detect and treat any congenital infection. Confirmatory evidence that toxoplasmosis has been unusually prevalent in Barton-on-Humber may be obtained as a result of this work.

Conclusions

The most probable cause of the difference in incidence of stillbirths between the three districts of north Lincolnshire is infection with *Toxoplasma gondii*. Of the 19 stillbirths which occurred in Barton-on-Humber at least 3, and possibly as many as 10, are likely to have been due to toxoplasmosis. In only three cases could another cause for the stillbirth be definitely established, and the dye-test titres of two of these three mothers were among the three lowest titres observed in the series. The high incidence of malpresentation in Barton-on-Humber during this time could be due to toxoplasmosis, there being evidence in three out of the six breech presentations that the foetus was already dead or deformed prior to the onset of labour. If 10 of the 19 stillbirths were due to toxoplasmosis the remaining nine due to other causes would represent a rate of 28.2. This is still higher than the rates for England and Wales, but the difference is not significant.

Summary

Significant differences in perinatal mortality among three areas of Lincolnshire over a three year period are shown to be due to variation in stillbirth rate. Investigation of possible causes of this showed that there was a significantly higher incidence of cytoplasm-modifying antibody to *T. gondii* in the women whose babies had been stillborn, when compared with a group of mothers who had been delivered of live babies in the same month and in the same place. The two groups did not differ greatly in age, parity, or in any other respect. The hypothesis that toxoplasmosis may have been the cause of these stillbirths is discussed.

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FULMINATING ULCERATIVE COLITIS

RECENT EXPERIENCE IN MANAGEMENT

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During the last few years new surgical and medical measures have become available for treating very severe acute episodes of ulcerative colitis. Some experience has now been gained in the use of these measures, and the time seems opportune for a review of some of the results obtained so that recommendations can be made for the future. We have studied the results of different treatments in a group of patients with very severe acute " fulminating " colitis and have tried to answer three questions: (a) Can treatment with corticotrophin or cortisone induce a remission in a " fulminating " episode of colitis ? (b) When should surgical treatment be undertaken and what operation should be performed ? (c) Does previous treatment with corticotrophin or steroid drugs influence the outcome of surgical treatment in these patients ? Because " fulminating " episodes of colitis are uncommon and because the early years of treatment with steroid drugs have necessarily been exploratory, some of our conclusions can only be tentative, but from them we suggest a course of action for trial in the future.

Selection of Cases

Our aim has been to study a group of the most severe cases of ulcerative colitis seen at St. Mark's and the Central Middlesex Hospitals from 1951 to 1959. As we wished to select cases of acute colitis, we have not included in the series patients ill with serious metabolic disturbance, haemorrhage, or perforation of the colon, unless these complications were preceded by a severe exacerbation of the disease. Our selection has been made on account of the severity of the illness and without reference to the treatment given or its outcome. A definition of fulminating colitis has been impossible to achieve. No group of criteria adequately defines the severity of the illness. For example, neither fever nor tachycardia is adequate as a criterion, because three of our patients were critically ill with a high fever but a pulse rate less than 120 a minute, two were apparently overwhelmed by the illness with a pulse rate consistently above 150 a minute but with slight

fever, and several had a fever of 103–104° F. (39.4–40° C.) but have not been included in this series as they did not appear to be very ill.

In our selection we took account of fever, tachycardia, abdominal distension, mental changes, and biochemical disturbance, but eventually we came to rely mainly on the clinician's recorded impressions of the severity of the patient's illness and his memory of it as one that caused him great anxiety. Brooke (1956) has said that a fulminating episode of colitis "beggars exact definition," and suggested as criteria "severe toxaemia, pyrexia to 103–104° F. (39.4–40° C.), lethargy verging on coma, and serious alteration of blood chemistry." One or more of these criteria is present in 30 of our 32 cases.

The results of medical treatment described here cannot be regarded as representing the success rate among unselected cases of fulminating colitis, as several patients were transferred to the two hospitals when medical treatment elsewhere had failed.

Clinical Features of our Patients

The records of 520 patients admitted to St. Mark's and the Central Middlesex Hospitals for the treatment of ulcerative colitis during 1951 to 1959 have been examined and from them 32 patients have been selected for study.* Brief details of these patients are set out

*The proportion (6%) of patients selected accords well with the 10% of Brooke's (1956) surgical series and the proportion in other series, such as that of Crile and Thomas (1951).

in Table I. In it our criteria for fever and tachycardia have been a temperature of more than 103° F. (39.4° C.) or a pulse rate of more than 120 a minute (any higher figure is shown) on four out of any seven consecutive days. The biochemical data show the most abnormal results during the illness. Clinical descriptions are taken as far as possible verbatim from the notes written at the time of the illness and are then enclosed in inverted commas. Where data are not available (as, for example, when a patient died within four days of admission) no entry is made in the Table.

Pathological Observations

A careful study made of the colon removed surgically at the height of the illness in 16 of our patients reveals features which explain some of the difficulties in the clinical management of this illness. Though mucosal ulceration was always very extensive, we were surprised to find that the mucosa of the caecum (and sometimes of the ascending colon also) was intact in 10 patients (Fig. 1) and that only in six was the whole colonic mucosa ulcerated; in all 16 the terminal ileum was normal. Histologically the wall of the colon showed grossly dilated blood-vessels and separation of muscle fibres by oedema. This intensely vascular base of the ulcers probably exudes fluid rich in protein, because the total serum protein was 4.5 g./100 ml. or less at one time in 7 out of the 17 of our patients in whom it was estimated; two of these patients (Cases 5 and 25) developed hypoproteinaemic oedema.

TABLE I.—*Clinical Details of the Patients (see Text for Explanation of Abbreviations). Patients are Numbered in the Order in which their Treatment is Described. Lines Separate Groups who Received Different Treatments*

Case No.	Age and Sex	Fever	Pulse	Abdominal Distension	Mental State	Protein g./100 ml.	Na mEq/l.	K mEq/l.	Remarks
1	M 40	0	—	Moderate	Drowsy	4·0	114	4·1	"Acute toxic," gross loss of weight
2	F 33	0	150	Slight	Normal		125	4·8	Very weak, unable to move. Died
3	M 25	+	120	,,	,,	4·0	118	4·2	"An ill toxic patient"
4	M 48	0	150	,, 0	Drowsy	6·6	132	5·6	"Intensely toxic"
5	M 83	0	—	Moderate	Very drowsy	4·3	132	3·3	"Fulminating, acute." Gross oedema. Died
6	M 42	0	—	Slight	Drowsy		137	3·9	"A fulminating episode"
7	M 67	+	—	0	Drowsy. Confused	5·0	135	3·8	"Very toxic"
8	F 22	+	130	Moderate	Confused		137	3·7	"Typhoid state"
9	F 42	0	120	,,	Normal		135	4·7	"Toxic." Steady deterioration
10	M 31	0	120	,,	Confused	6·5			"Extremely ill"
11	F 34	+	120	,, 0					"Very ill"
12	F 67	0	—	Slight	Normal				"Very ill indeed." Died
13	M 24	0	—	Moderate	Confused	5·0	98	5·2	"Most severe toxic state"
14	M 51	+	—	,,	Drowsy				"Going rapidly downhill"
15	F 30	0	—	,,	Normal				"Considerable toxicity." Increasing distension
16	F 19	0	120	Slight	Apathy		115	3·8	"Very toxic fulminating colitis"
17	F 32	+	120	Moderate	Normal	4·5			"Acute toxic state"
18	F 57	0	—	,,	,,		130	4·8	Emergency colectomy; increasing distension
19	F 40	+	120	0	,,	6·5			"More and more toxic"
20	F 28			Moderate	Confused				Emergency colectomy; distension and delirium
21	F 42	0	—	,,	Drowsy		137	4·8	"Intensely toxic." Died
22	M 32	+	—	0	Normal		141	5·5	"More and more toxic"
23	F 24	0	160	Slight	,,	5·4	118	3·5	"Overwhelming toxaemia, deteriorating steadily"
24	M 33	0	120	Moderate	Drowsy. Confused	5·8	122	3·8	"Ill and toxic." Died
25	M 44	0	130	Gross	Drowsy	3·5	123	2·3	"Very ill." Gross oedema. Died
26	M 28	+	120	0	Normal	5·4	115	4·3	"Critically ill." Died
27	F 27	+	120	Slight	,,	3·0	122	5·1	"Disease is rampant"
28	M 19	0	140	,,	,,	6·0	124	5·2	"Toxic; condition very poor." Died
29	F 30	+	120	0	,,		125	4·6	Emergency colectomy life-saving
30	F 22	+	120	Moderate	Drowsy		130	4·1	"Gravely ill"
31	M 42	0	130	Gross	Normal	5·5		5·2	"Extremely toxic." Died
32	M 51			0	Apathy	4·5			"Intensely toxic; profound apathy." Died

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Not only were the ulcers large but they were also deep (Fig. 1), and penetration into the muscle coat was noted in 13 out of 16 patients. The inflammation had often spread through the muscle to involve the serosa, which was adherent to neighbouring structures in 10 out of the 27 patients who came to operation. This spread of inflammation into the muscle seems a likely

FIG. 1.—Case 14. Colon removed at operation, showing the contrast between the dilated right side of the colon with normal mucosa and the almost complete loss of mucosa with exposure of the circular muscle fibres on the left side. The ileum and caecum were normal both on inspection and on histological examination.

cause for the characteristic friability of the bowel wall in fulminating colitis. Extension of the ulceration into muscle was not necessarily associated with clinical abdominal distension in this series.

Results of Treatment

Cortisone and Corticotrophin

Seven patients were given a trial of cortisone or corticotrophin during a fulminating episode; three of them recovered without operation (Cases 4, 6, and 7).

Cases 1 and 2.—Both these patients were given cortisone, 200 mg. daily, without benefit.

Case 3.—This man was given corticotrophin, 120 units daily, for four days when he was admitted with two weeks' history of very severe colitis. As he improved only slightly, emergency ileostomy and subtotal colectomy was performed. At this operation the bowel was torn and his recovery was delayed by sepsis.

Case 4.—This patient did not apparently benefit from treatment with corticotrophin gel, 60 units daily, but later he slowly improved with general medical measures and was discharged well four months after admission.

Case 5.—A vigorous man of 83 had always enjoyed good health until the onset of severe colitis. Within five weeks he was grossly oedematous, without evidence of cardiac failure and with a low serum albumin of only 2 g./100 ml. Corticotrophin gel, 80 units daily, did not help him, and he died two weeks later.

Case 6.—This patient had had two milder episodes of colitis during the previous seven years. When admitted to hospital one month after a further exacerbation he was drowsy, had persecutory delusions, and was running a high fever. His condition did not alter while he was given corticotrophin gel, 80 units daily for three days, but when the dose was increased to 120 units daily there was a dramatic fall in temperature (Fig. 2) with a corresponding improvement in his well-being. He continued to improve, and was discharged free of symptoms after six weeks.

Case 7.—This patient had always been healthy until diarrhoea began abruptly, with the passage of three or four watery, often blood-stained, stools every hour. After three weeks of this he felt weak, lost his appetite, and began to vomit. He was admitted to hospital one week later a very ill man, wasted, dehydrated, and running a high fever (Fig. 2). Despite intravenous replacement therapy and chloramphenicol, his condition worsened over the next few days and he became drowsy and confused. Within a day of starting treatment with corticotrophin, 120 units daily, his mental state cleared and his temperature fell (Fig. 2). Three days later this note was made: " Has responded dramatically to corticotrophin, general condition now good, eating well and cheerful, less urgency of bowel action and no blood in stools." He continued to improve slowly and returned to work in normal health, passing one constipated stool each day, four months after his symptoms began.

Of the five patients who were given corticotrophin, two responded to a dose of 120 units daily. One of them did not respond to 80 units daily but did so to 120 units daily. Perhaps in fulminating colitis bigger doses of corticotrophin are needed than those in use at present.
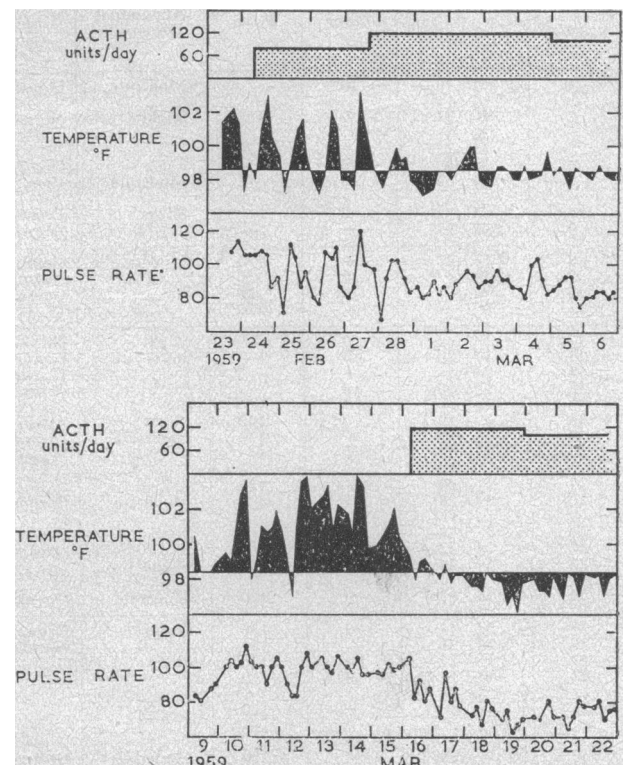

FIG. 2.—Temperature charts of Case 6 (above) and 7 (below), showing response to 120 units of corticotrophin daily and the lack of response to 80 units daily in Case 6.

Surgery Without Preliminary Corticotrophin or Steroid Drugs†

Opinion is divided on whether immediate colectomy and ileostomy should be performed or whether a preliminary ileostomy only should be undertaken, with subtotal colectomy as an elective operation later. Immediate colectomy with removal of the ulcerated inflamed bowel is the rational procedure, but there are powerful arguments against it ; for instance, these patients are so ill that they may not be able to withstand such a major operation or the colon may be so fragile at the height of the illness that it tears when an attempt is made to remove it.

Preliminary ileostomy was performed four times in our series, each time because the surgeon favoured this policy. The results are set out in Table II. It will be seen that all the patients recovered and there was a satisfactory improvement in the general condition of two out of the four patients. Pathological examination showed that the colon was healing at the time of subsequent colectomy in every case, though in Case 10 the bowel was torn during mobilization ; it may be significant that this colectomy was done only two weeks after the ileostomy.

Immediate colectomy was performed in 13 patients (Table III), of whom three died, four made a complicated recovery, and six recovered uneventfully. We think that at present these results must be considered satisfactory in this very severe disease. Could any of the deaths, however, have been avoided if ileostomy alone had been performed ?

Case 21.—This patient, a woman aged 42, died after a severe rectal haemorrhage on the eighth post-operative day. Necropsy revealed bilateral bronchopneumonia and ulceration of the rectal mucosa but no bleeding-point.

We do not think that this death can be attributed to the colectomy ; in fact, the portion of diseased bowel remaining caused her death.

Case 12.—A woman of 67 had had mild colitis for three years, and was admitted to another hospital with a very severe exacerbation. During the next five days she lapsed into stupor with high swinging fever and abdominal distension. She was transferred to St. Mark's Hospital for immediate operation, and subtotal colectomy with ileostomy was performed. A perforation of the caecum was found sealed to the sigmoid colon. For five days she improved slowly, but then her temperature rose and fatal circulatory collapse ensued. Necropsy revealed peritonitis.

Case 24.—This man, aged 33, was at work three weeks before he died, when a severe exacerbation of his procto-sigmoiditis prostrated him. As his condition deteriorated during medical treatment, with a rising pulse rate and increasing lethargy, operation was decided upon. During the 36 hours before operation he became mentally confused and his abdomen became distended. At laparotomy the caecum and ileum were found to be greatly distended, the colon was acutely inflamed, and ascitic fluid was present. Subtotal colectomy was undertaken as it was feared that the colon might perforate spontaneously if ileostomy alone were performed ; as it was, the colon was torn during mobilization. After operation his blood-pressure could not be maintained and he died 15 hours later. Necropsy revealed no local cause of death.

It is possible that these two patients might have been saved by a lesser operation, though the first was so ill

†These patients were not given corticotrophin or steroid drugs for a variety of reasons ; some were treated in the years before these drugs were commonly used, some were not given the drugs because they were so ill when admitted that it was thought dangerous to delay surgical treatment, and some because there were complicating factors such as healed pulmonary tuberculosis.

TABLE II.—*Results of Treatment with Ileostomy Followed by Colectomy in Patients who had not Received Treatment with Corticotrophin or Steroid Drugs*

Case No.	Post-operative Course	Interval until Colectomy	Colectomy	Time in Hospital after Ileostomy
8	Violent toxic psychosis for 3 weeks	15 weeks	Straightforward. Uneventful recovery	12 weeks
9	Good response. No complications	10 months	Colon adherent but removed intact. No complications	7 weeks
10	Acute delirium for 6 days	2 weeks (elective)	Colon torn at operation with subsequent pelvic abscess	9 weeks (including colectomy)
11	Good response. Ileostomy dysfunction	3 weeks (elective)	Straightforward. No complications	9 weeks (including colectomy)

TABLE III.—*Results of Immediate Colectomy in Patients who had not Received Treatment with Corticotrophin or Steroid Drugs*

Case No.	Adherent Colon	Colon Torn	Post-operative Course	Time from Operation to Discharge
12	Yes	? (Sealed pre-op. perforation)	Deteriorated after fair initial response. Died 7th day. Necropsy—peritonitis	
13	No	No	Confusional state for 4 weeks	8 weeks
14	,,	,,	Exacerbation of bronchitis	5 ,,
15	,,	,,	No complications	4 ,,
16	,,	,,	,, ,,	4 ,,
17	Yes	Yes (also pre-op. perforation)	Partial wound separation	7 ,,
18	No	No	No complications	4 ,,
19	,,	,,	,, ,,	13 weeks (includes rectal excision)
20	,,	,,	,, ,,	3 weeks
21	Yes	,,	Bronchopneumonia. Later massive rectal haemorrhage ; died next day. Necropsy: bilateral bronchopneumonia	
22	No	,,	Burst abdomen	11 weeks (pan-procto-colectomy)
23	,,	,,	No complications	5 weeks
24	,,	Yes	Irreversible shock. Died	

that it is doubtful if any measure could have saved her. Despite careful observation the severity of the second patient's illness was underestimated and he was operated upon too late.

We cannot make a direct comparison between preliminary ileostomy and immediate colectomy because there are only four of the former in this series. These cases represent 4 out of 10 preliminary ileostomies performed as treatment for acute colitis at St. Mark's Hospital during the period 1951-9. The other six patients were severely ill, but not so ill as to be included in this series. The results of ileostomy in these cases were as follows:

Girl aged 18.—Continued deterioration. Immediate improvement after subtotal colectomy.

Man aged 61.—Excellent result. Uneventful colectomy.

Woman aged 56.—Continued deterioration. Died after proctocolectomy.

Woman aged 63.—Died after two days. Generalized peritonitis from perforation of sigmoid colon.

Man aged 66.—Satisfactory recovery, but complicated by pneumonia.

Man aged 20.—Continued deterioration. Colon torn at colectomy ; died from intra-abdominal sepsis.

The poor results in these cases suggest that the results of ileostomy in our four patients were fortuitously favourable and that ileostomy alone cannot be relied upon to check the downhill course of severe colitis.

This lesser operation may be necessary because a patient's condition precludes more extensive surgery. It may be advisable if inspection at laparotomy suggests that the colon is especially apt to perforate during mobilization, owing to extensive adhesion to other structures or to fragility of its wall as a result of distension and inflammation. We consider that the results from immediate colectomy shown in Table III justify this as the operation of choice in most cases.

Does Treatment with Corticotrophin or Steroid Drugs Influence the Results of Surgical Treatment ?

Of the eight patients who received these drugs during the three months before operation, four died and only two made an uncomplicated recovery. Why were the mortality and morbidity so high in this group ? In considering this, we shall first present the results in the whole group (Table IV) and then discuss the fatal cases.

Table IV shows that the colon was torn during colectomy rather more often in this group than in the group (Table III) who had not received corticotrophin

TABLE IV.—*Results of Immediate Colectomy after Treatment During the Previous Three Months with Corticotrophin or Steroid Drugs*

Case No.	Length of Steroid Treatment	Adherent Colon	Colon Torn at Operation	Post-operative Course	Time from Operation to Discharge
1	16 days	Yes	No	No complications	4 weeks
2	9 ,,	Yes	Yes	Fatal circulatory collapse. Died	
3	5 ,,	No	,,	Pelvic abscess and wound sepsis	8 ,,
25	8 weeks	,,	No	Fatal circulatory collapse. Died	
26	10 ,,	Yes	,,	Subphrenic, pelvic, and intraperitoneal abscesses. Died	
27	5 ,,	No	Yes	Intra-abdominal abscesses and faecal fistula	6 months (colectomy and ileo-rectal anas-tomosis)
28	3 ,,	,,	No (pre-op-erative perfora-tion)	Pelvic abscess, sep-ticaemia, and pul-monary infarct. Died 25th day	
29	8 ,,	,,	No	No complications	4 weeks

or steroid drugs. We cannot correlate this occurrence with adherence of the colon to neighbouring structures, with the duration of steroid treatment, or with the length of the illness. There was one spontaneous perforation of the colon before operation in each group. This is in keeping with the findings of others that treatment with steroids does not increase the likelihood of spontaneous perforation of the bowel (Truelove and Witts, 1955 ; Goldgraber *et al.*, 1957).

Important lessons can be drawn from the fatal cases.

Case 2.—A woman aged 33 continued to deteriorate rapidly despite cortisone treatment. At the time of operation she was emaciated and weak, and a purpuric rash had appeared. The bowel was very adherent and was torn twice during mobilization, with gross peritoneal soiling. She collapsed immediately after operation and died five days later. The operation was not covered with cortisone.

Case 26.—A man aged 28 was critically ill, with a fever of 102-3° F. (38.9-39.5° C.), when he was transferred for operation after treatment with prednisone for 10 weeks. Subtotal colectomy and ileostomy was performed with cortisone cover, and, though there was no obvious soiling of the peritoneal cavity, subphrenic, pelvic, and intra-abdominal abscesses subsequently developed. In the interval before these were drained there was severe fluid and

electrolyte disturbance (blood urea, 252 mg./100 ml.) due to the associated ileus. This was partially corrected (blood urea, 140 mg./100 ml.) before a second operation for draining the abscesses, which was not covered with cortisone. He died from circulatory collapse, unresponsive to intra-venous hydrocortisone and noradrenaline, which developed two days later.

Both these patients had steadily deteriorated during medical treatment, and surgery was eventually under-taken as a last resort. This appears to have been the primary fault, but, in addition, both were operated upon without cortisone cover. At the time of the first patient's illness the need for extra cortisone at the time of operation was not yet appreciated. Beween his two operations the second patient presented a most difficult metabolic problem ; so much attention was given to this that the need for cortisone cover at the second operation was overlooked.

Case 28.—A youth aged 19 began to deteriorate while being given cortisone, 200 mg. daily, and the physician decided that medical treatment had failed. Urgent opera-tion was not undertaken, and spontaneous perforation of the caecum occurred four days later. Emergency subtotal colectomy and ileostomy was done, but subsequent intra-abdominal sepsis proved fatal.

This patient became worse while being treated with cortisone. The spontaneous perforation that occurred emphasizes the need for early operation if steroid treat-ment fails. During a period of medical treatment an initial sense of urgency may abate.

Case 25.—This patient was well for six weeks after a two-months course of corticotrophin. Profuse diarrhoea then began, and he was readmitted one week later with gross oedema (total serum protein 3.5 g./100 ml.), haemoconcen-tration (P.C.V. 54%), and hypokalaemia (2.7 mEq/l.). He improved with fluid and electrolyte replacement during the six days before his operation ; there was then no evidence of haemoconcentration, his serum electrolytes were normal, but he was still grossly oedematous. He collapsed after uneventful subtotal colectomy and ileostomy. It seems unlikely that the collapse was due to cortisone lack, because he was given 200 mg. of hydrocortisone daily, beginning the day before operation.

This patient had gross oedema and a low serum protein ; the problem was the same in Case 5. Fluid and electrolyte deficiencies were made good in both, but no vigorous attempt was made to replace protein, one of the most urgent needs in this type of case.

These results of the first few years of steroid treat-ment are disturbing, but results should be better in the future if some of these causes of failure are avoided.

Results in Miscellaneous Group

Case 30.—A woman aged 22 was admitted to hospital four weeks after her symptoms of colitis began. She was drowsy, her abdomen was distended, and she ran a fever of 103-4° F. (39.4-40° C.) for the first six days. Emergency colectomy was being considered, when spontaneous improve-ment began without specific treatment and she was discharged six weeks later in complete remission.

Case 31.—An emergency laparotomy was undertaken when this patient, a man aged 42, was admitted to hospital with a most unusual degree of abdominal distension and in a severely toxic state. On incising the peritoneum a grossly dilated and adherent transverse colon was accidentally opened ; it was brought to the surface as a colostomy. An ileostomy was performed at a second operation but he died of peritonitis.

Case 32.—A man aged 51 was moribund when admitted to hospital and died before any treatment could be given.

Discussion

One in three of the patients whose cases are described died as a result of the illness. This startling fact requires analysis if the mortality is to be less in years to come. One patient (Case 32) was moribund when first seen. Of the rest it is important to emphasize that only 4 out of 31 patients were treated successfully by medical means alone ; two of these successes can be attributed to corticotrophin. Only one patient (Case 5), aged 83, died without attempted surgical treatment ; of the 26 patients operated upon, eight died (four of these without preliminary treatment with corticotrophin or steroid drugs). This mortality stands in marked contrast to the five deaths which occurred after 113 elective colectomies for ulcerative colitis at St. Mark's Hospital during the same period (Ewart and Lennard-Jones, 1960). In order to achieve better results, either operation must be avoided in the fulminating state or, if this is not possible, the patient must be in better condition when he is operated on ; techniques which reduce the risk of perforation of the friable bowel at operation (Brooke, 1959) are also needed. A better medical regime might achieve remission in more patients. When a remission cannot be induced the emphasis must be on energetic metabolic replacement and early operation.

At present physicians perhaps have too much faith in corticotrophin or steroid drugs. The large-scale trial of cortisone in ulcerative colitis (Truelove and Witts, 1955) showed that this drug can induce a remission but does so less often in " severe " than in moderate or mild cases. Their criteria‡ for describing the illness as " severe " denoted patients who were ill but not as desperately ill as were those described here. It seems reasonable to suppose, therefore, that corticotrophin and steroids will be even less effective in a fulminating episode than in the more usual severe acute or chronic cases. Perhaps larger doses than at present usually given deserve cautious trial—for example, Cases 6 and 7—without placing too much reliance on this treatment. Kirsner et al. (1959) give 20–40 units of corticotrophin daily by intravenous infusion in fulminating colitis and up to 160 units daily by intramuscular injection in severe colitis. Since corticotrophin is more potent than cortisone in the treatment of relapses (Truelove and Witts, 1959) we suggest the use of this drug rather than cortisone for these critically ill patients.

If corticotrophin and steroid drugs are possibly given undue prominence, other measures may be receiving too little notice. Firstly, our analysis has emphasized the importance of replacing the protein and electrolytes which these patients have lost and are losing. Two of our patients (Cases 5 and 25) died mainly from metabolic depletion, particularly of the serum proteins, and in many others metabolic disturbance was obviously one very important cause of their prostration. When protein loss is severe, replacement with transfusions of whole blood and plasma (preferably drawn from a small panel of donors) would seem the best immediate treatment. Secondly, recent work has demonstrated a bacteraemia of portal-vein blood at elective colectomy for ulcerative colitis (Brooke and Slaney, 1958 ; Brooke,

‡Severe diarrhoea (six or seven motions a day) with macroscopic blood in stools. Fever (mean evening temperature more than 99.5° F. (37.5° C.), or a temperature of 100° F. (37.8° C.) or more on at least two days out of four). Tachycardia (mean pulse rate more than 90 a minute). Anaemia (haemoglobin 75% or less). E.S.R. much raised (more than 30 mm. in 1 hour).

1959) and a septicaemia in some patients after operation (Slaney and Brooke, 1958). It seems reasonable to take a blood culture from all patients with fulminating colitis, as some of them may have a septicaemia also. The general experience of broad-spectrum antibiotics in ulcerative colitis appears to be unfavourable, and 10 of our patients were given antibiotics without effect ; clinicians are also rightly afraid of secondary infection of the bowel by drug-resistant staphylococci, as in the following case.

Case 23.—A woman aged 24 had been given tetracycline, 2 g. daily, as treatment for a severe exacerbation of colitis, but her condition had deteriorated steadily, so that when admitted to hospital she appeared overwhelmed by the illness, with a pulse rate persistently above 160 a minute. A severe pharyngitis was noted and throat swabs yielded a profuse growth of *Staph. pyogenes* resistant *in vitro* to tetracycline and penicillin, and only slightly sensitive to erythromycin. Stool culture yielded *Staph. pyogenes* of the same phage pattern, also insensitive to antibiotics ; blood culture was sterile. Treatment with intravenous erythromycin was ineffective, but she made a rapid and uneventful recovery after subtotal colectomy. The operation specimen revealed confluent ulceration of almost the whole colonic mucosa.

Of the six patients who were given a course of insoluble sulphonamides, two probably benefited. We have no experience of salicylazosulphapyridine in the treatment of very severe colitis ; Bargen (1955) does not recommend its use in fulminating colitis. As so many of the complications after colectomy were due to intra-abdominal sepsis, a trial of neomycin given pre-operatively seems worth while. Lastly, and just as important, Paulley (1956) and others have emphasized the value of dealing with the emotional upheavals found in many of these patients. It is clear that in this disease the physician must be prepared to give much time in getting to know the patients and their problems. He needs to gain their confidence, deliberately seek sources of emotional strain, and deal with the problems sympathetically as they arise, and actively support their morale more than in most other illnesses.

At present the indications for surgery are usually failure to improve during medical treatment, or the appearance of progressive abdominal distension, which is regarded as a sinister sign of impending perforation of the colon. In some of our cases—for example, No. 28—there was disaster because surgery was delayed. The operation of choice is still under discussion—a strong case has been made for preliminary ileostomy by Cattell (1953), but many surgeons now favour immediate colectomy (Aylett, 1959 ; Brooke, 1959 ; Goligher, 1959). We consider that the results presented here favour immediate colectomy but emphasize the dangers of perforation of the bowel during mobilization.

From our findings, some of which can only be tentative, we suggest a trial of the following scheme of management :

A Suggested Regime of Management for Trial

General.—The management of these patients is a matter for both physician and surgeon. As soon as the severity of the illness is recognized—and the severity is not always at once obvious—they should see the patient together and continue this close co-operation from day to day. A vigorous attempt should be made both to make good the metabolic depletion already present and to keep pace with further losses, not only of haemoglobin, fluid, and electrolytes, but also of protein. A blood culture is taken to detect a

septicaemia. It is important to gain the patient's confidence and to help with any emotional problems which may have precipitated the illness.

Corticotrophin.—(a) *The patient has not received corticotrophin or steroid drugs :* Give 120 units of corticotrophin daily for four days to test the response of the patient's illness to this drug, provided that delay in undertaking operation appears justifiable. (b) *Corticotrophin or steroid drugs have been given :* From a knowledge of the dose given a decision must be made whether these drugs received an adequate trial. If they did, corticotrophin should not be given ; if not, a cautious trial of 120 units of corticotrophin daily for four days seems justifiable.

Indications for Surgical Treatment.—Unless operation is deliberately delayed for a trial of corticotrophin it should be performed as soon as the patient's obvious metabolic deficiencies have been met. Further delay is not permissible except when the disease appears to be going into remission after energetic general medical treatment. If a trial of corticotrophin is undertaken urgent operation is indicated if (a) there is no dramatic response to this drug and all other medical measures within four days ; (b) the patient's condition deteriorates at any time during the treatment ; or (c) after an initial successful response to corticotrophin a severe relapse occurs while he is still receiving the treatment.

Type of Operation.—We consider that the best procedure is immediate subtotal colectomy and ileostomy. If, however, the patient's general condition is desperate, or if inspection at laparotomy suggests that the colon is especially apt to perforate during mobilization, ileostomy alone may be preferable.

Summary

The results of treatment in 32 patients with very severe acute ulcerative colitis have been analysed.

The results of medical treatment were disappointing ; one patient died without an attempt at surgical treatment, two patients responded to conservative measures, and two apparently responded to corticotrophin, 120 units daily (one of these patients did not respond to corticotrophin, 80 units daily).

Four patients were treated by ileostomy alone and all of them recovered. Reasons are given for supposing that these results were fortuitously favourable.

Twelve patients who had received no corticosteroid treatment were treated by immediate subtotal colectomy and ileostomy ; three of them died and six made an uneventful recovery. It is suggested that this is the operation of choice in most cases.

Seven patients who had received corticosteroid therapy were treated by immediate subtotal colectomy and ileostomy ; four of them died and two made an uneventful recovery. There was a dangerous deterioration in the condition of three of these patients during pre-operative medical treatment ; two patients were not given extra cortisone at the time of operation. The colon was torn during colectomy rather more often among patients who had received corticosteroids than among those who had not received these drugs.

From our findings we suggest a possible regime for trial in the management of these very ill patients.

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LOCAL CORTICOSTEROID TREATMENT IN SEVERE ATTACKS OF ULCERATIVE COLITIS

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Since 1955 considerable experience has been acquired in the use of corticosteroid solutions applied locally within the colon by means of a rectal drip for the treatment of ulcerative colitis. The initial studies showed that mild and moderate attacks were often checked abruptly, so that the patient became symptom-free in a few days, though a minority of attacks failed to respond (Truelove, 1956, 1957). A special feature of these early studies was that the water-soluble corticosteroid, hydrocortisone hemisuccinate sodium, was shown by serial biopsy of the mucosa to produce striking histological improvement in those patients showing a favourable symptomatic response. Consequently this agent, or another water-soluble corticosteroid, prednisolone 21-phosphate, has since been the agent of choice for this form of treatment.

Since these early studies, local corticosteroid treatment has been tested in two independent controlled therapeutic trials, carried out in Oxford and Leeds respectively, both of which were conducted on the so-called " double-blind " system with neither the physician nor the patient knowing whether a particular treatment was corticosteroid or " dummy." Both studies yielded convincing evidence that local corticosteroid treatment usually caused a rapid cessation of mild and moderate attacks of ulcerative colitis, whereas it was exceptional for a patient to undergo spontaneous loss of symptoms when given the dummy treatment (Truelove, 1958 ; Watkinson, 1958). Subsequently it has been found that local corticosteroid treatment is twice as likely to bring about a rapid clinical remission as a comparable dose of corticosteroid given by mouth, but that it is even more efficient to use combined systemic and local corticosteroid therapy consisting of prednisolone by mouth and hydrocortisone hemisuccinate sodium by rectal drip (Truelove, 1960).

All these published studies were concerned with the value of local corticosteroid therapy in mild or moderate attacks of ulcerative colitis, and it has sometimes been assumed that this form of treatment is useful only in such attacks and has little or no place in the management of a severe attack. In reality, local