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Nerve Changes in Morphea*

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Thirty-nine peripheral nerves in dermis of 12 morphea patients were analysed for ultrastructural changes. Changes found in the mesenchymal parts of the nerves, i.e. epi-, peri- and endoneurium, were myxedematous changes, collagen fibril degradation, cell infiltration and abnormal fibrosis. The infiltrating cells were lymphocytes and plasma cells as well as mast cells and myofibroblast. Perineural cells were assumed to be one of the origins of myofibroblasts. The axons and the Schwann cells showed slight signs of degeneration. (Received December 23, 1982.)

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Dermal nerves in plaques of morphea are occasionally surrounded by cell infiltrates (4). The infiltrating cells are lymphocytes, plasma cells and fibroblast-like cells. Ultrastructurally, filamentous membranous material has been found outside the basal lamina of Schwann cells (9). Dermal nerves may be involved in the pathological process of morphea, since a segmental distribution of the plaques has sometimes been seen. However, details of the nerve changes and their signficance are obscure.

MATERIAL AND METHODS

Twelve patients, one male and 11 female, aged betwen 16 and 74 years, were studied. Nine of the patients showed single or a few plaques of morphea, while 3 presented multiple plaques. In 6 cases, the plaques were located on the trunk, in 5 cases on the lower extremities, and in one case on the arms. Six patients showed distinct lilac rings in the periphery of the plaques. The ages of the plaques ranged between one month and 10 years (average 3.7 years).

The skin biopsies were taken with a 3-mm manual punch, within the sclerotic areas of the plaques, in the peripheries of the plaques, and from the uninvolved skin of a symmetrical area (8 cases) or near the plaques (4 cases). The skin specimens were fixed in 6% glutaraldehyde in 0.2 M cacodylate buffer, pH 7.4, with 7.5% sucrose, then osmicated, dehydrated and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate and studied under a JEOL 100 CX electron microscope at 8 0 kV.

OBSERVATIONS

Of 39 nerves found in the biopsies, 33 were composed of several Schwann cells with axons and endoneurium enclosed by perineurium. One was myelinated, while the other 32 nerves were unmyelinated. Five of the 33 nerves were found within the sclerotic areas, 10 in the peripheral zones and 18 in uninvolved skin (Fig. 1). The changes in the 33 nerves differed in combinations of the findings in each component of the nerve tissue, as summarized in Fig. 1. Six of the 39 nerves consisted of single Schwann cells with axons without perineurium. They were found in both sclerotic plaques and lilac rings.

Axons and Schwann cells. Eight nerves showed degenerative products of cytoplasm such as vacuoles, lipid-droplets and accumulations of glycogen particles (Fig. 2). Thickenings and multiple layers of the basal lamina around the Schwann cells were also found. *Endoneurium.* Seventeen nerves

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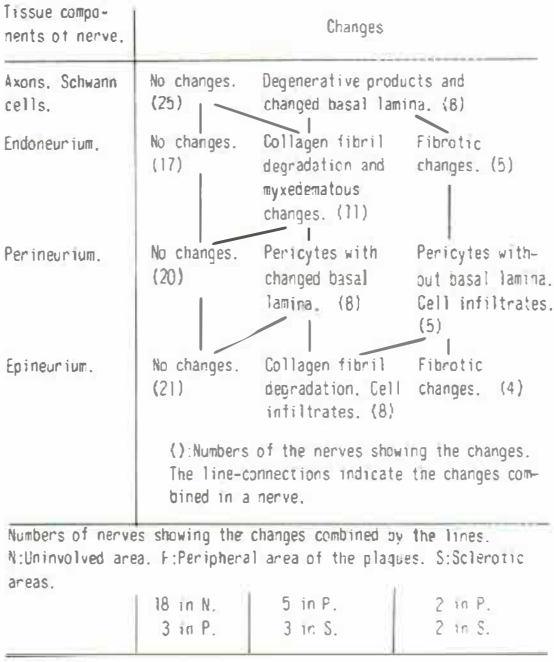


Fig. 1. The changes of nerves in morphea.

were unchanged. Luse bodies and elastic fibres (Figs. 2, 3) were also found. Eleven nerves showed glycosaminoglycan figures, amorphous material, and collagen fibrils with zig-zag margins in the widened interfibrillar space of the endoneurium (Fig. 2). Five nerves showed collagen fibrils with various diameters of their round or oval cut-surfaces, ranging from 30 to 130 nm (Fig. 3, 4). The axial periodicity was 60 nm. Disarranged fibrils were rarely found. *Perineurium.* Twenty nerves showed complete circles of perineurium. In some places the basal lamina of the pericytes was dislocated, and some were lacking on the endoneural surfaces of the perineurium. Eight nerves showed interrupted circles of perineurium. The pericytes of the perineurium (Figs. 2, 5) contained distinct granular endoplasmic reticula, ribosomes, pinocytotic vesicles, cytoplasmic filaments with cell-membrane thickenings and invaginated nuclei.

The basal lamina of the cells was thickened either partially or as a whole, and it also showed dislocation and interruptions. The other five nerves showed cytoplasmic structures of pericytes identical with those of the above described cells, but they lacked basal lamina completely (Figs. 3, 4). Such pericytes did not encircle the endoneurium. Plasma cells, lymphocytes and mast cells have migrated into the perineurium. *Epineurium.* Seven nerves showed dispersed bundles of collagen fibrils, granular material and collagen aggregates (Fig. 5 B). Five nerves revealed collagen fibrils with varying diameter of the round and oval cut-surfaces and with an axial periodicity of 60 nm. *Single Schwann cells with axons.* The nerves showed no endo- and perineurium (Fig. 6). Two of the six nerves presented degenerative products in the Schwann cells. The basal lamina of the Schwann cells partially enclosed the cell surfaces. Some of the nerves showed pericyte-like cells close to the Schwann cells. The cells contained granular endoplasmic reticula and cytoplasmic filaments, while no definite basal lamina was noted. The cells were seen enclosed by compact bundles of collagen fibrils.

DISCUSSION

The present study demonstrated that the mesenchymal components of peripheral nerves are involved in the sclerotic process. The changes were identical with those in dermis with myxedematous changes, collagen degradation, cell infiltration and abnormal fibrosis (12). Acid glycosaminoglycan figures in the widened spaces of the endoneurium represent myxedematous changes such as have been described in the dermis of localized sclero-

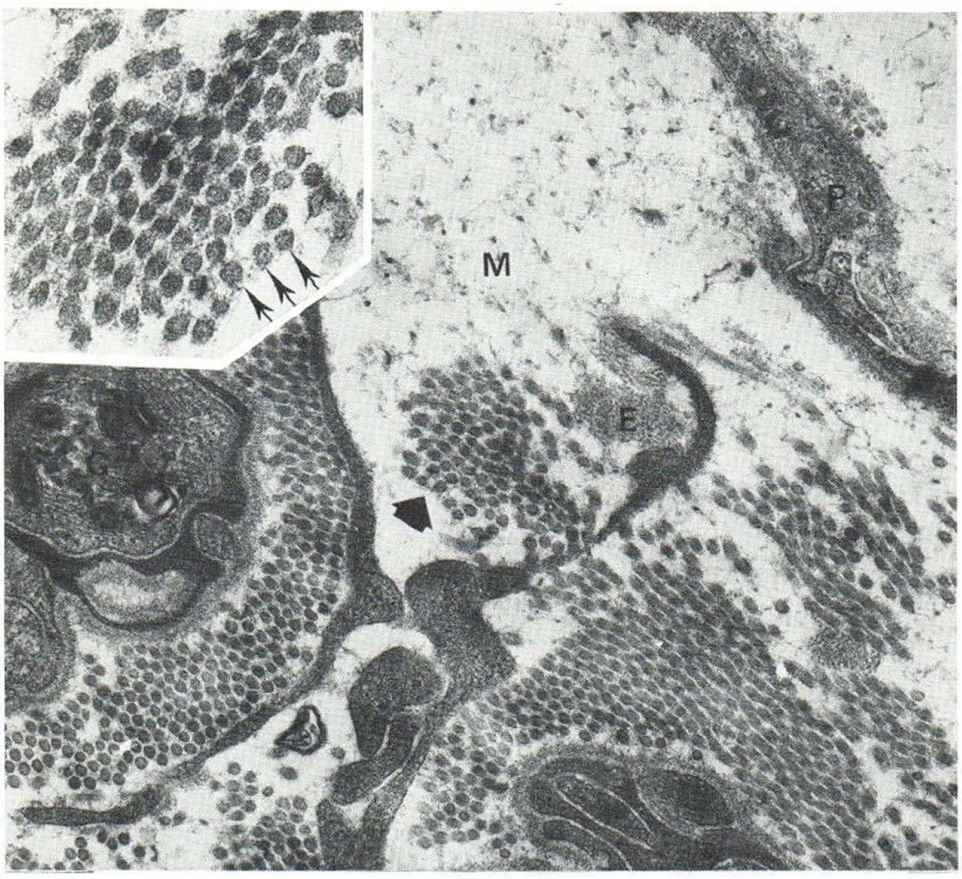
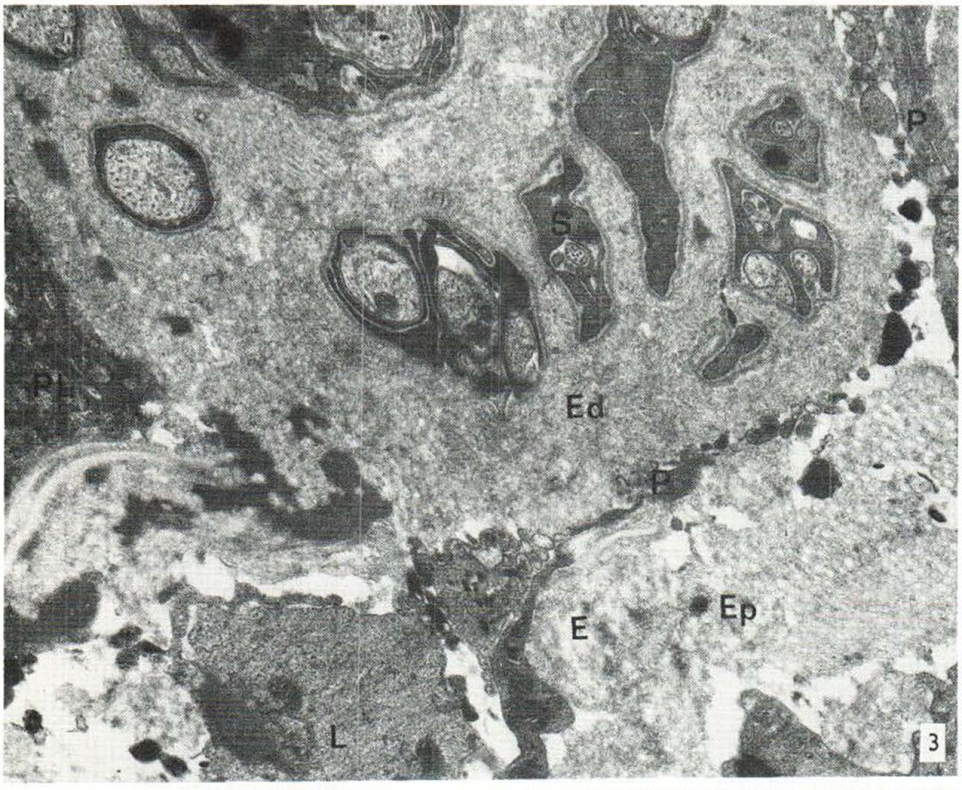


Fig. 2. A nerve shows glycogen particles (*G*) in the axon. Endoneurium is myxedematous (*M*) with numerous glycosaminoglycan figures. Pericytes (*P*) show irregular basal lamina, pinocytotic vesicles, ribosomes and granular endoplasmic reticula. Elastic fibres (*E*). The arrow-pointed area appears in the inset which show collagen fibrils with zig-zag margins (arrows). ×25 800, ×51 600 (inset).

derma (10, 12). The zig-zag margins of collagen fibrils have been shown in experiments of collagen fibril degradation by both bacterial and cellular collagenase (13). Collagen aggregates have been found in the dermis of various skin diseases such as inflammatory, degenerative and tumour conditions, as well as in experiments on culture and collagenase influence (7, 13). The aggregates represent in situ degradation of collagen fibrils by cells.

The dermis of scleroderma showed collagen fibrils having small (30–40 nm) and large (130–140 nm) diameters (3, 11, 12, 16). Thin collagen fibrils represent newly formed fibrils (2). Endoneural collagen fibrils of normal skin are 28–47 nm wide, while epineural fibrils are 40–80 nm wide (1). Sclerotic areas of scleroderma contained thick fibrils in the compact bundles (11, 12). The collagen fibrils in the dermis of the lilac ring also showed abnormal shapes such as unevenly thick and bifurcated fibrils and also disarranged fibrils (12). The present findings in the nerves are identical with those earlier reported in scleroderma, though disarrangements and abnormal shapes were not found in the present study.

Lymphocytes, plasma cells, macrophages, mast cells and fibroblast-like cells occurred in the cell infiltrates, in agreement with other studies (4, 12). The perineural cells with



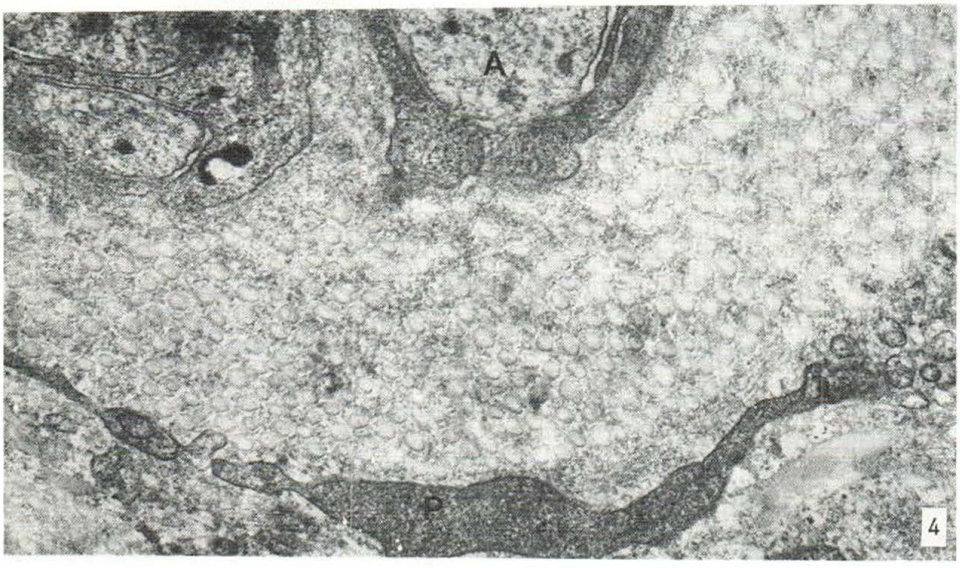


Fig. 3. A nerve with cell infiltrate of plasma cells (*PL*) and lymphocytes (*L*). Pericytes (*P*) have no basal lamina and show their interrupted circle around the nerve. The collagen fibrils of the endoneurium are thinner than those of the epineurium, though the collagen fibrils in both parts show variations in diameter. Elastic fibres (*E*). Schwann cells (*S*). Endoneurium (*Ed*). Epineurium (*Ep*). ×13 050.

Fig. 4. A nerve showing endoneural collagen fibrils of varying diameter. Pericytes (*P*) show neither basal lamina nor cell contact to the neighbouring pericytes. Axon (*A*). ×26 100.

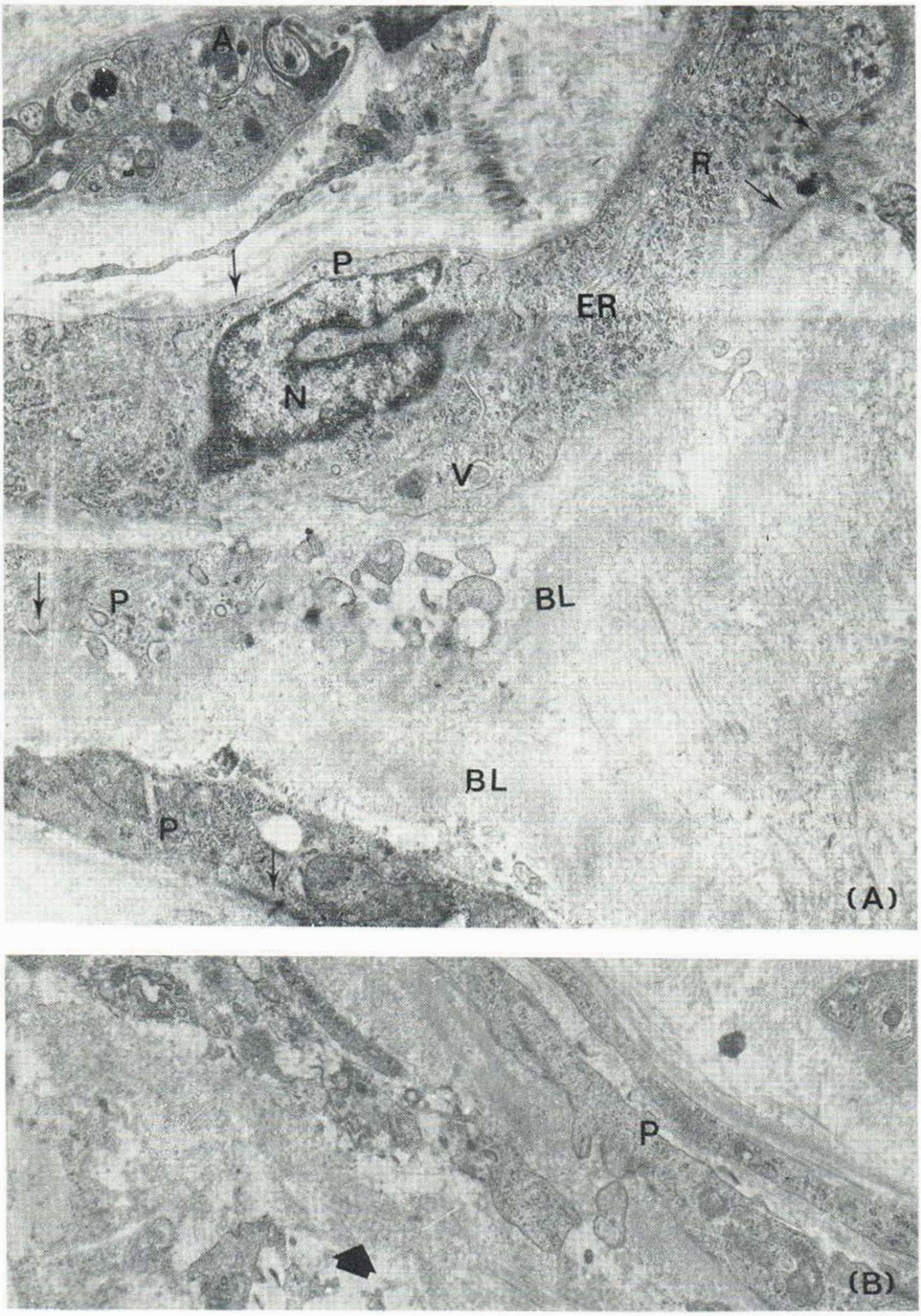


Fig. 5. A: A nerve with pericytes (*P*) showing an invaginated nucleus (*N*), numerous granular endoplasmic reticula (*ER*), ribosomes (*R*), pinocytotic vesicles (*V*), intracytoplasmic filaments with cell membrane thickenings (arrows). Basal lamina of the epineural surface (*BL*) is thickened, dislocated and interrupted. Axon (*A*). B: Epineurium of the same nerve, showing collagen aggregates (arrow). Pericytes (*P*). ×13 200.

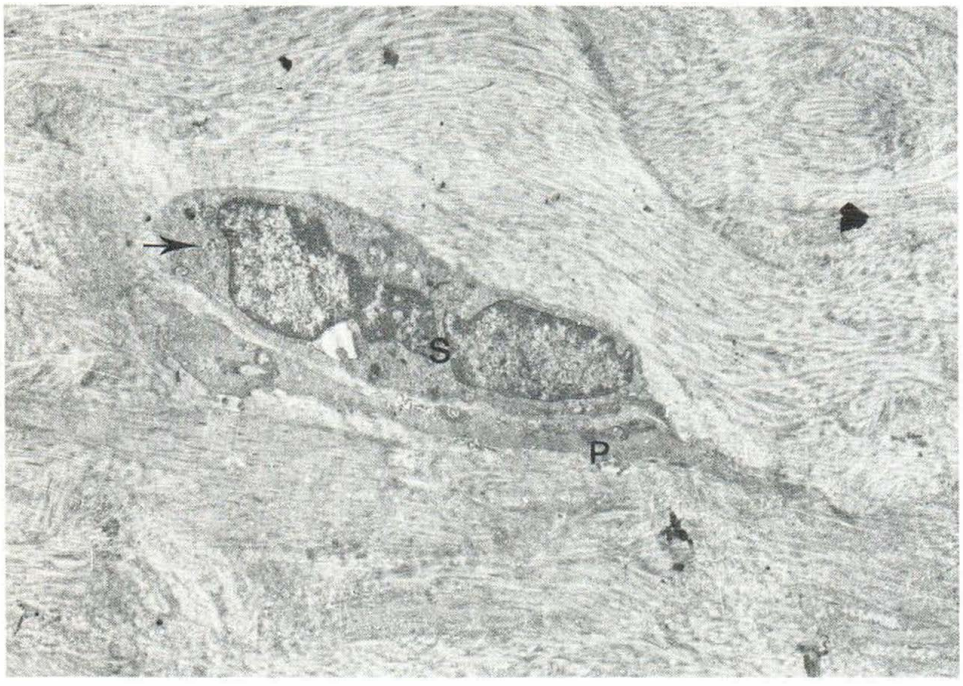


Fig. 6. A Schwann cell (*S*) with axons (arrows) and a cell without basal lamina, assumed to be a pericyte (*P*), is enclosed in compact bundles of collagen fibrils. ×5280.

ribosomes, granular endoplasmic reticula and changes of basal lamina suggesting increased activity were noteworthy in the pathological processes. Perineural cells are of mesenchymal origin. The cells in adult nerves have no cytoplasmic characteristics of either fibroblasts or Schwann cells; the cells were considered primitive smooth muscle cells (15). Polyribosomes, granular endoplasmic reticula and pinocytotic vesicles characteristic of fibre-forming cells were also noticed in the perineural cells (15). In regenerating peripheral nerves after crushing, fibroblast-like cells around axons and Schwann cells gradually are transformed into typical perineural cells with basal lamina (14). In cutaneous nerves of 14-week-old human embryos, the perineurium was composed of collagen fibrils and flattened fibroblast-like cells without basal lamina (6). In morphea, fibre-forming cells have cytoplasmic characters of both pericytes and fibroblasts. The cells were identified as myofibroblasts (18). Myofibroblasts secrete collagen type I and III and are assumed to originate from perivascular cells, not from smooth muscle cells. Stem cells in perivascular areas have been suggested to be the source (17). As to ultrastructure, perineural and perivascular cells are identical (pericytes). In organ culture of human adult skin, fibroblast-like cells grow from pericytes of vessels and nerves (8). The fibroblast-like cells in vitro are known to be of mesenchymal origin (5), and so are myofibroblasts (17). The present findings suggest that pericytes of nerves are precursors of myofibroblasts in morphea.

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