ANTIBIOTIC-RESISTANT STAPHYLOCOCCAL PSEUDOMEMBRANOUS ENTERITIS

BY

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Fatal pseudomembranous 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 pseudomembranous 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 pseudomembranous 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 pseudomembranous 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, Bargen, 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 (tetracycline)—(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 staphyloccal ileocolitis where no antibiotic was administered.

A post-operative case of staphylococcal enteritis is recorded here following the prophylactic use of streptomycin and phthalysulphathiazole (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 phthalysulphathiazole, 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
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. 1.—The gross appearance of the pseudomembrane covering a segment of the ileum.

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, × 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.

**Table**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Streptococcus faecalis</em></th>
<th><em>Bact. coli</em></th>
<th><em>Proteus vulgaris</em></th>
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<td>Penicillin</td>
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<td>Streptomycin</td>
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<td>Erythromycin</td>
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*S* = Sensitive. *R* = Resistant.

Fig. 3.—A part of the pseudomembrane showing pus cells, fibrin, and a colony of staphylococci. Gram's stain, × 350.
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 phthahlylsulphathiazole, 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-ethanol 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-
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