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Non-proliferative Lesions of the Hematopoietic System in Rats

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INTRODUCTION

Terminology used to describe non-proliferative lesions of the hematopoietic system in rats is quite varied. Since this species is utilized in both research and testing, proper diagnosis and characterization of non-proliferative hematopoietic lesions in this species is important. This guide presents a biologically accurate, morphologic classification of non-proliferative lesions of the hematopoietic system in rats. The authors have placed each of the non-proliferative lesions into one of the following classifications: congenital, disturbances of growth, degenerative, vascular, inflammatory and miscellaneous.

LYMPH NODES

Degenerative Changes

Lymphoid Necrosis (Figure 1)

Lymphoid necrosis can be multifocal or diffuse and can involve T cell areas, B cell areas, or both. It is characterized by fragmentation of cells with pyknotic or karyorrhectic nuclei, often accompanied by phagocytic macrophages. Individual cell necrosis may be present within the germinal centers of antigen-stimulated nodes undergoing rapid lymphocyte proliferation. Diffuse necrosis of both T and B cell areas has been observed after irradiation (11), exposure to viruses (10), injection of bacterial endotoxin (2), and exposure to certain chemotherapeutic or immunosuppressant drugs (15). Lymphoid necrosis can also occur as an agonal event associated with hypoxia and stress, presumably due to the release of endogenous glucocorticoids (3).

Infarction (Figure 2)

Lymph node infarctions are uncommon, and are generally observed secondary to a predisposing condition, such as polyarteritis nodosa. Infarctions are characterized by diffuse coagulation necrosis of the tissue with loss of nodal architecture, although a peripheral rim of viable lymphocytes may survive. Consolidation of the node, with replacement of the parenchyma by collagen and mineralization of necrotic tissue, may be present, depending on the chronicity of the lesion. Abdominal lymph nodes are more likely to be affected due to their proximity to diseased blood vessels.

Mineralization (Figure 3)

Mineralization is a secondary effect of tissue damage observed infrequently in lymph nodes. It appears as basophilic crystalline mineral deposits within necrotic or degenerating tissue, and is most likely to be associated with an infarction or neoplasm. Mineralization of arteriolar

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walls may occur occasionally in the paracortical region.

Fibrosis (Figure 4)

Fibrosis is characterized by an increase in collagenous stroma with resulting distortion of normal tissue architecture. It invariably occurs as a sequela to inflammation, necrosis, or neoplasia. It may involve only the capsular surface in an animal with peritonitis, or it may affect localized or diffuse portions of the parenchyma such as fibrotic encapsulation of an abscess, granulation tissue around a hematoma, or fibrosis within an infarcted neoplasm.

Pigmentation (Figures 5, 6)

Hemosiderin is the most common pigment found in lymph nodes. It consists of brown granular material within the cytoplasm of macrophages. It is most likely to be found within the medullary cords and lymphatic sinuses of nodes exhibiting sinus erythrocytosis. Macrophages containing hemosiderin pigment stain iron-positive and PAS-positive (20). Other pigments, that are not iron or PAS-positive, may also be found within macrophages and reticular cells lining sinuses. These substances are usually of finer grain than hemosiderin and range from pink to pale tan in color. Their origin is not certain. They may represent metabolic breakdown products such as lipofuscin, or they may represent insoluble material cleared from the blood or respiratory tract. A number of inhaled, ingested, and injected chemicals induce sinus histiocytosis in the lymph nodes in which macrophages contain inert or insoluble pigmented test substance (3).

Lymphoid Atrophy/Depletion (Figure 7)

Lymphoid atrophy, or depletion, is observed as a sequelae to any disease or toxic condition that causes lymphoid necrosis. It is also seen as a spontaneous finding in aged rats where it may affect B cells and/or T cells. Follicular atrophy is characterized either by the presence of a few follicles, small follicles, or no follicles. Paracortical, or T cell atrophy, is perhaps more common in aging rats and may parallel involution of the thymus. In paracortical atrophy, lymphoid follicles are present, but parenchymal areas around the follicles are hypocellular. Plasmacytosis may be prominent in animals with T cell atrophy.

Vascular Changes

Sinus Erythrocytosis/Erythrophagocytosis (Figures 8, 9)

Sinus erythrocytosis, characterized by the presence of free red blood cells within the lymphatic sinuses, generally occurs as a result of hemorrhage in organs or tissues drained by the affected node. In acute lesions, there is no cellular reaction. In chronic lesions, there may be erythrophagocytosis by macrophages, crystallization of hemoglobin from degenerate red blood cells, and accumulation of hemosiderin pigment within lymphatic sinuses.

Hemal lymph nodes, which resemble normal nodes except that some of their sinuses contain blood instead of lymph, are found occasionally in rats in the perirenal area (8).

Lymphatic Ectasia (Figure 10)

Synonyms: lymphatic sinus ectasia, lymphangiectasis, lymphangiectasia, cystic ectasia, lymphatic cysts

Dilated or cystic sinuses are common spontaneous findings in the lymph nodes of aging rats, particularly in the mesenteric, mediastinal, and paralumbar nodes. Diffuse ectasia tends to be associated with lymphoid atrophy and usually involves the medullary portion of the node, although subcapsular lymphatic dilation can also be present. Cystic lymphatic ectasia occurs less frequently and may be found in any node. Cysts range from microscopic size to 8 mm in diameter. They contain a few cells, including erythrocytes, and a pale, pink homogenous fluid (1). They are lined by endothelial cells. Incidences of lymphatic ectasia in an aged rat population vary from 5 to 26% (8).

Vascular Sinus Ectasia (Figure 11)

Synonyms: angiectasis, vascular sinus dilation, peliosis, telangiectasis

Vascular sinus ectasia is similar, but less common than lymphatic ectasia. It is characterized by dilation of thin vascular channels (sinuses), located within the medullary cords. It should be distinguished from hematoma or early hemangioma. It is distinguished from the former by the presence of endothelial lining cells, and from the latter by hypertrophic and/or hyperplastic vascular endothelium and in some cases, the absence of fibrosis and the regular distribution of dilated vessels within the medullary cords. Collagenous stroma is minimal.

Thrombosis (Figure 12)

Thrombosis is observed infrequently in the lymph nodes of rats. It is characterized by the formation of a solid mass within the lumen of a blood vessel. It is composed largely of fibrin and platelets and may contain a small number of trapped red blood cells.

Inflammatory Changes

Abscess (Figure 13)

Abscesses may be acute or chronic. They are generally the result of an infectious or antigenic substance reaching the lymph nodes via the bloodstream or lymphatics. Abscesses are characterized by a central area of necrosis in which neutrophils are the predominant inflammatory cells. The abscesses make up the eosinohilic portion of a hemotoxalin and eosin (H&E) section. They are surrounded by variable amounts of fibrous

connective tissue whose density is dependent on the chronicity of the lesion. Acute abscesses have a soft to liquefied central area due to the high enzyme content of neutrophils. Chronic abscesses are surrounded by fibrous connective tissue and may have solid caseous central cores. Certain infectious agents, particularly poorly degradable substances with a high lipid content of their capsule or cell wall, are more likely to produce caseous necrosis. Abscesses were more common in rats prior to the development of specific pathogen free (SPF) animals. Corynebacteria species, cultured from submandibular lymph node abscesses, were one of the more commonly isolated etiologic agents.

Acute Inflammation, (Figure 14)
Synonym: acute lymphadenitis

Aggregates of inflammatory cells are occasionally seen in lymph nodes without necrosis or abscess formation in the node. Such infiltrates usually occur in lymph nodes that are draining acute or chronic ulcerative lesions of the skin or intestinal tract, including ulcerated neoplasms. They are most likely to be found in superficial nodes draining the skin and in the cecal or mesenteric nodes draining the intestines (17). Inflammatory cells, primarily neutrophils and macrophages, may be present in the capsule, subcapsular sinuses, and medullary cords. Inflammatory infiltrates must be distinguished from extramedullary hematopoiesis and granulocytic leukemia. Extramedullary hematopoiesis usually has megakaryocytes and other hematopoietic elements intermixed. Granulocytic leukemia has a high proportion of immature myeloid cells as well as multiple organ involvement.

Chronic Inflammation, (Figure 15)
Synonym: chronic lymphadenitis

The term "chronic lymphadenitis" is generally applied to animals exhibiting chronic abscesses, as described above, in which the normal lymphoid architecture may be partially or completely obliterated by the destructive process. "Lymphadenitis" should not be used to describe lymph nodes that are subjected to chronic antigenic stimulation. In the latter case, there is generally a secondary immune response characterized by hyperplasia of the lymphoid follicles, germinal center formation, and plasmacytosis of the medullary cords and paracortical region. In some cases, lymphoid atrophy, rather than hyperplasia, is seen along with plasmacytosis of the medullary cords, particularly in older animals. Chronic antigenic stimulation of a node may also result in hyperplasia of the follicular dendritic cells that trap and present antigen to the lymphocytes. Dendritic cell hyperplasia is characterized by a diffusely cellular node in which tingible body macrophages with large irregular nuclei and pale cytoplasm are scattered throughout the tissue producing the "starry sky" appearance. Sinus histiocytosis may occur as a component of chronic inflammation. Histiocytes are normally present within the medullary sinuses where they trap and remove exogenous and endogenous pigments, erythrocytes, micro-organisms, and insoluble foreign materials such as particles derived from food, air, and drugs (17). Any disease or condition that causes an increase in absorption of such materials may result in sinus histiocytosis of the associated lymph nodes. The mesenteric and peribronchial lymph nodes are most likely to be affected.

Granulomatous Inflammation, (Figure 16)
Synonym: granulomatous lymphadenitis

Granuloma formation within the paracortical and medullary cord regions is a common finding in rats, particularly of mesenteric lymph nodes. Affected lymph nodes show multiple small aggregates of macrophages with abundant pink to tan colored (on H&E staining) cytoplasm (1, 8). Hemosiderin or lipofuscin pigment may be present in the granulomas (20), or they may contain poorly degradable substances, possibly from the feed. Such granulomas rarely show degenerative changes and are not associated with other forms of inflammation.

SPLEEN

Congenital Changes

Accessory Spleen (Figure 17)

Small pieces of splenic tissue (capsule, red and white pulp, trabeculae) may rarely be found in the mesentery or omentum, and attached to visceral organs of rats. The accessory spleen can be seen grossly as a small red nodular lesion in these tissues. Histologically, all normal components of the spleen may be seen (capsule, red and white pulp, trabeculae). The etiology may be congenital or related to previous trauma to the spleen.

Disturbances of Growth

Abnormal growth of the spleen is rare in rats. Enlarged spleens are usually due to those processes described in other sections.

Capsular Cyst (Figure 18)

Capsular cysts occur as small or large cysts on the capsular surface of the spleen of rats. The cysts are lined by endothelial cells and are filled with eosinophilic fluid. They may be of lymphatic origin or from previous trauma.

Degenerative changes

Degenerative changes may be found in any of the cellular elements in the spleen in its various anatomical regions. For examples, lymphocytes in red and white pulp may show vacuolated and other degenerative changes after exposure to toxins. Focal and diffuse changes in

capsule components can be seen after intraperitoneal injection and induction of peritonitis.

Lymphoid Hypoplasia (Figure 19)

Lymphoid hypoplasia is found in nude rats. There are few or no small lymphocytes in T cell zones (PALS) and the white pulp is smaller than normal. The spleen may be smaller than normal in size and weight. Loss of lymphocytes from B or T cell zones is often seen after necrosis in chemical toxicity (16, 18), viral infections and after irradiation.

Lymphoid Atrophy/Depletion

Loss of lymphocytes from B or T cell zones is often seen after necrosis in chemical toxicity, viral infections and after irradiation.

Pigmentation (Figure 20)

Pigments of various types (most often hemosiderin and lipofuscin) are found in aging rats and after chemical exposure. Differentiating features of pigments requires histochemical procedures (20).

Hemosiderosis. Hemosiderosis is an age-related lesion in rats. Hemosiderosis may also be related to old hemorrhage. Accumulation of iron-positive pigment is found in the red pulp of aging rats. The presence of a small amount of hemosiderin pigment in the spleen is considered normal. Special stains are sometimes required to determine if the pigment is hemosiderin. It may arise from normal hemoglobin breakdown or to chemically-induced methemoglobinemia or autoimmune hemolytic anemia, as seen in LGL lymphoma (leukemia).

Lipofuscin. Lipofuscin is an acid fast pigment, probably from oxidative breakdown of lipids, that can be found in aging rats.

Lipid Accumulation (Figure 21)

Lipid accumulation occurs as either a focal or diffuse accumulation and is a rare spontaneous lesion in rat spleen. It has been reported in rats exposed to some aromatic amines (aniline, para-chloroaniline). These lesions are usually associated with focal fibrosis and sarcoma development. The lipid accumulation may be focal or almost nodular. The lesion may appear similar to angiolipoma of humans.

Mineralization

Mineralization is often found after necrosis induced by chemical agents. It is not found as an aging lesion in rat spleen. Capsular mineralization may be found. Mineralization may also be observed in old areas of hemorrhage. Mineralization may also rarely be observed in the walls of vessels.

Fibrosis (Figure 22)

Fibrosis may involve both the capsular surface, as well as parenchymal tissue.

Fibrosis, Capsular. Focal or diffuse fibrosis of the splenic capsule can be seen in rats with peritoneal metastatic tumors and in rats exposed to some aromatic amines. Fibrosis may be associated with chronic inflammation.

Fibrosis, Parenchymal. Parenchymal fibrosis of the spleen occurs as a focal or diffuse parenchymal (red pulp) lesion and can be seen as rare aging lesions in rats but is more commonly induced by some aromatic amines (aniline, para-chloroaniline). It is also sometimes associated with LGL leukemia. Focal areas of the red pulp become fibrotic with loose or dense collagenous tissue. Hemangiomas, hemangiosarcomas and other sarcomas may arise within areas of fibrosis. Grossly, scars may be seen.

Cell Death

Individual cell death (apoptosis, or individual cell necrosis) in splenic cell components, as well as those in other tissues, often occurs after exposure to toxins. The differentiation of apoptosis from cell necrosis may be difficult.

Apoptosis. Apoptosis is a distinct mode of cell death that is responsible for deletion of cells in normal tissues (6,7). The process can be quantitated and may be increased or decreased by xenobiotics. Markers for apoptotic cells are used for tissues. Normal age-matched controls are important for determining levels of apoptosis. Individual cell necrosis, not a component of normal apoptosis, may be found after low doses of toxins.

Necrosis. Necrosis may affect white pulp, red pulp, trabeculae or the capsule. Necrosis of white pulp may include necrosis of marginal zone cells, B cell zone lymphocytes, or T cell zone lymphocytes. Red pulp necrosis may be of hematopoietic or vascular cells, or trabeculae. Necrosis of the capsule can be seen in various conditions. Chemicals, viruses and irradiation are etiologies of splenic necrosis.

Vascular Changes

Hemorrhage (Figure 23)

Hemorrhage occurs after chemical exposure, irradiation and some viral infections. It may be focal or diffuse. Congestion is a common finding in the rat spleen. The method of euthanasia is often a cause.

Periarteritis

Periarteritis was found more frequently in aging rats in past years than it is today. It may involve trabecular arteries and is similar to that seen in other tissues.

Infarction

Infarction of the spleen has been seen in rats with LGL and other leukemias. Sometimes vascular lesions are seen also. Grossly, these areas appear as scars.

Inflammatory changes

Inflammation in the spleen may be acute or chronic, suppurative, fibrinous, or granulomatous. Lesions are usually seen within the red pulp. However, splenic inflammation is not common in rats as a spontaneous lesion or after experimental procedures. Infectious agents may cause these lesions.

Inflammation, Acute/Chronic (Figure 24)

Severe suppurative inflammation in associated tissues may result in suppurative splenic inflammation. Chronic inflammation is rare.

Inflammation, Granulomatous (Figure 25)

Injection of granuloma-inducing agents (e.g., BCG) or infection with granuloma-causing agents may produce granulomas in the spleen. Also, a rare spontaneous lesion in F344 rat spleens is characterized by foci of macrophages forming small nodules.

Miscellaneous Changes

Mesothelial Hypertrophy (Figure 26)

The mesothelium can be focally or diffusely hypertrophied. Mesothelial hypertrophy can be seen on the splenic capsular surface in rats with peritoneal metastatic tumors, peritonitis and other conditions.

THYMUS

CONGENITAL CHANGES

Ectopic Parathyroid/Thymus (Figure 27)

Synonym: aberrant parathyroid

Aberrant or ectopic thymic tissue is sometimes seen in the parathyroid gland and aberrant or ectopic parathyroid is sometimes seen in the thymus of rats. At approximately day 13 of gestation in the rat, the thymus and parathyroid migrate caudally. The organs separate from each other on day 15 when the thymus moves down into the thorax. Thymic tissue becomes thin in the neck and breaks up into small fragments. These fragments may be found in the thorax close to or embedded in the thyroid gland (3). It is necessary to identify the presence of pale staining clusters of thymic epithelial cells and/or Hassall's corpuscles within these foci in order to be certain that they represent ectopic thymic tissue. Ectopic thymic tissue must be differentiated from simple lymphoid aggregates. In addition, fragments of ectopic thyroid and/or parathyroid tissue, of normal histolic appearance, may be found adjacent to or embedded within the thymus. These findings are not common, and no toxicological significance has been attached to them.

Disturbances of Growth

Physiological Involution (Figure 28)

Synonym: atrophy

The thymus of the rat reaches its maximum size in young adult rats and then begins to slowly decrease in size with age beginning at sexual maturity. This normal decrease in size is commonly referred to as physiological involution. Both lymphocytic and epithelial components decrease in size in normal involution, although atrophy is more pronounced in the cortex than in the medulla. The thymus of a two year old rat is quite small as a result of a decrease in size in both the cortex and medulla. As involution progresses with age, cuboidal to columnar epithelial cells become more prominent in the medulla and may form cysts. In advanced cases of involution, infiltration of adipose tissue is pronounced in the cortex.

Some pathologists record this finding in older rats as either atrophy or physiological involution. Others regard this finding as a normal change and do not record it as a lesion. The benefit of recording this finding is that some toxicants can cause an atrophy of the thymus. Although the age-related reduction of thymic tissue is a normal process and not a pathologic lesion, it can be useful in toxicologic studies to grade the degree of aging in order to investigate the influence of test substances on the rate of aging (7).

Degenerative Lesions

Lymphoid Necrosis (Figure 29)

Necrosis of the cortical lymphocytes may occur as a direct effect of toxicants or secondary to debilitation and stress as a result of an elevated level of endogenous corticoids (13, 16). It may be especially prominent in rats sacrificed in a moribund condition.

Necrosis may consist of either individual cell necrosis or more advanced necrosis characterized by large clumps of nuclear debris.

It has been reported that cytostatic chemicals result in atrophy and necrosis of the thymus of rats (4). Imai reported a decrease in the number of thymic lymphocytes, as well as abundant pyknotic thymic lymphocytes, cellular debris, and hemorrhage (4).

Fibrosis (Figure 30)

Fibrosis is an uncommon lesion of the thymus of rats, but it is sometimes seen as a secondary to chronic inflammation that may occur as a result of a gavage injury.

Mineralization

Mineralization is an uncommon finding in the thymus of rats. It may be observed in old areas of hemorrhage.

Vascular Lesions

Hemorrhage (Figure 31)

Focal or multifocal hemorrhage may be seen in the thymus and is more commonly seen in the medulla than the cortex. It is usually more common in sacrificed animals and may be observed as an agonal lesion in rats anesthetized with CO_2.

Stefanski et al (13) state that in the absence of necrosis or other lesions, these areas of extravascular erythrocytes are generally attributed to necropsy technique or dissection-induced artifact and are not considered to be a vascular lesion. Vitamin K deficiency in rats may cause thymic hemorrhage.

Inflammatory Changes

Inflammation (Figures 32, 33)

Primary inflammatory changes in the thymus of rats are rare. Inflammation may occur as a result of extension of inflammation from other tissues, particularly as a result of gavage injury.

miscellaneous changes

Epithelial Cysts (Figure 34)

Epithelial cysts are common findings in the involuted thymus of aged rats. These cysts are believed to be either remnants of the thymopharyngeal duct or are believed to develop as a result of dilatation of thymic tubular structures (13). They are often associated with epithelial glandular hyperplasia (1).

BONE MARROW

disturbances of growth

Atrophy (Figure 35)

Synonym: hypocellularity

Bone marrow atrophy may be focal, multifocal or diffuse. It is characterized by well demarcated areas with a decrease in the number of hematopoietic cells, an increase in the number of fat cells and an increased prominence of reticular stroma. Diffuse atrophy is usually observed in old rats, especially those sacrificed in a moribund condition. In young rats it is associated with decreased weight gain or reduced weight. It may be associated with chemical administration. Focal or multifocal hypocellularity is rarely observed and is more common in female rats. The aging process results in fatty replacement of bone marrow in long bones.

Degenerative changes

Fibrosis (Figure 36)

Synonym: myelofibrosis

Myelofibrosis is characterized by an increase in reticulum and collagenous fibers with decreased number of hematopoietic cells. This lesion must be distinguished from focal atrophy, fibrous osteodystrophy and stromal hyperplasia. Focal fibrosis is usually observed in young rats and it may occur secondarily as a result of injury, inflammation, or necrosis.

Necrosis (Figure 37)

Bone marrow necrosis is characterized by focal or diffuse nuclear pyknosis, karyorrhexis, cytoplasmic vacuolization, and lysis. It may result from infections, toxins or inflammatory processes. Bone marrow necrosis can also be induced with chemicals. It may also be associated with malignancies, leukemia, lymphoma, metastases, vascular obstruction (thrombosis) or hemorrhage in the acute stage due to the vascularity of the tissue.

Infarction

Occlusion of blood vessels that supply blood to the bone marrow may lead to infarction. It may also be associated with infection, growing malignancies, metastases or vascular obstruction (thrombosis).

Pigmentation (Figure 38)

Hemosiderin pigment is sometimes found in the bone marrow. It is present in macrophages and may be associated with old hemorrhage. An iron stain such as Prussian blue may be helpful in determining hemosiderin pigment.

Vascular Lesions

Hemorrhage (Figure 39)

Escape of blood from the vessels in the bone marrow is referred as hemorrhage. In old hemorrhage where brown pigment (iron positive) accumulation is observed in the endothelial cells, the lesion should be referred to as hemosiderosis. In some cases these lesions may be associated with bone marrow necrosis.

Inflammatory Lesions

Inflammation (Figure 40)

Inflammatory lesions of rat bone marrow are rare. Focal granulomatous lesions have been reported and are more common in females than in males (9). They are characterized by accumulation of macrophages, having oval, elongated or fusiform nuclei and abundant pale eosinophilic cytoplasm. These lesions can be induced by

some chemicals. Bacterial sepsis with acute inflammation has rarely been observed.

Miscellaneous Lesions

Lymphoid Follicles

Lymphocytes are found in the normal marrow population and are dispersed singly among hematopoietic and fat cells. Lymphoid cells may also be present in aggregates or lymphoid follicles with well developed germinal centers but are not usually found in untreated rats.

DISCUSSION

The previously described lesions may be found in both control and treated rats. The use of immunocytochemistry can further define the nature of these lesions.[14]

Hematopoietic tissues are commonly fixed in 10% neutral buffered formalin along with the remaining tissues of the animals. This is satisfactory for light microscopy. However, if the investigator anticipates the use of immunocytochemistry on hematopoietic tissues, special procedures or fixatives may be needed. Cell surface antigens and immunoglobulins may require frozen sections or Bouin's, B-5 or Zenker's fixation. Predigestion with trypsin or another protease may enhance immunoreactivity of immunoglobulins in formalin-fixed rodent tissue. Frozen sections are required for many cell surface antigens found on hematopoietic cells. Bouin's fixative is a good fixative for demonstrating immunoglobulins in cells in paraffin-embedded tissue sections.

Immunocytochemistry can serve as a valuable adjunct in diagnosing non-proliferative hematopoietic lesions in rats, especially in paraffin-embedded tissues. Specific antigens may be localized in cells and tissues, and the immunoreactivity of polyclonal and monoclonal antibodies to these antigens provide a more accurate basis in the diagnosis and also aid in understanding the pathogenesis of these lesions. Both specific and nonspecific staining patterns may be focal or diffuse and may be categorized by localization as tissue, nuclear, cell membrane, nuclear membrane, cytoplasmic-diffuse, cytoplasmic-focal, or granular, whole cell (nucleus and cytoplasm and extracellular) (19).

Many techniques are available and many commercial kits can be obtained (e.g., ABC, PAP, immunogold). Antigen retrieval methods using antigen retrieval solutions and microwave pretreatment of tissue sections may allow detection of some cell surface antigens in paraffin embedded sections (12).

Many rat leukocyte antigens can be detected using frozen sections of rat tissues. A thorough evaluation of them for use in paraffin sections, especially after antigen retrieval has not been made. The following table lists a number of antibodies along with their source.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

LYMPH NODE

Degenerative Changes

Lymphoid Necrosis

1. Focal, multifocal or diffuse
2. Fragmentation of cells with pyknotic or karyorrhectic nuclei
3. Often accompanied by phagocytic macrophages

Infarction

1. Uncommon finding
2. May be secondary to polyarteritis nodosa

Table 1 - Selected Rat Hematopoietic Antibodies Immunoreactive on Paraffin-Embedded Sections and Frozen Sections.

Antibody	CD Number	Commercial Source	Cells Expressed in	Optimal fixative
Lysozyme	N/A	DAKO	macrophages/histiocytes	formalin
ED-1	N/A	Chemicon, Harlan	macrophages/histocytes	formalin
Ig Kappa, IgG, IgA, IgM	N/A	Harlan	B lymphocytes	Bouin's Zenker's, B-5, frozen
OX33	CD45RA	Harlan	B cells	frozen
OX-8	CD8	Harlan	cytotoxic/suppressor T lymphocytes/LGLs	frozen, Bouin's, B-5, Zenker's, formalin (with trypsin digestion)
W3/25	CD4	Harlan	Helper T Macrophages	frozen

3. Diffuse coagulation necrosis with loss of nodal architecture
4. Peripheral rim of viable lymphocytes may survive
5. Replacement of parenchyma with collagen and mineralization

Mineralization

1. Secondary effect of tissue damage
2. Basophilic crystalline mineral deposits within necrotic or degenerating tissue
3. Most likely to be associated with infarction or neoplasm

Fibrosis

1. Increase in collagenous stroma with resulting distortion of normal tissue architecture
2. Occurs as a sequelae to inflammation, necrosis or neoplasia

Pigmentation

1. Deposition of pigment
2. Present in cytoplasm of macrophages
3. Most likely to be present in medullary cords and lymphatic sinuses
4. Hemosiderin is most common
5. Other pigments may be found within macrophages and reticular cells lining sinuses
6. Special stains may be required for differentiation

Lymphoid Atrophy/Depletion

1. Sequelae to disease or toxin resulting in necrosis
2. May affect B cells or T cells
3. Follicular atrophy characterized by presence of a few, small or no follicles
4. Paracortical or T cell atrophy characterized by the presence of lymphoid follicles, but parenchymal areas around follicles are hypocellular

Vascular Changes

Sinus Erythrocytosis/Hemorrhage

1. Presence of free red blood cells within lymphatic sinuses
2. Usually occurs as a result of hemorrhage in organs or tissues drained by affected node
3. In chronic lesions, accompanied by macrophages, crystallization of hemoglobin from degenerate red blood cells, erythrophagocytosis, and accumulation of hemosiderin pigment

Lymphatic Ectasia

1. Dilated or cystic lymphatic sinuses
2. Spaces are lined by endothelial cells
3. Dilated sinuses contain a few cells, including erythrocytes, and a pale, pink homogeneous fluid
4. Most common in mesenteric and mediastinal lymph nodes

Vascular Sinus Ectasia

1. Dilatation of vascular channels, sinuses within medullary cords or subcapsular sinuses
2. Sinuses lined by endothelial cells
3. Sinuses contain erythrocytes

Thrombosis

1. Solid mass within lumen of blood vessel
2. Composed of fibrin, platelets and may contain trapped red blood cells

Inflammatory Changes

Abscess

1. May be acute or chronic
2. Generally result of infections or antigenic substance
3. Central area of necrosis in which neutrophils are predominant inflammatory cell
4. Surrounded by variable amounts of fibrous connective tissue

Acute Inflammation

1. Aggregates of neutrophils without necrosis or abscess formation
2. Commonly found in superficial nodes draining skin or mesenteric nodes draining intestinal tract
3. Must be distinguished from extramedullary hematopoiesis and granulocytic leukemia

Chronic Inflammation

1. Associated with chronic abscesses
2. Normal lymphoid architecture may be partially or completely obliterated

Granulomatous Inflammation

1. Multiple small aggregates of macrophages/ histiocytes
2. Hemosiderin or lipofuscin pigment may be present
3. Most commonly found in mesenteric lymph nodes

SPLEEN

Congenital Changes

Accessory Spleen

1. Small pieces of splenic tissue present separate from spleen in mesentery, omentum or exocrine pancreas

Disturbance of Growth

Capsular Cyst

1. Cyst-like structures on capsular surface of spleen
2. Lined by endothelial cells
3. Filled with homogeneous eosinophilic fluid
4. May be of lymphatic origin

Degenerative Changes

Lymphoid Hypoplasia

1. Found in nude rats
2. Few or no small lymphocytes in T cell zones (PALS)
3. Decrease in white pulp

Lymphoid Atrophy/Depletion

1. Loss of lymphocytes of B or T cell zones
2. Often seen after necrosis in chemical toxicity, viral infections or after irradiation

Pigmentation

1. Pigment may be either hemosiderin or lipofuscin
2. Both pigments are more common in aging rats
3. Small amount of hemosiderin considered normal
4. Hemosiderin is iron positive
5. Lipofuscin is acid fast

Lipid Accumulation

1. Focal or diffuse accumulation
2. Characterized by presence of empty clear vacuoles

Fibrosis

1. May be focal, multifocal or diffuse
2. May involve capsule or parenchymal tissue
3. Capsular involvement may be due to peritoneal metastatic tumors or peritonitis
4. Parenchymal fibrosis occurs as fibrotic areas with loose or dense collagen in the red pulp

Mineralization

1. May occur in capsule or parenchyma
2. May be observed in areas of old hemorrhage
3. Basophilic crystalline mineral deposits within necrotic or degenerating tissue

Apoptosis

1. Distinct mode of cell death responsible for deletion of cells in normal tissues
2. Not associated with inflammation
3. Characteristic biochemical feature is cleavage of nuclear DNA
4. Presence of apoptotic bodies

Necrosis

1. Cell death characterized by nuclear pyknosis, karyorrhexis or karyolysis associated with increased cytoplasmic eosinophilia
2. May affect white pulp, red pulp, trabeculae or capsule
3. Necrosis of white pulp may include marginal zone cells, B cell zone lymphocytes or T cell zone lymphocytes
4. Red pulp necrosis may be of hematopoietic or vascular cells or trabeculae

Vascular Changes

Hemorrhage

1. Presence of erythrocytes outside of vascular channels
2. May be focal, multifocal or diffuse
3. May follow chemical exposure, irradiation and viral infections

Periarteritis

1. Accumulation of inflammatory cells around periphery of vessels and within vessel walls
2. Small muscular arteries commonly affected
3. Varies from an acute inflammation with neutrophils and fibrinoid necrosis of vessel walls to a chronic inflammation with infiltration of lymphocytes

Infarction

1. Cell death as result of vascular occlusion
2. Occlusion often not identified microscopically
3. Secondary hemorrhage

Inflammatory Changes

Acute Inflammation

1. Infiltration of neutrophils
2. Usually associated with inflammation in adjacent tissues

Granulomatous Inflammation

1. Foci of macrophages forming small granulomas

Miscellaneous

Mesothelial Hypertrophy

1. Focal or Diffuse
2. Increase in size and prominence of mesothelial cells on capsular surface of spleen
3. Usually secondary to peritoneal metastatic neoplasms, peritonitis and related conditions

THYMUS

Congenital Changes

Ectopic Parathyroid/Thymus

1. Aberrant or ectopic thymic tissue in parathyroid gland
2. Ectopic thymic tissue contains pale clusters of thymic epithelial cells and/or Hassall's corpuscles
3. Aberrant or ectopic parathyroid tissue in thymus
4. Ectopic parathyroid tissue usually embedded in thymus

Disturbances of Growth

Involution/Atrophy

1. Normal physiological change

2. Begins at sexual maturity
3. Decrease in both lymphocytic and epithelial components but more pronounced in cortex than medulla
4. Some toxicants may increase or enhance this process

Degenerative Changes

Necrosis

1. Consists of either individual cell necrosis or more advanced necrosis with prominent nuclear debris

Mineralization

1. Uncommon finding
2. May be found in areas of old hemorrhage
3. Basophilic crystalline mineral deposits within necrotic or degenerating tissue

Vascular Changes

Hemorrhage

1. Presence of erythrocytes outside of vascular channels
2. Focal, multifocal or diffuse
3. More common in medulla

Miscellaneous Changes

Epithelial Cysts

1. Dilatation of thymic tubular structures
2. Common in involuted thymus
3. Often associated with glandular hyperplasia

BONE MARROW

Disturbances of Growth

Atrophy/Hypocellularity

1. Well demarcated areas containing a decrease in the number of hematopoietic cells
2. Focal, multifocal or diffuse

Degenerative Changes

Myelofibrosis

1. Increase in reticulum and collagenous fibers with decreased number of hematopoietic cells
2. May occur as a result of injury, inflammation, or necrosis

Hematopoietic Cell Necrosis

1. Cell death characterized by nuclear pyknosis, karyorrhexis cytoplasmic vacuolization and lysis
2. May be associated with malignancies, leukemia, metastases or vascular obstruction

Infarction

1. Cell death as a result of vascular occlusion
2. Occlusion usually not visible microscopically
3. May be associated with malignancies and metastases

Pigmentation

1. Brown granular pigment in cytoplasm of macrophages
2. Most commonly hemosiderin
3. May be associated with old hemorrhage
4. Can be confirmed with special stains for iron

Vascular Changes

Hemorrhage

1. Presence of free red blood cells outside of vascular channels
2. May be associated with necrosis
3. Hemosiderin pigment may be present in old hemorrhages

Inflammatory Changes

Granulomatous Inflammation

1. Focal granulomatous lesions characterized by accumulations of macrophages with oval, elongated or fusiform nuclei and abundant eosinophilic cytoplasm

Miscellaneous Changes

Lymphoid Follicles

1. Aggregates of lymphocytes that appear normal within marrow
2. Germinal centers are prominent

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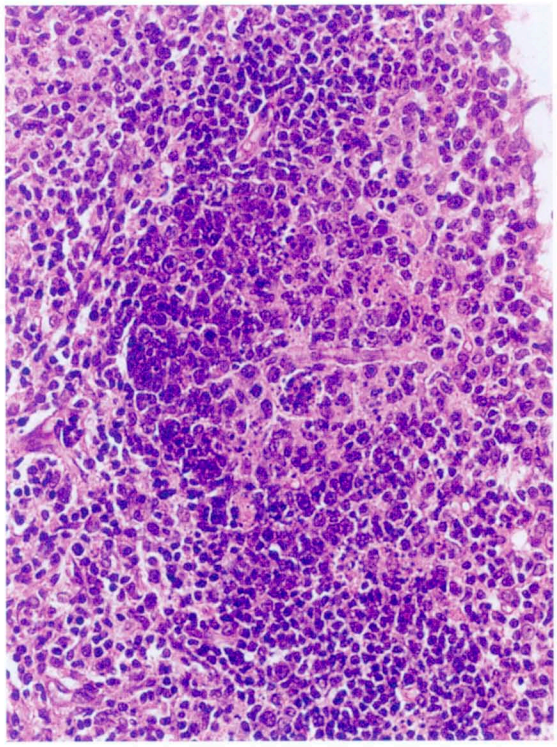

Fig. 1 *- Necrosis, lymph node from a rat administered E. coli toxin.*

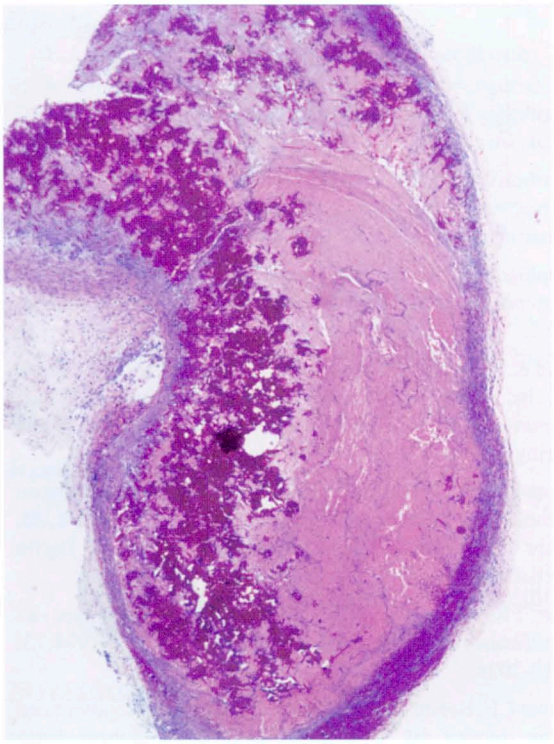

Fig. 2 *- Infarcted lymph node.*

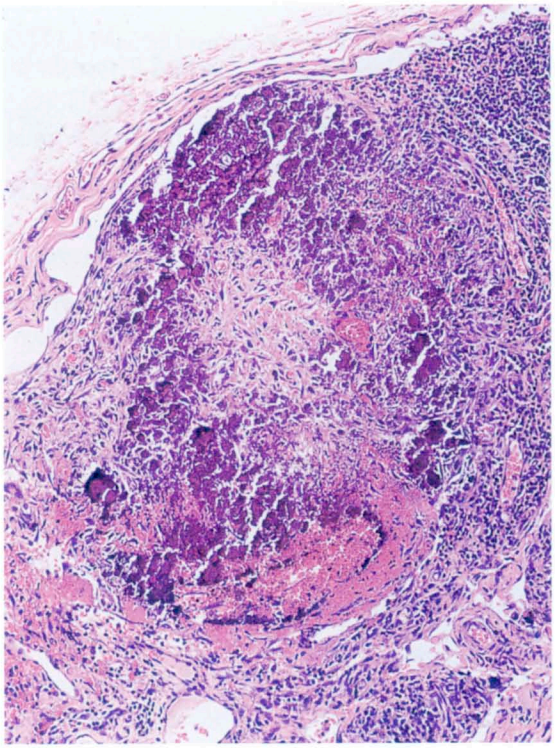

Fig. 3 *- Mineralization, lymph node.*

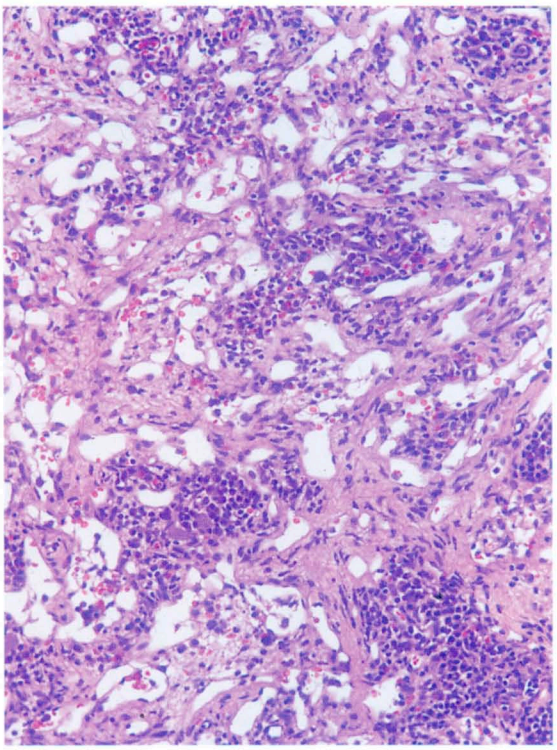

Fig. 4 *- Fibrosis, lymph node.*

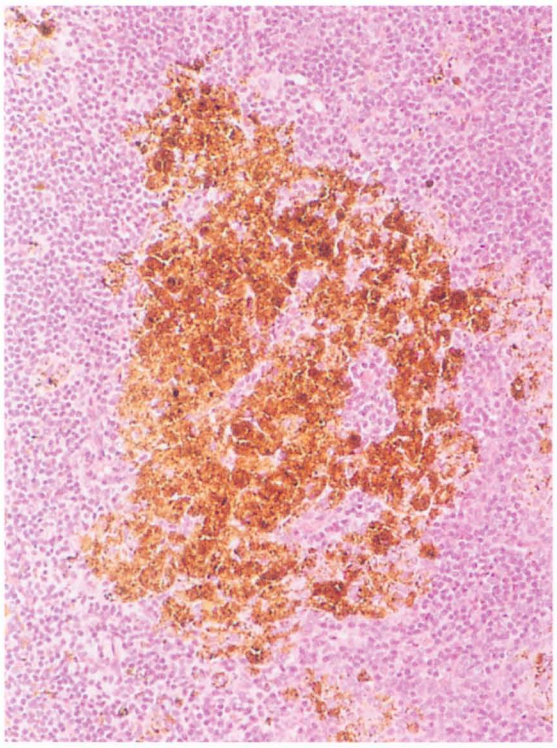

Fig. 5 *- Hemosiderin pigment, lymph node.*

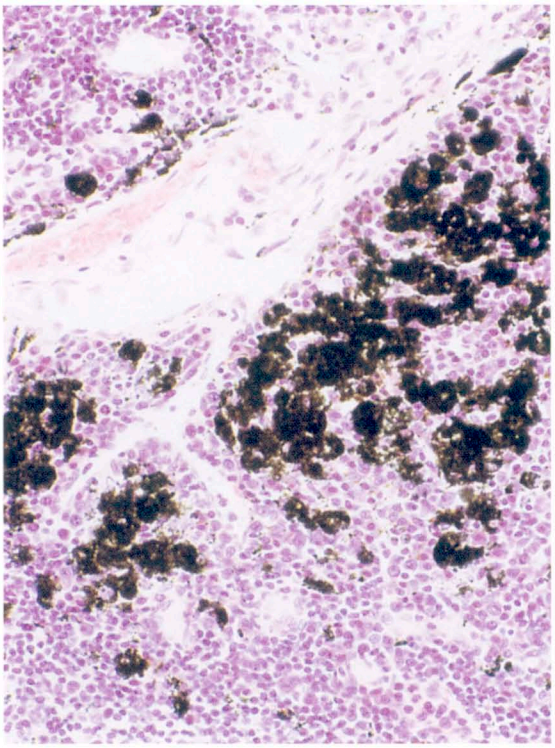

Fig. 6 *- Black treatment-related pigment , lymph node.*

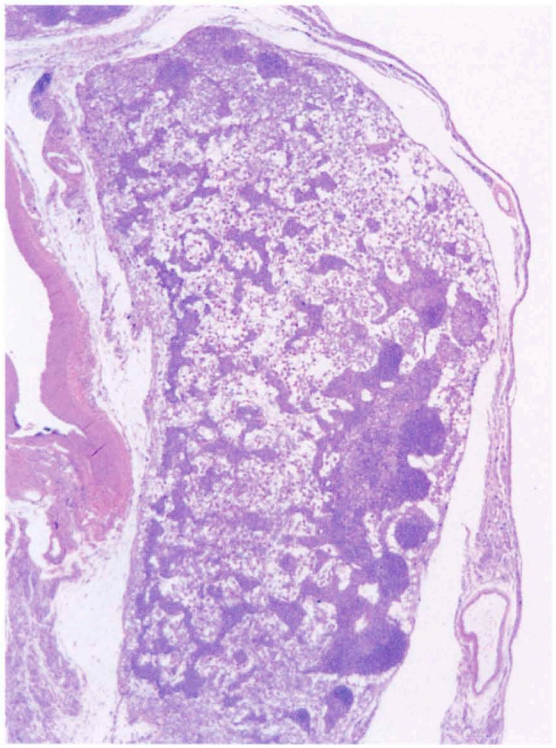

Fig. 7 *- Generalized atrophy, lymph node.*

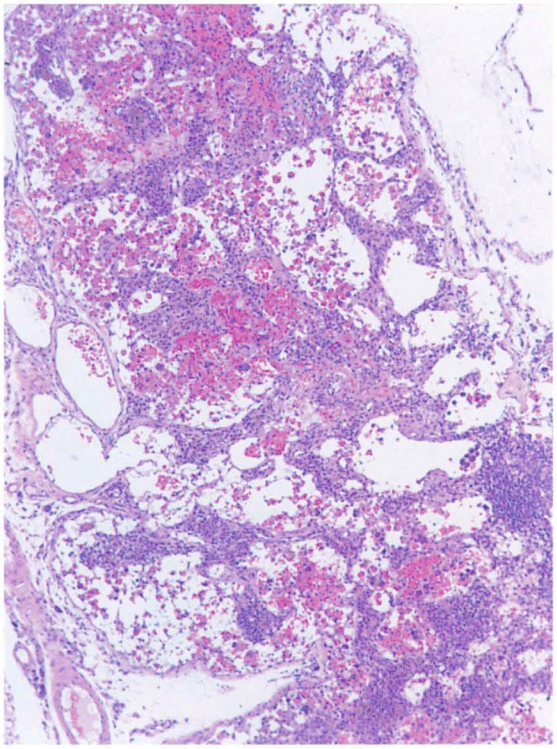

Fig. 8 *- Sinus erythrocytosis, lymph node.*

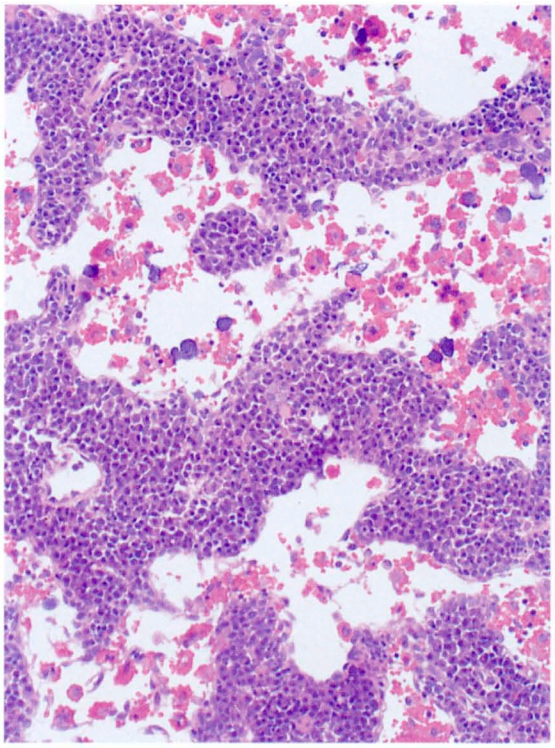

Fig. 9 - *Erythrophagocytosis, lymph node.*

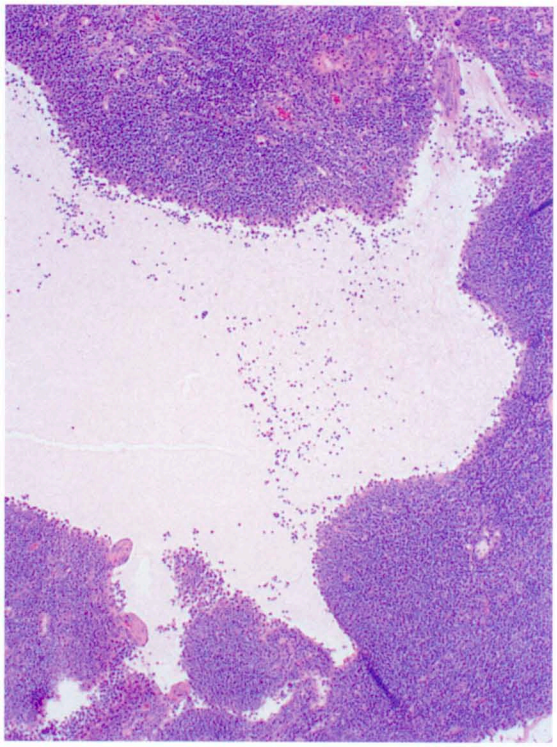

Fig. 10 - *Lymphatic ectasia, lymph node. Note eosinophilic fluid.*

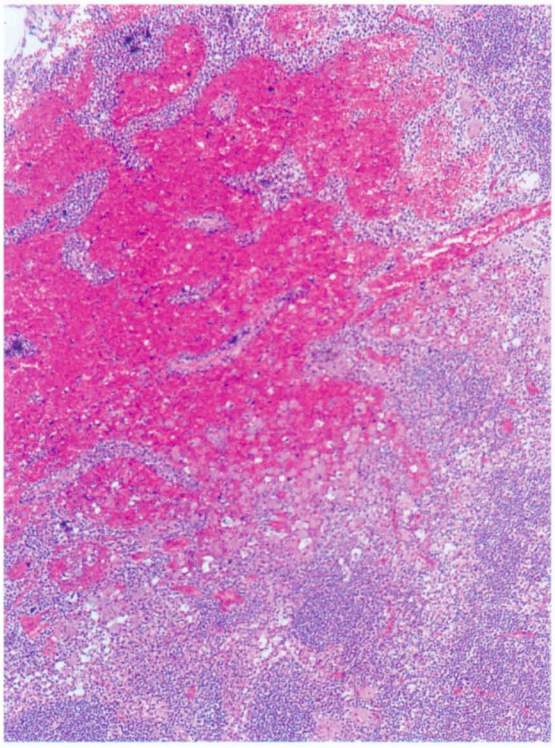

Fig. 11 - *Vascular ectasia, lymph node.*

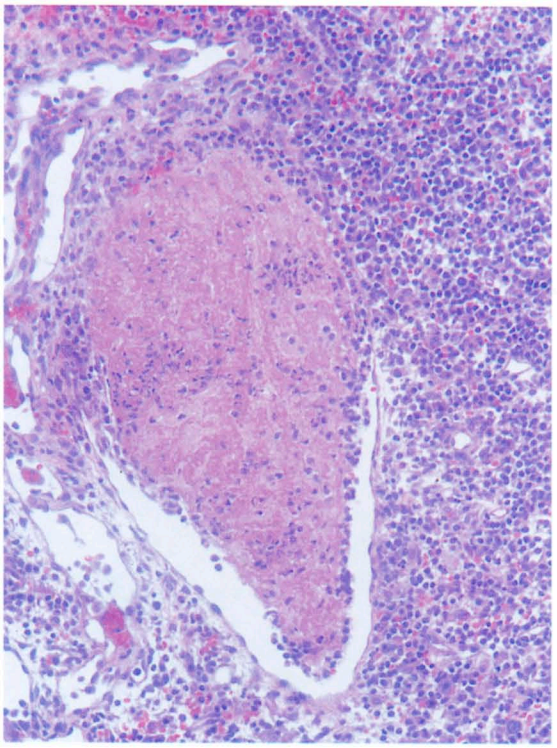

Fig. 12 - *Thrombosis, lymph node.*

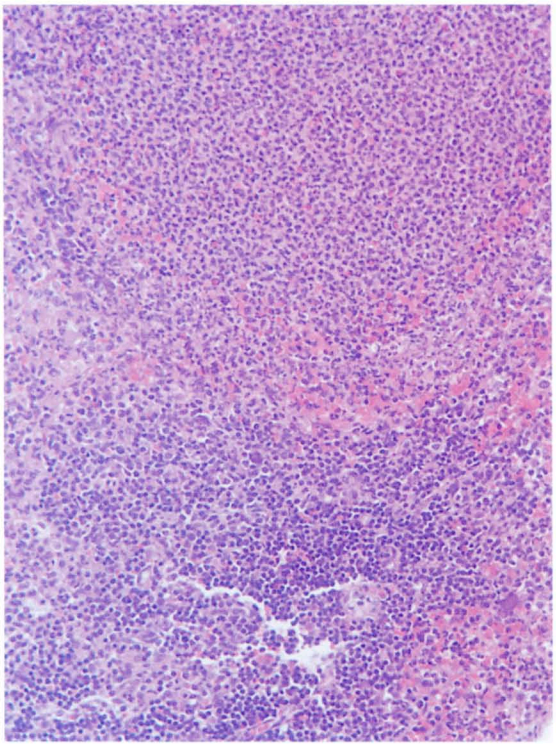

Fig. 13 - *Abscess, lymph node.*

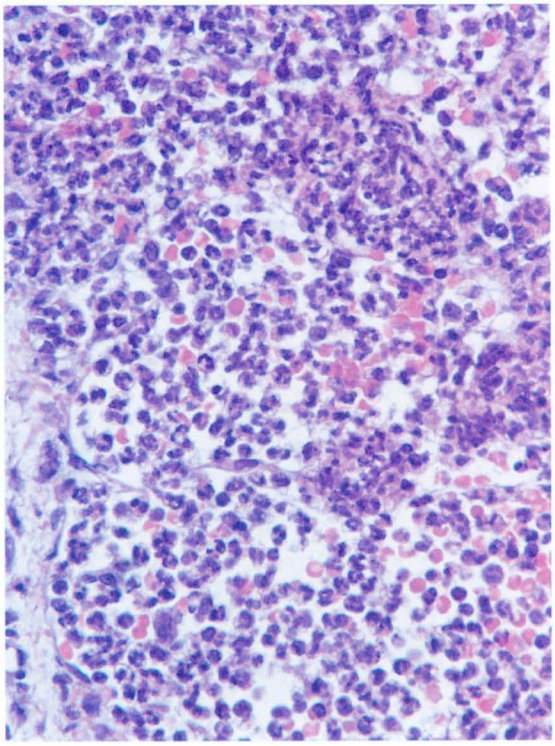

Fig. 14 - *Acute inflammation, lymph node. Note mature neutrophils.*

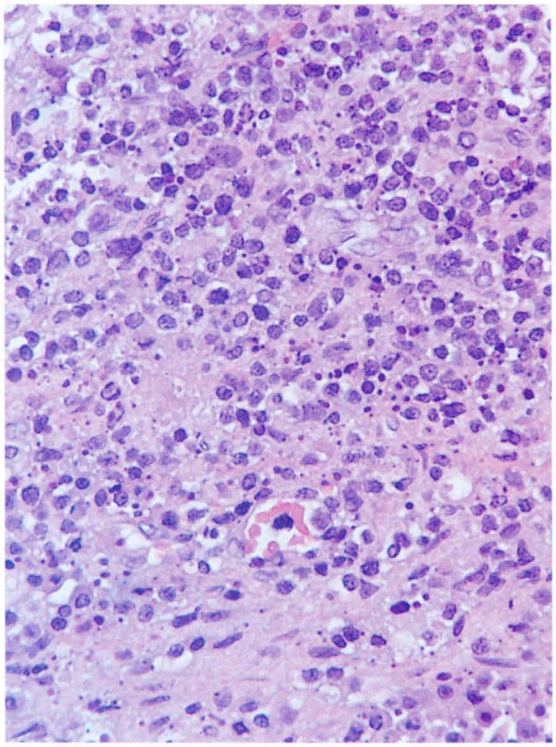

Fig. 15 - *Chronic inflammation, lymph node.*

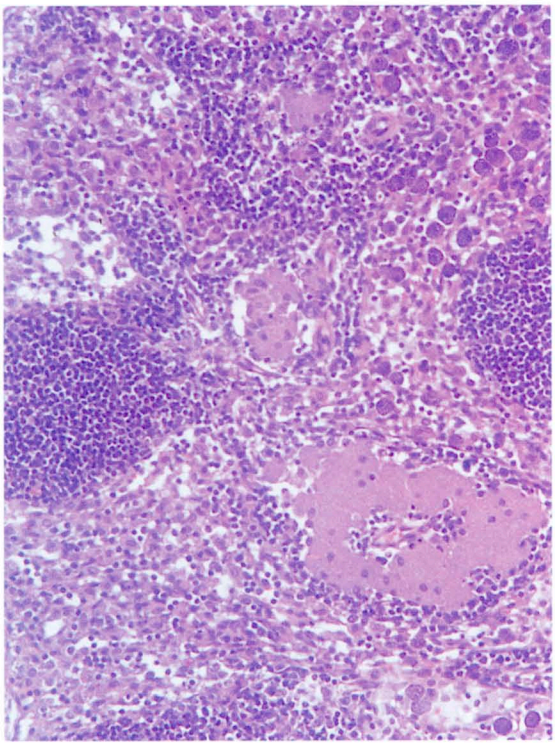

Fig.16 - *Granulomatous inflammation, lymph node.*

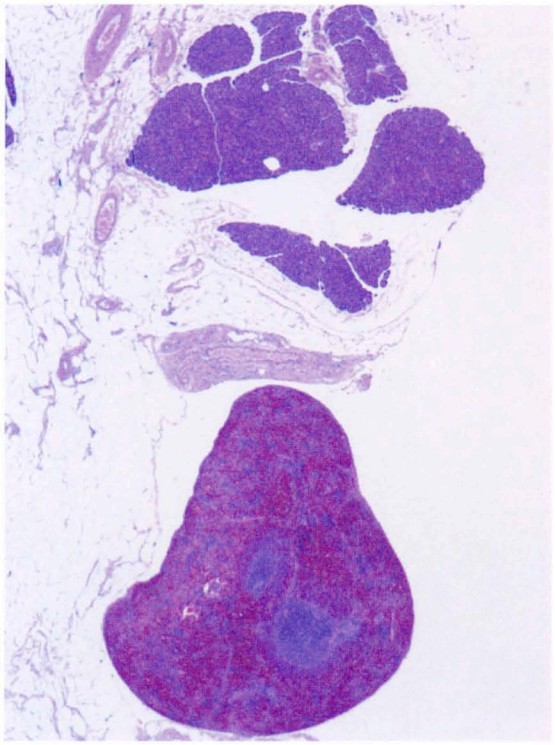

Fig. 17 - *Accessory spleen.*

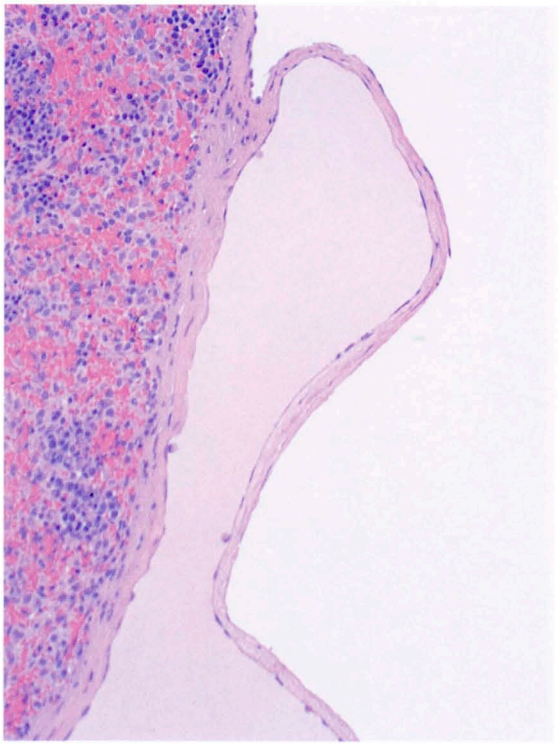

Fig.18 - *Splenic capsular cyst. Note endothelial cells and eosinophilic material.*

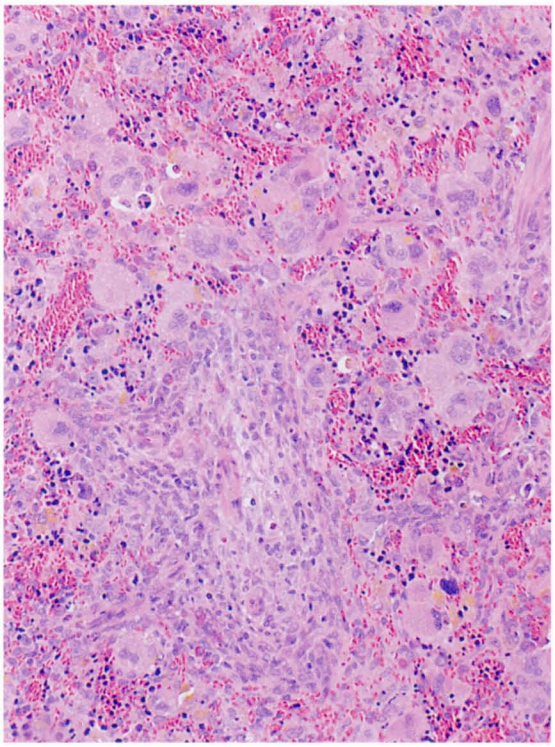

Fig. 19 - *Lymphoid hypoplasia, spleen from a nude rat. Note decreased white pulp.*

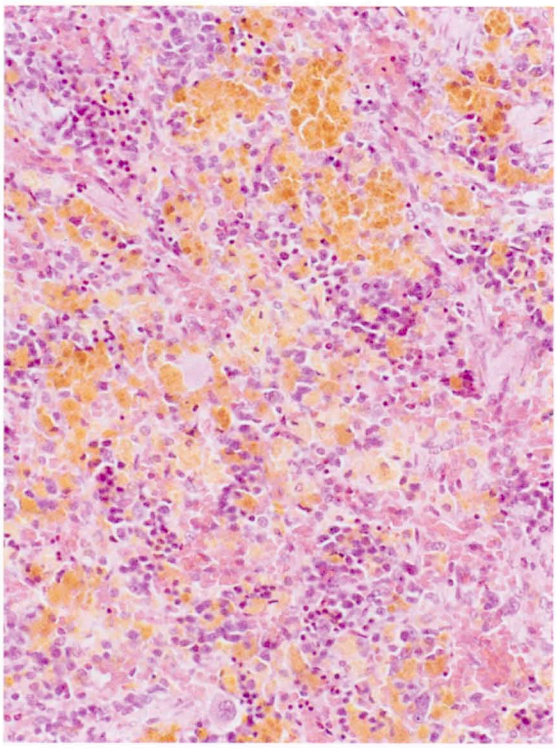

Fig. 20 - *Hemosiderin, spleen.*

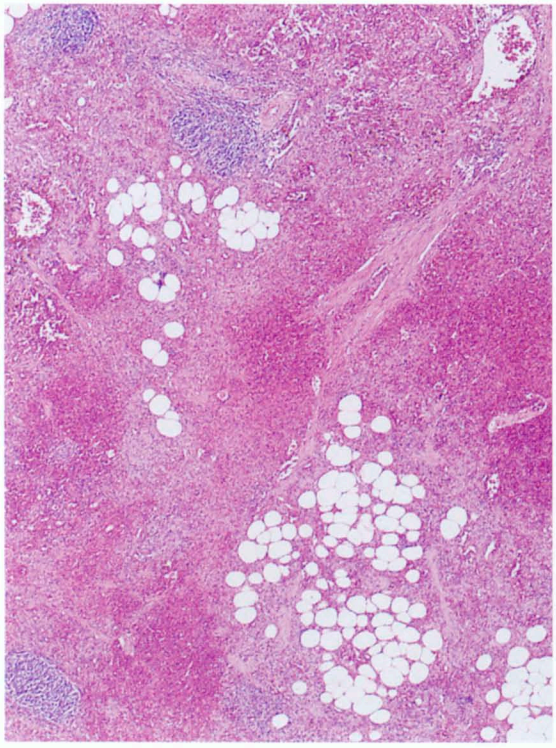

Fig. 21 - *Lipid accumulation, spleen.*

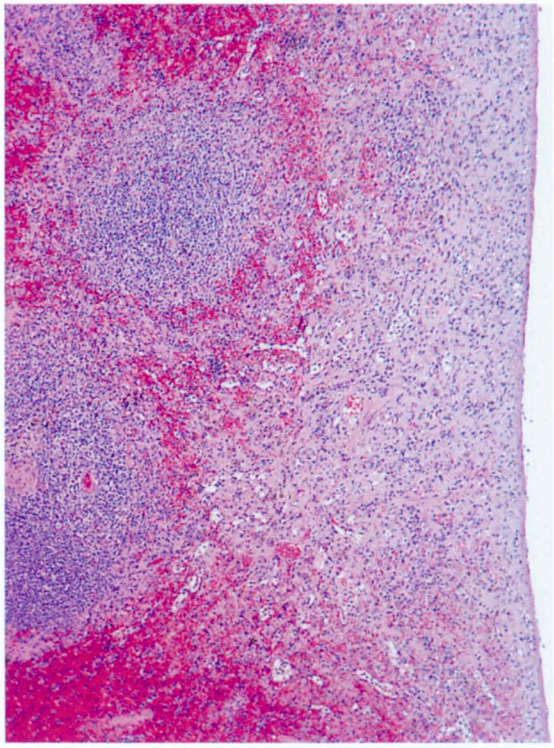

Fig. 22 - *Fibrosis, splenic capsule, extending into the parenchyma.*

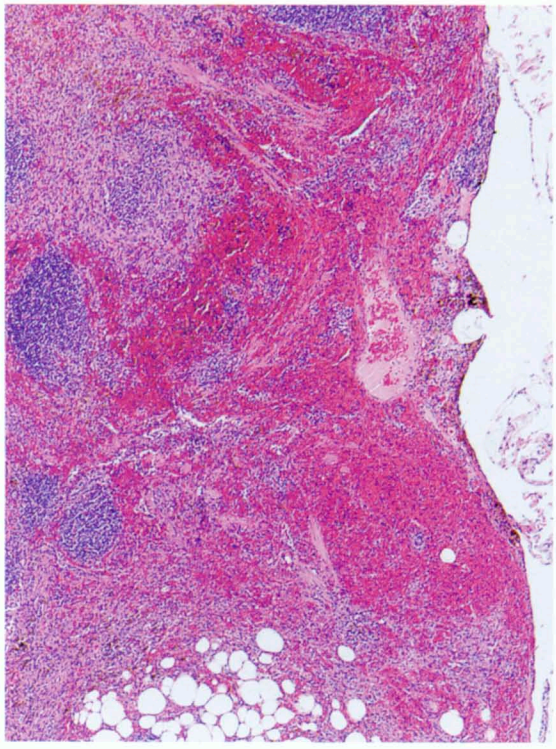

Fig. 23 - *Hemorrhage, spleen.*

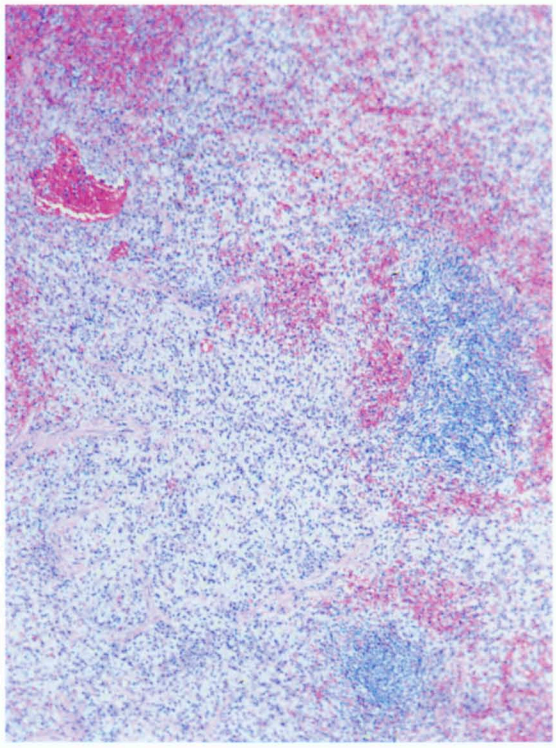

Fig. 24 - *Chronic inflammation, spleen.*

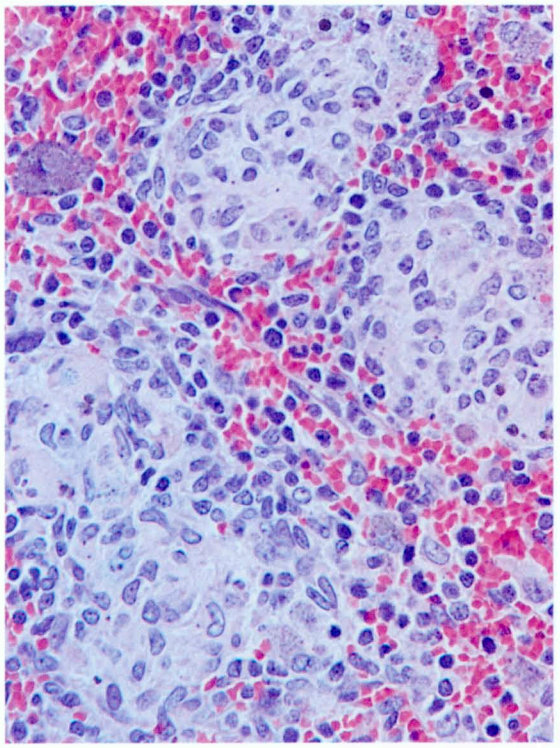

Fig. 25 - *Granulomatous inflammation, spleen.*

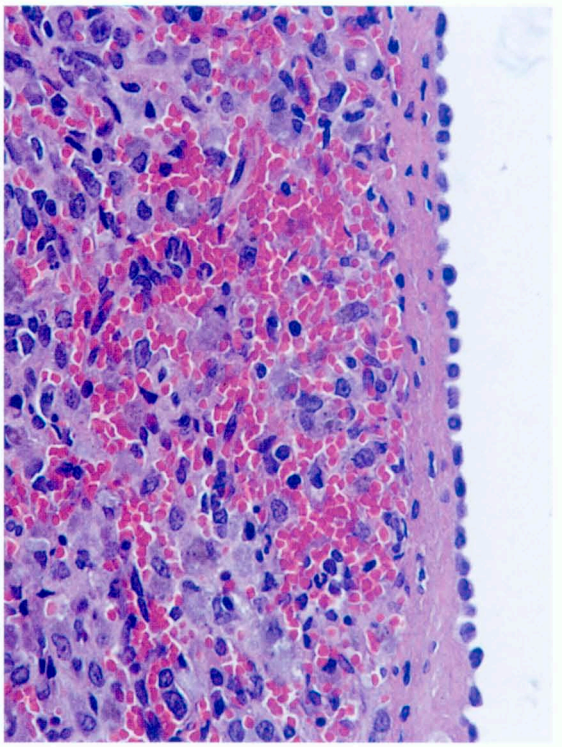

Fig. 26 - *Mesothelial hypertrophy, capsular surface of spleen.*

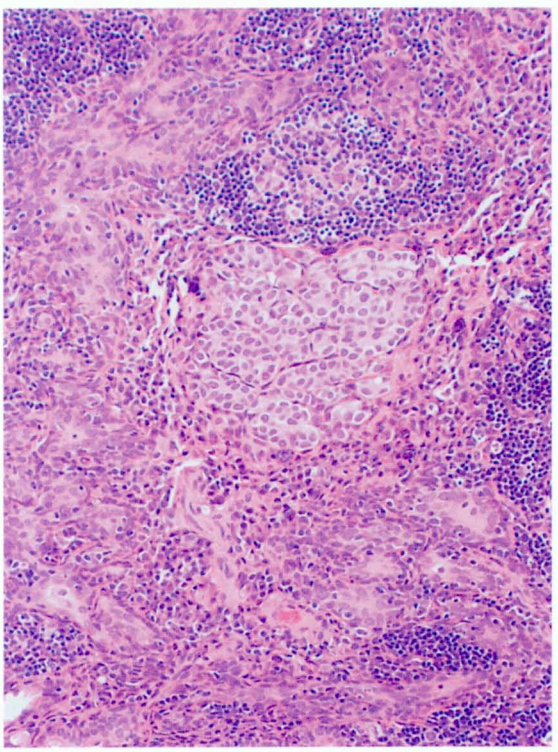

Fig. 27 - *Ectopic parathyroid, thymus.*

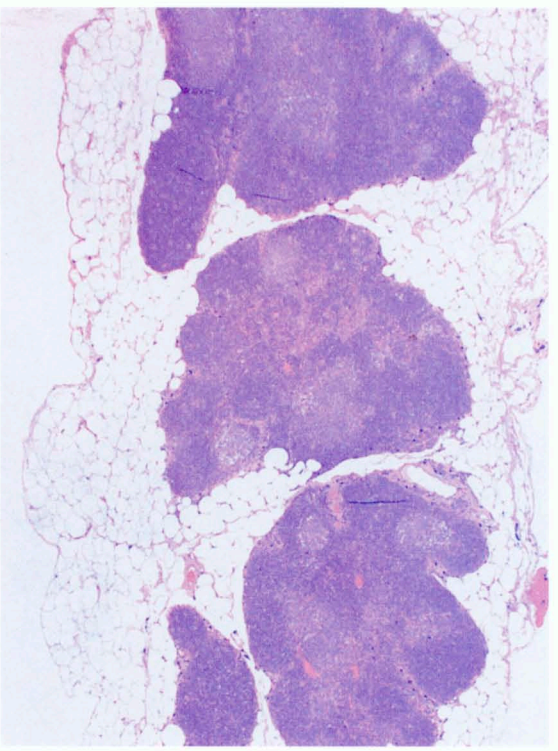

Fig. 28 - *Physiologic involution (atrophy), thymus of a sexually mature rat.*

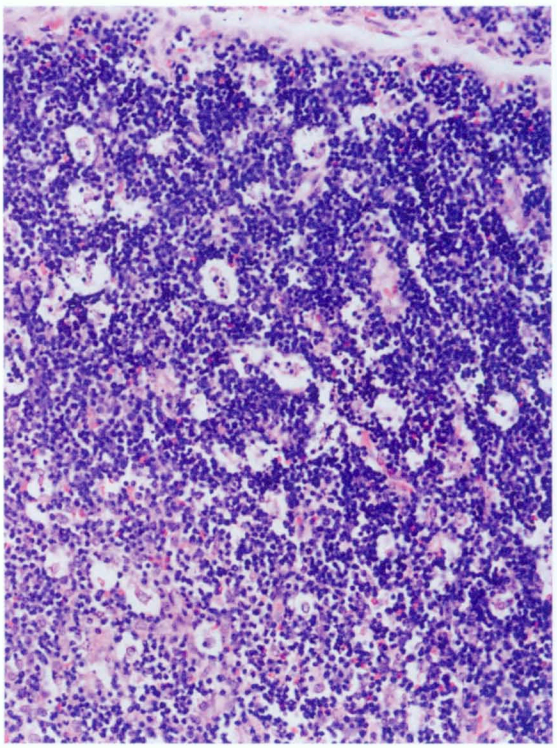

Fig. 29 - *Lymphoid necrosis, thymus.*

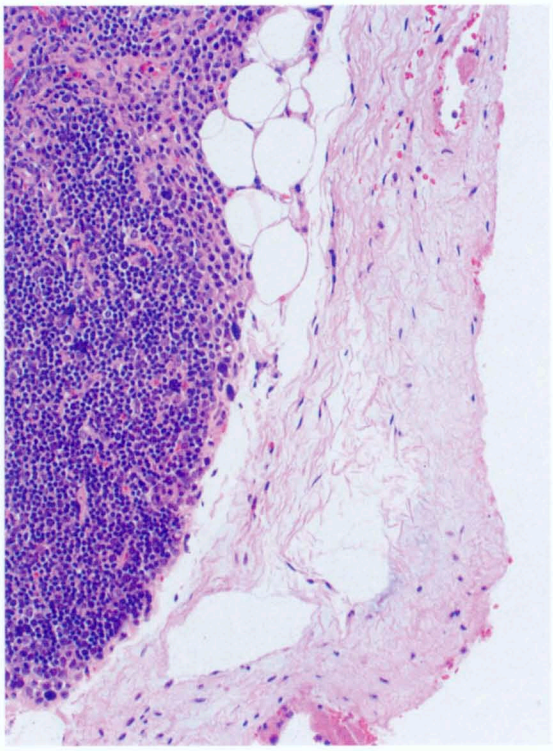

Fig. 30 - *Fibrosis of capsular surface, thymus.*

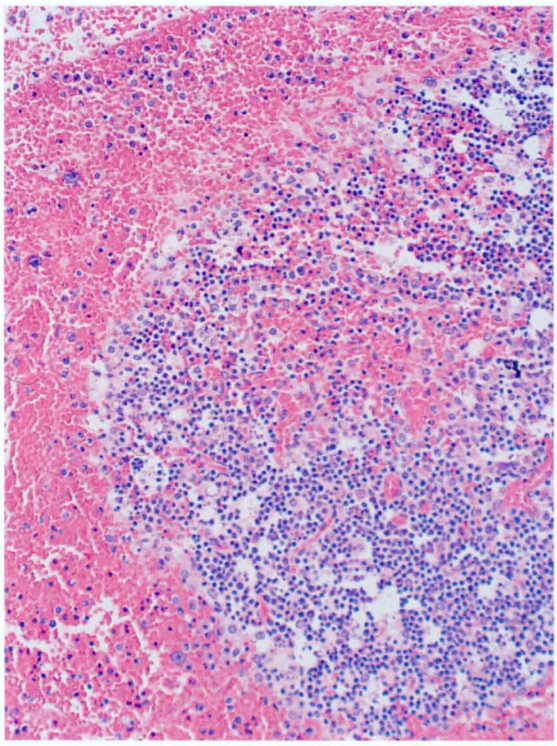

Fig. 31 - *Hemorrhage, thymus.*

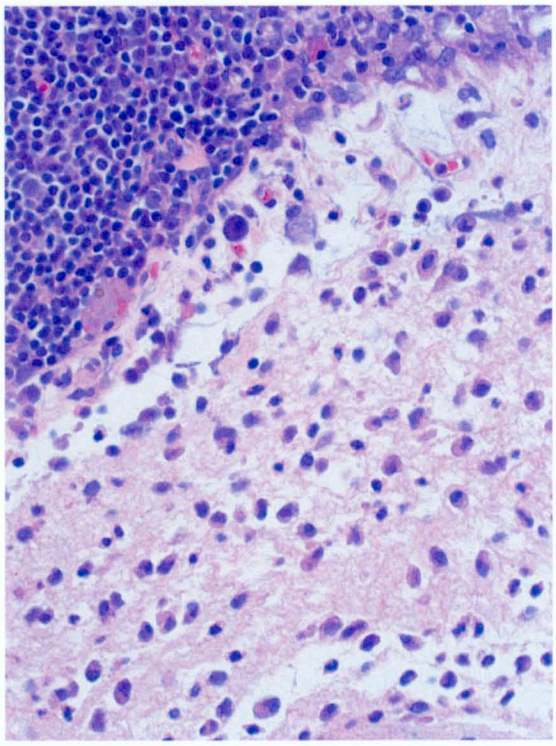

Fig. 32 - *Acute inflammation, thymus, from gavage injury.*

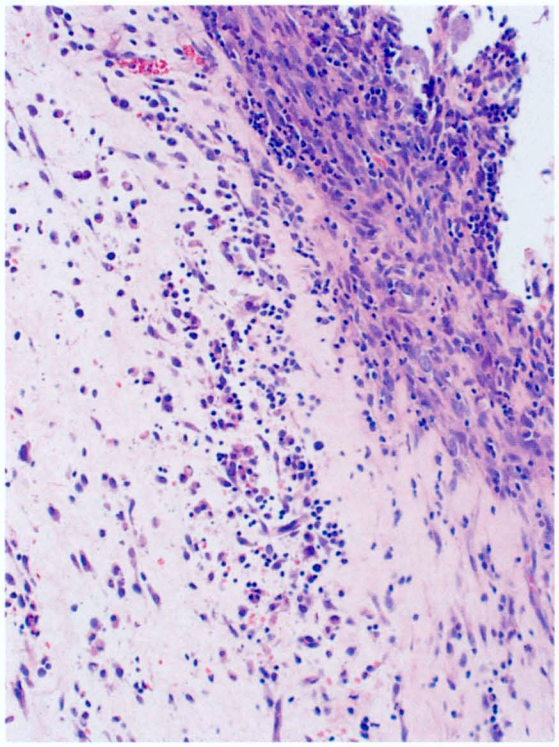

Fig. 33 - *Chronic inflammation, thymus. Note increase in collagen.*

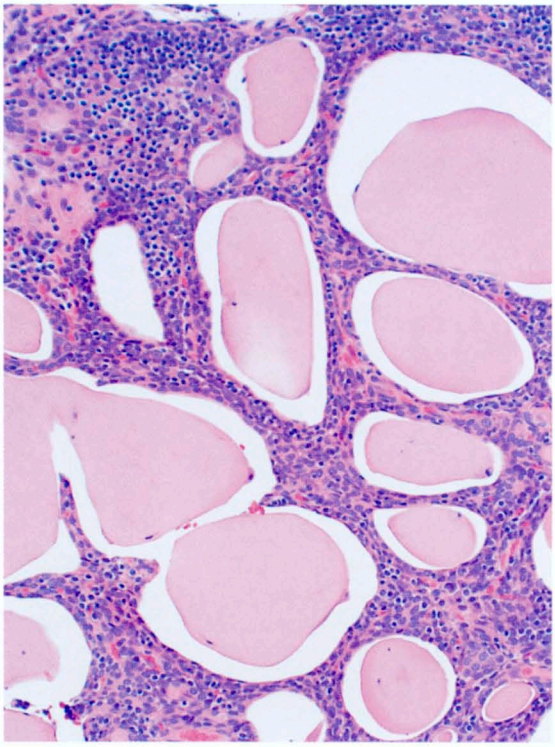

Fig. 34 - *Epithelial cysts, thymus.*

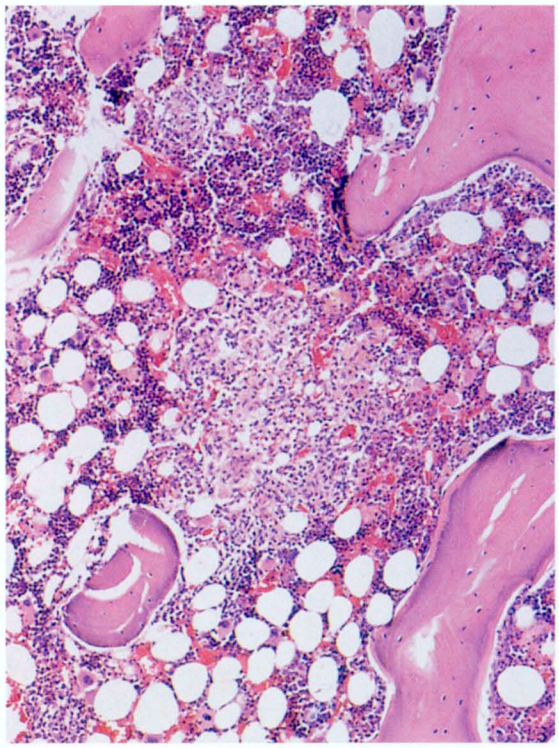

Fig. 35 - *Focal atrophy, bone marrow.*

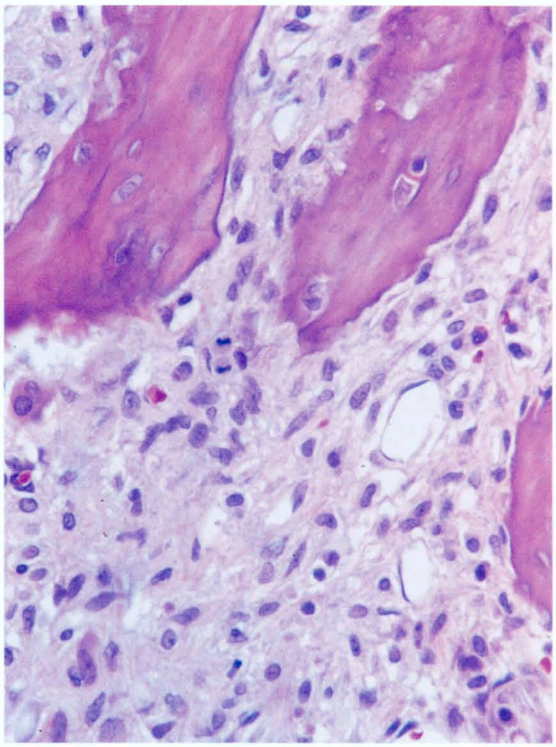

Fig. 36 - *Myelofibrosis, bone marrow.*

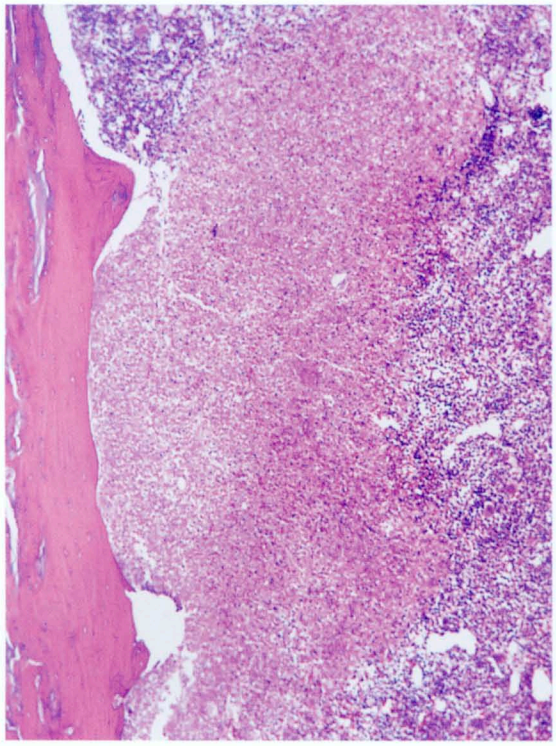

Fig. 37 *- Necrosis, bone marrow.*

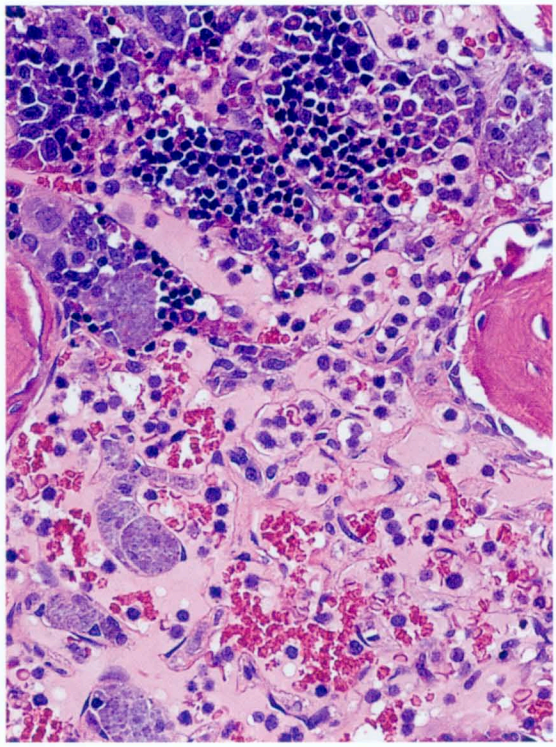

Fig. 38 - *Pigmentation, bone marrow.*

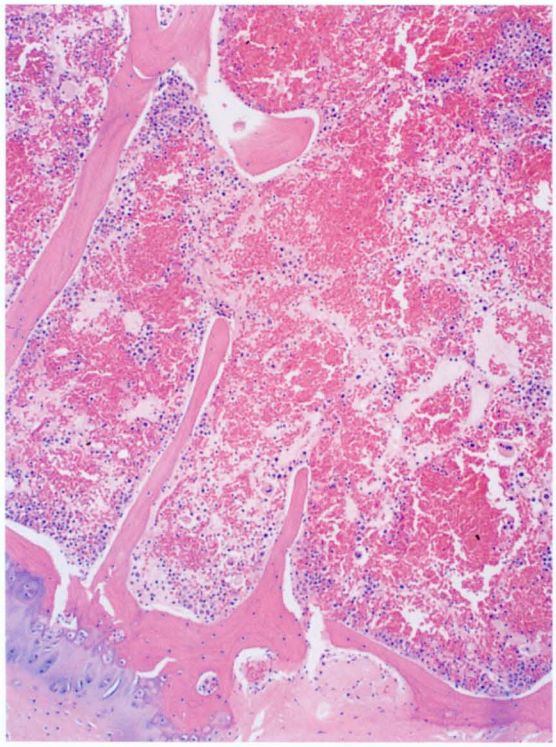

Fig. 39 - *Hemorrhage, bone marrow.*

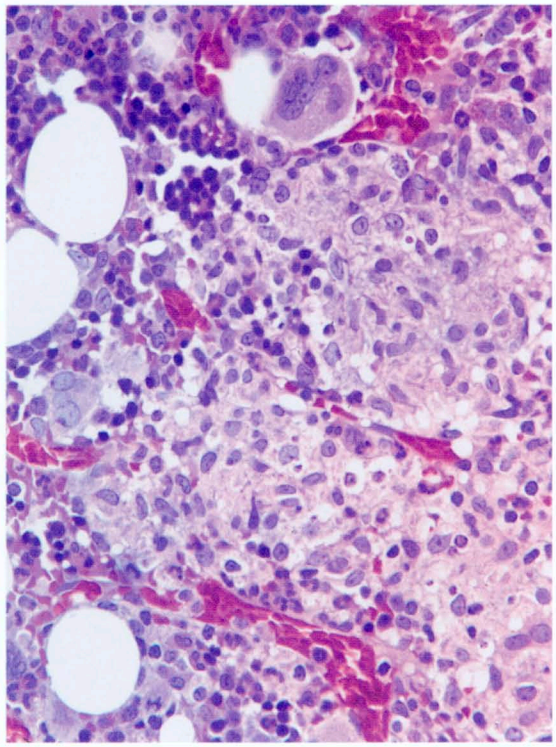

Fig. 40 - *Granulomatous inflammation, bone marrow.*