colonic disorders their use rests on flimsy experimental evidence. In general the effect of atropine is to depress colonic motility (Jackman and Bargen, 1938), but results may be inconstant and variable. For example, in one study (Kern *et al.*, 1951) the normal therapeutic dose of 0.6 mg. of atropine given intravenously had no effect on one occasion, while on another occasion the same dose given subcutaneously resulted in a supression of motility. In general the effect of even larger doses (1 mg.) was slight and of short duration, usually less than 30 minutes.

This paper indicates a definite effect of Mebeverine on colonic motility. Of particular interest is the suggestion from these results that Mebeverine has a more marked proportional response in patients with colonic hypermotility than in patients with normal or diminished motility. This would be a useful quality, as the aim of therapy in a motility disorder is not to produce the abnormal state where all motility is abolished but to restore an abnormally active or incoordinate bowel to a more normal pattern of activity. To date the evidence for the effectiveness of Mebeverine has rested on animal experiments, and it is well known that such evidence may have only a limited significance in human therapeutics (Rowlands, 1959). This paper, however, demonstrates a definite effect on human motility of a musculotropic agent given intravenously. There are, however, differences in response—that of the small intestine and proximal colon being minimal, while the response of the sigmoid colon is distinct. It may be that the therapeutic effectiveness will be shown to reflect this specificity.

From time to time assessments have been made of the effect of anti-spasmodic preparations on the course of the irritable bowel syndrome, but as far as is known this is the first attempt to study the effect of an anti-spasmodic preparation in a double-blind controlled way. The difficulties in such an assessment are great, particularly as no objective criteria of effectiveness are available. Indeed, this fact would seem to underline the necessity of assessing symptomatic therapy in as unbiased a way as possible. One further difficulty in the way of such an investigation is the lack of any objective criteria of diagnosis. The diagnosis of an irritable colon is vague and at best is one of exclusion. The association of the symptoms of lower abdominal pain and disturbance of bowel habit with the colon rests on no secure basis and is only presumptive, and it is conceded that the symptom complex studied may be the end-result of a number of functional or pathological processes.

It is likely, however, that Mebeverine has an effect on the colon, and that, moreover, in these patients over a period of three months the abdominal cramps and disturbance of bowel habit improved to a greater degree using the active preparation Mebeverine than the identical inert control tablet. It would appear that it is a useful preparation in such patients. The usefulness is enhanced by the fact that there are virtually no side-effects. This is a considerable advantage over the standard anticholinergic preparations, where for therapeutic effectiveness it is usually necessary to give dosages which affect not only the target organ but also other sites in the body.

Summary

A new anti-spasmodic preparation which has a direct musculotropic effect has been studied.

Mebeverine results in a diminution of exaggerated colonic motility as tested by the measurement of intraluminal pressures in the sigmoid colon in man.

In a double-blind controlled trial assessed by sequential analysis Mebeverine was shown to be superior to a placebo preparation in relief of symptoms assumed to be arising from the irregular activity of the lower alimentary tract.

I am grateful to n.v. Philips-Duphar for supplies of Mebeverine and to Mr. W. Strik for the statistical analysis of the results, also to Dr. F. Avery Jones and Dr. T. D. Kellock for permission to study patients under their care.

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Recurrent Acute Renal Failure: Report of Two Cases

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Records of two separate episodes of acute renal failure in the same patient are extremely rare. This paper describes two cases in which a second episode of acute oliguric renal failure occurred during the recovering diuretic phase after the first attack.

In the first patient a Gram-negative septicaemia was implicated on both occasions. The second patient had initially acute renal failure after trauma, and the development of a Gram-negative septicaemia during his recovery caused a second episode of renal failure.

Case 1

First Episode: Renal Failure Due to Post-operative Septicaemia.—A man of 44 with a two-year history of dyspepsia from a chronic duodenal ulcer came to hospital with a history suggestive of acute appendicitis. A gangrenous retrocaecal appendix which had perforated at the base, with local peritonitis, was removed. The wound was drained. After operation he remained febrile, and by the second day abdominal distension and hypotension had developed. The wound was re-explored for suspected general peritonitis, but a paralytic ileus was the only finding. Blood culture before the second operation was positive for *Escherichia coli*. He was oliguric from the second day after appendicectomy (Fig. 1, a), and a diagnosis of acute renal failure due to post-operative septicaemia was made. Haematemesis began on the fifth day, and the urea level rapidly rose, to reach 500 mg./100 ml. by the seventh day, when haemodialysis was performed. He required haemodialysis again on the

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9th and 12th days. Regional heparinization was employed for each dialysis. Despite an increasing urine output he remained criticially ill. The serum bilirubin level rose to 6 mg./100 ml. and liver-function tests showed marked impairment. He continued to bleed steadily from the gastro-intestinal tract. Continued antibiotic therapy and repeated transfusions resulted in a gradual improvement, and by the 19th day his jaundice was fading, bleeding had ceased, and a continued diuresis had lowered the urea level to 62 mg./100 ml. Blood cultures were negative and antibiotics were discontinued.

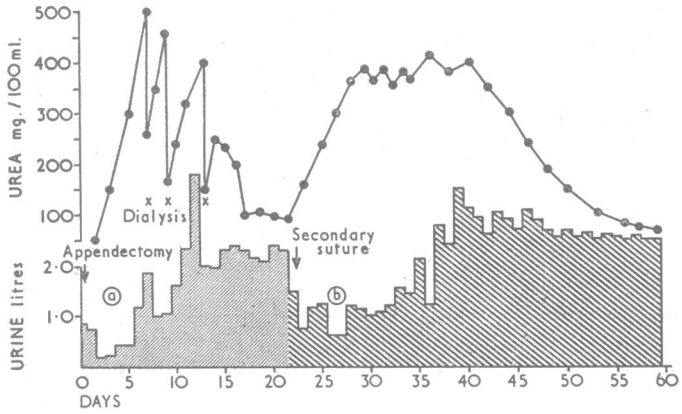

FIG. 1.—Course of renal failure in Case 1.

The gridiron wound had failed to heal and omental fat was protruding between the sutures, so on the 22nd day the wound was resutured under general anaesthesia.

Second Episode : Renal Failure Due to Recurrent Septicaemia.—Several hours after this operation he became grossly hypotensive, with a rigor and a fever of 39° C. A diagnosis of recurrence of septicaemia was made, and his hypotension responded after four hours to further antibiotic therapy and intravenous fluids. Blood culture did not reveal any organisms. This episode was followed by a second period of oliguria (Fig. 1, b). The urea level again rose rapidly to levels of 400 mg./100 ml. and he developed fresh gastro-intestinal bleeding. He responded to repeated transfusions and a stepwise diuresis was eventually sustained at 2–3 litres daily. A right-femoral-vein thrombosis was an additional complication. The urea level began to fall for the second time from the 41st day, and thereafter he improved rapidly. A barium-meal examination during convalescence revealed a chronic duodenal and a gastric ulcer. His wound, which had again broken down with omental protrusion, was resutured—this time under local anaesthesia with antibiotic cover—without event. He was discharged after 60 days with a serum urea level of 75 mg./100 ml. One year after the appendicectomy he was very well, had regained 3 stone (19 kg.) in weight, and had resumed his job. The only urinary symptom was nocturia, requiring him to get up twice nightly. There were no ulcer symptoms, and his incisional hernia was easily controlled by a surgical corset. No repair of this is contemplated. The urea level was 70 mg./100 ml., serum electrolytes were normal, there was no proteinuria or cellular deposit, and the creatinine clearance was 63 ml./minute.

Case 2

First Episode : Post-traumatic Acute Renal Failure.—A man of 40 was hit by a car and was unconscious on admission to hospital. He was hypotensive and oliguric. The hypotension responded rapidly to colloid and blood replacement, but he remained oliguric despite a test infusion of mannitol. His injuries included a severe pelvic fracture, and cystography revealed compression of the bladder by a considerable pelvic haematoma but no evidence of extravasation of urine. Post-traumatic acute renal failure was diagnosed and he remained oliguric for 10 days. He required haemodialysis on two occasions. He had mild right upper quadrant abdominal pain, which was initially treated conservatively. A stepwise increase of the urinary output from the 10th day began to lower the urea level by the 13th day (Fig. 2, a), and on the 20th day the urea level had fallen to 48 mg./100 ml.

However, at this stage his abdominal pain increased in severity ; there was persistent vomiting and guarding beneath the right costal margin, with abdominal distension. He was thought to have a possible intestinal obstruction as a result of the pelvic haematoma, or a delayed rupture of the liver. Laparotomy was performed under penicillin and tetracycline antibiotic cover, and, in view of his previous episode of renal failure, a constant infusion of 10% mannitol was given throughout the operation. The findings were a small pelvic abscess containing old blood clot, which was evacuated and drained, and a tense, acutely inflamed gall-bladder. Cholecystectomy was performed, and the mucosa of the gall-bladder was found to be haemorrhagic with acute inflammatory oedema, but no stones were present. The daily urine output was less than 1 litre for 48 hours after operation ; it then increased to 2 litres (Fig. 2, b), and the urea level, which showed a transient rise after surgery, had fallen by the fifth post-operative day to 54 mg./100 ml. The pelvic swab had grown *E. coli*.

Second Episode : Renal Failure Due to Post-operative Septicaemia.—On the sixth day after cholecystectomy he had a sudden rigor, with a fever of 39.5° C., and developed profound hypotension. A Gram-negative septicaemia was diagnosed, and he was treated with vigorous fluid replacement, mannitol infusion, and chloramphenicol therapy on the basis of sensitivities from the previous abscess culture. Blood culture done at the time of his collapse subsequently grew *E. coli* with a similar sensitivity pattern. His hypotension responded rapidly, but a second episode of oliguria developed, lasting six days (Fig. 2, c). The blood urea level again rose rapidly, and acute renal failure due to *E. coli* septicaemia was diagnosed. Two further haemodialyses were required for this episode, which was complicated by cardiac arrhythmia, right-lower-lobe consolidation, and a generalized bleeding tendency. A stepwise diuresis ensued, and 18 days after his cholecystectomy (38th day

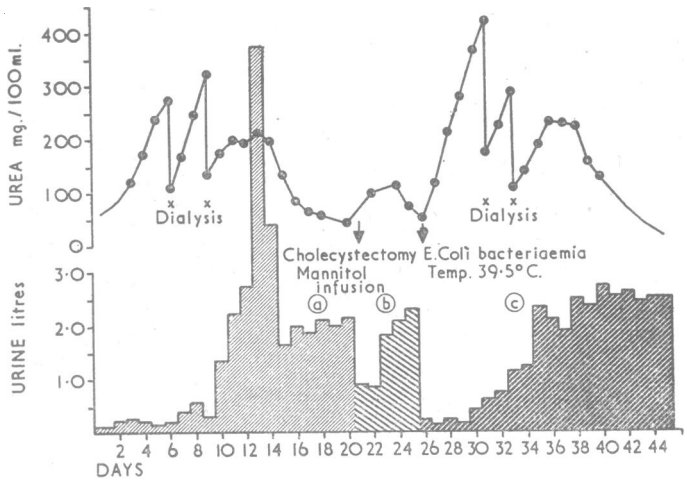

FIG. 2.—Course of renal failure in Case 2 (multiple injuries and acute cholecystitis).

after trauma) the urea level again began to fall ; and his progress thereafter was rapid. He was discharged after 50 days with a blood urea level of 25 mg./100 ml.

On review three months later he had no symptoms and his pelvic fractures had united soundly. The urea level was 40 mg./100 ml., serum electrolytes and urine examination were normal, and the creatinine clearance was 123 ml./minute.

Discussion

Two episodes of acute renal failure in the same patient would seem to be extremely rare. In previous reports a considerable time interval existed between the two attacks (Bluemle *et al.*, 1959 ; Gray and North, 1960).

In the two cases described here the second episode occurred during the diuretic phase following a typical attack of acute oliguric renal failure.

In Case 1 the separate nature of the two episodes of acute renal failure was strongly suggested by the typical pattern in each incidence of oliguria accompanied by progressive clinical and biochemical uraemia, followed by a gradually developing

diuretic phase with resolution of uraemia. An obvious renal vascular insult with severe hypotension was apparent on both occasions as a precipitating cause, Gram-negative septicaemia being proved for the initial attack and clinically suspect for the second. The inadvisability of the wound resuture being undertaken without institution of antibiotic therapy was apparent on retrospect, and the second severe collapse and subsequent renal failure highlights the nephrotoxicity of a Gram-negative bacteriaemia. In the first episode the time period from the onset of oliguria to the onset of spontaneous lowering of the urea level, which is a more reliable index of the severity of the course of acute renal failure than the period of oliguria (Niall, 1963), was 12 days, and in the second instance it was 20 days. Although the patient was in excellent health one year later, residual impairment of renal function existed.

Case 2 illustrates even more strikingly the danger of bacteriaemia developing as a complication during the course of acute renal failure. When it was apparent that an operation during the diuretic phase of his acute renal failure was unavoidable because of the development of an acute abdominal emergency, the danger of precipitating a second episode was thought to be considerable, especially in view of our previous experience. Pre-operative hydration and blood replacement during operation were accordingly screened carefully, aided by determinations of blood volume. Antibiotic therapy was begun, although no previous evidence of infection existed, and a mannitol infusion given during the operation was continued thereafter for 24 hours. A transient post-operative oliguria with a rise in the urea level was noted, but a brisk diuresis then lowered the urea level again towards normal. However, the collapse due to Gram-negative septicaemia six days after operation, although treated early and vigorously, resulted in a second severe episode of oliguric renal failure requiring two haemodialyses. The respective times from onset of oliguria to fall in urea level were 13 days on the first and 11 days on the second occasion.

Gram-negative septicaemia, both as the origin and as a complication of acute renal failure, is a major cause of morbidity and mortality in most centres, and these two cases emphasize its hazards.

Recurrence of acute renal failure in the second patient was not prevented by antibiotic therapy and mannitol infusion, although mounting clinical and experimental evidence affords support for the protective effects of a mannitol-induced osmotic diuresis in renal failure from other causes (Barry *et al.*, 1961).

The lack of protective effect of mannitol in a patient recovering from acute tubular necrosis may perhaps have been predicted from the failure of mannitol given during the previous cholecystectomy to prevent a short period of post-operative oliguria, although mannitol has been effective in reversing post-operative antidiuresis in patients with pre-operative renal impairment due to a variety of diseases (Seitzman *et al.*, 1963).

It is possible that additional protection may be provided by the use of dextran of low molecular weight (Rheomacrodex) in bacteriaemic shock, not by virtue of its diuretic effect, which is minor (Rabelo *et al.*, 1962; Matheson *et al.*, 1964), but perhaps by its action in improving the microcirculation in low-flow states (Gelin and Zederfeldt, 1960).

Finally, these patients afford opportunity for speculation on the pathogenesis of acute oliguric renal failure. Such instances of recurrence of renal failure, with two episodes following each other so closely, appear to suggest a functional vascular aetiology rather than an organic tubular necrosis (Finckh, 1962).

Summary

Two patients, each having two separate episodes of acute renal failure, are recorded. The second attack on each occasion occurred during the recovering diuretic phase after a typical episode of acute oliguric renal failure. In the first patient recurrence of a Gram-negative septicaemia was responsible. The second patient developed a Gram-negative septicaemia during convalescence from post-traumatic acute renal failure.

These cases highlight the nephrotoxicity of Gram-negative septicaemia, and it is of interest that mannitol was found to be ineffective in preventing renal failure in the second patient.

I am grateful to Mr. C. Schneider for permission to publish the details of the second patient's illness.

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Primary Hyperparathyroidism Resembling Rickets of Late Onset

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Primary hyperparathyroidism is rare in childhood and early adolescence, and may present special difficulties in diagnosis. Delay in treatment is dangerous, since children are prone to develop severe hypercalcaemia (Nolan, Hayles, and Woolner, 1960), and may suffer irreversible mental impairment (Anspach and Clifton, 1939; Harmon, 1956). Moreover, bone disease, if present, may cause rapidly progressive deformity resulting in prolonged or permanent incapacity.

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Important aspects of primary hyperparathyroidism in childhood were encountered in the patient described in this report. The osseous manifestations were of unusual interest, comprising osteitis fibrosa cystica, osteosclerosis, and metaphysial changes simulating rickets. There was a neurological disturbance resembling chorea.

Case Report

A 14-year-old schoolboy was admitted to Brisbane Hospital on 18 February 1964. He had been well until two years previously, when his scholastic performance began to deteriorate and his cheer-