

# NON-PROLIFERATIVE LESIONS OF SOFT TISSUES AND SKELETAL MUSCLE IN RATS

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## INTRODUCTION

Soft tissues comprise three principle elements, namely cells, extracellular fibers, and ground substance. The plasticity of the fixed mesenchymal cells in combination with the proliferative potential of blood vessels and the recruitment of mobile cells such as lymphocytes, granular leukocytes, and macrophages in response to injury can give rise to a bewildering array of histological appearances. Although such responses may be considered physiological and self-limiting, they can be proliferative in nature. In this monograph, therefore, the term *non-proliferative* refers to *non-preneoplastic* and *non-neoplastic* changes. As a consequence, one of the diagnostic challenges in the assessment of pathological changes in soft tissue is making a distinction between reactive but self-limiting conditions and autonomous neoplastic lesions of mesenchymal cells. Careful recording of the nature, intensity, and duration of the inflammatory response of the soft tissues to implanted or injected substances is important in the assessment of the local tolerability of agents intended for contact with human tissues.

While skeletal muscle contains a range of connective tissue elements similar to other soft tissues, its bulk is predominantly composed of highly specialized skeletal muscle cells or fibers. These cells form a syncytium by fusion of fetal myoblasts to produce a muscle fiber whose length is often many thousand times greater than

its diameter. Although the principles of pathological changes in muscle are similar to other tissues of the body, its unusual cellular structure and its contractile nature give rise to a constellation of pathological changes that need to be considered separately.

Like neurons, skeletal muscle cells become differentiated early in the course of development and their post-natal growth is limited by the addition of cytoplasm to their mass. Hence, regeneration of muscle cells after injury takes place only on a limited scale.

The general system of nomenclature of rat skeletal muscle fiber types is based on the ATPase reaction (1) or modifications (2). When this reaction is performed at pH 9.4, type I fibers show low myofibrillar ATPase activity. Type II fibers show greater ATPase reactivity and can be divided into categories on the basis of inhibition of the reaction at successively lower values of pH. Thus, in the rat, type IIA fibers are inhibited at pH 4.5, type IIB at pH 4.3, and type IIC at pH 3.9 (3).

## MORPHOLOGY

## SOFT TISSUES

### *Inflammation, Necrosis, Granulation Tissue, and Fibrosis (Figures 1-3)*

Localized inflammatory processes in soft tissues usually develop as a consequence of local trauma,

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ulceration, infarction, injection or implantation of foreign materials into soft tissues, or their extravasation from blood vessels (4, 5). Systemic effects of xenobiotics may also occasionally result in damage to the soft tissue. Histologic features are those of inflammation and repair which may be modified by the nature and duration of the damage and type of tissue involved. Damage to adipose tissue and skeletal muscle may give rise to additional characteristic histological features (see below).

Initially, tissue damage or necrosis is accompanied by variable degrees of hemorrhage and edema and infiltration by acute inflammatory cells, followed by infiltration by mononuclear leukocytes. Within two or three days, there is proliferation of fibroblasts and angiogenesis giving rise to so called "granulation tissue". Subsequently, fibroblasts synthesize significant amounts of collagen, usually reaching a peak by about the third week. Remodelling of collagen ultimately occurs to produce mature scar tissue possessing high tensile strength.

If the inflammatory process is prolonged, chronic inflammation develops. This condition is characterized by the presence of an infiltrate composed predominantly of lymphocytes, plasma cells, and macrophages. A foreign body reaction with giant cells, abscess, or microcyst formation may also develop. Minerals can also be deposited at the site of injured tissue (dystrophic mineralization). This is characterized by fine or coarse granular deposits staining intensely with hematoxylin or positively with von Kossa stain. Iron pigments may also be found, particularly in macrophages when hemorrhage has occurred.

Healing may be delayed or incomplete, or there may be overgrowth of fibrous tissue and fibroblasts forming lesions such as hypertrophic scars or keloids. The differential diagnosis between an exaggerated fibroblastic response to tissue injury and a benign tumor (fibroma) is usually made on the basis of size and growth pattern. Neoplasms are usually large and show evidence of nodularity with compression of local tissues and adjacent organs.

### ***Granuloma (Figures 4 & 5)***

A granuloma is an aggregate of unattached cells composed predominantly of histiocytes associated with a variable but usually sparse infiltrate of polymorphonuclear leukocytes, connective tissue cells, and proliferating blood vessels. It should be kept in mind that a granuloma represents a localized form of an inflammatory reaction in which the range of cell types is similar to that found in the reparative phase of the inflammatory process but in which the histiocytic component is predominant and granulation tissue minimal. The terms, granulomatous infiltrate or granulomatous inflammation, may be applied to a more extensive infiltrate of predominantly

histiocytes and macrophages.

While granulomas may form as a local reaction to foreign materials, they can develop widely in soft tissue as a response to infectious agents, as an immunological or non-immunological granulomatous inflammatory reaction, or as an expression of altered cellular function of the monocyte/macrophage series.

### ***Fat Necrosis, Steatitis (Figures 6-8)***

Focal damage to fat cells occurs under a variety of circumstances. Focal fat necrosis is typically found in acute pancreatitis and is characterized by the presence of white foci in adipose tissue. Histologically, evidence of necrosis is usually lacking but there is a sparse accumulation of inflammatory cells including macrophages and giant cells. Clefts representing dissolved cholesterol crystals may also be seen. Occasionally, reactive changes in fibroblasts, blood vessels, and other connective tissue cells may occur. This may become highly proliferative and give rise to a pseudosarcomatous appearance.

A form of more generalized fat damage affecting adipose tissue in the rat has been termed "steatitis" (6, 7). This condition is believed to be the result of vitamin E or antioxidant deficiency which may develop as a consequence of excess dietary polyunsaturated fatty acids with at least three double bonds, such as found in fish or linseed oil (7). This form of fat damage is characterized by the presence of widespread small yellow foci composed of clusters of macrophages laden with small lipid vacuoles and lipofuscin pigment. The lipofuscin pigment is resistant to paraffin wax embedding and acid fast, and shows yellow autofluorescence in fluorescent light. Inflammatory cells are characteristically sparse in these lesions.

### ***Elastosis***

Elastosis or solar elastosis is found in the superficial connective tissue of the skin in man and animals following chronic exposure to sunlight or artificial ultraviolet light. In rats exposed for long periods to ultraviolet light, there is accumulation of thickened, basophilic elastic fibers in the upper dermis. Cellularity is usually poor and there may be a sparse scattering of chronic inflammatory cells (8, 9). The overlying epidermis may also show evidence of atrophy.

### ***Mineralization***

Mineral deposits can occur in the subcutaneous and soft tissues of the rat either following local tissue injury (dystrophic) or under circumstances that favor generalized mineralization, such as high dietary calcium:phosphate ratio and treatments that mobilize body calcium stores. When calcium balance is disturbed, the soft tissues most commonly affected in the rat appear to be natural trauma sites such as around the limbs and, in

females, the mammary tissues (10).

Histologically, mineralization appears as fine or coarse granular deposits or massive aggregates that stain intensely with hematoxylin and positively with histochemical stains for calcium. These deposits may be accompanied by foreign body giant cells, an acute or chronic inflammatory reaction, or a fibroblastic response (10).

## SKELETAL MUSCLE

### *Necrosis and Inflammation (Figures 9-12)*

The characteristic process of muscle degeneration, inflammation, and repair is observed following intramuscular injection of myotoxic agents. In the first few hours following injection, fibers become rounded and hyalinized with pyknotic nuclei. Myofibers often exhibit focal or segmental necrosis because of their length and multiple nuclei (11). Necrotic fibers are surrounded by variable degrees of hemorrhage and edema (12). Within 24 hours, affected fibers become overtly fragmented and macrophages can be seen. By day three, lesions are composed of numerous infiltrating macrophages accompanied by proliferating myoblasts which may form myotubules with long chains of nuclei. After five days, there are numerous regenerating muscle fibers characterized by basophilic cytoplasm, vesicular nuclei, and prominent nucleoli.

Satellite cells around intact muscle fibers in the region of necrotic muscle may also show activation. Affected satellite cells show increased cytoplasmic volume and mitotic activity and are separated from skeletal muscle fibers by an unusually wide space which may contain prominent basal lamina (13).

Finally, regenerating fibers subsequently enlarge and, by three weeks after injury, the muscle tissue becomes essentially normal although fibers may retain some central nuclei (14). Although regeneration following local damage is surprisingly complete, muscle fibers may not regenerate after severe, extensive, or repeated damage, and as a consequence fibrous scarring may follow.

It should also be noted that skeletal muscle degeneration and necrosis can occur after systemic exposure to various xenobiotics such as the inhibitors of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase (15) and cytostatics.

### *Hypertrophy*

Hypertrophy of muscle fibers may be focal or diffuse. Focal compensatory hypertrophy may occur in muscle showing atrophic alterations. Diffuse hypertrophy may occur in response to increased exercise or as a response to prolonged exposure to excessive growth factors, such as growth hormone (16) or growth-

promoting xenobiotics (17). Hypertrophy is characterized histologically by an increase in muscle fiber diameter, but this may be difficult to assess without morphometric analysis.

### *Atrophy (Figure 13)*

Atrophy of skeletal muscle may result from degenerative processes originating in muscle fibers or be secondary to denervation (denervation atrophy). Both types of atrophy can be induced experimentally in the rat. Moreover, atrophy of skeletal muscle occurs spontaneously in rats with advancing age, although whether the changes result from primary muscle degeneration or changes in the nerve supply is disputed.

The nature of an individual muscle fiber is determined by its innervation, and the distribution of fiber type varies between muscles. As a consequence all fibers supplied by an individual neuron are of the same type. For instance, the soleus muscle in the F344 rat is comprised of over 80% of type I fibers whereas the extensor digitorum longus contains mainly type II fibers (2). Normally, different fibers are intermingled randomly within a muscle. Consequently, if a neuron supplying a muscle motor unit dies, the muscle fibers supplied by that unit undergo atrophy and take on a compressed angular profile, which is a characteristic histological feature of denervation atrophy.

Ultimately, surviving intramuscular axons form collateral branches that connect with denervated fibers which then display histochemical characteristics of the type determined by the new innervation. A characteristic grouping of the fibers into homogeneous groups of fiber type rather than the checkerboard pattern of normal muscle develops following reinnervation (3). Furthermore, if a neuron supplying the enlarged motor unit degenerates, atrophic fibers are more likely to be grouped together and surviving fibers may undergo compensatory hypertrophy to give a characteristic histological pattern of both atrophy and hypertrophy.

Atrophy from non-neurogenic causes, such as those induced by the administration of myotoxic xenobiotics, is usually characterized by the presence of myopathic changes such as necrotic or rounded hyaline fibers, centrally nucleated cells, and split fibers (see below), and by the lack of angulated fibers. The muscle atrophy and increased protein catabolism that follows chronic administration of corticosteroids in the rat is characterized by an uncomplicated reduction in the size of type II fast twitch fibers (18). Experimentally induced thyrotoxicosis affects type I fibers (11).

In the aging rat, atrophy of muscle fiber occurs predominantly in the hind limbs. There is atrophy of muscle fibers, increased variation in muscle fiber size, accumulation of degenerative inclusion bodies, lipofuscin, and lipid droplets, and increased connective tissue

(19). The presence of angular fibers suggests that the changes may result from spinal degeneration. However, spinal nerve lesions are not consistently observed in all affected animals (20).

### ***Degenerative (Myopathic) Alterations (Figure 14)***

Pathologic insults to muscle may lead to a variety of cytopathic changes in muscle fibers. The precise nature of the changes is dependent on the nature of the damage. Following systemic administration of agents which have a direct myotoxic effect, such as 6-mercaptopurine, vincristine, and emetine, muscle fibers exhibit rounding, vacuolation, and hyalinization with loss of myofibrils, targetoids, and split fibers (21).

Some agents inducing systemic phospholipidosis produce vacuolation of skeletal muscle cells. Muscle vacuoles usually appear empty in routinely processed sections stained with hematoxylin and eosin but stain dark blue in toluidine blue stained plastic embedded sections. Ultrastructural examination shows that they are composed of lamellated membranous inclusions associated with lysosomes.

Round cytoplasmic basophilic bodies of up to 3 $\mu$ m in diameter composed ultrastructurally of laminated membranous material (spheromembranous bodies) have been described in the muscles of rats treated with vincristine, colchicine, and chloroquine (22, 23, 24, 25). Central nuclei may also be seen as a non-specific change (26).

### ***Mineralization (Figure 11)***

Mineralization of dystrophic or metastatic type may be observed within skeletal muscle. It shows histological characteristics which are similar to mineralization in other tissue (see above).

## **DISCUSSION**

Degenerative or inflammatory alterations are seen sporadically in the soft tissues and muscles of laboratory rats, usually either as a result of local trauma or age-related degenerative diseases. Systemic administration of xenobiotics may induce generalized alterations in soft tissue. Occasionally, localized tissue damage can be induced by agents administered systemically. Examples of this phenomenon are produced by ergot derivatives which have been shown to induce peripheral vasoconstriction of sufficient intensity to produce soft tissue necrosis (27).

An important part of the toxicologic assessment of polymeric materials for biomedical applications and injectable therapeutic agents is the development of an

understanding of their tolerability within the soft tissues and muscle. This assessment relies heavily on the histopathologic examination of the tissue reaction to the materials when they are implanted or injected into soft tissue or muscle of laboratory animals. Histological criteria and various scoring systems employed in grading of the tissue reaction have been reviewed by Autian (28). It is important to record the intensity and duration of the known pathological sequence of inflammation and note any alterations in the response. Because experimental protocols vary, it is important to have comparative data from agents of known irritant potential to reach an overall assessment of how human tissue will tolerate a new substance. Moreover, it is necessary to show any compromise to the healing process. Hence, tissue sampling should take place over the course of healing to assess the completeness of the repair process.

## **RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA**

### ***SOFT TISSUE***

#### ***Inflammation***

##### **Early**

1. Necrosis
2. Edema
3. Hemorrhage
4. Infiltration by polymorphonuclear leukocytes (peak 1 to 2 days)
5. Infiltration by mononuclear leukocytes (peak 3 to 4 days)

##### **Later**

1. Proliferation of fibroblasts (starts at about 3 days, peaks about 5 or 6 days)
2. Angiogenesis (starts at about 3 days)
3. Collagen synthesis (peaks at about 3 weeks)

##### **Associated features**

1. Macrophages and foreign body giant cells (may contain iron pigment)
2. Abscess formation
3. Cyst or microcyst formation
4. Mineralization

#### ***Granuloma***

1. Discrete cellular aggregates predominantly of histiocytes
2. Sparse infiltrate of other cells such as polymorphonuclear leukocytes, blood vessels, and fibroblasts

#### ***Fat Necrosis***

1. White foci in adipose tissue
2. Sparse accumulation of macrophages and giant

cells, some of which may show foamy cytoplasm

3. Cholesterol clefts
4. Variable fibroblastic and angioblastic response

### **Steatitis**

1. Widely distributed small yellow foci in adipose tissue
2. Clusters of macrophages with small lipid-laden cytoplasmic vacuoles
3. Macrophages contain acid fast cytoplasmic lipofuscin pigment which shows yellow autofluorescence in fluorescent light

### **Elastosis**

1. Accumulation of thickened basophilic elastic fibers in upper dermis
2. Basophilic fibers stain for elastic
3. Sparse chronic inflammatory infiltrate
4. Overlying epidermis shows actinic alterations

### **Mineralization**

1. Usually found at sites of tissue injury or in trauma sites
2. Fine or coarse granules staining intensely with hematoxylin
3. Stain with histochemical reactions for calcium

## **SKELTAL MUSCLE**

### **Inflammation**

1. Necrosis, edema, and hemorrhage
2. Rounded, hyalinized fibers with pyknotic nuclei (first few hours)
3. Fragmentation of muscle fibers (24 hours)
4. Polymorphonuclear leukocyte infiltrate (peak at 1 to 2 days)
5. Infiltration of macrophages and proliferation of myoblasts, may form myotubules with long chains of nuclei (day 3)
6. Regeneration of basophilic muscle fibers (day 5)
7. Repair complete (3 weeks)

### **Hypertrophy**

1. Enlargement of muscle fibers

### **Atrophy**

1. Loss of muscle fiber size, angulation
2. Replacement by adipose tissue

### **Degenerative (Myopathic) Alterations**

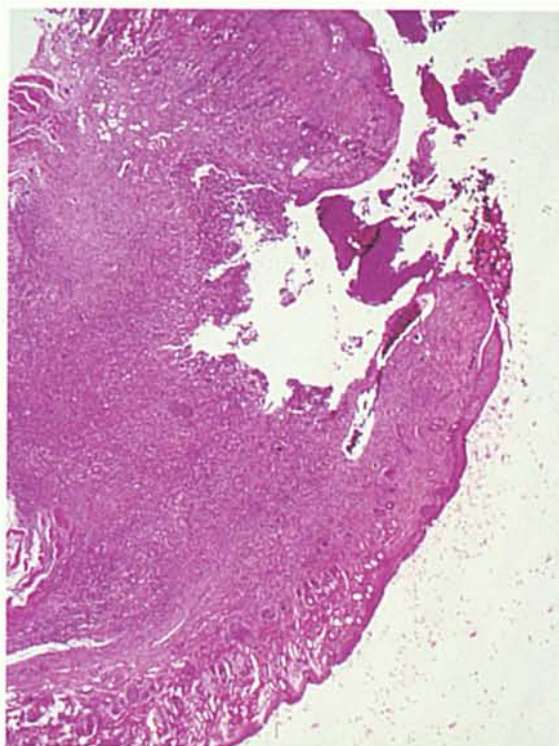
1. Vacuolation of fibers
2. Basophilic cytoplasmic droplets (phospholipid)
3. Targetoid fibers
4. Split fibers
5. Hyaline changes

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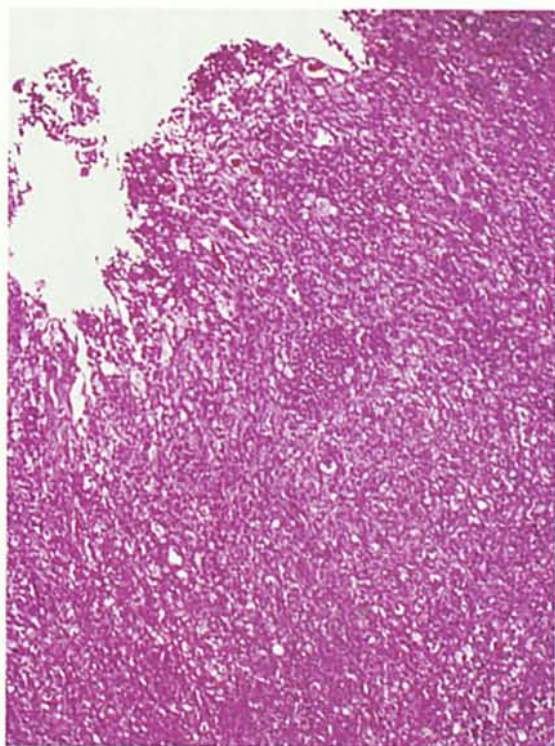
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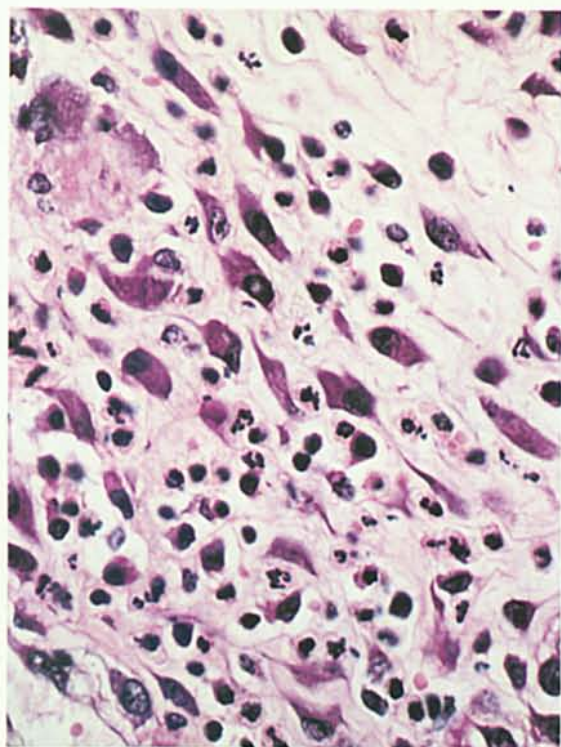
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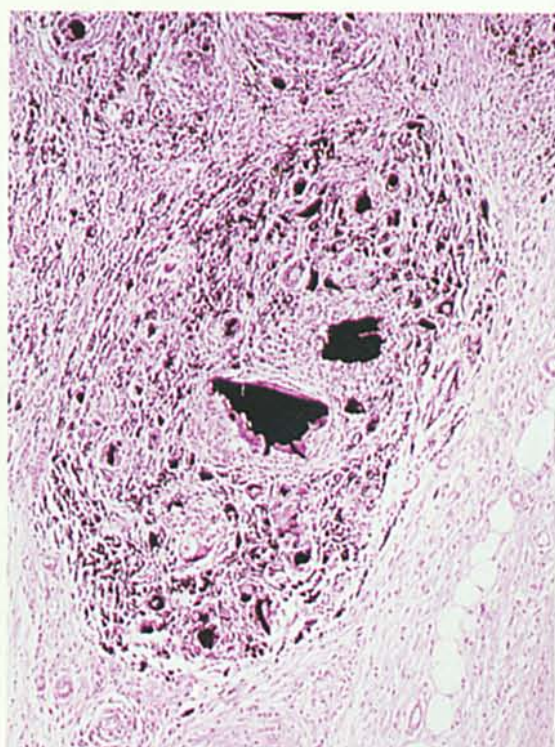
*Fig. 1 – Inflammation; subcutaneous tissue. Focus of chronic pyogenic inflammation (H&E).*



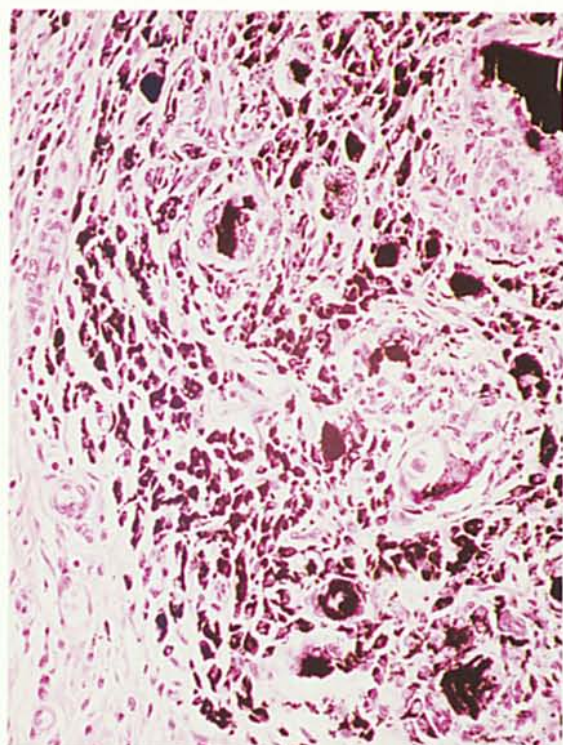
*Fig. 2 – Higher power view of the inflammatory process in Fig. 1 (H&E).*



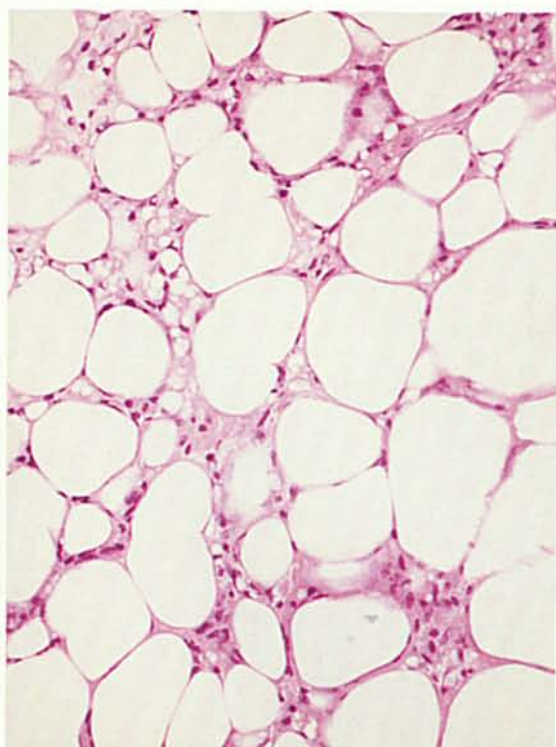
*Fig. 3 – Inflammation and fibrosis; subcutaneous tissue. Tissue from an aged rat showing an inflammatory and fibroblastic reaction to spontaneous trauma (H&E).*



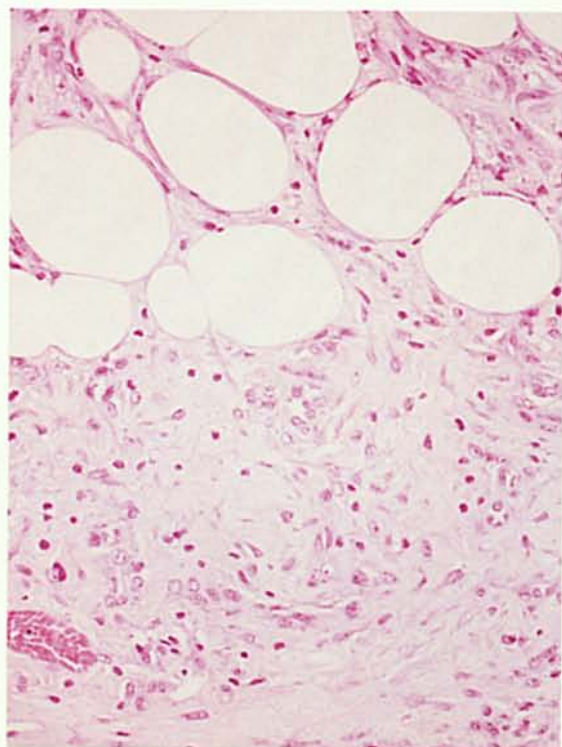
*Fig. 4 – Granuloma; subcutaneous tissue. Granuloma formed around injected carbon particles (H&E).*



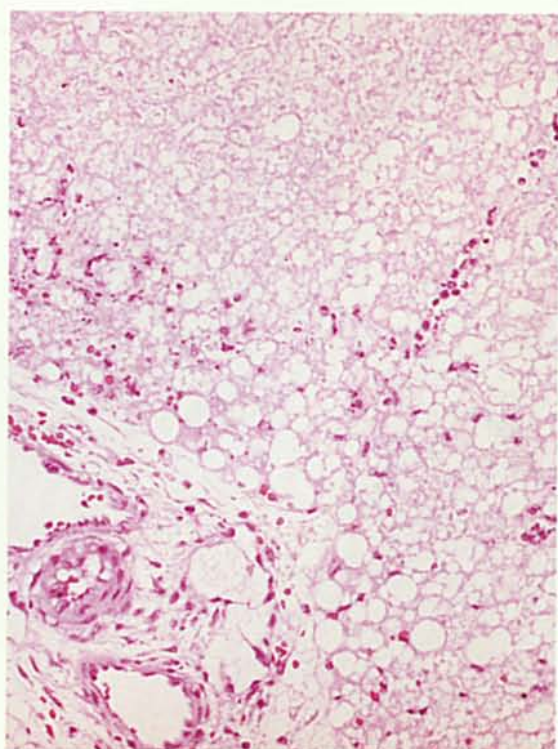
*Fig. 5 – Higher power view of Fig. 4 showing macrophages and foreign-body giant cells (H&E).*



*Fig. 6 – Fat necrosis. Omentum from an aged rat showing fat necrosis with lipid laden macrophages (H&E).*

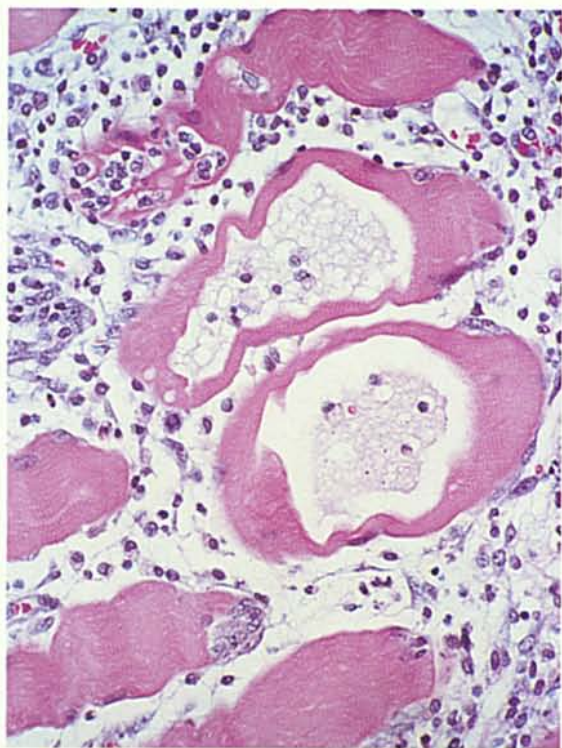


*Fig. 7 – Fat necrosis. Omental fat of an aged rat showing a zone of reactive but benign fibroblastic proliferation (H&E).*

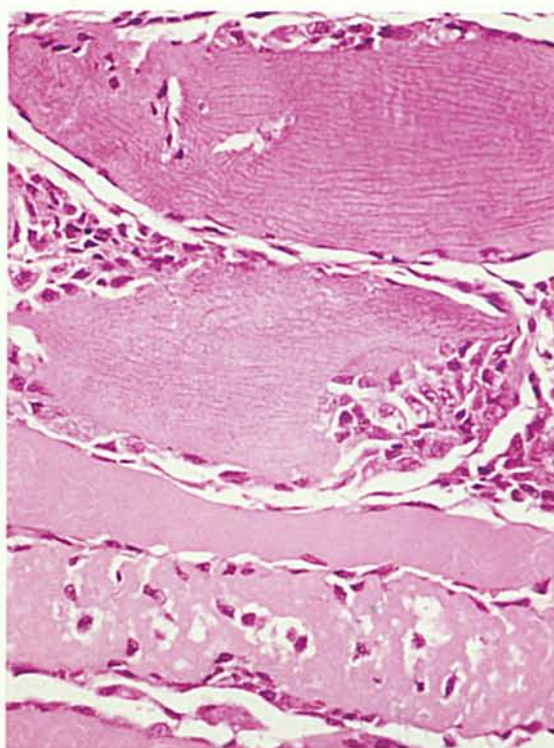


*Fig. 8 – Fat necrosis. A confluent sheet of acute fat necrosis which has formed in the subcutaneous tissues of a rat following oral administration of a xenobiotic (H&E).*





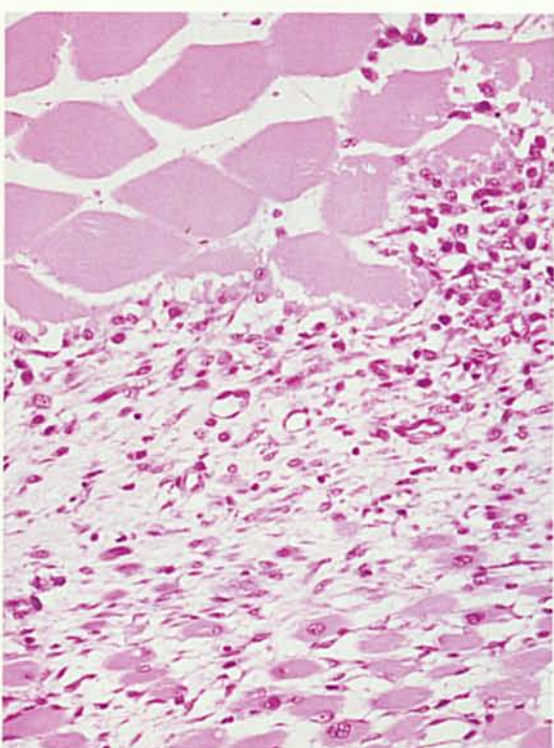
*Fig. 9 – Necrosis and acute inflammation; skeletal muscle (H&E).*



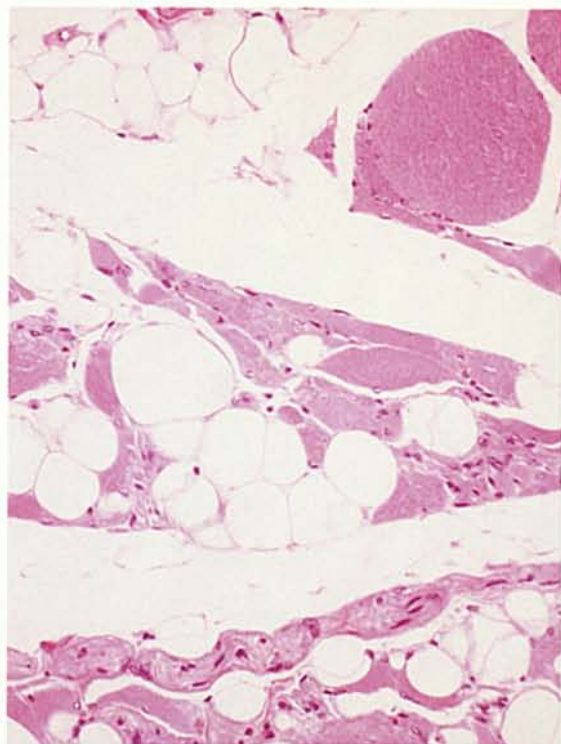
*Fig. 10 – Mineralization, necrosis, and inflammation; skeletal muscle. Muscle fibers showing degeneration four days after administration of an irritant substance (H&E).*



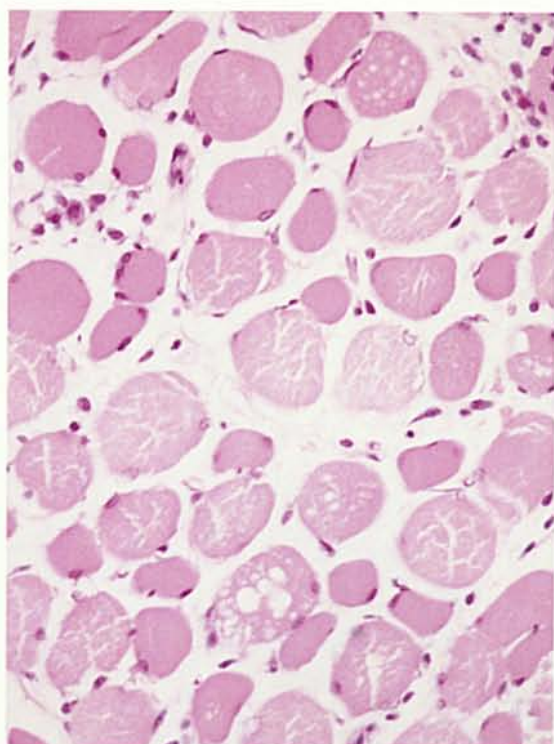
*Fig. 11 – Similar to Fig. 10 stained for calcium. Fine linear deposits of mineral are visible within degenerate muscle fibers (von Kossa).*



*Fig. 12 – Inflammation; skeletal muscle. A zone of necrosis and associated inflammatory and repair response 10 days after injection of a moderately irritant substance (H&E).*



*Fig. 13 – Atrophy; skeletal muscle. Severe atrophy of quadriceps muscle fibers and replacement by fatty tissue in a 2-year old Wistar rat (H&E).*



*Fig. 14 – Degenerative alterations; skeletal muscle. Quadriceps muscle fibers showing vacuolar degenerative alterations in a Wistar rat treated chronically with an aldose reductase inhibitor (H&E).*