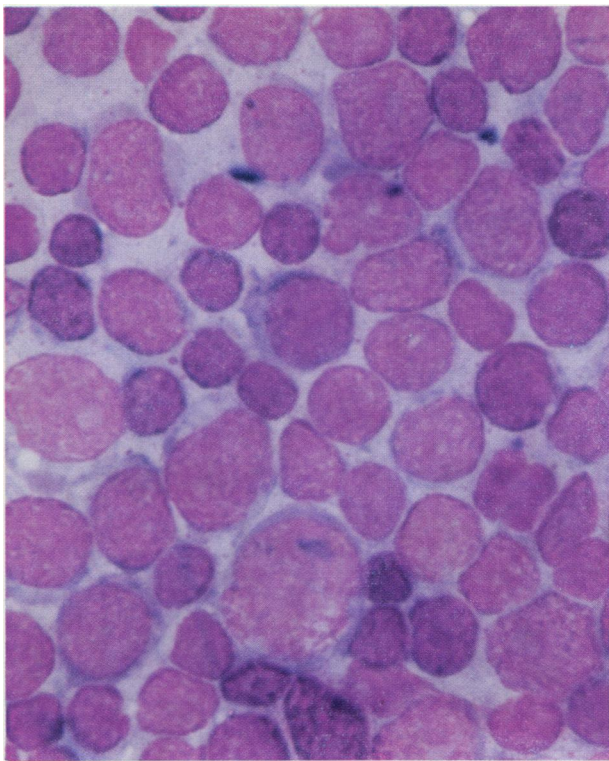
B. Lymphoblastic lymphosarcoma (cat).



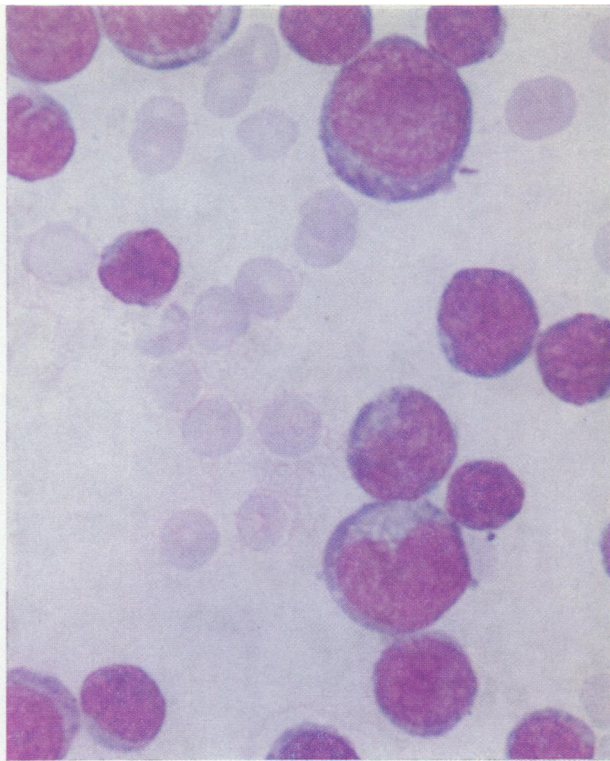
C. Polymorphocytic lymphosarcoma (ox).



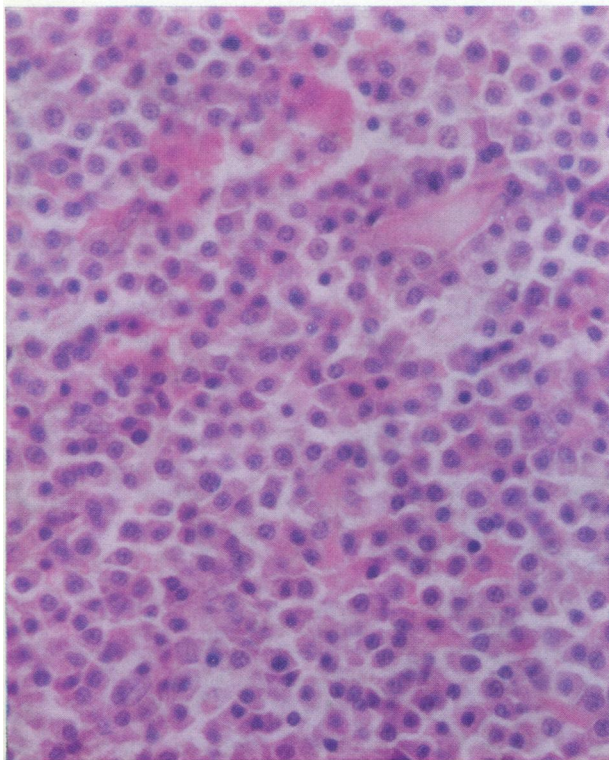
D. Histioblastic lymphosarcoma (cat).



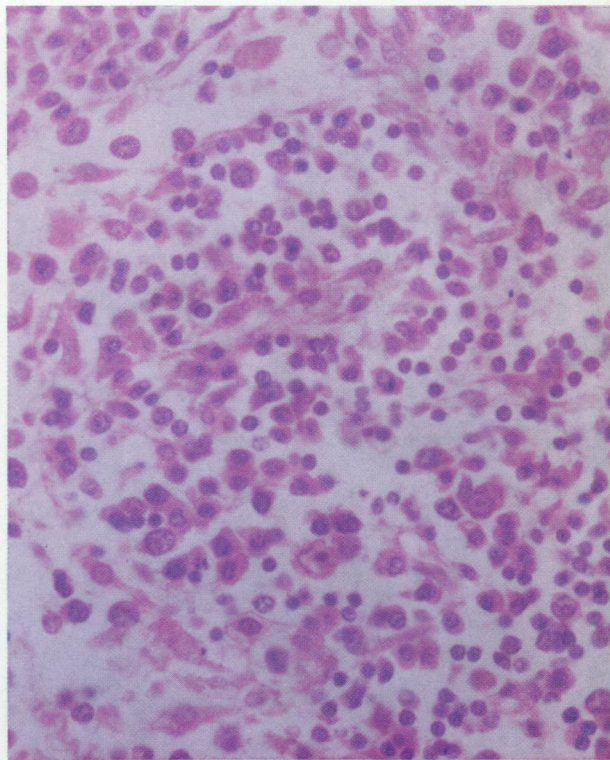
A. Lymphoblastic leukaemia; Leishman's (dog).



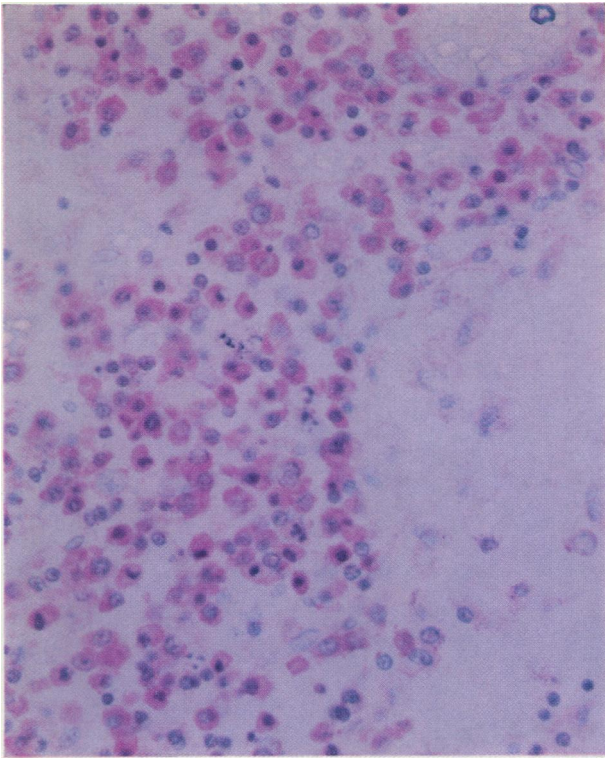
B. Lymphoblastic leukaemia, bone marrow imprint; Leishman's (ox).



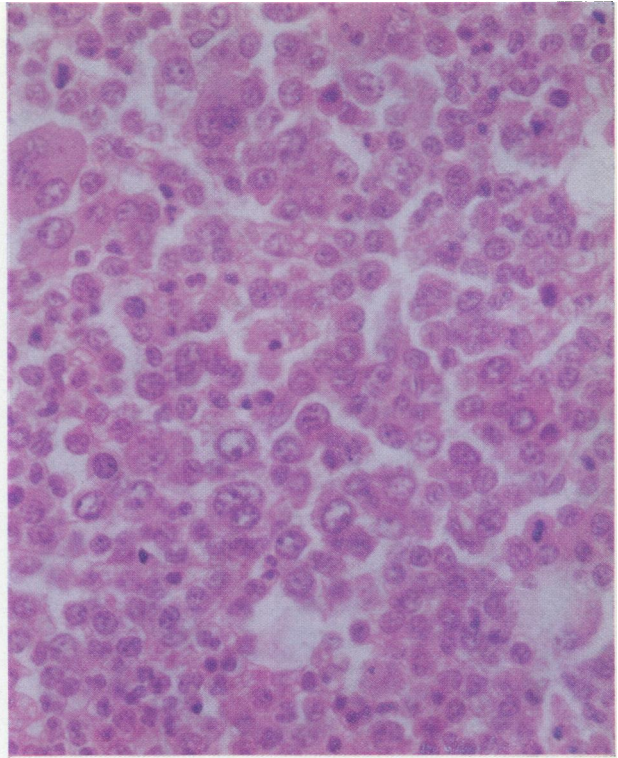
C. Myeloma (dog).



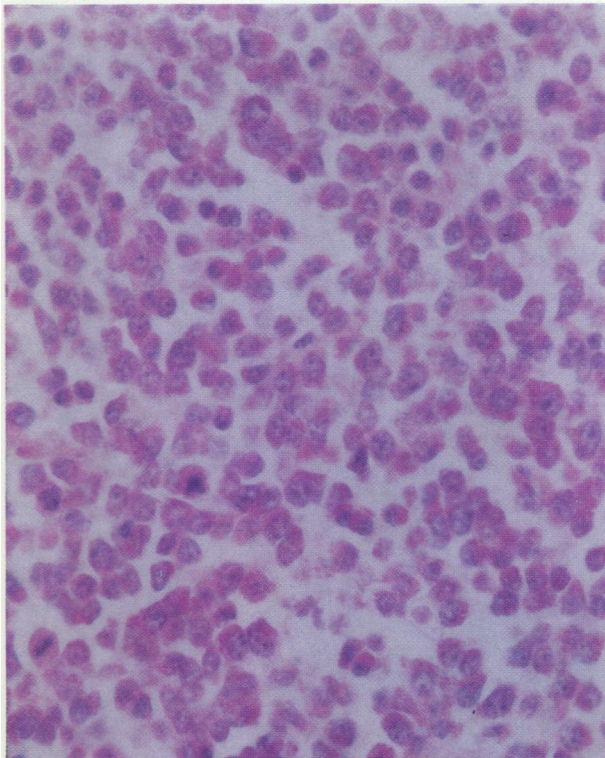
D. Primary macroglobulinaemia (Waldenström); haemalum and eosin (dog).



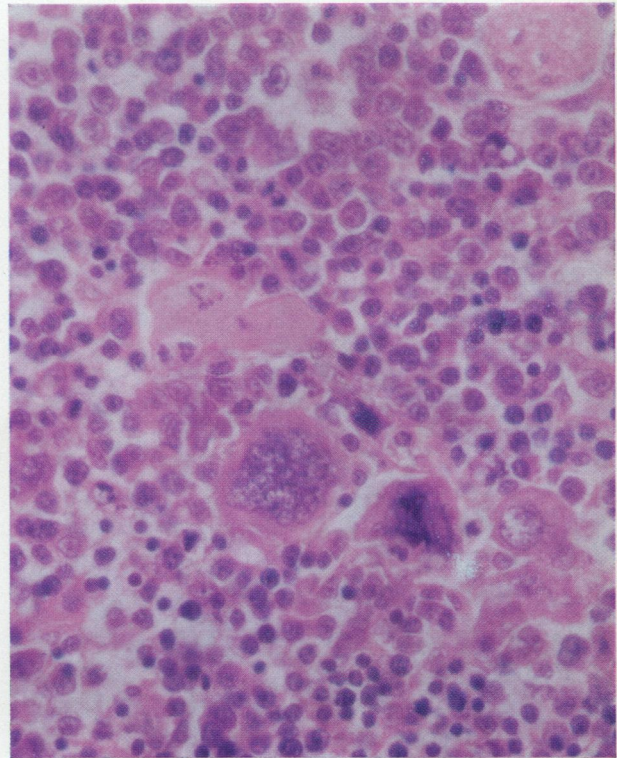
A. Primary macroglobulinaemia (Waldenström);
Unna-Pappenheim (dog).



B. Myeloid leukaemia, poorly differentiated (dog).



C. Myeloid leukaemia, well differentiated, eosinophilic
(ox).



D. Panmyelosis (cat).

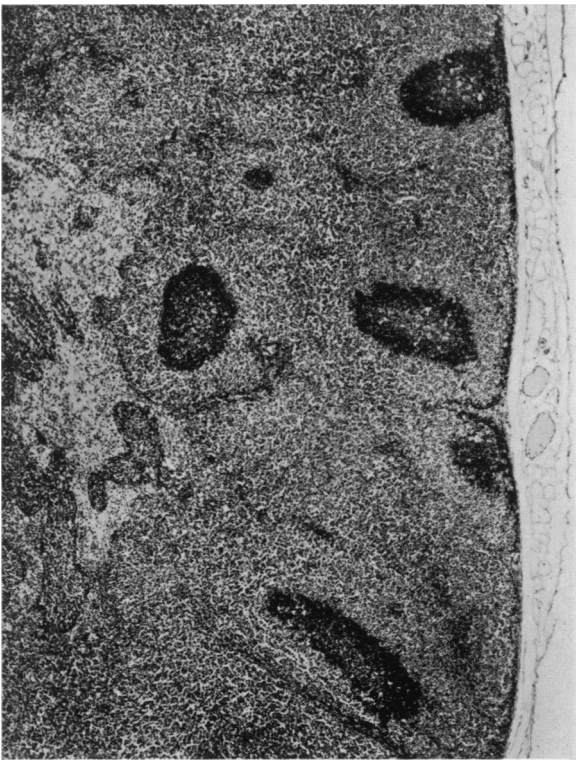


Fig. 1. Lymphosarcoma, lymph node; haemalum and eosin (cat).



Fig. 2. Lymphosarcoma, spleen (cat).

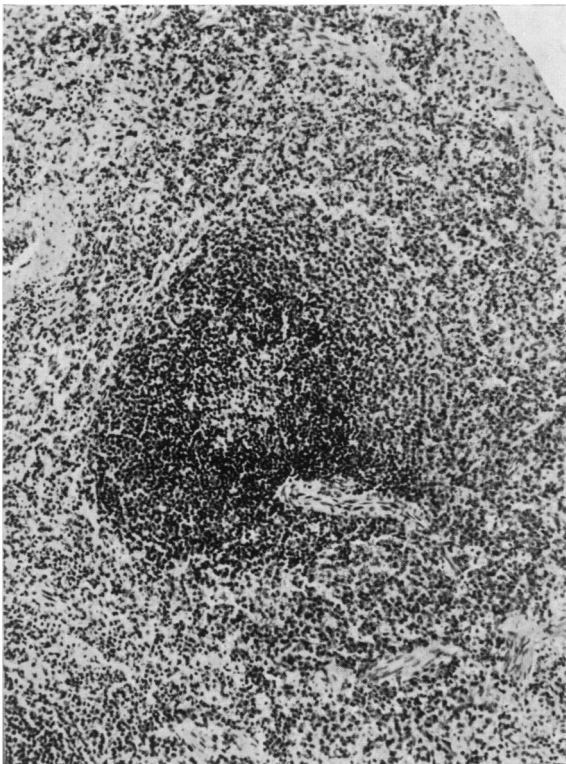


Fig. 3. Lymphosarcoma, spleen (cat).



Fig. 4. Lymphosarcoma, Peyer's patch (cat).

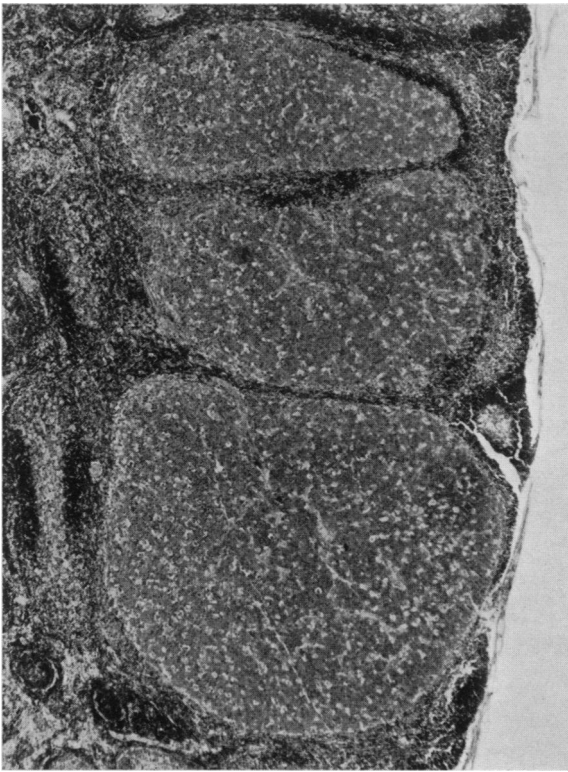


Fig. 5. Lymphosarcoma, lymph node (cat).

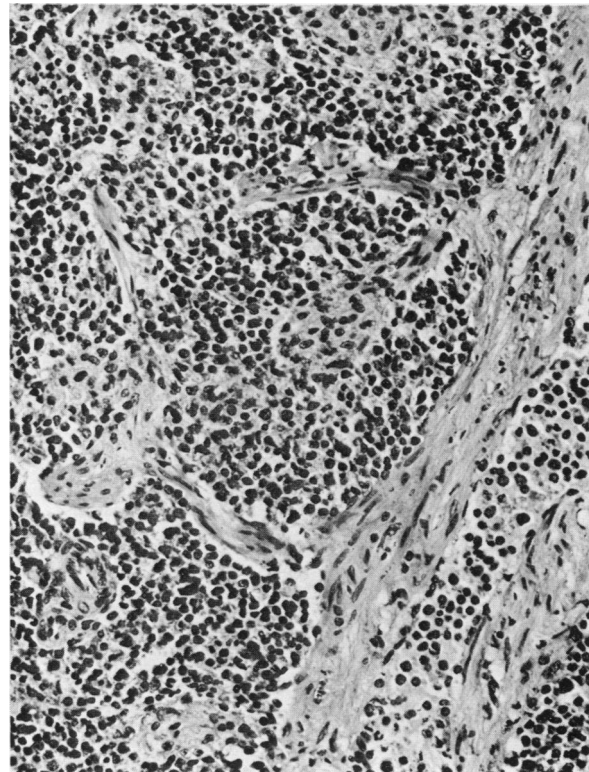


Fig. 6. Lymphoblastic leukaemia, spleen (cat).

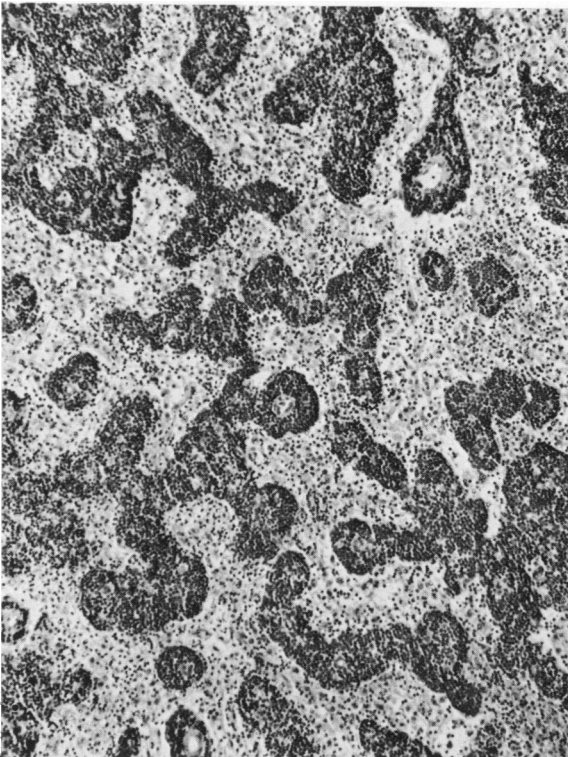


Fig. 7. Lymphoblastic leukaemia, lymph node (cat).

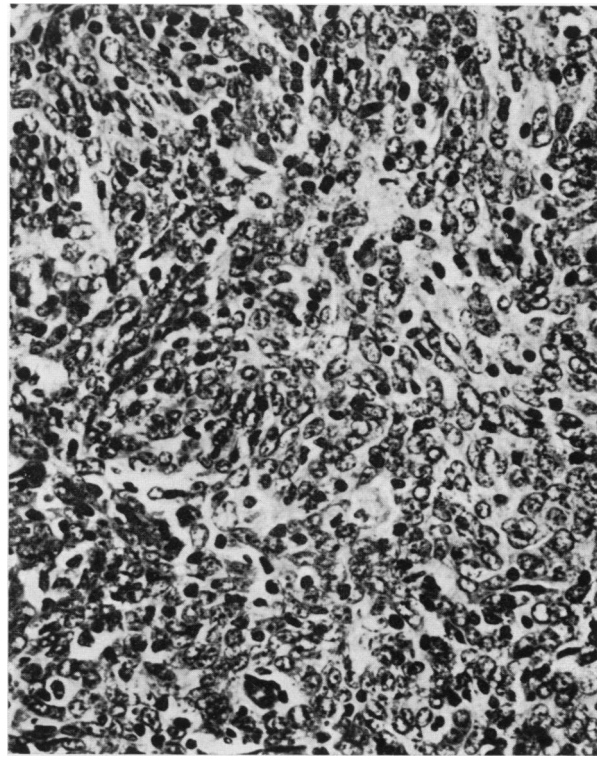


Fig. 8. Thymoma, predominantly epithelial (ox).

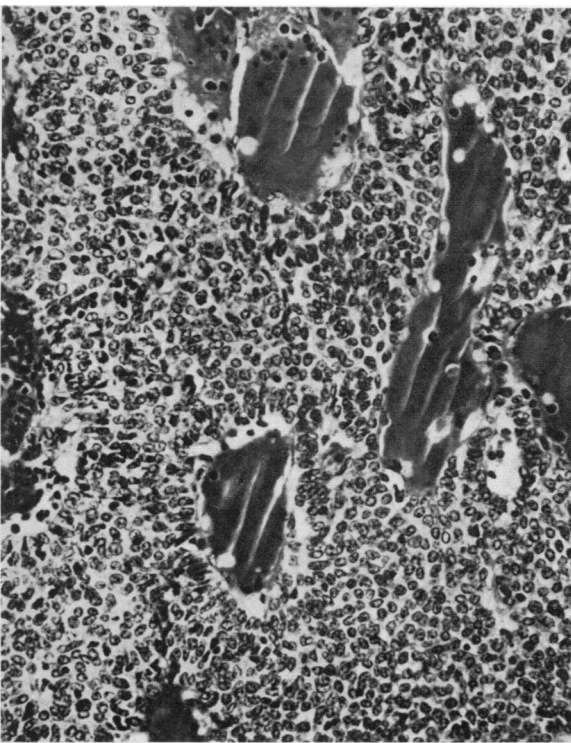


Fig. 9. Thymoma, predominantly epithelial (ox).

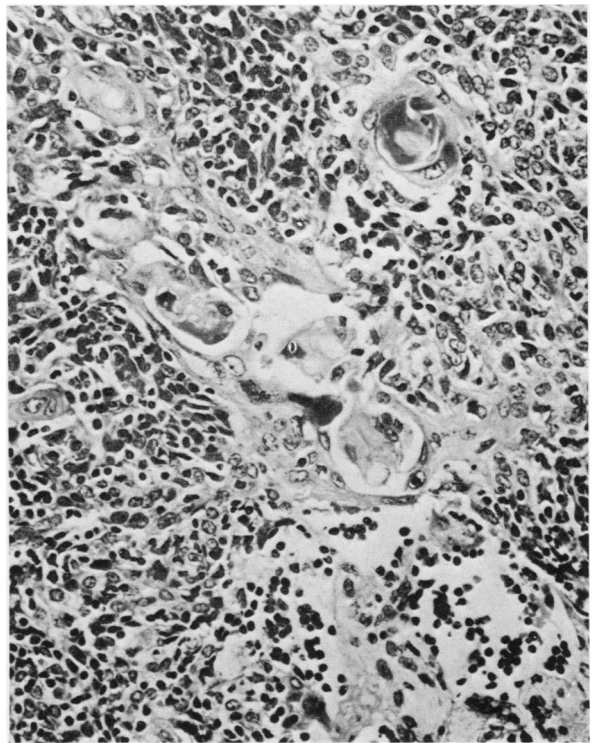


Fig. 10. Thymoma, predominantly epithelial (ox).

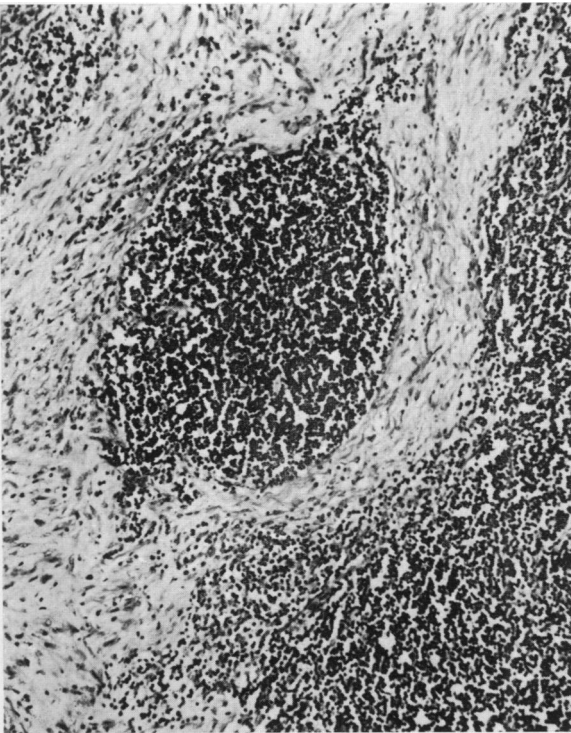


Fig. 11. Thymoma, predominantly lymphocytic (ox).

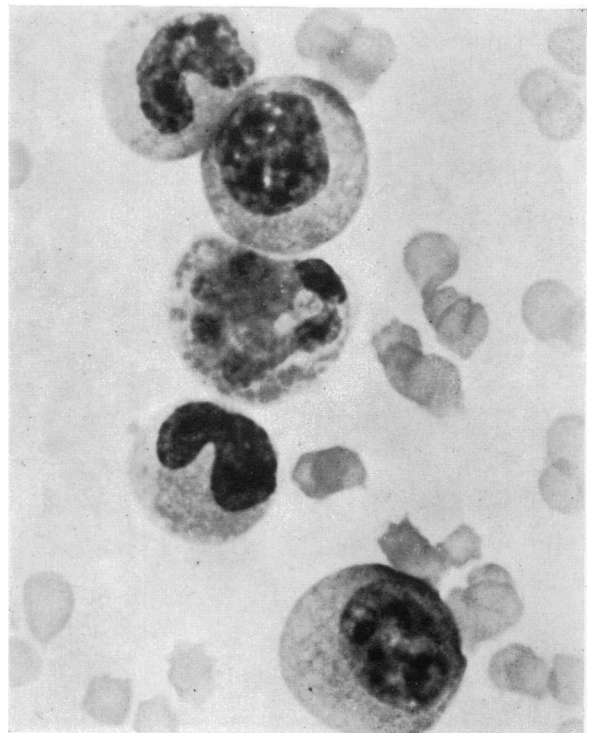


Fig. 12. Myeloid leukaemia, well differentiated, neutrophilic (dog).

Fig. 13. Acute erythraemia ; Giemsa (cat).

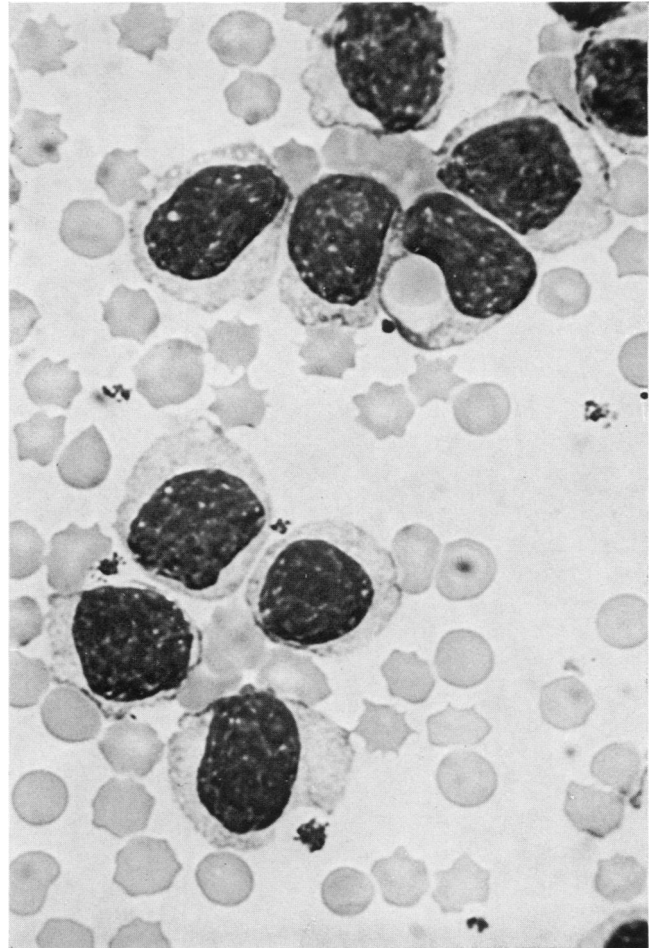
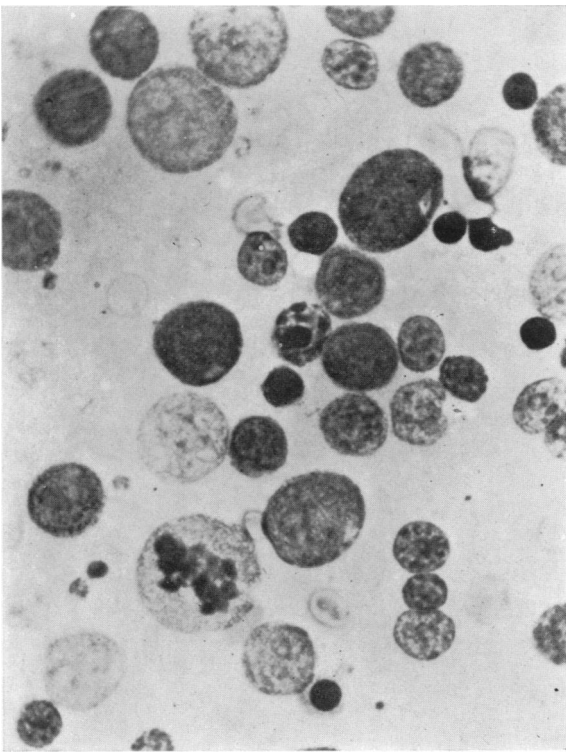


Fig. 14. Monocytoid leukaemia ; Leishman's (ox).

clumped chromatin. The staining affinity of the cytoplasm may be weakly basophilic, amphophilic, or moderately eosinophilic. In poorly differentiated tumours, the cells are pleomorphic, differing in size and shape, and some contain multiple nuclei; in such cases, only a proportion of the cells are recognizable as plasmacytes or plasmablasts. Mitoses may be moderately frequent or rare.

2. *Myeloma* (Plate IIC). A systemic neoplasm of plasma cells that vary in their degree of differentiation. It shows discrete masses in, or diffuse infiltration of, the bone marrow, and often involves the spleen, lymph nodes, and viscera. There is usually an accompanying monoclonal gammopathy, and light chain complexes (Bence-Jones protein) may be found in the serum or urine.

3. *Primary macroglobulinaemia* (*Waldenström*) (Plate IID and Plate IIIA). A lymphoproliferative disease occurring primarily in lymph nodes and the spleen. There is an accompanying monoclonal gammopathy of 19S immunoglobulin and there may be a high viscosity syndrome. The neoplastic cells have the appearance of a mixture of lymphocytes, plasma cells, and cells with a range of lymphoid morphology and pyroninophilic cytoplasm.

E. *Thymoma* (Fig. 8–11)

This must be distinguished from the more common thymic lymphosarcoma. The thymoma is a localized and usually benign primary tumour of the thymus in which both the epithelial and lymphoid elements of the normal thymus proliferate. The proportion of these two elements varies in individual cases, which are classified according to the predominant type of cell.

1. *Predominantly epithelial*. Most thymomas are of this type. They are composed of irregular masses of cells subdivided by broad fibrous bands and are usually encapsulated. The tumour cells are plump and elongated with fairly abundant cytoplasm that is faintly eosinophilic. The nuclei are oval with small nucleoli and fine chromatin granules. There is no reticulin between the cells and PAS-staining is negative. Mitoses are rare. Lymphocytes are scattered among the epithelial cells, both singly and in small aggregates. Eosinophils are present in small numbers. Fluid-containing cysts are common in these tumours and often small calcispherites can be seen. Only rarely are rudimentary Hassall's corpuscles present.

2. *Predominantly lymphocytic*. The neoplasm consists of masses of small lymphocytes, subdivided by prominent bands of fibrous tissues. Small cords or

groups of epithelial cells can be seen among the lymphocytes. Occasional eosinophils and plasma cells are present. In some cases, an amorphous, eosinophilic matrix is formed focally throughout the tumour; this may represent old fibrin deposition. The lymphoid cells of the tumour have the appearance of normal small lymphocytes. Mitoses are rare.

II. MYELOID NEOPLASMS

A. *Myeloid leukaemia* (Plate IIIB, C and Fig. 12)

A systemic neoplasm of cells of the granulocyte series, in which the bone marrow and blood are principally affected. The malignant cells invade haematopoietic and other organs by the haematogenous route as described in lymphatic leukaemia. In poorly differentiated cases, the majority of leukaemic cells are myeloblasts and early members of the series; evidence of differentiation, on which the diagnosis depends, may be apparent in only a small proportion of the cells. The use of histochemical techniques with peroxidase, Sudan black, etc., is essential for accurate recognition of the cell series. In well-differentiated cases, the majority of leukaemic cells are later members of either the neutrophil or eosinophil series, with a preponderance of myelocytes and metamyelocytes.

B. *Erythroleukaemia*

In this form, there is proliferation of cells of both the erythrocytic and granulocytic series. The erythroid element is truly neoplastic and must be distinguished from the marked extramedullary or reactive haematopoiesis that may accompany lymphatic or myeloid leukaemia. Abnormal red-cell precursors, often with numerous megaloblastic forms, are a striking feature of this neoplasm. The granulocytic component may vary in the degree of differentiation, as in simple myeloid leukaemia.

C. *Acute erythraemia* (di Guglielmo) (Fig. 13)

In this neoplasm, the malignant cells are members of the erythrocytic series and include blast cells, erythroblasts, and normoblasts; it is the erythroid analogue of myeloid leukaemia. As in the other leukaemias, the bone marrow and blood are mainly affected, together with haematogenous infiltration of other organs. Abnormal red-cell precursors including megaloblastic forms are commonly seen. Failure to respond to folic acid and Vitamin B₁₂ therapy are prerequisites for diagnosis.

D. *Polycythaemia vera*

In this condition, there is an absolute increase in erythrocyte mass and often leukocytosis, thrombocytosis, and hypervolaemia. The condition may terminate in erythroleukaemia or myeloid leukaemia.

E. *Megakaryocytoid leukaemia*

This neoplasm of megakaryocyte precursors arises in the bone marrow and may spread to involve haematopoietic organs, but megakaryocytes do not usually appear in the blood. The neoplastic cells are mainly megakaryoblasts—indistinguishable from other haemocyto blasts in their morphology—and promegakaryocytes, which are readily recognized by their large size and partially lobulated nuclei; the nuclei are not condensed as in mature megakaryocytes and they contain nucleoli. Abnormal forms with aberrant mitosis occur.

F. *Panmyelosis* (Plate IIID)

In this neoplasm of bone marrow cells, members of the erythrocytic, granulocytic and megakaryocytic series participate. Malignant cells from these series replace the normal marrow and appear in the blood. Invasion of haematopoietic and other organs *via* haematogenous routes is seen. This condition may be difficult to differentiate from myeloid leukaemia with marked extramedullary haematopoiesis. The distribution of the malignant cells in sites where extramedullary haematopoiesis does not normally occur, together with the fact that a high proportion of the total lesion is composed of erythrocytic and megakaryocytic cells, distinguishes this condition.

G. *Myelosclerosis*

Myelosclerosis, or intramedullary fibrosis, usually accompanies—or supervenes during the course of—some form of myeloid neoplasia. There may be an associated myeloid metaplasia or osteosclerosis. It is not known whether myelosclerosis with myeloid metaplasia can arise as a primary disease in animals or whether it is always a secondary feature of myeloid neoplasia.

H. *Myeloproliferative disease, unclassified*

Occasional cases of neoplasms of bone marrow origin do not conform to any of the categories described. Too few examples have been seen in animals to permit generalization, but individual cases may show features suggestive of myelosclerosis, with myeloid metaplasia and well-differentiated granulocytic leukaemia.

I. *Monocytoid (monocytic) leukaemia* (Fig. 14)

This neoplasm of monocytes and their precursors involves principally the bone marrow and blood stream. The cell type is recognizable by its size (15–18 μm), and abundant cytoplasm, which has a characteristic “ground glass” appearance and may contain fine azurophilic granules. The nuclei may be oval or indented, and central in position, containing one or more nucleoli. In some cases, a striking feature may be phagocytic activity, so that, in blood films, monocytes containing engulfed red cells or platelets form a valuable diagnostic marker. Phagocytic activity can also be tested *in vitro*.

III. MAST CELL TUMOURS

Mastocytomas are common in the dog but also occur in other species. The most frequent site is the skin, but systemic forms involving lymph nodes and the spleen with dissemination to the liver and other organs are found in dogs, cats, and cattle.

A. *Mastocytoma*

1. *Well differentiated.* The mast cells in this tumour show a wide range of granulation both between and within cases. The cells have a pale oval nucleus and a cuboidal or polygonal cytoplasm that usually appears pale red or clear in formalin-fixed, H-&E-stained material. Some tumours show very poor granule formation and diagnosis is helped by fixing in Carnoy's fluid and staining with astra blue-safranin or toluidine blue.

The cells characteristically occur in packets and infiltrate tissues by long, streaming, closely applied lines of cells.

2. *Poorly differentiated.* This is a form of mastocytoma in which there is considerable pleomorphism, with the formation of bizarre cells that may be multinucleated. Granulation may be minimal and the fixation and staining methods mentioned above may be required.

B. *Malignant mastocytosis*

This is a systemic and disseminated mast cell neoplasm affecting primarily the lymphoid organs. In the cat, hepatosplenomegaly is marked. The cell type is the same as that described for mastocytoma; usually the disease can be recognized by the packets of cells with uniform nuclei and clear cytoplasm found in nodes and in the splenic red pulp. In some cases, cellular pleomorphism, as described under “poorly differentiated”, may be seen.