EPITHELIAL OVERGROWTHS AND DIVERTICULA IN THE GUT OF RATS FED ON A HUMAN DIET

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Although diverticulosis and diverticulitis are by no means rare conditions in human pathology, yet the aetiology is far from clear. Probably no one factor is responsible for all cases. Thus the occurrence of diverticula in rats fed on a human diet seemed to warrant systematic investigation in the hope that the findings might be not without bearing on the pathological process in man.

"A long-term experiment with rats on a human dietary" was begun at the Rowett Institute in December, 1932, and was described in 1935 (Orr, Thomson, and

FIG. 1.—Gut of rat affected with epithelial overgrowths. S = Stomach. C = Colon.

Garry). In this experiment two groups of Lister hooded rats, bred from the same stock, have been reared for six generations under exactly similar environmental conditions except for diet. One group received a ration closely approximating to that eaten by a working-class community in Scotland as ascertained by a dietary survey (Davidson, *et al.*, 1933); this will be referred to as the "experimental group." The other group, known as the "supplemented group," received the same diet with an additional supply of milk and green food.

During the course of the experiment a spontaneous epidemic with an organism of the *Salmonella* class broke out in the colony and caused a high death rate from gastro-enteritis, especially in the experimental group. During routine post-mortem examinations it was found that many animals showed nodular swellings or thickenings in the distal part of the small intestine and in the proximal and intermediate colon. These were found only in animals over 100 days old—that is, in adult animals.

Macroscopic Appearance

In the small intestine the lesions were mostly in the distal ileum on the anti-mesenteric border. The size varied, probably according to the age of the lesion, from that of a small pin-head to that of a cherry, and was thus sometimes three or four times the diameter of the gut. In cases of long standing the large number of individual nodules gave the gut the appearance of a string of beads (Fig. 1). In the large intestine the wall of the proximal and intermediate colon was usually thickened to form a stiff hard mass often studded with small sessile nodules. The distal part of the colon, the rectum, was free from such lesions. In the advanced stages there were adhesions to the omentum and to adjacent loops of bowel. On incision both small and large bowel lesions were found to have large loculi, in many instances filled with pus, and the growth often encroached on the gut lumen, reducing it to a small channel. Sometimes it was possible to see a small opening communicating between the loculi and the gut lumen. Thus there was a striking resemblance to the condition observed in man, both with respect to the macroscopic appearances and to the sites of the lesions.

Microscopical Appearance

Histologically the lesions were essentially the same in the small and in the large guts. The chief characteristic was extreme glandular proliferation with penetration of the muscular coats; in some cases this proliferation extended into the adherent omentum. In the majority an inflammatory reaction was present and there was often profuse round-cell infiltration. In the later stages there was abscess formation. In certain regions caseation occurred, not

FIG. 2.—Transverse section through a nodule in the ileum. GL = Gut lumen. D = Diverticulum.

unlike that seen in tuberculous foci. Attempt at repair could be seen, as instanced by the presence of fibrous tissue.

Fig. 2 illustrates a transverse section through the middle of a lesion in the ileum showing direct communication with the gut lumen and consequent formation of a diverticulum. Fig. 3 represents a section of the colon in the same rat showing extreme glandular proliferation on one side of the lumen and a sessile nodule under the serous coat. Fig. 4 illustrates in one of the largest nodules the characteristic microscopical appearance; the epithelium retained its normal structure, there was no satisfactory evidence of penetration of the basement membrane, and in no case were metastases found. There was, then, no evidence for malignancy in the stages at which the lesions were examined.

Probably the natural history of a nodule is as follows. For some unknown reason the glandular epithelium proliferates and penetrates the muscular coats, tending all the

time to retain its acinous form; the acini are prone to infection, and inflammation follows often with necrosis.

A condition of somewhat similar nature was described by Leitch in 1924. He put such foreign bodies as human gall-stones, pebbles, and pitch pellets into the gall-bladder of guinea-pigs. As a result there was destruction of the lining membrane of the gall-bladder and then repair by an epithelium which in the majority of cases proliferated to such an extent that it penetrated and destroyed the wall of the gall-bladder. Nevertheless the acinous arrangement of the epithelium persisted, and cytologically

FIG. 3.—Transverse section through a lesion in the colon. A points to subserous nodule.

FIG. 4.—Section through a nodule; note the dilated acini and round-cell infiltration.

there was no real evidence for malignancy. But, since these epithelial overgrowths invaded neighbouring organs such as the liver or penetrated tissue adherent to the gall-bladder, Leitch reported that the process was malignant. However, in 1933 Burrows repeated and confirmed Leitch's results, but definitely decided that the condition induced was not malignant in the true sense of the word. The microscopical appearances illustrated by these two workers are remarkably like those described here.

Incidence of Lesions

The gut lesions were first noted in the winter of 1933-4, when the experiment had been running for about one year. Since then until the end of the experiment this year a number of rats have continuously been found to be affected. Of seventy-six animals in which either the small or the large bowel or both were concerned fifty-four were

fed on the experimental diet and twenty-two on the supplemented diet. In those on the defective diet the lesions were usually more extensive. The number of rats with gut lesions in each generation on the experimental and supplemented diets have been compared with the total number of rats in each generation living beyond a hundred days, the age above which lesions have been observed. This is shown in the table.

Generation	Experimental Diet			Supplemented Diet		
	Number with lesions	Number surviving 100 days	Incidence	Number with lesions	Number surviving 100 days	Incidence
Parental ..	2	29	% 6.9	2	30	% 6.7
F1 ..	14	234	6.0	3	205	1.5
F2 ..	29	129	22.5	1	94	1.1
F3 ..	7	53	13.2	8	107	7.5
F4 ..	2	12	16.7	8	112	7.1
General incidence	54	457	11.8	22	548	4.0

Since the environmental conditions of the two groups were identical apart from diet, and these were bred from the same stock, this higher incidence would seem at least to indicate that the nutritional level of the diet is one factor in the aetiology. No more than this can be said at present. The original dietary experiment in which this outbreak occurred has now been concluded. Further similar dietary experiments, however, are being continued, and the rats in these experiments will be examined for these nodules.

It seems, then, that we have in these rats a pathological process which macroscopically has all the appearances of diverticulosis and diverticulitis in man. Microscopically, apart from the inflammatory processes common to both, the resemblance ceases. However, since the aetiology of diverticulitis in man is obscure, since relatively little work has been done on the histopathology of this condition in man, and since the lesions here described have appeared in rats, especially in elderly rats and in rats on a human diet known to be far from perfect, it does seem worth while putting this condition on record in the hope that it may stimulate interest in the essential pathological processes of diverticulosis and diverticulitis in man. Moreover, we have been unable to find any reference in the literature to this condition in rats.

Summary

In rats fed on a low-grade human diet an unusual kind of epithelial proliferation was observed in the small and large guts. This resulted in multiple diverticula, which penetrated the entire thickness of the bowel wall. Macroscopically there was a striking resemblance to diverticulitis as seen in man, but microscopically we were forced to regard this change as an acquired heterotopia. Throughout the period of observation no evidence for malignancy was detected.

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