

# Proliferative Lesions of Soft Tissues and Skeletal Muscle in Rats

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## INTRODUCTION

The histologic diagnosis of proliferative lesions in soft tissues is one of the more difficult issues in tumor pathology in view of the inherent plasticity of mesenchymal cells and the variability of tumors that develop from them. They may show skeletal or smooth muscle, vascular, fatty, fibrous or histiocytic differentiation patterns. The more common neoplasms — fibrous histiocytomas, histiocytic sarcomas and some vascular tumors can be confidently diagnosed from routine hematoxylin and eosin stained sections. The remaining lesions usually need histochemical, immunohistochemical or ultrastructural confirmation (Fisher, 1990).

Soft tissue is regarded as non-epithelial extraskelatal tissue, excluding the reticuloendothelial system and supporting cells of parenchymal organs (Enzinger and Weiss, 1988). Soft tissue tumors are traditionally classified histogenetically according to the adult tissue they resemble. The employment of immunohistochemistry and electron microscopy, however, suggests that many of them, at the time of diagnosis, show incomplete differentiation (Fisher 1990). It is important to emphasize also that mixed differentiation patterns occur (Brookes, 1986) and that there is a close histogenetic relationship between soft tissue neoplasms and bone tumors (Hajdu, 1986). In some classifications of human soft tissue tumors, those showing peripheral nerve differentiation are included because tumors arising from nerves pose similar problems in

diagnosis and therapy. Experimental tumors of peripheral nerves are usually classified separately (Carter, 1973; Greaves and Barsoum, 1990).

## MORPHOLOGY

### TUMORS OF FIBROUS TISSUE

#### *Fibroma (Figure 1)*

This term is limited to nodules or masses composed of dense interwoven bands of collagen, interspersed with a scattering of small fibroblasts with little or no cellular pleomorphism or mitotic activity. These lesions are localized and usually solid although focal myxomatous degeneration is seen.

Fibromas are occasionally seen in untreated aged rats. They need to be distinguished from mammary fibroadenomas in which atrophy of glandular elements has occurred and poorly cellular fibrous histiocytomas.

#### *Fibrosarcoma (Figure 2)*

The diagnosis of fibrosarcoma is limited to monomorphic sarcomas composed of spindle cells with oval nuclei and basophilic cytoplasm arranged in interlacing fascicles or interwoven in a typical herringbone pattern. They have variable mitotic activity and collagenous intercellular matrix.

Ultrastructural examination shows the spindle cell to be fibroblastic. The cytoplasm is usually dominated by rough endoplasmic reticulum either as slender profiles or dilated by moderately electron-dense amorphous material.

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Fibrosarcoma cells contain cytoplasmic intermediate filaments (7-10 nm diameter) of the vimentin type (Virtanen et al., 1981; Miettinen et al., 1982). Thin filaments (4-6 nm diameter) arranged in bundles near the cell membrane and focal condensations or dense bodies suggestive of myofibroblast differentiation have also been described in rat fibrosarcomas (Katenkamp and Neupert, 1982).

Fibrosarcomas are locally invasive neoplasms, spreading widely in skeletal muscle with relatively late and infrequent metastatic spread.

#### ***Tumors of Fibrohistiocytic Type (Figures 3-7)***

Malignant fibrohistiocytic tumors, have been characterized in the rat where they occur spontaneously (Greaves and Faccini, 1981) or can be induced by various chemicals, metals and inert subcutaneous implants (Konishi et al., 1981; Nii et al., 1982; Greaves et al., 1985; Sakamoto et al., 1986; Lumb et al., 1987). Similar neoplasms occur in other species including dog, cat, horse (Ford et al., 1975; Gleiser et al., 1975; Renlund and Pritzker, 1984), mouse (Stewart 1979; Faccini et al., 1990) and hamster (Greaves 1990).

Histological features are variable. They form a spectrum ranging from a well-ordered storiform or cartwheel pattern of plump spindle cells to a highly pleomorphic mixture of spindle cells, small rounded cells, multinucleated and bizarre giant cells. A mononuclear or polymorphonuclear infiltrate is also sometimes seen and blood vessels can be prominent. Collagen formation is usually marked in spindle cell zones and myxoid change can develop. Hemorrhage, necrosis and focal accumulation of iron pigment also occurs. Giant cells may contain multiple hyperchromatic nuclei within abundant eosinophilic cytoplasm features suggestive of skeletal muscle differentiation. However, cross-striations are not seen and myoglobin is not detected in the tumor cell cytoplasm by immunocytochemical techniques.

Enzyme cytochemical study of these neoplasms have shown the presence of lysosomal enzyme activity characteristic of tissue histiocytes (Greaves et al., 1985; Sakamoto, 1986). Ultrastructural features are those of both fibroblasts and histiocytes and in addition a small number of primitive mesenchymal cells are found (Greaves et al., 1985).

Most fibrous histiocytomas in the rat are malignant neoplasms and show extensive local infiltration into surrounding soft tissues with infrequent metastatic spread to lymph nodes, lungs and liver relatively late in their development (Greaves and Faccini, 1981; Mii et al., 1982). Localized fibrous lesions showing a uniform storiform pattern, abundant collagen formation and relatively little mitotic activity appear to be benign neoplasms in the rat (Greaves and Faccini, 1981).

Study of cell lines and fibrous histiocytic neoplasms

induced by subcutaneous implantation of inert materials in rodents suggests that these tumors are derived from a primitive local tissue mesenchymal cell rather than a cell of histiocytic lineage (Greaves, 1989; Greaves and Barsoum, 1990).

Although in man monocyte-macrophage markers have been demonstrated in some examples of malignant fibrous histiocytoma (Strauchen and Dimitriu-Bona, 1986), several intermediate filament subtypes may also be expressed, including reactivity with anti-cytokeratin antibody (Fisher, 1990). Therefore, these data are consistent with the hypothesis that malignant fibrous histiocytomas originate from locally-derived pluripotential primitive cells.

#### **TUMORS OF HISTIOCYTIC TYPE**

##### ***Histiocytic Sarcoma (Malignant Histiocytoma) (Figures 8-10)***

These are composed of rounded or oval histiocytic or epithelioid cells with abundant eosinophilic cytoplasm and rounded, oval or indented nuclei. Mitotic activity is variable. A characteristic but not essential feature is the presence of benign-looking multinucleated giant cells similar to foreign body giant cells, Langhan's cells or osteoclasts. In some tumors these multinucleated cells may be numerous.

Another striking histological feature is the presence of well-defined zonal necrosis frequently surrounded by palisading tumor cells. Collagen formation is not marked although focal fibrosis and a storiform pattern of spindle cells may be occasionally found. Ultrastructural study features include indented or irregular nuclei, abundant electron lucent cytoplasm with variable numbers of cytoplasmic organelles, interdigitating cytoplasmic margins and little or no intercellular collagen fibers or ground substance.

These neoplasms may be multicentric, prone to infiltrate local tissues and spread along serosal surfaces so that the primary site may not be evident. Metastases may be found in the lungs, liver, lymph nodes and peritoneal cavity (Ward et al., 1981). An association between a large burden of histiocytic sarcoma cells and the presence within proximal renal tubular cells of prominent cytoplasmic hyaline droplets which immunostain for lysozyme has been established in the rat (Hard and Snowden, 1991). The biological behaviour of histiocytic sarcoma is similar to lymphoma.

Although the histiocytic sarcoma possesses certain histological features in common with fibrous histiocytomas, notably their histiocytic appearances and enzymatic characteristics, (Barsoum et al., 1984), it appears that unlike fibrous histiocytomas they are probably of true histiocytic lineage rather than derived from a

pluripotential mesenchymal stem cell. For this reason, they have a close histogenetic relationship to neoplasms of haemopoietic and lymphatic systems.

### **TUMORS OF ADIPOSE TISSUE**

#### ***Lipoma (Figure 11)***

These lesions are soft, lobulated masses of mature fat cells separated by connective tissue. Focal fibrosis, fat necrosis and inflammatory cells may be found but myxoid areas, cellular pleomorphism and marked mitotic activity are not seen because these features are considered to be those of liposarcomas. When the connective tissue stroma is very prominent, some authors employ the term, fibrolipoma. Lipomas are found at any soft tissue site but they are most frequently located in subcutaneous tissue, the thoracic or abdominal cavity.

#### ***Hibernoma (Brown Fat Tumor) (Figures 12 and 13)***

This neoplasm is characterized histologically by brown fat differentiation. Tumor cells are round, oval or polygonal with dense basophilic nuclei of variable size and pale foamy cytoplasm which stains with the oil red O stain for fat in frozen sections. Electron microscopic study shows numerous mitochondria and small lipid droplets. Usually these neoplasms are well demarcated and show no definite histological evidence of malignancy. However, nuclear pleomorphism, marked mitotic activity, local tissue invasion and pulmonary metastases have been reported in rat neoplasms of this type and some should therefore be regarded as liposarcomas (Coleman et al., 1980; Stefanski et al., 1987).

Hibernomas are rare in rats as well as other animals. They develop in the anatomical location of brown fat, notably the back, neck, mediastinum and posterior abdominal wall (Coleman, 1980; Al Zubaidy and Finn, 1983; Stefanski et al., 1987).

#### ***Liposarcoma (Figure 14)***

The diagnosis of liposarcomas depends on the positive identification of fat forming cells, lipoblasts. These cells vary from primitive mesenchymal cells with fine lipid droplets to larger rounded or oval cells with large central or eccentric nuclei and large cytoplasmic fat vacuoles which stain positively for fat (oil red O or osmium). Brown fat differentiation is sometimes seen. The stroma is usually well vascularized and a myxoid appearance may also be evident (Greaves and Barsoum, 1990). Spindle cells and undifferentiated cells are also found and mitotic activity may be intense, in which case the differential diagnosis of pleomorphic malignant histiocytoma should be entertained. Liposarcomas occasionally develop spontaneously in aged rats (Port et al., 1979).

### **TUMORS OF STRIATED MUSCLE**

#### ***Rhabdomyosarcoma (Figures 15–18)***

The diagnosis of rhabdomyosarcoma is often difficult and depends on the histological identification of rhabdoblats which are characterized by eosinophilic cytoplasm containing fibrillary material around the nuclei and cross striations, myofilaments well-stained with PTAH, glycogen as well as immune reactive desmin and myoglobin.

Identification of rhabdomyoblasts remains difficult because a variety of other sarcomas contain large tumor cells with abundant eosinophilic cytoplasm which superficially resemble rhabdomyoblasts most notably pleomorphic malignant fibrous histiocytoma. This difficulty is compounded by the tendency of many sarcomas to infiltrate along skeletal muscle fibers so that degenerate or altered skeletal muscle cells appear as integral parts of the neoplasms. Indeed, care must be taken in the immunocytochemical demonstration of myoglobin, a muscle-specific constituent. It has been shown that myoglobin can be taken up into the cytoplasm of totally unrelated neoplasms when they infiltrate skeletal muscle and this myoglobin may be present in sufficient quantities to stain immunocytochemically. It has also been shown that even with the use of a specific anti-rat myoglobin antiserum, the small, round primitive cells within rat rhabdomyosarcomas do not stain although multinucleated and mature spindle-shaped rhabdomyoblasts stain strongly (Takahashi et al., 1988).

In view of these difficulties, an unequivocal diagnosis of rhabdomyosarcoma can be made only when there is clear evidence of skeletal muscle differentiation in tumor cells. This can be shown by cross striations with light microscopy, the presence of Z lines ultrastructurally, or immunocytochemical demonstration of myoglobin in parts of the tumor distant from normal skeletal muscle.

Rat rhabdomyosarcomas may be composed of mononuclear, polygonal or elongated spindle cells. Spindle cells are often arranged in bundles and may show features of muscle differentiation such as abundant eosinophilic cytoplasm with cross striations (Glaister, 1981). Multinucleated giant cells may also be seen. (Allen et al., 1975; Altmansberger et al., 1985; Hildebrand and Biserte, 1978). Ultrastructural study shows a variety of cell types ranging from immature cells with a prominent Golgi to well-differentiated rhabdomyoblasts with myofibrils and Z bands (Hildebrand and Biserte, 1978).

There is no fully substantiated report of rhabdomyoma occurring in the laboratory rat.

## TUMORS OF SMOOTH MUSCLE

### *Leiomyoma (Figure 19)*

Benign tumors of smooth muscle are found in the soft tissues of aged rodents, although they are more common in the female genital organs or other tissue with abundant smooth muscle such as the gastrointestinal tract. They are characterized histologically by interlacing bundles of uniform spindle cells with typically blunt ended or cigar shaped nuclei. Palisading of nuclei may be evident. The cell cytoplasm may contain perinuclear vacuoles. Myofibrils are characteristically demonstrable as linear streaks which stain blue with phosphotungstic acid hematoxylin and red by Masson trichrome stain. Mitotic activity is low. Indeed any undue mitotic activity and cellular pleomorphism should be taken as evidence of potential malignancy. These neoplasms show fairly consistent immunocytochemical staining for desmin.

Ultrastructural features include a cytoplasm packed with thin filaments with focal densities, some mitochondria, sparse profiles of endoplasmic reticulum and a Golgi apparatus situated adjacent to the nuclear poles, micro-pinocytic vesicles and dense plaques at the points of attachment of myofilaments to the cell membrane. A poorly developed basal lamina may be present.

### *Leiomyosarcoma (Figure 20)*

This neoplasm is similar to the leiomyoma but mitotic activity and cellular pleomorphism are more marked. Clinicopathological studies of human leiomyosarcomas have suggested that the degree of mitotic activity is more predictive of biological behaviour than cellular pleomorphism or other cytological features. As such neoplasms are frequently not well differentiated, the distinction between leiomyosarcoma and fibro-sarcoma or Schwann cell neoplasm may be particularly difficult at the light microscope level, although immunocytochemical staining for desmin and protein S-100 is helpful. The presence of desmin supports the diagnosis of leiomyosarcoma. S-100 is often present in Schwann cell neoplasms but electron microscopy is especially helpful in the diagnosis of peripheral nerve sheath tumors.

### *Peripheral Nerve Tumors (Schwannoma) (Figures 21 and 22)*

A difficult differential diagnosis is the distinction of Schwann cell neoplasms from spindle cell tumors of other types. Schwannomas are characterized by the presence of areas composed of compact spindle cells with indistinct cytoplasmic borders and elongated and frequently twisted nuclei. The cells are arranged in fascicles and show prominent palisading of nuclei giving rise to so-called Verocay bodies. At ultrastructural level, the cells show a

prominent external lamina, elongated cytoplasmic processes, desmosomal-like intercellular junctions, laminated cytoplasmic inclusions suggestive of myelin sheaths. They typically contain immune-reactive S-100 protein (Gough et al., 1986). However, some of these features are found in other spindle cell tumors and S-100 protein can be expressed in cells of non-neurogenic type (Egan et al., 1986).

The sarcoma with characteristic cystic features, described by MacKenzie and Garner (1973), is of uncertain histogenesis. These tumors are found in the subcutaneous tissues, around the salivary glands in the mesentery and female genital tract in aged rats. They are characterised histologically by solid sheets of small round, angulated or spindle cells lying in a loose pale matrix. The tumors show cystic spaces of variable size containing pale proteinaceous material and lined 'by condensed rounded or cuboidal' cells. Ultrastructural study has revealed no differentiated features to suggest a cell of origin. However, they stain immunocytochemically with antisera to S-100 protein, which has led to the suggestion that they are of Schwann cell origin (Turusov 1989; Leininger and Jokinen 1990).

### **SARCOMA, NOS (NOT OTHERWISE SPECIFIED)**

Few histological types of mesenchymal tumors have been described in the rat. However, in view of the potential variety of histological appearances of neoplasms of mesenchymal cells, it may not always be possible to make a precise diagnosis of all rat soft tissue tumors. This is especially true if the pathologist does not have adequately fixed material available for ultrastructural examination or a battery of appropriate antisera for immunocytochemical demonstration of antigens. It is appropriate to classify such neoplasms as sarcoma, NOS.

## DISCUSSION

Soft tissue neoplasms are relatively uncommon spontaneous tumors in rats but reported incidences vary. The incidence is usually greater in males than in females but usually less than 10% of untreated animals in historical control data from long-term carcinogenicity studies (Goodman et al., 1979, 1980; Kroes et al., 1981; Solleveld et al., 1984). However, in life-span studies it has been shown that their incidence may increase above 10% after the age of two years (Solleveld et al., 1984). Mesenchymal sarcomas also develop in rats following local injection of chemical carcinogens, some metal salts, at sites of repeated injection of innocuous agents or around implantation sites of inert substances.

The classification used in the diagnosis of human soft tissue tumors can be applied to rat neoplasms. However, the biological behaviour of soft tissue neoplasms has been less well characterised in the rat. Nevertheless; study of human mesenchymal sarcomas has shown that the most important factors predicting biological behaviour are size and histological features (Brennan 1989). This suggests that cellularity, degree of differentiation, amount of stroma, vascularity, extent of necrosis and number of mitoses are more important as indicators of behaviour than precise cell type.

Immunocytochemical techniques are increasingly being used in the analysis of experimental soft tissue sarcomas (Barsoum et al., 1984; Altmannsberger et al., 1985; Gough et al., 1986). Immunocytochemistry provides another method of cell identification and has given insights into the histogenesis of soft tissue sarcomas (Brookes, 1986). However, it has become increasingly evident in both human and animal soft tissues that aberrant or unexpected antigen expression can occur. The presence of a given histochemical marker should not be the cause of confusion provided that immunocytochemistry is performed with rigorous control procedures and applied within the context of other appropriate clinical and morphological data, including electron microscopy.

## **NOMENCLATURE AND DIAGNOSTIC CRITERIA**

### ***TUMORS OF FIBROUS TISSUE***

#### ***Fibroma***

1. Dense fibrous mass
2. Abundant interwoven bands of collagen
3. Small, sparse spindle cells with small dense nuclei
4. Little or no mitotic activity

#### ***Fibrosarcoma***

1. Solid fibrous mass
2. Monomorphic interwoven fascicles of plump spindle cells sometimes arranged in a herringbone pattern
3. Variable mitotic activity, may be marked
4. Collagen content variable
5. Local invasion

### ***TUMORS OF FIBROHISTIOCYTIC TYPE***

#### ***Fibrous Histiocytoma (benign)***

1. Fibrous mass
2. Storiform or cartwheel pattern of spindle cells
3. Little cellular pleomorphism and mitotic activity

4. Abundant intercellular collagen

#### ***Fibrous Histiocytoma (malignant)***

1. Solid fibrous homogeneous mass, large lesions show ulceration of overlying skin
2. Variable histology ranging from storiform pattern of uniform plump spindle cells to a highly pleomorphic pattern of bizarre spindle cells and tumor giant cells
3. Variable mitotic activity
4. Abundant but variable amount of interstitial collagen and ground substance
5. Widespread infiltration and invasion of local tissues
6. Occasional metastases in lung, liver and other organs

### ***TUMORS OF HISTIOCYTIC TYPE***

#### ***Histiocytic Sarcoma, Malignant Histiocytoma***

1. Fleishy, yellowish, homogeneous mass in soft tissues, occasionally diffuse
2. Uniform histiocytic or epithelioid cells
3. Variable number of benign-looking foreign body or Langan's type giant cells, may be numerous
4. Punched-out zones of necrosis with peripheral palisading of tumor cells
5. Mitotic activity may be marked
6. Highly invasive with early spread to lymph nodes, lungs, liver and other internal organs

### ***TUMORS OF ADIPOSE TISSUE***

#### ***Lipoma***

1. Soft lobulated fatty mass
2. Mature fat cells
3. Devoid of significant mitotic activity, cellular pleomorphism, necrosis or myxoid change

#### ***Hibernoma***

1. Lobulated pale yellowish mass in posterior thoracic or abdominal region or in the mediastinum
2. Fairly uniform rounded cells with abundant fine cytoplasmic lipid droplets and central, round nuclei
3. Mitotic activity and cellular pleomorphism usually low but may be marked and associated with invasion and metastatic spread (liposarcoma)

#### ***Liposarcoma***

1. Fatty mass of variable appearance
2. Lipoblasts present
3. Cellularity and mitotic activity variable but spindle cells, primitive undifferentiated cells, myxoid zones and necrosis may be evident

**TUMORS OF STRIATED MUSCLE****Rhabdomyosarcoma**

1. Fleishy mass frequently showing necrosis and hemorrhage
2. Usually pleomorphic with rhabdomyoblasts, immature spindle and mononucleated rounded or polygonal cells
3. Rhabdomyoblasts characterized by eosinophilic fibrillary cytoplasm with myofilaments, cross striations, immunocytochemical staining for myoglobin and ultrastructural evidence of Z bands
4. Locally invasive with metastatic spread

**TUMORS OF SMOOTH MUSCLE****Leiomyoma**

1. Spindle cells arranged in fascicles with some palisading of nuclei
2. Nuclei typically blunt-ended
3. Cytoplasm contains longitudinal myofilaments, desmin immune reactivity and perinuclear vacuoles
4. Little or no mitotic activity and pleomorphism not a prominent feature

**Leiomyosarcoma**

1. Similar to leiomyoma but more pleomorphic and with mitotic activity

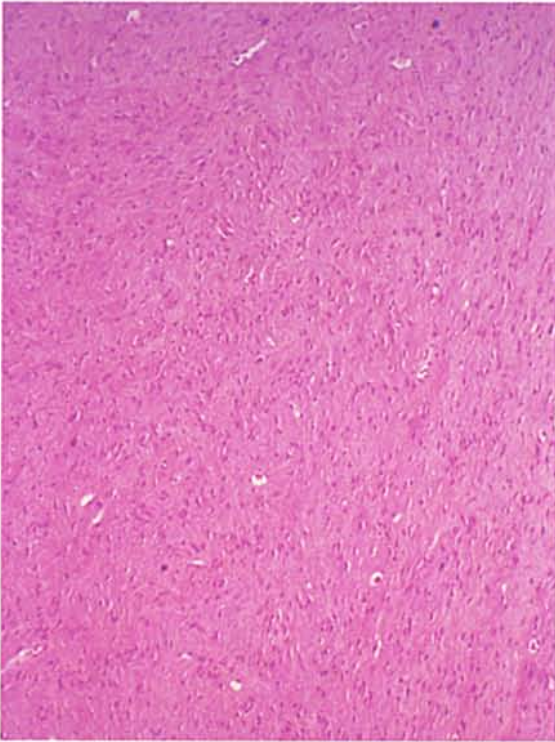
**SARCOMA, NOS (NOT OTHERWISE SPECIFIED)**

1. Mesenchymal tumor without recognizable light microscopic differentiation
2. Where possible, without ultrastructural differentiation and specific immunohistochemical markers

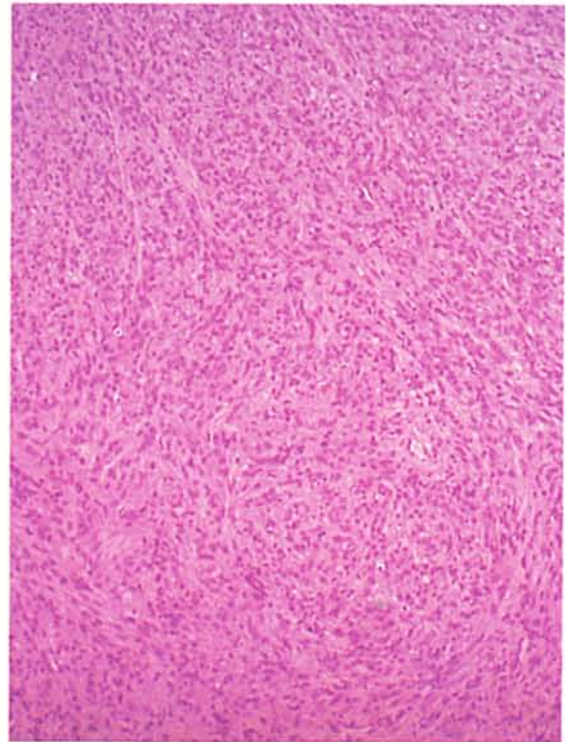
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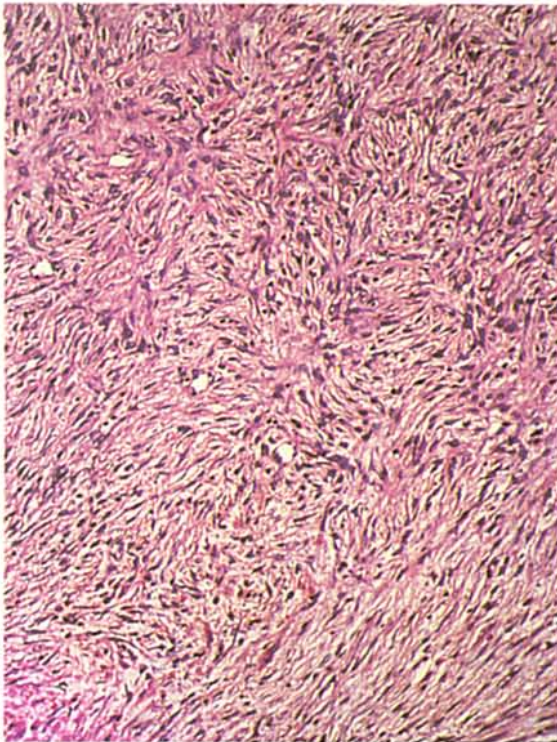
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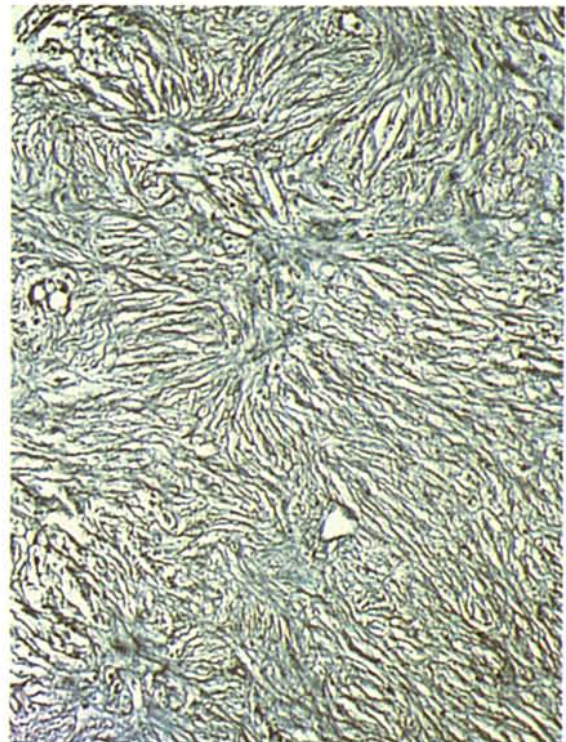
*Fig. 1 – Moderately cellular fibroma showing marked intercellular collagen formation. Cell nuclei are fairly uniform and show little or no mitotic activity (H x 25).*



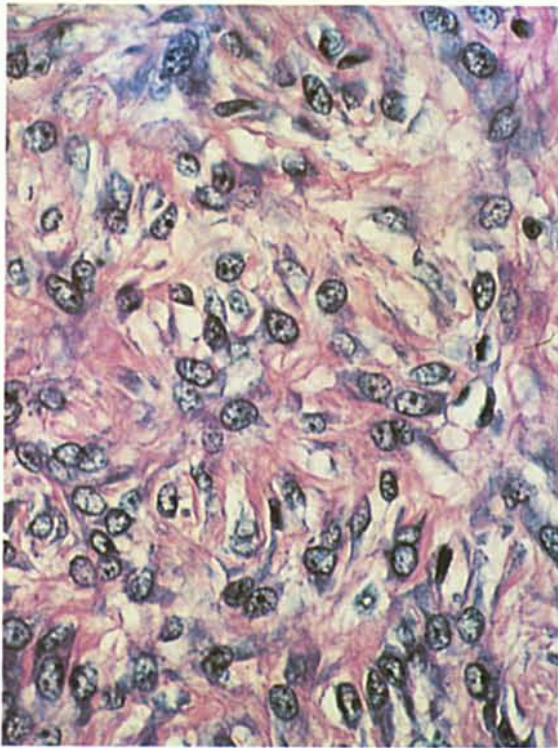
*Fig. 2 – Fibrosarcoma showing a monomorphic pattern of collagen-forming spindle cells arranged in bundles (H&E x 25).  
hjj*



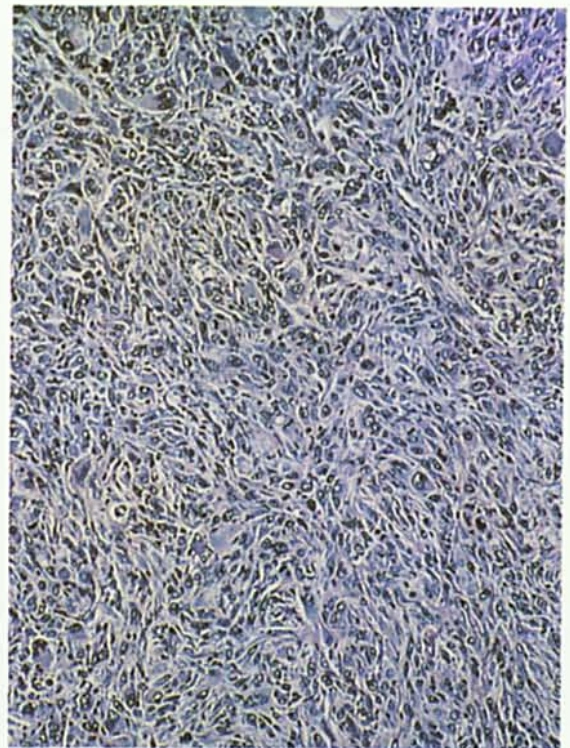
*Fig. 3 – Fibrous histiocytoma from a male Sprague-Dawley rat. It is composed of well-ordered spindle cells arranged in the typical cartwheel or storiform pattern (H&E x 40).*



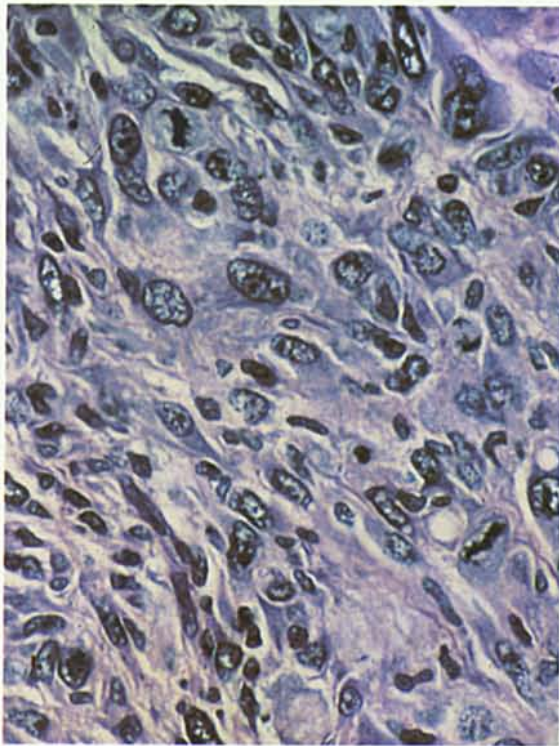
*Fig. 4 – Same tumour as in Figure 3 showing the presence of numerous reticulin fibres. The storiform pattern is also evident (Reticulin x 40).*



*Fig. 5 – High power view of a fibrous histiocytoma from a male Sprague-Dawley rat. In this field the spindle cells are arranged in a storiform pattern and contain fairly uniform, plump vesicular nuclei (H&E x 160).*



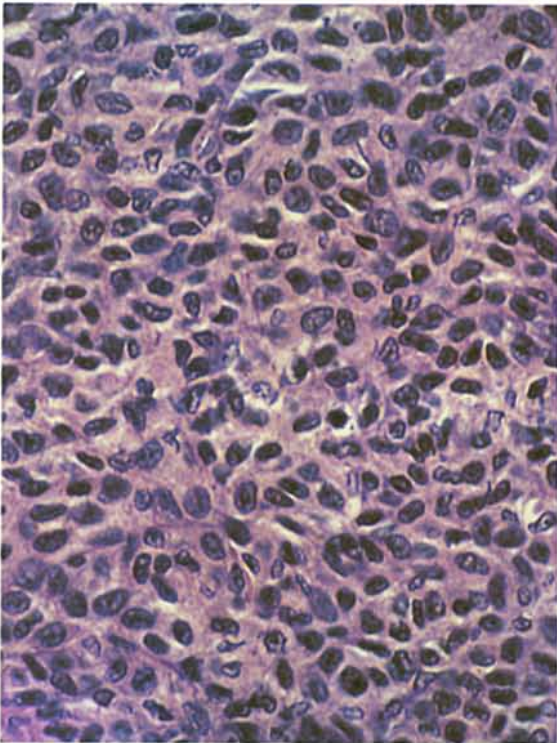
*Fig. 6 – Fibrous histiocytoma of pleomorphic type found in a male Sprague-Dawley rat. Although the storiform pattern of spindle cells is evident, the overriding feature is of marked cellular pleomorphism (H&E x 40).*



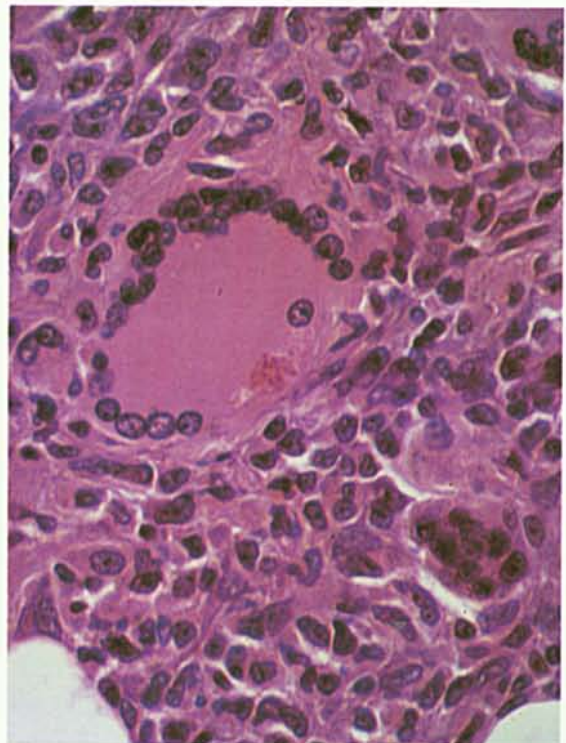
*Fig. 7 – Higher power view of the tumor seen in Figure 6 showing a highly pleomorphic pattern of spindle cells and giant cells with highly irregular nuclei. Mitotic activity is evident in this field (H&E x 160).*



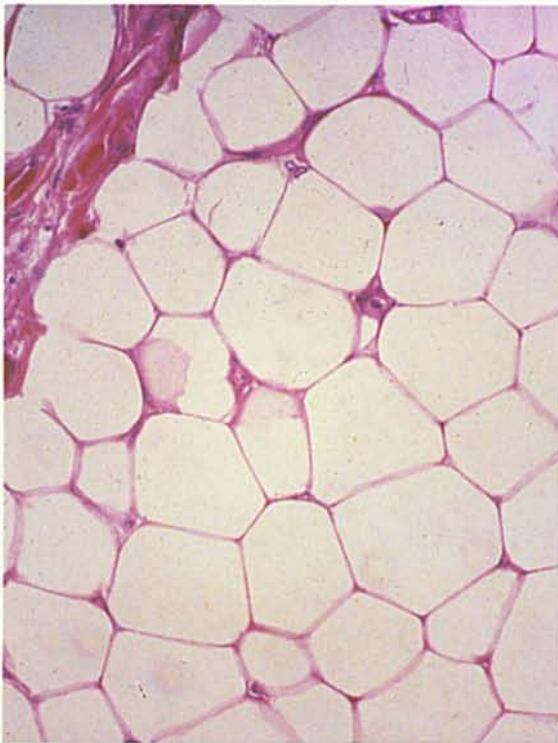
*Fig. 8 – Low power view of a histiocytic sarcoma from a male Sprague-Dawley rat showing the characteristic feature of zonal necrosis surrounded by a rim of prominent, radially arranged hyperchromatic nuclei (H&E x 40).*



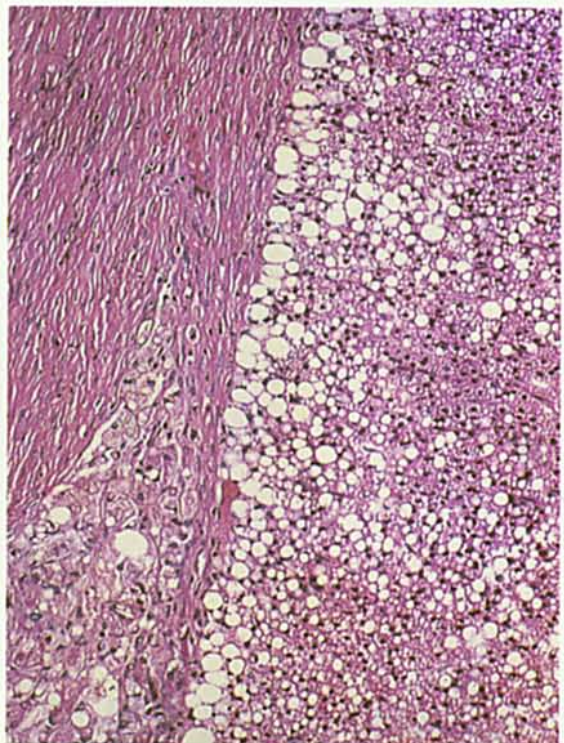
*Fig. 9 – Histiocytic sarcoma from a female Sprague-Dawley rat composed of uniform histiocytic cells showing abundant eosinophilic cytoplasm with indistinct cell margins and ovoid or indented nuclei (H&E x 160).*



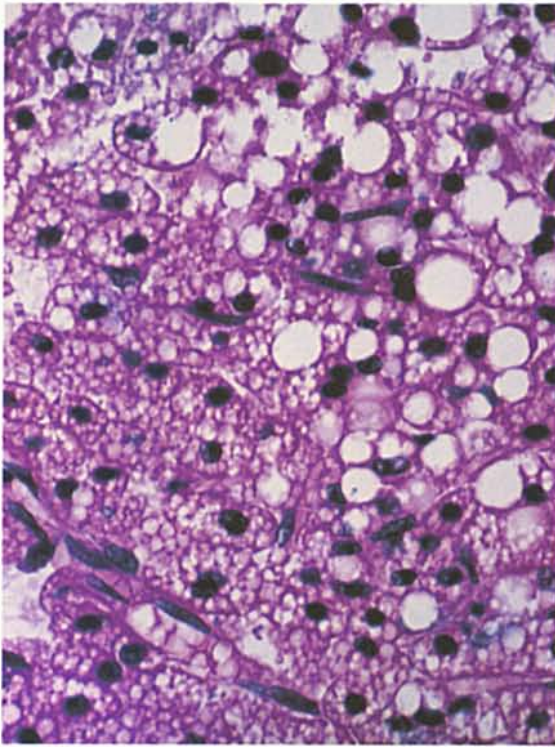
*Fig. 10 – Another histiocytic sarcoma found in a female Sprague-Dawley rat containing benign-looking epithelioid or Langhans type multinucleated giant cells (H&E x 160).*



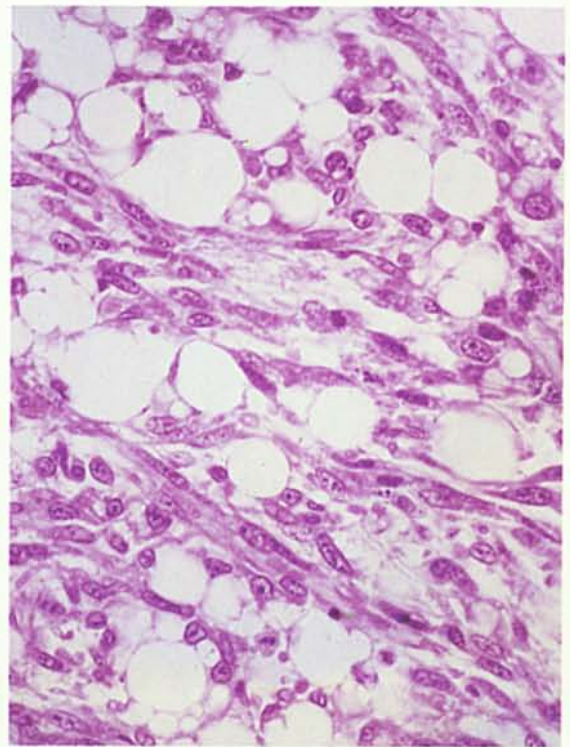
*Fig. 11 – Lipoma from the subcutaneous tissue of a Wistar-derived rat showing mature fat cells and fine fibrous septa (H&E x 50).*



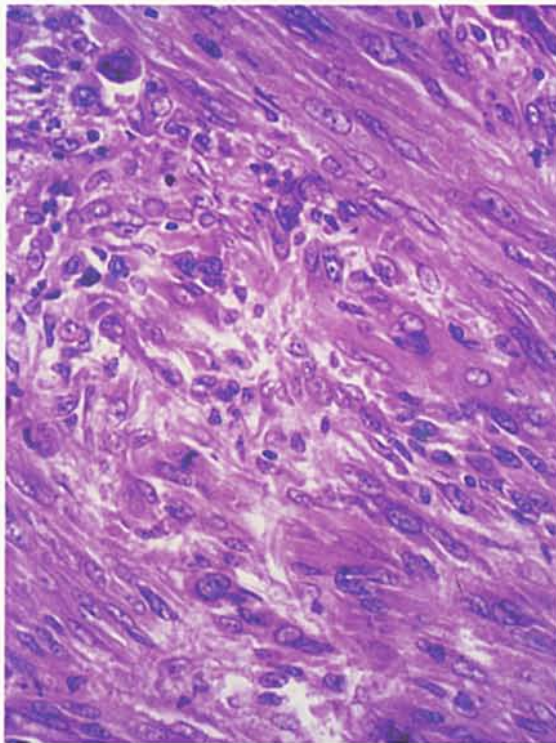
*Fig. 12 – Hibernoma from the thorax of a male Sprague-Dawley rat showing the typical foamy, lipid-laden cells with dense rounded nuclei. A fibrous capsule is seen in this field, penetrated by a band of tumour cells (H&E x 40).*



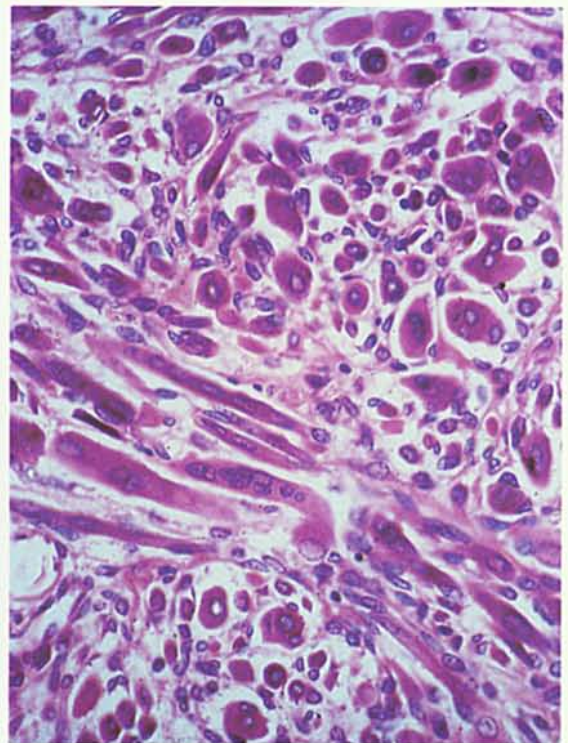
*Fig. 13 – Higher power view of the tumor seen in figure 12 showing cytological detail of fine and coarse cytoplasmic lipid droplets and dense, round centrally placed nuclei (H&E x 160).*



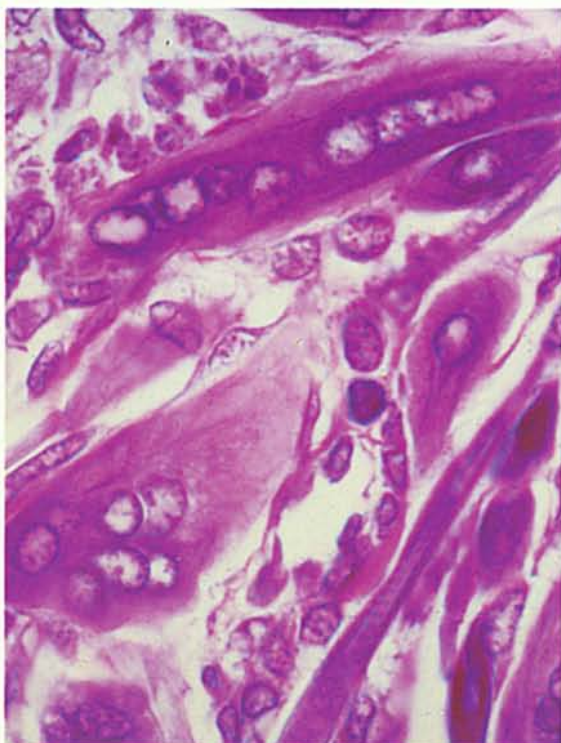
*Fig. 14 – Liposarcoma from the soft tissues of a rat showing presence of typical lipoblasts and zones of less-well differentiated spindle cells with evidence of considerable mitotic activity (H&E x 25).*



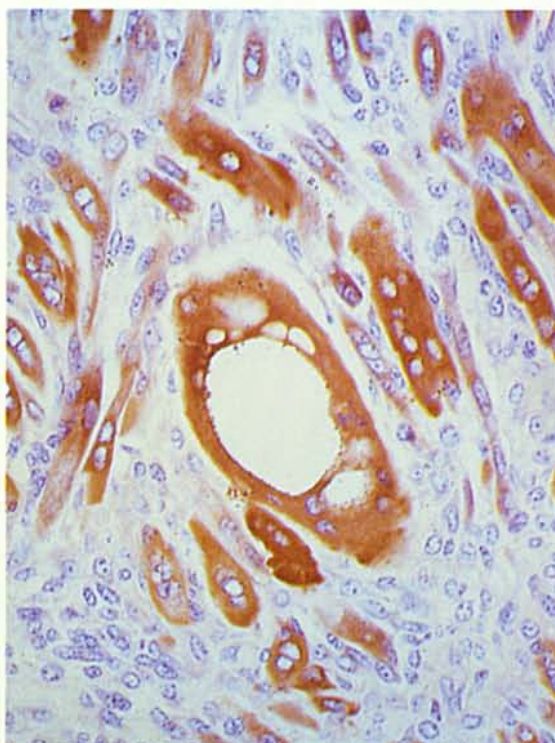
*Fig. 15 – Pleomorphic rhabdomyoblastoma from soft tissues of a Wistar-derived rat composed of small poorly differentiated cells mixed with pleomorphic rhabdomyoblasts with abundant eosinophilic cytoplasm. Both strap-like and multinucleated rounded giant cells are evident in this field (H&E x 80).*



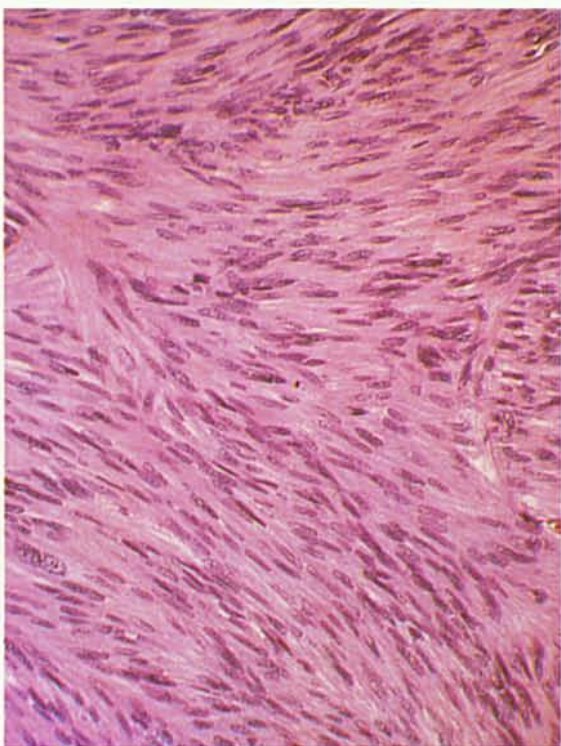
*Fig. 16 – Zone within a pleomorphic rhabdomyosarcoma showing pleomorphic spindle cells with abundant eosinophilic cytoplasm and evidence of mitotic activity (H&E x 80).*



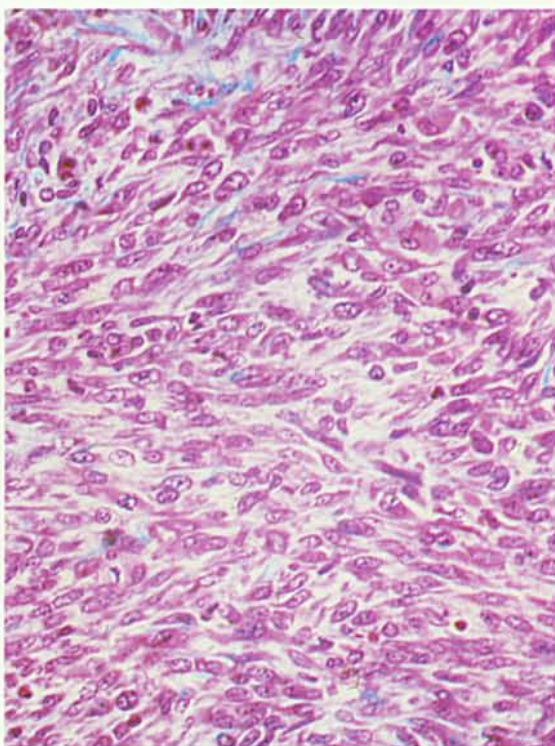
*Fig. 17 – Same tumor seen in Figure 15 stained with phosphotungstic acid hematoxylin to show clear evidence of cross-striations in a strap-like rhabdomyoblasts (Phosphotungstic acid hematoxylin x 200 oil immersion).*



*Fig. 18 – Same tumor as above stained for myoglobin. Well-differentiated cells stain well, primitive cells are poorly stained (Immunoperoxidase x 40).*



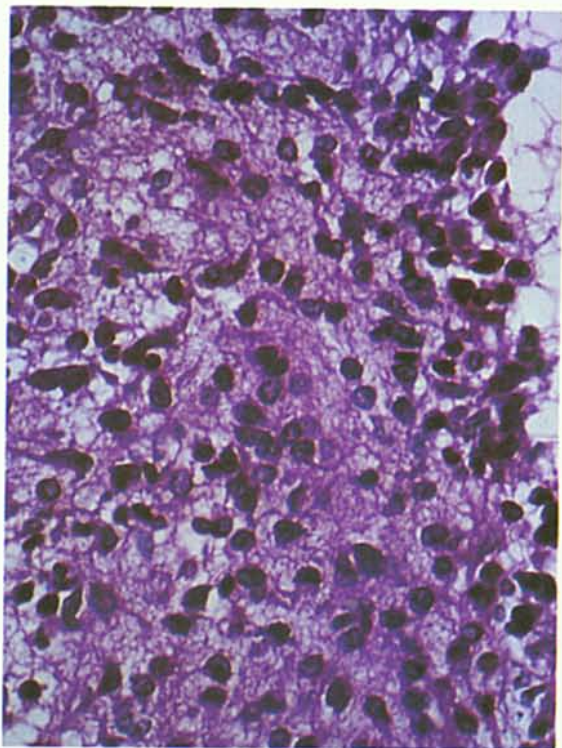
*Fig. 19 – Leiomyoma from a Wistar-derived rat showing fascicles of well-differentiated smooth muscle cells (H&E x 60).*



*Fig. 20 – Leiomyosarcoma from a Wistar-derived rat showing a typical cellular appearance with spindle cells showing hyperchromatic nuclei, mitotic activity but little intercellular collagen (Trichrome x 80).*



*Fig. 21 – Malignant schwannoma with cystic features found in the neck region of a male Sprague-Dawley rat (H&E x 40).*



*Fig. 22 – Higher power view of the tumor seen in Figure 21 (H&E x 160).*