PANETH CELL METAPLASIA IN ULCERATIVE COLITIS

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The pathologic diagnosis of ulcerative colitis is reached by exclusion. In the absence of specific infective agents or lesions, the pathologist depends principally upon the clinical history, the characteristic gross appearance of the ulcers, and the striking tendency for pseudopolyp formation. However, the identification of certain microscopic changes may be helpful in many cases, notably the presence of cryptitis, nonspecific ulceration, focal granulomas, etc. We have recently become interested in another microscopic alteration—Paneth cell metaplasia—a lesion which was described by Hertzog[1] in a single case of ulcerative colitis 13 years ago but which apparently has not been mentioned in any modern treatise on the pathology of the disease.[2-7]

Paneth cells are normally present in the mucosa of the small intestine, but most authorities state that they are absent from the normal colon.[8,9] Nevertheless, it should be noted that Bloch[10] found numbers of these cells in the large intestine of newborn infants although they could not usually be demonstrated at older ages. However, he did find Paneth cells in one adult with appendicitis, and Hertzog[1] noted them in 3 of 25 diseased colons—in the case of ulcerative colitis mentioned above and in two cases of tuberculous typhlitis. Our interest in these cells stems from an accidental observation made during the microscopic study of a segment of colon removed surgically from an individual with long-standing ulcerative colitis. On preliminary examination the impression was gained that Paneth cells were almost as numerous in the colonic crypts as they were in the mucosa of the accompanying segment of terminal ileum (Fig. 1). The metaplastic change was so striking that it stimulated us to search for it in tissue from other surgically treated cases of ulcerative colitis in our hospital and in an associated institution. The results of this review and of the observations in a comparable number of colons resected for other diseases are the basis of the present report.

MATERIAL AND METHOD

Tissue was obtained from all cases of ulcerative colitis that had been treated by partial colectomy in our hospital over a period of 10 years. Since only 4 such cases

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were available, the series was augmented by 6 additional specimens from cases of ulcerative colitis treated surgically at Victoria Hospital, London, Ontario. Multiple sections of the colon were cut at intervals from the paraffin blocks already available from each of these 10 cases; they were stained with hematoxylin and eosin and examined microscopically for the presence and the incidence of Paneth cells. The exact procedure was to count the number of glands in as many low power (× 70) microscopic fields as possible, the maximum number of microscopic fields counted in any one case being 100. The number of glands containing one or more Paneth cells was then noted. To avoid counting the same gland twice in any one microscopic field, only the bases of the crypts were considered; similarly, the only Paneth cells counted were those at the bases of the same crypts. The criterion for the diagnosis of Paneth cells was the presence of large eosinophilic granules, supranuclear in position, lying in the cytoplasm of cells at the bases of the crypts[9] (Fig. 2).

Similarly, the incidence of Paneth cells was determined in colons which had been resected for diseases other than ulcerative colitis. Ten such specimens were obtained from our own files or from Victoria Hospital. Most of them were examples of partial colectomy performed for adenocarcinoma. The search for Paneth cells in this material was made from blocks of tissue as far distant as possible from the sites of neoplasm.

No attempt has been made to determine the incidence of Paneth cell metaplasia of the colon in necropsy material as it was suspected that postmortem autolysis might interfere with the staining qualities of the specific cytoplasmic granules.[1]

Observations

Each of the 10 cases listed in Table I fulfilled the criteria described for ulcerative colitis, both pathologically and clinically. They have been listed in the table in the order of duration of symptoms. The percentages of glands showing the presence of one or more Paneth cells at the bases of crypts in each case of ulcerative colitis are given in the same table. It will be noted that the number of crypts showing the presence of these cells varied from 0.6 per cent to 30 per cent (average 19.6 per cent) and that, with the exception of case 8, there was a reasonable correlation between the incidence of Paneth cells and the clinical duration of disease. This is in marked contrast to the number of Paneth cells found at the bases of crypts in the control specimens (Table II), in which the average number was only 0.3 per cent.

The number of Paneth cells found in any one crypt in the cases of ulcerative colitis varied considerably; generally, 1 or 2 of these cells were found although occasionally as many as 5 could be distinguished. In addition, a diminution in the number of crypts per low power field, compared with that in the control group, was present in the ulcerative colitis. This has been noted previously by Lumb.[5]

No Paneth cells were seen adjacent to areas of recent acute ulceration unless evidence of previous damage was present; nor were their granules ever noted within a crypt abscess. The cells were usually found in areas which were interpreted as regenerated or previously damaged mucosa. In these locations the crypts were often irregular, the mucosa thinner

than normal, and the submucosa scarred. In one instance, Paneth cells were seen in the depth of a crypt which was, or appeared to be, affected by cryptitis at a different level (Fig. 3); and in another, a small clump of cells which contained a few eosinophilic granules lay at the margin of a micro-abscess. These latter findings, although suggestive of an association between Paneth cells and cryptitis, were by no means definite.

TABLE I

THE INCIDENCE OF PANETH CELL METAPLASIA OF THE COLON IN ULCERATIVE COLITIS

Case no.	Age (yr.)	Sex	Duration of disease (yr.)	No. of low-power fields counted	Total crypts counted	Av. no. of crypts per low-power field	Total no. of crypts with one or more Paneth cells	Percentage of crypts with one or more Paneth cells
1	47	F	20	43	245	6	63	26.0
2	37	M	17	100	649	6	174	27.0
3	39	F	16	94	585	6	174	30.0
4	32	M	13	100	935	9	252	27.0
5	49	M	10	100	928	9	243	26.0
6	29	M	9	100	682	7	124	18.0
7	20	F	4	38	255	7	31	12.0
8	21	M	1½	98	780	8	191	24.0
9	20	F	1½	52	418	8	20	5.0
10	36	F	1	55	311	6	2	0.6
							Average	19.6

TABLE II

THE INCIDENCE OF PANETH CELL METAPLASIA IN "NORMAL" COLONS

Case no.	Age (yr.)	Sex	No. of low-power fields counted	Total crypts counted	Av. no. of crypts per low-power field	Total no. of crypts with one or more Paneth cells	Percentage of crypts with one or more Paneth cells
11	72	M	100	1114	11	3	0.3
12	76	M	100	1407	14	2	0.1
13	57	M	100	1102	11	3	0.3
14	63	M	100	1348	13	8	0.6
15	68	M	100	1234	12	2	0.2
16	80	F	100	1187	12	1	0.1
17	77	F	100	979	9	14	1.4
18	74	F	100	1182	12	0	0.0
19	65	M	100	1125	11	4	0.4
20	45	M	100	1320	13	0	0.0
						Average	0.3

DISCUSSION

Contrary to the views expressed in earlier reports,[1,8,9] our results indicate clearly that Paneth cells are present in the mucosal crypts of most "normal" colons. However, their numbers are so sparse that they can only be demonstrated by a searching examination of many microscopic fields in a particular specimen. On the other hand, their number

has been found to be enormously increased (even as much as 300 fold) in association with the regenerative phase of ulcerative colitis (Tables I and II).

The obvious question arises: Are such large numbers of Paneth cells in the colon of any importance in the initiation of ulcerative colitis? We doubt if this is so because of the definite suggestion in our cases that the more long-standing the disease process, the greater the number of Paneth cells (Table I). Indeed, we found very few of them in the colon from one individual (case 10) who had suffered from symptoms for only one year. This being the case, the presence of Paneth cells in association with long-standing ulcerative colitis must be interpreted as a metaplastic alteration—as the differentiation of previously undifferentiated cells at the bases of colonic crypts. They are therefore regarded as the result, rather than the cause, of colonic inflammation or regeneration. This is analogous to the intestinalization of gastric mucosa found in chronic gastritis. This interpretation, however, does not necessarily mean that Paneth cells in these locations have no pathogenetic significance; it does not eliminate the possibility that they may assist in perpetuating the disease.

The exact function of the Paneth cells in man is still a mystery. At one time they were presumed to secrete the ferments of the intestinal juice,[11] and this view has had a certain amount of support in recent publications. For example, Blaschko and Jacobson,[12] citing van Weel, asserted that Paneth cells in the ileum of the rat produced a proteolytic exoenzyme, dipeptidase. Marques de Castro, Sasso and Saad[13] also presented evidence that the secretion of these cells in the ant eater was capable of digesting chitin, whereas in the rabbit it digested scleroprotein. If it can be shown that the Paneth cells of man have similar or related proteolytic actions, their liberation into the lumens of colonic crypts offers a possible explanation for the production of micro-abscesses (cryptitis) and for the spreading mucosal inflammation which are such characteristic features of the disease.[4,6] This hypothetical mechanism should apply particularly in patients in remission, since with normal dehydration of the fecal stream there would be less dilution of the liberated ferments and more chance of a local histolytic effect. Further support to this suggestion is found in the observation that even surgically defunctioned colons were subject to continuing active inflammation and ulceration.[4] The words of Warren and Sommers[6] are also pertinent: "Presence of early lesions [cryptitis] in a uniform location within the crypts, even though scattered along the course of the intestine, suggests . . . that the irritant is being released by the mucosa. The possible role of such agents as proteolytic enzymes in ulcerative colitis already has

aroused much clinical interest, but their origin from the colonic mucosa has not been considered previously and now requires further investigation."

More information on the functions of Paneth cells is therefore required, and in particular on the possible proteolytic action of their granules. Until this information is available, the significance of Paneth cell metaplasia in the pathogenesis of ulcerative colitis must remain speculative. This is particularly so since we have not yet succeeded in demonstrating, unequivocally, Paneth cells in intimate association with a micro-abscess in a single colonic crypt.

Summary

A searching examination of many microscopic fields of colons resected surgically for ulcerative colitis, and for other diseases, has revealed Paneth cells in the colonic crypts of most of the specimens. They were exceedingly sparse in "normal" colons, but their numbers were markedly increased in cases of ulcerative colitis (as much as 300 fold). The widespread Paneth cell metaplasia of the large intestine is considered to be the result, rather than the cause, of ulcerative colitis. On the other hand, the possibility that Paneth cells in the colonic crypts may be important perpetuating agents of the disease has not been eliminated.

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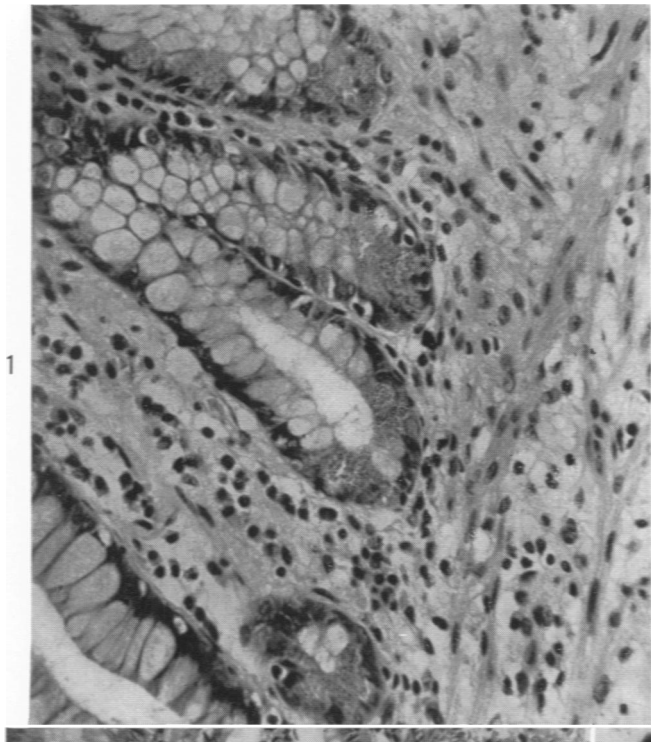
LEGENDS FOR FIGURES

Photographs were prepared from sections stained with hematoxylin and eosin.

FIG. 1. Four crypts in the large intestine of a case of long-standing ulcerative colitis (case 5). Each crypt has numbers of Paneth cells at its base. × 300.

FIG. 2. A single colonic crypt containing numerous Paneth cell granules, supranuclear in position, at the base of the crypt. × 600.

FIG. 3. The crypt of Lieberkühn on the left contains a micro-abscess at one level. At the base of the crypt, shown in the box and magnified on the right, there are several Paneth cells. Left, × 200; right, × 600.



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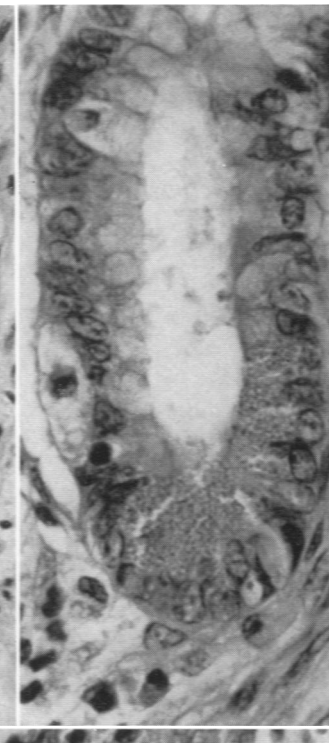

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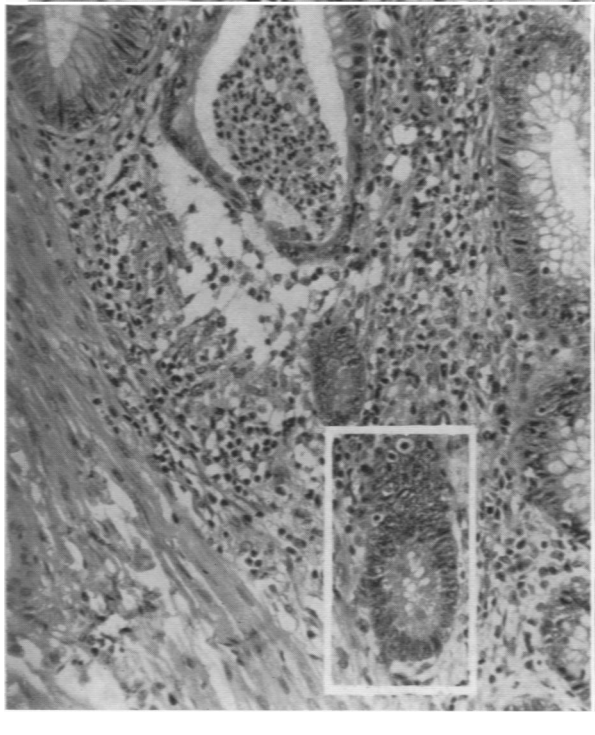

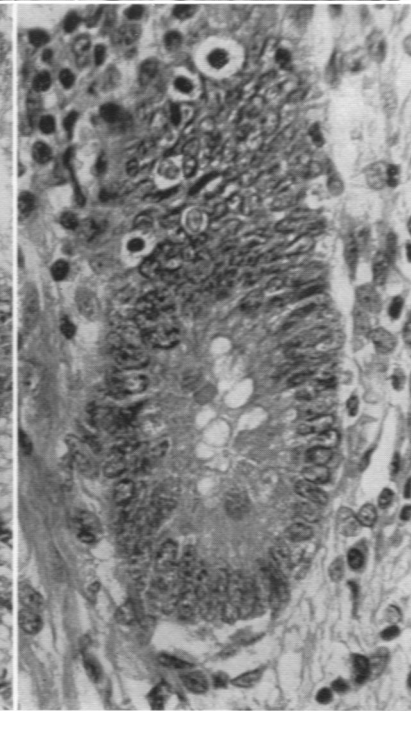

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