Acta Dermatovener (Stockholm) 50: 355–373, 1970

PSEUDOXANTHOMA ELASTICUM

A Clinico-pathological Study

Lis Danielsen, Takasi Kobayasi, Hans-Walther Larsen, Knud Midtgaard and Hans Ewald Christensen

From the Departments of Dermatology, Ophthalmology and Pathology, Rigshospital, University of Copenhagen, Denmark

Abstract. Nine patients (group 1) with skin lesions typical of pseudoxanthoma elasticum (PXE) and 3 patients (group 2) with angioid streaks without visible skin eruptions were examined. *Clinical findings.* Besides the typical skin lesions 1 patient of group 1 showed lesions on the oral mucosa. Frequent appearance of vascular disease was observed in both groups, and gastro-intestinal hemorrhage in 2 patients of group 1. *Ophthalmoscopical findings.* All 12 patients had angioid streaks, 6 presented *peau d'orange* configuration, 2 had salmon spots and 6 had macular changes. The final stage with diffuse choroidal sclerosis and atrophy was not represented in this material. No differences were observed between the two groups. *Light microscopic findings.* The skin specimens from all the patients of group 1 and 1 patient of group 2 showed characteristic changes of the elastic tissue and calcification. The finding of calcification also in evidently normal elastic fibers indicate that calcification is the primary event in PXE. A reduced amount of normal collagen fibers and a large amount of reticulin fibers were observed in the lesions. This alteration is considered secondary to the elastic tissue changes. The gastric wall from 1 patient of group 1 showed calcification of the internal elastic lamina of the smaller arteries, dilation of the veins and capillaries and a mucosal erosion. *Electron microscopic findings.* The skin specimens from all the patients of group 1 and 1 patient of group 2 showed pronounced changes of elastic tissue. Extremely dense material, probably calcification, was present in the elastic fibers. The calcification occurred inside the elastic fibers. As no previous elastic fiber degeneration was observed inside the PXE lesions, these studies also support the notion that calcification is considered the primary lesion in PXE. Compact or loose masses of a thready material were found surrounding some of the altered elastic fibers. This material closely resembles fibrin, despite the absence of banding. Many collagen fibrils in the areas around the calcified elastic fibers and inside the thready material showed twisting and often they were irregularly arranged. These collagen changes are considered to be secondary to elastic tissue changes, or to the occurrence of the thready material.

The term pseudoxanthoma elasticum (PXE) is now used for a systemic disease particularly involving the skin, the eyes and the cardiovascular system (40). The condition shows a heredity of recessive type (16 *b*).

In this disease characteristic yellowish papules in the skin were first described by Rigal (42) in 1881 and by Balzer (1) in 1884, and these lesions were regarded as atypical xanthomas. In 1896 the skin disease was distinguished from the xanthomatoses and named pseudoxanthoma elasticum by Darier (9) because of affected elastic fibers.

In 1889 Doyne (11) described lesions in the ocular fundus, which in 1892 were named "angioid streaks" by Knapp (32). The connection between the skin lesions and angioid streaks was pointed out by Grönblad (22) and Strandberg (43) in 1929. This relationship occurs frequently (5, 23) and has given rise to the term "Grönblad-Strandbergs disease". PXE may, however, occur without angioid streaks, and angioid streaks may occur without evidence of systemic disease (16 *a*). In the latter case PXE may, however, be the basic disorder. Angioid streaks have also been described in association with ostitis deformans (Paget, 29, 36), Ehlers-Danlos's syndrome (21) and sickle cell disease (18, 19). Angioid streaks is a slowly progressive degenerative condition in the ocular fundus, characterized by ruptures particularly in the elastic lamina of Bruch's membrane and frequently associated with macular degeneration (5, 10).

Many authors (4, 5, 20, 22, 24, 46, 47) have called attention to the involvement of the vas-

Table I. *Clinical study of patients with PXE lesions in the skin and/or angioid streaks*

Patient no.	Age (years)	Sex	PXE lesions in skin	Leg cramps	Claudication	Calcification in lower leg vessels on X-ray	Angina pectoris	Calcification in aorta on X-ray	Heart shadow increased on X-ray
Group 1: mean age 41 years									
1	35	♀	+	−	−	−	−	−	−
2	37	♂	+	−	−	+	+	−	−
3	29	♂	+	−	−	+	−	−	−
4	54	♀	+	−	−	+	−	−	−
5	48	♂	+	−	−	−	−	−	−
6	50	♂	+	−	+	+	+	−	+
7	62	♀	+	−	−	+	−	−	+
8	36	♂	+	+	+	+	−	−	−
9	20	♀	+	+	−	−	−	−	−
Group 2: mean age 49 years									
10	48	♀	−	−	−	−	−	−	−
11	38	♂	−	−	−	−	−	−	−
12	61	♂	−	−	+	+	+	+	+

cular system, as evidenced by degeneration of the arterial elastic tissue and early, widespread arteriosclerosis. Bleeding into the gastro-intestinal tract has been reported frequently (3, 5, 6, 12, 20, 31, 39, 40, 47, 48).

The problem, whether the basic defect in PXE is in elastic or in collagen fibers has been debated (15, 25, 39, 40, 45). Ultrastructural studies have demonstrated changes in the elastic tissue in PXE (26, 28, 39), while implication of the collagen fibers is still uncertain. The presence of calcification in the affected elastic fibers has been shown by various methods (14, 17, 20, 26, 28, 38, 39), but the pathogenesis of this finding is obscure. Recent examinations indicate calcification of the elastic fiber as the primary event in PXE (20, 26, 28) in contrast to previous suggestion of a primary degeneration of elastic tissue in this disease.

MATERIAL

The material consists of 9 patients with typical skin lesions and angioid streaks (group 1), and 3 patients with angioid streaks but without visible skin lesions (group 2). Group 1 includes 4 women and 5 men, group 2, 1 woman and 2 men. Their age is listed in Table I. In the material there are two pairs of siblings (nos. 2 and 3 in group 1, and nos. 10 and 11 in group 2).

For light and electron microscopic studies biopsies were taken in group 1 from typical skin lesions of the neck, groin, antecubital, axillary or abdominal region. In group 2 biopsies were taken from normal appearing skin of the antecubital region or neck.

In addition, specimens from the resected gastric and duodenal wall of Patient 2 were studied with the light microscope.

METHODS

For light microscopic studies the sections from skin specimens were stained with standard hematoxylin-eosin, orcein stain for detection of elastic fibers, Foot's silver impregnation for detection of reticulin fibers, and in 10 cases alizarin red S and in 2 cases calcium red and van Kossa's staining for detection of calcium. The sections from 2 patients of group 1 were also stained with Pearl's method and the Turnbull blue method for detection of iron. Sections from the gastric and duodenal wall were stained with hematoxylin-eosin, orcein and silver impregnation.

For electron microscopic studies the specimens were fixed in a 4% glutaraldehyde solution, buffered at pH 7.4 with phosphate salts, for 1 hour at 4°C. For after-fixation 1% osmic acid solution in 0.1 M phosphate buffer at pH 7.4 was used. After stepwise dehydration in increasing concentrations of ethanol the specimens were embedded in epoxy resin, and ultrathin sections were cut by a Reichert OM 2 ultramicrotome. The sections were stained by combined technique using uranyl acetate and lead citrate, and studied by a Siemens Elmiscop I.A. operated at 80 kV with double condensors.

Clinical and Pathological Studies

Clinical history

The presence of skin eruptions was observed by the patient himself in only 6 out of 9 cases.

Hypertension (mmHg)	Epigastric burning	Hematemesis and melena	Upper gastrointestinal X-ray
–	–	–	
–	+	+	Duodenitis at 22 years
–	+	–	Duodenal ulcer at 25 years
–	–	–	
170/90	+	+	Gastritis at 25 years
150/100	–	–	
160/90	–	–	
–	+	–	Duodenitis at 35 years
–	–	–	
–	–	–	
200/110	–	–	
220/120	+	–	Duodenal ulcer at 61 years

Three patients had noticed eruptions since about the age of 6 years, 2 patients since the age of 25 years, 1 patient since he was 30 years. Symptoms from the cardiovascular system and gastrointestinal tract are shown in Table I. Patient 12 was sympathectomized for hypertension at the age of 47 years and recently he suffered from heart infarction. Patient 2 had three attacks of gastro-intestinal hemorrhage. Melena was observed at the age of 22 years. At the age of 35 he had violent melena and hematemesis, and a partial resection of his stomach was performed. The mucosa of the resected stomach showed petecchial bleedings but no ulcers. At the age of 36 years diffuse bleeding from the remaining part of the stomach was observed by gastroscopy. Patient 5 had melena and hematemesis at the age of 25 years.

Clinical findings

All the patients of group 1 showed the typical skin changes: cutaneous deposits of yellow material, arranged in papules or linear masses, mainly parallel to the skin lines, often dilating the follicle openings (Fig. 1). The alterations were mainly confined to the flexural folds, most frequently to the neck, groins, antecubital and axillary folds, less often to the abdominal wall and the popliteal folds. The skin appeared slack in 2 patients; broad scars were seen in the skin of 3 patients. No alterations were seen in the skin of the patients of the second group. In 1 patient of group 1 yellow lesions were found in the buccal mucous membrane. Other details of findings are shown in Table I.

Ophthalmological study

In 11 out of 12 patients the diagnosis was established by the ophthalmologist. Three cases were discovered by chance and 8 cases because of a history of failing vision in one or both eyes. The age of the patients ranged from 20 to 62 years. One patient was examined only once, while the

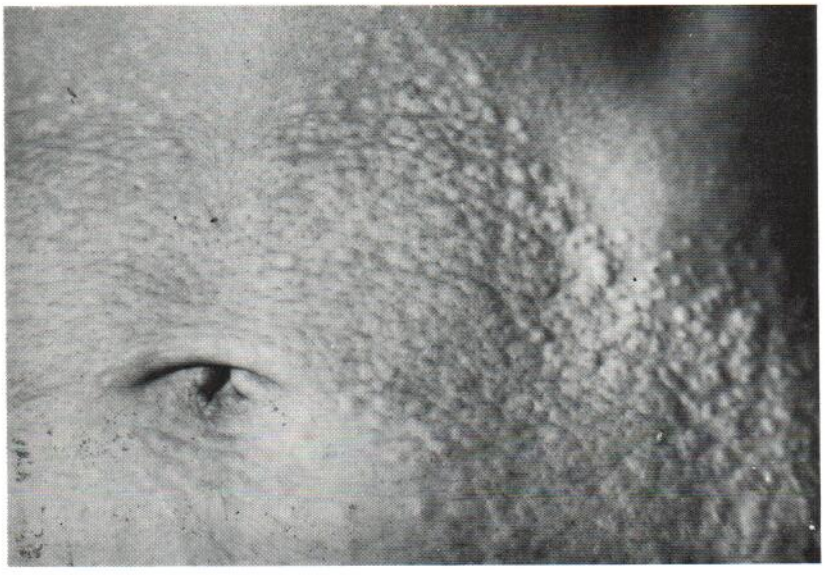

Fig. 1. PXE lesions in the abdominal region seen as papules and linear masses parallel to the skin lines. Note dilating of the follicle openings.

Table II. *Ophthalmological findings in patients with PXE lesions in the skin and/or angioid streaks*

Sex	Age (years)	Corrected vision Right (R) and Left (L) eye	Fundus changes at the last examination				Follow-up period (years)
			Angioid streaks	*Peau d'orange* configuration	Salmon-spots	Macular changes	
♀ 1	35	R 6/6	+	+	+	–	
		L 6/24	+	+	+	–	2
♂ 2	37	R 6/6	+	–	–	–	
		L 6/6	+	–	–	–	1
♂ 3	29	R 6/6	+	+	–	–	
		L 6/6	+	+	–	–	3
♀ 4	54	R 6/9	+	–	–	–	
		L 2/60	+	–	–	+	1
♂ 5	48	R 1/60→CF	+	–	–	+	
		L 6/12→HM	+	–	–	+	5
♂ 6	50	R 1/36→6/24	+	–	+	+	
		L 6/36→6/18	+	–	+	+	5
♀ 7	62	R 6/60→3/60	+	–	–	+	
		L 6/12→6/60	+	–	–	+	3
♂ 8	36	R 6/9	+	+	–	+	
		L 6/12	+	+	–	+	1/2
♀ 9	20	R 6/6	+	+	–	–	
		L 6/6	+	+	–	–	Single exam.
♀ 10	48	R 6/9→CF	+	+	–	+	
		L 1/60→HM	+	–	–	+	8
♂ 11	38	R 6/6	+	+	–	–	
		L 6/6	+	+	–	–	3
♂ 12	61	R 6/9→6/18	+	–	–	–	
		L 6/9→6/18	+	–	–	–	1

remaining patients were followed-up from half a year to 8 years. All stages of angioid streaks, except the final, were represented in the material. The fundus changes were bilateral in all cases, but the eyes were most often unequally affected. Ophthalmoscopically, there was no difference between the fundus changes observed in groups 1 and 2. The clinical findings are grouped in Table II.

As stated above, the patients showed almost all developmental phases of angioid streaks. During the follow-up period a progression of the fundus lesions was observed in several cases.

In the early stage where angioid streaks were observed as the sole phenomenon, vision was unaffected. Angioid streaks were present in all eyes. They were seen as fine or broad, brown, red or greyish bands with tapering ends, situated beneath the retinal vessels (Fig. 2 *a*). The streaks resembled blood vessels and were often bordered by some pigmented or whitish lines. The streaks frequently anastomosed near the optic disc, forming an irregular ring around it, and then radiation towards the equatorial region.

Six out of 12 patients presented coarse granulation in the perimacular and macular area, giving rise to the so-called *peau d'orange* configuration (Fig. 2 *b*). In 2 cases this change was also present in the fundus periphery (Fig. 2 *c*). The *peau d'orange* lesion caused no visual disturbances.

In 2 patients scattered yellowish-white or whitish spots, known as salmon-spots, were present in the fundus periphery (Fig. 2 *d*).

In 6 out of 12 patients subretinal or choroidal hemorrhage or the sequelae of this, was seen in one or both eyes. Two of these patients were over 50 years of age. Only 1 patient presented this lesion at an age of 36 years. The hemorrhages were usually confined to the macular area (Fig. 2 *e*) and central vision was therefore seriously damaged in all these eyes. The hemorrhages were observed to disappear and be replaced by a connective tissue scar (Fig. 2 *f*), giving the lesion a close resemblance to the scar stage of disciform macular degeneration.

In Patient 1 the reduced vision was due to an occlusion of a branch of the central retinal artery, and in Patient 11 caused by a heavy sclerosis and possibly partial occlusion of some of the retinal arteries in connection with hypertension.

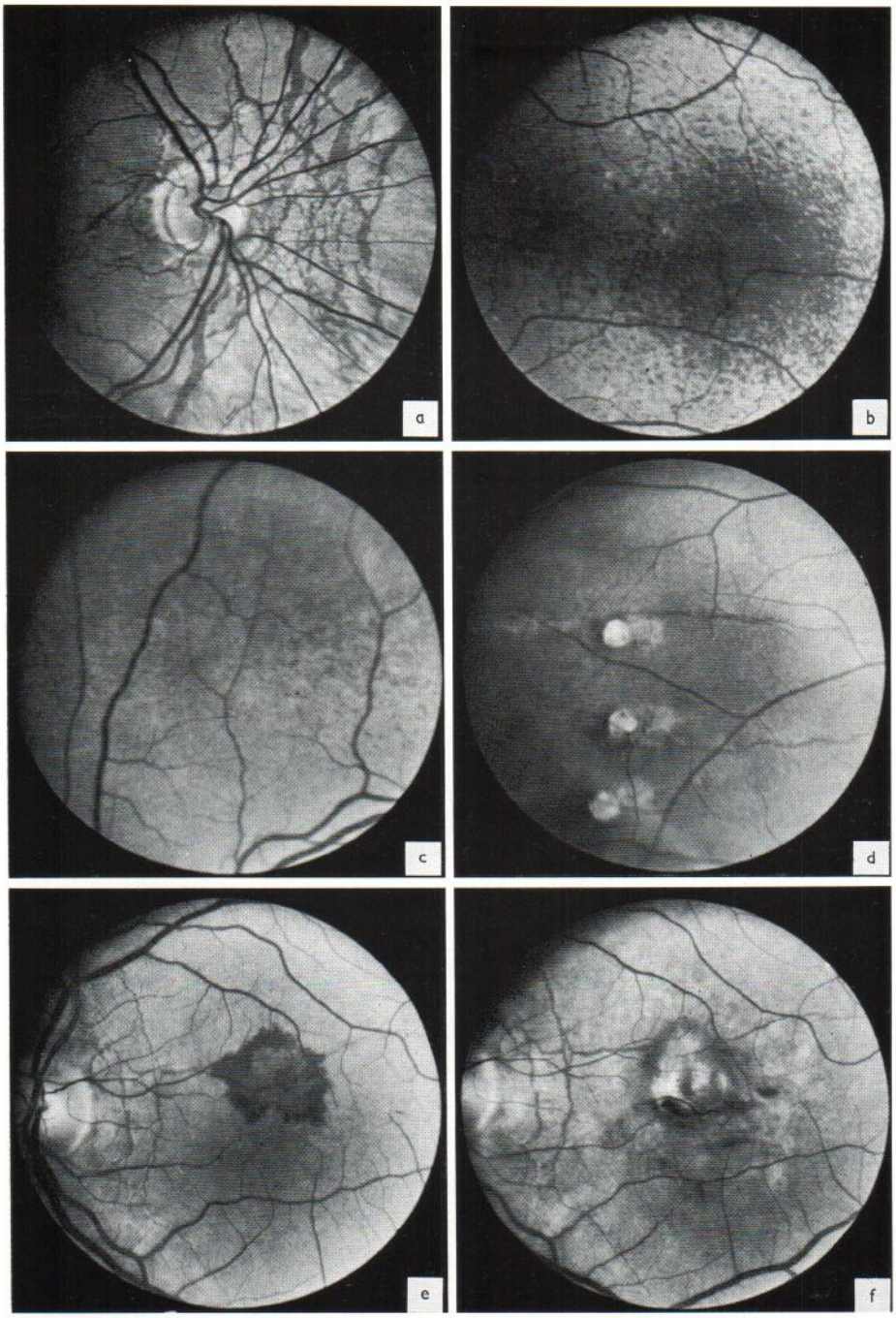

Fig. 2. (*a*) (From Patient 3, right eye) showing a dense network of angioid streaks around the optic disc. (*b*) (from Patient 3, left eye) showing coarse granulation (*peau d'orange* configuration) in the perimacular area. (*c*) (from Patient 11, left eye) showing coarse granulation (*peau d'orange* configuration) in the fundus periphery. (*d*) (from Patient 6, right eye) showing salmon-spots and angioid streaks in the fundus periphery. (*e–f*) (from Patient 5, left eye) showing a sub-retinal hemorrhage in the macular area and the scar stage, about 1 year later. The angioid streaks show some progression.

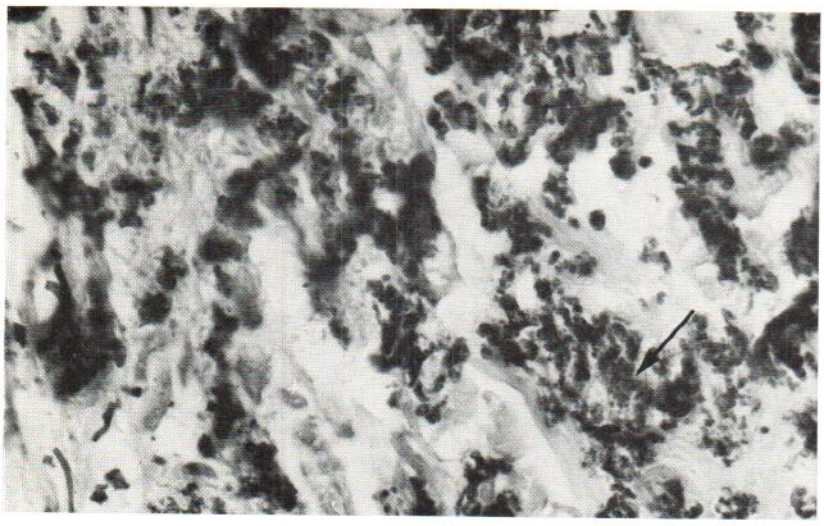

Fig. 3. Fragmented masses of elastic tissue presenting a granular structure and uneven staining (*arrow*). × 400. Orcein stain.

Light microscopic study

In group 1 alterations were observed in both elastic and collagen fibers in the middle and lower part of the corium. In the middle part these changes were present in all cases, in the lower part in most of the cases.

The elastic tissue appeared as fragmented mas-

Fig. 4. A few normal collagen fibers (*thick arrow*) are dispersed among a large amount of diffusely spread reticulin fibers (*fine arrow*). × 200. Silver impregnation.

Fig. 5. Same area as Fig. 4. Note fragmented and granular elastic tissue (*arrow*) located in the same areas as the reticulin fibers. × 200. Silver impregnation and orcein stain.

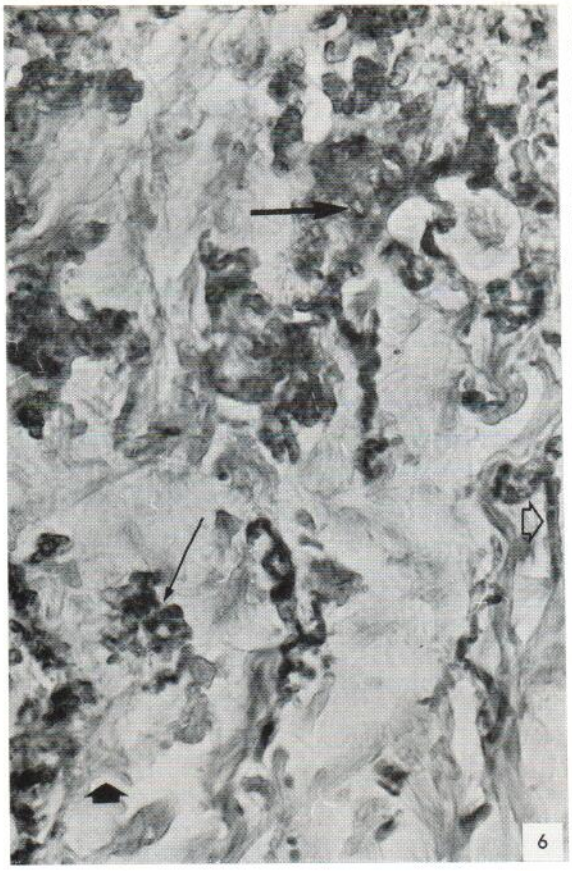

Fig. 6. (× 500, Calcium red stain) and *Fig. 7.* (× 500, orcein re-stain): Same arrows indicate same areas. Granular calcium is seen in a normal-looking elastic fiber (*framed arrows*) and in elastic tissue showing granulation (*fine arrows*). Annular calcium is seen mainly in elastic tissue presenting granulation (*thick arrows*). Note, that the pattern of calcification in the calcium red stain partly correspond to the pattern of granulation in the orcein stain. In the orcein stain, an area presenting uneven staining shows no calcification (*broad arrows*).

ses presenting a granular structure and uneven orcein staining (Fig. 3).

The amount of normal collagen fibers was reduced in the affected areas, while reticulin fibers were present in large amounts (Fig. 4). In 8 patients the remaining few normal collagen fibers were dispersed among a large amount of diffusely spread reticulin fibers (Fig. 4). In 1 patient nets of reticulin fibers were located in patchy areas with fewer but normal collagen fibers. The surrounding collagen appeared as in normal corium. A section stained for elastic as well as for reticulin fibers showed fragmented and granular elastic tissue located to the same areas as the reticulin fibers (Fig. 5).

In areas showing granulation of the elastic tissue calcification was demonstrated by staining with hematoxylin-eosin, alizarin red S and van Kossa's method, in calcium red staining as annular or granular patterns (Fig. 6). A few normal looking elastic fibers did contain calcium (Figs. 6 and 7). Iron was not demonstrated in any sections.

In group 2, no granulation of the elastic fibers was seen in Patients 11 and 12, while in Patient 10 a little area in the deep part of the corium revealed changes in the elastic tissue similar to those observed in group 1. In the same area nets of reticulin fibers were present, while the collagen appeared normal in the other 2 patients. In Patient 10, in the area showing fragmentation and granulation of the elastic tissue, deposits of calcium were observed. No deposits

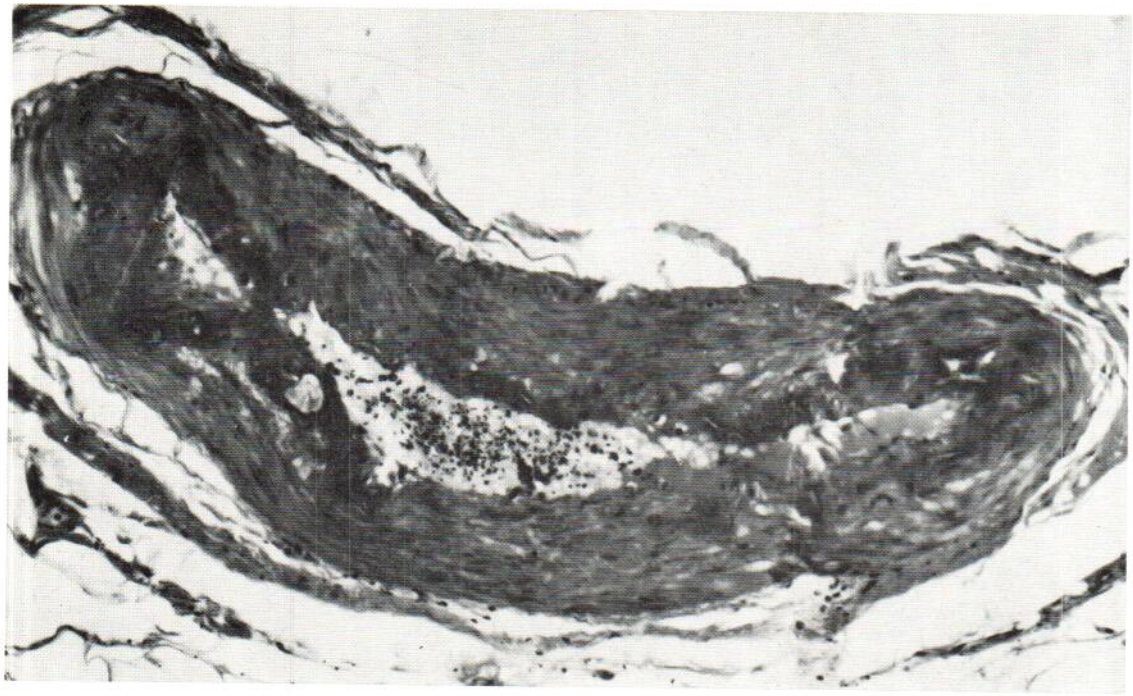

Fig. 8. A smaller artery in the periduodenal fat shows patchy calcification of the internal elastic lamina. Arteriosclerosis of the intima. × 200. Hematoxylin-eosin stain.

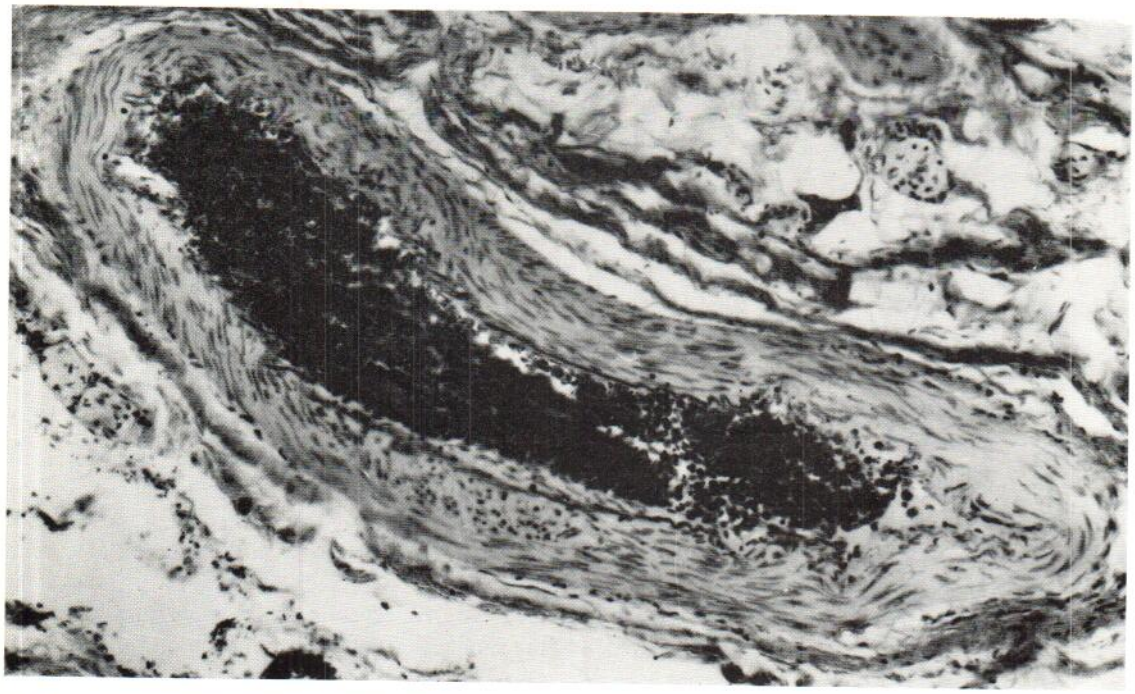

Fig. 9. The same vessel as Fig. 8 orcein stained. The internal elastic lamina is ruptured. × 200.

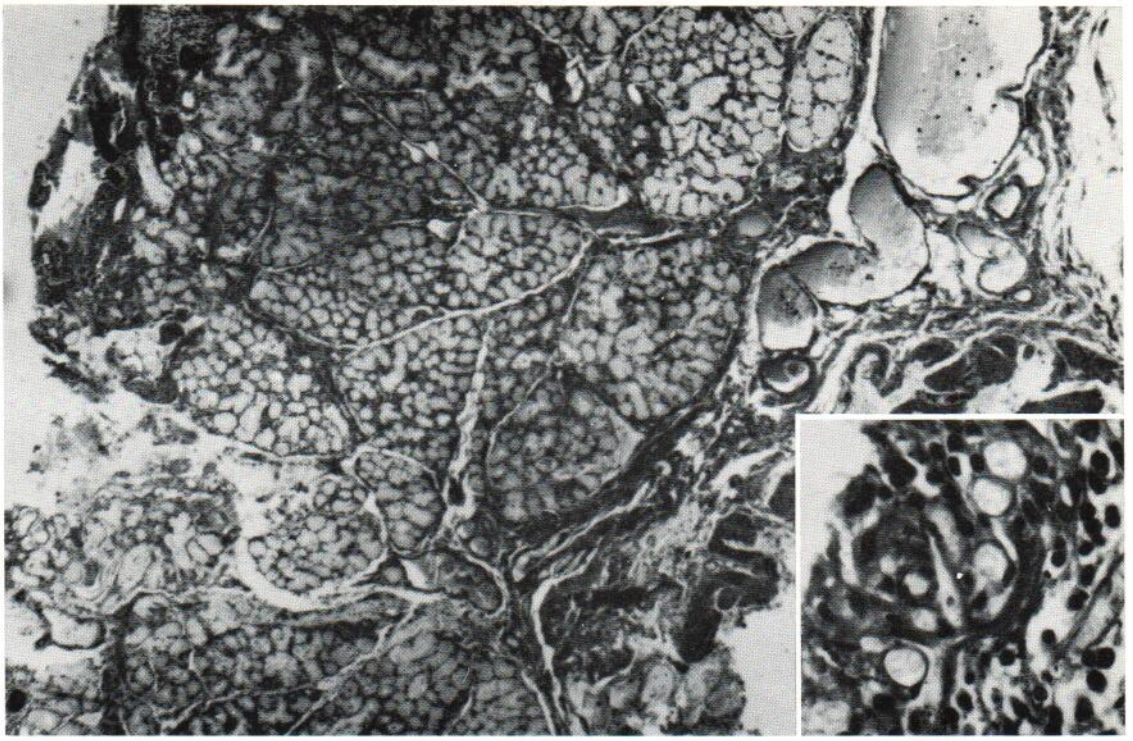

Fig. 10. Gastric mucosa showing erosion and necrotic tissue. The mucosal and submucosal veins are widely dilated. × 55 hematoxylin-eosin stain. *Inset:* Area of Fig. 10 at magnification × 550. Note ectasia of the mucosal capillaries.

of calcium were seen in sections from Patients 11 and 12.

In the gastric submucosa and the periduodenal fat the small arteries showed patchy calcification of the internal elastic lamina (Fig. 8). In addition, arteriosclerosis was noticed in the intima (Fig. 8). Orcein staining showed ruptures in the internal elastic lamina of these vessels (Fig. 9). Reticulin fibers were not observed in the affected areas. The veins and capillaries of the gastric mucosa and submucosa were widely dilated at certain places (Fig. 10). In one of these an erosion with necrotic tissue and pronounced surrounding interstitial hemorrhage was present.

Electron microscopic study

In all specimens from patients in group 1 pronounced changes were observed in many of the elastic fibers in the middle part of the corium. The fibers were often irregularly shaped and some of them showed holes of various sizes and shapes (Fig. 11). The holes were empty or contained a granular or fibrillar material. Extremely dense material, probably calcium salts, was found inside areas of both irregular and normally shaped elastic fibers (Figs. 11 and 12). The dense material assumed annular (Fig. 12) or bizarre forms (Fig. 11), or appeared as granules (Figs. 12 and 13) or thin stripes reminding of calcium apatite crystals (Fig. 14). The dense material was often found completely surrounded by normal appearing matrix (Fig. 12), but dense material was also observed without any relation to the matrix (Fig. 13). Compact or loose masses of a thready material were found surrounding some of the calcified elastic fibers (Fig. 15). In the peripheral zone this material showed longer and more distinct threads forming bundles (Fig. 16). The threads did not show banding. In some areas the thready material showed round holes. The holes were either empty or contained a spot of granular material centrally or a thin ring peripherally (Figs. 15, 17 and 18). The rings showed transverse banding (Fig. 17) or a lamellar arrangement (Fig. 18). In some areas

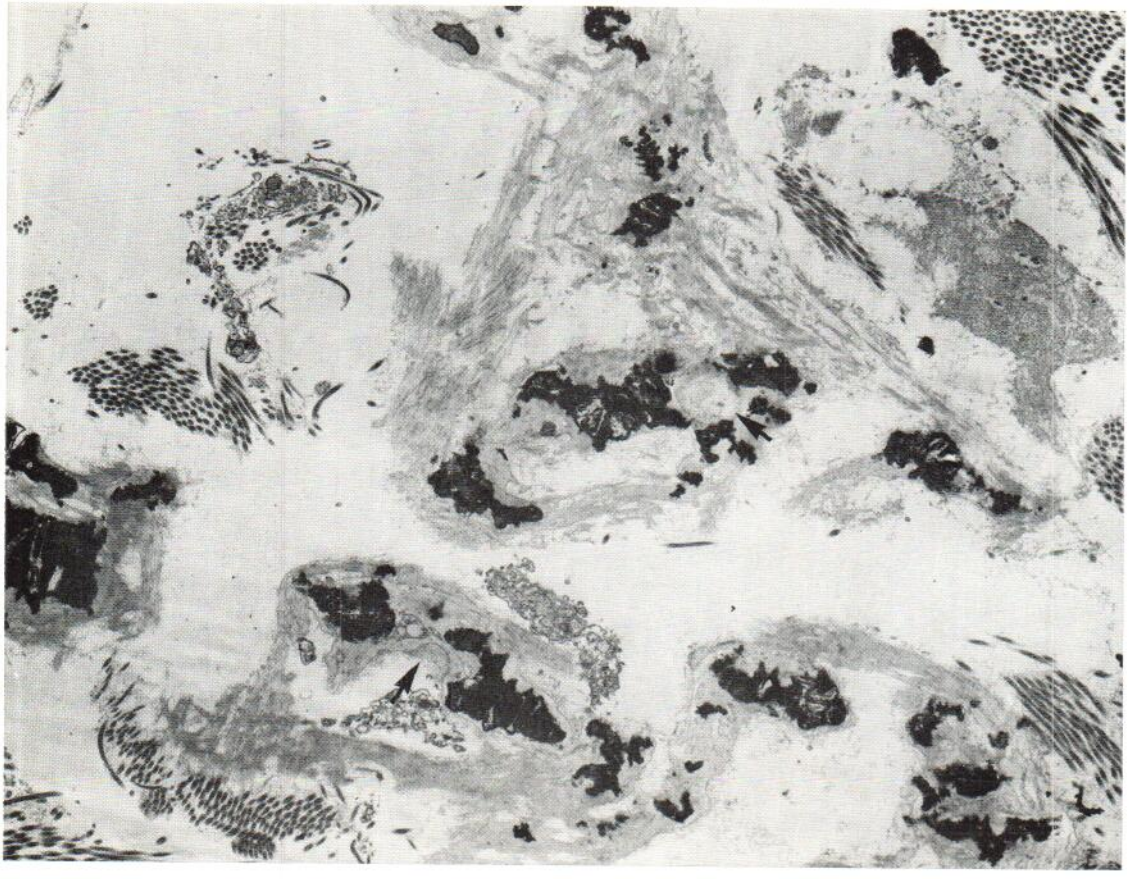

Fig. 11. Irregularly shaped elastic fibers with holes of various sizes and shapes, and dense material, calcification, arranged in bizarre forms. The holes are empty or contain granular or fibrillar material (*arrows*). × 6 700.

the thready material contained collagen fibrils (Figs. 15, 16 and 23) and normal elastic fibers. Many collagen fibrils inside and outside the material showed twisted figures as described below (Figs. 16 and 23).

In group 2, Patient 10 showed alterations of the elastic fibers and appearance of a thready material as in group 1. Patients 11 and 12 showed no changes of elastic fibers similar to those found in the PXE-patients of this study.

In some biopsies from the neck of patients from both groups the upper part of the corium showed changes similar to those observed in senile elastosis (2, 8). These findings do probably not represent PXE-alterations. None of the degenerated elastic fibers in these areas were observed to contain calcium deposits.

In group 1, collagen fibrils were often irregularly arranged (Fig. 16) and showed wide variations in the diameter (Figs. 19 and 23), ranging from 300 to 7 000 Å (Fig. 20). The small fibrils had an almost round cut-surface, while the cut-surface of larger fibrils was flower-like (Fig. 19). The center of the larger fibrils resembled a normal small collagen fibril, while the periphery appeared split into subunits, lending the fibril an irregular shape (Fig. 19). In the longitudinal sections, wire-like figures appeared twisted along the axes of the fibrils (Fig. 21). The periphery of the twisted collagen fibrils showed subunits approximately 100 Å wide (Fig. 22). The axial periodicity of the twisted collagen fibrils showed values identical with normally figured collagen fibrils. The twisted collagen fibrils were often observed in collagen bundles with a loose structure and in the surroundings of calcified elastic fibers

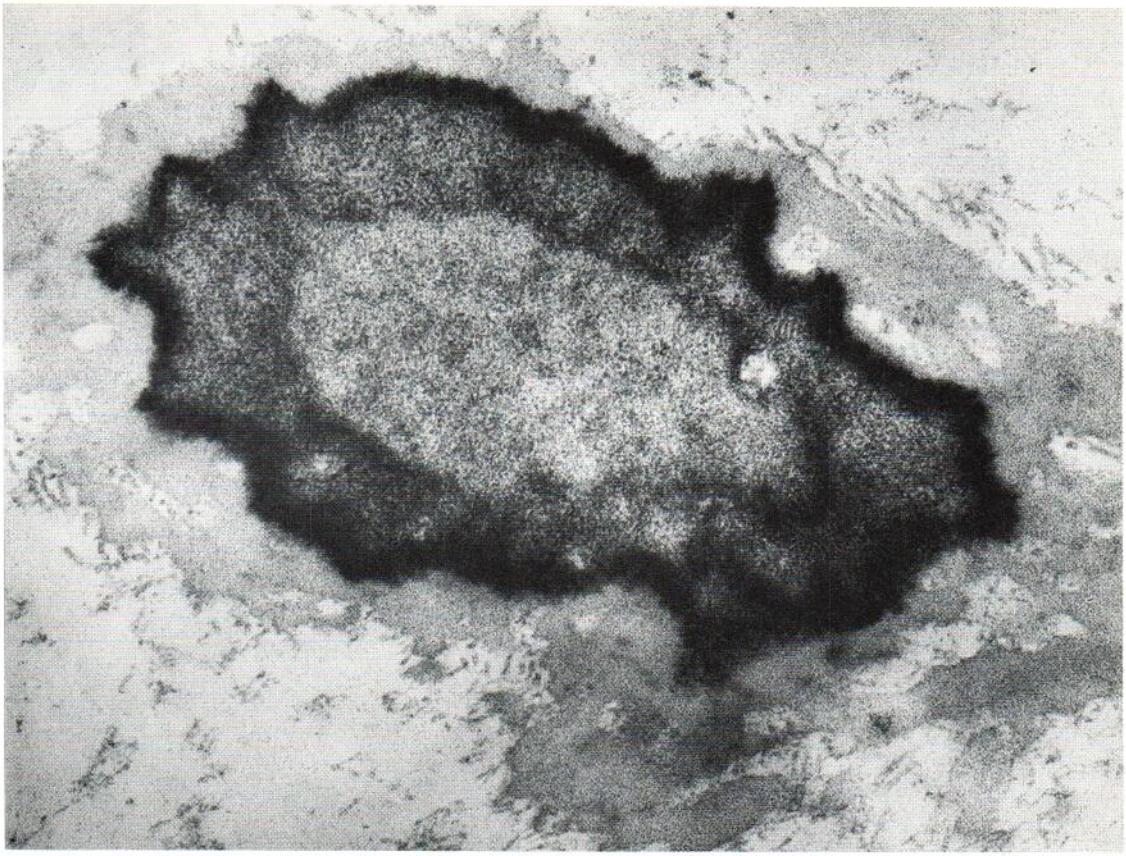

Fig. 12. Calcification inside an elastic fiber. There is an extremely dense annular border, enclosing dense granules centrally. × 54 000.

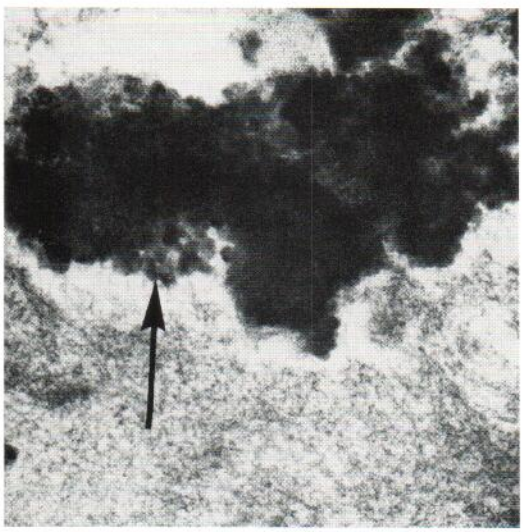

Fig. 13. Calcification appearing as dense granules (*arrow*) and surrounded by thready material. × 60 000.

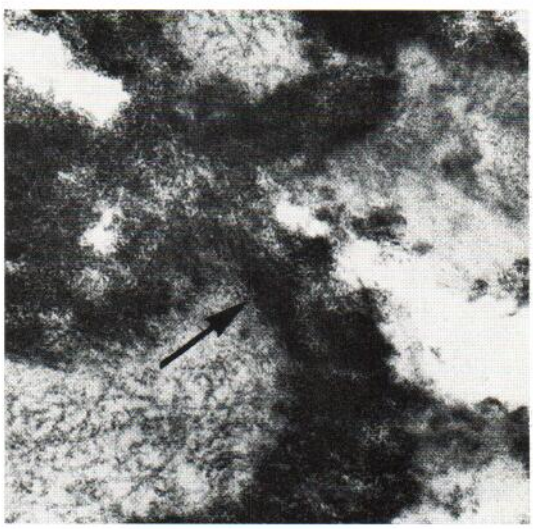

Fig. 14. Calcification appears as fine stripes (*arrow*) reminding of calcium apatite crystals. × 60 000.

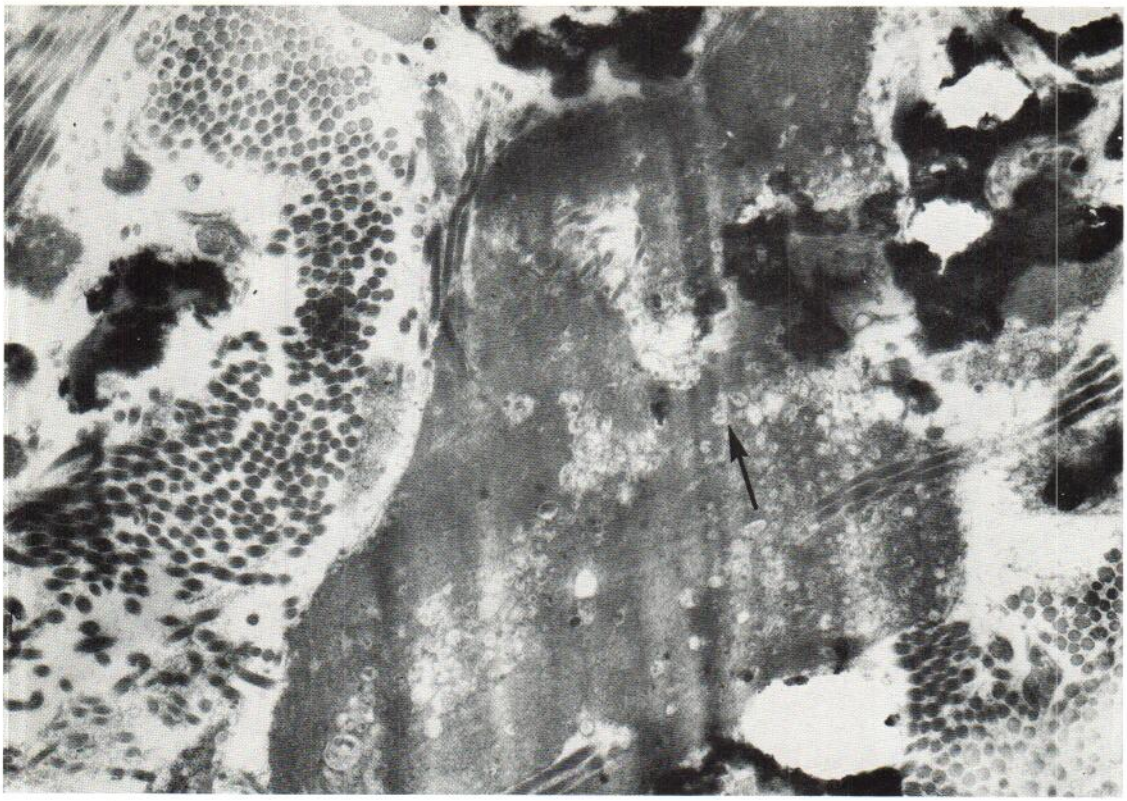

Fig. 15. Compact masses of the thready material surrounding calcified elastic fibers. Round holes and collagen fibrils are seen inside the material. Some holes contain a granular material centrally (*arrow*). × 14 500.

(Fig. 23). The number of such twisted fibrils varied from one patient to another. Two patients showed twisting of almost all collagen fibrils in the most heavily affected collagen bundles. Six patients showed many twisted fibrils, and 1 patient only a few in the worst bundles.

In all the patients of group 2, a few collagen fibrils showed identical alterations as described for group 1.

In addition to the collagen fibrils and the elastic fibers mentioned, two other types of fibril were observed in both groups, in group 1 occasionally in large amounts (Fig. 24). One of these fibril types showed an almost uniform thickness of about 100 Å and a more or less granular appearance. They showed no branchings, but a continuity with elastic fibers. The other type showed large variations in thickness, ranging from approximately 80 to 250 Å, but no periodic banding. They had a homogeneous appearance and branchings.

DISCUSSION

The clinical appearance of the skin alterations of all the patients of group 1 and of the lesions in the oral mucosa of one correspond to earlier reports on PXE (6, 20, 40). Besides in the mouth, mucosal lesions have been described in the vagina, rectum and stomach (20). The time of onset of the skin lesions cannot be determined with certainty, as the lesions were not always observed by the patient. However, some lesions were noticed during childhood. This is in accordance with previous reports, which include a case of skin lesions noted at birth (20, 47). In contrast, Case 10 showed no clinical skin manifestations, but she must be grouped as a case of PXE because of typical light and electron microscopic changes.

The frequent appearance of vascular disease in patients of both groups confirm earlier reports on PXE (4, 5, 6, 12, 20). The occurrence of gastrointestinal hemorrhage in patients with PXE has

Fig. 16. Long distinct bundles of thready material mixed with irregularly arranged collagen fibrils. Some collagen fibrils show twisting (*arrow*). × 15 600.

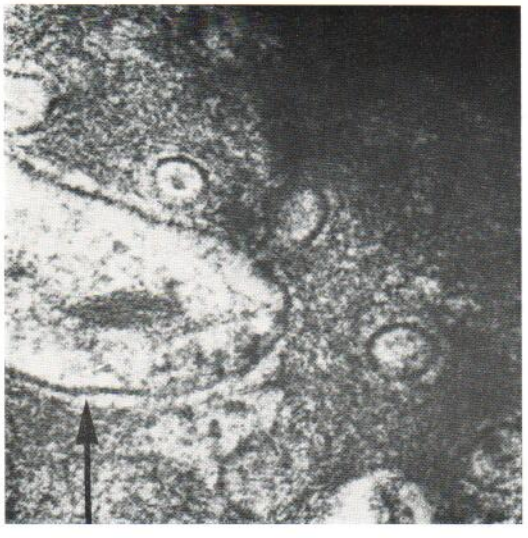

Fig. 17. The holes in the thready material are bordered by thin rings showing banding (*arrow*). × 60 000.

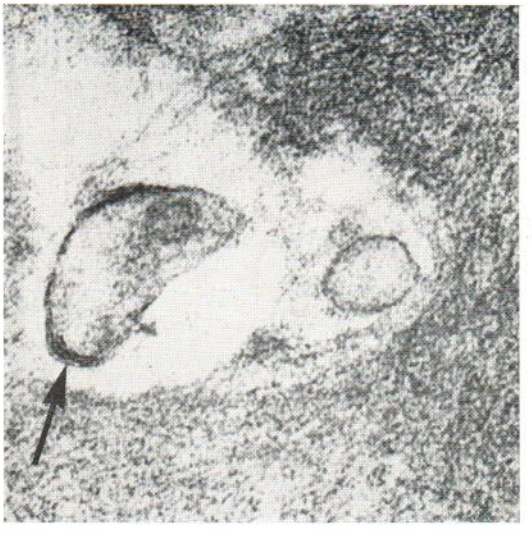

Fig. 18. A hole in the thready material containing a dense ring with lamellar arrangement (*arrow*). × 120 000.

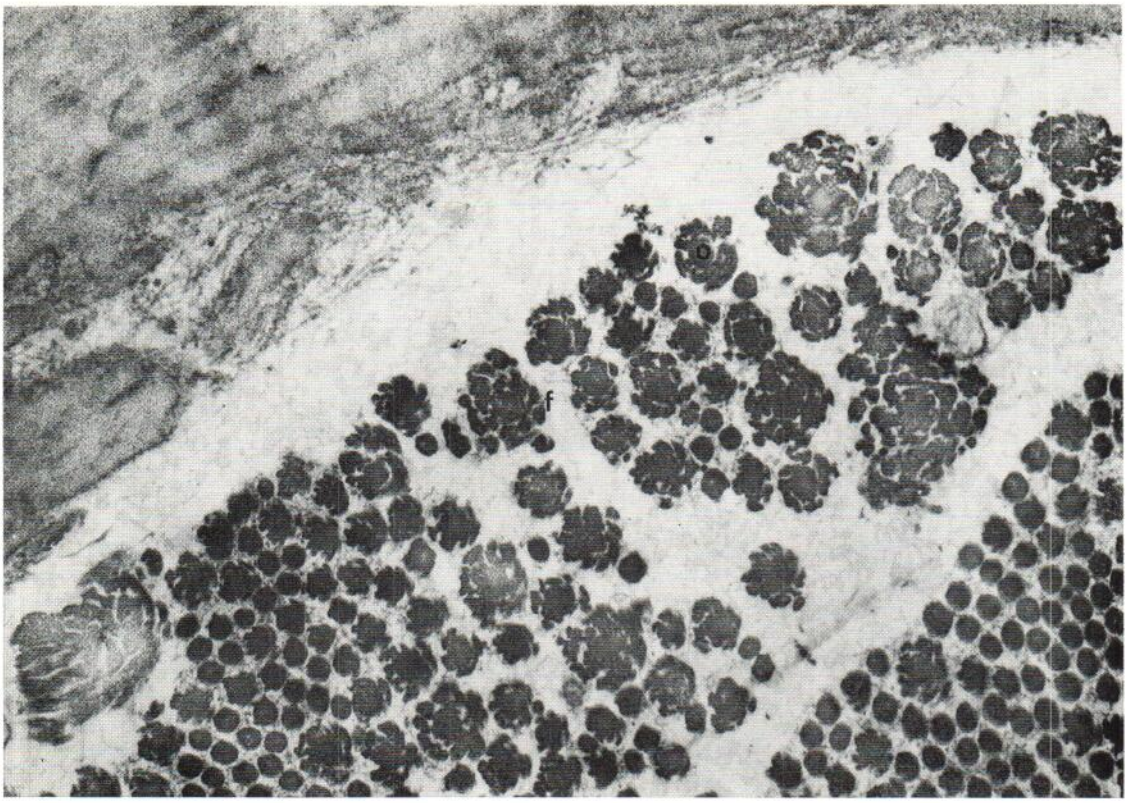

Fig. 19. Cut-surfaces of collagen fibrils showing large variations in diameter and flower-like shapes (*f*). Note normal small fibrils (*o*) in the centre. × 38 500.

also been reported previously (3, 5, 6, 12, 20, 31, 39, 40, 47, 48). The observation in 1 patient of hemorrhage due to scattered petecchial lesions in the gastric mucosa is typical of the disease (20).

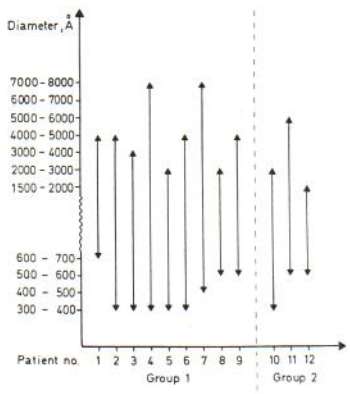

Fig. 20. Ranges of diameters of skin collagen fibrils in patients with PXE.

The fundus changes in this material are of the type previously described by Grönblad (23) and Larsen (37). The final stage presenting diffuse choroidal sclerosis and atrophy was, however, not found in any of our cases. No ophthalmoscopical differences were observed between the groups showing skin manifestations or not.

The light microscopic findings of pathological elastic tissue and heavy calcification in the middle and deep part of the corium in group 1 are well known (20, 28). Granulation of elastic tissue is characteristic of PXE, but not pathognomonic, considering that it has also been observed in cutis laxa (30). The granularity in PXE seems to be partly caused by the presence of calcium salts, partly by uneven stainability of the elastic tissue (compare Figs. 6 and 7). In cutis laxa no calcification has been observed (30). The finding of calcification in normal-appearing elastic fibers accords with the report of Goodman and co-workers

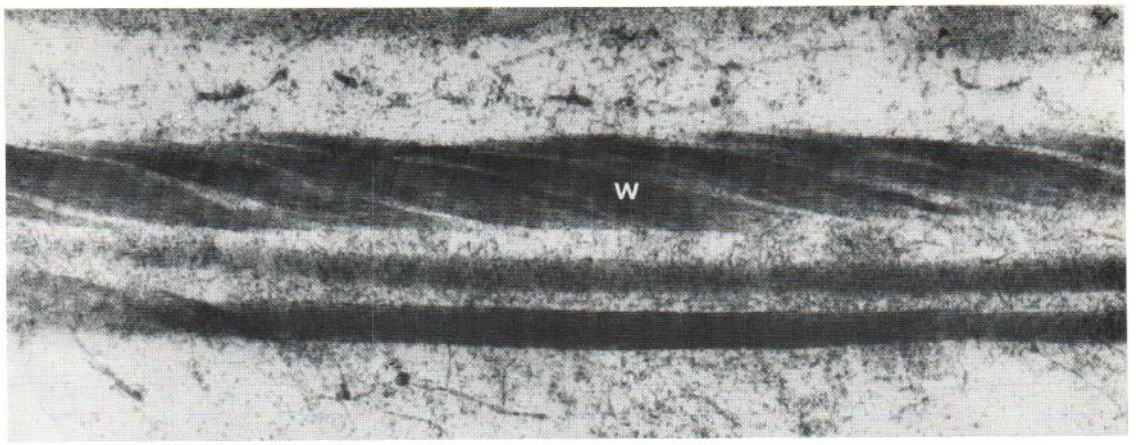

Fig. 21. Wire-like collagen fibril (*w*) in longitudinal section. The axial periodicity of wire-like and straight fibrils are identical. × 51 800.

(20) and support their suggestion of calcification as the primary alteration in PXE.

Reticulin fibers around the altered elastic tissue and between the collagen bundles have previously been observed (15, 25). This morphological change of collagen we consider a secondary response to alteration in the elastic tissue.

The histological finding of skin changes typical for PXE in 1 patient of group 2 is similar to an observation made among others by Goodman and co-workers (20).

Alterations in the vessels of the gastric and duodenal wall as in Patient 2 have been observed previously (31, 40, 48). The observations support the suggestion of Goodman and co-workers (20), that changes in the elastic tissue of the gastric vessels may cause stasis in the mucosa and a tendency to hemorrhage.

When compared with the histochemical findings, the extremely dense material showing annular and bizarre figures is most likely to be interpreted as deposits of calcium salts. As ultrastructural degeneration inside the elastic fibers, similar to that seen in senile elastosis, was only found in the upper part of the corium in the biopsies from the neck, and as calcium deposit was the only visible abnormality in some of the fibers in the PXE-lesions, our findings accord with the reports of Huang and co-workers (28) and Hashimoto & Di-Bella (26) and support their suggestion of calcification as the primary event in PXE. The changes of the elastic fibers frequently found in the affected areas are possibly a reaction to the presence of calcification. As in the present study, Huang and co-workers (28) found a "granulo-fibrillar" material among collagen fibrils, at the envelope of the elastic fibers and in relation to large areas of dense material. However, our findings cannot support their theory that calcification takes place primarily in the granulo-fibrillar material in the perielastic tissue, as we found calcification surrounded by matrix inside the elastic fiber. Our findings thus

Fig. 22. Oblique section of twisted collagen fibrils. They show 100 Å wide subunits (*arrow*). × 60 000.

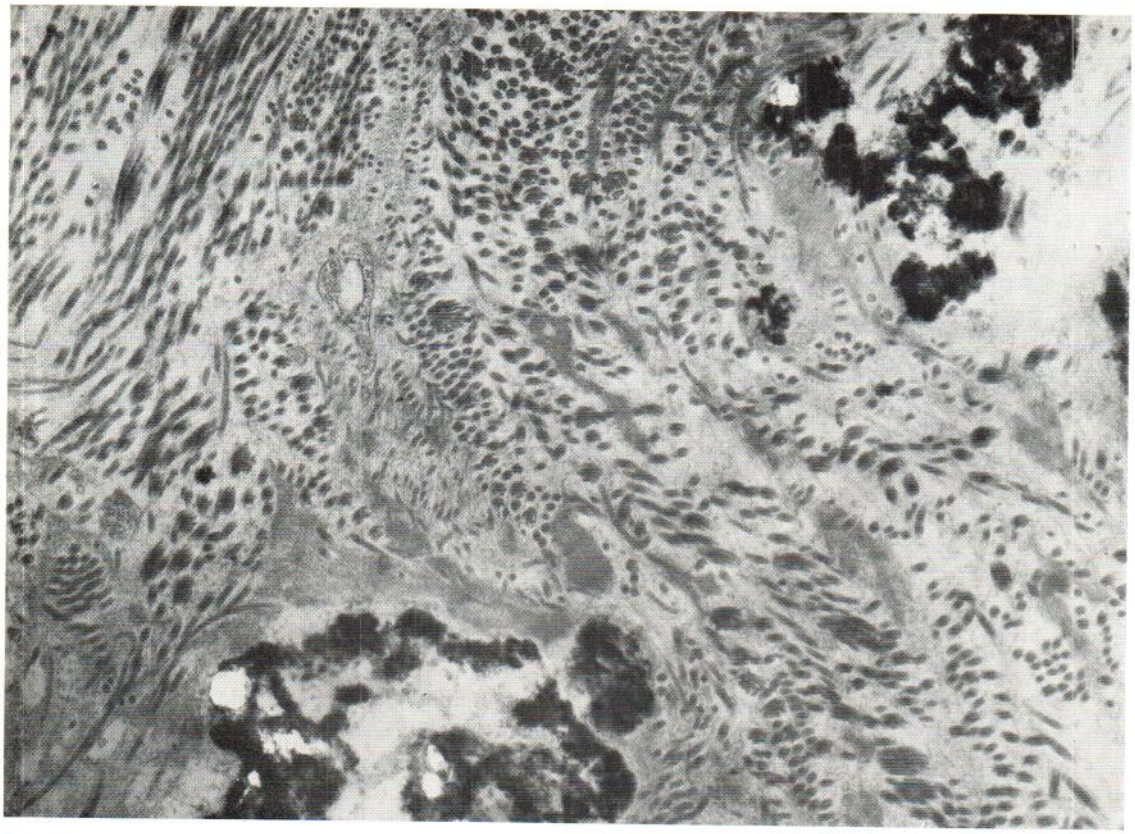

Fig. 23. Collagen bundles showing a loose structure and flower-like collagen fibrils. × 24 600.

indicate, in agreement with those of Hashimoto & DiBella (26) that calcification takes place inside the elastic fiber.

The nature of the masses of thready material surrounding the calcified elastic fibers is unknown. Hashimoto & DiBella (26) observed amorphous substances with only a faint indication of a fibrous structure. They suggested that these substances possibly might be some abnormally increased ground substance. A material, similar to that found in our study, is observed in the Arthus phenomenon of the rabbit (35) and in human atherosclerotic lesions (27). The material present in the atherosclerotic lesions was identified by Haust et al. (27) as fibrin. This fibrin showed a periodic striation which could not be demonstrated in the thready material of the PXE lesions in our study. However, fibrin does not invariably show banding (27).

Rings and spots of granular material similar to those observed in the holes of the thready material in the present study have been observed inside the degenerated elastic fibers in senile elastosis (8). The lamellar arrangement of some of the rings is similar to that of myelin (13). The nature of the spots could not be determined.

Collagen fibrils showed the usual distinct transverse banding, but the thickness of the fibrils varied considerably. The flower-like and wire-like figures of the thick collagen fibrils may develop by the twisting of thin fibrils around the original fibril. Teller & Vester (44) have also described thin fibrils in PXE, and Hashimoto & DiBella (26) findings reminding of our flower-like figures in the thick collagen fibrils. The flower-like figures are not specific of PXE as similar figures have been observed in amyloidosis (41) and in carrageenin granuloma of the rat (33). In skin of normal human subjects similar figures have also been observed, although

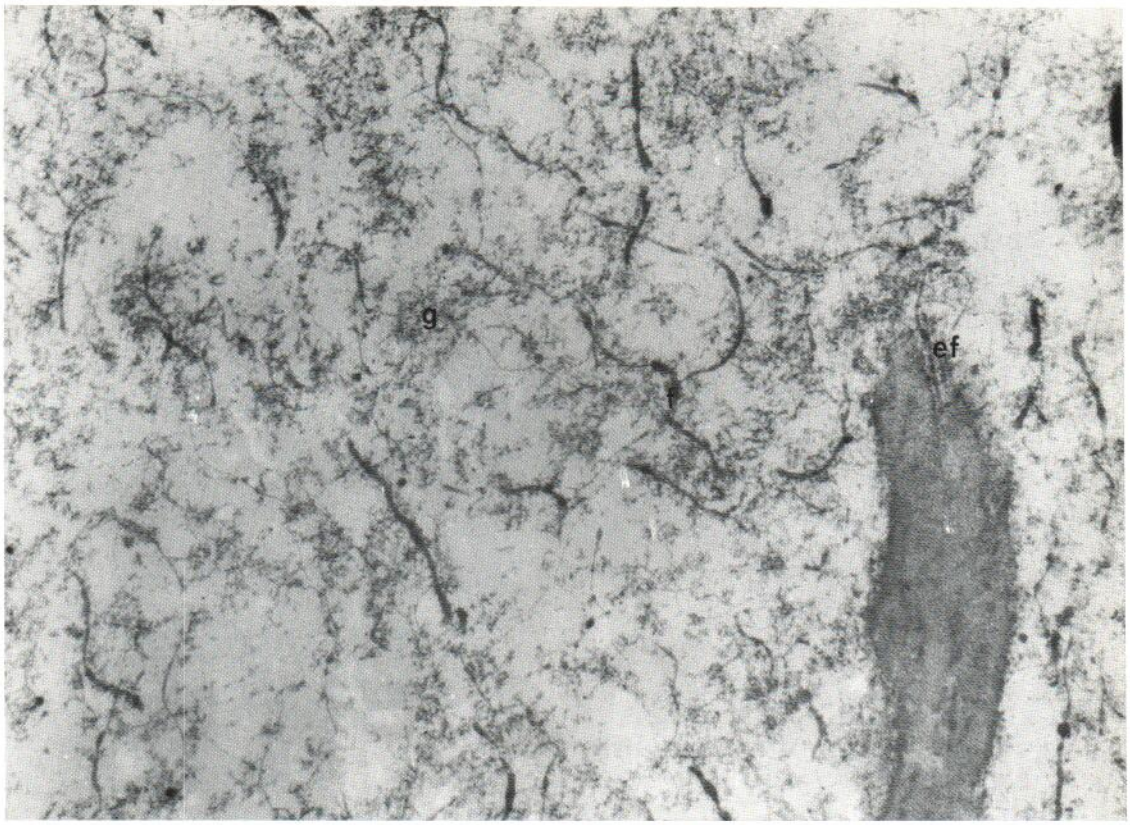

Fig. 24. Loose thread-like material (*g*) and two types of thin fibrils around an elastic fiber. One type of these fibrils (*ef*) shows an almost uniform thickness, granular appearance and a continuity with the elastic fiber. The other type (*f*) shows variations in thickness, branching and a homogeneous appearance. × 44 700.

the number was usually much less (7). The irregularly arranged and the twisted collagen fibrils observed in the PXE electron micrographs might correspond to the reticulin fibers observed in the histologic sections and are like those considered to represent a reaction to calcification of elastic fibers. However, the presence of the thready material also might cause such alterations in collagen.

The thin, granular, non-branching fibrils of uniform thickness, which showed a continuity with the elastic fibers must be considered elastic fibrils. The nature and function of the homogeneous, branching fibrils, which could be distinguished from elastic and collagen fibrils, are unknown. A further description of these fibrils will appear in a separate paper (34).

One of the 3 patients in group 2 showed submicroscopic as well as light microscopic alterations of elastic fibers, indistinguishable from those found in group 1. However, only a few collagen fibrils showed ultrastructural changes in this patient.

In group 2, the presence of PXE was proven in Patient 10 by light microscopy by the typical granulation and calcification of the elastic tissue. Furthermore, this patient showed reticulin fibres like those present in group 1, and electron microscopic findings indistinguishable from those observed in group 1.

Even if, besides angioid streaks, the only pathological sign indicating PXE in Patient 11 was hypertension, this patient is still considered to have PXE, as he is a brother of Patient 10.

Patient 12's hypertension was so severe that sympathectomy had to be performed at the age of 47. At the age of 61 he presented widespread arteriosclerotic lesions. Although angioid streaks

were present, neither the light nor the electron microscopic examinations could demonstrate PXE in this patient.

ACKNOWLEDGEMENTS

The authors wish to thank Svend Petri, M.D., who placed the gastric mucosa at our disposal, for helpful advice.

We also wish to thank Mrs Nancy Hansen, Miss Lise Fredebo and Mr John Winther for their valuable technical assistance.

REFERENCES

1. Balzer, F.: Recherches sur les Caractères Anatomiques du Xanthelasma. Arch Physiol Norm Path 4 *(3. Serie):* 65, 1884.
2. Banfield, W. G. & Brindley, D. C.: Preliminary observations on senile elastosis using the electron microscope. J Invest Derm *41:* 9, 1963.
3. Brandt, N. J.: Gastro-intestinal blødning ved pseudoxanthoma elasticum. Ugeskr Læg *123:* 1245, 1961.
4. Carlborg, U.: Studies of circulatory disturbances, pulse wave velocity and pressure pulses in larger arteries in cases of pseudoxanthoma elasticum and angioid streaks. A contribution to the knowledge of the function of the elastic tissue and the smooth muscles in larger arteries. Acta Med Scand, Suppl. *151:* 14, 1944.
5. Carlborg, U., Ejrup, B., Grönblad, E. & Lund, F.: Vascular studies in pseudoxanthoma elasticum and angioid streaks. Acta Med Scand, Suppl. *350:* 3, 1959.
6. Connor, P. J., Juergens, J. L., Perry, H. O., Hollenhorst, R. W. & Edwards, J. E.: Pseudoxanthoma elasticum and angioid streaks. A review of 106 cases. Amer J Med *30:* 537, 1961.
7. Danielsen, L. & Kobayasi, T.: Ultrastructural changes of dermal elastic and collagen fibers in normal subjects. To be published.
8. — Electron microscopy of dermal elastic fibers in actinic (senile) elastosis. To be published.
9. Darier, J.: Pseudoxanthoma elasticum. Mh prakt Derm *23:* 609, 1896.
10. Domke, H. & Tost, M.: Zur Histologie der "Angioid Streaks". Klin Mbl Augenheilk *145:* 18, 1964.
11. Doyne, R. W.: Choroidal and retinal changes; the result of blows on the eyes. Trans ophthal Soc UK *9:* 129, 1889.
12. Eddy, D. D. & Farber, E. M.: Pseudoxanthoma elasticum. Internal manifestations: a report of cases and a statistical review of the literature. Arch Derm (Chicago) *86:* 729, 1962.
13. Finean, J. B.: Electron microscope and X-ray diffraction studies of a saturated synthetic phospholipide. J Biophys Biochem Cytol *6:* 123, 1959.
14. Finnerud, C. W. & Nomland, R.: Pseudoxanthoma elasticum. Proof of calcification of elastic tissue; occurrence with and without angioid streaks of the retina. Arch Derm (Chicago) *35:* 653, 1937.
15. Fisher, E. R., Rodnan, G. P. & Lansing, A. I.: Identification of the anatomic defect in pseudoxanthoma elasticum. Amer J Path *34:* 977, 1958.
16. Franceschetti, A., François, J. & Babel, J.: Les héredo-dégénérescences chorio-rétiniennes, *a:* p. 561 *b:* p. 573. Masson, Paris, 1963.
17. Friedmann, M.: Ein Beitrag zur Kenntnis des Pseudoxanthoma elasticum (Darier). Arch Derm Syph (Berlin) *134:* 151, 1921.
18. Geeraets, W. J. & Guerry, D.: Angioid streaks and sickle-cell disease. Amer J Ophthal *49:* 450, 1960.
19. — Elastic tissue degeneration in sickle-cell disease. Amer J Ophthal *50:* 213, 1960.
20. Goodman, R. M., Smith, E. W., Paton, D., Bergman, R. A., Siegel, C. L., Ottesen, O. E., Shelley, W. M., Pusch, A. L. & McKusick, V. A.: Pseudoxanthoma elasticum. A clinical and histopathological study. Medicine (Baltimore) *42:* 297, 1963.
21. Green, W. R., Friedman-Kien, A. & Banfield, W. G.: Angioid streaks in Ehlers-Danlos syndrome. Arch Ophthal *76:* 197, 1966.
22. Grönblad, E.: Angioid streaks—pseudoxanthoma elasticum. Acta Ophthal (København) *7:* 329, 1929.
23. — "Angioid streaks"—Pseudoxanthoma Elasticum—Der Zusammenhang zwischen diesen gleichzeitig auftretenden Augen- und Hautveränderungen. Acta Ophthal (København) *10,* Suppl. *1:* 3, 1932.
24. Grönblad, E. & Carlborg, U.: Pseudoxanthoma elasticum — en kärlsjukdom. Nord Med *5:* 579, 1940.
25. Hannay, P. W.: Some clinical and histopathological notes on pseudoxanthoma elasticum. Brit J Derm *63:* 92, 1951.
26. Hashimoto, K. & DiBella, R. J.: Electron microscopic studies of normal and abnormal elastic fibers of the skin. J Invest Derm *48:* 405, 1967.
27. Haust, M. D., Wyllie, J. C. & More, R. H.: Electron microscopy of fibrin in human atherosclerotic lesions. Immunohistochemical and morphologic identification. Exp Molec Path *4:* 205, 1965.
28. Huang, S.-N., Steele, H. D., Kunnar, G. & Parker, J. O.: Ultrastructural changes of elastic fibers in pseudoxanthoma elasticum. A study of histogenesis. Arch Path *83:* 108, 1967.
29. Hugonnier, R. & Royer, J.: Manifestations oculaires au cours de la maladie de Paget. Bull Soc Ophtal Franc p. 393, 1959.
30. Hult, A. M., Goltz, R. W. & Midtgaard, K.: The dermal elastic fibers in cutis hyperelastica (Ehlers-Danlos syndrome) and in cutis laxa (generalized elastolysis). A histological histochemical and electron microscopical study. Acta Dermatovener (Stockholm) *44:* 415, 1964.
31. Kaplan, L. & Hartman, S. W.: Elastica disease. Case of Grönblad-Strandberg syndrome with gastrointestinal hemorrhage. Arch Intern Med (Chicago) *94:* 489, 1954.
32. Knapp, H.: On the formation of dark angioid streaks as an unusual metamorphosis of retinal hemorrhage. Arch Ophthal (Chicago) *21:* 289, 1892.
33. Kobayasi, T.: Ultrastructure of carrageenin granuloma in rats. To be published.
34. — Microfibrils of corium. To be published.

35. Kobayasi, T.: Ultrastructural changes of the Arthus phenomenon of rabbit. To be published.
36. Larmande, A. & Margaillan, A.: Maladie de Paget et syndrome de Groenblad-Strandberg. Bull Soc Franc Ophtal *70:* 206, 1957.
37. Larsen, H.-W.: Manual and Color Atlas of the Ocular Fundus, pp. 91, 254. Munksgaard, Copenhagen, and Saunders, Philadelphia, 1969.
38. Lobitz, W. C. & Osterberg, A. E.: Pseudoxanthoma elasticum: Microincineration, J Invest Derm *15:* 297, 1950.
39. Loria, P. R., Kennedy, C. B., Freeman, J. A. & Henington, V. M.: Pseudoxanthoma elasticum. (Grönblad-Strandberg syndrome). A clinical, light- and electron-microscopic study. Arch Derm (Chicago) *76:* 609, 1957.
40. McKusick, V. A.: Heritable Disorders of Connective Tissue, ed. 3, p. 286. C. V. Mosby Company, Medical Publishers, St. Louis, 1966.
41. Merker, H. J., Shibolet, S., Sohar, E., Gafni, J. & Heller, H.: Alterations in fine structure of collagen in amyloidosis. Naturwissenschaften *53:* 527, 1966.
42. Rigal: Observation pour servir à L-Histoire de la Cheloide Diffuse Xanthelasmique. Ann Derm Syph (Paris) *2:* 491, 1881.
43. Strandberg, J.: Pseudoxanthoma elasticum. Z Haut Geschlechtskr *31:* 689, 1929.
44. Teller, H. & Vester, G.: Elektronenmikroskopische Untersuchungsergebnisse an der kollagenen Interzellularsubstanz des Koriums beim Pseudoxanthoma elasticum. Derm Wschr *136 (51):* 1373, 1957.
45. Tunbridge, R. E., Tattersall, R. N., Hall, D. A., Astbury, W. T. & Reed, R.: The fibrous structure of normal and abnormal human skin. Clin Sci *11:* 315, 1952.
46. Urbach, E. & Wolfram, S.: Über Veränderungen des elastischen Gewebes bei einem autoptisch untersuchten Falle von Groenblad-Strandbergschen Syndrom. Arch Derm Syph (Berlin) *176:* 167, 1937.
47. Wolff, H. H., Stokes, J. F. & Schlesinger, B. E.: Vascular abnormalities associated with pseudoxanthoma elasticum. Arch Dis Child *27:* 82, 1952.
48. Woo, J. C. & Chandler, F. W.: Pseudoxanthoma elasticum with gastric hemorrhage: Report of a case. Ann Intern Med *49:* 215, 1958.

Received May 11, 1970

Lis Danielsen
Department of Dermatology
Rigshospital
Blegdamsvej 9
DK-2100 Copenhagen Ø
Denmark