Virchows Archiv A Pathol Anat (1988) 413:287–296

Virchows Archiv A
Pathological Anatomy and Histopathology

Collagenous colitis: histologic, morphometric, immunohistochemical and ultrastructural studies. Report of 21 cases*

Sven Widgren, Rachid Jlidi, and Jeremiah N. Cox
Department of Pathology, Centre Médical Universitaire, Geneva University, CH-1211 Geneva-4, Switzerland

Summary. We examined 129 colonic biopsies from 21 patients with collagenous colitis, most of whom presented with diarrhoea. Morphometric measurements gave a mean thickness of the subepithelial collagen deposit of 19.5 $\mu \pm 5.1$. The trapped fusiform and/or stellate cells within the deposits were identified immunohistochemically as myoid cells, being positive with antibody against smooth muscle cell alpha-actin. Ultrastructurally, these cells have all the characteristic features of myofibroblasts. Similar cells are also present along the crypts, where they were formerly referred to as pericryptal fibroblasts. Although there is still much debate as to the pathogenesis of this condition, we would like to suggest that collagenous colitis is a disease of pericryptal myofibroblasts. During their migration and maturation into the subepithelial region they may synthesize an excess of collagen, under some yet unknown or undefined stimulus/stimuli.

Key words: Collagenous colitis – Myofibroblasts – Myoid cells – Immunohistochemistry – Ultrastructure

Introduction

Since Lindström's (1976) first description of collagenous colitis, over 100 cases have been documented in the European and American literature. Forty-eight cases were reviewed by Rams et al. (1987) in the English literature. Sixty-three other cases have been described in French and German publications, or later on in English. Bogomoletz (1983) has discussed this pathological entity extensively, but other authors have questioned its identity (Whitehead 1979; Güller and Anabitarte 1981; Williams and Rhodes 1987). The latter authors are of the opinion that the clinical spectrum appears to be too wide and that the histological change is of questionable importance. We have collected 21 cases from our files, and have studied their histological features, the morphometry of the lesions and their immunohistochemical and ultrastructural features.

Material and methods

Rectal and colonic biopsies from 21 patients (13 women, 8 men), examined between 1982 and 1986, were fixed in a 10% formalin-mercury solution, dehydrated and embedded in paraplast, and cut at 5 μ. Sections were stained with haematoxylin-eosin, van Gieson-elastin, Gomori, Giemsa, Congo red and the periodic acid Schiff (PAS) reaction.

Morphometric measures were performed following Weibel's method (Weibel et al. 1966) by counting points and intersections on a grid adapted to an automatic stage M 20 Wild microscope. Ten normal colonic biopsies from matched sex and age subjects were used as controls. Mast cells were counted on the same instrument (10 high power fields/case) on Giemsa stained slides.

The immunohistochemical studies were performed using the Avidin-Biotin-Complex (Kit Vectastain, Nector Labs., Burlingame, USA); the following antibodies were used: anti-alpha-actin smooth muscle and anti-desmin (both through the courtesy of Prof. G. Gabbiani); anti-vimentin (Amersham International, Amersham, UK), and anti-keratin AE1 (Immunostick, Bedford, UK). In addition material from 3 cases was also snap frozen in isopentane in liquid nitrogen. These were cut on a cryostat and stained with the same antibodies using the indirect immunofluorescence method. Anti-laminin (Calbiochem, Hoechst-Behring, La Jolla, USA) was also applied to these sections.

In 5 cases a second biopsy was fixed in 2% glutaraldehyde

* Presented in part at the Pathologists' Meeting "Sillon Rhône-Alpes", Grenoble, 18 June 1987, and at the Annual Meeting of the Swiss Society of Pathology, Feldkirch, 6–7 November 1987

Offprint requests to: S. Widgren

Table 1. Collagenous colitis: clinical data[a]

13 F:8 M (1.6:1)	
Age: 56.8 y (31–79)	
Diarrhoea	8
Abdominal pain	4
Constipation	3
Rectorrhages	2
Laxative abuse	1
Steatorrhoea	1
ND	5

[a] Clinical features of 21 patients

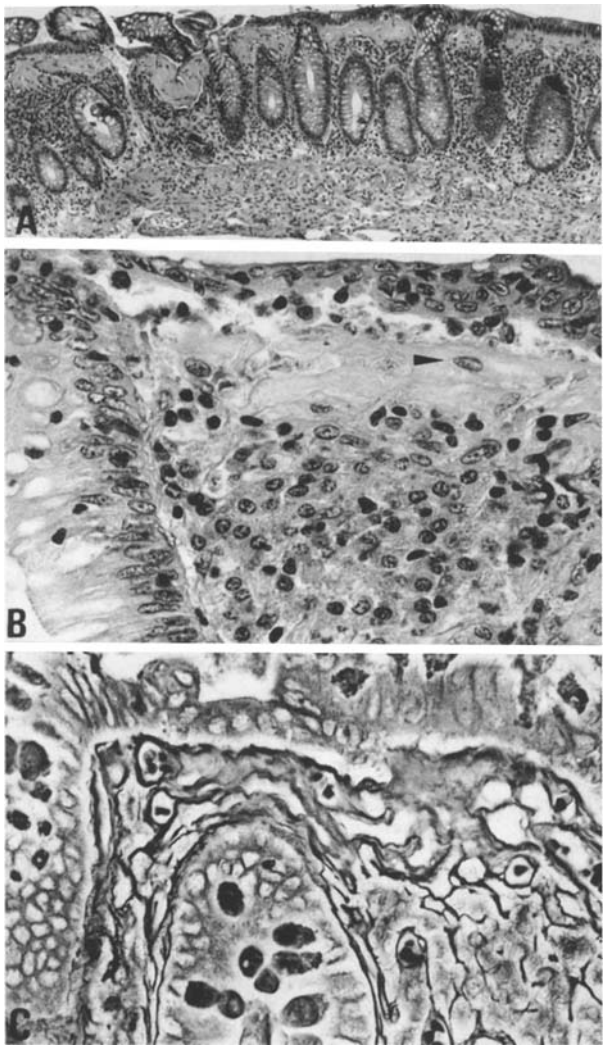

Fig. 1. (**A**) Collagenous colitis: subepithelial collagen band with irregular distribution; moderate to heavy lymphoplasmocytic infiltration of lamina propria (Haematoxylin-Eosin, 23.5×). (**B**) Detail: isolated fusiform cells (*arrow head*) trapped within the collagen band (Haematoxylin-Eosin, 530×). (**C**) The collagenous band is distinctly separated from the basal membrane and does not extend along the crypts (Gomori silver impregnation, 530×)

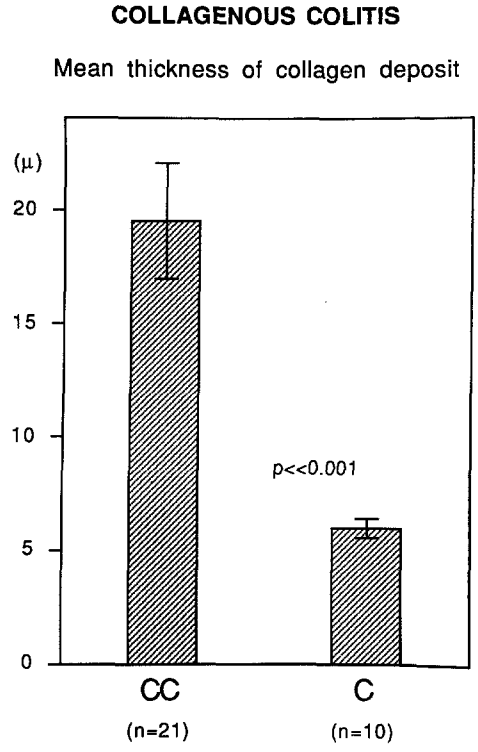

Fig. 2. Mean thickness of collagen deposit of patients (*CC*) compared with the thickness of the basal membrane in controls (*C*)

for electron microscopic studies. The material was rinsed in S-collidin buffer; ultra thin sections were cut with an ultramicrotome (Ultratome LKB), stained with uranyl-acetate and lead nitrate, then examined with a Philips EM 300 electron microscope at 80 kV.

Clinical presentation. Of the 21 patients (13 women and 8 men) with ages ranging between 31 years and 79 years (average 56 years), detailed clinical histories were obtained from 18. They are summarized in Table 1. Three patients were known to be suffering from hypothyroidism, one from sarcoidosis and another from scleroderma. All biological examinations were normal except for one patient who presented with an abnormal D-xylose test. Colonoscopy was normal in 12 patients; one patient had an erosion of the recto-sigmoid mucosa, and another hyperaemia of the colonic mucosa. Repeated searches for parasites in the stools were negative.

Control biopsies in 7 cases helped in following the evolution of the lesions. These were identical in appearance in one case and slightly or markedly improved in the other cases after 1 to 3 years, despite clinical improvement and disappearance of the symptoms in most of these cases.

Results

Pathology

A total of 129 biopsies from 21 patients were studied (mean 6.1 specimens/patients), taken from various parts of the colon and rectum, the majority in the sigmoid. Control biopsies were obtained

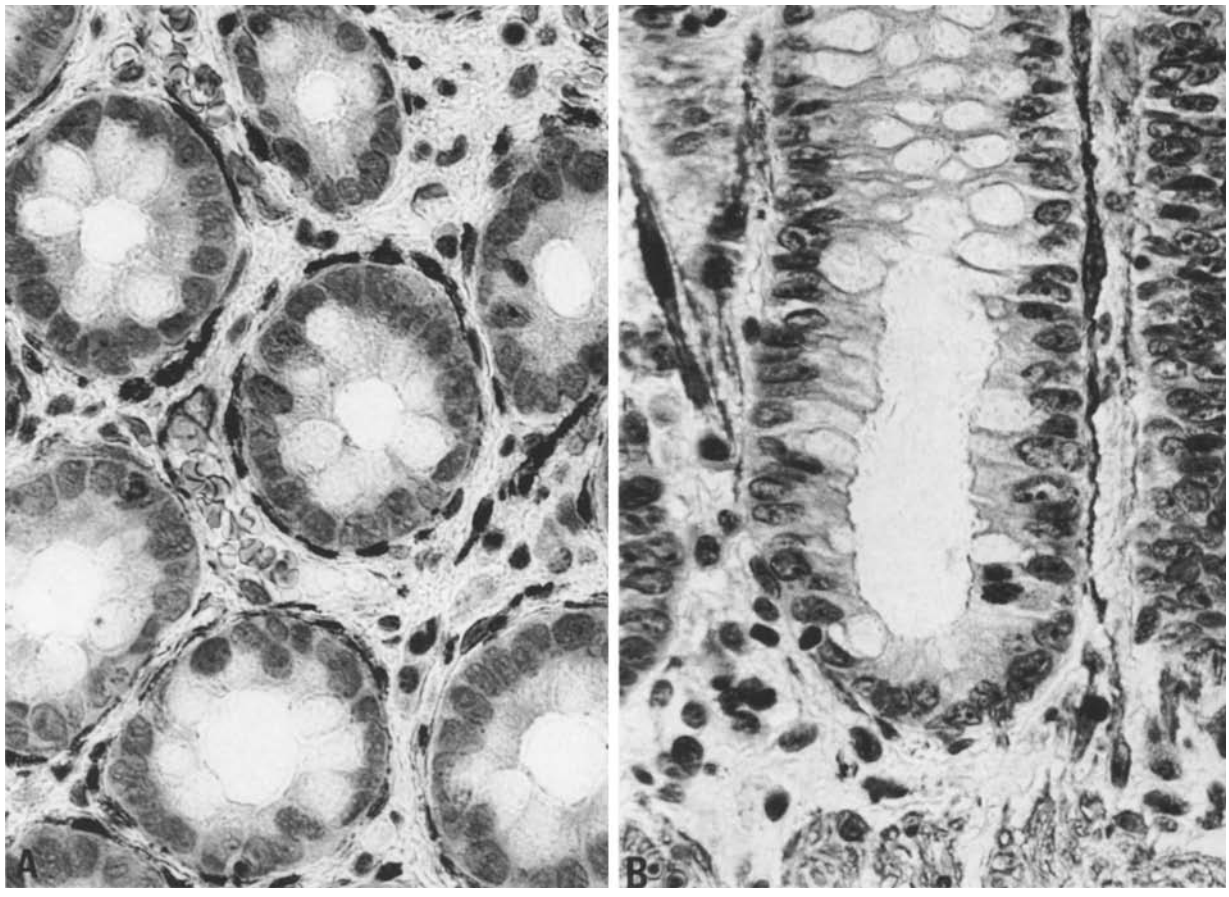

Fig. 3. Marked staining of pericryptal cells indicating their myoid nature. (**A**) With antibody against smooth muscle alpha-actin (530×); (**B**) With antibody against desmin (530×)

from 7 patients. In all cases there is a collagen band, of variable thickness, under the overlying surface epithelium (Fig. 1 A and B). It must be emphasized that the collagen band is irregularly distributed as demonstrated in the figures mentioned. Variations in the thickness of the deposits according to the site of the biopsy could not be evaluated.

This band is pale pink with HE, slightly positive with PAS, red with van Gieson-elastin, does not stain with Congo red and is not birefringent under polarized light, indicating its collagenous nature. The Gomori silver impregnation shows that the material is closely apposed to the basal membrane, and does not extend along the crypts (Fig. 1 C). It contains thin capillaries and occasional isolated, elongated cells, or fragments of cells. The surface epithelium is cylindrical in most cases. In 2 cases only it is eroded, and in 5 cuboidal. In 10 patients, it is infiltrated by occasional lymphocytes, which are accompanied by rare granulocytes in 9 cases. The crypts are not modified; in 6 cases there is an occasional lymphocyte infiltrating the crypt cells. No crypt abscesses are seen. The lamina propria has a lymphoplasmacytic infiltrate of varying intensity, accompanied by rare eosinophils and mast cells.

Slides stained with HE were used for morphometry and the measurements therefore included the basal membrane. The combined thickness of the collagen band and the basal lamina varies between 11.3 μ and 31.5 μ (mean: 19.5 μ ± 5.1) among the 21 cases studied (Fig. 2). The value of the controls (basal membrane) is between 4.3 μ and 6.4 μ (mean: 5.8 μ ± 0.8). The statistical difference between the two groups is $p \ll 0.001$, thus highly significant.

The mast cell count shows an average of 9.5 ± 1.12 (0–42) in 20 patients. In 10 controls, the average is 8.1 ± 4.70 (0–14). The statistical difference ($p < 0.5$) is not significant.

The anti-laminin antibody, specific for basal membranes, delineates this structure as a thin subepithelial membrane in all the cases as well as the controls. In the 17 cases tested with the alpha-actin

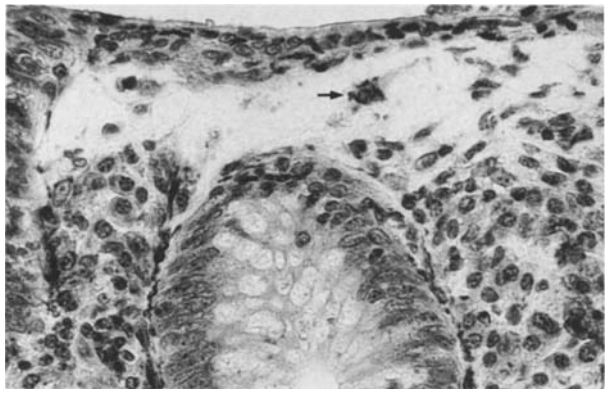

Fig. 4. Fusiform cells trapped within the collagen band, stained positively with smooth muscle alpha-actin (*arrowhead*) (530 ×)

smooth muscle antibodies, the pericryptal cells (Fig. 3A), the muscularis mucosae and the blood vessel walls are strongly positive. In 10 of these, the isolated cells within the collagen bands are also stained (Fig. 4). Staining with anti-desmin antibody in 16 cases reveals a positive reaction of pericryptal cells (Fig. 3B). In one case only a few cells within the collagen band are positive. Few pericryptal cells are stained with anti-vimentin antibody (2 out of 8 cases), whereas the anti-keratin antibody is negative.

On electron-microscopic examination the collagen deposits are intimately fused with the sub-epithelial basal membrane (Fig. 5). They are composed of collagen fibres measuring 20 to 30 nm

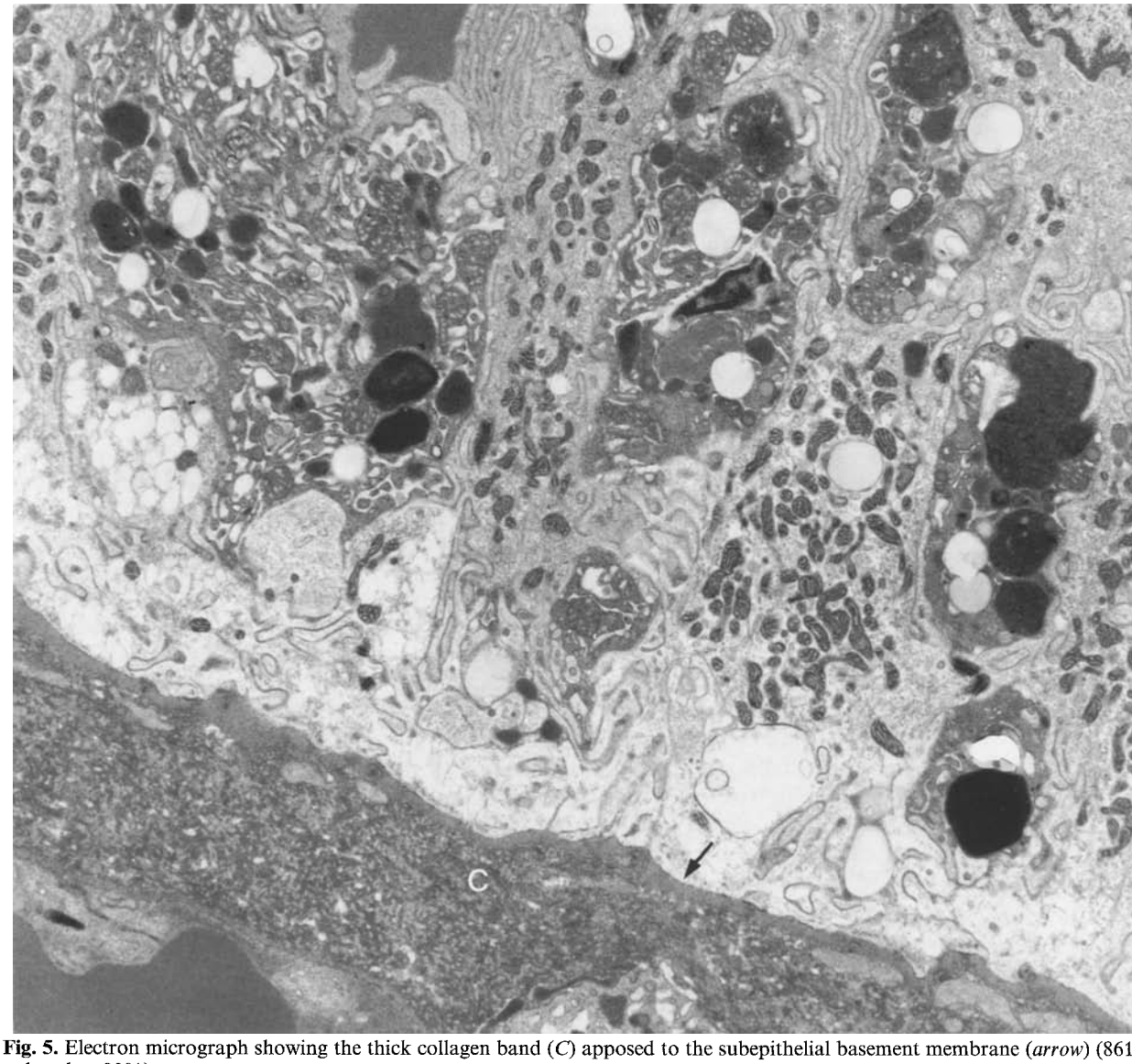

Fig. 5. Electron micrograph showing the thick collagen band (*C*) apposed to the subepithelial basement membrane (*arrow*) (8610 ×, reduced to 90%)

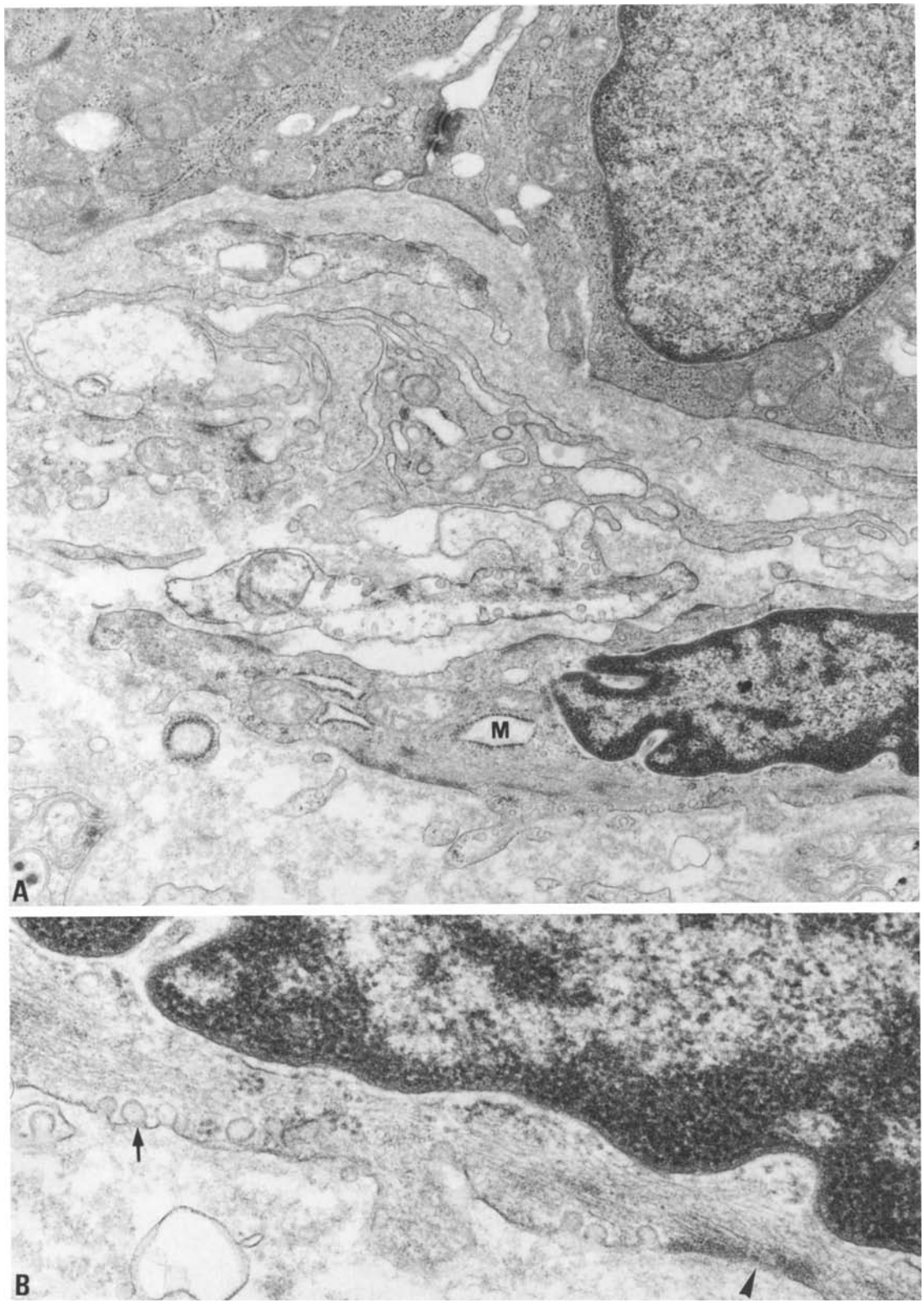

Fig. 6. (**A**) Myoid cell (*M*) trapped within the collagen band (18470×, reduced to 90%); (**B**) Detail showing numerous cytoplasmic microfilaments abutting on attachment device (*arrowhead*); notice several pinocytic vesicles (*arrow*); (58100×, reduced to 90%)

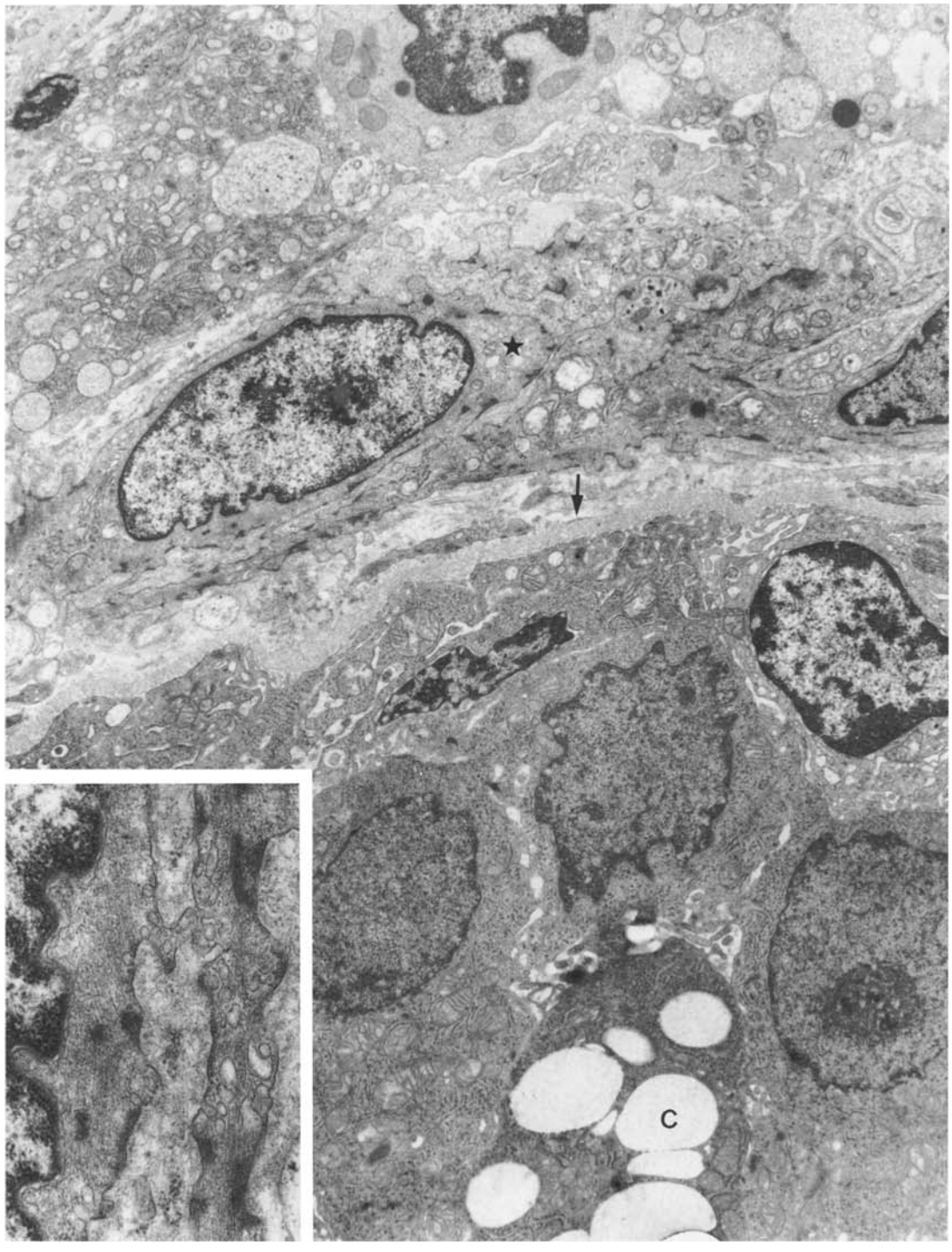

Fig. 7. Electron micrograph of crypt (*C*) with basement membrane (*arrow*) and a pericryptal cell (*) showing microfilaments and pinocytotic vesicles (6500 ×, reduced to 90%); detail in insert (10600 ×, reduced to 90%)

in diameter with an axial perodicity of about 60 nm. They are densely packed, sometimes forming fascicles without any organisation or are arranged parallel or concentric to imprisoned vessels. Sometimes they are dispersed within an amorphous ground substance, and in no instance do they extend along the crypts. The basal lamina is not significantly modified. However, in some places, it seems not to be delineated very well from the collagen fibres. The small vessels trapped within the collagen are not modified. Most important are occasional cells within the bands, sometimes

fusiform or stellate in shape (Fig. 6). Cytoplasmic expansions are also seen. The cytoplasm of these cellular elements contains microfilaments arranged in bundles which converge towards attachment devices of the cellular membrane. The cell membranes, in addition, show pinocytotic vesicles. The cytoplasm contains a well developed Golgi apparatus, and the rough endoplasmic reticulum is conspicuous in some cells, scarce in others. The mitochondria are few, and lysosomal vesicles and glycogen are in variable amounts. The pericryptal cells with their folded nuclei and their elongated cytoplasm show identical features to those observed in the cells described above (Fig. 7), but their rough endoplasmic reticulum appears less abundant.

Discussion

The clinical manifestations of collagenous colitis may be variable but most often present as a chronic watery, non-haemorrhagic diarrhoea accompanied, in most instances, with abdominal pain. The symptoms may last for months or years (Bogomoletz 1983; Giardiello et al. 1987; Lindström 1976; Rams et al. 1987). Women are most frequently affected; the average age of the patients is 56 years. Fourteen of the 21 patients in this series presented either with chronic watery diarrhoea or abdominal pain, or both. In addition, 2 patients had rectal haemorrhage, probably in connection with haemorrhoids.

Ulcerative colitis and Crohn's disease can be excluded on clinical presentation, biological tests and the colonoscopic features. The latter investigation revealed a hyperaemic, friable colonic mucosa in a few cases (Bogomoletz 1983; Rams et al. 1987) as was observed in one of our patients. Another presented with a recto-sigmoideal erosion. The condition has also been documented in association with other diseases including rheumatoid arthritis, polyarthritis, hypo- or hyperthyroidism or simple thyroid nodules (Giardiello et al. 1987; Jessurun et al. 1987; Maroy and Moullot 1984; Rams et al. 1987). One of the patients in our series had scleroderma, one hypothyroidism, and one sarcoidosis, another had been submitted to radiotherapy after hysterectomy. None had ulcerative colitis or Crohn's disease (Jessurun et al. 1987). Finally the features found in our cases and in most of those published in the literature have, in our opinion, nothing in common with minimal change colitis (Elliott et al. 1982) or microscopic colitis (Kingham et al. 1982), although Levine et al. (1987) are of the opinion that the latter condition and collagenous colitis are related entities, because microscopic colitis may precede collagenous colitis in some patients.

The histological appearance, as first described by Lindström (1976), is characterized by a thick collagen band situated below the superficial epithelial lining of the colonic or rectal mucosa, the lamina propria of which contained moderate to marked numbers of plasma cells (Jessurun et al. 1987). The same authors emphasized that the surface epithelial cells appeared cuboidal or flattened; that degenerative features were common, and that this change was accompanied by focal or patchy lymphocytic infiltration; they noted also surface epithelial detachment in about half their cases. In our series however, only 2 cases showed erosion, and 5 a cuboidal appearance; in 10 patients there was a slight lymphocytic infiltration. Other reports have shown that the mucosa may show minor histological changes (Bogomoletz et al. 1980; Flejou et al. 1984). Giardiello et al. (1987) have insisted on the abundance of mast cells in the lamina propria, observation that our counts did not confirm.

The thickness of the collagen deposit has been the subject of numerous studies. Some authors (Rams et al. 1987) have noted a variation between 7 μ and 100 μ, others (Bogomoletz 1983) between 7 μ and 60 μ. According to Jessurun et al. (1987), the overall mean thickness of the subepithelial collagen thickening of 15 cases was 14.5 μ. This variation between different authors might be the result of several factors including the fixative, or the various methods, often subjective, employed in measuring (Bogomoletz 1983; Fausa et al. 1984). The distribution and thickness of the collagen deposits are varying (Wang et al. 1987; Jessurun et al. 1987). In a few cases (Pariente and Maître 1986; Pieterse et al. 1982; Rams et al. 1987; Debongnie et al. 1984; Eaves et al. 1983) the collagen deposit diminished in thickness or disappeared in control biopsies after treatment. However these observations could be questioned, since, as already mentioned, the distribution and thickness of the deposits are known to be quite variable. The morphometric method used in this study gave a mean value of 19.5 μ ± 5.1 μ with a range between 11.3 μ and 31 μ, which is statistically highly significant, when compared with the thickness of the basal membrane of the controls, the means of which was 5.8 μ ± 0.8 μ (range: 4.3 μ to 6.4 μ). These results are comparable to those of Bogomoletz et al. (1980) (between 4.6 μ and 6.9 μ) ,but higher than those of Giardiello et al. (1987) (between 2.3 μ ± 12. μ).

Ultrastructurally, the collagen deposit was made up of fibres measuring between 20 nm and 30 nm in diameter with an axial periodicity of 60 nm (Bogomoletz et al. 1980; Flejou et al. 1984). They were arranged sometimes in bundles, but not necessarily oriented parallel or perpendicular to the surface as has been reported by some authors (Fausa et al. 1984; Yeshaya et al. 1984). They were often arranged parallel or concentric to the vessels (Guarda et al. 1983; Stubbe-Teglbjaerg and Thaysen 1982) and only rarely were they found scattered in an amorphous granular interstitial substance. The subepithelial basal membrane was not notably altered as has been indicated by others (Galian et al. 1982; Flejou et al. 1984; Serin et al. 1986) but it was sometimes not clearly separated from the collagen deposit, as was also observed by Bamford et al. (1982). It is important to underline that the collagen band was restricted to the sub-epithelial surface region and did not involve the pericryptal basal membrane as has been noted by numerous authors (Bogomoletz 1983). The entrapped cells, often referred to as fibroblasts (Bamford et al. 1982; Farah et al. 1985; Flejou et al. 1984; Grouls et al. 1982; Guarda et al. 1983; Pariente et al. 1985; Rask-Madsen et al. 1983; Gardiner et al. 1984) were found to have the ultrastructural features of myofibroblasts (Gabbiani et al. 1972). Kaye et al. (1964) referred to the latter cells as pericryptal fibroblasts, as a result of their studies both in man and rabbits and, in their Fig. 11, described a striking thickness and density of the collagen table. This may represent the first histological description of the disease not yet identified as collagenous colitis. Hwang et al. (1986) considered the cells to be activated with some synthetic activity, whereas pericryptal cells of the upper and middle portion of the crypts were probably activated myofibroblasts. The detailed description of the pericryptal cells of normal colonic mucosa by Richman et al. (1987) leaves no doubt as to the myofibroblastic nature of these cells and these findings are identical to our observations.

Most of the immunohistochemical descriptions of the mucosa in collagenous colitis have dealt with the types of collagen found in the deposit (Birembaut et al. 1982; Flejou et al. 1984; Loo et al. 1985; Mason and Jewell 1985) but, to the best of our knowledge, little or no attention has been given to the immunohistochemical characterization of the cells within the deposit. In about half of the cases these cells stained positively with the monoclonal antibody for alpha-actin smooth muscle, an isomorphic actin specific for smooth muscle (Skalli et al. 1986). Apart from one case, they did not stain with anti-desmin antibody specific for the intermediate filaments of smooth muscle cells in general.

Interestingly, all the pericryptal cells, both in the cases studied and the controls, were strongly positive with the alpha-actin smooth muscle as well as with the anti-desmin antibody. Recently Richman et al. (1987), using a new monoclonal antibody (PR_2D_3), the antigen of which is not altogether identified, concluded that pericryptal cells in the colon were myofibroblasts and thus are in agreement with our own findings. These staining properties that we have observed would indicate that the pericryptal cells as well as those within the collagen bands are myoid cells (Skalli et al. 1987).

The cause(s) and pathogenesis of the disease remain obscure. In one case with active secretion of chloride, in which prostaglandin A_2 levels were elevated, Rask-Madsen et al. (1983) speculated that prostaglandins may be the local mediators of this secretion. The inflammation of the lamina propria suggested to Pieterse et al. (1982) the hypothesis that there was an underlying infectious agent. Rams et al. (1987) are of the opinion that it is an inflammatory disease of undetermined origin, "whether infectious or non infectious is unknown". The hypothesis of an autoimmune disease has been proposed by only one group of authors (Jessurun et al. 1987), and still needs further verification. Based on the hypothesis of Bogomoletz (1980) and Grouls et al. (1982), we would like to propose another pathogenesis. Collagenous colitis is possibly a disease of the pericryptal myofibroblasts, which may occur during their migration towards the subepithelial region. In the pericryptal site, they probably fulfill a contractile action on the crypts, as was also suggested by Richman et al. (1987). In the course of their maturation, during their migration towards the extremity of the crypts and the subepithelial region, they acquire a fibroblastic function and synthesize collagen precursors, which, under some unknown stimulus, are produced in excess, and constitute the collagen deposit which is the morphological marker of collagenous colitis.

Acknowledgements. We wish to thank Prof. Giulio Gabbiani for advice and suggestions, and for providing anti-desmin and anti-smooth muscle alpha-actin antibodies; Mrs. Marie-Claire Peclet, Miss Béatrice Conne, Miss Christine Magnin, Mrs. Ingrid Fuglister and Mr. Miladin Jovanovic and his team, for technical assistance; Mrs. Claire-Lise de Marignac for typing the manuscript; Mssrs. Jean-Claude Rumbeli and Etienne Denkinger for the photographs; Mr. G. Rapin for the graphic work.

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Accepted May 6, 1988