Summary

During the last few years it has proved possible to recognize a group of patients with ulcerative colitis in whom removal of milk and protein-containing milk products from the diet has been followed by marked improvement in the clinical course of the illness. In five of these patients milk has been reintroduced into the diet, and on every occasion this has been followed in a few days or weeks by a frank attack of ulcerative colitis. One patient was tested twice on separate occasions, so that there were six such events in all.

From previous studies in which patients in clinical remission were being treated with "dummy" tablets, it is possible to arrive at an estimate of the risk of spontaneous relapse in a patient with ulcerative colitis. Taking an outside figure for this risk, it can be shown that it was very unlikely that the six relapses would have occurred by chance alone. In other words, there was almost certainly a causal connexion between the reintroduction of milk into the diet and the subsequent relapse.

There was a highly significant positive correlation between the time a patient was symptom-free while on a milk-free diet and the time taken to clinical relapse after reintroduction of milk into the diet. This finding is compatible with the notion of these relapses representing an immunological type of response to milk proteins, with the reactivity of the colonic mucosa varying according to the length of time since it was last exposed to the allergen.

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ULCERATIVE COLITIS

A FOLLOW-UP INVESTIGATION WITH MUCOSAL BIOPSY STUDIES

BY

A. P. DICK, M.D., F.R.C.P.

AND

M. J. GRAYSON,* M.B., M.R.C.P.

Addenbrooke's Hospital, Cambridge

The object of this study has been to follow up an unselected series of cases of ulcerative colitis, including proctosigmoiditis, after an interval of 5 to 10 years, with particular reference to the presence of mucosal histological abnormalities in relation to the clinical state of the patient. It seemed of especial interest to find out what proportion of patients, apparently recovered, showed persistent abnormalities in the mucosa. It was also felt that the follow-up results of an unselected series would be of value. Of the many large reported series of ulcerative colitis, in some instances followed up for long periods, the majority come from a special centre (Sloan, Bagen, and Gage, 1950) or hospital dealing with diseases of this type (Cullinan and

MacDougall, 1957), which would tend to draw the more severe cases or, alternatively, is concerned with in-patients only, such as the series of Rice-Oxley and Truelove (1950). Cases of proctitis and proctosigmoiditis have been included because there does not appear to be any fundamental distinction between such cases and those with more extensive involvement of the bowel.

The cases in our series were all referred to a provincial hospital centre, serving a mixed rural and urban population, and which was, for part of the area, the only hospital available. Some of the cases were seen initially at smaller local hospitals.

The series consisted of 94 patients, first seen by one of us (A.P.D.) between 10 and 5 years ago (April, 1949, to September, 1954).

Type of Case

The types of case comprising the series are summarized in Table I. The cases were classified according to the extent of disease into three groups—namely, proctosigmoiditis, left-sided colitis, and total colitis—and into three grades of severity—mild, moderate, and severe. There were no cases of right-sided or segmental colitis, although some may have started in this way before they were seen. Two cases in which typical total ulcerative colitis was associated with regional ileitis (Crohn's disease), proved by laparotomy and histological section, were seen for the first time during the same period as the cases under review. Whether regional ileitis represents a different type of tissue reaction to a similar mucosal disturbance or whether it is in fact an entirely different disease—a problem discussed by Lumb (1951) and Crook (1957)—is uncertain, but to avoid controversy these two cases have been excluded.

TABLE I.—Type of Case

	Total No. of Cases		Mild		Moderate		Severe	
	M	F	M	F	M	F	M	F
Proctosigmoiditis	9	36	6	21	3	14	—	1
Left-sided colitis	7	14	2	4	3	9	2	1
Total colitis	8	20	1	1	1	3	6	16

The extent of the disease was determined mainly by barium-enema examination. Cases were classified as "left-sided" when there were no changes in the barium enema proximal to the splenic flexure, although some of these may have had more extensive mucosal abnormalities. Cases where more than the left side of the colon was involved were classified as "total," although in some the whole colon was probably not involved. In cases of "proctosigmoiditis," in which group are included those with proctitis only, radiological abnormality was either absent or limited to the sigmoid region. In some of these patients, in whom there was no doubt on sigmoidoscopic grounds that the disease was confined to the rectum, a barium enema was not performed.

It appeared that some of the cases of total and left-sided colitis had begun as proctitis, and in a few, seen early in the disease, sigmoidoscopic and radiological evidence of this retrograde progression was available. A history of rectal bleeding, without diarrhoea, usually implies that the disease is confined to the rectum; and, indeed, of our 36 female cases of proctosigmoiditis, nine had no diarrhoea at any stage and in every instance the disease was confined to the rectum. Of the 28 patients

*Now at St. George's Hospital, London.

with total colitis, three gave a history of rectal bleeding for about six months before diarrhoea developed. Of the 21 patients with left-sided colitis, seven gave a history of initial bleeding, varying in duration from a few weeks to 15 years before the onset of diarrhoea. It appears reasonable to assume that these 10 cases of colitis had begun as proctitis, and, if they are added to the 45 patients with proctosigmoiditis, then 10 out of 55 cases of proctosigmoiditis eventually developed left-sided or total colitis.

Cases were classified as mild, moderate, or severe, according to their condition at its worst. They were regarded as mild when there was no constitutional upset and the symptoms were insufficient to interfere appreciably with the patient's mode of life; moderate when there was fairly severe diarrhoea or bleeding with some degree of constitutional disturbance and ill-health; and severe when there was considerable constitutional disturbance, severe diarrhoea, and at some stage the patient was seriously ill.

Age at Onset and Clinical Course

The age at onset of the cases is shown in Table II. It should be mentioned that few patients under 14 years attend the clinics to which the patients in this series were referred. The youngest patient, at onset, was a boy of 14 years with proctosigmoiditis, and the oldest at onset a woman aged 63, also with proctosigmoiditis.

TABLE II.—Age at Onset

		<21	21–	26–	31–	36–	41–	45–	51–	56–	61–
Procto-sigmoiditis	M	3	1	3	—	—	—	—	2	—	—
	F	2	4	7	5	2	6	4	3	—	3
Left-sided colitis	M	—	1	—	3	—	1	1	—	1	—
	F	1	2	2	2	2	2	1	—	1	1
Total colitis	M	1	2	2	—	—	1	2	—	—	—
	F	5	5	2	5	1	1	—	—	1	—
Total	..	12	15	16	15	5	11	8	5	3	4

The clinical course run by these cases is given in Table III. The way in which ulcerative colitis behaves is so variable that it is impossible to make any simple and yet comprehensive classification. The cases have therefore been grouped into those in which there was one attack, relapsing cases where the duration of the relapse has not exceeded six months, relapsing cases becoming chronic, and cases which had been chronic from the start. This classification has been made entirely on the presence or absence of symptoms without regard to other findings. Cases have arbitrarily been called chronic when symptoms had persisted without relief for more than six months, although many such patients were in clinical remission at the time of follow-up.

TABLE III.—Clinical Course

	One Attack		Relapsing		Relapsing Becoming Chronic		Chronic from Onset	
	M	F	M	F	M	F	M	F
Proctosigmoiditis	—	3	6	22	—	2	3	9
Left-sided colitis	1	—	5	10	—	1	1	3
Total colitis	2	2	2	9	1	6	3	3

Treatment

During the period when the cases were first seen substantial changes took place in the methods of treatment available. Routine supportive measures with suitable diet, mucilages such as "iso-gel," constipating

agents, and antispasmodics were used, and in the more severe cases blood transfusion and correction of electrolyte imbalance as necessary. Twenty-three patients had one or more courses of treatment with A.C.T.H., the earlier cases having been reported elsewhere (Dick and Beckett, 1954). Five patients received oral cortisone or prednisone at some stage, but in no case was long-term treatment with oral corticosteroids used. The results of A.C.T.H. therapy were similar to those in most reported series (Kirsner and Palmer, 1951; Truelove and Witts, 1959) and to those obtained with cortisone (Truelove and Witts, 1954, 1955). Hydrocortisone retention enemas (Truelove, 1956, 1957) were used in 21 cases, 7 of which also had systemic steroid therapy. In 66 cases admission to hospital was required at some stage.

In the management of these cases a common-sense supportive psychological approach was used, with the discussion of any difficulties or anxieties to which the patient would admit. A few patients in whom the emotional disturbance was obviously severe were referred for expert psychiatric advice. Four were treated with electroplexy. In two patients, who showed definite depressive features, a remission followed the treatment, being dramatic in one. Two other patients of hysterical personality received this treatment on the grounds that there might be a depressive element in their emotional disturbance, but neither showed any response.

Nine patients had an ileostomy and total colectomy. One patient died in the post-operative period, his condition before operation having been extremely poor. This occurred in the early days of steroid therapy, and pre-operative treatment would now be regarded as inadequate. The remaining eight patients have done well and are leading normal lives. Five of these operations were carried out for severe chronic disease which could not be controlled by medical means. In three instances the operation was carried out for fulminating attacks, which could not be controlled by steroids, and in one of them perforation had occurred.

Mortality

Four patients died from severe or fulminating ulcerative colitis, including one mentioned above who had an ileostomy and colectomy. These deaths all occurred in 1952 or earlier, and it is felt that three of these patients might have survived with modern management.

A man aged 27 with an eight-years history of colitis which involved the whole colon, died from a carcinoma of that organ. This has been discovered a year before his death and a colectomy was performed, but he died from secondary deposits. Thus, including this case, five patients died of ulcerative colitis, making a mortality due to the disease of 5.3% of the 94 cases.

Five patients died from other causes: one each from carcinoma of the pancreas, carcinoma of the hepatic duct, cerebral thrombosis, heart failure of unknown origin, and diverticulitis with pericolic abscess.

Present Investigation

Excluding the 10 patients who had died, and eight who were alive and well after surgical treatment, the remaining 76, if not already attending the clinic, were asked to do so for review. Sixty-five attended; in 10, information was obtained by letter from the patient or

his doctor, and in only one case was there a complete failure of follow-up.

A clinical assessment was carried out on the 65 patients and a sigmoidoscopy performed in all but three. A mucosal biopsy was taken from the area of the rectosigmoid junction under direct vision with a special biopsy instrument passed through a sigmoidoscope. The instrument used is based on the principle of Wood's flexible gastric biopsy tube (Wood, Doig, Motteram, and Hughes, 1949), but has a rigid tube—following the example of Truelove, Horler, and Richards (1955)—and was made for us by the Genito-Urinary Manufacturing Company. A knuckle of mucosa is sucked into a hole of 3.5 mm. diameter on the side of the head of the tube. Suction is applied at a pressure of between 5 and 10 cm. of water, measured on a gauge connected to the rubber tubing between the instrument and a 20-ml. syringe. Inside the head of the instrument is a cylindrical blade, which is drawn downwards, cleanly cutting off the indrawn knuckle of mucosa.

A barium enema was not performed as part of the follow-up examination as it was not justifiable in patients who were well or had minimal symptoms, because of the discomfort involved, the risk of causing an exacerbation, and the possible radiation hazard, most of the patients having had one or more such examinations in the past.

State at Follow-up

Of the 94 patients, 55 (58%) were free of symptoms at the time of follow-up. Many of them, however, had been free of symptoms for only a short period and might be expected to relapse again. A further 8 (8.5%) were in good health, having had an ileostomy and colectomy.

TABLE IV.—*State at Follow-up. Cases Where Information was Obtained Only by Letter from Patient or Doctor are Shown in Parentheses*

	Symptom-free for			Symptoms		Colectomy (Alive)	Death From			Failed Follow-up
	2 Years and Over	Between 24 and 6 Months	6 Months or Less	Mild	Moderate		Colitis	Carcinoma Coli	Other Causes	
Proctosigmoiditis	7 (+3)	11 (+2)	9	5 (+1)	3	1	—	—	3	—
Left-sided colitis	4 (+2)	2	5 (+1)	4	1	—	—	—	1	1
Total colitis	4 (+1)	—	4	3	3	7	4	1	1	—
Total	15 (+6)	13 (+2)	18 (+1)	12 (+1)	7	8	4	1	5	1

It was difficult to assess the outcome in relation to the severity of the disease at its worst, because so many of the severe cases have been treated by colectomy. Except in the few patients who have had one relatively brief attack of the disease, it was also difficult to relate the total duration of active disease with the subsequent outcome. Symptomatology does not always mirror the state of the mucosa, particularly in the recovering phase of the disease. For this reason it is usually impracticable to ascribe a definite duration of active disease to any given case.

There did not appear to be any difference between the sexes as regards the outcome at the time of follow-up, with the exception of cases of proctosigmoiditis. All the nine male patients with this form of the disease were in clinical remission, whereas 9 of the 36 female patients were still having symptoms.

Half of the patients who were symptom-free were still keeping to some sort of low-residue diet or taking a mucilage, or both—in some instances for many years since they last had symptoms. Some patients had found that a departure from their diet resulted in a return of symptoms, but in many it was merely due to a fear of departing from a regime on which they had become symptom-free.

Sigmoidoscopic Appearances

Of the 65 patients who were interviewed, sigmoidoscopy was carried out in 62. The examination was impossible in one patient on account of an anal stricture which was thought to be due to complete perineal tear at previous childbirth and not to colitis. In one case the examination was not carried out on account of pregnancy, and in a third it was declined.

The findings on sigmoidoscopy in relation to the presence of symptoms or to the duration of freedom from symptoms are shown for the different types of disease in the accompanying diagram. None of the

Relationship of clinical state to sigmoidoscopic appearances.

patients at the time of follow-up had a severely inflamed mucosa, and the appearances have been classified into normal and three categories of abnormality. When the mucosa was granular, with the absence of visible vessels, but either of a normal colour or very slightly redder than normal, the appearance has been called "quiescent." In the presence of granularity with definite reddening and some degree of friability, but without ulceration or an obviously juicy oedematous appearance, it was labelled "slightly active." The mucosa was called "moderately active" when it showed a frankly oedematous appearance with more marked friability and reddening, sometimes with occasional superficial ulcers. In only two cases were a few small pseudopolyps seen in the rectum and lower sigmoid, but we have taken the mucosal appearance itself as the guide in this classification of activity.

The point of interest which emerges from the diagram is the large number of patients who showed an abnormal although quiescent appearance of the mucosa and who had been free of symptoms for long periods, in one instance for seven years. It is appreciated that the sigmoidoscopic appearance of the rectum and lower sigmoid may not reflect what is happening higher in the colon, but all of these patients previously had involvement in this region. The patient with moderate symptoms and a "quiescent" appearance of the

mucosa is a highly nervous subject whose symptoms have always been out of proportion to the severity of her disease.

Colonic Mucosal Biopsy

A biopsy was obtained from the region of the rectosigmoid junction with the instrument described above. The size of the specimen varied from 0.3 by 0.2 by 0.2 cm. to 0.1 by 0.1 by 0.1 cm. This seemed to depend to some extent on the normality or otherwise of the mucosa. A larger amount of normal mucosa than of oedematous and more rigid mucosa tended to be drawn into the hole in the instrument. As a general rule bleeding from the biopsy site was either absent or negligible, but in one patient bleeding was troublesome and necessitated admission to hospital for observation. Out of a total of approximately 300 biopsies done with this instrument for other purposes, there have been only two cases of appreciable bleeding, one of which necessitated transfusion.

The specimen obtained was satisfactory for histological examination in all but the three instances discussed later. There is no reason to suppose that this method of taking the specimen produces any appreciable distortion of the histological appearance or that the histology of the specimens differs from that of those taken with biopsy forceps, as in the study of Lumb and Protheroe (1955).

We have not carried out a series of mucosal biopsies on normal controls, but in 10 cases of nervous diarrhoea or "mucous colitis" a biopsy taken with this instrument has shown histological appearances which were normal in all respects.

The three points which have been taken as criteria of abnormality in the mucosa are, firstly, abnormalities of glandular pattern; secondly, the presence of an excess of chronic inflammatory cells; and, thirdly, the presence of neutrophil polymorphonuclear leucocytes. We have not considered oedema of the lamina propria, evidence of hyperaemia, or the presence of micro-abscesses, except in so far as the latter are included under the finding of polymorphonuclear leucocytes. It has not been possible to comment on changes deep to the

mucosa, as more than a small amount of submucosa is only rarely present in the specimen.

The glandular changes found included a widening, irregularity, forking, or clubbing of the glands, which may appear sparse in number. A few plasma cells, lymphocytes, and monocytes are always present in the mucosa, but an excess was noted. The presence of more than a very occasional neutrophil polymorphonuclear leucocyte around the glands was taken as being abnormal.

The presence of histological abnormalities in relation to the sigmoidoscopic signs, and the presence or absence of symptoms, is shown in Table V. In three instances the biopsy specimens were inadequate in size for an assessment of the glandular pattern to be made. All three were obviously abnormal in showing a large excess of chronic inflammatory cells.

Of the 62 cases, 14 (23%) showed a normal histological appearance of the mucosa and 48 (77%) an abnormal. In those with symptoms, 18 biopsies were abnormal and one was normal. The discrepancy in this latter case, where the patient had proctosigmoiditis with definite symptoms, may have been due to the fact that the changes were much more marked in the lowermost 2 to 3 in. (5 to 7.5 cm.) of the rectum than they were at the site from which the biopsy was taken at the rectosigmoid junction, although the mucosa did look abnormal at this site.

Of the patients who had been free of symptoms for six months or less, 14 out of 17 (82%) still showed an abnormal mucosal histology, whereas in those who had had no symptoms for more than six months, 16 of the 26 (62%) had persistent histological change. Of six who had been free of symptoms for four or more years, three had an abnormal and three a normal mucosa.

During the period of up to 6 months from the last symptoms a high proportion of cases have an abnormal mucosa. After this period there does not, on the figures available, seem to be any correlation between the duration of freedom from symptoms and the disappearance of mucosal histological abnormality. Apart from the time interval, the other two possible factors to which the persistence of histological change may be related are the actual duration for which the patient had active disease and its severity.

The difficulty of assessing accurately the duration of active disease has already been mentioned. So far, however, as this has been possible, there did not appear to be any correlation between the time for which the disease had been active and the persistence of mucosal abnormality after an interval of freedom from symptoms of six months. The exception to this was that two patients who had had only one attack lasting about three months in each instance had made a complete histological recovery. In the remaining eight of the ten patients who had a normal mucosa the duration of active disease was not significantly different from that in 16 patients in whom histological abnormality had persisted, after freedom from symptoms for six months.

On the other hand, among patients in whom the mucosa had remained abnormal there was a high proportion who had had severe or moderate disease. Of the 10 cases with a normal mucosa seven were classified as mild; eight of the 10 had proctosigmoiditis, and each of the remaining two had had only one attack of colitis. Of the cases with persistent histological change, nine had been classified as moderate or severe and seven as

TABLE V.—*Relationship of Clinical State, Sigmoidoscopic Appearances, and Histological Findings*

Clinical State	Sigmoidoscopy	Histology	Abnormal Glandular Pattern	Excess of Chronic Inflammatory Cells	Presence of Polymorphs
With symptoms	Normal 0				
	Ab-normal 19	Normal 1 Ab-normal 18*	0 15	0 15	0 9
No symptoms for 6 months or less	Normal 4	Normal 3 Ab-normal 1	0 1	0 0	0 0
	Ab-normal 13	Normal 0 Ab-normal 13†	0 12	0 9	0 3
No symptoms for 6 months to 2 years	Normal 7	Normal 3 Ab-normal 4	0 4	0 3	0 1
	Ab-normal 5	Normal 2 Ab-normal 3	0 2	0 2	0 1
No symptoms for over 2 years	Normal 8	Normal 4 Ab-normal 4	0 4	0 3	0 1
	Ab-normal 6	Normal 1 Ab-normal 5	0 4	0 3	0 2

* Two of these specimens were inadequate for assessment of glandular pattern.

† One of these specimens was inadequate for assessment of glandular pattern.

mild. In this group of 16 patients, 11 had proctosigmoiditis, including the 7 mild cases.

We cannot say whether any of the cases with a normal mucosa would have been found to show abnormality had more specimens been taken, and, particularly in cases of recovered proctosigmoiditis, whether some abnormality might have been shown had a specimen been taken from lower down, where perhaps the disease had been more severe. It may be that more patients symptom-free after this disease have a persistently abnormal mucosa than would appear from our figures.

With three exceptions the glandular pattern was abnormal where there was any other abnormality in the biopsy specimen, excluding from consideration the biopsies where the specimen was of insufficient size for us to estimate this feature. In 12 patients an abnormal glandular pattern was the only deviation from normal in the biopsy specimen. An abnormal glandular pattern may be the only change that persists, and in a third of those patients who had been free of symptoms for more than two years, but whose mucosae were still abnormal, this was in fact the only change.

Correlation of Sigmoidoscopic and Histological Appearances

The relation between the sigmoidoscopic appearances and the mucosal biopsy changes are shown in Table VI. The fact that in some instances the histology of the mucosa is abnormal when the sigmoidoscopic appearances are normal is of considerable interest, but not surprising. Conversely, however, the presence of an abnormal-looking mucosa with normal histology is more difficult to understand. The mucosa of one patient described as "slightly active" on sigmoidoscopy in which histology proved to be normal has already been mentioned, and it is thought that the specimen may have been taken above an undoubtedly active proctitis. The three patients whose mucosa was thought to be abnormal but quiescent on sigmoidoscopy, and in whom the histology was normal, showed slight but definite changes identical with those in many others in whom the histology was abnormal. The reason for this discrepancy between the sigmoidoscopic and the histological findings in these three cases is not clear, and is discussed later.

TABLE VI.—*Correlation of Histological and Sigmoidoscopic Appearances*

Sigmoidoscopic Appearances	No.	Histological Appearances			
		Normal	Abnormal Glandular Pattern Alone	Chronic Inflammatory Cells Present	Acute and Chronic Inflammatory Cells Present
Normal ..	19	10	3	4	2
Quiescent ..	26	3	9	9	5
Slightly active	9	1	0	2	6
Moderately active ..	8	0	1	3	4
Total ..	62	14	13	18	17

Three abnormal specimens were insufficient in size to assess the glandular pattern. In the remaining abnormal biopsies an abnormal glandular pattern was present, with the exception of three other specimens where the presence of inflammatory cells was the only abnormality.

Discussion

Any comparison of the outcome in different reported series of cases of ulcerative colitis is made difficult, if not impossible, by the fact that the duration, severity, and type of case are often not described in detail. It seems probable that our series includes a greater proportion of milder cases than most other reported series.

Rice-Oxley and Truelove (1950) make the point that the highest mortality occurs in the first attack. It follows, therefore, that the more cases in a series which are first seen after their first attack, the better is the overall outcome likely to be. In our series, 25 patients were seen during the period of six months after the first onset of symptoms and a further 22 when symptoms had been present for between 6 and 18 months. The remaining 47 had their first symptoms at any time from 18 months to 25 years before they were seen by us. Viewed from this aspect also, it would seem likely that our series includes a higher proportion of milder cases. However, this survey is not intended to assess the prognosis in ulcerative colitis, as its main interest lies in the persistence of colonic mucosal abnormalities in the presence of clinical recovery.

Slaney and Brooke (1959) reviewed the literature and reported their own experience of the incidence of carcinoma of the colon in association with ulcerative colitis. It is perhaps surprising that only one case of carcinoma, that of a 26-year-old man with an eight-year history of total colitis, has been found in our series, which includes many patients with a long history. There were 33 patients in whom the duration of disease at the time of follow-up was over 10 years, and 15 of these had total colitis. Of these 15 patients three had had the condition for over 30 years, one for over 20 years, four for between 15 and 20 years, and seven for 10 to 15 years.

Colonic mucosal biopsy with the instrument described has proved a satisfactory method of obtaining a specimen adequate for histological study in practically all instances. The appearance of an excessive number of chronic inflammatory cells, and of more than occasional polymorphonuclear leucocytes, are obvious abnormalities about which there are rarely difficulties in interpretation. The assessment of an abnormal glandular pattern is, however, occasionally more difficult. The glands may show widening, irregularity, forking, and clubbing, and they frequently appear to be sparser than normal. A study of glandular size has been made by Dr. G. K. S. Roberts (personal communication) mainly on our material, and is to be published shortly. It seems that there is almost always an increase in the external diameter, and in the diameter of the lumen, of the glands in cases of ulcerative colitis, both in an active and in a quiescent phase.

The significance of this disturbance of glandular pattern and size is not known. Where there has been more severe disease with extensive shedding of the mucosa, with inflammation and subsequent fibrosis of the submucosa, a thin regenerated layer of mucous membrane with very sparse "stumpy" glands may be seen. This appearance is very different from the abnormal glandular pattern, discussed above, seen in the milder case, in which it is thought that only superficial ulceration of the mucosa has occurred. Why the glandular pattern assumes this abnormal form is not clear, but it was the most constant change in our cases. Whether it is the result of superficial ulceration and inflammation, or whether it represents some special reaction peculiar to this disease, is not known.

In patients with symptoms there was good correlation between sigmoidoscopic and histological findings; only one patient, discussed earlier, whose mucosa was sigmoidoscopically abnormal had normal histological appearances. Half of the patients with symptoms

showed active inflammation, as indicated by the presence of polymorphs in the mucosa.

In patients who had been without symptoms for six or less months, the great majority, 14 out of 17, had an abnormal mucosa histologically, and in 13 of these it also appeared abnormal on sigmoidoscopy. However, the patients without symptoms for more than six months were different. About one-half showed a normal appearance by sigmoidoscopy and the other half abnormal, but of the 15 cases whose appearances were normal eight had an abnormal mucosa microscopically. This finding emphasizes the value of histological examination in ascertaining whether the mucosa has returned to normal, and indicates the value, on occasion, of mucosal biopsy in retrospective diagnosis.

Conversely, the finding of normal mucosal histology in patients who were judged to be sigmoidoscopically abnormal was surprising. The three possible explanations of this anomaly are erroneous interpretation of sigmoidoscopic appearances, unrepresentative biopsy specimens, and the possibility that some of the macroscopic changes regarded as being indicative of mild quiescent colitis might have been the result of disturbances which were not microscopically apparent. The reddening of the mucosa and the disappearance of the normally visible larger vessels are due to hyperaemia and oedema, both of which may be difficult to interpret on a small specimen, and neither change is considered in our criteria of histological abnormality. The cause of mucosal granularity, the most characteristic change of all, remains obscure.

In patients who have symptoms the mucosa is nearly always histologically abnormal, and during the six months after the cessation of symptoms a high proportion of cases still have an abnormal mucosa. After this period, about half the patients still show histological abnormality. There was no difference between the proportion of cases with an abnormal mucosa among those free of symptoms from six months to two years compared with those who had been free for over two years. With the passage of time after the first six months, we suspect that there is no increase in the proportion of cases in which the mucosa reverts to normal. Our figures suggest this, but the numbers are too small to draw any significant conclusion.

Summary

A series of 94 unselected cases of ulcerative colitis have been followed up after a period of 5 to 10 years.

Five patients had died either directly or indirectly from the disease, and five from other causes. Eight patients still under observation were alive and well but had been treated by ileostomy and colectomy.

Of the remaining patients, who had been treated medically, 55 were free of symptoms, 19 were having symptoms, and one could not be traced.

Sigmoidoscopy and colonic mucosal biopsy were carried out in 62 patients. In patients with symptoms, sigmoidoscopy was always abnormal and the histology almost always so. In those free of symptoms for six or less months, a high proportion had an abnormal mucosa, on both naked-eye and microscopical examination. Less than half the patients who had been symptom-free for over six months showed an abnormal sigmoidoscopic appearance, but a greater proportion had histological abnormality. Of 19 symptom-free

patients in whom sigmoidoscopy was normal nine had an abnormal mucosa microscopically.

Apart from the grossly disorganized glandular pattern found in the regenerated mucosa of severe cases, an abnormal glandular pattern is frequently seen in milder cases of ulcerative colitis and may be the only abnormality which persists.

Histological abnormality may persist, with or without an abnormal sigmoidoscopic appearance, for many years, perhaps indefinitely, in patients who have apparently recovered from ulcerative colitis.

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INTRARECTAL TREATMENT OF 100 CASES OF ULCERATIVE COLITIS WITH PREDNISOLONE-21-PHOSPHATE ENEMATA

BY

S. G. FLAVELL MATTS, M.B., Ch.B., M.R.C.P.Ed.
Senior Medical Registrar, The Royal Hospital,
Wolverhampton

Ulcerative colitis is a disease for which many and varied treatments have been tried. Intrarectal injections as an aid to therapy were first suggested by Hurst (1921), but met with little success at that time. A slow-drip method of giving these solutions was first mentioned by Martin (1925), but his variation of intrarectal treatment was equally unsuccessful. It was not until the work of Truelove (1956, 1957) and Watkinson (1958) that the slow-drip method of intrarectal therapy was really shown to be effective. The active agent that Truelove infused was a solution of freshly prepared hydrocortisone hemisuccinate, and this method was found to be valuable. However, its rather complicated nature appeared to delay its general adoption into the treatment of the disease, especially in out-patients (Lennard-Jones *et al.*, 1960).

Recently a more simple method of giving intrarectal therapy has been described (Matts, 1960a, 1960b). The active agent here infused was a solution of prednisolone-21-phosphate. As the results of using this appeared encouraging, further work on the subject was justified.