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Pathology of the alimentary tract in *Salmonella typhimurium* food poisoning

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SUMMARY The pathology of the alimentary tracts of nine patients dying of *Salmonella typhimurium* infection is reviewed. Two patients had previous gastric operations, supporting previous reports that such patients are more susceptible to food poisoning. Four had no parietal (oxyntic) cells in the gastric mucosa, suggesting hypo- or anacidity. Only one had acute gastritis. None had acute enteritis, but in half of the patients, subtle histological changes suggested an 'enteropathy'. Acute diffuse colitis with abundant crypt abscesses, without stromal abscesses in the lamina propria, was the most constant finding and reparative features started very early, and occurred in later deaths. Under ideal circumstances this crypt abscess is readily distinguished from that of idiopathic ulcerative colitis, but can be confused with the crypt abscess of acute bacillary (sonne) dysentery. While the florid colonic changes may have settled in the late deaths, active inflammation is commonly present in the appendix mucosa on histology. The pathology of the alimentary tract in *S typhimurium* infection differs from that of *S typhi* and *S paratyphi* infections. There is little evidence of gastroenteritis, although subtle changes occur in the stomach and small intestine. The features are those of acute diffuse colitis with histological appendicitis, distinguishable from idiopathic ulcerative colitis.

Statistics suggest that the incidence of food poisoning in the United Kingdom is increasing.[1] Food poisoning is commonly referred to as 'gastroenteritis', implying inflammation of the stomach and small intestine. During an outbreak of *S typhimurium* (phage type 32) infection in the west of Scotland in 1968, it was surprising to find virtually no gastritis, or enteritis, and that the predominant histological lesion was an acute diffuse colitis.[2] Further experience has been gained from *S typhimurium* infection of other phage types and from other salmonella subtypes.[3] Other publications[4–11] have confirmed the colitis component of *S typhimurium* infection, but the findings in the stomach and small intestine remain un-reported. Indeed, the colonic findings have not been adequately described. In this paper the pathology of the alimentary tract in nine patients dying from *S typhimurium* infection, involving at least four phage types is described. The first necropsy was done before phage typing had been routinely accepted.

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Methods

NECROPSIES

The nine necropsies were carried out as soon after death as possible. Two loops of jejunum and two of sigmoid colon were sent for microbiological examination and virology. Blood samples from the right auricle were also taken for culture and Widal tests.

The necropsy was standard with the gastrointestinal tract being dissected out and opened with the minimum of handling. Hosing with water and sponging was avoided to allow inspection of the luminal contents and the undisturbed mucosal surfaces.

After formalin fixation standard sets of blocks for histological examination were taken from the gastric fundus, jejunum, jejuno-ileal region, ileum, appendix, and from the ascending, transverse and descending colon. These were chosen to include any obvious pathology at these sites. In all 27 blocks of stomach, 43 of small intestine, 27 of appendix and 90 of colon were examined. All tissue was paraffin embedded and stained with haematoxylin and eosin. Standard special stains were carried out when thought necessary.

Results

PATIENTS

Clinical data are shown in Table 1. Patient 1 developed diarrhoea and vomiting when less than one month old. No pathogen was isolated from watery stool specimens during the 10 days in another hospital. After recovery the infant remained well for seven days when less severe diarrhoea developed. On the second admission no pathogen was cultured from a number of stool specimens and the illness settled with gain in weight after two weeks. Pyrexia, however, developed two weeks later – that is, 10 days before death. Penicillin was given, but had no effect. Blood culture four days before death (34 days after the second admission) yielded *S typhimurium*. The stools became loose again on the day before death. These observations, in conjunction with the histology, suggest that the infant's alimentary *S typhimurium* illness was about one day's duration.

Patients 4–7 were ill at home, then admitted to other hospitals before being transferred to Ruchill Hospital. Patient 6 became ill on transit to Tunisia, and circulatory complications to her left leg arose while there. Medical attention was given in Tunisia, but an emergency disarticulation at the hip joint was undertaken within two days of her return to Glasgow. She was in a very toxic state and she died six days later.

NECROPSY FINDINGS

1 *Stomach*

Two patients (5 and 7, Table 1) had undergone gastric surgery. Patient 5 had hypertrophic and patient 9 very atrophic gastric mucosa. Acid-secreting cells were not identified in four (50%) of the stomachs (Table 2). Only one patient (no. 2) had acute gastritis with abundant crypt abscesses (Fig. 1). Very occasional minor crypt abscesses and epithelioid granulomata in the mucosa indistinguishable from Crohn's disease, were present in patient 7. Thus, gastritis was florid in only one patient who was one of the four patients not showing oxyntic cells.

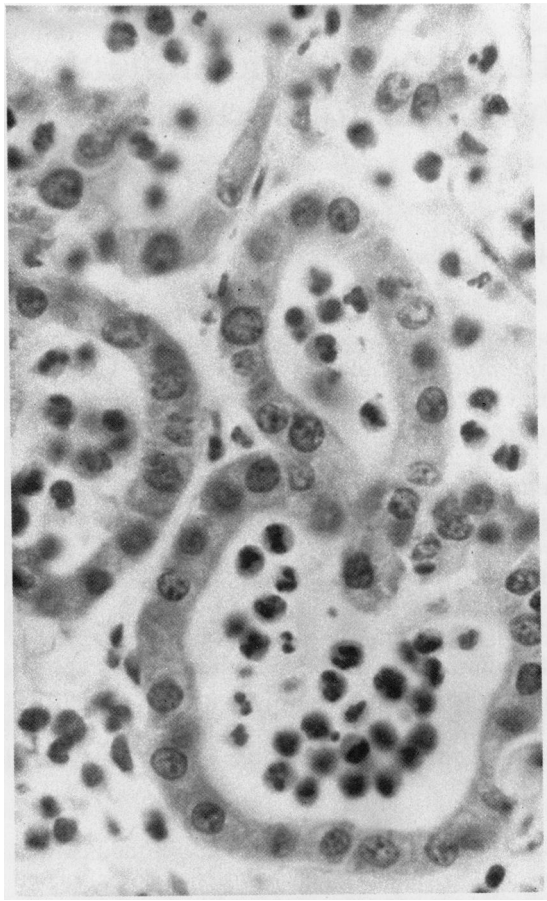

Fig. 1 *Patient 2. Stomach. Crypt abscesses lined with nondescript cubical and squamoid epithelium with high nucleus/cytoplasm ratios. H and E. Original × 1000.*

2 *Small intestine*

The macroscopic abnormalities were minimal with mild swelling and oedema of some of the mucosal ridges. In four patients (2, 3, 4 and 9) the terminal ileum was reddened and suggested a reflux ileitis.

Histological examination showed that in four cases the small bowel was normal (4, 6, 8 and 9). The villi were normal in height and width. Of the other five cases only one (2) had well established acute inflammatory changes while in the remaining four these were mild (Table 3). This took the form of occasional crypts plugged by mucin and macrophages with ingested nuclear debris. Some crypts were lined by nondescript 'embryonal-like' cells with prominent nucleoli and haematoxyphilic cytoplasm (Fig. 2). Occasional capillary thrombi were observed and some perivascular inflammation in the lamina propria. No granulomas or fissures were seen and Peyer's patches were not prominent.

Thus only one patient had a well established enteritis with recognisable crypt abscesses and four had mild 'enteropathic' changes.

3 *Large intestine*

Three colons (nos. 2, 3 and 4) were grossly normal, two were collapsed (1 and 7), two (6 and 8) were moderately dilated. Patient 8 had diverticulosis of the sigmoid and a 15 μl abscess in the pouch of

Table 1 *Data concerning nine patients dying with* Salmonella typhimurium *infection ranked by duration of illness*

Patient no	*Sex*	*Age at Death*	*Days ill at home/ on holiday*	*Days ill in hospital*	*Total days ill until death*	*Previous alimentary surgery*	*Other conditions antemortem or at necropsy*	*Organism isolated from*	*Phage type*
1	M	2mth	<1	10	—	Nil	Marasmic on admission. At necropsy, dehydrated	Blood culture Faeces negative	?
			<1	38	<39*(1)				
2	F	65y	2	1	3	Nil	Atrial fibrilln. Myoc. fibrosis	Faeces positive One bl. culture neg.	32
3	M	65y	5	2	7	Nil	Permanent tracheotomy after laryngectomy. No metastases	Bl. culture pos. Faeces negative	32
4	M	6y	>1	7	>12	Nil	Lymphatic leukaemia under treatment	Faeces positive Bl. culture pos.	U252
			—	4					
5	M	62y	6	3	16	Repairs of perforations Gastro-jejun	Uraemia due to renal tubular necrosis	Faeces positive One bl. culture neg.	32
				7					
6	F	43y	11	1	19	Nil	Ac. gangrene of L. leg with oper. hip disarticulation	Faeces and bl. culture pos.	1a
			—	7					
7	M	48y	8	13	23	Partial gastrectomy	Low-grade pul. tub. Mitral + aortic stenosis SBE (S. viridans)	Blood culture pos.	32
			—	2					
8	F	81y	21	8	29	Nil	Metastases to brain, cord, liver, lung of ovarian cancer. Involuting zoster	Faeces antemortem, pus pelvic abscess PM both pos. Blood culture not done	204c
9	F	67y	1	57	58	Cholecy-stectomy	Asthma, Rheum. arthr. Bilat. pulm. art. emb.	Faeces pos. Nine bl. culture neg.	204c

* Two separate admissions to hospital, with seven days at home between episodes and histology suggests that *S. typhimurium* infection was terminal and unrelated to the earlier episodes. (See text.)

Table 2 *Summary of histological findings in the stomach*

No	Parietal (oxyntic) cells	Chronic gastritis	Intestinal metaplasia	Acute crypt abscesses	Acute inflammation of lamina propria	Granulomata in lamina propria
1	Specimen not taken					
2	−	−	−	++++	++	−
3	−	++	++	±	−	−
4	−	+	++	−	−	−
5	+	+	+	−	−	−
6	−	−	−	−	−	−
7	++	++	−	±	−	+
8	++++	++	−	−	−	−
9	++++	−	−	−	−	−

Douglas with no connection to diverticula, from which *S typhimurium* was cultured. Two had toxic dilatation, of the whole colon (no 5) or of the caecum and ascending colon only (no 9). Patient 9 also had diverticulitis.

The mucosa was grossly normal in patients 1, 5, 6 and 9 (apart from the diverticulitis) despite the histology in patient 1, and the toxic megacolon in patients 5 and 9. In patient 8 the mucosa was patchily red. The mucosal ridges were red throughout in patient 2, while the mucosa was diffusely red beyond the splenic flexure in patients 3 and 4. The mucosa of patient 7 was cyanotic from the sigmoid flexure. All these features might have been ignored, if the history of a diarrhoeal illness had not been available. There was no melaena, or bloodstaining in any case.

The histological features are summarised in Table 4. Patient 1 showed universal loss of the mucosal surface and the exposed lamina propria displayed shallow diffuse fibrinoid necrosis along the entire bowel wall covered by haematoxyphylic (Gram negative) bacteria (Fig. 3). The columnar cells lining the lower halves of the crypts had prominent eosinophilic nucleoli, hyperchromic nuclei, raised nuclear/cytoplasmic ratios and abundant mitotic activity. Crypt abscesses were absent. The lamina propria showed oedematous granulation tissue with new capillary loops growing into the zone of fibrinoid necrosis. Some capillaries showed fibrin/platelet thrombi. The deeper lamina propria and the submucosa contained a mixed inflammatory infiltrate.

Varying mucosal surface repair with crypt abscesses occurred in all acute deaths. Patient 2 (three day illness) showed abundant crypt abscesses (Fig. 4) rich in eosinophil leucocytes, neutrophil polymorphs, plasma cells, lymphocytes, mononuclear cells, and desquamated crypt lining cells. A few crypts were ballooned with squamoid lining cells at the sides and necks, but at the bases, cells were stratified upon one another. The lamina propria showed no stromal abscesses. Scattered haemorrhages and very scanty capillary thrombi were

Table 3 *Summary of histological findings in the small intestine*

No	Protein-rich vesicles at villous tips	Acute focal enteritis with crypt abscesses	Plasma cells in lamina propria considered to be excessive	Non-differentiated crypt columnar epithelium with no brush border, high nucl/cyto ratio, prominent nucleoli	Excessive exfoliation of lining cells into crypt lumen	Inspissated mucin plugs in crypt lumina	Capillary thrombosis in villous stroma and/or lamina propria	Perivenous cuffing by lymphocytes and/or neutrophil polymorphs in submucosa
1	++	−	−	−	−	−	−	−
2	−	++	−	+	−	±	±	±
3	−	±	++	±	±	−	−	−
4	−	−	−	−	−	−	−	−
5	−	±	++	±	±	−	−	−
6	−	−	−	−	−	−	−	−
7	−	±	++	±	±	−	−	−
8	−	−	−	−	−	−	−	−
9	−	−	−	−	−	−	−	−

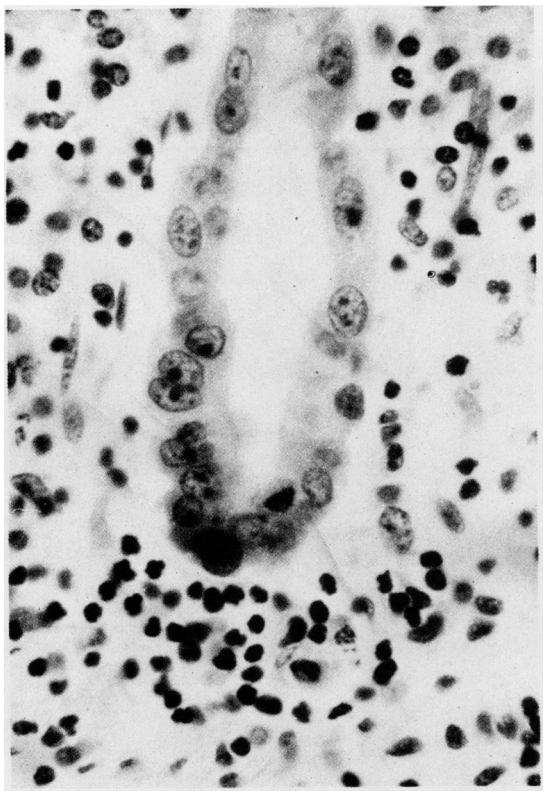

Fig. 2 *Patient 3. Small intestine. Crypt of Lieberkühn lined by cubical 'embryonal' epithelium. Lymphocytes (? cleaved) are at the crypt base, in the lamina propria. H and E. Original × 1000.*

present. The submucosa was very oedematous with mild cellulitis and lymphangitis.

Patient 3 (seven days) had a non-differentiated columnar surface epithelium (Fig. 5). Patient 5 (16 days) had ballooned crypts, some with mucin plugs, others with cell debris and a few showed abscesses. Most crypts were rich in goblet cells. Patient 6 (19 days) had tall crypts with abundant goblet cells, but there were isolated ballooned crypts with cell debris in the lumen, and flattened epithelium round their walls. The superficial lamina propria showed persisting necrosis. Patient 7 (23 days) had tall crypts (Fig. 6) rich in goblet cells, a normal quota of goblet cells on the surface and a moderately dense infiltration of lymphocytes superficially in the lamina propria – that is, where fibrinoid necrosis is assumed to have been. Patients 8 (29 days) and 9 (58 days) had no additional features.

All patients had subtle acute diffuse colitis with crypt abscesses in most and evidence of repair. Granulomata and fissures were absent. While histological recovery could occur by two weeks (no 4), evidence of continuing infection could still be seen at four weeks (no 8).

4 *Appendix*

All appendices appeared grossly normal, but were studied histologically in patients 2 to 9 (Table 5).

Appendicitis was most severe in patient 3 with zones of fibrinoid necrosis, scanty crypt abscesses, and excessive mucopus in the lumen. Patient 7 showed an epithelioid granuloma in the lamina propria, similar to the stomach findings. The inflammatory changes were more severe in the appendix than in the colon of the same patient, although *in toto* there was more inflammation in the colon.

Discussion

This series suggests that the young and the elderly are most likely to die from food poisoning, but it also shows that patients need not be debilitated. The patients had clinical states similar to those reported by Dickinson and Pickens.[13]

The relative absence of gross features at necropsy

Table 4 *Summary of the histological findings in the large intestine*

No	*Superficial fibrinoid necrosis*	*Crypt abscesses*	*Ballooned crypts*	*Non-differentiated epithelium*	*Reappearance of goblet cells*	*Stromal inflammation of lamina propria*	*Lymphocytic infiltration in superficial lamina propria mucosae*	*Paneth cells per inch of colon wall*
1	++++	–	–	++	–	+++	–	–
2	–	++++	±	+++	–	++	–	–
3	–	++	++	+++	±	–	–	–
4	–	–	–	–	++	–	–	±
5	–	+	+	±	+++	–	–	–
6	+	–	±	±	+++	–	–	–
7	–	–	–	–	++++	–	++	–
8	–	±	±	±	++++	–	+	±
9	–	–	–	–	++++	–	–	–

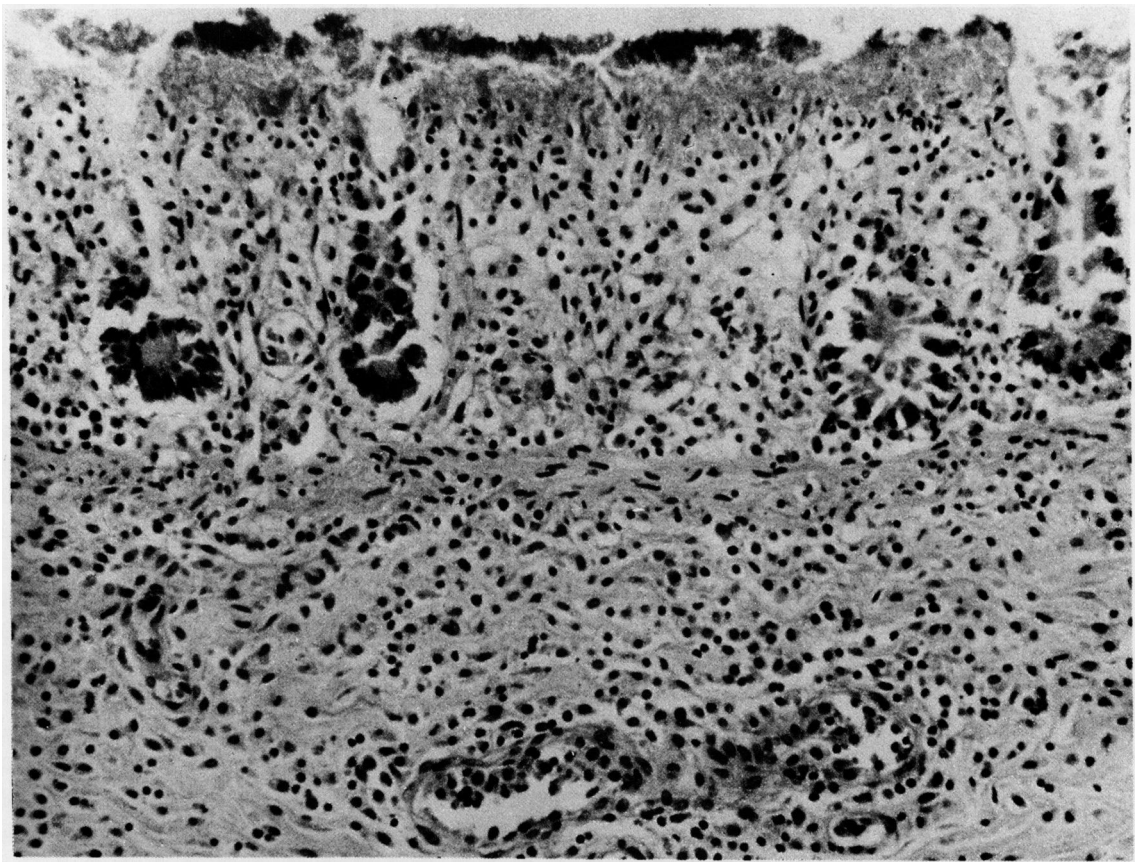

Fig. 3 *Patient 1. Large intestine. Representative field. Incomplete haematoxyphilic layer of bacilli (Gram-negative) overlying a shallow fairly even layer of fibrinoid necrosis into which new capillary loops are migrating from the lamina propria. The crypts of Lieberkühn are lined by non-differentiated columnar cells, squamoid at the crypt necks. The submucosa shows widespread cellulitis and the venules show pavementing by neutrophil polymorphs. H and E. Original × 250.*

Table 5 *Summary of the histological findings in the appendix*

No	*Superficial fibrinoid necrosis*	*Crypt abscesses*	*Ballooned crypts*	*Non-differentiated epithelium*	*Epithelioid cell granuloma*	*Pus in the lumen*	*Excess mucin in the lumen*	*Hyperplastic mucosa*	*Paneth cells per circumference of organ*
1	Not taken								
2	−	±	−	−	−	±	−	−	0
3	++	+	−	−	−	+	++	−	1
4	−	−	±	++	−	−	−	−	20
5	−	±	−	−	−	−	−	−	10
6	−	±	+	−	−	++	−	+	50
7	−	−	−	−	+	−	−	+	40
8	−	−	−	−	−	−	−	−	5
9	−	−	−	−	−	−	−	−	1

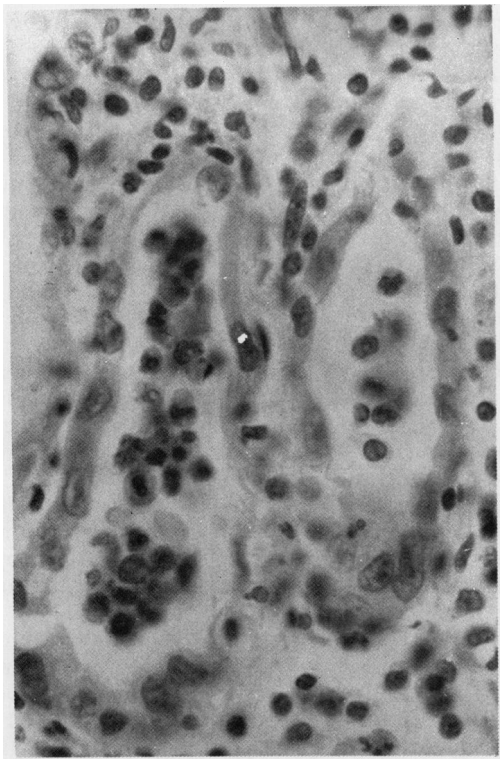

Fig. 4 *Patient 2. Colon. Three adjacent crypts of Lieberkühn lined by primitive squamoid epithelium with prominent nucleoli. The more cellular crypt abscess contains neutrophil polymorphs, an eosinophil leucocyte, mononuclear cells and a few lymphocytes. H and E. Original × 1000.*

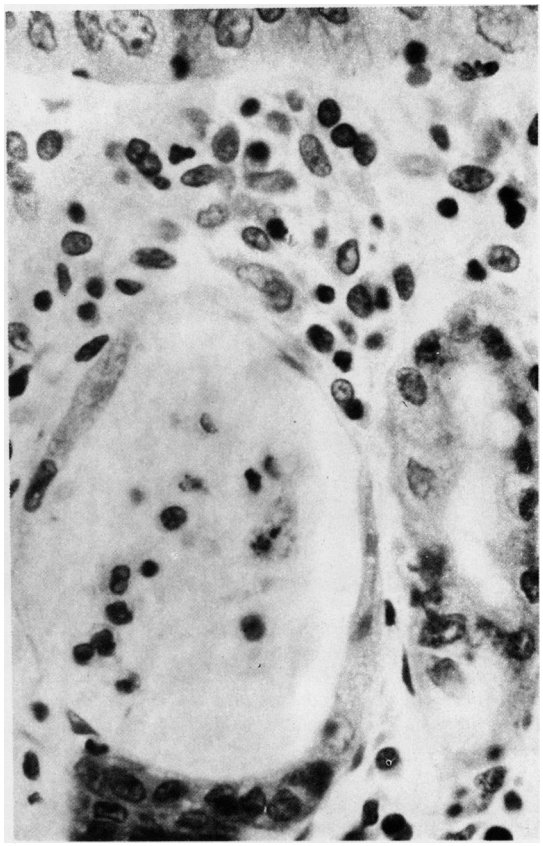

Fig. 5 *Patient 3. Colon. Early goblet cell differentiation in the right-hand crypt. Florid repair in the left-hand crypt has caused stratification at the base, with ballooning. The contents are equally neutrophil polymorphs, lymphocytes and cell debris. The surface bears non-differentiated columnar cells, and goblet cells are absent. H and E. Original × 1000.*

can be misleading. Histology of the gastric mucosa showed no parietal cells in half the subjects, reinforcing ideas of Hurst in 1934[14] and others,[15–18] that patients with hypo- or anacidity, or with stomach operations are more susceptible than normal persons to food poisoning. The relative absence of acute gastritis is important.

The absence of swollen ulcerated Peyer's patches and the paucity of acute inflammation in the small intestine are important but there were changes which were difficult to explain. Generalised enteritis was not recorded in any patient, only one showing focal enteritis, but in about half there was evidence of repair of the crypts and mucosal surfaces by a non-differentiated epithelium. The infection is occasionally choleraic,[19 20] a cholera toxin like enterotoxin has been reported recently,[21 22] and three patients (nos 2, 3 and 5) had excessive fluid in the bowel to simulate paralytic ileus at necropsy. This discovery fails to explain the observations reported above, because there is no sloughing or ulceration of the small bowel mucosa on biopsy in true cholera.[23] The small intestines of four patients (nos 4, 6, 8 and 9) showed no histological abnormality, and therefore a cholera like enterotoxin might have been present in these cases. The 'enteropathy' of four patients (nos 2, 3, 5 and 7) may be the consequences of the action of the cytotoxin which has been described in the last two years,[24] and it is interesting that phage type 32 was responsible for the illness of these four patients (Table 1). This illness has been described previously as 'salmonella gastro-enteritis', but in the present study gastritis and enteritis were minimal. A more satisfactory term therefore may be salmonella food poisoning.[13] It is noted that 'infantile gastro-enteritis' shows no gastritis or enteritis on

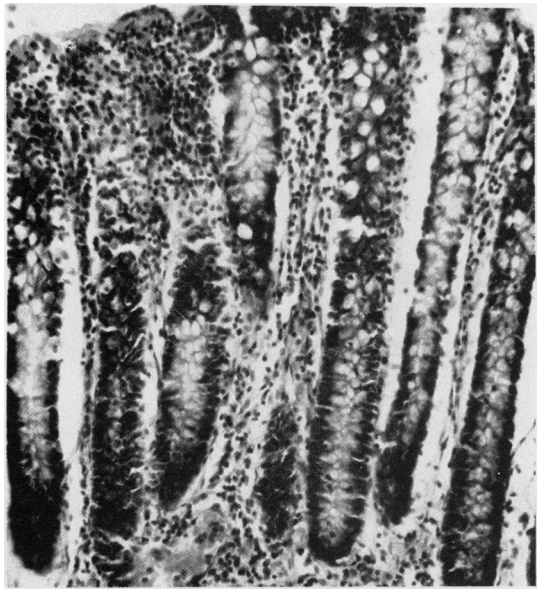

Fig. 6 *Patient 7. Colon. The crypts are deeper than normal, and possibly more numerous than normal, with a normal quota of goblet cells. There is a condensation of lymphocytes however in the lamina propria immediately below the surface layer, where the layer of fibrinoid necrosis may have existed. H and E. Original × 250.*

histology, but, when associated with specific types of *Escherichia coli,* commonly shows acute ileitis.[25–27] *S typhimurium* infection caused 'gastro-enteropathy' in only half of this series, but in contrast, Yersinia infections[12 28–30] may cause enteritis and ileitis severe enough to need laparotomy. No such infections have been seen in this department[31] which serves medical units only. Whether or not salmonella infections may cause chronic ulcerative enteritis[32] remains uncertain.

S typhimurium causes greatest histological damage in the colon.[2–11] In this country the illness may be confused with bacillary dysentery, or idiopathic ulcerative colitis. Patients with idiopathic ulcerative colitis may develop superinfection by *S typhimurium.*[33] The gross changes in the colons of the patients of this series were minimal, and toxic megacolon can occur (patients 5 and 9).[34]

A pathologist should be able to distinguish idiopathic ulcerative colitis from *S typhimurium* infection. In untreated ulcerative colitis the inflammatory cells are entirely neutrophil polymorphs with dumb-bell type abscesses with one part in the crypt of Lieberkühn and the other in lamina propria. In the author's experience the crypt abscess in *S typhimurium* infection is never of dumb-bell shaped type. Most cells are neutrophil polymorphs, with eosinophil leucocytes, lymphocytes, plasma cells and mononuclear cells or macrophages. This appearance is indistinguishable from that seen in Sonne dysentery in Glasgow, but Flexner dysentery crypt abscesses may involve the lamina propria. The author has no experience with campylobacter infections but the description by Price *et al*[35] suggests that the changes resemble those of Flexner dysentery.

Superficial fibrinoid necrosis of the colon of patient 1 is unique but similar areas are evident in the colon of patient 6 and the appendix of patient 3 (Tables 4 and 5), as well as in a death from *S enteritidis* infection (infra). The sequence of repair in other colons suggests that all experienced similar damage. The inference is that diffuse superficial fibrinoid necrosis is the earliest lesion in the colon, and is distinct from pseudomembranous colitis.[36]

The changes reported in this series of fatalities may not be representative of survivors, but some practical generalisations may be made. Although these patients had a single episode of infection, diarrhoea settled fairly rapidly after admission to hospital. The colon could be histologically normal by 12 days, (patient 4, Tables 1 and 4), and certainly by 58 days (patient 9). Colonic inflammatory activity could persist for 19 days, (patient 6, Tables 1 and 4) and subtle minor activity was still present at 29 days, (patient 8, Table 4). Thus, histological normality may take six weeks to return. This suggests that with a continuing diarrhoeal illness, the possibility of idiopathic ulcerative colitis should not be considered until after two months unless a biopsy within this interval shows classical histology in conjuction with several negative faecal and blood specimens. There need not be a community outbreak of food poisoning, as isolated cases of salmonella infection occur.

Histological appendicitis is part of the process. Repair is not as advanced in the appendix as it is in the colon of the same patient, and given the correct circumstances, appendicitis requiring operative treatment may evolve.[37–39]

The four patients reported by Story and Hanbury[40] had different alimentary tract histology. It is possible that polyarteritis nodosa contributed more to the pathology of their case 1 than the authors believed. The gross and histological pathology could be very variable, but the colon appearances were not changed appreciably. Their patient 1 had a hospital acquired infection, a situation that has become more common[41] and was probably the case in patient 1 of this report. Review of the literature disclosed that colonic ulceration (? ulcerative colitis) was reported in some studies, but none recorded acute diffuse ulcerating colitis.[40] Appendicitis was identified as a complication.[40]

The author has gained experience from seven necropsies with *S aberdeen* (1 case), *S brandenburg* (1), *S enteritidis* (1), *S heidelberg* (2), *S panama* (1) and *S virchow* (1) infections and has examined colonic biopsies from patients surviving *S typhimurium* infection. All had features similar to those reported here. Scanty gastric crypt abscesses occurred with *S enteritidis* only. *S enteritidis* infection failed to show enteritis (or enteropathy),[3] whereas the two examples of *S heidelberg* food poisoning showed extensive small bowel damage as well as colitis.[3] Thus, the combined series of 16 patients suggests that not all salmonellae carry the enterotoxin[21 22] or cytotoxin,[24] and that yet other possible mechanisms have to be sought to explain the undoubted gastric and small intestinal clinical features. Superficial fibrinoid necrosis occurred in the colon with *S enteritidis* as described above in patients 1, 3 and 6. The lack of gross features in the alimentary tract of all these patients is re-emphasised, and some patients with infective diarrhoea will inevitably be categorised as having minimal change colitis.[42]

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