

ULTRASTRUCTURAL CHANGES IN SCLEROMYXEDEMA¹

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Abstract. Skin biopsy specimens from a 60-year-old patient with paraproteinemia and generalized changes of the skin typical of scleromyxedema were studied with the electron microscope. The dermis was dominated by collagen fibrils and accumulations of peculiar connective tissue cells, while elastic tissue was sparse and in some areas completely absent. Large, sharply demarcated areas of a filamentous material were occasionally observed. The collagen fibrils were often surrounded by thin filaments with a periodic segmentation and by many glycosaminoglycan (mucopolysaccharide) filaments. The elastic fibres contained large amounts of elastic fibrils and small amounts of a homogeneous matrix. The cytoplasm of the above-mentioned cells was dominated by lysosomes in different stages of development, often occupying almost all the cytoplasmic area. The collagen fibrils were found in close relation to these cells, frequently inside invaginations of the cells. Furthermore, collagen fibrils were observed free in the cytoplasmic area and inside the lysosomes, indicating lysosomal degradation of collagen.

Key words: Myxedema; Collagen; Elastic tissue; Lysosomes; Immunoglobulins

Scleromyxedema (generalized lichen myxedematosus) is a rare disorder characterized by a widespread lichenoid eruption and a diffuse thickening of the skin (8, 19, 21). The dermis contains large amounts of acid glycosaminoglycans and many large stellate and elongated cells, resembling fibroblasts (8, 19, 21). In addition, a paraprotein in the serum has been observed in many cases (23).

We present electron microscopic findings in a case of scleromyxedema.

MATERIAL

The patient was a 60-year-old woman with an itching widespread skin eruption which had developed over a period of 20 years. Nodular and lichenoid greyish-red waxy papules were present in large areas of the skin, particularly on the

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face and in the flexural folds, the lichenoid papules often presenting a linear arrangement (Fig. 1). Nodules were also observed in the mucosal area of the lower lip. The eruption was accompanied by a diffuse thickening of the skin, most pronounced in the skin of the face, arms and hands. In addition, large erythematous areas containing hyper- and hypopigmentations of a reticular pattern were present on the torso. X-ray examinations showed the presence of calcifications in the skin or subcutis of the fingers. No evidence of multiple myeloma were found. The serum contained a paraprotein, type G, L. The values of thyroxin and cholesterol in serum were normal.

Skin biopsies were taken from the antecubital and axillary regions and prepared for both light and electron microscopic studies. A sternal marrow puncture was also performed.

METHODS

Light microscopy. The skin biopsies were fixed in a 4% lead subacetate solution. Paraffin sections were stained with hematoxylin and eosin, toluidine blue, alcian blue, congo red, and with the methods of van Gieson and Mallory. The sternal marrow was prepared according to the usual procedure.

Electron microscopy. The specimens were fixed in glutaraldehyde 6% in Veronal acetate buffer (pH 7.2) with 7.5% sucrose and then osmicated. After stepwise dehydration in increasing concentrations of ethanol the specimens were embedded in epoxy resin, and ultrathin sections were cut with an LKB ultramicrotome. Some of the sections were stained according to a combined technique using uranyl acetate and lead citrate, and the others were stained with ruthenium red (13). A Siemens electron microscope (Elmiskop IA) was operated at 80 kV with double condensers for the study.

OBSERVATIONS

Light microscopy. The skin biopsies showed an increased amount of ground substance in the dermis, presenting metachromatic staining with toluidine blue and a blue stain with alcian blue. The congo red staining did not disclose any amyloid material. The collagen fibres partly presented a homogenization and partly a splitting of the fibre structure. A

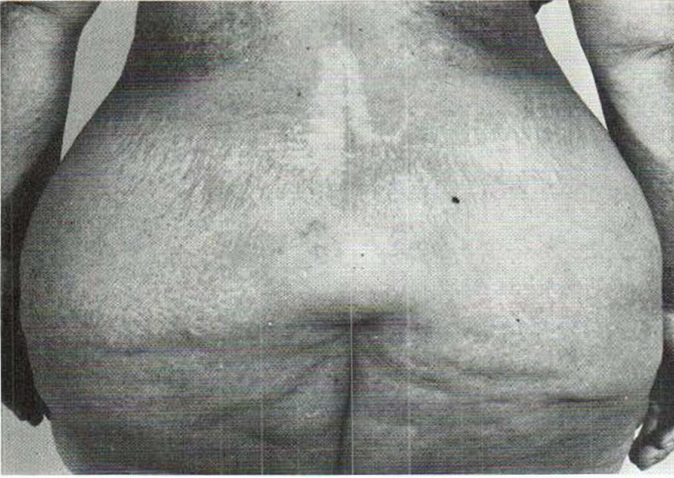


Fig. 1. Lichenoid papules in a linear arrangement.

few elastic fibres were observed. Many large, often stellate, mononuclear cells were noticed as well as the presence of fibroblasts and mast cells.

The sternal marrow showed no abnormalities.

ELECTRON MICROSCOPY

The dermis was dominated by collagen fibrils and accumulations of peculiar connective tissue cells.

Some of the collagen fibrils appeared in thick

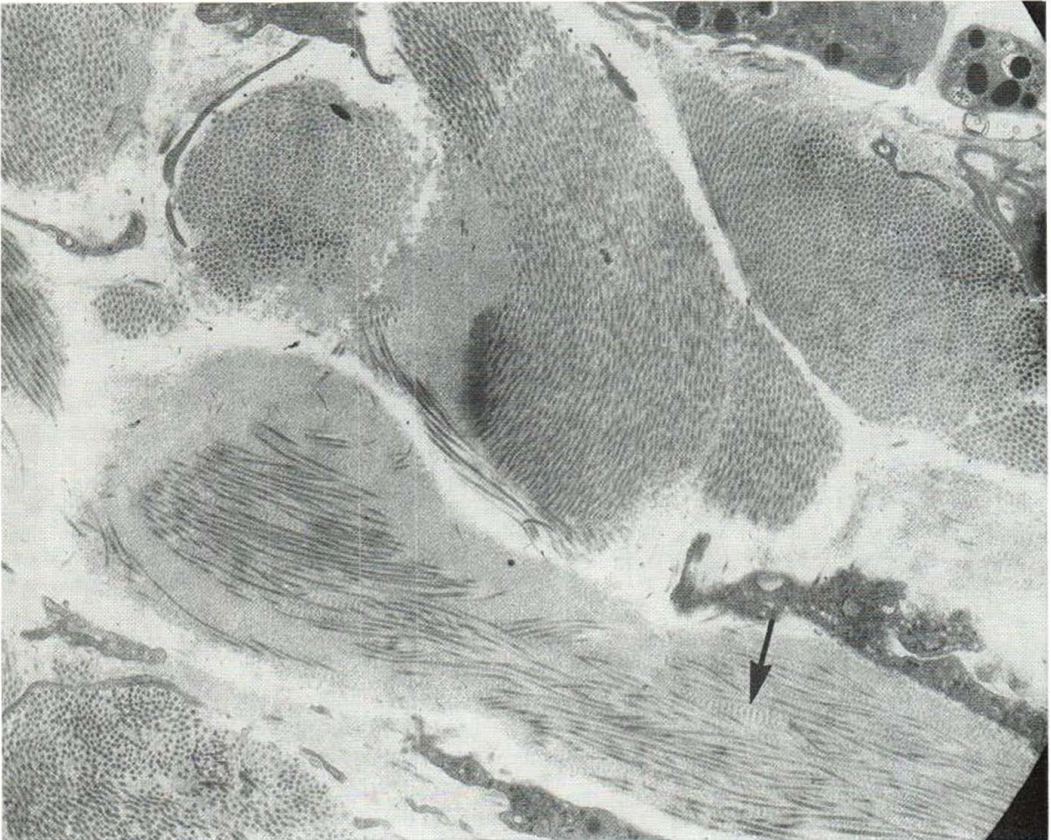


Fig. 2. Thin, parallel filaments with a periodic segmentation (arrow) are seen among collagen fibrils. The collagen fibrils are embedded in a granular material. $\times 10\,000$.

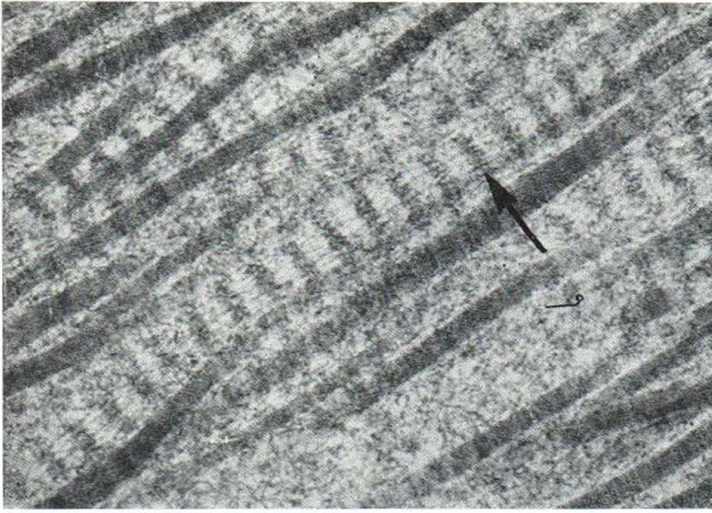


Fig. 3. Thin filaments with a periodic segmentation (arrow) are seen among collagen fibrils. The filaments contain light and dark segments of about equal size appearing at intervals of about 100 nm. $\times 60\ 000$.

bundles, while others presented an irregular arrangement. The individual collagen fibrils were often surrounded by a granular material and in many areas by thin parallel arranged filaments with a periodic segmentation (Figs. 2, 3). These filaments contained light and dark segments of about equal width, appearing at intervals of from 85 to 100 nm. The filaments were particularly often observed around the vessels. In addition, many glycosaminoglycan filaments (14) were seen around the collagen fibrils (Fig. 4). The ruthenium red staining demonstrated the mucopolysaccharide nature of these filaments (Fig. 5) (13).

In some areas, elastic tissue was absent, while

other areas contained elastic fibrils forming round masses or oblong fibres (Fig. 6). Occasionally a homogenous matrix could be observed inside areas of elastic fibrils. 'Senile' degeneration of the elastic fibres was rarely seen (4).

Large, sharply demarcated areas of a filamentous material were occasionally observed (Fig. 7). These filaments appeared thinner and more densely packed than elastic fibrils. The filamentous material showed no relationship to the dermo-epidermal junction.

Beside fibroblasts with a well developed endoplasmic reticulum and mast cells, accumulations of peculiar cells were seen in many areas (Fig. 8). The cytoplasm of these peculiar cells contained large

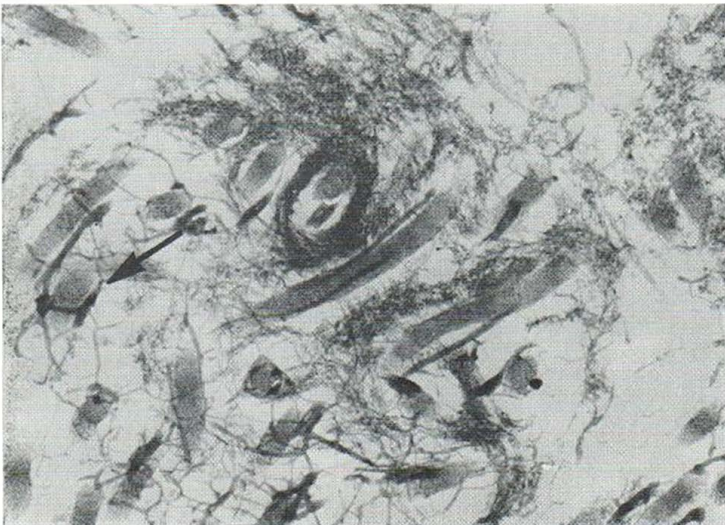


Fig. 4. Many glycosaminoglycan filaments (arrow) are seen around irregularly arranged collagen fibrils. $\times 60\ 000$.

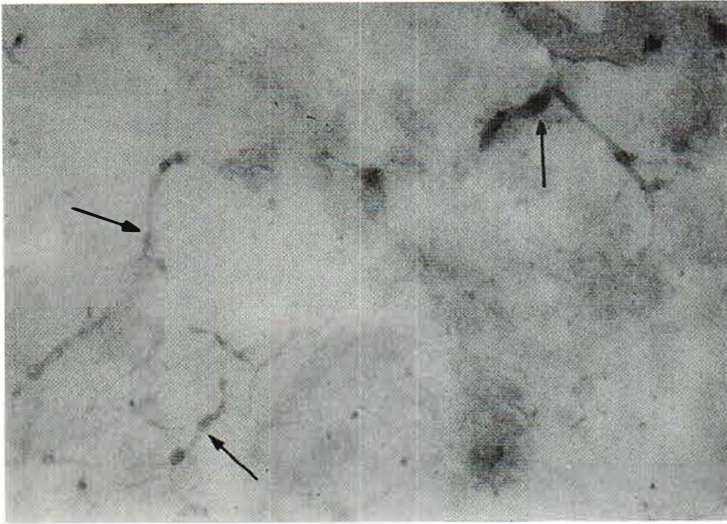


Fig. 5. Glycosaminoglycan filaments (arrows) stained with ruthenium red. $\times 60\ 000$.

amounts of lysosomes, often occupying most of the cytoplasmic area. Some of the lysosomes were composed of electron-dense granules and electron-dense round or oblong bodies. However, most of the lyso-

somes appeared as vacuoles with a heterogeneous content, particularly dominated by vesicles and multilamellar bodies (Fig. 9) (25). Some of the vacuoles were extremely dilated. Multilamellar bod-

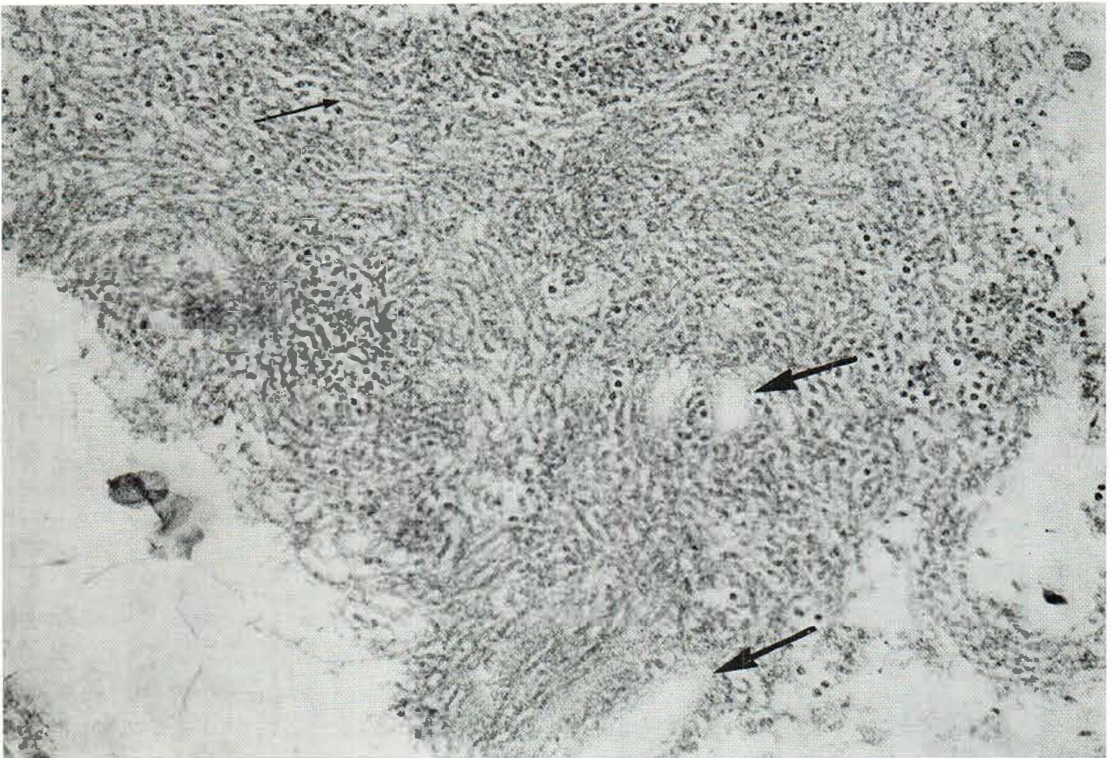


Fig. 6. Large amounts of elastic fibrils (thin arrow) with small amounts of homogeneous matrix, (thick arrows). $\times 60\ 000$.

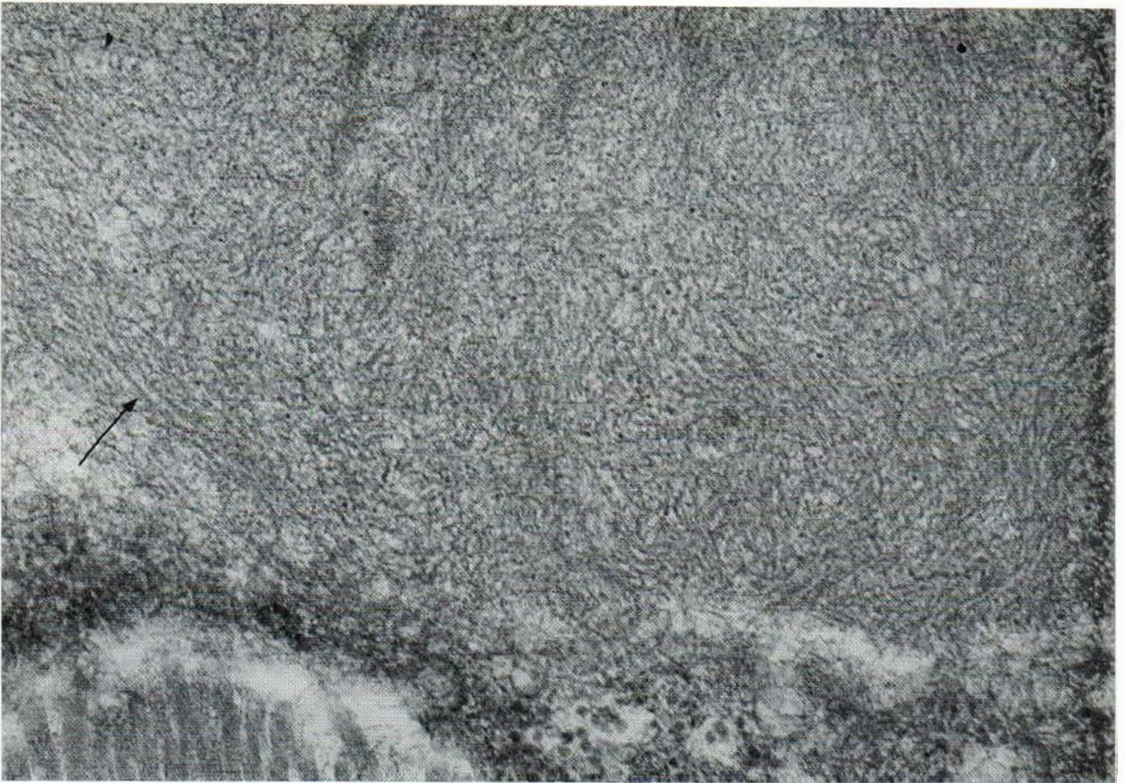


Fig. 7. A filamentous material with filaments (*arrow*) appearing thinner and more densely packed than elastic fibrils. $\times 60\ 000$.

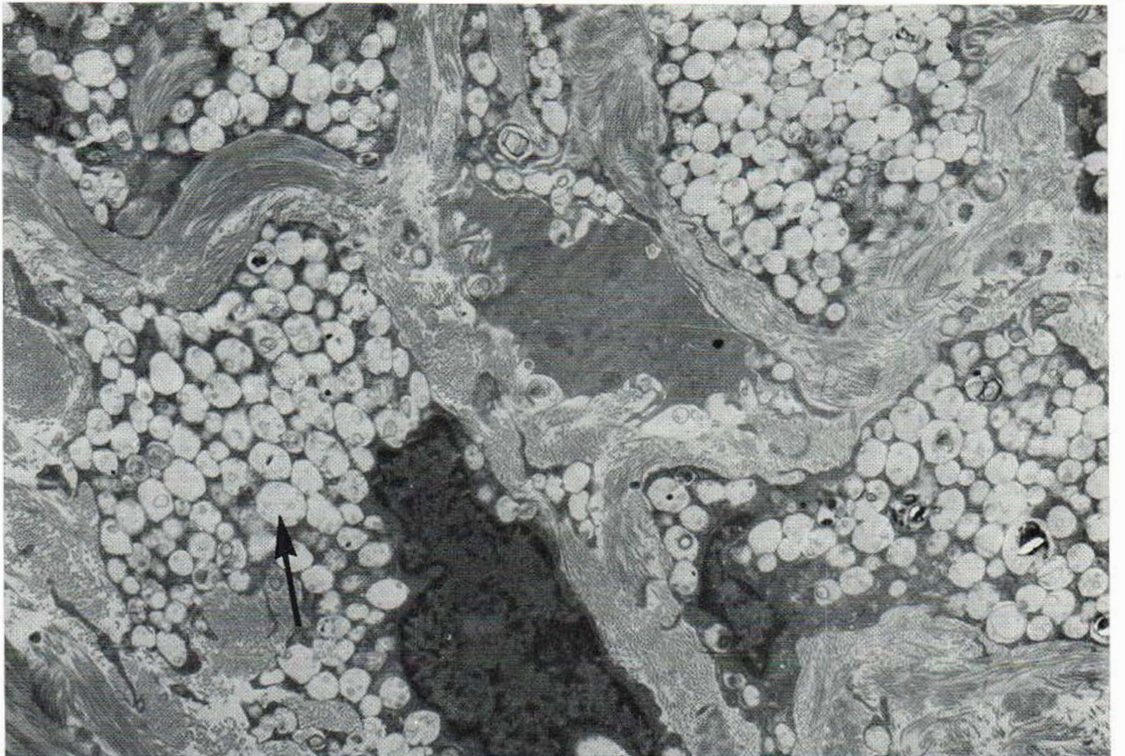


Fig. 8. Peculiar cells are surrounded by collagen fibrils. The cytoplasm of the cells contains large amounts of lysosomes (*arrow*), occupying almost all the cytoplasmic area. $\times 6\ 000$.

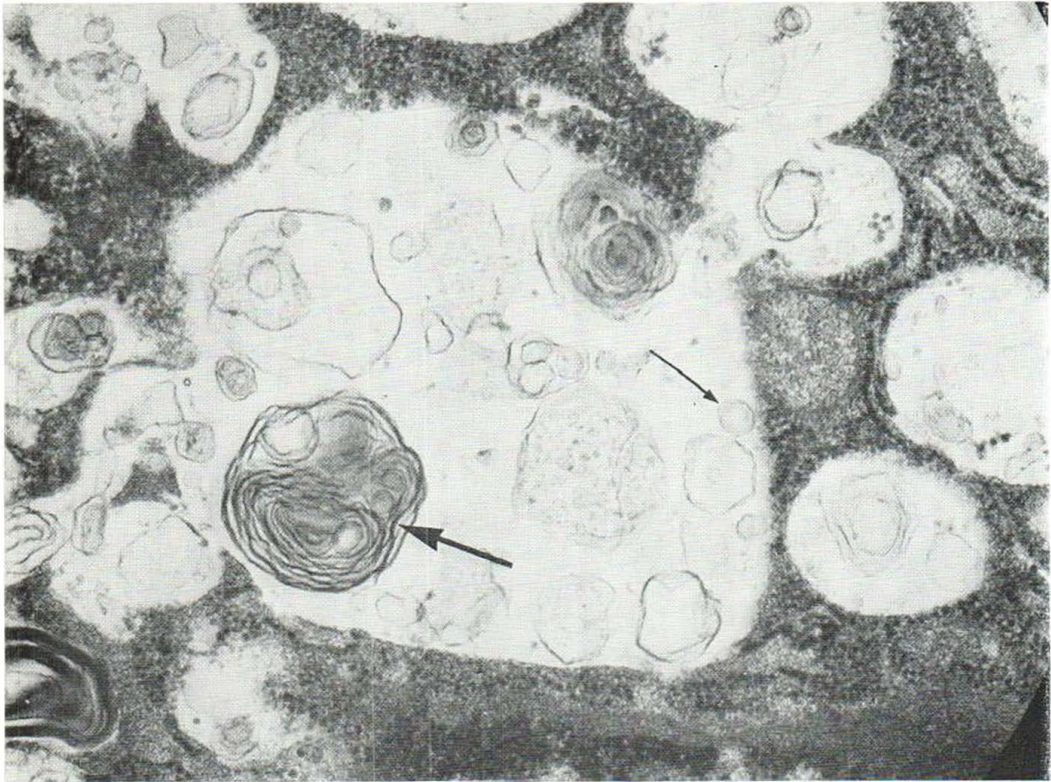


Fig. 9. Multilamellar bodies (*thick arrow*) and vesicles (*thin arrow*) are seen inside an extremely dilated lysosome. $\times 40\ 000$.

ies and vesicles were also observed free in the extracellular space. The collagen fibrils were found in close relation to these cells, frequently inside invaginations of the cells. Furthermore, collagen fibrils were observed both free in the cytoplasmic area (Fig. 10) and inside the lysosomes (Figs. 10, 11). A light granular material often surrounded these intralysosomal collagen fibrils (Fig. 11). The mast cells were located among such cells rich in lysosomes. The mast cell granules contained dense homogeneous and coarse granular material. The latter material often showed a light periphery and an enclosing membrane which indicate degranulation (Fig. 12).

DISCUSSION

The thin parallel filaments observed in this study show a segmentation reminiscent of that of collagen fibrils, though appearing with a somewhat wider periodicity and without subfractions. Similar filaments have been observed in tissue cultures of fibro-

blasts (7, 29), in the skin of scleroderma (15, 17) and occasionally in normal skin (5), and have been suggested to represent precursors of collagen fibrils (7, 15, 17). The presence of these filaments in large amounts in the skin of scleromyxedema might thus indicate an active new-formation of collagen in this disease.

However, in recent studies, Hentzer & Kobayasi suggested that a degradation phenomenon is probably responsible for the presence of these filaments (12). Histograms performed by Pilgram et al. (22) have shown the mean collagen fibril diameter to be decreased in scleromyxedema. The authors (22) discussed the possibility that this finding might indicate neogenesis, impaired maturation, or accelerated ageing of the collagen fibril. While a close association between segmented filaments and acid glycosaminoglycans has been observed in colloidal iron preparations of fibroblast cultures (29) the present study showed many glycosaminoglycan filaments (13, 14) around collagen fibrils. An increased

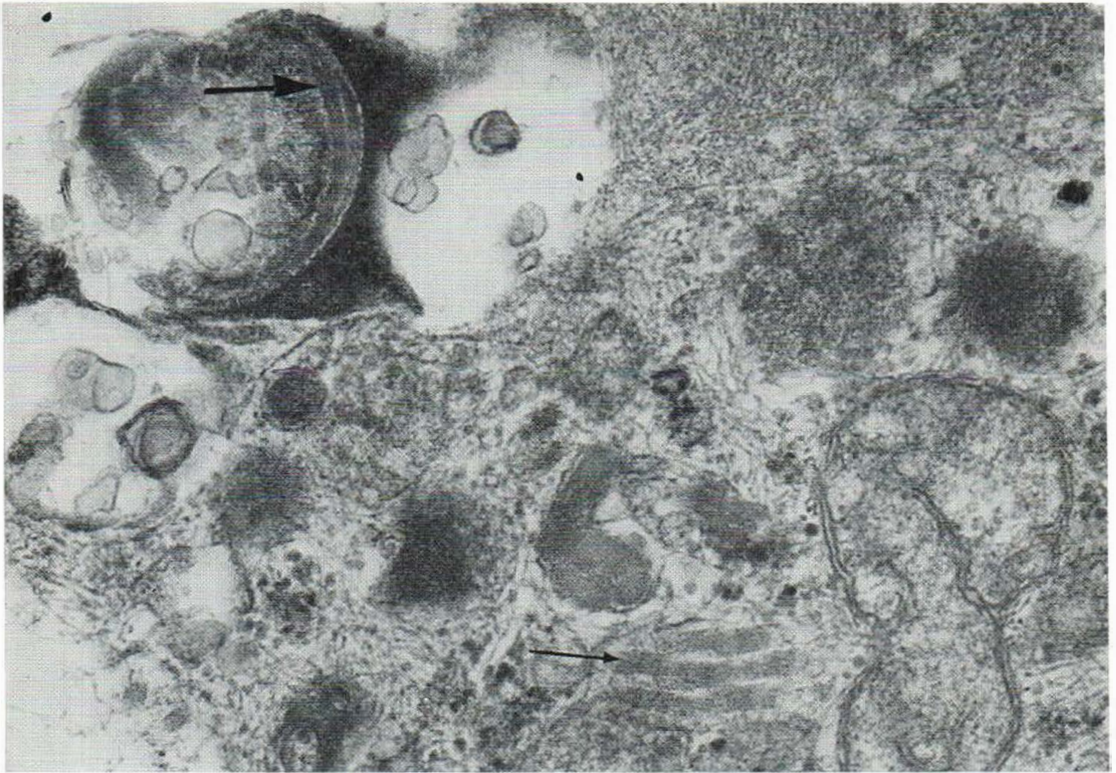


Fig. 10. Collagen fibrils are seen free inside the cytoplasm (thin arrow) and inside a lysosome (thick arrow). $\times 60\ 000$.

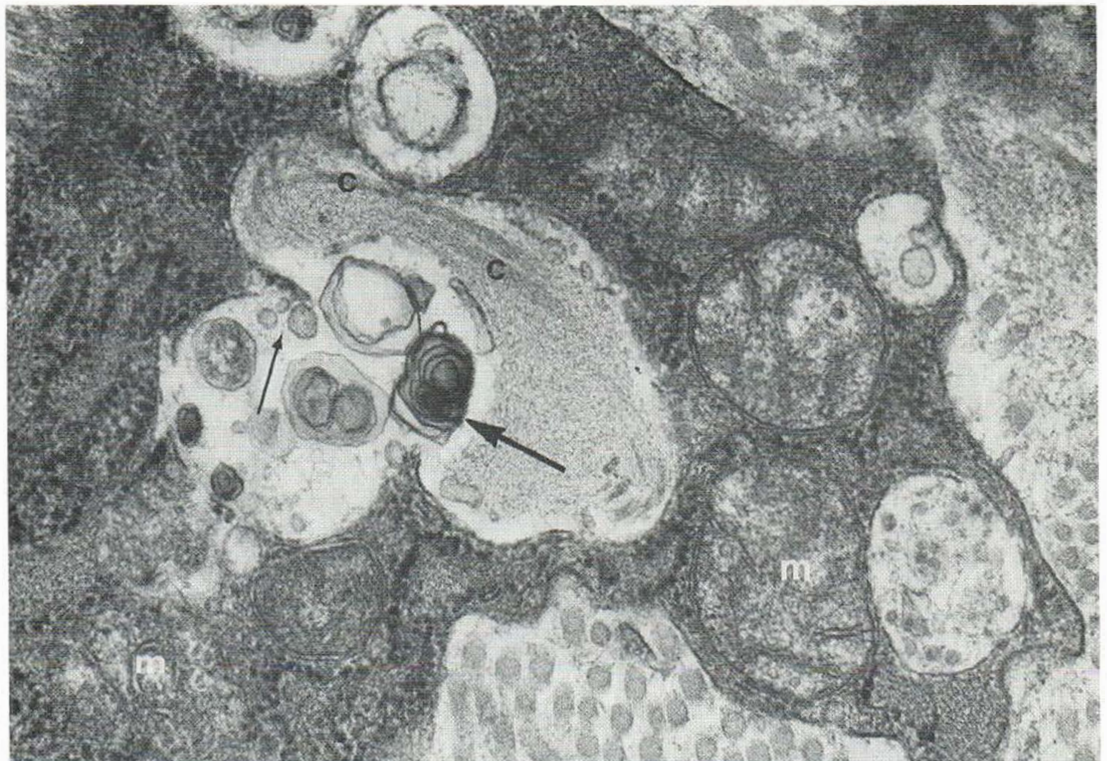


Fig. 11. Multilamellar bodies (thick arrow), vesicles (thin arrow) and collagen fibrils (*c*) are seen inside a lysosome. The collagen fibrils are surrounded by a light, granular material. (*m*) shows mitochondria. $\times 60\ 000$.

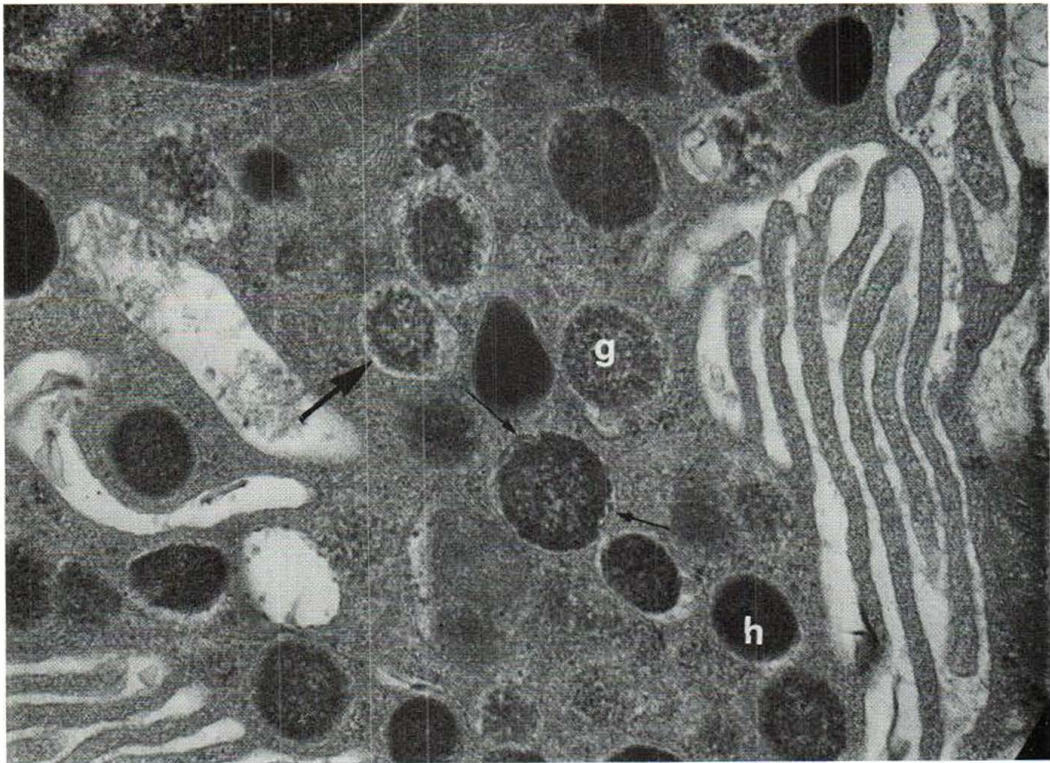


Fig. 12. The mast cell granules exhibit dense homogeneous (h) and coarse granular material (g). Distinct, enclosing mem-

brane is indicated by a thick arrow and scrolls characteristic of mast cell granules by thin arrows. $\times 40\ 000$.

amount of acid glycosaminoglycans is known to be typical of scleromyxedema skin (8, 19).

As elastic fibrils represent young elastic tissue (9, 24), their presence in large amounts compared with the amount of the homogeneous matrix in scleromyxedema skin suggests an active new-formation of elastic fibres in this disease. This suggestion concurs with the report of Hardmeier & Vogel (11). These authors observed an increase in elastic fibres and particularly of the elastic fibrils in 2 patients with scleromyxedema. The possibility that the reduced amount of matrix in our patient could have been caused by inhibitory factors as suggested for a disease with deficiency in elastase inhibitor (1) is less likely.

The large masses of a filamentous material observed in the present study contain filaments similar to those of the filamentous bodies demonstrated in localized scleroderma (17) and in systemic lupus erythematosus skin (10, 16). These filamentous bodies have been suggested to be identical with the 'hyaline bodies' found in immunofluorescence and

histochemical studies on several dermatoses (17, 27). The hyaline bodies contain immunoglobulins (27). Immunofluorescence studies of skin biopsy specimens from a patient with scleromyxedema have shown the presence of an IgG protein with the same specificity as a monoclonal globulin found in the serum of that patient (3). Tissue cultures have demonstrated the synthesis of a monoclonal IgG protein in both skin and bone marrow in scleromyxedema (18). Recently, it has become evident that in many instances, amyloid fibrils represent tissue deposits of fragments of immunoglobulin proteins related to Bence Jones protein (6). However, the question whether the presence of filamentous masses is related to the presence of a paraprotein in scleromyxedema skin remains unanswered.

The close association of collagen fibrils to cells observed in the present study was previously noted by Hardmeier & Vogel (11). Their suggestion of an activated degradation of collagen in scleromyxedema is further supported by our finding of accumulations of cells rich in lysosomes and with collagen fibrils

inside some of the lysosomes. As the function of lysosomes is known to be related to autolytic enzymic destruction, this finding indicates an active lysosomal degradation of collagen fibrils in this disease. The multilamellar bodies observed inside the lysosomes are considered to be undigested end products (20). It is still not known whether the destruction of collagen normally occurs extracellularly or intracellularly, or both. Ultrastructural evidence of intracellular degradation of collagen has been reported only exceptionally (20, 26, 28). Collagen fibrils were present in large amounts in our study, despite the evidence of an active lysosomal degradation of these fibrils, suggesting either hampered extracellular (?) degradation or an active new-formation of collagen fibrils. Elastic fibres were few, despite the evidence of an active new-formation of elastic tissue, thus suggesting an active cellular degradation also of elastic fibres in this disease. The 'senile' extracellular degeneration of elastic fibres was less pronounced than that found in normal subjects of a corresponding age (4). Similar cells rich in lysosomes as observed in the present study have been reported in other mucopolysaccharidoses such as Hurler's and Hunter's disease (2).

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