

## ACQUIRED CUTIS LAXA (GENERALIZED ELASTOLYSIS): LIGHT AND ELECTRON MICROSCOPIC STUDIES

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**Abstract.** The case is described of a 44-year-old man with acquired cutis laxa.<sup>1</sup> The primary clinical manifestation was an erythema of the chest. Gradually there developed persistent circumscribed lesions in other areas of the skin, spreading into large erythematous plaques with loose skin. Slight restrictive ventilatory insufficiency, elongation of the vocal cord and diverticulosis of the colon were also found, indicating a chronic and widespread disorder. Skin biopsies showed diminution and degeneration of the elastic fibres. The light-microscopic features were subdivided in relation to the various skin manifestations. Ultrastructure of the skin showed various amounts of electron-dense, amorphous material and loosely bound microfibrils in and around elastic and collagen fibres as well as some microfibrils with knobs in the interfibrillar and interfibrillar space of the collagen. Most of the collagen fibres, however, were found normal. It is suggested that the first changes in the elastic fibres induced an inflammatory response and mild mucinous changes of the collagen fibres. Furthermore elastic fibres seemed to be replaced by newly formed collagen.

**Key words:** Acquired cutis laxa; Elastic fibre; Collagen; Microfibrils

Cutis Laxa (CL) or generalized elastolysis is a very rare disease which involves not only the skin but also internal organs such as lungs, heart, aorta and gastro-intestinal tract. In some cases pulmonary emphysema may lead to heart failure and death (5, 19).

Two types of CL have been recognized, congenital and acquired. Both show the same clinical and histological changes. The onset of the congenital form is at birth or during the first months of life, while the onset of acquired CL is in later life. The congenital form may have a family history for the disorder (5). Episodes of edema in the congenital form and urticaria or allergic reactions to drugs

such as penicillin in the acquired form have been suggested to be predisposing factors. Acquired CL is rarer than the congenital form; we found only 14 cases in the literature (9, 17 og 18). This paper presents a case of acquired CL and describes the histological features of the skin on light and electron microscopy.

### CASE REPORT

A 44-year-old man noted the onset of his disorder at the age of 41 in August 1975. He had undergone surgery for bilateral inguinal hernias in 1953 and 1954, and in 1971 was treated for a fracture of the lumbar spine. Otherwise, he had previously been healthy until the first skin manifestations appeared. The disease began with a reddish spot on the chest. Gradually there developed persistent circumscribed lesions with mild itching at other sites of the skin, mainly on the trunk. In September 1975 he was examined and a biopsy was taken by a local dermatologist who suspected a fixed drug eruption due to phenacetin, which the patient was taking for low back pains. In spite of discontinuing this analgetic, no improvement was found. The patient also noted loss of appetite and lost 10 kg in weight during the ensuing months.

In May 1976 he was admitted to our department. His

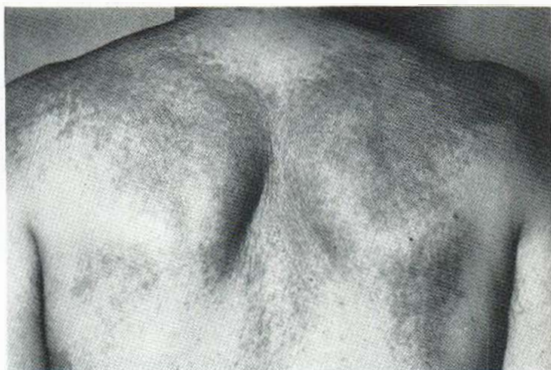


Fig. 1. Large erythematous plaques on the back.

<sup>1</sup>This case was presented at the 5th European Meeting on Electron Microscopy applied to Cutaneous Pathology, Copenhagen, May 1978.

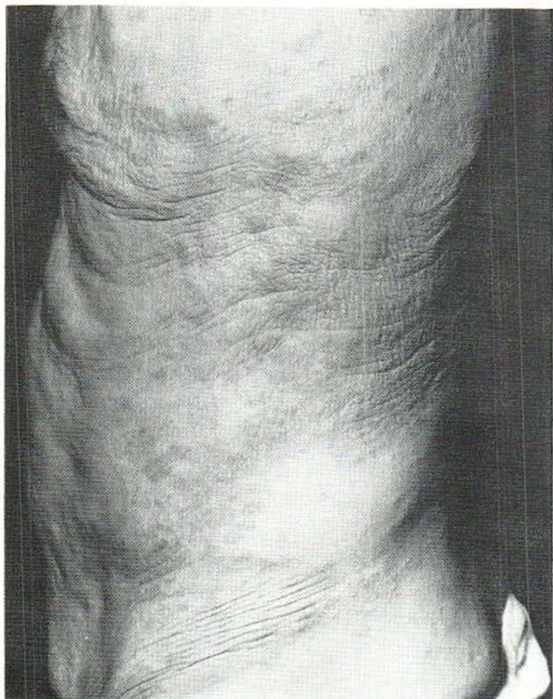


Fig. 2. Trunk skin with erythematous plaques, deep furrows and loose skin.

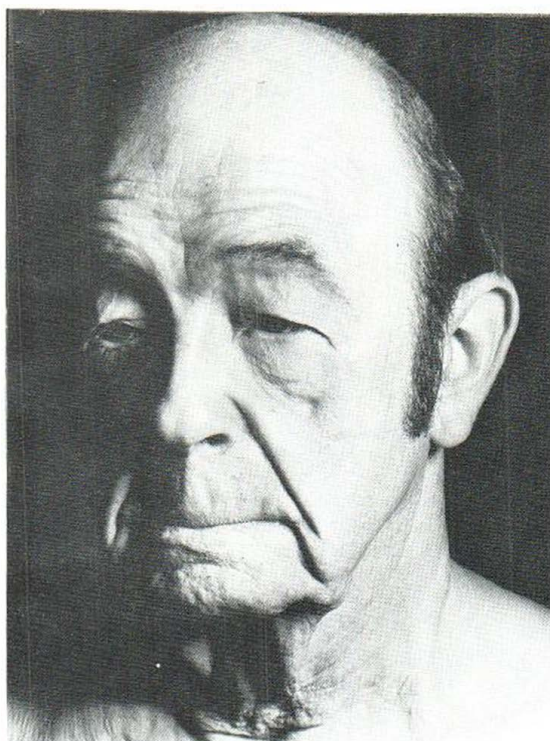


Fig. 3. Face of the patient, aged 44, showing drooping eyelids, nasolabial folds and cheeks.



Fig. 4. Verhoeff stain, showing conspicuous diminution and fragmentation of the elastic fibres and increased quantities of collagen bundles ( $\times 40$ ).

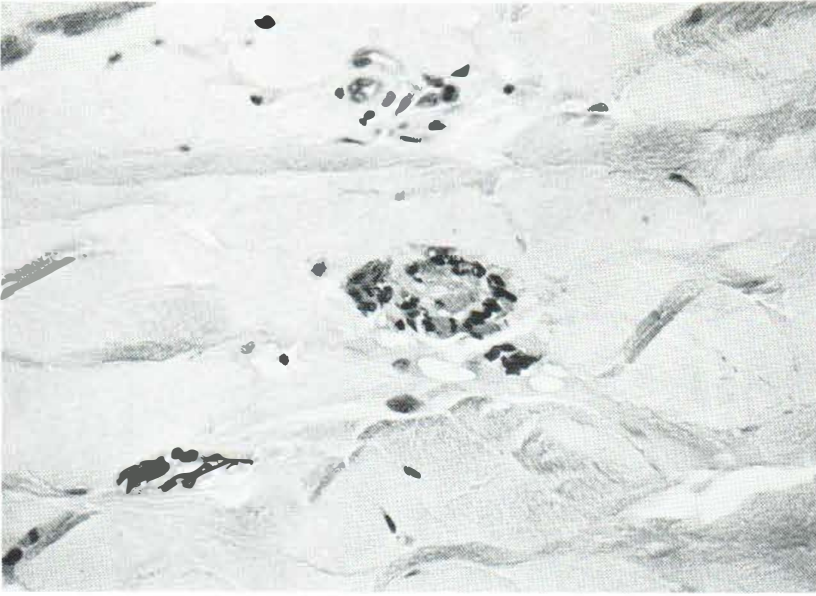


Fig. 5. Giant cell, showing phagocytosis of degenerative elastic fibres (Verhoeff stain,  $\times 250$ ).

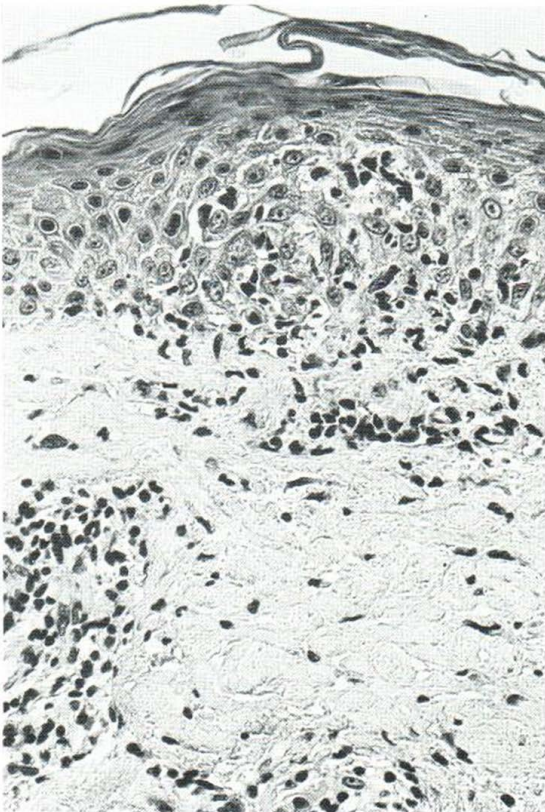


Fig. 6. Lymphocytic infiltration and exocytosis of lymphocytes (Hematoxylin-eosin stain,  $\times 230$ ).

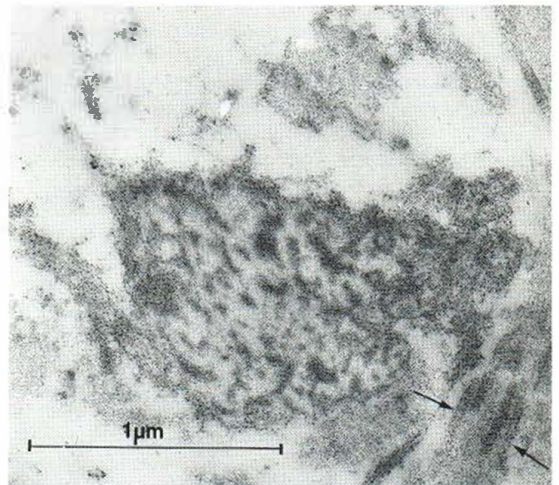


Fig. 7. Each remaining elastic fibre in the lesion shows a normal amorphous matrix with skeleton fibrils (arrows) ( $\times 32\,000$ ).

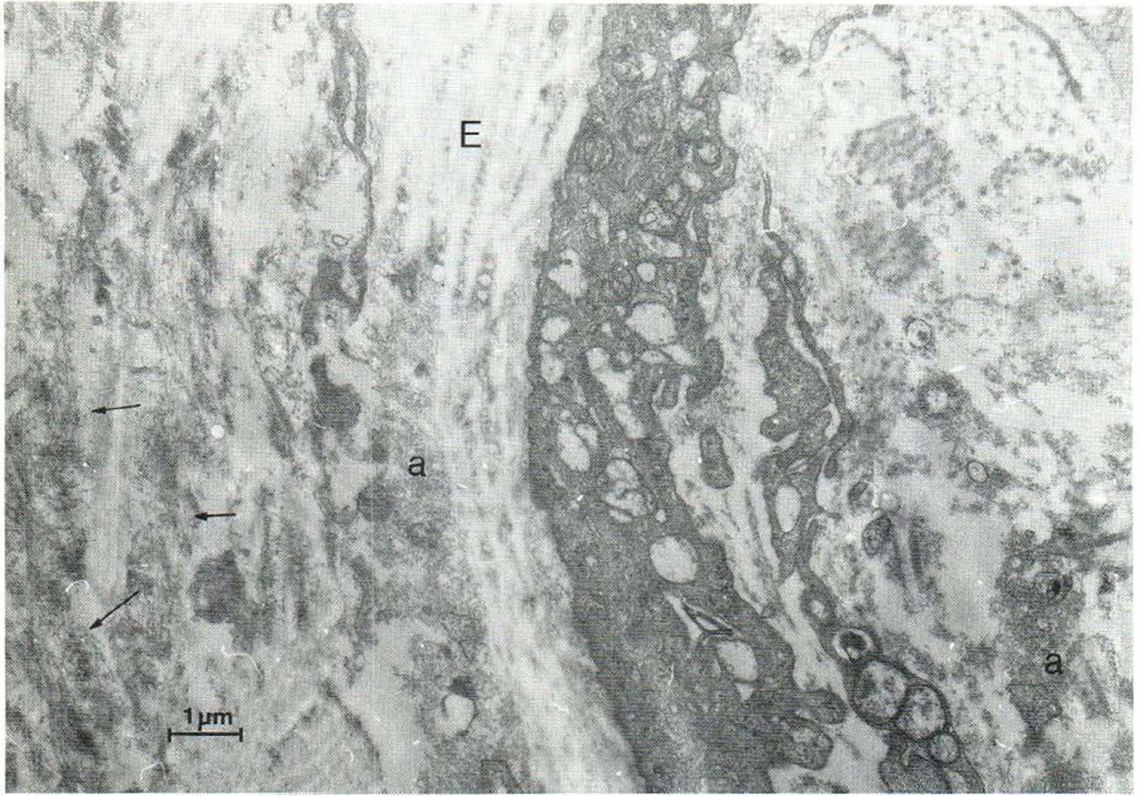


Fig. 8. Numerous loosely bound microfibrils (arrows) and electron-dense amorphous materials (a). E = elastic fibre ( $\times 9000$ ).

family history was found negative for skin diseases as well as for parental consanguinity.

At physical examination, relatively demarcated, large erythematous plaques were seen, mixed with normal-appearing skin on the neck, shoulders, back (Fig. 1), chest and groins. At the center the erythema and swelling regressed, to be followed by mild hyperpigmentation. Lung and heart stethoscopy were normal, the blood pressure was 140/80 mmHg and a neurological examination revealed no abnormalities. A biopsy was taken which showed non-specific dermatitis and the tentative diagnosis was erythema perstans.

In March 1977 the patient was hospitalized again as he felt increasingly tired and the skin changes had progressed, this time displaying increased furrowing (Fig. 2). Examination of the skin now also showed larger erythematous plaques than before, not only on the trunk but also on the upper extremities. He looked older than his age. The upper eyelids were drooping and the cheeks were sagging (Fig. 3). Sometimes his voice had an abnormal tremor. We suspected cutis laxa and skin biopsy confirmed this diagnosis.

Penicillamine therapy was started in May 1977 on trial basis, 150 mg daily, gradually increasing to maximum 900

mg daily. No objective improvement was seen except for a slight weight gain.

Laboratory tests failed to reveal any significant abnormalities in blood or urine. The following tests all gave normal or negative results on one or more determinations: hemoglobin, white blood count, differential count, platelet count, urine samples for protein and sugar, erythrocytes, sedimentation rate, coagulation survey, analysis of stool for blood and fat, rheumatoid factor, Wasserman's reaction, antistreptolysin titer, antinuclear antibody, fasting blood sugar, glutamic pyruvic transaminases, alkaline phosphatases, uric acid, serum creatinine, serum creatinine phosphokinase, serum and immuno-electrophoresis, serum zinc and serum copper. Our standard patch tests were normal too. Roentgenograms of chest and stomach were normal, while a colon X-ray demonstrated diverticulosis of the sigmoid colon. The electrocardiogram was normal.

#### MATERIALS AND METHOD

Since the first examination of this patient in May 1976, six biopsies have been taken, with 12 specimens including

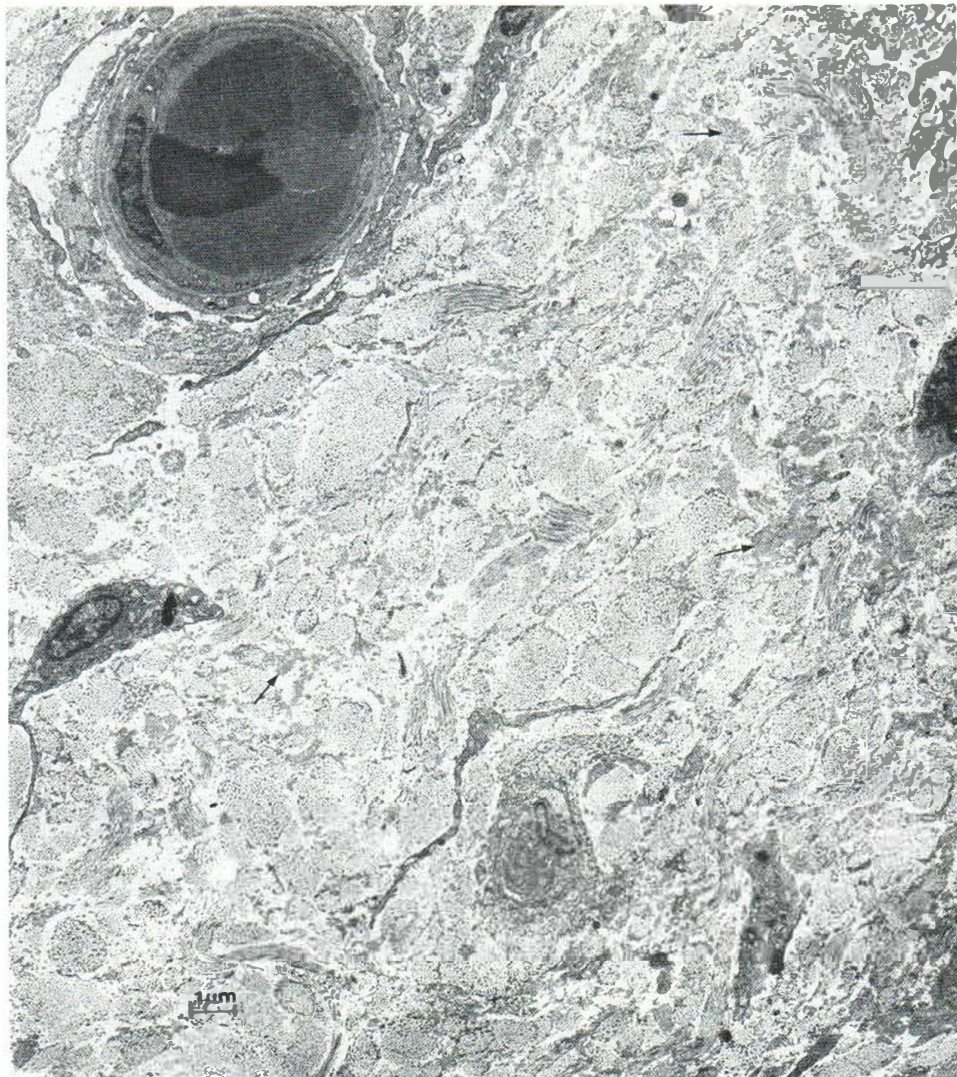


Fig. 9. Upper dermis of normal-appearing skin, showing semimyxomatous state with various amounts of electron-

dense, amorphous materials (arrows) in the interspace of collagen ( $\times$  4000).

normal appearing skin. Most were removed from the erythematous plaques on non-light-exposed areas. The first and second biopsies were taken before penicillamine treatment, the fifth when the patient had just completed one year on this therapy and the sixth 1½ months after therapy had been finally discontinued. Each part of the specimens was fixed in Bouin's solution or 10% buffered formalin solution, embedded in paraffin wax and 5  $\mu$ m sections cut and stained with hematoxylin-eosin, Verhoeff, periodic acid Schiff, Alcian blue (pH 2.7) and Von Kossa.

Parts of the fifth and sixth biopsies were fixed immediately in cold 3% glutaraldehyde buffered to pH 7.4 with cacodylate, followed by postfixation in 1% osmic acid with the Veronal buffer (pH 7.4) and dehydrated with

a graded concentration of ethanol, passed through propylene oxide and embedded in Epon 812. Ultrathin sections cut on an LKB ultramicrotome were stained with uranyl acetate and lead citrate solution. JEM-100B and Siemens Elmiskop 1A electron microscopes were used for the examination.

Parts of the second, fifth and sixth biopsy specimens were also immediately frozen for direct immunofluorescence microscopy.

## RESULTS

### Light microscopy

The various skin biopsy specimens taken from lesions in different stages of development from 1976

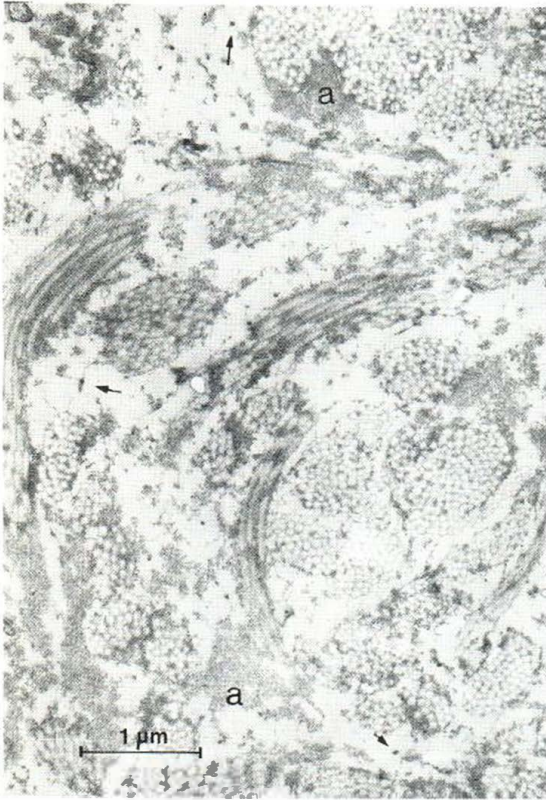


Fig. 10. Collagen covered with electron-dense, amorphous materials (a) and some microfibrils with knobs (arrows) in the interspace of collagen bundles. The mean diameter of the collagen fibrils was 50 nm in the upper dermis of this biopsy (5th) ( $\times 16000$ ).

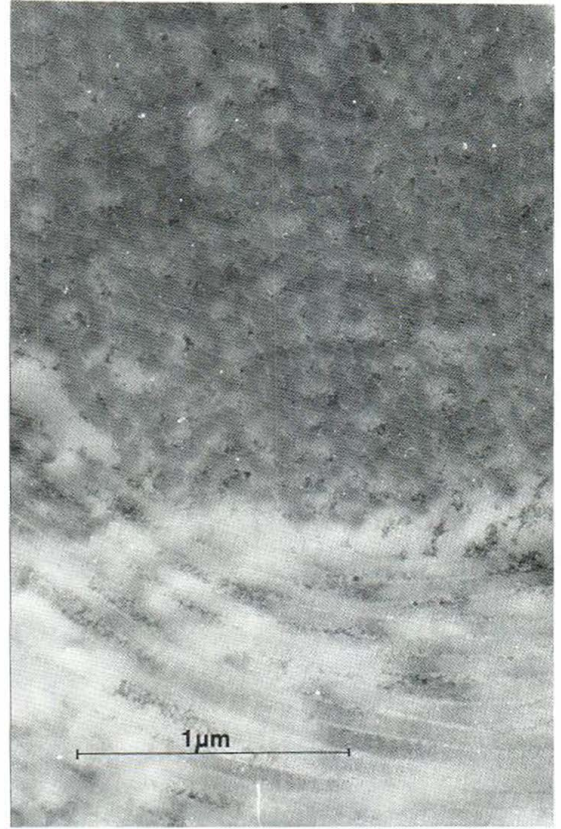


Fig. 11. Collagen fibrils with a normal periodicity and diameters ranging between 60 and 80 nm in the upper dermis (6th) ( $\times 36000$ ).

to 1978, all showed essentially similar findings. The primary change seemed to be in the elastic fibres, which were almost completely absent or diminished in all layers especially in the papillary, middle and lower portion of the dermis (Fig. 4). Each fibre was thinner than normal, shortened, fragmented or granular. Foreign body type giant cells were seen, some of which showed phagocytosed elements of the degenerative elastic fibres (Fig. 5). These findings were observed in Verhoeff elastic stained sections. Hematoxylin-eosin stains showed a slight atrophy of the epidermis and mild to moderate lympho-histiocytic infiltrations in the upper third of the dermis, sometimes with fibromatous changes of collagen bundles in the lower two-thirds of the dermis.

Relatively severe lymphocytic infiltration with exocytosis in the epidermis was observed in one specimen taken from an erythematous area of the

skin (Fig. 6). All biopsies showed a somewhat semimyxomatous state of the upper dermis. Alcian blue and PAS stains, however, did not stain the substance between the collagen bundles. Kossa stain failed to demonstrate any insoluble calcium in any of the specimens. Direct immunofluorescence stains were negative except for a slight positive IgG at the basal membrane in one biopsy.

#### Electron microscopy

Ultrastructure of two specimens from erythematous plaques showed essentially the same changes. There was conspicuous diminution of the elastic fibres. Each of the few remaining elastic fibres had a normally amorphous matrix with skeleton fibrils surrounded by microfibrils which exhibited normal staining properties both in longitudinal and cross section (Fig. 7) (7).

Varying amounts of electron-dense amorphous

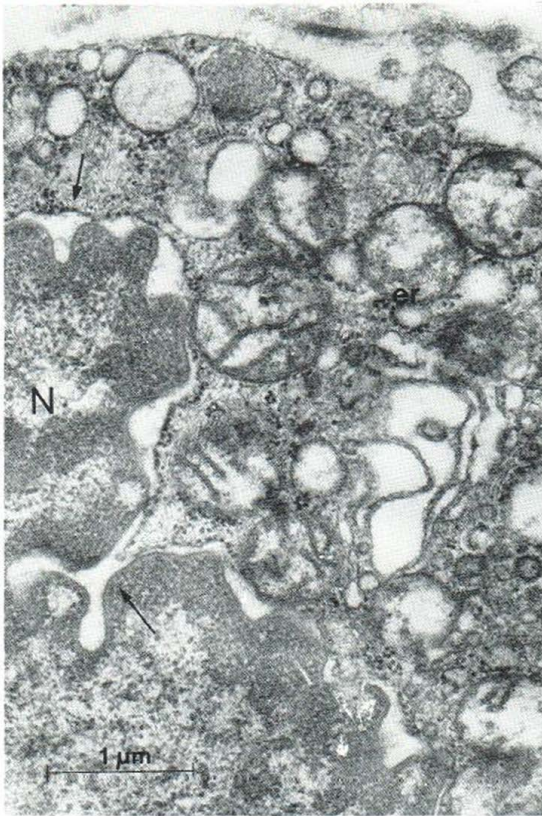


Fig. 12. The rough endoplasmic reticulum (*er*) and the nuclear envelope (arrows) of fibroblast is dilated or cystic. (*N* = nucleus) ( $\times 18000$ ).

materials and loosely bound microfibrils were seen to embed the collagen bundle and to cover some of the elastic fibres and cells (Figs. 8–10). The same was also observed in the interfibrillar spaces. These two substances were conspicuous in the upper dermis and sometimes existed in a mixed state. The nature of the electron-dense grains is unknown, but has been suggested to represent degenerated elastic fibres (1).

Additional findings were some microfibrils with knobs—which might be mucin—in the interfibrillar and interfibrillar space of collagen (Fig. 10) (12). In one section (Fig. 9) glycosaminoglycan filaments were found rather frequently. Similar findings have been observed in actinic elastoses (3). Individual collagen fibrils were basically normal with a normal periodicity and a diameter of about 60 nm in the upper dermis and about 100 nm in the middle and lower dermis. They were arranged in parallel (Fig. 11). Occasionally, larger than normal collagen bun-

dles and some irregularity in the diameter of the collagen fibrils were seen. Some fibroblasts which encircled or touched many collagen fibrils and elastic fibres were noted. The rough endoplasmic reticulum and nuclear envelope of the fibroblasts were dilated or cystic (Fig. 12). A few mast cells were seen which showed no degranulated figures. Some macrophages were also found surrounding the elastic and collagen fibres as well as the abnormal substances (Fig. 13). The macrophages seemed to be relatively inactive because of the undeveloped lysosomes and phagosomes in their cytoplasm. Other elements including blood vessels, epidermal cells and epidermal–dermal junctions showed no significant changes.

On comparing two biopsies, the fifth was found to show a wide interfibrillar and semixymomatous state of the upper dermis and many destroyed collagen bundles with a diameter of 50 nm in each fibril replaced by amorphous materials (Figs. 9, 10), while the sixth showed a tendency toward the increased collagen bundles with some irregularity in the diameter of each fibril. The differences in the biopsies may be due to the different stage of CL or to the influence of penicillamine.

The findings in normal-appearing skin were essentially the same as those seen in the involved areas, though the degree of change was much less severe.

## DISCUSSION

The findings of diverticulosis of the colon, the restrictive ventilatory insufficiency and elongation of the vocal cords indicate that internal organs as well as the skin are involved at the same time and that the disorder is a systemic disease. Whether the inguinal hernias were related to the disorder cannot be determined. They had occurred 20 years before the clinical diagnosis was established.

Some authors have stated that erythema multiforme, allergic reactions to penicillin, urticaria, neuroangioma and vesicular eruptions can be found prior to the onset of this disorder (17, 18). In our patient the initial diagnosis was erythema perstans. Verhagen & Werdeman (19) described a disease in young children with features resembling CL but without any internal involvement which might represent an abnormal reaction to the bite of an arthropod. They called the condition "postinflammatory elastolysis and cutis laxa". Convit and co-



Fig. 13. Macrophages (*M*) encircling remaining elastic fibres (*E*) ( $\times 9000$ ).

workers presented similar findings in a patient after injection of Mitzuda antigen and BCG vaccine (2). We know of no predisposing factor in our case. The intake of phenacetin may or may not be related to the onset of the disorder.

The acquired form of CL is, as stated, a very rare

disease and only 14 cases have been reported in the literature. Twelve were collected and considered in detail by Reed and co-workers (17). Most were accompanied by internal involvements such as emphysema and diverticulosis of several organs. Since their report, 2 cases of acquired CL as-

sociated with multiple myeloma have been described (9, 18). One began after an allergic reaction to penicillin.

Histopathologically the biopsy specimens seemed to display four disease stages. Stage I showed mild involvement of the elastic fibres alone. These fibres were found shortened, fragmented, or granular. In stage II these changes advanced and were followed by a lymphocytic reaction, primarily in the upper dermis. In stage III the lymphocytic infiltration was replaced by histiocytes which began active phagocytosis of the abnormal elastic fibres. As a result of this cleansing action there were no more elastic fibres stained with elastic staining in the dermis and macrophages decreased. This represents stage IV. Clinically, stage I appears normal, stage II shows an erythematous appearance and stage III displays some minute furrows besides erythema. In stage IV the erythema has regressed, to be followed by loose and sagging skin.

At the patient's latest visit, all four stages were represented at the same time, mainly on the trunk and upper arms, showing progression to the margin of the chronic process where no more elastic fibres were found to be formed. These findings may indicate that the disorder has an acquired autoimmune mechanism involving the elastic fibres.

When observed by electron microscopy, the specimens seemed to be compatible with stage III, whereas by light microscopy, which showed conspicuous diminution of the elastic fibres with elastic staining, stage IV seemed more likely. The ultrastructural findings would also seem to support the theory advanced by Hashimoto & Kanzaki that synthetic abnormalities of elastin underlie the pathogenesis of cutis laxa (9). Numerous microfibrils produced by fibroblasts were found, but only in a loosely bound state and did not combine to form elastic fibres. This means that these microfibrils might be elastic microfibrils or protofilaments as described by Hashimoto & Di Bella which are negative with elastin staining on light microscopy.

The varying amounts of electron-dense amorphous materials may be a result of the degeneration of remaining elastic fibres visualized by elastin staining on light microscopy. Some of these amorphous materials as well as the small amounts of microfibrils with knobs may be derived from collagen. The first changes in the elastic fibres may influence the metabolism of collagen. However our findings indicate that synthesis of collagen has,

generally speaking, been normal and that the elastic fibres have been replaced by newly formed collagen fibres.

Furthermore, normal-appearing skin showed changes of CL on electron microscopy due to the presence of amounts of amorphous, electron-dense materials, small amounts of loosely bound microfibrils and some microfibrils with knobs. We do not believe that penicillamine therapy for one year affected these ultrastructural changes in our patient, except maybe for the rather wide interfibrinous state of the upper dermis in one biopsy. Hulth and co-workers (10) described the ultrastructure of congenital CL. They observed large and small segments of dense granules of the elastic fibres, which are compatible with the varying amounts of electron-dense, amorphous substances in our patient. The present findings should be differentiated from senile degeneration, scleromyxedema, scleroderma and Ehlers-Danlos syndrome. The elastic fibres of senile degenerations show, on electron microscopy, the appearance of "tiger stripes" as well as a reduced number of collagen fibrils (3, 12-13). Scleromyxedema has an increase in the number of fibroblasts and each collagen fibril is richly coated with ground substance (glycosaminoglycan) (4, 6). Increased collagen synthesis with highly active fibroblasts and a high content of acid glycosaminoglycan are seen in scleroderma (4, 6 and 8). Ehlers-Danlos syndrome shows mainly a deficient production of collagen (10, 16).

Several theories on etiology, including copper deficiency and a familial deficiency of serum alpha-1-antitrypsin, have been proposed (2, 5, 14, 17). Wilson's disease generally requires prolonged treatment with penicillamine which preserves low levels of serum copper and sometimes causes many skin manifestations, including friability, cutis hyperelastica as well as elastosis perforans serpiginosa (16). Elastosis perforans serpiginosa shows an increase in abnormal elastin, as against the decrease in elastic fibre in CL (16, 20). Two examinations of copper levels in our case were both within normal limits and penicillamine therapy was started after the diagnosis of CL had been made.

There is at present no specific treatment for this disorder. Penicillamine, which apparently has some effect on a number of collagen diseases, was used in a therapeutic trial. The clinical and histological changes produced by this medication are described above. Penicillamine was administered again after

the last biopsy was taken for electron microscopy, to alleviate the worsening symptoms. However, this therapy has since been discontinued due to the lack of any visible effect. The patient is now on a trial with azathioprin.

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