ANTIBIOTIC-RESISTANT STAPHYLOCOCCAL PSEUDO-MEMBRANEOUS ENTERITIS

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Fatal pseudomembraneous enterocolitis is characterized clinically by diarrhoea, dehydration, electrolyte imbalance, metabolic acidosis, and peripheral circulatory collapse; the state of the patient has been aptly likened to that found in Asiatic cholera. Pathologically the intestinal mucosa shows acute inflammation, varying from a mild to a severe necrotizing process with pseudomembrane formation, and affecting the small intestine more frequently and more severely than the large. When the lesion is confined to the small intestine the condition is then naturally referred to as pseudomembraneous or necrotizing enteritis.

Cases of enterocolitis from whose faeces *Staphylococcus pyogenes* is isolated are usually referred to as staphylococcal enterocolitis to differentiate them from the other cases of pseudomembraneous enterocolitis where no such organism has been isolated (Dearing and Heilman, 1953; Prohaska, Govostis, and Taubenhaus, 1954; Pettet, Baggenstoss, Dearing, and Judd, 1954; Hofer and McCaskey, 1954). However, Pettet *et al.* (1954) could find no difference in the naked-eye or histological appearance of the bowel in either condition.

Before the antibiotic era pseudomembraneous enterocolitis had been described following various abdominal operations, e.g., those on the stomach, colon, and uterus (Finney, 1893; Penner and Bernheim, 1939). In contrast to its post-operative occurrence, Kleckner, Barger, and Baggenstoss (1952) reported 14 cases associated with cardiac disease, with neoplastic obstruction of the colon, or with infections—all without a preceding operation.

Many cases, fatal and non-fatal, of antibiotic-resistant staphylococcal enterocolitis have now been reported after the use of antibiotics. Kramer (1948) described a case following the oral use of streptomycin for gastro-enteritis in an infant. Fairlie and Kendell (1953), Terplan (1953), and Fowler (1955) have published cases following the

prophylactic use of a combination of penicillin and streptomycin in surgery. Both post-operative and non-operative cases have followed the administration of chlortetracycline (aureomycin) and oxytetracycline (terramycin)—(Jackson, Haight, Kass, Womack, Gocke, and Finland, 1951; Dearing and Heilman, 1953; Gardner, 1953; Hay and McKenzie, 1954; Barber and Burston, 1955). On the other hand, Herrell, Nichols, and Martin (1953) have described three non-fatal cases of staphylococcal ileocolitis where no antibiotic was administered.

A post-operative case of staphylococcal enteritis is recorded here following the prophylactic use of streptomycin and phthalylsulphathiazole (sulphathalidine) in the pre-operative preparation of the intestine.

Clinical History

The patient, a 43-year-old man, was referred on July 19, 1955, to the Out-patient Department with a five-week history of vague pains in the region of the left iliac fossa. He had passed one watery motion a day for the past six months, but no blood or mucus. Slight tenderness and fullness were found over the sigmoid colon. He had a history of trauma to the lower anterior abdominal wall 12 months previously. A barium enema revealed slight deformity of the sigmoid colon, which was thought to be most probably due to a carcinoma.

He was admitted to hospital on August 13. The haemoglobin was 15 g. per 100 ml. blood and white blood cells were normal. He received phthalylsulphathiazole, 2 g. six hourly, until the second post-operative day, amounting to 40 g. in all, and 1 g. streptomycin by mouth daily for the last four pre-operative days, followed by 1 g. intramuscularly daily for the first two post-operative days, amounting in all to 6 g. A laparotomy was performed on August 18. No tumour was found, but the omentum was adherent to the sigmoid colon; these adhesions were divided and the appendix removed.

His progress was satisfactory until 5 p.m. on the second post-operative day, when he complained of

FIG. 1.—The gross appearance of the pseudomembrane covering a segment of the ileum.

abdominal distension and passed a large diarrhoeal stool. At 6 p.m. he was pale and cyanosed, his pulse was weak and rapid, blood pressure was 60 mm. Hg systolic, and his condition was one of severe peripheral circulatory collapse. Phthalylsulphathiazole and streptomycin were discontinued and 600,000 units of penicillin injected intramuscularly. Examination of the plasma showed urea 95 mg.%, protein 6.5 g.%, P.C.V. 55%, chloride 85 mEq. per l., sodium 142 mEq. per l., potassium 5.2 mEq. per l., bicarbonate 9.25 mEq. per l. An intravenous saline drip was immediately started and noradrenaline added, but despite 6 litres of normal saline and 1 litre M/6 sodium lactate administered during the night and the following morning, he continued to deteriorate and passed into a coma at noon on the third post-operative day, and died shortly afterwards. He had passed three further diarrhoeal stools during the night, and towards the end had faecal incontinence. A stool passed during the morning of the day of death was sent to the laboratory for examination.

Necropsy

Necropsy was performed 24 hours after death, the body having been kept in the refrigerator during that time.

The body was that of a muscular man with a left lower paramedian abdominal incision. The lungs showed basal collapse and acute bronchitis of the lower lobes. The heart and coronary arteries were normal.

The oesophagus, stomach, and duodenum were normal. The peritoneal surfaces of the bowel showed no naked-eye evidence of inflammation. The small and large intestine were grossly dilated and distended, and on opening the intestine large quantities of liquid faeces, amounting to several

litres, escaped. The mucosal surface of the small bowel, particularly of the ileum, was covered with a yellowish-grey, friable pseudomembrane (Fig. 1). This membrane varied from small patches to large diffuse areas several feet in extent, and was easily peeled off, so partially removing the mucosa. The large bowel showed a few petechial haemorrhages in the mucosa of the transverse colon, but no membrane was seen. The mesenteric glands were inconspicuous. The liver showed a few small areas of pale yellow opaque discoloration under the capsule and extending a few centimetres into

FIG. 2.—The pseudomembrane shows partial separation, and is composed of necrotic debris, pus cells, and fibrin. The basal cells of the mucosal glands are intact. Haematoxylin and eosin, $\times 45$.

its substance. The spleen was normal in size and the cut surface was soft. Normal-sized kidneys showed cloudy swelling.

Permission for examination of the brain was refused.

Histology

Histological examination of the jejunum and ileum showed the pseudomembrane adherent in some areas and partly separated in others (Fig. 2). The membrane was composed of fibrin, large numbers of pus cells, and cellular debris; colonies of Gram-positive cocci were easily seen throughout all parts of the membrane (Fig. 3). The mucosal

glands showed varying degrees of necrosis, but usually, even in the most severely affected areas, the basal parts were intact and viable. Scattered cocci were seen in the necrosed glands and the intervening stroma, though they were inconspicuous compared with the colonies found in the pseudomembrane. The stroma between the mucosal glands showed oedema and dilatation of the blood vessels. Sections of the large bowel showed largely intact mucosal glands and round cell infiltration of the mucosal stroma; the appearance was not remarkable.

Sections of the liver, spleen, and kidneys showed cloudy swelling; no organisms were seen in sections stained by Gram's method.

Bacteriology

Specimens of faeces collected before and after death were examined.

Gram-stained films showed large numbers of Gram-positive lanceolate diplococci (*Streptococcus faecalis*), moderate numbers of Gram-negative coliform bacilli, and small numbers of staphylococci in bunches; no pus cells were seen.

Cultures on MacConkey's medium grew numerous colonies of *Bact. coli*, *Streptococcus faecalis*, *Proteus vulgaris*, and a few colonies of *Staphylococcus aureus*; nutrient agar containing 0.25% beta phenylethyl alcohol (Lilley and Brewer, 1953) gave a mixed growth of *Staphylococcus aureus* and *Streptococcus faecalis* and *Proteus vulgaris* and *Bact. coli* were inhibited; Ludlam's medium (Ludlam, 1949) gave mixed growth of *Staphylococcus aureus* and *Streptococcus faecalis* and all coliform organisms were inhibited. Cultures for *Salmonella*, *Shigella*, and *Clostridium welchii* were negative. The *Staphylococcus aureus* was coagulase positive. The antibiotic sensitivities of the organisms cultured from the faeces were determined by a simple filter-paper-disc diffusion technique, using Oxford staphylococcus as a control.

It will be seen from the table that all the organisms isolated from the faeces were resistant

FIG. 3.—A part of the pseudomembrane showing pus cells, fibrin, and a colony of staphylococci. Gram's stain, $\times 350$.

TABLE
ANTIBIOTIC SENSITIVITIES OF ORGANISMS ISOLATED FROM FAECES

	Penicillin	Streptomycin	Chloramphenicol	Oxytetracycline	Chlortetracycline	Erythromycin
<i>Staphylococcus aureus</i> . .	R	R	S	S	S	S
<i>Streptococcus faecalis</i> . .	S	R	S	S	S	S
<i>Bact. coli</i>	R	R	S	S	S	R
<i>Proteus vulgaris</i> . . .	R	R	R	R	R	R

S=Sensitive. R=Resistant.

to streptomycin, which had been the only antibiotic used pre-operatively and before the start of the fatal illness; the *Staphylococcus pyogenes* was resistant to both penicillin and streptomycin. The phage-type of the staphylococcus was 52/77; no means were available to test for enterotoxin production, and so it is unfortunately not possible to say in this case whether the organisms produced enterotoxin.

Discussion

In this case fatal diarrhoea occurred unexpectedly on the second post-operative day and developed into a fulminating cholera-like illness lasting 22 hours, following a simple abdominal operation. Streptomycin had been used in the pre-operative preparation of the bowel, and a *Staphylococcus aureus* isolated from the faeces before and after death was found resistant to penicillin and streptomycin. As no case of staphylococcal enteritis has yet been described following the use of phthalylsulphathiazole, there are no grounds for incriminating it.

Bact. coli and *Streptococcus faecalis*, both resistant to streptomycin, were considered to be present in normal numbers in the faeces, and the staphylococcus was not the predominant organism. Nutrient agar containing 0.25% beta phenyl-ethyl alcohol (Lilley and Brewer, 1953) and Ludlam's medium (Ludlam, 1949) were found to be suitable selective media because they inhibited the Gram-negative coliform organisms. Fowler (1955) also found enterococci and coliform bacilli associated with staphylococci in his cases following the pre-operative use of a combination of penicillin and streptomycin. Hence it appears that the elimination or severe reduction of the faecal flora of the large bowel is not an essential prerequisite in the establishment and growth of staphylococci in the small intestine. In contrast, staphylococci are usually found in more or less pure culture in cases following the use of the broad-spectrum antibiotics (Gardner, 1953; Dearing and Heilman, 1953; Pettet *et al.*, 1954).

The pathogenesis of antibiotic-resistant staphylococcal enterocolitis is not yet clear, and the patient-staphylococcal-antibiotic relationship is not fully understood. Hofer and McCaskey (1954) summarized the mechanisms which may play a role in antibiotic-resistant infection or superinfection into three groups: (1) environmental factors where, for instance, the antibiotic used may so alter the bacterial flora of the body that resistant organisms become predominant. (2) Stimulation of bacterial growth by antibiotics: they are care-

ful to point out that this is not a clinically established fact, although it can be demonstrated *in vitro* with penicillin. (3) Tissue alterations: under this heading they point out that broad-spectrum antibiotics may cause clinical vitamin-B deficiency by eliminating the synthesizing bacteria of the normal intestinal flora. They suggest that alterations in the flora of the large bowel induced by the broad-spectrum antibiotics and resulting in vitamin-B deficiency states may also favour acute enterocolitis as a result of local tissue alteration. Barber and Burston (1955) state that streptomycin-resistant variants of staphylococcus can grow in the presence of streptomycin, that these variants develop with rapidity, and that a few days' treatment is sufficient for them to become predominant. Hence the predominance of a streptomycin-resistant variant in this case is not surprising. Fairlie and Kendall (1953) support the view that antibiotics might actually stimulate staphylococci to pathogenicity or toxin production, because some of their cases showed symptoms as early as 24 hours after giving antibiotics. However, in this case the patient had been receiving streptomycin for six days before the onset of symptoms. Since *Streptococcus faecalis* and *Bact. coli* of the normal faecal flora were not found to be greatly reduced or eliminated, it does not appear that the mechanism of tissue alteration was operative in this case.

Cregan and Hayward (1953) investigated the bacterial flora of the healthy small intestine, using samples removed directly from the lumen of the small bowel with a syringe at gynaecological operations. They found that the jejunum and the greater part of the ileum contained a transient flora chiefly of Gram-positive organisms of oral type, which were regarded as contaminants passing through with the ingesta. Because of the apparent inability of these organisms to become resident, they deduced that an antibacterial mechanism, distinct from the stomach mechanism, must be operating in the small bowel. Blacklock, Guthrie, and Macpherson (1937), investigating the nature of this mechanism, could draw no definite conclusion and thought that many factors combined to keep the small bowel fairly sterile.

If the existence of the antibacterial mechanism of the small intestine is accepted, it would then appear that one of the factors in the production of staphylococcal enteritis is that, in certain circumstances, this mechanism is no longer able to withstand an antibiotic-resistant staphylococcus, aided, perhaps, in some unknown way by the corresponding antibiotic. The relative roles played by the staphylococcus and the antibiotic are not understood, but there can now be little doubt that

combined they are capable of causing enteritis in certain cases.

In the treatment of this disease the antibiotic or antibiotics which the patient has been receiving are stopped and replaced by one to which the staphylococcus is sensitive. In this country at the present moment erythromycin will be the antibiotic of choice, as Barber and Burston (1955) found none of their strains resistant to it. They make an important plea that this antibiotic should be used only for infections resistant to all other antibiotics, and rigidly reserved for this purpose, as resistance to it rapidly develops. The fluid loss must be made good. Prohaska *et al.* (1954) claim good results using corticotrophin, but no staphylococci were isolated in their cases. The use of corticotrophin for a short period in severe cases of staphylococcal enteritis would not appear to be contraindicated, provided that an antibiotic to which the staphylococcus is sensitive is administered at the same time. The prophylactic use of streptomycin in surgical, and presumably in non-surgical, cases in an environment harbouring staphylococci is inevitably accompanied by a certain risk of staphylococcal enteritis.

Summary

Pseudomembranous enteritis is characterized clinically by diarrhoea, dehydration, electrolyte imbalance, and peripheral circulatory collapse; pathologically by necrotizing enteritis with formation of a false membrane. Cases which show staphylococci on examination of the faeces are referred to as staphylococcal enteritis.

A case of post-operative staphylococcal enteritis following the use of streptomycin in the pre-operative preparation of the bowel is described. The staphylococcus isolated from the faeces was associated with *Bact. coli*, *Streptococcus faecalis*, and

Proteus vulgaris. Selective media were useful in the isolation of the staphylococcus in the presence of the Gram-negative coliform organisms.

The small intestine showed necrotizing inflammation and a pseudomembrane, the latter being composed of fibrin, pus cells, and colonies of staphylococci.

It is suggested that an antibacterial mechanism normally present in the small bowel may be concerned in its pathogenesis.

Treatment consists of stopping the offending antibiotic and administering one to which the staphylococcus is sensitive; the fluid and electrolyte balance must be promptly corrected.

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REFERENCES

- Barber, M., and Burston, J. (1955). *Lancet*, **2**, 578.
 Blacklock, J. W. S., Guthrie, K. J., and Macpherson, I. (1937). *J. Path. Bact.*, **44**, 321.
 Cregan, J., and Hayward, N. J. (1953). *Brit. med. J.*, **1**, 1356.
 Dearing, W. H., and Heilman, F. R. (1953). *Proc. Mayo Clin.*, **28**, 121.
 Fairlie, C. W., and Kendall, R. E. (1953). *J. Amer. med. Ass.*, **153**, 90.
 Finney, J. T. M. (1893). *Bull. Johns Hopk. Hosp.*, **4**, 53.
 Fowler, B. J. (1955). *Brit. med. J.*, **1**, 1313.
 Gardner, D. L. (1953). *Lancet*, **2**, 1236.
 Hay, P., and McKenzie, P. (1954). *Ibid.*, **1**, 945.
 Herrell, W. E., Nichols, D. R., and Martin, W. J. (1953). *J. Amer. med. Ass.*, **152**, 1601.
 Hofer, J. W., and McCaskey, G. M. (1954). *Arch. intern. Med.*, **93**, 44.
 Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., and Finland, M. (1951). *Ann. intern. Med.*, **25**, 1175.
 Kleckner, M. S., Bagen, J. A., and Baggenstoss, A. H. (1952). *Gastroenterology*, **21**, 212.
 Kramer, I. R. H. (1948). *Lancet*, **2**, 646.
 Lilley, B. D., and Brewer, J. H. (1953). *J. Amer. pharm. Ass. (Sci. ed.)*, **42**, 6.
 Ludlam, G. B. (1949). *Monthly Bull. Minist. Hlth (Lond.)*, **8**, 15.
 Penner, A., and Bernheim, A. I. (1939). *Arch. Path. (Chicago)*, **27**, 966.
 Pettit, J. D., Baggenstoss, A. H., Dearing, W. H., and Judd, E. S. (1954). *Surg. Gynec. Obstet.*, **98**, 546.
 Prohaska, J. V., Govostis, M. C., and Tautenhaus, M. (1954). *J. Amer. med. Ass.*, **154**, 320.
 Terplan, K. (1953). *Amer. J. Path.*, **29**, 595.