Virchows Arch. Abt. A Path. Anat. 350, 166—178 (1970)

Scleroderma Hyalopathy*

J. GÄRTNER

Univ.-Augenklinik Mainz (Direktor: Prof. Dr. A. Nover)

Received January 26, 1970

Summary. One of the eyes of a 46-year old patient, suffering from scleroderma for 7-years, was examined electronmicroscopically. Corresponding to the slit-lamp and ultrasonic findings six months before death, a severe destruction of the vitreous body with marked fibrosis was found. The similarity of these changes to those observed in the perivascular space of the retinal vessels is discussed.

Zusammenfassung. Ein Auge eines 46 Jahre alten, seit 7 Jahren an Sklerodermie erkrankten Patienten wurde elektronenmikroskopisch untersucht. Entsprechend den biomikroskopischen und echographischen Befunden 6 Monate vor dem Tod, ergab sich eine schwere Glaskörperdestruktion mit deutlicher Fibrose. Die Ähnlichkeit dieser Veränderungen mit denjenigen, die im perivasculären Raum von Netzhautgefäßen beobachtet wurden, wird diskutiert.

Changes of the vitreous body in scleroderma (progressive systemic sclerosis) have already been demonstrated in biomicroscopic and ultrasonic studies. The eyes of 10 patients with progressive systemic sclerosis showed in 8 cases a destruction of the vitreous body, which was either premature in beginning or more progressed in advanced age (Gärtner, Löpping and Holzmann, 1967; Gärtner and Löpping, 1968).

The present paper deals with electronmicroscopic observations on the vitreous body and on the retinal vessels of one of the cases reported in the papers cited above.

Case Report

A 46-year old man (case 3; Gärtner, Löpping and Holzmann, l. c.) suffered from progressive systemic sclerosis since 7 years. He had typical cutaneous symptoms of scleroderma. No visceral manifestations were evident until one month before the death. In the last year of his life, he was treated with 1 mg Celestan and 15 mg Primolut-Nor dayly.

From the side of the eyes, the patient has always been in good health with exception of a keratitis on the right eye in early childhood. Six months before death, when he was seen in the eye hospital, only occasionally mouches volantes were complained. Visions were as follows: OD, $5/20+1{,}0+1{,}5$ axis $0°=5/12$ (old corneal scar); OS, $5/3+0{,}5=5/3$. The lens was clear. Fundus examination revealed no pathological signs; especially the vessels were normal. Vitreous study revealed a remarcable destruction, comparable to the senile vitreous body destruction in advanced senile age. The objective evaluation of the vitreous body destruction was possible by means of A-mode ultrasonography. The echogram of both eyes showed numerous echoes within the zero-line representing the vitreous space (Fig. 1).

* Supported by the „Deutsche Forschungsgemeinschaft".

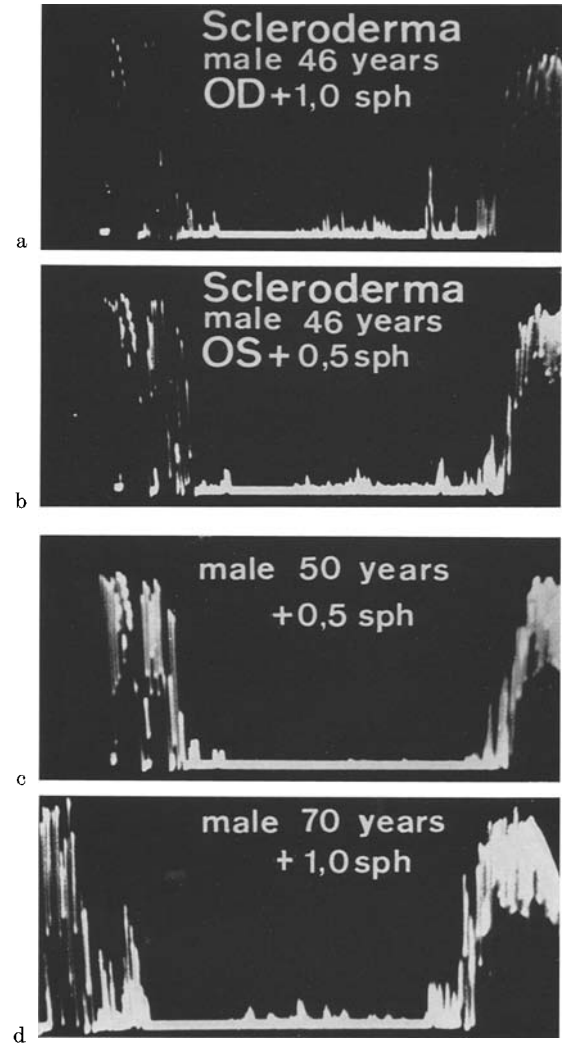

Fig. 1a—d. Discleral echograms from both eyes of a patient suffering from scleroderma (a, b). For comparison: Echograms of two healthy persons (c, d). The long zero line represents the vitreous space. In the echograms of the sclerodermic eyes, this line shows numerous echo peaks very close to each other. This is caused by a severe vitreous body destruction, similar to the senile vitreous body destruction of the 70-years old man (d). Within the zero line of the echogram of the 50-years old man, representing a practically undestructed vitreous, only very few small echoe peaks appear (c). A-mode machine, Kretztechnik Model 7,000. Transducer with a frequency of 6 Mc. *Abbreviations: BM* basement membrane, *CL* capillary lumen, *MC* Müller cell, *NPE* nonpigmented ciliary epithelium, *PVS* perivascular space, *VB* vitreous body

One month before death, suddenly symptoms of uremia with severe hypertension developed. The blood pressure, formerly 140/70, raised on 240/140 mm Hg. Fundus examination showed the picture of a retinitis angiospastica. The patient was treated with Ismelin and

Presinol. There was a diminution in blood pressure until death, but the patient remained oliguric and uremic, and died with severe respiratory and cardiac insufficiency.

Necropsy. Histologic sections of the lung showed interstitial fibrosis. Pleural fibrosis was present. The heart weighed 550 gm (body weight 75 kg). It showed marked left ventricular hypertrophy. Acute-subacute glomerulonephritis. Fibrosis of the testes. Uncommon granulomas of the liver, partially with giant cells. Gynecomastica after therapy with gestagens.

The brain showed marked edema. Spotlike fibrosis of the leptomeninges. Fibrosis of the adventitial structures of the brain- and meningeal vessels. Homogeneous appearance of the wall of the brain vessels, especially of the arterioles. Perivascular sponginess, partially as a result of the edema, partially in the form of glial microscars (beginning status cribriformis).

Method

The left eye of the patient was obtained seven hours after death. Immediatly after the enucleation, the eye was immersed in ice-cold Ringer solution and opened by an equatorial incision. The portion containing the ora serrata was further dissected, so that flat pieces including choroid, pars plana and peripheral retina were isolated. These specimens were then fixed in 2% Zetterquist-buffered osmium tetroxide, dehydrated in a graded series of acetone, embedded in durcupan (Fluka), sectioned on a Reichert ultramicrotome Om U2 and photographed with an electron microscope Zeiss EM 9 A.

Only the changes of the loose connective tissue in the vitreous body and in the perivascular space of the retinal vessels interested for this investigation. Therefore the post-mortem time factor could be neglected. It is known, that post-mortem autolysis does not necessarily occur very rapidly after the death (Pease, 1964; Pau Lussen and Hübner, 1966). Especially this is the case with the post-mortem changes of the collagen. In our material, the fibroblasts of the vitreous body cortex show a remarkable good preservation of the cell organelles (see Fig. 6).

Observations

The peripheral retina and the pars plana epithelium show large clefts and vacuoles and wide empty spaces between the Müller cells resp. the nonpigmented epithel cells. Typical peripheral cystic degenerations are not visible.

The vitreoretinal basement membrane on both sides of the ora serrata is 450—700 A thick; including the lamina rara. On the pars plana side it is multilayered, as it is frequently observed in the region of the pars plana of aged human eyes (Gärtner, 1966a). On both sides of the ora serrata are defects and fragmentations in the course of the basement membrane. The fragmented basement membrane material scatters about in the neighbouring vitreous body cortex.

The fine collagen fibrils (vitrosin fibrils) of the vitreous cortex on both sides of the ora serrata form a more or less loose network. At many places they are rather densely packed, so that they seem to be increased in number. Their arrangement is irregular, as it is otherwise observed in the vitreous of senile eyes (Figs. 2,3). The single fibrils have a diameter of approx. 80 Å. A faint, indistinct cross-striation is visible. The intervals between the bands are difficult to measure; their length is 50—100 Å (Fig. 4). No over-period is evident. There is no difference in the structure of the fibrillar network on both sides of the ora serrata. At some places over the posterior part of the pars plana, zonular fibres are intermingled with the fibrillar network of the vitreous body cortex. They consist of fibril-bundles, which are either densely packed or are in a more loose connection with each other (Fig. 5). The single fibrils have the same appearance and show the

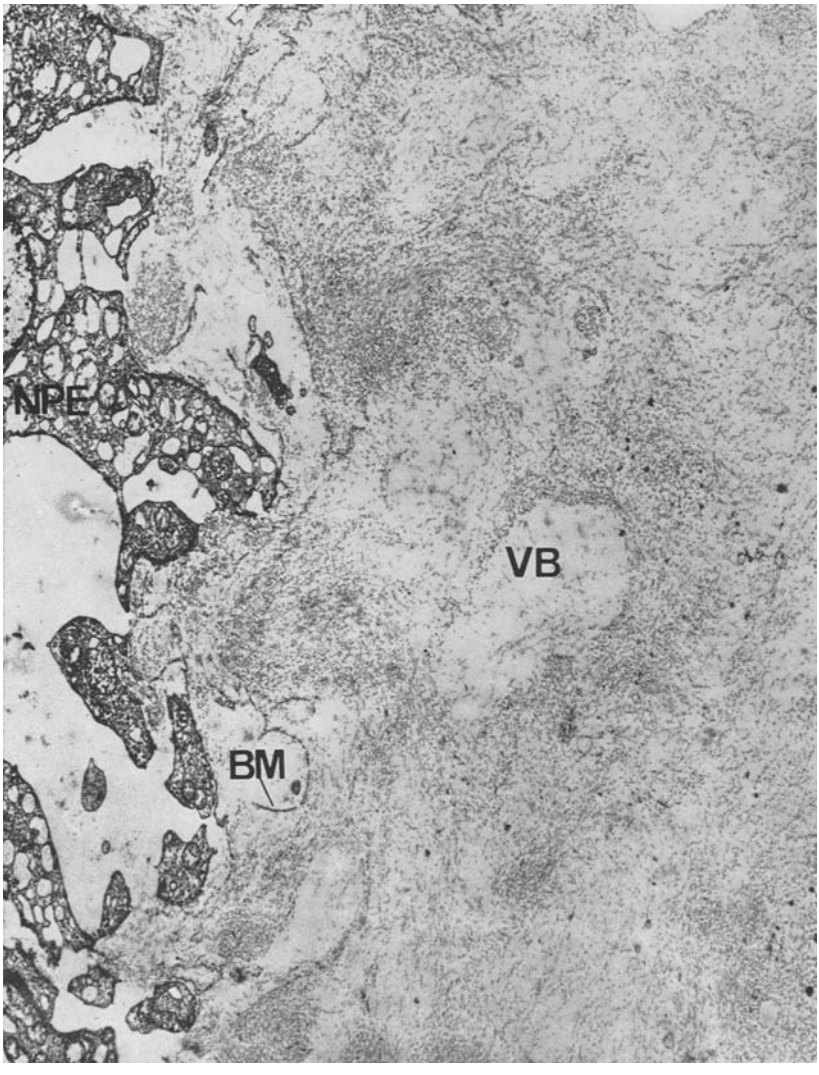

Fig. 2. Ora serrata region, pars plana side. The basement membrane is fragmented and detached at many places. The fibrillar network of the vitreos body cortex shows an irregular texture with spotlike densifications. Uranyl-acetate permanganate. 5,000:1

same type of cross-striation as those of the surrounding vitreous body cortex. The length of the individual intervalls between the bands varies between 50 and 120 Å. Within the closely packed fibril-bundles, overperiods of approx. 400 Å are visible.

The cells in the vitreous body cortex have the appearance of typical fibroblasts. The cytoplasm contains numerous vesicles, a well developed rough-surfaced endoplasmic reticulum, free ribosomes, secretory granules and mitochondria with

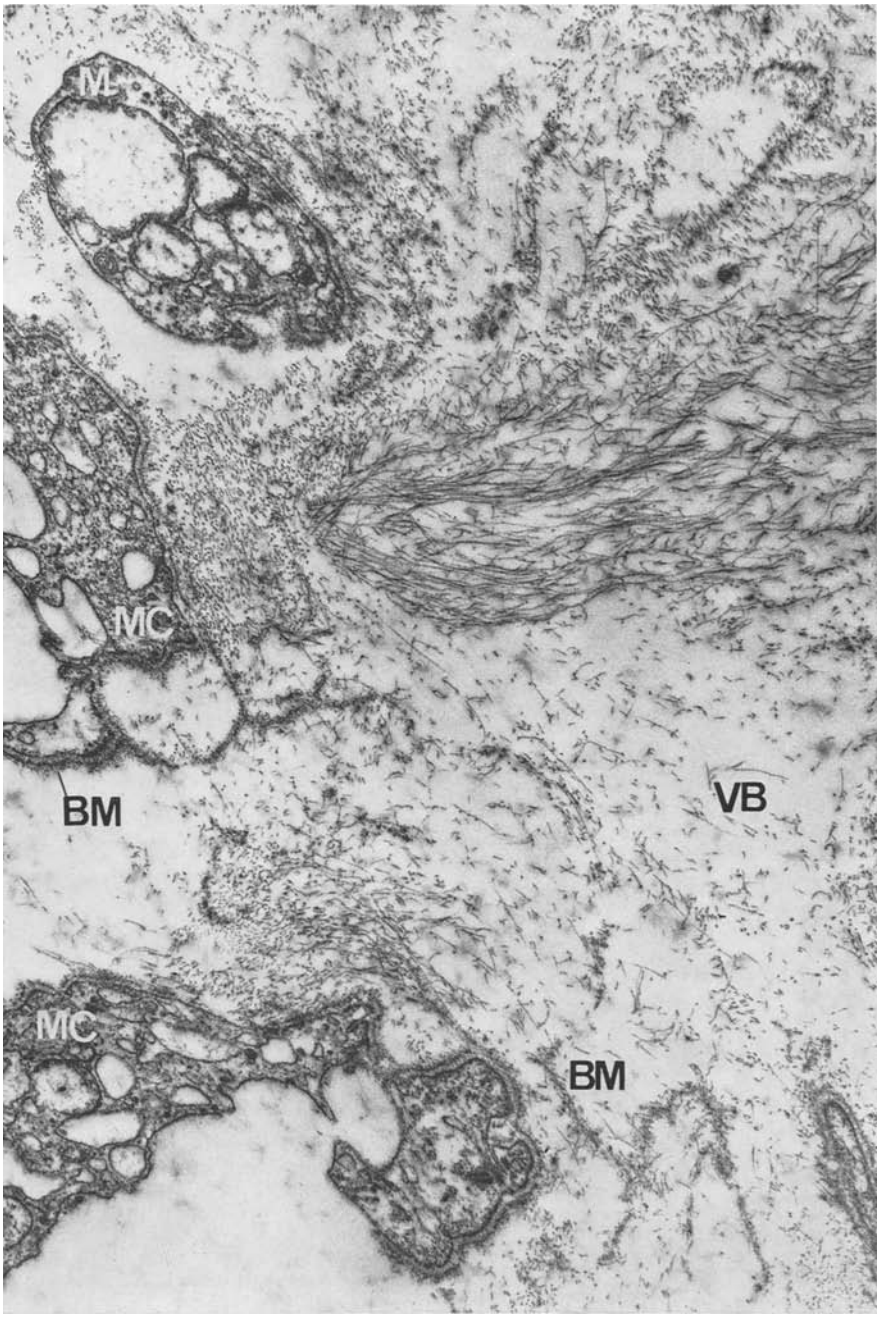

Fig. 3. Ora serrata region, neural retinal side. The changes of the marginal glial cells (atypical Müller cells) and of the vitreous cortex are very similar to those found anterior to the ora serrata. Uranyl-acetate permanganate. 21,000:1

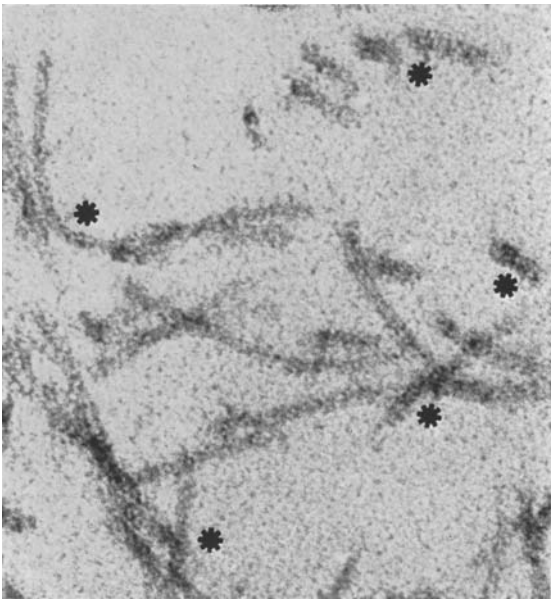

Fig. 4. Ora serrata region, pars plana side. Vitrosin fibrils. The fine structure of the single fibrils seems to be unaffected by the patient's disease. Their diameter is fairly constant. At some places axial periodicity should be noted (asteriks). Uranyl-acetate permanganate. 240,000:1

cristae mitochondriales. Also the outer membrane of the nuclear envelope is in good preservation. Much of the cells show numerous vitrosin fibrils adhering to the cell membrane (Fig. 6).

In the peripheral neural retina, near the ora serrata, some capillaries and venules could be examinated.

Contrary to the findings in infants and normal adults, the outer surface of the capillary basement membrane is not in direct contact with the basement membrane of the surrounding glial elements. Between the capillary basement membrane and the surrounding glial cells extends a rather large perivascular space, filled with abundant fine fibrils (Figs. 7, 8). Small islands of electron-dense, fine granular substances and the remains of damaged cells are scattered throughout the fibrillar network. The fibrils have the same diameter and the same type of cross-striation as the fibrils in the vitreous body cortex, including the single fibrils of the zonular fibres. At some places they form closely packed fascicular bundles (Fig. 8).

The capillary basement membrane is not remarkably thickened.

The findings at the venules, where a perivascular space normally exists, correspond to the findings at the capillaries. The perivascular space is filled with abundant fine fibrils, much greater in number than it is the case in normal eyes of the same age.

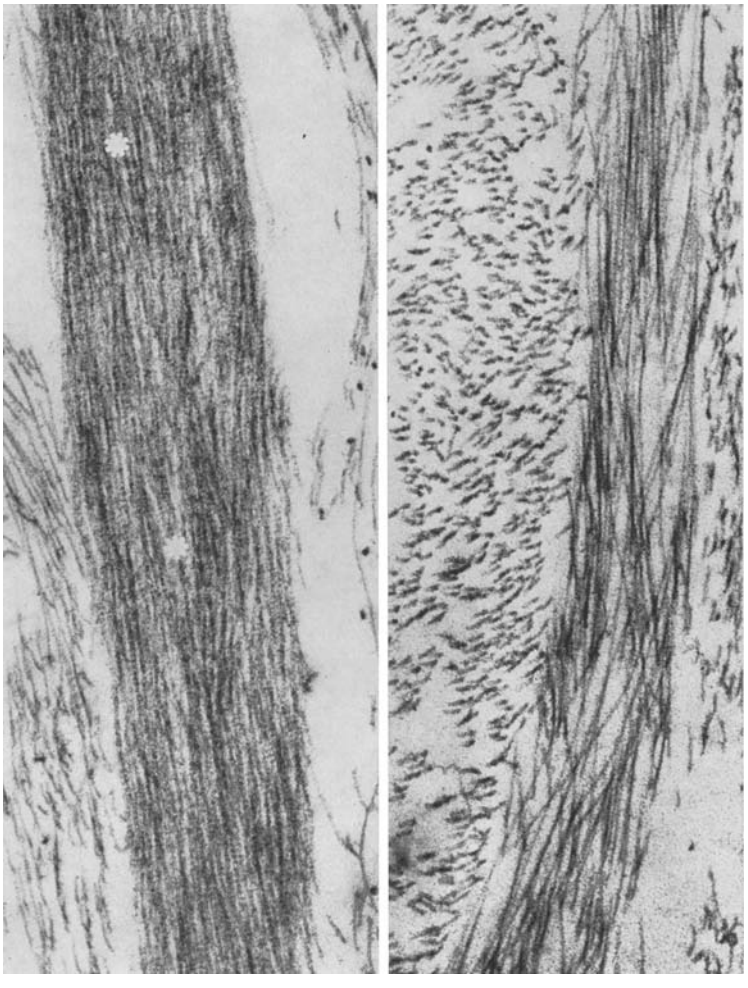

Fig. 5. Ora serrata region, pars plana side. Zonular fibres, consisting of bundles of fine fibrils. The single fibrils are not distinguishable from the vitrosin fibrils. One of the fibres appears to be unaffected by the patient's disease. Over-periods of 400 Å are evident (asteriks). The other fibre shows a very loose connection of its fibril-bundles. Uranyl-acetate permanganate. 60,000:1

The continuity of the glial basement membrane around the perivascular space of the capillaries and the venules is interrupted at many places. Fragmented basement membrane material scatters about in the neighbouring perivascular space.

Discussion

As a part of the mesenchymal tissue the vitreous body may be involved in systemic disorders, manifested by connective tissue and/or vascular alterations (Gärtner and Löpping, 1968). This is the case with arteriosclerosis, resulting in the fibrosis both of the retinal perivascular space and of the vitreous body cortex,

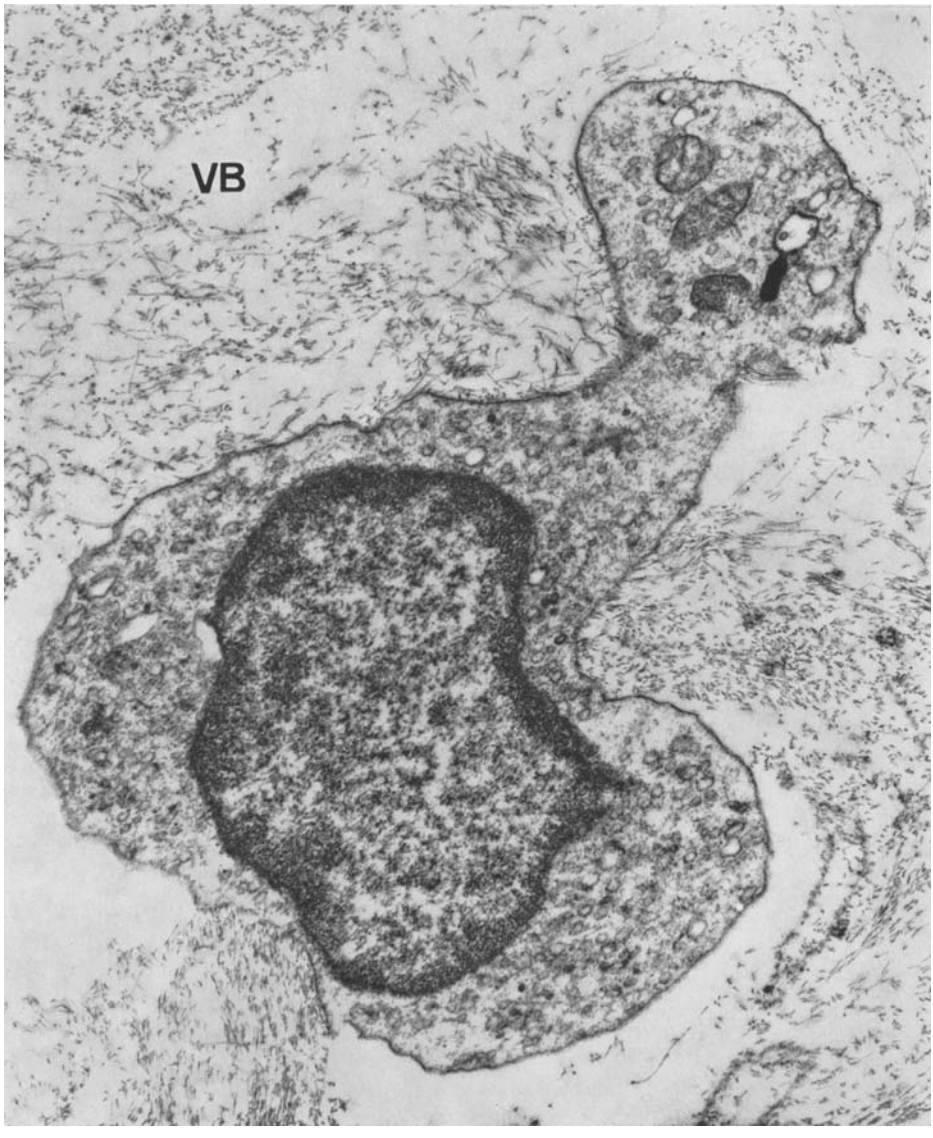

Fig. 6. Ora serrata region, pars plana side. Fibroblast of the vitreous body cortex. Uranyl-acetate permanganate. 21,000:1

and this may also be the case with scleroderma. It must be called in mind, that the sclerogenic factors in arteriosclerosis do not only involve the connective tissue of the vessels (Hauss, Junge-Hülsing, Gerlach, 1968) and that, on the other hand, scleroderma may be regarded as a progressive systemic sclerosis, or as a sclero-vasculopathy (Korting and Holzmann, 1967).

In advanced arteriosclerosis of the retina each capillary contains numerous fine fibrils in a pathologically developed perivascular space (Ikui, Mimatsu, Sugu

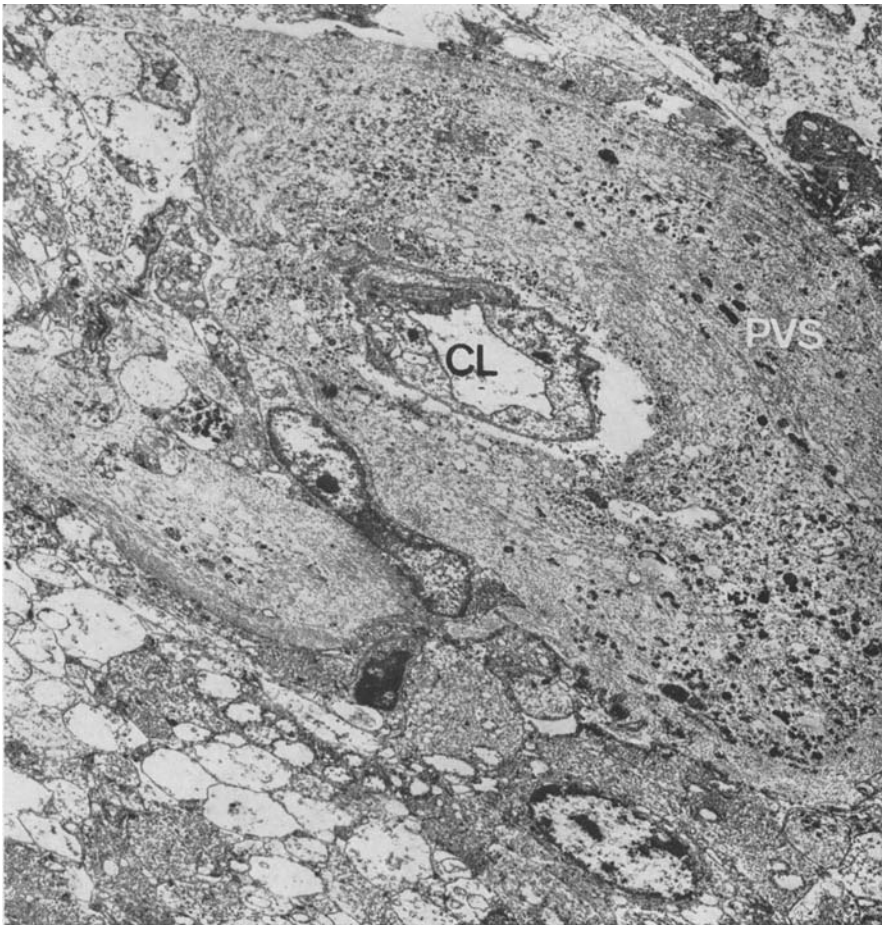

Fig. 7. Ora serrata region, neural retinal side. Retinal capillary. A pathological perivascular space has developed. It is filled with abundant fine fibrils. The perivascular neuropile shows marked edema and, at other places, an increased number of glial filaments. Uranyl-acetate permanganate. 5,000:1

and Tominaga, 1964; Gärtner, 1966b; Irinoda, Matsuyama, Kimura and Tamara, 1967). In the vitreous body cortex of such eyes similar changes are observed: The regular network of the vitrosin fibrils at many places is transformed into a very irregular texture of densely packed fibril aggregations, clinically known as "senile vitreo-retinal adhesions". Thus the fibrosis in the retinal perivascular space and in the vitreous body cortex of senile arteriosclerotic eyes may be regarded as correlated lesions, probably resulting from an alteration in the ground substance-fibril relation (Gärtner, 1965a, 1967, 1970a).

It is now commonly accepted, that the mature collagen fibres in sclerodermatous tissue are normal, but that there exists a quantitative increase in fine collagen fibrils from the type of the microfibrils. Possibly, an alteration of a ground

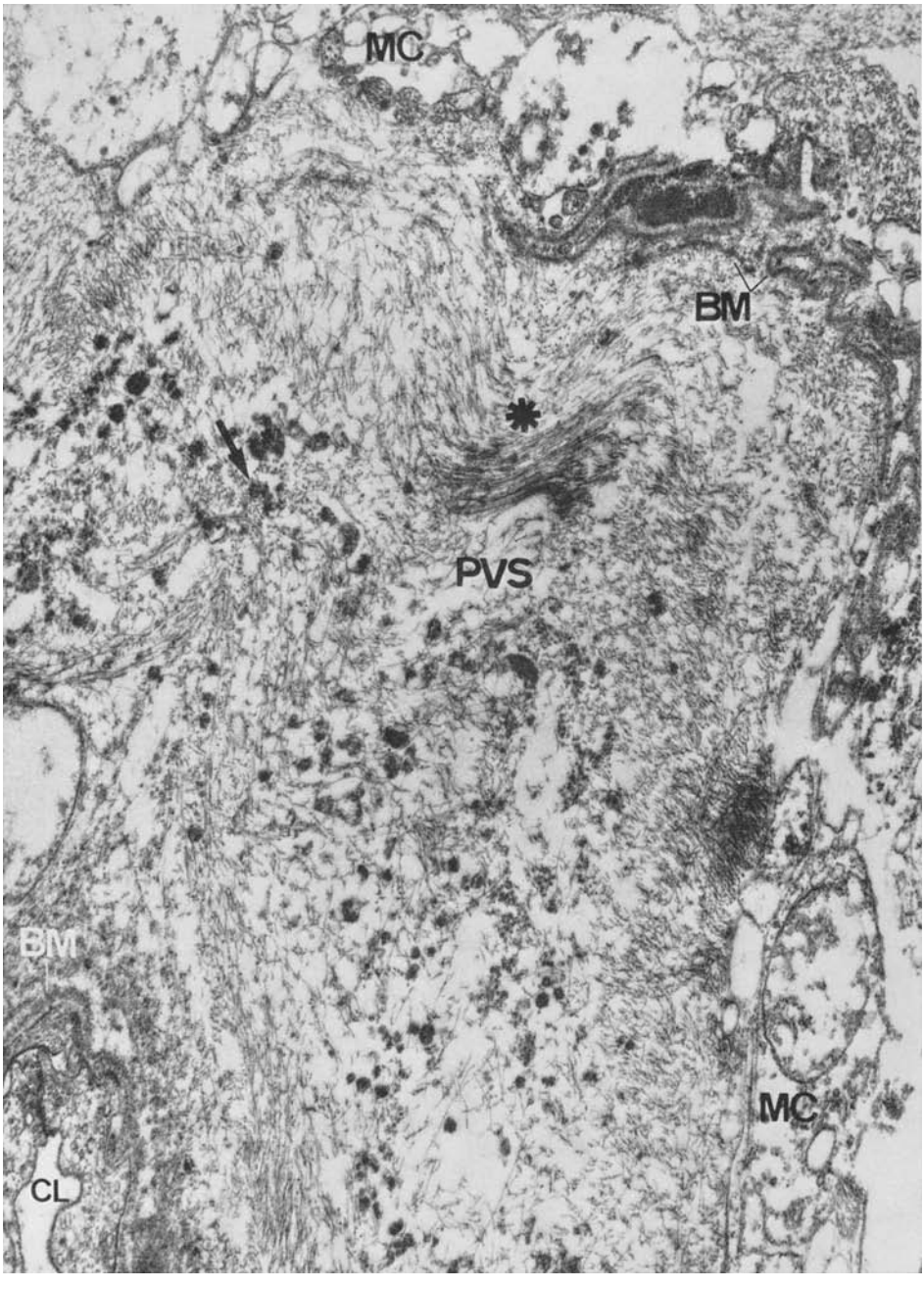

Fig. 8. Ora serrata region, neural retinal side. The pathological perivascular space around a retinal capillary is filled with abundant fine fibrils. At some places, they form densely packed bundles, which are sectioned transversally (arrow) or in longitudinal direction (asterik). Uranyl-acetate permanganate. 21,000:1

substance component such as a polysaccharide protein complex in combination with collagen may be the primary lesion (see Sackner, 1966; Korting and Holzmann, l. c.). As well as in arteriosclerosis, this could explain the fibrotic alterations both in the vitreous body and in the perivascular space.

After the results of the biomicroscopic and ultrasonic examination six months before the patient's death, the destruction of the vitreous body must have been present already at this time. As to the fibrosis of the perivascular space, ophthalmoscopy six months before the patient's death revealed no pathologic findings. This is no proof against a possible manifestation of the capillary and venous changes at this time, because the fundus periphery was not examinated. It is known, that the capillary blood flow to the skin is greatly reduced in scleroderma.This is assumed to be the result of an increase in collagen which produces obliteration of the arterioles and capillaries (Brown, O'Leary and Adson, 1930). Study of the renal histology in patients with scleroderma dying from nonrenal causes revealed a strikingly high incidence of renal vascular sclerosis (Sackner, l. c.). It our opinion, it seems therefore more reasonable to relate the severe perivascular fibrosis to scleroderma than to the terminal hypertension. Ashton, Coomes, Garner and Oliver (1968) suggest, that the retinopathy of scleroderma may be due to hypertensive damage potentiated by the underlying connective-tissue process.

As shown by lightmicroscopic (Dejean, 1958; Pau, 1969) and electronmicroscopic (Gärtner, 1965b, 1969, 1960b, 1970c) investigations, the zonule fibres are a special differentiation of the vitreous body framework, that is of collagen. Therefore alterations of the fine structure of the zonular fibres in scleroderma should be expected.

In our case, most of the fibril-bundles of the zonula (possibly "vitreozonules", Kaczurowski, 1967) appear without pathological changes. Other zonular fibres show a very loose aggregation of their fibrillar subunits. This may be an effect of the elastic properties of the zonular fibres, but could also be caused by the supposed alteration of the interfibrillar ground substance in sclerodermatous connective tissue. By slit-lamp examination, in the present case as well as in the other cases of our series clinically no displacement of the lenses was observed. However, bilateral subluxation of the lens possibly related to scleroderma is reported by Sackner (l. c.) in the case of a 51 year old female negro.

It seems of interest, that in the present case interstitial and perivascular amyloid was found not in the skin, but in other organs: Thyroid, mammary gland, testis, epididymis, and sceletal musculature (Holzmann, Korting and Missmahl, 1969). Histochemical procedures used for the identification of amyloid were no more possible in our material. Electronmicroscopically, the fascicles of microfibrils within the perivascular space of some retinal vessels seem not unlike to the fascicles of filaments, identified as amyloid in the so-called "drusige" degeneration of the arteries of the cerebral cortex in old age (Schlote, 1965).

The ophthalmic manifestations of scleroderma lately have been reviewed by Stucchi and Geiser (1967) and by Horan (1969). Changes of the vitreous are not reported in these papers. Our clinical and electronmicroscopical observations give evidence, however, that vitreous body destruction with fibrosis must be regarded as one of the features of this systemic disease.

I am grateful to Prof. Korting, Univ.-Hautklinik Mainz, for allowing me to examine the clinical notes of the patient. Prof. Bredt and Prof. Hempel, Pathologisches Institut der Universität Mainz, kindly permitted me to examine the post mortem findings of the present case.

References

Ashton, N., Coomes, E. N., Garner, A., Oliver, D. O.: Retinopathy due to progressive systemic sclerosis. J. Path. Bact. **96**, 259—268 (1968).

Brown, G. E., O'Leary, P. A., Adson, A. W.: Diagnostic and physiologic studies in certain forms of scleroderma. Ann. intern. Med. **4**, 531 (1930) (Cited by Sackner).

Dejean, Ch.: Embryologie du corps vitré. In: Ch. Dejean, G. Leplat et Fr. Hervouet, L'embryologie de l'oeil et sa tératologie. Paris: Masson & Cie. 1958.

Gärtner, J.: Die Feinstruktur der Glaskörperrinde des menschlichen Auges an der Ora serrata im Alter. Albrecht v. Graefes Arch. klin. exp. Ophthal. **168**, 529—562 (1965a).

— Elektronenmikroskopische Untersuchungen über Glaskörperrindenzellen und Zonulafasern. Z. Zellforsch. **66**, 737—764 (1965b).

— Die Feinstruktur der Netzhaut des menschlichen Auges im Gebiet seniler peripherer cystoider Degenerationen. Albrecht v. Graefes Arch. klin. exp. Ophthal. **169**, 38—61 (1966a).

— Elektronenmikroskopische Beobachtungen zur Morphologie der Blut-Hirnschranke an Netzhautgefäßen des Menschen. Albrecht v. Graefes Arch. klin. exp. Ophthal. **171**, 134—161 (1966b).

— Beziehungen zwischen Fundusdiagnostik und Elektronenmikroskopie, dargestellt am Beispiel der Glaskörperrinde in der Ora-serrata-Gegend. Mod. Probl. Ophthal. **5**, 154—169 (1967).

— Die vitreoretinale Grenzschicht und ihre Bedeutung für die Pathogenese der Netzhautabhebung. In: Amotio retinae. Bücherei des Augenarztes, Heft 53, hrsg. von W. Doden. Stuttgart: Ferd. Enke 1970a.

— The fine structure of the zonular fibre of the rat. Development and aging changes. Z. Anat. Entwickl.-Gesch. **130**, 129—152 (1970b).

— The fine structure of the zonular fibre of the human eye. With special reference to the aging changes. (In preparation.) (1970c).

— Löpping, B.: Der Glaskörper bei systematischen Bindegewebsveränderungen. Untersuchungen mit Ultraschall. Ber. dtsch. ophthal. Ges. **68**, 40—44 (1968).

— — Holzmann, H.: Über Glaskörperveränderungen bei Sklerodermie. Arch. klin. exp. Derm. **229**, 110—116 (1967).

Hauss, W. H., Junge-Hülsing, G., Gerlach, U.: Die unspezifische Mesenchymreaktion. Zur Pathogenese der reaktiven Mesenchymerkrankungen. Stuttgart: W. Thieme 1968.

Holzmann, H., Korting, G. W., Missmahl, H. P.: Perikollagene Amyloidablagerung in Haut und inneren Organen bei Sklerodermie. Klin. Wschr. **47**, 390—391 (1969).

Horan, E. C.: Ophthalmic manifestations of progressive systemic sclerosis. Brit. J. Ophthal. **53**, 388—392 (1969).

Ikui, H., Mimatsu, T., Sugi, K., Tominaga, Y.: Histological studies of vascular changes in the retina in hypertension. Light and electron microscopic investigations. Jap. J. Ophthal. **8**, 35—62 (1964).

Irinoda, K., Matsuyama, S., Kimura, T., Tamura, H.: Some aspects of fundus changes in hypertension. XX Concilium Ophthalmologicum Germania 1966, Acta Pars I, p. 237—248 (1967).

Kaczurowski, M. I.: The surface of the vitreous. Amer. J. Ophthal. **63**, 419—428 (1967).

Korting, G. W., Holzmann, H.: Die Sklerodermie und ihr nahestehende Bindegewebsprobleme. Stuttgart: G. Thieme 1967.

Pau, H.: Die Struktur des Glaskörpers in Beziehung zu embryonalen Blutgefäßen und Glaskörperrindenzellen. Albrecht v. Graefes Arch. klin. exp. Ophthal. **177**, 261—270 (1969).

Paulussen, F., Hübner, G.: Feinstrukturelle Untersuchungen an formalinfixiertem Sektionsmaterial. Zbl. allg. Path. path. Anat. **109**, 557 (1966).

Pease, D. C.: Histological techniques for electron microscopy, 2nd ed. New York and London: Academic Press 1964.

Schlote, W.: Amyloidnatur der kongophilen, drusigen Entartung der Hirnarterien. Acta neuropath. (Berl.) **4**, 449—468 (1965).

Stucchi, C. A., Geiser, J. D.: Manifestations oculaires de la sclerodermie generalisée. Docum. ophthal.('s-Grav.) **22**, 72—110 (1967).

Prof. Dr. J. Gärtner
Univ.-Augenklinik
D-65 Mainz
Langenbeckstr. 1