returned with a severe exacerbation. There followed a period on the placebo, the relief being just as great as when she had been taking the drug. The day she began taking the placebo coincided with the achievement of her life's ambition, for she began her medical studies, having previously been a nurse. She soon stopped having ulcers, and had a complete remission. This continued for six months, whether or not she was taking corlan tablets.

Discussion

The advantage of drug over placebo has clearly been demonstrated in 16 out of 17 patients serving as their own controls. When considering all the patients together the degree of ulceration was reduced by about 50%, and the reduction could often be maintained for three to six months. It is interesting to note that in Figs. 2 and 3 the effect of the drug was almost the same when the patients knew they were receiving the active preparation as when they were unaware of the nature of the tablets. Nevertheless, any complete remissions were probably the result of the natural history of the disease rather than the result of the drug, since one occurred with the placebo and two others have been maintained for three months without treatment.

That the response to the drug over a period of time was not as constant as in Fig. 3 does not necessarily mean that the drug is no longer effective, but may rather reflect the periodicity of the severity of the ulceration, as is also shown by the difference between the ulceration at the beginning of the trial and while on the placebo.

That psychological factors play an important part is suggested not only by the difference between the effect when the active preparation preceded the placebo and vice versa, but in the history in Case 3, illustrated by Fig. 4, when the remission is plainly not the result of any therapy but perhaps the personal satisfaction of beginning medical studies. The smaller effect of the active preparation over the inactive one when the former was given first can also be accounted for by the feeling of well-being that these patients experience when at last they obtain some relief, even though only partial, from their severe ulceration.

No side-effects have been noted in patients treated in this way, but it has been my experience, so far, that only the Mikulicz type of ulceration responds in this manner, and that the type of recurrent ulceration with multiple shallow erosions of herpetiform type is made worse, not better, by local hydrocortisone therapy.

Thus in the treatment of the Mikulicz type of recurrent ulceration, tablets containing 2.5 mg. of hydrocortisone hemisuccinate given four times a day are of value in reducing by half the degree of ulceration, especially during acute exacerbations. Remissions are not induced nor are they maintained by the treatment in the type of case that is severe enough to warrant this therapy. Since it in no way cures or prevents these troublesome ulcers, four tablets a day for eight weeks would appear to be enough to help a patient during a particularly severe bout of ulceration. The resultant relief from pain may induce such a feeling of well-being that the ulceration may remain at a less severe level for a month or two, after which another period of therapy could then be tried if desired.

Summary

Assessment of the value of topical hydrocortisone hemisuccinate in the treatment of patients suffering from recurrent Mikulicz's aphthae has been undertaken by a double-blind controlled clinical trial. The results show that, compared with the placebo, the drug reduces by about 50% the number of ulcer days and of new ulcers per patient, per eight-weeks period.

Our thanks are due to Glaxo Laboratories Ltd. for providing the active and inert tablets, and to Guy's Hospital Medical Illustration Department for preparing the charts.

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BACTERIAL FLORA OF THE SMALL INTESTINE IN ACUTE INTESTINAL OBSTRUCTION

BY

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In acute obstruction of the small intestine the bowel above the site of obstruction soon becomes filled with fluid which is feculent, both in colour and in odour. When appropriate treatment is deferred, fluid of this nature may eventually be vomited.

It has usually been assumed that the flora of this fluid is closely akin to that of normal faeces. Moreover, it has generally been believed that the small intestine is inoculated with organisms by retrograde spread from the large bowel. A search of the literature of the past 60 years has not revealed any detailed investigation of the bacterial flora in intestinal obstruction in man.

In the work reported here, samples of intestinal content were taken at operation from many levels of the small bowel by aspiration of its content through hypodermic-needle punctures of the bowel wall. The specimens were then examined bacteriologically.

The results show that the small intestine above an obstruction contains a profuse flora of faecal type. This is abnormal. In contrast, the small intestine below the obstruction is either sterile or yields only a scanty growth. This is normal (Cregan and Hayward, 1953; Cook, Elliott, Elliot-Smith, Frisby, and Gardner, 1957). This leads to the conclusion that the profuse flora of faecal type present above an obstruction of the small intestine is acquired by ingestion.

Materials and Methods

Patients Studied.—Twenty-seven patients with intestinal obstruction were examined (Table I). Twenty-three obstructions were of the small intestine and were caused by herniae (9), bands or adhesions (10), obturation (2), volvulus (1), paralytic ileus (1). The bowel was considered to be gangrenous in two patients with strangulated herniae. The remaining four obstructions were in the large intestine, and were caused by diverticulitis (2) or carcinoma (2). The duration of the obstructions ranged from 6 hours to 10 days. No patient was accepted for study if any chemotherapy had been used.

Collection of Specimens.—Samples were taken in the following order: (*a*) stomach contents aspirated by

intragastric tube introduced before operation; (*b*) bacteriological swab of peritoneal fluid from the region of the obstructed bowel; (*c*) bacteriological swab of fluid from the hernial sac where appropriate; (*d*) bowel washing from the small intestine within 30 cm. below the point of obstruction, except when the obstruction was too near the ileo-caecal valve to allow such a specimen to be obtained; (*e*) bowel washing from within 30 cm. above the point of obstruction; (*f*) bowel washing from the first loop of jejunum distal to the duodeno-jejunal flexure; (*g*) bowel washing from the middle small bowel when the obstruction was in the terminal ileum or colon; and (*h*) bowel washing from the terminal ileum when the obstruction was in the colon.

All samples from the small intestine were taken during the emergency operation for relief of the obstruction. A gauge 21 needle was inserted obliquely through the bowel wall on its antimesenteric aspect while an assistant occluded the bowel lumen 3 cm. above and below the puncture, using either a clamp as illustrated (Fig. 1) or

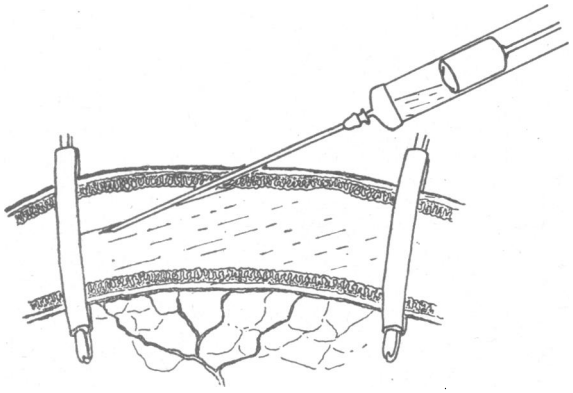

FIG. 1.—Method of sampling contents of small intestine.

preferably the more gentle grip of gloved fingers. Then 2 ml. of sterile Ringer's solution was instilled and washed to and fro from syringe to bowel lumen. The bowel washing was then withdrawn and examined bacteriologically.

Whenever possible the collapsed intestine below the site of obstruction was sampled before the obstructing factor was relieved. For this reason the band obstructions were approached by wide laparotomy incision, and the McEvedy (1950) technique was adopted for femoral herniae. Despite this, it was sometimes impossible to avoid partial relief of the obstruction during the early manipulations to determine its cause.

Bacteriological Examination

Immediately the collection of specimens was complete the following media were inoculated with the swab or with 2 drops (0.06 ml.) of the bowel washings or gastric aspirate: horse-blood agar and plain desoxycholate agar, incubated aerobically at 37° C.; horse-blood agar incubated anaerobically at 37° C. with 5–10% carbon dioxide.

The method of inoculation and interpretation of results on a quantitative basis was the same as that described by Cregan and Hayward (1953). The amount of growth was graded as follows: +/− or +, a scanty flora, normal in the small intestine and stomach; ++ and +++, a profuse flora, abnormal at these two levels of the gastro-intestinal tract.

The plates were examined at intervals up to at least five days' incubation and all species isolated were identified as fully as possible. Staphylococci were classified according to the criteria of Shaw, Stitt, and Cowan (1951) and *Candida* species according to Martin, Jones, Yao, and Lee (1937). The systematic table recommended by Swift (1952) was used for streptococci, while *Bact. coli* and *Bact. aerogenes* were subdivided into types according to Wilson and Miles (1955). All other species were identified by reference to *Bergey's Manual* (Breed, Murray, and Smith, 1957). For convenience the species were classed as either oral or faecal types as shown in Table II.

Direct smears of all specimens were made and examined after staining by Gram's method. These observations were correlated with the results of culture, and provided a check on the adequacy of the range of media and conditions of incubation used.

TABLE I.—*Gastro-intestinal Flora in Intestinal Obstruction*

Case No.	Level	Duration	Cause	Quantitative Results						
				Stomach	Jejunum	Mid-gut		Ileum		Colon
						Above	Below	Above	Below	
1	Mid-gut	1 day	Hernia	—	+++F	+++F	±F			
2	,,	1 ,,	,,		++O+++F	+++F	+F			
3	,,	2 days	,,		+++F	++O+++F	—			
4	,,	3 ,,	,,		++O++F	++F	±F			
5	,,	3 ,,	Adhesion		+++F	+++F	±F			
6	,,	3 ,,	Volvulus		+++F	+++F	±F			
7	,,	4 ,,	Hernia		+++O+++F	++O+++F	—			
8	,,	4 ,,	,,	++F	++F	++F	±F			
9	,,	7 ,,	Adhesion	+++F	+++F	+++F	+++F			
10	Ileum	6–12 hours	,,		—	+++F				
11	,,	12 ,,	,,		+O+F			+O+F	—	
12	,,	12 ,,	Hernia		±O	+O+++F		+O+++F	±F	
13	,,	1 day	Adhesion		—			++F	++F	
14	,,	2 days	Obturation	++F	++O++F			+++F	—	
15	,,	3 ,,	Adhesion		+++F	+++F		+++F	+++F	
16	,,	4 ,,	Hernia		++O+++F			++O+++F	—	
17	,,	4 ,,	,,					+++F	—	
18	Terminal ileum	2 ,,	Adhesion		—			+++F		
19	,,	3 ,,	,,	++F	+++F	+++F		+++F		
20	,,	3 ,,	Obturation		+++F	+++F		+++F		
21	,,	4 ,,	Adhesion	+++O+++F				++O+++F		
22	,,	10 ,,	,,	++O++F	++O++F			++O++F		
23	,,	2 ,,	Ileus		+++F	+++F		+++F		
24	Colon	1 day	Diverticulitis		+O	+O		±O+F		+++F
25	,,	2 days	,,		+F	+++F		+++F		+++F
26	,,	7 ,,	Carcinoma		+++F	+O++F		++F		
27	,,	14 ,,	,,		+++F	+++F		+++F		

The thick vertical lines denote level of obstruction. O indicates a flora of oral type and F indicates a flora of faecal type; ± to +++ indicate the degree of growth; — indicates no growth.

Results

Samples from Small Intestine Distal to the Point of Obstruction

Of the 16 samples taken 13 were either sterile (6) or contained a scanty flora (7). The remaining three (Cases 9, 13, and 15) yielded a profuse faecal flora which in each case was identical with the flora proximal to the obstruction. Two of these three cases were due to bands which were disturbed before the samples could be taken, and the other was regarded, at operation, as being incompletely obstructed. It was concluded that these three samples were mixed with material from above the point of obstruction and should be neglected in assessing the results.

The results, as set out in Table I, show that the small bowel contains only its normal scanty flora below any complete obstruction regardless of its level, of its duration, and of its cause.

Samples Proximal to the Point of Obstruction

Specimens from the small intestine immediately proximal to the point of obstruction contained a profuse faecal flora in 22 of the 23 cases of small-bowel obstruction and in three of the four cases of large-bowel obstruction. Of seven patients in whom obstruction had been present for less than 24 hours (Cases 1, 2, 10, 11, 12, 13, and 24) six yielded only a scanty growth from the stomach or jejunum. In contrast, of the 17 patients in whom the obstruction had been present for more than one day, only two (Cases 18 and 25) yielded a scanty flora in the proximal small intestine. It seems clear from these observations that, given time, an abnormal profuse flora of faecal type develops in the small intestine above any obstruction, regardless of its level or its cause.

It was observed that there was a correlation between distension of the small intestine and the presence of an abnormal flora. A profuse faecal flora was obtained from all 18 samples taken from distended bowel, whereas all five samples taken from bowel which appeared normal at operation yielded either sterile (2) or scanty (3) cultures. The six gastric samples which grew faecal flora were turbid and frankly feculent.

A list of the bacterial species and the number of occasions on which each was found in specimens of small-intestine and stomach contents that were quantitatively abnormal (+ + or + + + growth) is given in Table II. Species of faecal type predominate, but oral-type organisms were occasionally isolated.

TABLE II.—*Nature of Abnormal Flora in Small Intestine in Intestinal Obstruction*

Species of Faecal Type	No. of Isolations	Species of Oral Type	No. of Isolations
Bact. coli type 1	22	*Str. mitis*	9
Cl. welchii	22	*Str. MG*	6
Paracolon sp.	18	*Staph. saphrophyticus*	3
Bacteroides sp.	14	*H. parainfluenzae*	2
Str. faecalis	11	*Str. salivarius*	2
Proteus mirabilis	9	*N. sicca*	1
Bact. aerogenes type 1	5	*Str.* group C	1
Bact. coli intermediate type	3	*Lactobacillus* sp.	1
Cl. multifermentans	3	*H. aphrophilus*	1
Veillonella parvula	3	*C. xerosis*	1
Candida albicans	3		
Cl. tetanomorphum	2		
Anaerobic streptococcus	2		
Bact. coli irregular type	2		
Cl. tertium	1		
,, *bifermentans*	1		
,, *capitovale*	1		
,, *cochlearium*	1		
Achromobacter butyri	1		
Alcaligenes faecalis	1		

Number of patients with a profuse (abnormal) flora = 25.

Coliforms were isolated from all of the 25 patients who showed an abnormal flora, and generally outnumbered other species present. Usually two or more "coliform" species were isolated from each patient, *Bact. coli* type 1 being found most frequently. *Clostridium welchii* was present in 22 patients, but in 10 of these in relatively small numbers. *Bacteroides* species were present in 14 patients, an incidence which is less than in normal faeces (Eggerth and Gagnon, 1933).

Peritoneal and Hernial-sac Swabs

Peritoneal swabs (13) and hernial-sac swabs (6) were always sterile when the bowel was viable. In two patients with strangulated femoral herniae of four days' duration the bowel was found at operation to be gangrenous. In one of these patients both peritoneal and hernial-sac swabs were sterile. In the other patient the peritoneal swab was sterile but the hernial sac yielded a pure culture of *Proteus mirabilis*, though a mixed faecal flora (*Proteus mirabilis, Bact. coli* intermediate type 1, *Cl. welchii, Cl. multifermentans*) was present in the lumen of the herniated bowel.

Discussion

Many investigations into the bacteriology of experimental intestinal obstruction have been carried out, particularly in dogs (Whipple, Stone, and Bernheim, 1913; Meleney, Berg, and Jobling, 1927; Harper and Blain, 1945; Rabinovici and Fine, 1952). Though results from these experiments are not directly applicable to man, they agree in the main with the results of this investigation.

Williams (1926, 1927) investigated the flora in intestinal obstruction in man during life. However, his specimens were restricted to vomitus or swabs from the bowel lumen at the site of resection when this proved necessary. His bacteriological techniques were directed to the isolation of *Cl. welchii*, and little interest was taken in the many other organisms present. Williams also reported on the flora of the small bowel at necropsy in patients who had died of intestinal obstruction or peritonitis. However, the results tabulated by Blacklock, Guthrie, and Macpherson (1937) show that post-mortem bacteriological studies do not reliably reflect the situation before death.

The direct sampling technique used in the present investigation has yielded a clear picture of the flora in the lumen of the stomach and small intestine in the presence of obstruction. Bacteriological techniques used have allowed the isolation and full identification of all micro-organisms present within the bowel lumen.

The results of this investigation presented two different pictures, which are illustrated in Figs. 2 and 3. These are diagrams of two typical simple obstructions (Cases 12 and 14). In Fig. 2 the obstruction had been established for 12 hours, and in Fig. 3 for 48 hours. It will be seen that both distension of the small bowel and the presence of a profuse faecal flora above the obstruction extend proximally with the passage of time, whereas the small bowel below the obstruction contains only a scanty flora irrespective of the duration of obstruction. Though the diagrams represent obstructions in the ileum, no difference in bacterial flora was found in obstructions at other levels. Similarly, the nature of the obstructing agent did not affect the bacteriological picture.

These findings fail to support the belief that the profuse faecal flora in the small bowel and stomach proximal to an obstruction is derived directly from the

colon (Penman and Pullan, 1958). Instead the abnormal flora must be derived from above, either from ingested foods and fluids or from the oro-nasopharynx. That this is so is shown clearly by the findings (Fig. 4) in one hernial obstruction (Case 16). The faecal type of flora proximal to the obstruction could not have been derived from the distal bowel because of the zone of oral type bacteria present within the herniated loop. If faecal bacteria had passed through this segment by retrograde spread they would rapidly have overgrown the less robust oral type of bacteria in the herniated loop.

Since the profuse faecal flora present above an intestinal obstruction is derived from ingestion, the species of micro-organisms found in this study must be continually contaminating the healthy small intestine. However, the healthy small intestine contains so few micro-organisms that the species present have been regarded as only transient contaminants (Cregan and Hayward, 1953). Thus the healthy small bowel must possess the ability to prevent the establishment of these species as a resident flora. This ability is independent of the gastric germicidal barrier (Cregan, Dunlop, and Hayward, 1953). The nature of the mechanisms involved in preventing the establishment of a resident flora in the small intestine is not fully understood. However, it is clear that arrest of onward passage of bowel contents alters conditions in the small intestine above the point of obstruction so radically that organisms of faecal type proliferate rapidly. These findings have practical significance.

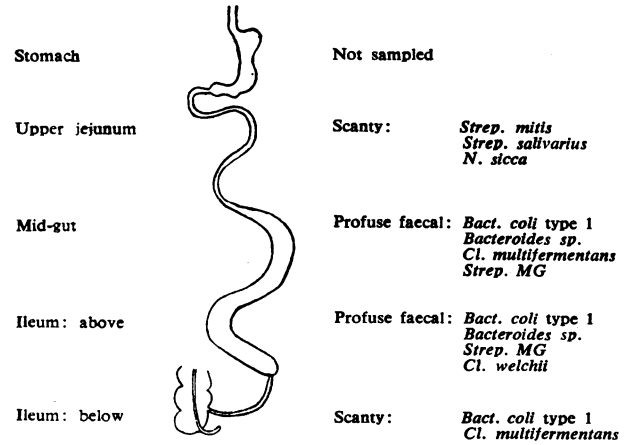

FIG. 2.—Case 12. Typical early ileal obstruction (12 hours).

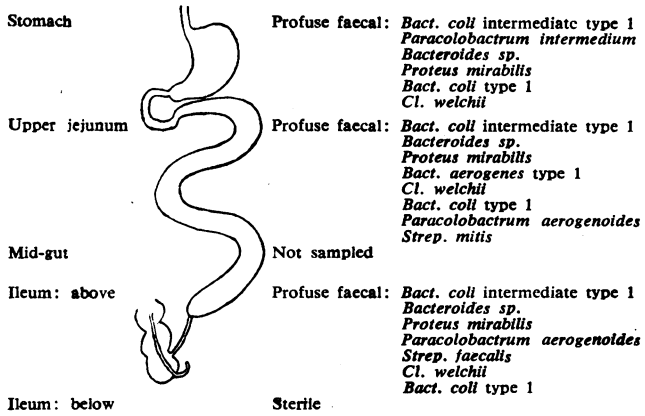

FIG. 3.—Case 14. Typical late ileal obstruction (48 hours).

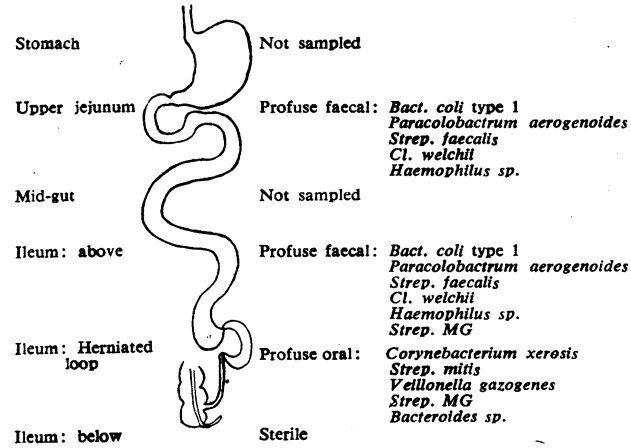

FIG. 4.—Case 16. Late obstruction with herniated loop of ileum.

Infective complications are common after surgery for intestinal obstruction. They range from minor wound infection to peritonitis with subphrenic or pelvic abscess and even to septicaemia. The bacterial flora of secondary peritonitis (Gillespie and Guy, 1956) and of a high proportion of wound infections after gastro-intestinal surgery (Ralston and Cowling, 1959) resembles that of the contents of the small intestine proximal to an obstruction. Hence any soiling of the peritoneum or wound with these contents is dangerous. In addition to an immaculate aseptic surgical technique, the parenteral administration of a suitable antibiotic pre-operatively should help by saturating the tissues of the host so as to protect them in the event of accidental soiling. It is recommended that immediately before operation either 250 mg. of tetracycline should be given intravenously in a saline infusion or alternately 1 mega unit of penicillin and 0.5 g. of streptomycin should be given intramuscularly. These doses should be repeated six-hourly post-operatively.

Summary

The bacteriology of the content of the small intestine in intestinal obstruction has been investigated. Samples were taken from the bowel at many levels, both above and below the obstruction. A profuse flora, predominantly of faecal type, was demonstrated above the point of obstruction. The longer the duration of the obstruction the further proximally did this flora extend.

The small bowel below the site of complete obstruction was sterile or contained only a scanty transient flora.

It is postulated that the infection in the lumen of the bowel above an obstruction is derived from ingested food and fluids or oro-nasopharyngeal secretions and not from a retrograde spread from the colon as has been thought hitherto.

We thank Dr. Nancy Hayward for constant help and advice, especially to one of us (R. F. B.), Professor S. D. Rubbo for helpful criticism, and the surgical staffs of the Alfred and Royal Melbourne Hospitals for their co-operation.

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TREATMENT OF TRICHURIASIS WITH DITHIAZANINE IN A HOSPITAL FOR MENTAL DEFECTIVES

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Since the publication of our preliminary report (Paine *et al.*, 1959) on the treatment of six patients known to be infected with trichuriasis, it has been possible to plan a controlled trial experiment with dithiazanine and arrange a full-scale treatment programme of all whipworm carriers at Coldharbour Hospital.

While the preliminary trial appeared to provide evidence of the efficacy of dithiazanine against human trichuriasis, the number of patients treated was small, and it was thought that the results might have been influenced by previous trials with other anthelmintics. Moreover, no control group of patients had been studied and there had been no long-term follow-up examinations to determine the possibility of relapse or reinfection.

Controlled Trial

Method

Twenty-four patients known to be infected with whipworm were chosen, 12 being selected for treatment with dithiazanine and 12 to serve as controls. Some attempt was made to match the individual patients for treatment and control in respect of their pre-treatment egg counts, and it was possible to allocate an approximately equal number with light and medium infections to each group. No claim is made, however, that a patient's whipworm load can be estimated from his faecal egg count.

The treatment group received dithiazanine orally, as "telmid" tablets, in the same dose as that used in the preliminary trial—that is, 200 mg. three times a day for five days, regardless of age and weight. The patients' weights in this trial ranged from 60 to 151 lb. (27 to 68.5 kg.). In view of the possible association between vomiting and failed treatment in the preliminary trial, the five-day course of dithiazanine was extended on this occasion by one additional 200-mg. dose of the drug for every dose interval when vomiting occurred. A tendency to constipation had been noted in the previous trial, and patients in both treatment and control groups therefore received two "senokot" tablets on each of the five treatment days, followed by two tablets three times weekly for the next two weeks.

Pre-treatment egg counts were carried out by the Stoll (1947) technique, since this method gives some indication of the severity of the whipworm infestation. Ten days after the completion of treatment, further faecal examinations were made by De Rivas's (1928) concentration technique, giving either positive or negative results only.

From the first day of treatment, a careful search was made for the adult whipworm, all faecal specimens being examined for 10 days, and, thereafter, one specimen weekly for three weeks. The worms were immediately placed in distilled water at room temperature, where they remained for 24 hours so that any motility might be noted.

All patients were observed for possible side-effects, and ward records were kept of the four-hourly temperatures, daily blood-pressures, and the incidence of vomiting and diarrhoea in each case. Pyrexia was taken to mean an axillary temperature of at least 99° F. (37.2° C.), and temperatures were recorded over a period of three weeks, commencing two days before treatment. Blood-pressures were taken for a 10-day period, also beginning two days before treatment. Vomiting was charted once for each dose interval in which it occurred, and diarrhoea when two loose motions occurred in one day.

Possible toxic effects from dithiazanine were investigated by means of haematological examinations, blood-urea levels, serum-protein estimations, and urine tests, before and after treatment; the post-treatment examinations being carried out between one and three weeks after the cessation of treatment. From two days before treatment, urine specimens from all patients were tested daily on the ward with "albustix" and "clinistix" for a period of three weeks, and any abnormal findings were sent for laboratory confirmation.

None of the patients selected had received anthelmintics during the two years preceding this trial.

Results

The results of the faecal egg counts are given in Table I. With one exception (Case 4), all the patients under treatment were rendered negative and all patients in the control group remained positive. Adult worms were recovered from all patients in the treatment group, but none from patients in the control group. The whipworms were discovered in faecal specimens between the third and sixth days of treatment, none being found thereafter. The worms were examined for motility, but all appeared to be non-viable. On the third day of treatment threadworms were seen in specimens from six patients in the treatment group.

Of the clinical findings shown in Table II, vomiting appears to be the only significant complication. This occurred in 7 of the 12 patients receiving dithiazanine but not at all in the controls. An analysis of the days