The course and prognosis of ulcerative colitis

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Part III Complications

One of the outstanding features of ulcerative colitis is the diversity of complications of the disease. They fall logically into two main groups: local complications in and around the large bowel, and remote or systemic complications affecting distant parts of the body. Some of these complications are so dangerous that they make a substantial contribution to the considerable fatality due to this disease.

Tables XXIV and XXV show the incidence of the main complications divided between 'first attack' cases and 'relapses', and further subdivided according to whether the complication occurred during the first referred attack or during the period of subsequent follow-up.¹ The right-hand column shows the overall incidence of these complications in our total series of 624 patients. This incidence must be regarded as an underestimate for two distinct reasons. First, in many cases we have had to rely purely on the case notes for our information, and some of the complications, especially minor examples, may not have been recorded in all instances. Secondly, it can be seen from Tables XXIV and XXV that these complications are numerous during the course of follow-up and therefore some patients who have so far escaped complications are almost certain to have one or more in the future.

LOCAL COMPLICATIONS

ISCHIO-RECTAL OR PARARECTAL ABSCESS Ischio-rectal abscess is a common complication, about one in 25 of our whole series having had one so far. Such an abscess may form at any time, either in a first attack or in a relapse of long-established disease. Sometimes the abscess may appear when the colitis is clinically quiescent, although sigmoidoscopy will reveal that the rectum and lower colon are inflamed.

An ischio-rectal abscess demands surgical drainage without delay. The abscess is often deep-seated so that formal surgery is required. It is one of the few

complications which are amenable to conservative surgery, leaving the colon intact.

Illustrative case history Mr. W. L. was first seen at this hospital in 1955, when he presented in his first attack of ulcerative colitis, at the age of 34 years. There was evidence of disease affecting the bowel from the transverse colon onwards, but the attack was mild, and he responded well to treatment with local hydrocortisone. Three months later, after a recurrence of symptoms, he developed a very large ischio-rectal abscess. This was opened and drained without any complications, and he made a satisfactory recovery. Since then, there has been no recurrence of symptoms.

FISTULA-IN-ANO This may present as an ischio-rectal abscess, but when the abscess bursts or is incised, persistent purulent discharge occurs. The internal openings into the rectum may be small or multiple, so that the surgeon must explore with a probe to find them. They seldom heal spontaneously. They can be treated by conservative surgery if not too severe and it is essential for the surgeon to open up all the tracks into the rectum. This usually means cutting through the sphincter muscles of the anus, but anal continence is nearly always recovered when the large exposed surface granulates and heals. Severe examples offer adequate justification for colectomy.

Fistula-in-ano resembles ischio-rectal abscess in being liable to present at any stage of the disease, from first attacks to recurrences of long-established disease, and also during clinical remissions. Its occurrence during a period of clinical remission always implies that there is active disease in the bowel, even though diarrhoea and the passage of blood per rectum may both be absent.

Ischio-rectal abscess and fistula-in-ano frequently occur in the same patient, 11 of our series having suffered from both.

Illustrative case history Mr. E. W. developed ulcerative colitis in 1937 at the age of 26, and subsequently

¹The Tables are numbered consecutively in Parts I to IV inclusive.

TABLE XXIV
LOCAL COMPLICATIONS

Local Complication	First Attacks			Relapses			Whole Series No.
	Before First Referred Attack	In First Referred Attack	During Follow-up	Before First Referred Attack	In First Referred Attack	During Follow-up	
Ischio-rectal abscess	1	4	6	2	5	8	26 (4.2%)
Fistula-in-ano	1	3	4	3	3	12	26 (4.2%)
Recto-vaginal fistula	—	4	3	—	1	3	11 (3.0%) ¹
Recto-vesical fistula	—	—	—	—	—	—	—
Entero-colic fistula	—	—	—	—	1	2	3 (0.5%)
Rectal prolapse	—	—	—	1	6	1	8 (1.3%)
Haemorrhoids	17	32	13	25	13	29	129 (20.7%)
Fibrous stricture	—	1	11	1	16	10	39 (6.3%)
Pseudo-polypoid	—	19	17	2	34	21	93 (14.9%)
Perforation	—	13	2	1	1	3	20 (3.2%)
Acute dilatation of the colon	—	2	—	1	6	1	10 (1.6%)
Massive haemorrhage	—	2	5	3	7	4	21 (3.4%)
Carcinoma of the colon	—	—	4	—	8	10	22 (3.5%)

¹Of 373 women in the series.

TABLE XXV
SYSTEMIC COMPLICATIONS

Systemic Complication	First Attacks			Relapses			Whole Series No.
	Before First Referred Attack	In First Referred Attack	During Follow-up	Before First Referred Attack	In First Referred Attack	During Follow-up	
Erythema nodosum	1	3	2	4	3	1	14 (2.2%)
Pyoderma gangrenosum	—	1	—	—	2	1	4 (0.6%)
Other skin eruptions	5	19	17	10	26	22	99 (15.9%)
Arthritis	1	4	3	8	10	9	35 (5.6%)
Ankylosing spondylitis	2	—	3	1	3	2	11 (1.8%)
Eye lesions	1	3	8	15	5	15	47 (7.5%)
Transient hepatitis	6	2	2	16	—	4	30 (4.8%)
Chronic hepatitis	3	2	1	5	2	3	16 (2.6%)
Renal disease	5	—	4	9	7	4	29 (4.6%)
Pulmonary embolism	—	—	2	1	6	1	10 (1.6%)
Venous thrombosis	1	6	8	6	14	5	40 (6.4%)
Oral aphthous ulceration	1	10	10	3	10	17	51 (8.2%)
Oral moniliasis	—	3	2	1	2	3	11 (1.8%)
Extensive moniliasis	—	1	—	1	1	—	3 (0.5%)
Osteoporosis	—	3	1	—	2	3	9 (1.4%)
Anaemia due to ulcerative colitis	—	36	13	8	52	18	127 (20.4%)
Other disorders of the blood	—	2	5	2	5	4	18 (2.9%)

suffered from the chronic intermittent form of the disease. He was first seen at the Radcliffe Infirmary in 1959, aged 48, in a mild relapse, the whole colon being affected. Treatment with local and systemic corticosteroids produced an early remission. However in 1960 he relapsed and presented with a painful swelling to the left of the anus which later discharged pus, and a small submucous fistula-in-ano. Two months later two more fistulous tracks had appeared, and these were subsequently laid open. They healed well, and no further fistulae developed. He has since had several mild recurrences of ulcerative colitis which have been treated satisfactorily without admission to hospital.

RECTO-VAGINAL FISTULA This is not infrequent among the female patients, there being 3% of the present series so affected. This condition gives rise to a profuse, foul, vaginal discharge. Spontaneous

healing seldom occurs. Conservative surgery is usually ineffective. Severe examples demand colectomy, but in this series there are two patients who have done well by being treated by a three-stage procedure consisting of double-barrelled ileostomy, conservative surgery to repair the fistula, and subsequent restoration of the continuity of the intestine.

Illustrative case history Mrs. P. V. developed severe ulcerative colitis involving the distal colon in 1957 at the age of 47 years. Treatment with local and systemic corticosteroids had little effect, and a recto-vaginal fistula developed five weeks after the onset.

Shortly afterwards she developed an ischio-rectal abscess, and this was opened and drained. At the same time a double-barrelled transverse colostomy was performed, and local hydrocortisone was applied to the diseased colon through the distal stoma. Two months

later an extensive, recently developed, fistula-in-ano was excised and she became symptom-free.

She was readmitted in 1960, having been well for over a year, and the recto-vaginal fistula was repaired. The colostomy was closed a few weeks later, and since then she has been in good health and has had no recurrence of the colitis.

RECTO-VESICAL FISTULA This must be rare in ulcerative colitis because no cases occurred in this series.

ENTERO-ENTERIC FISTULA This is an uncommon complication of ulcerative colitis in contrast to Crohn's disease, in which entero-enteric fistula is frequent. There were three patients with entero-colic fistula in the present series. One had a fistulous connexion between the tip of the appendix and the sigmoid colon, which was discovered at operation for carcinoma of the transverse colon complicating long-standing ulcerative colitis. The other two patients each had a fistula between the colon and a loop of small intestine.

An entero-enteric fistula demands surgical intervention with excision of the fistulous tract in addition to whatever other surgery appears necessary.

RECTAL PROLAPSE This is an occasional complication which develops during the course of an actual attack of ulcerative colitis when there is much diarrhoea. It is interesting that in the present series there was no example during the first attack of the disease. There is the possibility that the rectal musculature becomes altered as a result of repeated attacks of severe diarrhoea so that prolapse is liable to occur.

It is well known that, apart from ulcerative colitis, rectal prolapse chiefly occurs in infancy and in old age. In the present series, rectal prolapse occurred chiefly in patients aged 25 to 40 years, which further suggests that the disease itself creates the circumstances which lead to the development of the prolapse.

HAEMORRHOIDS These occur frequently in ulcerative colitis and appear to be one of the complications of diarrhoea. They also bulk largely in the case histories for the following additional reason. A patient may complain of passing bright blood on defaecation and be treated as a case of haemorrhoids by injection or actual haemorrhoidectomy. If the symptoms persist, it is not rare to find that the patient has the distal form of ulcerative colitis, which often causes bleeding without diarrhoea. We have seen many patients with ulcerative colitis who have given this type of history.

When severe prolapsed haemorrhoids occur during an actual attack of ulcerative colitis, they represent an unpleasant complication. It is best to treat them conservatively until the ulcerative colitis is quiescent and then to carry out haemorrhoidectomy as in any other patient.

FIBROUS STRICTURE This occurs in a small proportion of patients and is essentially a manifestation of chronic disease, as can be seen from Table XXIV.

It is not impossible for a fibrous stricture to form during the course of a first attack, and there was one such case in the present series, confirmed at surgical operation. Once the disease has become chronic, a stricture may become apparent at any time and one-third of the cases in the present series were diagnosed within five years of the onset of the ulcerative colitis. Patients with the chronic continuous form of the disease are more liable to stricture than those with the chronic intermittent form: but caution is necessary in the interpretation of this finding, because the presence of a stricture will itself cause chronic diarrhoea, and it is therefore difficult to distinguish between cause and effect unless repeated barium enema examinations have been made throughout the course of the disease.

Whenever a stricture is found, the possibility of carcinoma must be considered, but many of the strictures are fibrous with no evidence of malignancy. They are most frequent in the rectum and sigmoid colon but may occur in any part of the colon; they are occasionally multiple. A fibrous stricture is almost always an indication for surgical treatment, if only because the possibility of carcinoma must exist whenever a stricture is found and it is necessary to resect the lesion and to carry out histological examination before the distinction can be made with certainty.

Illustrative case history Mrs. J. M. was first seen at the Radcliffe Infirmary in 1959, when she presented in her first attack of ulcerative colitis at the age of 37 years. The disease pursued an intermittent course over the next two years and during this time she received treatment with local and systemic steroids. In April 1961 a stricture of the recto-sigmoid junction was diagnosed and the following operations were then performed: double-barrelled ileostomy (April 1961), resection of the sigmoid colon and upper rectum, with end-to-end anastomosis (May 1961), and closure of the ileostomy (August 1961). Pathological examination confirmed the fibrous nature of the excised stricture.

While the bowel was uncoupled, the colon was irrigated nightly with local hydrocortisone solution. After the final operation her symptoms were much less severe and all steroid therapy was stopped some weeks before discharge. Since then she has been seen regularly as an out-patient, and when last seen was in good health.

FIG. 13. *Pseudo-polyposis affecting the left half of the colon.*

PSEUDO-POLYPOSIS This is a consequence of severe ulcerative disease. The mucosa between the ulcerations becomes much swollen and raised above the general surface. Alternatively, the ulcerations may be the site of exuberant granulation tissue, which is later epithelialized. The condition can occur rapidly and is not infrequent during the first attack of the disease. It is most likely to occur in a severe attack of the disease, especially when the whole colon is involved, but the left half of the colon is the more liable to show pseudo-polypoid change and sometimes the process stops short at a particular point in the colon (Fig. 13). Once developed, the condition is likely to persist, but this is not invariable and complete regression to normality can occur over the course of time.

It is sometimes supposed that pseudo-polyposis may be a precancerous change. There appears to be no good evidence for this except that this complication is a measure of severe disease and may thus be an indirect indication that cancer of the colon is specially liable to occur. In the present series, only one patient with cancer of the colon complicating ulcerative colitis was known to have pseudo-polyposis preceding it.

The condition is not, in itself, a firm indication for colectomy.

PERFORATION OF THE COLON This is the most dangerous local complication of the disease. The colon does not form adhesions in ulcerative colitis and the consequence is that, if perforation does occur, it usually results in a generalized faecal peritonitis which is extremely dangerous. The complication is often hard to recognize because, although there are sometimes the classical signs of a perforation, the condition may produce few local signs and the only indication that some disaster has occurred is a marked deterioration in the general condition of the patient. In any case of doubt, an immediate plain x-ray examination should be made. When the patient is gravely ill, he should be examined by portable x-ray machine on his own bed; it is best to use a horizontal beam with the patient lying on his left side, so that any free gas between the right lobe of the liver and the thoraco-abdominal wall can be seen. The same film will also show if there is dilatation of the colon (see acute dilatation of the colon, below).

Perforation of the colon is specially liable to occur in the first attack of the disease. In the present series, among the 20 patients who suffered from perforation, there were 13 who developed this complication in the first attack. From our own data, perforation appears to be the only local complication with such a marked tendency to occur in the first attack.

The risk of perforation varies greatly according to the clinical severity of the attack of ulcerative colitis. In the present series the majority of perforations (16 cases) occurred in severe attacks, a few occurred in attacks classed as moderately severe (four cases), and none in attacks which were mild.

The common site of perforation was the sigmoid colon. The sites of perforation were as follows:—

Sigmoid colon	12
Descending colon	4
Caecum	2
Terminal ileum	1
Multiple sites (caecum, splenic flexure and descending colon)	1

One of the supposed dangers of corticosteroid therapy is that it may increase the risk of perforation of the colon. It is therefore important to record the fact that there has been no increase in the frequency of colonic perforation in the present series since the introduction of cortisone in 1952. If we confine ourselves to first attacks, when the population at risk is precisely known, and if we also exclude all mild attacks, none of which proceeded to perforation, we are left with the following data for severe and moderately severe attacks in relation to pre-cortisone and post-cortisone eras:—

No. of Patients in First Attack with Severe or Moderately Severe Disease		No. with Perforation
1938-52	59	8 (13.6%)
1953-62	55	5 (9.1%)

Perforation of the colon may be preceded by dilatation of the colon although often perforation occurs without any such premonitory manifestation. In fact, in the present series, only one patient developed perforation in association with severe dilatation of the colon.

Three-quarters of the patients who developed colonic perforation died. On studying our data, two salient facts emerge. First, there is the difficulty of recognizing the condition in life, because in half the patients with perforation in the present series, the complication was diagnosed only at post-mortem examination, and the possibility of colonic perforation had not been entertained by the physician during life. This emphasizes that plain x-ray examination with the patient in his own bed is an important diagnostic tool in any patient admitted in a severe attack of ulcerative colitis. Secondly, if emergency colectomy is to be performed, it must be carried out without delay, because death occurs quickly after a colonic perforation. Only five patients were treated by emergency surgery but three of them survived, in contrast to only two survivals among 15 patients treated conservatively. Even though an emergency colectomy is a hazardous operation in a patient who is already gravely ill, it offers the best chance of survival.

Illustrative case history Mr. W. H., aged 64, was admitted to the Radcliffe Infirmary on 9 October 1962 in his third attack of ulcerative colitis, having had symptoms for the previous six weeks. The attack was severe and there was evidence that the disease affected the bowel from the transverse colon onwards. He was treated with local and systemic corticosteroids in addition to general measures and blood transfusion, and showed some improvement over the next three weeks. On 30 October he complained, on waking, of feeling particularly unwell, but the possibility of perforation was not considered owing to the absence of more specific symptoms. Later in the morning his condition deteriorated and he complained of pain in the left iliac fossa. Localized tenderness and guarding were found, bowel sounds were absent, and a plain radiograph showed the presence of free gas in the abdomen. It was decided that laparotomy should be done at once, and operation revealed a perforation in the region of the splenic flexure. A subtotal colectomy with terminal ileostomy was performed. He recovered steadily without complication and, after his general health had improved substantially, the rectum and remaining sigmoid colon were removed by combined abdomino-perineal excision.

ACUTE DILATATION OF THE COLON Ten patients had evidence of marked dilatation of the colon, a complication which has sometimes been termed 'toxic megacolon' (Roth, Valdes-Dapena, Stein, and Bockus, 1959). The attack of ulcerative colitis in which this occurred was usually severe. Acute dilata-

tion of the colon may occur in either a first attack or a relapse of the colitis and is regarded as a dangerous complication, because it is thought to be a sign of impending perforation. In the present series only one patient was treated surgically; of the remaining nine patients, three died, but in one case death occurred shortly after admission to hospital. Of the three deaths, post-mortem examination in two patients showed that there was no perforation, and in the third, in whom there was no necropsy, there was no clinical evidence of perforation.

During recent years the importance of potassium deficiency has been appreciated as a cause of intestinal dilatation and paralysis, but some of our cases date from before this era and potassium studies were not made in them. Another known factor in the aetiology of the condition is the excessive use of anticholinergic drugs. Some authorities regard the occurrence of acute dilatation of the colon as an indication for immediate emergency colectomy; however, the present series shows that some cases can be managed conservatively with success. If a conservative approach to treatment is contemplated, it is first essential to take plain radiographs to exclude the presence of free gas as a sign of perforation of the colon, which usually calls for emergency colectomy. Blood electrolytes should be estimated, and any treatment with anticholinergic drugs stopped at once. Neither food nor drink should be given by mouth, and intubation of the gastrointestinal tract should be performed to enable gastrointestinal suction to be carried out. Control of water and electrolyte balance is achieved by intravenous therapy, and glucose and other suitable foods should also be given parenterally.

Illustrative case history Miss A. F. developed ulcerative colitis in 1952 at the age of 18, and subsequently had several attacks. She was admitted to this hospital in 1960 in a severe relapse. Diarrhoea had begun two weeks previously and for the week immediately before admission she had, in addition, abdominal pain, anorexia, and vomiting. On examination she was feverish and ill and the abdomen was very tense with slight tenderness in the left iliac fossa. A plain radiograph showed a greatly dilated colon with mucosal changes consistent with widespread colitis. There was no evidence, either on admission or subsequently, of free gas in the peritoneal cavity. She had not been treated with anticholinergic drugs and her serum potassium level was not lowered. It was decided to treat her conservatively and she slowly improved under the regime outlined above. Local and systemic corticosteroids were given to supplement the general measures. Blood electrolyte estimations and radiographs were repeated at frequent intervals throughout her illness and, although one month after admission a plain radiograph showed that there was still considerable colonic dilatation, her general condition continued to improve and she

was discharged a few weeks later. She has since been seen regularly as an out-patient; there have been no recurrences and she is at present in very good health.

MASSIVE HAEMORRHAGE We define as a massive haemorrhage in this disease a sudden bleed demanding urgent blood transfusion or continued heavy bleeding demanding massive transfusion. When so defined, massive haemorrhage is not a frequent complication (21 cases). It can usually be treated successfully by blood transfusion but exceptionally it is an indication for emergency colectomy.

Illustrative case history Mrs. R. W. was admitted to the Radcliffe Infirmary in 1957 in her first attack of ulcerative colitis. She was 34 years of age and was severely ill. The disease affected the whole colon and sigmoidoscopy showed a markedly inflamed and haemorrhagic mucosa. Her stay in hospital was notable for numerous episodes of exsanguinating haemorrhage from the bowel, all of which required immediate massive transfusion. Six weeks after admission, following one of these episodes, she complained of pain in the left iliac fossa. Local tenderness was present, but there was no evidence of free gas in the peritoneal cavity. Her general condition remained fairly good and it was considered that, as this might be a perforation resulting in a localized pelvic abscess, she should be treated conservatively with parenteral antibiotics in addition to the other treatment she was then receiving. She improved steadily after this further setback, but shortly afterwards had another very severe haemorrhage for which she received further urgent and repeated transfusions over the next few days. During her admission, which lasted for five months, she received a total of 64 pints of whole blood. Her treatment otherwise consisted of general measures, A.C.T.H., and both systemic and local corticosteroids. After discharge, she had one further rectal haemorrhage which responded rapidly to blood transfusion and corticosteroid therapy. Apart from this, she has remained in uninterrupted good health.

CANCER OF THE COLON This complication has occurred in 22 patients (3.5%) of the present series, with death in 17 of them. The complication is so important that it is dealt with separately in Part IV.

REMOTE OR SYSTEMIC COMPLICATIONS

ERYTHEMA NODOSUM This is well recognized as a complication of ulcerative colitis and fairly often occurs in association with arthritis. There were 14 patients in the present series who developed erythema nodosum, and all but one of them were women, a sex difference which is statistically significant. However, erythema nodosum is known to be more frequent in women than in men when it occurs apart from ulcerative colitis, so the marked sex difference in this disease may not have any special significance. Three patients in the present series had

an attack of erythema nodosum before the onset of the ulcerative colitis. In all but one of the remainder, the erythema nodosum coincided with a frank attack of ulcerative colitis, either the first attack or a relapse, while the one exception had the erythema nodosum two weeks before a relapse. Sometimes there are repeated attacks of erythema nodosum, and there were three such patients in the present series; in these patients, the erythema nodosum coincided with frank attacks of colitis.

Illustrative case history Miss M.S. was first seen at the Radcliffe Infirmary in 1940, when she presented in her first attack of ulcerative colitis at the age of 17 years. This attack was severe and the distal colon was affected. She was treated with general measures and transfusion but showed little improvement. She was still in hospital five months after admission when she developed erythema nodosum of both shins and, a few days later, an acute arthritis affecting the right elbow and wrist. These manifestations eventually subsided but she continued to have symptoms of colitis and two months later a second crop of lesions typical of erythema nodosum appeared. Throughout the whole of this admission she was very ill, with high fever and a much raised sedimentation rate. Her condition slowly improved and she was discharged some months later, although she had not gone into full clinical remission.

In 1946 she was readmitted in a sharp relapse and had at that time effusions into both knee joints and erythema nodosum of the legs and forearms. Since then she has had continuous bowel symptoms of varying severity, but has had no further attacks of erythema nodosum. She has had no medical supervision since 1946 and when seen by us in 1962 refused investigation and treatment, but it is almost certain, from her appearance and history, that she has gradually developed a severe degree of ankylosing spondylitis over the last 15 years.

PYODERMIA GANGRENOUSUM This rare and serious condition is virtually confined to ulcerative colitis and there were four such cases in the present series.

The essential lesion is an intra-epidermal bulla which is filled with a sterile milky fluid containing inflammatory cells. The surface of the bulla breaks down and scabbing occurs, sometimes with secondary infection. The bullae may be numerous and often coalesce so that the final result is an extensive area of scabbing, which may become gangrenous.

The condition is usually a complication of a severe attack of ulcerative colitis and is attended by marked constitutional symptoms, although it is hard to separate these from those of the colitis. The essential in treatment is to control the ulcerative colitis, either by corticosteroids or by colectomy; successful treatment of the colitis by either of these methods results in healing of the skin.

Although typically an acute complication, the condition may exist in a chronic form for months or

years, even when the symptoms of colitis are absent or slight. One such case occurred in the series and we have seen another recently.

Illustrative case history Mrs. E. W. developed ulcerative colitis in 1952 when she was 25 years old. Following her first attack she had many relapses, which were often associated with arthralgia and which responded to steroid therapy. During her second pregnancy, in 1957, she had another relapse of the colitis, during the course of which she developed a deep vein thrombosis of the right leg. Superficial ulceration of the leg, which later progressed to pyoderma gangrenosum, subsequently occurred, but immediately after delivery of her child both the colitis and the skin lesion improved greatly. However, a few weeks later there was a recurrence of ulceration and, some time afterwards, of the colitis. This relapse was treated with systemic corticosteroids in addition to general measures and, as the colitis improved, the ulcerated area on the leg healed. However a widespread crop of vesicles, particularly marked on the scalp, ears, and legs, then appeared. The vesicles coalesced and burst, to be replaced by extensive scabbing. All these lesions, which were typical of pyoderma gangrenosum, rapidly progressed and her general condition greatly deteriorated. Rectal hydrocortisone was added to the existing treatment, but no improvement occurred. Colectomy was seriously considered, but it was decided to try first the effect of very large doses of steroids. Accordingly, she was given 240 mg. of prednisolone daily and she responded dramatically. The diarrhoea quickly improved her general condition began to return to normal, and the skin lesions began to epithelialize. She was kept on this high dose of prednisolone for four weeks, and it was then reduced to a smaller maintenance dose for several more weeks. Healing of all the lesions continued steadily and there has been no recurrence of this complication. She was discharged in full clinical remission and she is at present in good health, although she has had one relapse of the colitis in the intervening period.

OTHER SKIN LESIONS These are numerous and diverse; 99 patients were affected, some with more than one type of lesion. In 13 patients the skin condition preceded the colitis, while in 86 patients it occurred either at, or after, the onset of the colitis. In 24 of these 86 cases the two conditions were considered to be unrelated, while in the remaining 62 patients skin lesions developed in relation to attacks of colitis.

A variety of skin reactions was noted in this latter group. In eight patients generalized rashes, mainly urticarial, were attributed to drugs (usually sulphonamides) or to serum sickness. Some patients developed mild forms of dermatitis, or macular and papular rashes. The largest group (13) had widespread erythematous lesions of varying severity and an additional three patients had definite erythema multiforme. Seven patients suffered from pustular rashes, four from superficial boils and abscesses,

while three had erysipelas. The remainder developed vesicular rashes, ulceration, eczema, abnormalities of pigmentation, or affections of the hair and nails.

Eighteen patients developed arthritis, eye lesions, or aphthous ulceration of the mouth at the same time as the skin condition.

ARTHRITIS This is a common complication of the disease. The usual form is a polyarthritis, which may affect either large or small joints. Involvement of a single large joint is fairly common. Sometimes the condition closely resembles rheumatoid arthritis, but it is known that the Rose-Waaler test is usually negative in the arthritis of ulcerative colitis (Bywaters and Ansell, 1958; Wright and Watkinson, 1959). There is often an effusion into the affected joints, but aspiration shows this to be sterile. The condition usually complicates a frank attack of ulcerative colitis but occasionally may precede the onset of the disease, and also may occur during periods of clinical remission.

When the colitis is treated effectively, the arthritis subsides. Corticosteroids have transformed medical treatment for the better in this respect. It has been said that 'arthritis and iritis constitute urgent indications for removal of the bowel' (Brooke, 1954) but this can no longer be regarded as a valid assessment, although some patients with arthritis may be found to require colectomy.

Thirty-five patients developed such an arthritis, which almost always coincided with either a first attack or a relapse of the colitis; in slightly less than half the cases the arthritis occurred simultaneously with erythema nodosum, aphthous ulceration, conjunctivitis, or a rash.

ANKYLOSING SPONDYLITIS This is less common than arthritis but is nevertheless not rare. Our present figure of 1.8% is certainly an underestimate of the frequency of the complication, because it covers only severe cases, and special study of patients with ulcerative colitis with this complication in mind reveals that early and minor changes of ankylosing spondylitis are fairly frequent. Whereas there is a heavy preponderance of male subjects when ankylosing spondylitis occurs in the absence of ulcerative colitis, the male : female ratio being about 10:1, in this disease the men are only about twice as frequently affected as the women.

In some patients, the ankylosing spondylitis precedes the symptoms of ulcerative colitis, as has been pointed out by Acheson (1960). There were three such patients in the present series.

Illustrative case history Miss M. D. was 28 years old when she had her first attack of ulcerative colitis in 1940

FIG. 14. *Ankylosing spondylitis in a woman with chronic ulcerative colitis.*

Shortly after she had recovered she had an attack of iritis which was later followed by a recurrence of bowel symptoms. Intermittent diarrhoea continued over the next three years and in one relapse an appendicostomy was performed and the bowel irrigated. In 1943 she had two more attacks of iritis and for the first time she noticed pain and stiffness of her back. These symptoms worsened and her back began to become fixed. In 1945 and 1946 she had two courses of deep x-ray treatment to the back, with some symptomatic relief. The colitis was largely inactive at this time, but in 1948 a fourth attack of iritis occurred and in 1950 she again experienced troublesome diarrhoea. She was referred to the Radcliffe Infirmary for the first time in 1951 and advanced ulcerative colitis involving the whole colon was found. A severe degree of ankylosing spondylitis was present and she experienced also, at that time, an attack of erythema nodosum and one of arthritis of the ankles. From 1952 onwards she has had extensive medical treatment for the colitis but this has continued to relapse, although less frequently and severely than during the first years of her illness. The spondylitis remained unchanged (Fig. 14) and the last radiograph, taken in 1960, showed extensive ankylosing spondylitis of the cervical, dorsal and lumbar spine, with marked bony fusion of the lumbar vertebrae.

EYE LESIONS These are common complications of ulcerative colitis. They were slightly more common in the women (8.9%) than in the men (5.6%) of this series but this small difference is probably of little account. Conjunctivitis is common, as are iritis and other forms of uveitis. Repeated attacks of the eye complication, usually coincident with frank attacks

of the colitis, are a special feature. These eye complications may also coincide with other remote complications of the disease, notably arthritis, skin lesions, and aphthous ulceration of the mouth.

Once again, our figures for this group of complications are almost certainly an underestimate, and this issue is being studied at present by our colleagues. The majority of patients with eye lesions had either conjunctivitis or iritis, two patients having both disorders. Conjunctivitis occurred in 20 patients, in all but three of them in direct association with an attack of colitis. Thirteen patients had one or more attacks of iritis and in three cases the first attack of iritis preceded the onset of ulcerative colitis. The remaining eye lesions were few: corneal ulceration, keratitis, blepharitis, and Sjögren's syndrome were the chief examples.

LIVER DISEASE The relationship between ulcerative colitis and liver disease is complex.

Transient hepatitis is fairly frequently associated with ulcerative colitis. Some patients have a past history of an attack of jaundice (presumably infective hepatitis from the available evidence) when they develop ulcerative colitis and there were 14 such patients in the present series. Three other patients gave a history of an attack of jaundice, also presumed to be infective hepatitis, that was followed immediately by the first symptoms of the colitis. The remaining 13 patients developed temporary hepatitis at varying times after the onset of the colitis.

There is often the possibility that such attacks of hepatitis are examples of homologous serum jaundice following blood transfusion and no diagnostic methods are yet available for establishing this hypothesis; two of the 13 cases developed jaundice at an appropriate interval after blood transfusion. Two other patients developed jaundice during chlorpromazine therapy, and were judged on the basis of investigations to be examples of drug-induced cholestatic hepatitis. Finally, one other patient was working with toxic chemicals in a factory and the jaundice was attributed to this.

In the remaining eight patients, no predisposing factor other than the ulcerative colitis could be found to account for the hepatitis. The precise reasons for this association remain to be determined but several distinct possibilities exist. First, ulcerative colitis may render the subject unduly prone to infective hepatitis. Secondly, the temporary hepatitis may be directly due to the ulcerative colitis, because liver biopsy studies have shown various abnormalities during acute attacks of ulcerative colitis in the majority of subjects (Kleckner, Stauffer, Bagen, and Dockerty, 1952; Brooke, Dykes, and Walker, 1961), and Brooke and

Slaney (1958) have been able to culture bacteria from the portal blood of the patients undergoing colectomy for the disease. Finally, some workers have considered both the hepatitis and the colitis to be separate manifestations of an auto-immune disease, especially as the sera of ulcerative colitis patients may give auto-immune reactions against liver as well as against colon (Broberger and Perlmann, 1959; Broberger, 1961).

In a similar way, there is a definite relationship between ulcerative colitis and chronic liver disease (usually cirrhosis) but the underlying mechanisms are not yet understood. In the present series, there were 16 cases of chronic liver disease, which is a far greater number than would be expected by chance. Sometimes the liver disease develops after the onset of the colitis but it appears to be equally common for ulcerative colitis to develop as a complication of chronic liver disease; in the present series, there were eight patients in each of these two groups. The combination of ulcerative colitis and chronic liver disease is dangerous and 11 of these 16 patients are already dead. In effect, this small group has contributed 10% of the total deaths in the whole series of 624 patients.

Case histories to illustrate the two distinct patterns are given below:—

Illustrative case history 1 Mrs. M. C. had her first attack of ulcerative colitis in 1939, when aged 30 years. She subsequently suffered from the chronic intermittent form of the disease. She was under medical supervision from 1947 onwards, when a stricture of the rectum was diagnosed, but the colitis did not improve. She was first referred to this hospital in 1951 when, at the age of 42, she had experienced for the first time a transitory episode of jaundice associated with pain in the right hypochondrium. She was found on examination to have a grossly enlarged liver and spleen, and there was evidence of long-standing ulcerative colitis involving the whole colon. Cholecystectomy and terminal ileostomy were performed; the thickened contracted gall bladder contained purulent fluid and when examined microscopically showed chronic atrophic cholecystitis. Biopsy of the liver showed chronic cholangiohepatitis. She recovered from the operations but over the next three years had persistent jaundice with frequent intestinal haemorrhages and a progressive tendency to bruise easily. A barium swallow done in 1955 showed oesophageal varices and she had a well-marked caput medusa around the ileostomy stoma. A liver biopsy obtained in the same year showed severe post-necrotic scarring with extensive fibrosis. An attempt to lower the portal venous pressure was made in 1955, by the now out-moded Talma-Morrison operation, but she died a few months later after a particularly severe haemorrhage from the ileostomy.

Illustrative case history 2 Mrs. A. S. was perfectly well until 1943, when, at the age of 20 and during the course of her first pregnancy, she developed jaundice. This cleared after a few weeks, only to recur in the weeks fol-

lowing premature delivery of a stillborn child. She was then well until 1944, when exactly the same sequence of events occurred during and after her second pregnancy which terminated in a full-term normal live birth. By 1945 the jaundice had faded and she remained well until 1946, when her third pregnancy was associated with severe pruritus, pale stools, and bile in the urine. Liver function tests showed some evidence of liver damage and the liver was found to be enlarged. She was discharged after the baby was born and was not seen again until her second admission in 1949. She had had pruritus continually since 1947 and jaundice had returned in 1949. She had also passed some blood per rectum but no cause was found for this. She had a high sedimentation rate and hepatosplenomegaly at this time.

She developed severe bloody diarrhoea and colic in 1951, and also had piles and marked anaemia. The diarrhoea lasted for five months during which time she became very oedematous, with a low serum albumin level, and had several small haematemeses. Throughout 1952 she had mild episodic jaundice and was next seen in 1953 with a recurrence of bloody diarrhoea, oedema and ascites, associated with fever. She was severely anaemic and several spider naevi were noted. The hepatosplenomegaly remained unchanged. She was treated with blood transfusion, antibiotics, vitamins, and corticosteroids, but her condition steadily deteriorated. She died in 1954 in hepatic coma associated with a marked exacerbation of intestinal bleeding.

Necropsy showed advanced cirrhosis of the liver with post-necrotic scarring, oesophageal varices, and severe ulcerative colitis involving the whole colon with the exception of the sigmoid colon and rectum. It was considered that the original illness was infective hepatitis and that recurrent subacute hepatitis had progressed to cirrhosis.

RENAL DISEASE There were 29 patients in the series with renal disease. In 12 patients this preceded the onset of the ulcerative colitis and there appeared to be no relationship between the two conditions. Of the remaining 17 patients, the biggest group suffered from renal infection, there being six cases of pyelitis and four of chronic pyelonephritis. All except two of these 10 patients were women. The only other examples worth noting were two cases of ureteric obstruction with subsequent pyonephrosis, due to carcinoma of the colon, and two cases of temporary renal failure after colectomy.

In effect, the association between ulcerative colitis and serious renal disease is not marked.

PULMONARY EMBOLISM Of the 10 patients with pulmonary embolism in the present series, nine were women, whereas in the hospital population as a whole the condition affects both sexes equally (Morrell, Truelove, and Barr, 1963). It is of interest that no cases were recorded in this series before 1950, and there is therefore the possibility that the use of cor-

corticosteroids has increased the risk. However, pulmonary embolism has become increasingly common in the total experience of this hospital during the past decade and its increased occurrence in ulcerative colitis may be no more than a reflection of this trend.

In each case, the pulmonary embolism was associated with a frank attack of ulcerative colitis, the latter being either severe (five cases) or moderately severe (five cases); in one instance the embolism occurred two days after total colectomy.

The range of ages affected was wide, the youngest patient being 18 and the oldest 76, but seven of the patients were under 45 years of age.

Pulmonary embolism was the immediate cause of death in five instances, and it is perhaps not unexpected that three of these patients were of an older age group, their ages being 59, 69, and 76 years.

Clinical signs of peripheral venous thrombosis preceding the pulmonary embolism were only apparent in half the patients, although necropsy revealed the presence of ante-mortem deep vein thrombosis in an additional three cases. It is possible that some deaths could have been avoided by the use of anticoagulant therapy. Anticoagulants were used, in this small group of cases, in only one instance (a patient who recovered) and their place in the management of venous thrombosis in ulcerative colitis will be discussed in the next section.

VENOUS THROMBOSIS OF LEGS This is a common complication of ulcerative colitis, there being 40 patients so affected in the present series. It may occur at any stage of the disease and there is little evidence that corticosteroid therapy has influenced the incidence. If we confine ourselves to first attacks of the disease in order to define the population at risk with precision, we have the following data for the pre-cortisone and post-cortisone eras:—

	<i>No. of Patients in First Attacks</i>	<i>No. with Leg Vein Thrombosis</i>
1938-52	108	5 (4.6%)
1953-62	142	7 (4.9%)

This is in contrast to the apparent rise in the number of pulmonary embolisms during the past decade, as mentioned in the preceding section.

The question of employing anticoagulants always arises whenever a leg vein thrombosis is recognized. It is our personal experience that the presence of ulcerative colitis is not a contraindication to this form of therapy, although it may increase the loss of blood from the bowel. Pulmonary embolism is so dangerous that this risk of increased blood loss from the bowel is worth accepting because it appears to be well established that anticoagulant treatment of leg vein thrombosis greatly diminishes the risk of

developing pulmonary embolism and renders it less dangerous if it does occur (Barritt and Jordan, 1960). In the present series, anticoagulant therapy was used in 10 patients with leg vein thrombosis and none of them sustained a pulmonary embolism. If we exclude three patients who died from pulmonary embolism without preceding clinical recognition of leg vein thrombosis, we have the following data:—

	<i>No. of Patients with Leg Vein Thrombosis</i>	<i>No. of Patients with Pulmonary Embolism</i>
With anticoagulants	10	0
Without anticoagulants	27	5 (18.5%)

No firm conclusion can be drawn from this information in view of the small numbers but the findings are in the direction which suggests that anticoagulants should be used.

APHTHOUS ULCERATION OF THE MOUTH This is a common complication of ulcerative colitis (51 patients in the present series) and is frequently severe during an acute attack. The pain of severe aphthous ulceration is often so extreme that it impedes eating and drinking and so may cause difficulties in the management of the colitis. Local hydrocortisone applied to the mouth as a mouthwash is sometimes beneficial in promoting rapid healing. Care must be taken not to miss an associated moniliasis if this treatment is being employed. Such attacks of severe aphthous ulceration frequently recur whenever the subject has an attack of the colitis.

Aphthous ulceration was more commonly associated with severe attacks of colitis (25 patients) than with moderate (11 patients) or mild attacks (seven patients). Five patients had ulceration while in remission, and one patient developed aphthous ulcers after colectomy. In five cases ulceration occurred some time before the onset of the colitis. Of the 51 patients, 11 were known to have recurrent bouts of mouth ulcers. In only four cases was moniliasis noted.

MONILIASIS Moniliasis of the mouth and throat is not very common. Its importance lies in the fact that in some patients extensive or generalized moniliasis may supervene and these forms of the disease are very dangerous. For this reason, moniliasis of the mouth should immediately be treated with Nystatin tablets to suck and these are usually effective. Generalized forms can also be treated with Nystatin, either locally or systemically. If this is not rapidly successful, Amphotericin B should be employed parenterally.

Oral moniliasis was recorded in 11 patients, and in

three of these cases there was extensive spread. Most cases occurred in the course of severe attacks of colitis. Of the three patients with generalized moniliasis of the gastrointestinal tract, two recovered after treatment with the antifungal agent, Nystatin, while one patient died (see below).

Illustrative case history Mrs. E. C. was in good health until the age of 43 when she had a large bowel intussusception, which was treated with a permanent left iliac colostomy. She remained in good health until 1953, when, at the age of 53 she had her first attack of ulcerative colitis. During the following two years she had recurrent attacks of colitis, and was first seen at this hospital in 1955 when she was admitted in a moderately severe relapse. There was evidence of widespread colitis with maximal changes in the right half of the colon and the rectum. During this admission she received systemic corticosteroids in addition to general medical measures and was discharged after four weeks showing very little improvement. A few days later she developed an extremely sore throat and mouth, with marked pain on swallowing and severe anorexia; she continued to have six to eight actions of the colostomy daily, the material consisting mainly of blood and mucus, and she was readmitted 12 days after discharge. On examination the mouth and throat were affected with thrush, some oral ulceration was present, and there was right-sided abdominal distension and tenderness. Swabs from the mouth grew *Candida albicans* and *B. aerogenes*, while culture of the colostomy discharge yielded yeasts and *C. albicans*. She was unable to take food and oral drugs, and was given intravenous saline to correct salt depletion and blood transfusions; these were supplemented by parenteral vitamins and Ferrivenin. She received A.C.T.H. daily throughout this admission, but apart from gentian violet applications to the mouth did not receive any treatment for the moniliasis. Although the oral moniliasis appeared to improve during the last few weeks of her admission she still could not take nourishment by mouth. She discharged herself, against medical advice, seven weeks after she had been readmitted and died two weeks later at home.

Her general practitioner recorded that the moniliasis had continued and that she had died, in effect, from malnutrition secondary to this.

OSTEOPOROSIS Osteoporosis was diagnosed in nine cases. This must be regarded as an underestimate of its true frequency, which would only be determined by systematic studies. Among these nine patients, the majority (seven) were women; and six of the nine were over the age of 60 years when osteoporosis was diagnosed. There were only two patients under the age of 45 and it may be of significance that both of them had been treated with corticosteroids. Among the older patients, only two out of seven had previously received corticosteroid therapy.

In six cases, the osteoporosis was purely a radiological diagnosis and there were no gross clinical

effects; but in the remaining three, obvious clinical manifestations were present, namely, fracture-collapse of a lumbar vertebra, collapse of cervical vertebrae with neurological symptoms and signs, and generalized aches and pains.

DISORDERS OF THE BLOOD

We include under this heading both anaemia secondary to ulcerative colitis and other miscellaneous blood disorders.

ANAEMIA SECONDARY TO LOSS OF BLOOD Ulcerative colitis may produce, as one of its more frequent complications, an anaemia of very variable severity. Persistent or recurrent loss of blood from the bowel, which may be the chief feature of the diarrhoea, or which may be so mild as to escape attention, will in almost all cases lead eventually to an iron-deficiency anaemia unless corrective measures are taken. It is probable that a far greater proportion of patients with chronic ulcerative colitis are kept under medical supervision at the present time than was formerly the case and so the extremely low levels of haemoglobin that used to occur are nowadays rarely seen. However, a severe degree of anaemia often arises in a surprisingly short time during the course of an acute attack of colitis, even in the absence of any frank episode of severe bleeding from the bowel. Various predisposing factors may also be present, as complications of the primary disease, and contribute substantially to the development of anaemia. Blood may be lost from carcinoma of the colon or rectum, or from associated haemorrhoids; and, among more remote complications, chronic hepatic or renal lesions may be important contributory causes.

We have defined anaemia as a haemoglobin level of 60% (9.0 g.) or less, occurring at any time during the course of the illness. Even having adopted such a stringent definition, we have found that 127, or 20.4% of the whole series of 624 patients, fulfilled this criterion. Haemoglobin levels between 60% and 80% were so common as to be almost universal.

The majority of the patients with anaemia had a hypochromic anaemia with evidence of moderate or severe iron deficiency. In some cases, particularly those occurring after isolated severe attacks of colitis involving heavy bleeding, the anaemia was normochromic at first. Studies employing red blood cells tagged with radioactive chromium have revealed that there is frequently a substantial loss of blood in the faeces in ulcerative colitis even if the symptoms are mild and in some cases when the patient is entirely symptom-free (Beal, Skyring, McRae, and Firkin, 1961).

Table XXVI shows the distribution of patients

TABLE XXVI

DISTRIBUTION OF PATIENTS ACCORDING TO SEVERITY OF ANAEMIA SECONDARY TO LOSS OF BLOOD

Haemoglobin (%)	No. of Patients		
	M(251)	F(373)	Whole Series (624)
<20	1	—	1
20-29	1	3	4
30-39	3	9	12
40-49	12	13	25
50-60	25	60	85
Total with values of 60% and below	42 (16.7%)	85 (22.8%)	127 (20.4%)

classified according to the lowest haemoglobin level recorded at any time during their colitis. It can be seen that 42 patients (25 women and 17 men) had a severe degree of anaemia, with haemoglobin levels below 50%, while, of these, 12 women and five men had levels below 40%.

It is noteworthy that in 13 of these 17 patients the anaemia had arisen before 1946, and that severe anaemia has become unusual during the past decade in spite of the far greater number of patients seen.

It is also noteworthy that nine of these 17 cases of severe anaemia developed this state within the first year of the onset of the disease. Indeed the chance of developing anaemia, as we have defined it with a haemoglobin level of 60% or less, appears to be maximal in the first year of the illness and to become steadily less likely to arise, although this may reflect medical treatment more than the natural history of the disease (Table XXVII).

TABLE XXVII

NUMBER OF PATIENTS DEVELOPING ANAEMIA SECONDARY TO LOSS OF BLOOD IN RELATION TO THE LENGTH OF HISTORY OF ULCERATIVE COLITIS

Length of History of Ulcerative Colitis before Diagnosis of Anaemia (yr.)	No. of Patients Developing Anaemia
<1	34
1-	18
2-	10
3-	8
4-	6
5-9 (average annual number)	4
10-19 (average annual number)	2
20-29 (average annual number)	1

Severe anaemia due to blood loss demands blood transfusion. Less severe grades can be treated successfully with iron, which sometimes needs to be given parenterally because oral iron is liable to be irritating to the bowel in patients with ulcerative colitis. In the present series, the anaemic patients were almost all treated along these lines.

OTHER DISORDERS OF THE BLOOD The other disorders of the blood were as follows:—

Blood Disorder	No. of Cases
Heinz body anaemia	7
Idiopathic thrombocytopenic purpura	3
Non-thrombocytopenic purpura	1
Pernicious anaemia	3
Coagulation defect due to severe liver disease	1
Christmas disease	1
Acquired haemolytic anaemia (auto-immune type)	1
Anaemia associated with polyarteritis nodosa	1

Heinz body anaemia is a particular type of haemolytic anaemia brought about by the action of various drugs, of which sulphonamides are an example. In the present series, all the cases were due to the use of sulphasalazine (salicylazosulphapyridine), and the first account of Heinz body anaemia occurring as a complication of this form of therapy came from this hospital (Spriggs, Smith, Griffith, and Truelove, 1958). Any patient who develops anaemia while on treatment with sulphasalazine should have the blood specially examined for this, as the changes are not evident in a standard blood film preparation.

There were four cases of purpura, of which three were thrombocytopenic and did not appear to be related to the use of drugs. The fourth case was an example of non-thrombocytopenic purpura which was attributed to either penicillin or sulphonamides, as the patient was on treatment with both, and the condition subsided soon after these drugs were withdrawn.

The three cases of pernicious anaemia appear to be much above the rate to be expected among 624 patients, especially as this includes a considerable number of young persons. With such a small number of cases this might be due to a chance sampling effect, but there exists the possibility that the two diseases have some connexion, especially as the two conditions have been described in the same patient (Perillie and Nagler, 1959). It is also of interest that one of the patients with pernicious anaemia had previously suffered from thyrotoxicosis, because the association between thyroid disease and pernicious anaemia is now well-established and they have close immunological similarities (Taylor, Roitt, Doniach, Couchman, and Shapland, 1962; Doniach, Roitt, and Taylor, 1963).

There were two cases of coagulation defects. One was an example of severe prothrombin deficiency due to chronic liver disease. The second was a patient with Christmas disease, which must be regarded as unrelated to the ulcerative colitis. The blood condition had a major effect upon the course of the illness, because the patient had a severe first attack and suffered from massive bleeding from the bowel. Medical management proved ineffective and he was treated by emergency colectomy, but died two days later.

There was one patient with acquired haemolytic

anaemia of the auto-immune type, giving a positive Coombs test. She also suffered from multiple sclerosis.

Finally, one patient suffered from severe anaemia in association with polyarteritis nodosa. This disease can itself affect any part of the gastrointestinal tract, and may exceptionally give rise to a bloody diarrhoea and thus mimic ulcerative colitis. It is therefore important to record that the ulcerative colitis developed nine years before the onset of symptoms attributable to the polyarteritis nodosa. The colitis was in complete clinical remission but the patient had a carcinoma of the colon which was detected by the finding of a palpable mass on ordinary clinical examination. Presumably the carcinoma could have contributed to the severe anaemia even though there was no obvious blood in the stools.

In considering this group of miscellaneous blood disorders associated with ulcerative colitis, it is impossible to avoid being struck by the fact that immunological disturbances are known to occur in several of them, namely, in pernicious anaemia, idiopathic thrombocytopenic purpura, acquired haemolytic anaemia, and polyarteritis nodosa. This is of interest as there is evidence of abnormal immunological reactions in ulcerative colitis, both in regard to auto-immune reactions and to dietary antigens (Broberger and Perlmann, 1959; Taylor and Truelove, 1961).

ASSOCIATED DISEASES

We have noted the incidence of a number of diseases, some of which have been said to be associated with ulcerative colitis. The main examples were as follows:—

Pulmonary tuberculosis		15 (2.4%)
Diabetes mellitus		10 (1.6%)
Gastric ulcer		7 (1.1%)
Duodenal ulcer		16 (2.6%)
Cholecystitis and/or gall-stones		10 (1.6%)
Mental illnesses		35 (5.6%)
Allergic diseases (asthma, hay fever, eczema)		16 (2.6%)
Thyroid disease		15 (2.4%)
Carcinoma other than of the colon (stomach 4; biliary tract 3; oesophagus 1; pancreas 1; breast 5; lung 1; prostate 1)		16 (2.6%)

All these diseases are common and it is impossible for us to say that the observed numbers exceed those to be expected in a random sample of the general population, especially when followed over the course of a number of years.

However, it may be of significance that, as far as carcinoma other than of the colon is concerned, there were nine cases involving other parts of the digestive

system, which raises the possibility that a widespread disturbance of the digestive system is present in ulcerative colitis.

CROHN'S DISEASE

Fourteen of the patients suffered from Crohn's disease of the small intestine in addition to the ulcerative colitis. The relationship between the two diseases is a strong one, and it is even conceivable that they are brought about by the same aetiological mechanisms. As primary Crohn's disease of the large bowel has become increasingly recognized in recent years, it is important to record that we are not here describing such cases. The question of combined Crohn's disease of the small intestine and ulcerative colitis is so confused that it will be discussed in a separate article.

DISCUSSION

The local complications have been briefly discussed in the body of the text and will not receive further attention here.

The frequency with which complications remote from the colon occur in this disease affords scope for speculation. There are two main possibilities to account for their occurrence. First, ulcerative colitis may be a generalized disease in which the brunt falls on the colon but in which many other organs are affected, to a greater or lesser extent, as an integral part of the illness. Secondly, all these complications may be secondary to the diseased colon, provided we exclude those due to malnutrition, those which may arise in any illness (such as venous thrombosis and pulmonary embolism), and those due to the side-effects of drugs.

A number of writers have suggested the possibility that ulcerative colitis may be a generalized disease merely because arthritis, erythema nodosum, skin rashes, eye lesions, chronic hepatitis, aphthous ulceration, and ankylosing spondylitis are frequently found in association with the colitis. The possibility gains some support from the finding that it is not unusual for one or more of these 'complications' to precede, often by years, the onset of the colitis. For example, Acheson (1960) found an association between ulcerative colitis and ankylosing spondylitis, and records the fact that in 19 patients the symptoms of ankylosing spondylitis preceded the symptoms of colitis and in 12 patients the diagnosis of ankylosing spondylitis was firmly established before the onset of bowel symptoms. In our series, three patients suffered from ankylosing spondylitis before the onset of any colonic symptoms. Similarly, although chronic hepatitis is well recognized as a complication of ulcerative colitis, in a number of patients the ulcerative colitis appears to develop in the course of

fully established chronic liver disease; in our own series, these two patterns were equally common, there being eight patients in each group. This is interesting in relation to so-called 'lupoid' hepatitis, an active chronic hepatitis in which L.E. cells are frequently found in the blood and which is considered by some workers to be an auto-immune disease. The particular point of interest is that Mackay and Wood (1962) give the case histories of 22 such patients and it is striking that five of them suffered from ulcerative colitis and in at least one of these patients the liver condition was fully established before the onset of the ulcerative colitis. Furthermore, circulating antibodies to liver have been demonstrated in the sera of some patients with ulcerative colitis (Broberger and Perlmann, 1959; Broberger, 1961). Another point possibly in favour of ulcerative colitis being a generalized disease, at any rate in some patients, is the fact that some of the remote complications frequently occur in the same patient. The remote complications which are specially likely to occur in the same subject, either concurrently or consecutively, are arthritis, ankylosing spondylitis, erythema nodosum, certain skin eruptions, aphthous ulceration of the mouth, and eye lesions. In brief, in these subjects, the skin and a variety of mucous and synovial membranes appear to share a common liability to become inflamed.

If we examine the evidence critically, it is apparent that none of the foregoing is sufficiently strong to make us regard ulcerative colitis as a generalized disease in its very nature. The fact that some 'complications' precede the colonic symptoms, often by years, is at first sight an unassailable piece of evidence in favour of the generalized disease theory. However, the exact starting point of ulcerative colitis may be difficult to determine and it is established that the colon may be inflamed as judged by sigmoidoscopic appearances and by the histological picture of biopsy specimens even though the patient is in perfect clinical remission. For example, in a systematic sigmoidoscopic and colonic biopsy study of the disease, it was found that more than half of the patients in clinical remission had obvious colonic inflammation by both these criteria (Truelove and Richards, 1956). Of course this refers to patients already known to have had an attack of ulcerative colitis, but many of these subjects, on close questioning, give a history of minor bowel disturbances long before they develop the overt symptoms of the disease. There is therefore the possibility that the colon may be inflamed from time to time in patients for a number of years before they come under close medical examination, and the fact that arthritis, ankylosing spondylitis, etc., may precede the classical bowel symptoms does not mean that

they were not secondary to an inflamed colonic mucosa. The difficulty that may exist in determining the exact time of onset of ulcerative colitis can be illustrated by a case in our recent personal experience.

A young man aged 20 presented with a severe attack of ulcerative colitis involving the whole colon for which he has since been treated with radical surgery. This was judged to be his first attack of the disease until it was found that there had been diarrhoea in his early childhood, attributed to rectal polyps, which were removed. This had been done in our hospital and the pathological specimens were still preserved. They showed changes typical of pseudo-polyps in active ulcerative colitis.

We therefore judge that there is no indisputable evidence in support of the generalized disease hypothesis. If we consider the other main alternative, namely, that the remote complications are a consequence of the colitis, it is plain that we do not know the mechanisms by which such complications could be brought about. One possibility is that the remote complications are brought about by immunological processes; for example, the ulcerative colitis might set up auto-immune reactions which could affect a variety of organs or there might be serological reactions to the bacterial flora of the large bowel or to dietary antigens, perhaps because such antigens may be absorbed readily through a damaged colonic mucosa. These are speculative possibilities which deserve experimental study but for which at present there is no conclusive evidence. On clinical grounds, the point most in favour of the remote complications being secondary to the colitis is the fact that total colectomy usually prevents their occurrence or, if they are already present, exerts a favourable influence upon their clinical course. Isolated examples have been published of complications of ulcerative colitis developing after colectomy; for example, Margoles and Wenger (1961) have described the occurrence of pyoderma gangrenosum in a patient six months after colectomy. However, such occurrences appear to have been so infrequent among the patients treated by pan-proctocolectomy and permanent ileostomy that we do not judge them to be a serious obstacle to accepting the theory that the remote complications are secondary to the diseased colon.

It is impossible at present to judge this major issue and the main value of a study such as the present one is to focus attention on the importance of the problem and the need for it to be studied, especially by laboratory methods.

SUMMARY OF PART III

The complications of ulcerative colitis fall logically into two main groups: local complications in and

around the large bowel and remote or systemic complications affecting distant parts of the body.

The main local complications in the present series of 624 patients were: ischio-rectal abscess, fistula-in-ano, recto-vaginal fistula, rectal prolapse, fibrous stricture, pseudo-polypoid, perforation of the colon, acute dilatation of the colon, massive haemorrhage, and carcinoma of the colon.

Perforation of the colon is worth special mention. It occurred only in attacks which were clinically either severe or moderately severe and was specially likely to occur in the first attack of the disease. It carried a high fatality rate and was sometimes not diagnosed until after death. Its incidence showed no increase after the introduction of corticosteroid therapy.

The main systemic complications were: erythema nodosum, pyoderma gangrenosum, various skin rashes, arthritis, ankylosing spondylitis, various eye lesions, liver disease, renal disease, peripheral venous thrombosis, pulmonary embolism, anaemia and other blood disorders, aphthous ulceration of the mouth, moniliasis, and osteoporosis.

The two systemic complications which made the biggest contribution to the mortality of the disease were liver disease and pulmonary embolism.

The incidence of some diseases which have been considered to show an association with ulcerative colitis is examined and discussed.

The frequency with which certain systemic complications occur in ulcerative colitis has suggested to some writers that ulcerative colitis may be a generalized disease, especially as these 'complications' may precede all bowel symptoms. This concept is discussed.

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Part IV Carcinoma of the colon

Over the last 35 years numerous papers relating to the association between ulcerative colitis and carcinoma of the colon have appeared (Bargen, 1928; Bargen, Jackman, and Kerr, 1938; Sauer and Bargen, 1944; Cattell and Boehme, 1947; Kasich, Weingarten, and Brown, 1949; Svartz and Ernberg, 1949; Sauer and Bargen, 1949; Gleckler and Brown, 1950; Sloan, Bargen, and Baggenstoss, 1950; Lyons and Garlock, 1951; Brown, Kasich, and Weingarten, 1951; Counsell and Dukes, 1952;

Dennis and Karlson, 1952; Weckesser and Chinn, 1953; Bargen, Sauer, Sloan, and Gage, 1954; Bacon, Yang, Carroll, Cates, Villalba, and McGregor, 1956; Goldgraber, Humphreys, Kirsner, and Palmer, 1958a and b; Rosenqvist, Öhrling, Lagercrantz, and Edling, 1959; Dawson and Pryse-Davies, 1959; Slaney and Brooke, 1959; Lindner, King, and Bolt, 1960; Bargen and Gage, 1960; Edling and Eklöf, 1961; Bruce and Cole, 1962).

The publication of so many series of cases with a