reference work. It is probably the method of choice for rare blood samples.

Intraerythrocytic enzymes appear to be reasonably stable under the conditions of storage.

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Haemorrhagic Necrosis of the Intestine

J. S. McKINNELL,* M.B., CH.B., D.PATH., F.C.PATH.; M. S. KEARNEY,† M.B., CH.B.

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The fact that necrosis of the bowel can occur in the absence of demonstrable occlusion of the mesenteric vessels has long been recognized. Kleckner, Bargen, and Baggenstoss (1953) recognized that enterocolitis occurred in heart disease, but Wilson and Qualheim (1954) seem to have been the first to define a specific syndrome occurring mainly in elderly subjects suffering from heart disease and characterized by patchy haemorrhagic necrosis of the intestinal mucosa unrelated to the distribution of the mesenteric arteries. These authors observed eight cases of acute haemorrhagic enterocolitis in one and a half years and discovered 12 similar cases in a survey of the hospital necropsy records between 1947 and 1953. Subsequently a number of American authors have described further cases of the same type: Ming and Levitan (1960) encountered 11 in three years among 698 necropsies; Glotzer and Shaw (1959) collected nine in a period of 10 years; Grosh, Mann, and O'Donnell (1965) described 10 cases seen in three years; in a study of hospital records over a 12-year period Berger and Byrne (1961) found 23 cases of massive bowel infarction in the absence of mesenteric artery or vein occlusion, though at necropsy the majority showed infarction in the distribution of the superior mesenteric artery and only a minority showed involvement of multiple segments at random sites; Fogarty and Fletcher (1966) studied 18 patients during five years; Drucker, Davis, Holden, and Reagan (1964) observed seven patients within two years. The last-mentioned authors discuss the pathogenesis. In a report from Australia, McGovern and Goulston (1965) recorded 33 cases in a 14-year period.

No series of exactly comparable cases seems to have been reported from this country. During the five months July to November 1964 we encountered 13 cases among fewer than 200 necropsies. Previous to this period such cases were very rare in the experience of one of us (J. S. McK.), and subsequently in the same hospital there have been only two similar cases among over 1,000 necropsies. The only unusual feature of the five months in question was that they were unusually dry; the rainfall in these five months totalled 3.5 in. (8.9 cm.), as compared with an average of 7 in. (17.8 cm.) for the same five months in the years 1947 to 1961. No other late summer and autumn since 1947 had been so dry.

Reports of two representative cases are given.

Case 1

The patient, a man aged 85, was admitted to hospital with a history of abdominal pain for some days, becoming more severe in the previous 24 hours.

On examination the transverse colon was distended and showed visible peristalsis. He was dehydrated. The rectum contained hard faeces. Levels of serum electrolytes were: sodium 134 mEq/l., potassium 3.5 mEq/l., chloride 86 mEq/l., and bicarbonate 29 mEq/l. The blood urea was 76 mg./100 ml. A provisional diagnosis of carcinoma of the colon was made. One litre of dextrose saline and one litre of Dacron's solution were infused in 12 hours, but the patient collapsed unexpectedly and died 48 hours after admission.

At necropsy the heart was of normal size. The myocardium was flabby. The valves were normal. The coronary arteries were moderately dilated and there was diffuse thickening of their walls, but there were no atheromatous plaques and no restriction of their lumina. The lungs were oedematous and congested. The liver was rather small and its surface was mottled, due to irregular patches of congestion. The gastric mucosa and the mucosa of the whole length of the small intestine were acutely congested, and gas bubbles were observed under the mucosa of the duodenum. There were small haemorrhages in the mesentery of the jejunum. The mucosa of the caecum was severely haemorrhagic and much thickened. In the transverse colon there were two segments in which the mucosa was greenish and the wall of the bowel thinned owing to dilatation. The mucosa of the pelvic colon was thickened and haemorrhagic, like that of the caecum. The aorta was well preserved for the age of the subject, and the superior and inferior mesenteric arteries and veins were patent. The kidneys showed some loss of cortical substance with coarse granularity of the subcapsular surface, suggestive of scarring due to senile arteriosclerosis. There was moderate dilatation of both renal pelves, the bladder was moderately dilated and trabeculated, and the prostate was enlarged.

On histological examination the more severely affected areas of the small intestine, the caecum, and the pelvic colon all showed essentially similar changes, consisting of haemorrhage into the mucosa and severe congestion of the submucosa with thrombosis

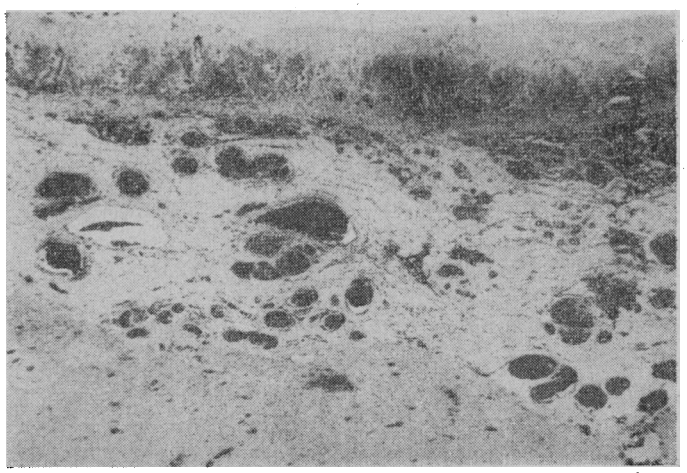

FIG. 1.—Case 1. Superficial necrosis of the mucosa with haemorrhage in the deeper zone. Severe congestion of the vessels of the submucosa with some oedema.

* Consultant Pathologist, Selly Oak Hospital, Birmingham 29.
† Surgeon Lieutenant, R.N.; late Registrar in Pathology, Selly Oak Hospital, Birmingham 29.

of a few small veins (see Fig. 1). Inflammatory cellular exudate was slight and diffuse in all coats. Large numbers of thick Gram-positive rods were present on the surface of the haemorrhagic mucosa. There were also large numbers of organisms in the mucosa and submucosa, and to a lesser extent in the other coats, but these were mainly Gram-negative rods. In the transverse colon affected areas showed thinning and necrosis of the mucosa with thinning of the wall of the colon, presumably due to dilatation of its lumen. Here organisms were less numerous, there being a few Gram-negative rods in the mucosa and submucosa. Culture of the small intestine revealed *Clostridium welchii* and *Escherichia coli*.

Case 4

This man, aged 75, had been treated by his family doctor for several years for congestive heart failure. He had been well maintained on diuretics and digoxin. On the day of admission he became jaundiced and complained of vague abdominal pain.

On examination he was obviously very ill, jaundiced, dyspnoeic, and cyanosed, with gross ankle oedema. He was pulseless and the heart sounds were inaudible. Shortly afterwards he had a massive rectal haemorrhage of fresh blood and died 33 hours after admission.

At necropsy there were bilateral pleural adhesions, and the lungs were oedematous and congested. Both ventricles of the heart were hypertrophied and dilated, and there was some dilatation of the atria. The myocardium was soft and flabby. The valves were normal and the coronary arteries showed only minimal atheroma. The heart weighed 505 g. There were several small acute ulcers of the gastric mucosa and petechial haemorrhages in patches at the cardiac end. From the duodenum to the rectum there was intense congestion, most severe in the duodenum, terminal ileum, and colon. The mucosa of the terminal ileum was haemorrhagic and thickened, with small irregular ulcers between thickened mucosal folds. The caecum was less severely congested and haemorrhagic, but there were a few ragged erosions and rounded ulcers 2 to 6 mm. in diameter. The mucosa of the anterior wall of the ascending colon was ulcerated in a strip 2 cm. wide. The distal half of the transverse colon and the descending colon showed the most severe changes. The mucosa was almost black, due to massive haemorrhage, and much thickened; areas up to 1.5 cm. in diameter were denuded of mucosa. There was no pseudomembrane. There were some calcified mesenteric lymph nodes. The mesenteric arteries and veins were patent and the aorta was only moderately atheromatous. Liver and kidneys showed cloudy swelling but were otherwise normal. The other organs showed nothing remarkable.

Histological examination showed much mucosal haemorrhage and a variable amount of necrosis and ulceration in the affected zones at all levels in the intestine. There was submucosal oedema and congestion with "thrombi" consisting mainly of aggregated red cells in small veins. Many Gram-negative rods and a few Gram-positive rods were found in the mucosa.

Clinical Picture

Table I summarizes the clinical features. Of the 13 patients, 12 were 64 years of age or older; the exception was a 45-year-old mentally subnormal woman who refused food and required tube-feeding. There were seven women and six men. Abdominal pain was a feature in seven cases. Vomiting was recorded in six patients and haematemesis in one of these. Diarrhoea occurred in four, and rectal bleeding in six. There was no abdominal pain in five cases. Terminal collapse was observed in 10 cases and severe peripheral cyanosis was recorded in three.

In 10 cases congestive cardiac failure had been present at some time, but only six of these were in failure at the time of admission to hospital. In two cases there was a recent myocardial infarct. In three cases there was no evidence of any heart disease. In two cases there was thrombocytopenia; one of these was uraemic owing to urinary tract infection. One case was on anticoagulant therapy with phenindione. In all cases the blood urea was above normal, but in the only three in which it was estimated on more than one occasion there was evidence of a steep rise between the onset of abdominal symptoms and death. In three cases significant nitrogen reten-

TABLE I.—*Summary of Clinical Features*

Case No.	Date of Death	Age	Sex	Duration of Symptoms	Abdominal Pain	Distension	Vomiting	Diarrhoea	Haematemesis	Rectal Bleeding	Cyanosis	Collapse	Heart Failure on Admission	Failure in Past	Type of Heart Disease	Blood Urea (mg./100 ml.) 1st	Blood Urea (mg./100 ml.) 2nd	Other Features
1	4/7/64	85	M	4 days	+	+	+	+	−	−	−	−	−	−	None	78	—	On phenindione. Prothrombin index 2·5
2	24/7/64	68	M	8 days	−	−	−	+	−	+	−	+	+		Myocardial fibrosis. Recent infarct	84	171*	
3	21/7/64	45	F	2 weeks	?	−	−	−	−	−	+	+	−	−	—	64	450	Mentally subnormal. Refused food or drink
4	22/7/64	75	M	2 days	Discomfort	−	−	−	−	+	+	+	+		Hypertensive	—	146*	Jaundice
5	23/7/64	69	M	1 day	−	−	−	−	−	+	−	+	+		Myocardial fibrosis	36	78	Carcinoma prostate
6	10/8/64	82	M	Weakness 4 days	−	−	−	−	−	−	+	−	+		Myocardial fibrosis. Coronary atheroma	—	195*	Recent prostatectomy. Urinary infection
7	5/9/64	76	F	3 days	+	−	+	−	−	−	+	+	−	+	Dilated heart. Unknown cause	—	92*	
	16/9/64	67	F	2 weeks	Slight	−	+	+	−	+	+	+	?	−	Adherent pulmonary embolus	—	136*	Purpura on arms and legs
9	24/9/64	80	F	Several weeks	+	+	+	−	+	−	−	−	−	Exertional dyspnoea	Fibrosis. Coronary disease	—	59*	
10	1/10/64	79	M	1 day	−	−	+	−	−	−	+	+	+		Recent myocardial infarct. Fibrosis	—	—	Chronic bronchitis and emphysema
11	17/10/64	69	F	Several days	+	+	−	−	−	+	+	+	+		Myocardial fibrosis. Coronary atheroma	91	—	Recent operation: strangulated omentum in femoral hernia
12	26/10/64	77	F	Weakness, anorexia 10 weeks	−	+	−	−	−	+	−	+	+	−	Anaemic	209		Megaloblastic anaemia. Hb 2·4 g./100 ml. Platelets 15,000
13	20/11/64	64	F	3 weeks	+	−	+	+	−	+	+	+	−	+	Auricular fibrillation	119	366	Purpura. Platelets 25,000. Digitalis overdose. Jaundice. Urinary tract infection

*Post-mortem values.

tion could have been the result of primary renal disease, there being evidence of pyelonephritis in two and carcinoma of the prostate in one. In three cases plasma potassium was low or rather low—3.5, 4, and 4.1 mEq/l.—while in one case it was raised to 5.6 mEq/l.

Table II summarizes the treatment which 10 of these patients had received before the terminal illness. Case 1 had no previous significant illness, and in Cases 7 and 10 our information is incomplete. One patient was known to have taken an overdose of digitalis in the period immediately before the onset of abdominal symptoms. The antibiotics had been given at varying intervals before the final catastrophe and do not seem to have played a significant part.

TABLE II.—*Summary of Drugs Which Had Been Administered Before the Onset of Symptoms*

Case	Digitalis	Thiazide Diuretics	Antibacterial Therapy	Other Drugs
1	–	–		
2	+	–	Sulphonamides	Phenindione. Choledyl
3	–	–	Penicillin. Tetracycline	Ephedrine. Aminophylline
4	+	+	Penicillin. Tetracycline	Oestrogens. Paracetamol. Stromba
5	–	–	Streptomycin	Paracetamol. Peritrate
6	–	–	Penicillin	
7	+	?		
8	+	+		
9	+	+		
10	?	?		
11	+	–	Erythromycin	Barbiturates
12	–	+		Ferrous sulphate
13	+	+		Mersalyl. Quinidine

Pathology

A characteristic feature was the patchy distribution of the changes, which consisted mainly of congestion of the mucosa, varying in degree from slight to very severe, accompanied by intramucosal haemorrhage which rendered the bowel wall thick and turgid, the mucosal surface being dark brown and slightly rough to the touch in those areas. In a few, as in Case 1, there were areas in which the wall of the colon was thinned, the mucosal surface being greenish and smooth; this phenomenon seemed to be secondary to dilatation of the colon proximal to haemorrhagic necrosis of the mucosa of the distal colon. In some cases the wall of the small intestine was diffusely plum-coloured and there was a little blood-stained fluid in the peritoneal cavity. In some such areas there were bubbles of gas in the submucosa. Fig. 2 gives a diagrammatic representation of the extent of involvement in the individual cases.

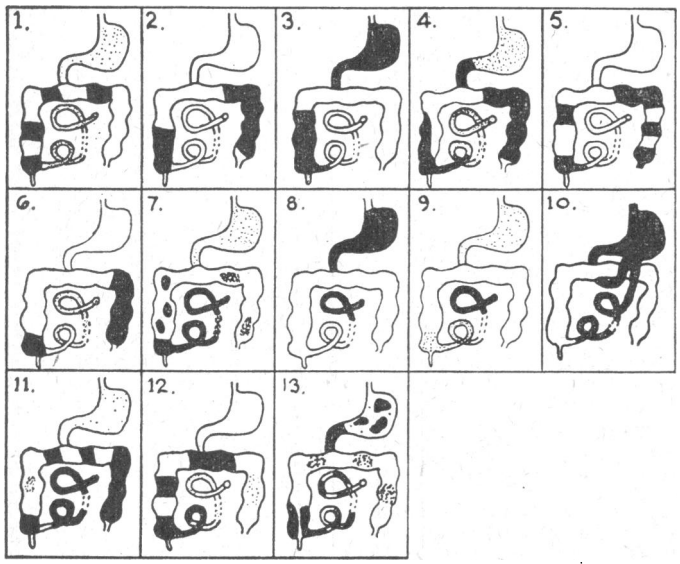

FIG. 2.—The solid black areas indicate haemorrhagic necrosis of the mucosa. The stippled areas indicate severe congestion with petechial haemorrhages.

Microscopically the characteristic features were haemorrhage into the mucosa with superficial necrosis. In the submucosa the veins were congested, some giving an impression of thrombosis, probably due to aggregation of red cells rather than to actual clotting, there being no obvious fibrin or platelet thrombi. In some cases there was oedema of the submucosa. Cellular inflammatory exudate was mainly slight, except in the few cases where there were areas of ulceration. The muscular and serosal coats were not greatly affected in most cases. In the dilated colon, where the mucosa was green and smooth, macroscopic examination showed necrosis of the thinned mucosa with almost no reaction.

Bacteriological Examination

Culture of the affected intestine, the small intestine being sampled when it was involved, gave in all cases a growth of *Cl. welchii*. All strains were tested for heat resistance, with negative results. This observation is of doubtful value, however, as the test was performed on cultures of the organism in Robertson's meat medium and not on the tissue itself: in these circumstances the spores may have germinated before being subjected to heat. The three strains which were tested were shown by toxin analysis to be of type A. Of the eight cases in which the other organisms present were identified, *E. coli* was recognized in five, *Streptococcus faecalis* in six, a *Klebsiella* in two, and *Pseudomonas pyocyanea* and *Sarcina* in one each. In three cases intestinal viruses were looked for, with negative results.

Discussion

Haemorrhagic necrosis of the bowel mucosa of patchy distribution occurring in elderly cardiac invalids has its own characteristics, but it shares some features with other types of acute non-occlusive intestinal necrosis. Among others, Dawson-Edwards and Morrissey (1955) and Kay, Richards, and Watson (1958) described cases of acute necrotizing colitis characterized by disseminated areas of congestion, necrosis, and ulceration of the mucosa. Not all of these cases could properly be described as "pseudomembranous" colitis, but they lacked the massive haemorrhage seen in the present series. These cases were predominantly postoperative and usually followed partial gastrectomy, though two cases of the series of Kay *et al.* were preceded by myocardial infarction. Undue operative shock was not a feature of either series and antibiotic administration was not thought to be an important factor. *Cl. welchii* was isolated in eight of the 14 cases described by Kay *et al.*, while in the other cases bacteriological examination was incomplete or omitted. Staphylococci were isolated in four cases. It is of interest that Howie, Duncan, and Mackie (1953) have demonstrated growth of *Cl. welchii* in the stomach after partial gastrectomy.

A number of types of necrotizing intestinal lesions have been described in which the causative agent seems to have been *Cl. welchii*. Cases of enteritis necroticans (*Darmbrand*) thought to have been due to ingestion of *Cl. welchii* from tinned meats were seen in Northern Germany in the summer of 1946 and again in 1947 (Jeckeln, 1947, 1948). The jejunum was most severely involved, but the ileum and the colon were occasionally affected. The disease was most severe in elderly patients and in young children, but occurred at all ages. Malnutrition may well have been a contributing factor. In those who survived the acute stage there was a tendency to perforation and stricture formation. A similar condition has been described in Papuan natives, caused by the consumption of poorly preserved pork in large quantities at times of festival (Murrell and Roth, 1963). Heat-resistant strains of *Cl. welchii* were incriminated in these outbreaks. The German strain is said to have been of type F (Zeissler and Rassfeld-Sternberg, 1949), while that from Papua was probably of type C.

Gas gangrene of the intestine has been described as a complication of leukaemia (Amromin and Solomon, 1962) and is not rare after haemorrhage from a peptic ulcer. Killingback and Lloyd Williams (1961) described six cases of necrotizing colitis of acute onset in previously well elderly subjects. Histological examination suggested the possibility of a clostridial cause. Resection of the affected colon was life-saving in three cases. Tate, Thompson, and Willis (1965) isolated a heat-resistant strain of *Cl. welchii* type A from a similar case.

The fact that we were able to grow *Cl. welchii* from all our cases may have been significant. Though *Cl. welchii* is a common inhabitant of the colon it can in our experience be isolated from the bowel in only about 70% of necropsies. The significance of heat resistance as a characteristic of food-poisoning strains of *Cl. welchii* has probably been exaggerated in the past, and there is some evidence to suggest that non-heat-resistant strains may also be capable of producing food poisoning (Taylor and Coetzee, 1966). The same consideration may well apply to the production of necrotizing enterocolitis in susceptible subjects, but even if *Cl. welchii* is a factor in precipitating this condition there are obviously important predisposing causes.

Among others, Marston (1962, 1964) stressed the role of ischaemia in the production of necrosis of the intestine. He also drew attention to the condition of haemorrhagic necrosis of the intestine occurring in dogs subjected to hypovolaemic shock. While we agree that anoxia is an important factor, the mesenteric arteries in our cases were not affected by atheroma to any significant degree, except in one case in which the inferior mesenteric artery was completely occluded and a plaque of atheroma was present in the main trunk of the superior mesenteric; and there was nothing in the histological sections to suggest anatomical occlusion of the small arteries, though in some cases apparent thickening of the walls of the small arteries relative to the area of the cross-section of their lumina suggested the possibility of spasm. Except for the two cases of myocardial infarction there was no reason to suspect shock as a primary factor. However, Corday, Irving, Gold, Bernstein, and Skelton (1962) have pointed out that mesenteric arteriolar spasm may result from cardiac arrhythmias and congestive heart failure as well as from hypotension and from the administration of vasopressor drugs.

Dehydration from diuretic therapy may aggravate both the arteriospasm and the congestion, favouring aggregation of red cells in the submucosal venules. Dehydration was perhaps a major factor in the youngest patient, who had been refusing food and drink. Prolonged treatment of congestive cardiac failure with thiazide diuretics tends to deplete the cells of potassium, even though serum potassium may remain normal. Though the effect of electrolyte imbalance on the intestine is complex, loss of cellular potassium tends to lower intestinal motility and may well favour proliferation of organisms in the small bowel.

The role of digitalis has been emphasized by Gazes, Holmes, Moseley, and Pratt-Thomas (1961); all their 10 patients seen in a period of 10 years had received large doses of digitalis and several were suffering from digitalis toxicity. They reviewed the evidence in the literature that digitalis causes pooling of blood in splanchnic vessels, possibly by causing spasm of hepatic veins or of portal venules. They also pointed out that a maintenance dose of digitalis may become toxic when potassium is lost from the body.

Treatment

The treatment of haemorrhagic enterocolitis is unsatisfactory. Laparotomy may have to be performed to rule out mesenteric vascular occlusion or necrotizing colitis, but resection of bowel should be avoided if possible. The administration of dextran of low molecular weights may improve the circulation in the intestinal wall, not so much by expanding the plasma volume as by favouring the disaggregation of red cells. Potassium depletion should be corrected. Vasopressors, especially angiotensin amide, should be avoided as being likely to increase vascular spasm. Judicious dosage of metaraminol or noradrenaline acid tartrate (levarterenol) may be less objectionable in the presence of septic shock (Smulyan, Cuddy, and Eich, 1964), but present opinion on the treatment of shock favours drugs which increase peripheral blood flow (*Brit. med. J.*, 1966). For this purpose either the alpha-adrenergic antagonist phenoxybenzamine or the quicker-acting beta-adrenergic receptor stimulator isoprenaline (du Toit, du Plessis, Dommisse, Rorke, Theron, and de Villiers, 1966) or orciprenaline, which is recommended by Shanks, Brick, Hutchison, and Roddie (1967) as being more easily obtainable, may be given. When using any of these drugs appropriate infusions should be administered to expand the blood volume to match the increased vascular bed. If we are correct in thinking that splanchnic vasoconstriction is an important cause of haemorrhagic enterocolitis this treatment should be instituted at the earliest possible moment, preferably before the development of the terminal collapse.

It would seem reasonable to administer anti-gas-gangrene serum and massive doses of antibiotics directed both against *Cl. welchii* and against the secondary invaders which may colonize the haemorrhagic and necrotic mucosa.

Summary

The clinical and pathological features of 13 cases of acute haemorrhagic enterocolitis which were seen in one hospital during an unusually dry spell in the summer and autumn of 1964 are described. It is suggested that, while the basic cause is probably reduction of the blood flow through the wall of the intestine, this is usually due to functional factors associated with heart failure and its treatment and not to anatomical lesions in the splanchnic blood vessels. It is also suggested that usually harmless organisms ingested in unusually large numbers owing to climatic conditions, and possibly proliferating in the intestinal contents owing to stasis, may have precipitated this haemorrhagic necrosis of the mucosa.

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