THE PANETH CELL IN HEALTH AND DISEASE

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Introduction

Paneth cells were discovered by Schwalbe in 1872 in a study of the gastro-intestinal glands of mice. Fifteen years later, in 1888, Paneth rediscovered them in the intestinal tract of the mouse and described their morphology, staining properties and function in great detail (Fig. 1). In 1891 they were discovered in man (Schäffer, 1891; Nicholas, 1891).

Paneth cells are found in the intestinal mucosa of a variety of animals which include a wide range of amphibians, reptiles, birds and mammals (Baecker, 1934). In the primitive animals such as lizards they are widely distributed throughout the epithelial surface of the intestinal tract (Nicholas, 1891). However, during the course of evolutionary development they become localized in the crypts of Lieberkühn. In man they are found normally in the fundus of the crypts of Lieberkühn (Fig. 2) of the small intestine and appendix, and have been reported in the colon (Hamperl, 1928; Verity *et al.*, 1962), stomach and pancreas (Helly, 1905). Their presence in the last three sites has not been generally confirmed. In the small intestine they occur in contiguous groups of up to 20 cells with no other cells between them. It has been estimated that they are found in about 75 per cent of crypts of jejunum and ileum and 50 per cent of crypts of duodenum. In the appendix they occur in much smaller numbers.

In diseases of the intestinal tract the number of Paneth cells normally present may be altered.

In the stomach there is proliferation in association with gastritis and gastric carcinoma. In the small intestine there is a diminution in number in the coeliac syndrome (Creamer and Pink, 1967). In the colon Paneth cells are found in increased numbers in ulcerative colitis (Watson and Roy, 1960; Paterson and Watson, 1961; Verity *et al.*, 1962), ' tuberculous typhlitis ' (Hertzog, 1937), other inflammatory conditions (Thorel, 1898), benign tumours (Thorel, 1898; Schmidt, 1905; Lendrum, 1948; Morson, 1955 and others) and carcinomas (Schmidt, 1905; Kerr and Lendrum, 1936; Lauren, 1961).

In addition to proliferation of the Paneth cell in response to disease, malignant proliferation can occasionally occur (Stern and Sobel, 1961; Holmes, 1965; Lewin, 1968).

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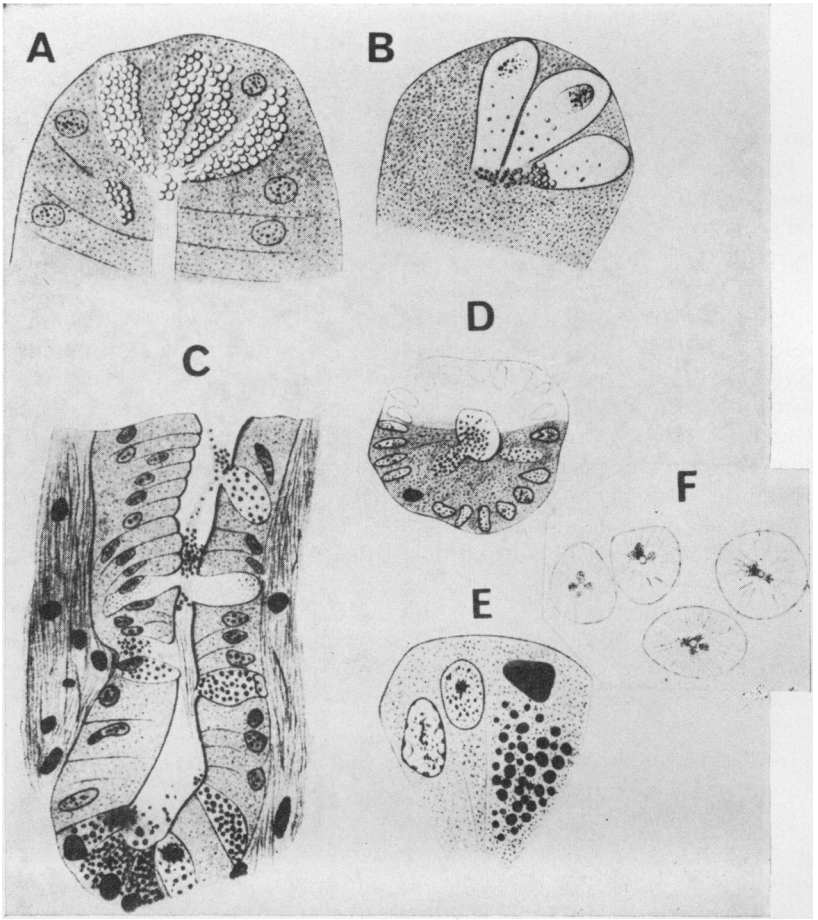


Fig. 1. The Paneth cell as illustrated by Paneth in 1888 (A), (B), (C), (D) and (E) and Schwalbe in 1872 (F). (A) Unfixed section of mouse intestine to show Paneth cells at fundus of crypts of Lieberkühn. (B) Same as (A), but after secretion of granules. (C) and (D) Same as (A) and (B), but its tissue fixed in picric acid and stained with haematoxylin. (E) To show difference in appearance of the Paneth cell nucleus from the nucleus of other cells. (F) The Paneth cell as illustrated by Schwalbe (1872).

The morphology of the Paneth cell is characteristic and is illustrated in Figure 3. It is a cone-shaped structure with its base adjacent to the basement membrane and apex bordering the lumen of the crypts of Lieberkühn. Its nucleus lies at the base of the cell. The cytoplasm contains large granules which are visible in fresh and fixed specimens and are situated in the upper half of the cell. They are refractile in the fresh state, vary in number and size and take up numerous dyes such as eosin, safranine, picric acid, acid fuchsin, azan stains, aniline dyes and others.

Under the electron microscope the cells possess a brush border and their cytoplasm contains many large membrane-bounded granules, an extensive Golgi apparatus and an elaborate endoplasmic reticulum (Dalton, 1951; Hally, 1958; Trier, 1963). These appearances resemble the pancreatic exocrine acinar cells.

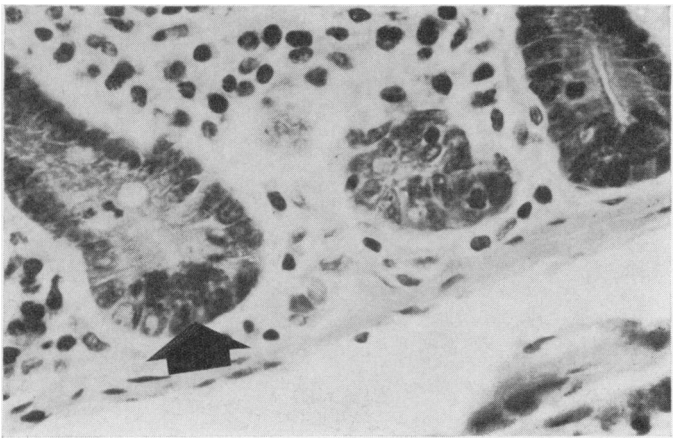


Fig. 2. Distribution of Paneth cells (arrowed) in the normal human jejunum. Cells lie at fundus of the crypts of Lieberkühn (Masson's trichrome × 200).

Studies on the chemical composition of the granules show a carbohydrate-protein complex, some free fat (Liu and Baker, 1963) and a small amount of phospholipid (Riecken and Pearse, 1966). The cytoplasm contains zinc (Stampfl, 1959). The protein moiety of the carbohydrate-protein complex contains amino, carboxylic, phenolic, tryptophan, arginine and tyrosine groups (Selzman and Liebelt, 1961; Taylor and Flaa, 1964). The carbohydrate component appears to vary from one species to another. Thus in the rat it is probably a mucoprotein or glycoprotein, whereas in the mouse an acid mucopolysaccharide is also present, and surrounds the granules. A large number of enzymes have also been demonstrated histochemically, within the granules. They include non-specific acid phosphatase, E600 resistant esterase, B glucosaminidase, mono-amine oxidase, ubiquinone, B glucuronidase, thiamine pyrophosphatase, succinate dehydrogenase, cytochrome-C-oxidase and

nicotinamide dinucleotide diaphorase (Riecken and Pearse, 1966). The latter authors conclude that the granules fulfil the enzymatic criteria of lysosomes and suggest that the demonstration of lysosomal activity and discharge into the intestinal lumen shows that the Paneth cell is a digestive gland of high efficiency.

Paneth cells are exocrine cells which discharge their granules into the intestinal lumen (Fig. 3). The secretory stimulus was thought to be food, but recently Trier *et al.* (1967) have shown that, in mice, secretion is continuous even during fasting and can be elicited by pilocarpine and inhibited by atropine. The nature of the secretions and function of the

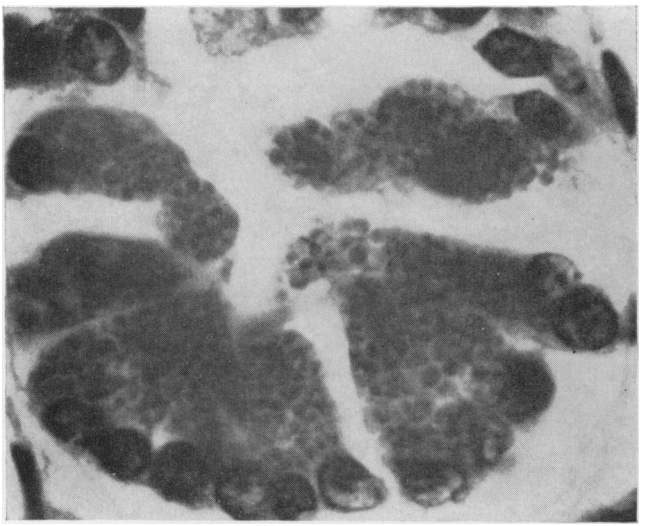


Fig. 3. High-power view of Paneth cells to show supranuclear granules and secretion of Paneth cell granules into lumen of crypts of Lieberkühn (phloxine tartrazine × 500).

cells has not been established. There are two main schools of thought, the one suggesting that they are zymogenic and the other that they are goblet cell precursors.

The arguments in favour of the goblet cell theory are the presence within the Paneth cells of intergranular cytoplasm with the staining characteristics of mucin and the presence of transitional cell forms, intermediate in structure between Paneth and goblet cells.

Against this is the fact that Paneth cells are absent from tissues containing large numbers of goblet cells (for example, the respiratory tree) and also that many investigators have been unable to find transitional cell forms.

Most people at present favour the zymogenic theory because of the close

morphological resemblance of the Paneth cells to the enzyme secreting pancreatic cells and because of the enzyme histochemical properties of the granules.

Original work

The object of my study was to investigate (1) the distribution of the Paneth cell in the normal human intestine; (2) the relationship of the Paneth cell to disease of the intestines; and (3) the function of the cell.

Distribution of the Paneth cell in the normal human intestines

The material examined consisted of autopsy, biopsy and operation specimens, details of which are summarized in Table I. The main problem of this study was the difficulty in obtaining suitable normal material.

TABLE I

MATERIAL EXAMINED FOR THE DISTRIBUTION OF THE PANETH CELL IN HEALTH

Material	*Number examined*	*Clinical details*
Autopsy	15	Death unrelated to gut
Jejunal biopsy	3	Investigation of steatorrhoea
Rectal biopsy	29	Colonic symptoms
Appendicectomy ..	37	Clinical appendicitis / Incidental removal
Terminal ileum ..	10	Ulcerative colitis
Foetuses	28	Termination of pregnancy Age 8 to 22 weeks gestation

TABLE II

PANETH CELL DISTRIBUTION IN THE HISTOLOGICALLY NORMAL ADULT AND FOETAL INTESTINE

	Small intestine		*Appendix*	*Colon*				
	Jejunum	*Ileum*		*Caecum*	*A.C.*	*T.C.*	*D.C.*	*Rectum*
Autopsy material ..	+ (6 of 6)	+ (6 of 6)		+ (3 of 10)	+ (1 of 13)	+ (1 of 15)	0	0
Biopsy material								
Jejunal ..	+ (3 of 3)							
Rectal ..								+ (1 of 29)
Operation specimens								
Appendix			+ (17 of 37)					
Terminal ileum ..		+ (10 of 10)						
Foetus	+ (2 of 28)			0	0	0	0	0

A.C. = Ascending colon. T.C. = Transverse colon. D.C. = Descending colon.

Autopsy specimens were adequate for finding Paneth cells in the small and large bowel, but unreliable for more detailed examination, because of autolysis. Thus, Paneth cells were found in all specimens of small bowel and four out of 15 specimens of large bowel. In the latter, they occurred in the caecum, ascending colon and transverse colon but not in these three sites in each case.

For detailed studies of Paneth cell distribution, histologically normal

biopsy and operation specimens were also examined, because these were well preserved as they were fixed immediately on removal. The results are shown in Table II. It was found that the jejunum and ileum contained about the same number of Paneth cells. However, whereas Hertzog (1937) reported them in about 75 per cent of all crypts of Lieberkühn, in this material they were found in almost every crypt. This discrepancy in results was probably because Paneth cells were not all found in one place in the crypts of Lieberkühn and would be missed unless serial sections were examined.

In appendices Paneth cells were found in about 75 per cent of specimens. Unlike the small intestine, they occurred only in about 8 per cent of the crypts and the number per crypt was small.

Amongst the rectal biopsies they occurred in only one specimen. Further evidence for the presence of Paneth cells in the normal colon is presented later.

The Paneth cell was found in two of the 28 embryos and foetuses ranging from eight to 22 weeks gestation. They occurred only in the small intestine of a 19 and 22 week foetus and occupied the same position as in the adult. Thus they were found to develop considerably earlier than previously reported (Schmidt, 1905). Goblet cells were found in foetuses from 11 weeks onwards, thus discrediting the hypothesis put forward by Bizzozero (1892) that the Paneth cell is a goblet cell precursor. Furthermore, ' intermediate ' cell forms were not seen.

The Paneth cell in disease of the intestinal tract in man

In every case the diagnosis was made on histological and not clinical grounds. An attempt was made to examine about 30 specimens of each disease because it was a large enough number to give a fairly accurate impression of resulting changes. In the case of rare diseases all the material available was examined.

Influence of disease of the small intestine and appendix on the Paneth cell (Table III)

Disease of the small intestine and appendix caused a fall in number of Paneth cells normally present. There were two exceptions:

1. Some cases of Crohn's disease in which there was an increased number of Paneth cells.
2. In chronic appendicitis, in which there was no change.

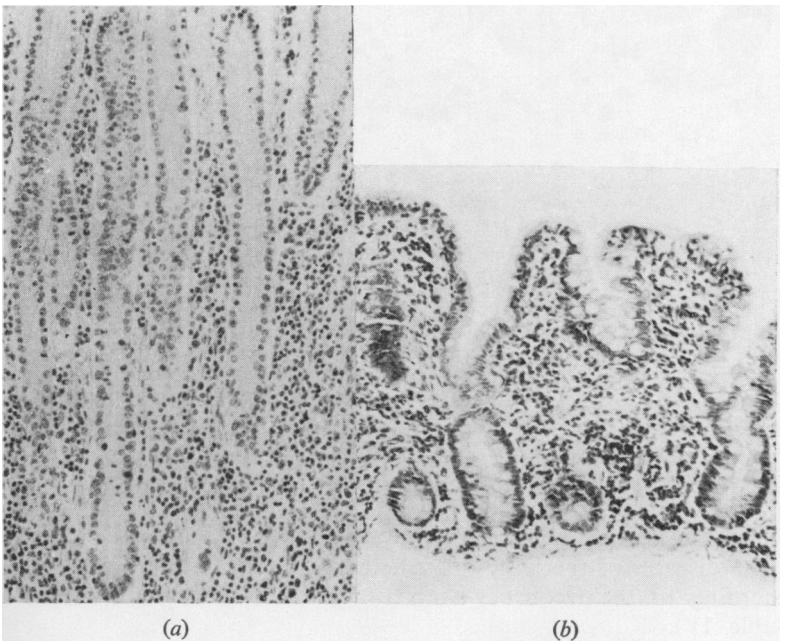
The factors responsible for the variation in number of Paneth cells were not the same in every disease. In Crohn's disease, ulcerative colitis with reflux ileitis and tumours, the reduction occurred in the diseased segments of intestine only, probably as a result of a non-specific injury (Fig. 4*a*).

In mucoviscidosis the most important abnormality appeared to be an inadequate or abnormal synthesis of granules, because many of the cells

TABLE III

INFLUENCE OF DISEASE OF THE SMALL INTESTINE AND APPENDIX ON THE PANETH CELL

Disease	*Effect on number of Paneth cells*
Small intestine	
Crohn's disease	Usually decreased Sometimes increased
Ulcerative colitis with reflux ileitis ..	Decreased
Mucoviscidosis	Decreased
Villous atrophy	Decreased
Tumours	Decreased
Appendix	
Acute appendicitis	Decreased
Chronic appendicitis	No change
Ulcerative colitis	Decreased
Crohn's disease	Decreased



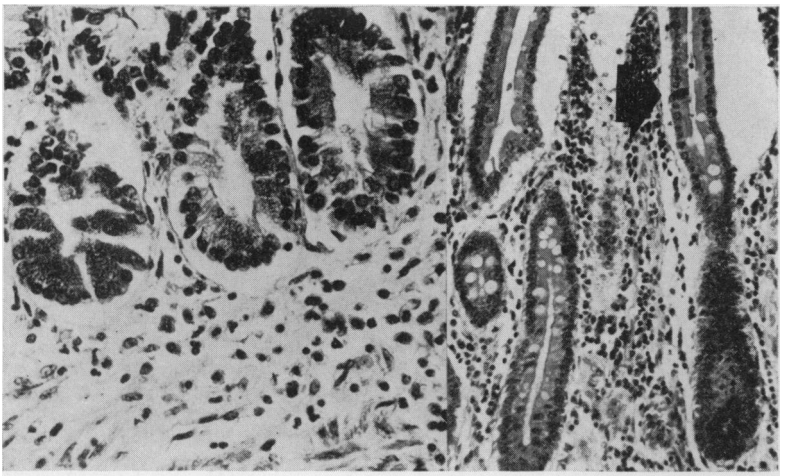
(*a*) (*b*)

Fig. 4. (*a*) Lymphosarcoma of ileum. Section of mucosa showing diffuse neoplastic infiltration and complete absence of Paneth cells (H. and E. × 57). (*b*) Per-oral human jejunum biopsy showing severe villous atrophy. Note absence of Paneth cells at fundus of crypts of Lieberkühn (H. and E. × 114).

contained small, poorly formed granules. This would not be surprising since specialized cells other than the goblet cells (for example, those in sweat glands) are also abnormal in this disease. Pressure atrophy of Paneth cells was responsible for a reduced number in areas containing cystically dilated crypts of Lieberkühn.

In villous atrophy the morphology of the mucosa changes to that of a large intestinal pattern and the Paneth cell depletion appears to be part of the mucosal reaction to injury (Fig. 4*b*).

Proliferation of Paneth cells occurred in Crohn's disease in areas showing mucosal regeneration, and in some specimens Paneth cells were



(*a*) (*b*)

Fig. 5. (*a*) Ileum in Crohn's disease. Mucosa shows proliferation of Paneth cells up the sides of the crypts of Lieberkühn (phloxine tartrazine × 177). (*b*) Ileum in Crohn's disease. Mucosa shows proliferation of Paneth cells, one of which is situated at the base of a villus (arrowed) (trichrome × 111).

actually seen on the intestinal villi (Fig. 5*a* and *b*). This was of great interest because it was also in areas of regeneration that proliferation of Paneth cells occurred in inflammations of the colon.

Influence of disease of the large intestine on the Paneth cell

The diseases of the large intestine could be divided into three groups according to the frequency with which the Paneth cells were found (Table IV).

In group I, which contained the developmental and functional disorders, Paneth cells were scant and were found in less than 5 per cent of specimens. They were probably unrelated to the intestinal disturbance and part of the normal distribution in the colon.

In group II, Paneth cells occurred in moderate numbers in 20 to 40

TABLE IV

FREQUENCY OF PANETH CELL OCCURRENCE IN DISEASE OF THE COLON AND INTESTINE

Percentage of Specimens with Paneth Cells

Group 1 *Between 0 and 20%*		*Group 2* *Between 20 and 40%*		*Group 3* *Between 70 and 90%*	
1. Diverticulosis	2 of 35 (5%)	1. Carcinoma of colon and rectum	26 of 65 (40%)	1. Ulcerative colitis	41 of 44 (93%)
2. Metaplastic polyps	0 of 16 (0%)	2. Adenoma of colon and rectum	10 of 38 (26%)	2. Crohn's disease	14 of 22 (64%)
3. Peutz Jegher's polyps	0 of 1 (0%)	3. Non-Specific rectal inflammations	6 of 26 (23%)	3. Diverticulitis	12 of 19 (63%)
4. Simple polyps	0 of 3 (0%)	4. Juvenile polyps of colon and rectum	1 of 4 (25%)		
5. Melanosis coli	0 of 3 (0%)				
6. Hirschsprung's disease	0 of 1 (0%)				
7. Muco-viscidosis	0 of 3 (0%)				

per cent of specimens. The diseases in this group consisted of the epithelial neoplasms and the rectal biopsies showing non-specific chronic inflammation. It also included the juvenile polyps. However, only one polyp out of four contained Paneth cells and this was severely inflamed. It appeared that the inflammation was responsible for the increase in Paneth cells.

In group III Paneth cells were found in very large numbers in 70 to 90 per cent of specimens. The diseases consisted of ulcerative colitis, Crohn's disease and diverticulitis, and the Paneth cells occurred most numerously in areas showing evidence of repair and healing.

It would appear from these figures that the functional and developmental disorders have no effect on the Paneth cell in the colon and that the inflammatory conditions are more potent stimulators of Paneth cell production than neoplasms (Table V).

TABLE V

INFLUENCE OF DISEASE OF THE LARGE INTESTINE ON THE PANETH CELL

Disease	*Effect on number of Paneth cells*
Carcinoma	Moderately increased
Polyps	
Epithelial	Moderately increased
Metaplastic	No change
Simple	No change
Peutz Jeghers	No change
Juvenile	Moderately increased
Diverticular disease	
Diverticulosis	No change
Diverticulitis	Greatly increased
Ulcerative colitis	Greatly increased
Crohn's disease of the colon	Greatly increased
Non-specific inflammation of the rectum	Moderately increased
Miscellaneous	
Melanosis coli	No change
Mucoviscidosis	No change
Hirschsprung's	No change
Idiopathic megacolon	No change

The above-mentioned figures did not reflect the true position because they failed to take into consideration the length of the specimen and the site of the lesion. The importance of the former is obvious, since one is more likely to find the Paneth cell in blocks from the whole colon than from one site alone. In our material invariably more blocks were taken in ulcerative colitis and Crohn's disease than in carcinoma, because in the first two total colectomy was almost always performed, whereas in the latter at most a hemicolectomy was done.

The site from which the section was taken was important in determining the likelihood of finding the Paneth cell. Table VI shows the percentage of specimens in which Paneth cells were found, grouped according to the site of the lesion. Paneth cells were found more frequently in the diseased

TABLE VI

PERCENTAGE OF SPECIMENS IN WHICH PANETH CELLS ARE FOUND GROUPED ACCORDING TO SITE OF LESION

Disease	*Proximal half of colon (caecum, ascending and transverse colon)*	*Distal half of colon (descending and sigmoid colon and rectum)*
Ulcerative colitis	38 of 44 (86%)	28 of 44 (64%)
Crohn's disease	3 of 4 (75%) (R. hemicolectomy)	1 of 6 (14%) (L. hemicolectomy)
	4 of 4 (100%) (Total colectomy)	3 of 4 (75%) (Total colectomy)
Diverticulitis		12 of 19 (63%)
Non-specific chronic inflammation		6 of 26 (23%)
Carcinoma colon	22 of 29 (82%)	4 of 35 (11%)
Adenomata		10 of 38 (28%)

proximal half of the colon than in the distal half. Therefore, taking site of the lesion into consideration, carcinoma of the proximal half of the colon was accompanied by the Paneth cell nearly as frequently as in ulcerative colitis and Crohn's disease. The relative frequency of the Paneth cell in diseases of the distal half of the colon remained unchanged.

Origin of the Paneth cells in the diseased colon

The increased number of Paneth cells in the large bowel could come either from cells migrating from the small intestine or from ones developing locally. The first possibility is unlikely because cells migrating along the mucosa should be seen on the surface epithelium and they have not been found there. Also I saw no evidence of migration of Paneth cells from small bowel to large bowel in specimens in which the ileum was anastomosed to the rectum.

Increased numbers of Paneth cells could develop locally either by the multiplication of Paneth cells normally resident in the colon or by the stimulation of Paneth stem cells. If the former occurs one would perhaps see some Paneth cells in the mitotic phase and an increased number in the crypts of origin. I have not seen mitotic figures in my material and in carcinoma and diverticulitis, Paneth cells were found usually singly

in the crypts. Since the Paneth cell is a distinctive cell and has never been shown to develop from the transformation of the other glandular cells of the mucosa, it is most likely to originate in the normal and diseased colon from stem cells *in situ.*

The animal experiments which will be described later lend further support for this theory.

The significance of changes in Paneth cell population

Black and Ogle (1948) have suggested that Paneth cells secrete a protective factor which inhibits the spread of tumours, because of the fact that carcinoma is so uncommon in the small intestine, where Paneth cells occur in large numbers, and so common in the colon, where Paneth cells are sparse. However, in the colon, if the Paneth cells do have a protective action, too few are produced to be of any practical significance.

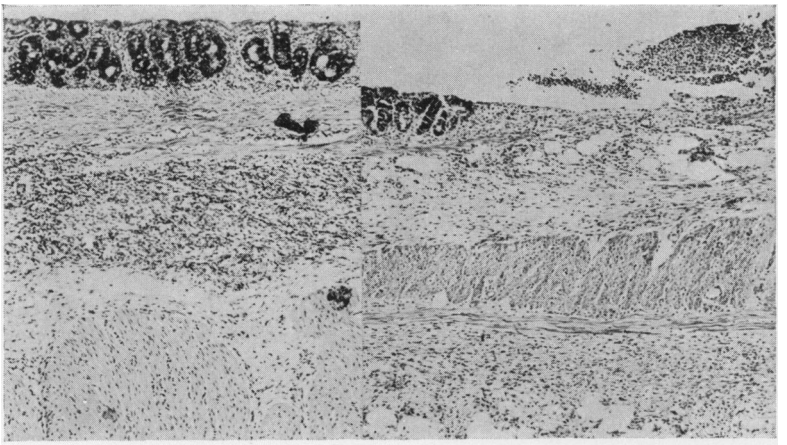
Large numbers of Paneth cells in the colon as in ulcerative colitis may be of some significance. If, as some believe, the Paneth cell produces a proteolytic peptidase, then an excessive number might cause mucosal damage by autodigestion, providing the peptidase was secreted in sufficient concentration and in the correct milieu. This may explain the difference in clinical behaviour between ulcerative colitis in which very many Paneth cells are found, and other inflammations in which there are far fewer Paneth cells. Once a sufficient number of Paneth cells are produced a self-perpetuating state may develop, in which Paneth cells cause tissue destruction, and the reparative process gives rise to new Paneth cells. The reason for the chronicity of ulcerative colitis and why the causative factor of the disease has never been found is presumably because by the time the patient is investigated it has long since ceased to act.

Experimental colitis

In order to understand more of the significance of Paneth cells in the diseased colon and the factors responsible for their appearance, experiments were undertaken to try and produce them in the colon of animals, whose intestinal morphology resembled the human intestine.

Experiments were chosen in which an immunological type of colitis was produced, because it seemed that these would be the most likely experiments to produce Paneth cells. Immediate and delayed types of hypersensitivity reactions were produced and artificially localized in the colon according to the methods of Kirsner (1961) and Bicks and Rosenberg (1962). The experiments were so designed to include the active and healing phases of the disease.

Both types of colitis produced the same changes in the guinea-pig colon. The active lesion was localized to the area of injury and showed severe inflammation. Histological examination of the early lesion showed leucocytic infiltration and distortion of the mucosal glands (Fig. 6*a*) and at a later stage there was necrosis of the mucosa with destruction of the



(*a*) (*b*)

Fig. 6. (*a*) Guinea-pig large intestine in experimental colitis showing an early lesion. There is diffuse leucocytic infiltration and distortion of glandular structures (trichrome × 125). (*b*) Guinea-pig large intestine in experimental colitis showing lesion at a later stage. Note inflammation and necrosis of mucosa (trichrome × 100).

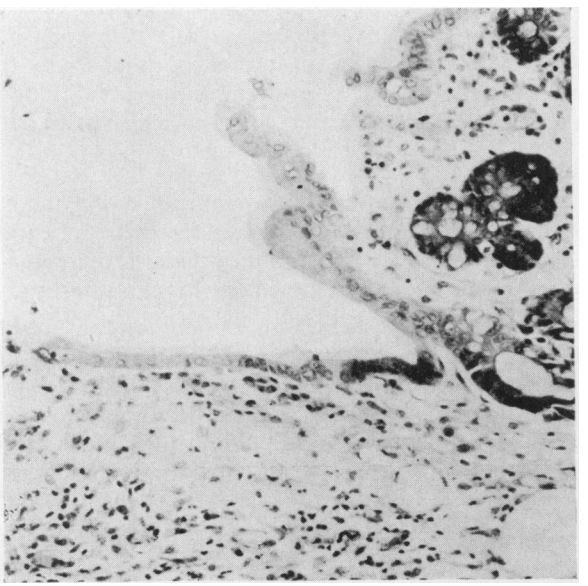


Fig. 7. Guinea-pig large intestine in experimental colitis showing healing phase. Note epithelialization of ulcerated mucosa and mild inflammation (trichrome × 150).

glandular crypts and heavy leucocytic infiltration (Fig. 6*b*). Paneth cells were not found. In the healing phase of the disease, mucosal repair and chronic inflammation were present but again there was no evidence of Paneth cells (Fig. 7).

There were two possible explanations for the absence of Paneth cells. Either the Paneth cell did not occur under any circumstances in the diseased guinea-pig colon or some factor other than destruction or repair was necessary for its appearance.

The first view seemed the most likely because no Paneth cells were found in the colons of 30 normal guinea-pigs and none were shown to develop by transformation of other cells. It is probable that there must be stem cells present for them to develop. This would explain why they were found in the diseased human colon because Paneth cells were normally present in the healthy organ, albeit in small numbers.

The only way to solve the question would be to repeat the experiments on another species of animal, with Paneth cells in its colon. However, from a preliminary study of the intestines of rabbits, mice and rats and a study of the literature, no such animal could be found.

Function of the Paneth cell

In the review of the literature, I mentioned that the consensus of opinion favours the zymogenic theory of function but that the nature of the enzymes secreted was obscure. One approach to the problem was to investigate the enzyme content of the cell to see whether there were any enzymes associated with the breakdown of protein, fat and carbohydrate constituents, which if liberated into the intestinal lumen could aid in the process of digestion.

The following enzymes were looked for: aminopeptidase, proteinase, non-specific esterase and lipase.

The aminopeptidase was distributed throughout the small intestine of man and the guinea-pig in the apical part of the cells covering the sides of the small intestinal villi and the upper parts of the crypts of Lieberkühn. In man there was a small amount of it in the cells at the fundus of the crypts which include the Paneth cells.

Proteinase was demonstrated in the Paneth cell granule of the rat by Adams and Tuqan (1961) and Adams and Bayliss (1961). I was unable to reproduce their results in man or the guinea pig.

Non-specific esterases occurred in the intestinal villi, the sides of the crypts of Lieberkühn and only faintly in the fundi of the crypts.

Lipase was not found. However, results are of doubtful value since with the tween method consistent results are seldom obtained.

Therefore, in man, the Paneth cell contains the same enzymes as the other epithelial cells of the small intestinal mucosa, but in smaller concentrations, and so would appear to have some digestive function.

SUMMARY

The Paneth cell is a morphologically distinct cell characterized by large supranuclear granules which are insoluble in distilled water and alkali and soluble in ether and alcohol.

The Paneth cell cytoplasm contains zinc. Its granules are stained by numerous dyes and consist of a carbohydrate protein complex, a small amount of phospholipid and possibly some neutral fat.

The cell has been shown to have an exocrine function. The nature of its secretions, however, are uncertain. The consensus of opinion favours a zymogenic function because of its morphological appearance and enzymatic characteristics.

The cell is widely distributed in the intestinal tract of vertebrates and during the course of evolutionary development becomes localized to the crypts of Lieberkühn.

In man in health it is found in large numbers throughout the small intestine but only sparsely in the appendix and colon.

In disease of the small intestine and appendix there is a fall in the number of Paneth cells normally present and the factors responsible for the fall are variable. In Crohn's disease there may be proliferation of the Paneth cell.

In disease of the colon the Paneth cells are unaffected in functional and developmental disorders and increased in inflammatory and neoplastic diseases. It is suggested that the Paneth cell proliferation originates from stem cells in the colon and not by metaplastic change of some other cells in the colonic mucosa. Animal experiments lend some support to this suggestion.

The variation in number of Paneth cells is probably of little significance in all diseases except ulcerative colitis and Crohn's disease of the colon, where they may produce a self-perpetuating destructive state.

In this lecture I have mentioned the known facts about the Paneth cell and the results of my experiments. However, basically we still do not know the true function of this interesting cell.

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