A clinico-immunological study of ulcerative colitis and ulcerative proctitis

ANNE HARDY SMITH AND IAN W. MACPHEE

From the Department of Surgery, University of Liverpool

SUMMARY Fifteen patients with ulcerative colitis and 11 patients with ulcerative proctitis have been observed and studied for periods ranging from one to 15 years. It is suggested that the clinical course of the two disorders is quite distinct. Further, while the serum immunoglobulins were within normal limits in ulcerative proctitis, significant increases in the serum α_2 -, β -, and γ -globulins and in the IgA and IgG concentrations were found in ulcerative colitis. Despite total colectomy for ulcerative colitis, the serum IgG and IgA concentration remained high and even after subsequent rectal resection the relative IgA concentration continued to increase. The significance of these findings is discussed.

Bloody diarrhoea without systemic disturbance and with mucosal changes confined to the rectum may not progress to frank ulcerative colitis. Haemorrhagic or ulcerative proctitis can, we believe, be differentiated from ulcerative colitis, even in its milder forms, on clinical and serological grounds. Autoimmune factors may be involved in the aetiology of ulcerative colitis but the results from tests *in vitro* for serum antibodies against alimentary antigens have been inconclusive (Polcak and Vokurka, 1960; Edgar, 1961; Gray, Walker, and Thompson, 1961; Henriksen, Gundersen, and Opsal, 1962; Soergel and Ingelfinger, 1964; Broberger, 1964; Harrison, 1965; Lagercrantz, Hammarstrom, Perlmann, and Gustafsson, 1966; Wright and Truelove, 1966; McGiven, Ghose, and Nairn, 1967).

The serum proteins and immunoglobulins were investigated in patients suffering from ulcerative colitis and ulcerative proctitis, and the clinical course of each of these conditions has been compared and contrasted.

Clinical Description and Methods

Fifteen patients with ulcerative colitis and 11 patients with ulcerative proctitis were studied.

ULCERATIVE COLITIS

The diagnosis of ulcerative colitis was made from the typical history, radiological examination by

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barium enema, sigmoidoscopy, and biopsy. The average age of the patients at the beginning of the study was 35 years (range 17 to 64) and the ratio of males to females was 6 to 9. The samples from patients with ulcerative colitis were subdivided into three groups (Table I).

Four patients whose symptoms were not thought severe enough to warrant surgery were placed in group A. They were treated at various times with salazopyrine and also with corticosteroids.

In three patients the immunoglobulins were studied just before total colectomy, in two just before and within a few weeks of operation, and in one patient three weeks after total colectomy (group B). Two of these patients were also studied after resection of the rectum, an operation carried out after resection of the colon.

A further five patients, all of whom had had total colonic resection carried out some years before, were studied from 16 months to 12 years after a subsequent resection of the rectum (group C). We can therefore assume that all active disease in the rectum and the colon had been removed in this group.

ULCERATIVE PROCTITIS

The diagnosis of ulcerative proctitis was based on normal barium enema appearances and the presence of multiple small superficial ulcers in the rectum, or on the basis of hyperaemia, a friable rectal mucosa which bled readily on examination,

Group	No. of Patients	Drug Therapy	Time of Investigation in Relation to Surgery	Comments
A	4	Salazopyrine and cortical steroids	No surgery	
B	6	Salazopyrine and cortical steroids	(a) Before colectomy (3 patients) (b) Before and within a few weeks of total colectomy (2) (c) Three weeks after total colectomy (1) Two patients were also studied after rectal resection.	Not responding to medical treatment and therefore more severe than group A
C	5	None	Sixteen months to 12 years after rectal resection following total colectomy	All active disease in the colon and rectum removed.

Table I Subdivision of the patients with ulcerative colitis

and the presence of excess mucus. The sigmoidoscopic appearances were progressively less severe at the upper end of the rectum. In all patients a biopsy of the rectal mucosa was taken and the subsequent report usually described hyperaemia and inflammatory changes in the mucosa and submucosa. The average age of the patients was 39 years (range 18 to 66) and the ratio of males to females was 6 to 5. Most of these patients were treated intermittently with salazopyrine.

SERUM PROTEINS AND IMMUNOGLOBULIN STUDIES

Serum samples were collected from each of the 15 patients with ulcerative colitis and the current group of 11 patients with ulcerative proctitis. The total protein was measured by the copper sulphate specific gravity method (Phillips, van Slyke, Dole, Emerson, Hamilton, and Archibald, 1943). Serum proteins were determined by cellulose acetate electrophoresis (Kohn and Feinberg, 1965). The concentrations of the serum immunoglobulins—IgA, IgM, and IgG—were measured using Hyland Immunoplates.

Tissue antigens were prepared from samples of human large and small intestine removed at sigmoidoscopy, colectomy, or at necropsy, and from fresh rat large and small intestine. Samples of rectal or colonic mucosa were obtained from five of the patients with ulcerative colitis and five of the patients with ulcerative proctitis. The human tissue samples were sometimes stored at -15°C before extraction. The initial extraction procedure was a modification of the methods used by Gajdusek (1958) and Webster (1965) using normal saline. The tissue residue was then re-extracted with Analar phenol at 65°C by the method of Westphall, Luderitz, and Bister as used by Broberger and Perlmann (1959). The electroimmunoprecipitation test was carried out as described by Webster (1965). Immunoelectrophoresis was carried out using the transfer method described by Kohn (1957, 1960, and 1966).

Results

CLINICAL STUDIES

Ulcerative colitis

In seven patients, the rectum was resected up to 12 years after total colectomy. In most a recrudescence of disease in the rectum occurred, as judged by the periodic discharge of blood and mucus from the rectum. Proctoscopy at the time revealed that the mucosa of the rectum was friable, bled easily, and occasionally ulcers were observed. In one patient in particular (no. 38) these bouts occurred in association with recurrence of iridocyclitis, skin rashes, joint pains, and swelling of the hands and feet, increased pain from ankylosing spondylitis, and activity of a duodenal ulcer. It is interesting to note that in the two years since resection of the rectum he still complains from time to time of these associated manifestations.

Ulcerative proctitis

With or without treatment by salazopyrine, complete resolution of the condition took place in the 11 patients in this series. In the patients receiving salazopyrine, blood and mucus disappeared from the stool while the rectal mucosa remained friable and readily bled on sigmoidoscopy.

In every case, the appearance of the rectum to 20 cm and beyond became normal and there has been no subsequent relapse up to a maximum of 14 years in the present series.

SERUM PROTEIN AND IMMUNOGLOBULIN STUDIES

The experimental results are shown in Tables II and III. The patients with ulcerative colitis and ulcerative proctitis had similar age distributions, and the difference in their results cannot be attributed to a difference in the age of the patients.

Serum protein concentrations were expressed

No. of Patients	Male	Female	Mean of Age Group ($\pm$ SD)	Mean Serum Concentration ($\pm$ SD)			
				Total Protein (g/100 ml)	Albumin (g/100 ml)	α_1 -Globulin (g/100 ml)	α_2 -Globulin (g/100 ml)
Ulcerative colitis 15	6	9	35.3 $\pm$ 14.2	6.7 $\pm$ 0.6	4.1 $\pm$ 0.7	0.2 $\pm$ 0.1	0.7 $\pm$ 0.2
Ulcerative proctitis 11	6	5	39.2 $\pm$ 17.0	6.1 $\pm$ 0.5	4.2 $\pm$ 0.7	0.2 $\pm$ 0.1	0.5 $\pm$ 0.1
Controls 37	17	20	37.2 $\pm$ 17.3	6.7 $\pm$ 0.5	4.6 $\pm$ 0.4	0.2 $\pm$ 0.1	0.6 $\pm$ 0.1

Table II Mean serum concentration in patients with ulcerative colitis, ulcerative proctitis, and in the controls

as g/100 ml serum and serum immunoglobulin concentrations as mg/100 ml serum. In addition the immunoglobulin concentrations were expressed as a percentage of the total immunoglobulin concentration (IgA + IgM + IgG) to show changes in their concentrations relative to overall changes in the total immunoglobulin concentration.

Where several samples had been obtained from one patient, a single sample was selected using random numbers, and results from this sample were used to calculate the mean values for the various groups of patients. The mean values from the ulcerative colitis patients were compared with those from the ulcerative proctitis patients (Tables II and III). In addition the mean values from groups A, B, and C of the ulcerative colitis patients were collated. Although the groups are small and the divisions somewhat arbitrary, the results from the three groups show some interesting trends.

Total protein and albumin

The group of patients with ulcerative proctitis had

a lower total protein concentration than either the group of ulcerative colitis patients or the controls (Table III). The ulcerative colitis patients in groups A and B had lower total protein concentrations than those in group C (Fig. 1). The albumin concentrations of both the ulcerative colitis patients and the ulcerative proctitis patients were significantly below that of the controls. The ulcerative colitis patients in group C had a mean albumin concentration which was significantly higher than that of the ulcerative colitis patients in groups A and B. The patients in group B had an even lower mean but a wider scatter.

α -Globulins

There were no significant differences between the mean concentrations of α_1 -globulin in the various groups of patients and the controls (Table III). The mean concentration of α_2 -globulin for the group of ulcerative colitis patients was significantly greater than that of either the controls or the patients with ulcerative proctitis (Table III). The ulcerative colitis patients in group B had a much higher concentration of α_2 -globulin than either

	Ulcerative Colitis and Ulcerative Proctitis		Ulcerative Colitis and Controls		Ulcerative Proctitis and Controls	
	Difference between Means	P	Difference between Means	P	Difference between Means	P
Total protein (g/100 ml)	0.6	0.005	0	—	— 0.6	0.005
Albumin (g/100 ml)	— 0.1	0.2	— 0.05	0.001	— 0.4	0.02
α_1 -Globulin (g/100 ml)	0	—	0	—	0	—
α_2 -Globulin (g/100 ml)	0.2	0.005	0.1	0.001	— 0.1	0.2
β -Globulin (g/100 ml)	0.2	0.005	0.2	0.001	0	—
γ -Globulin (g/100 ml)	0.3	0.005	0.2	0.05	— 0.1	0.3
IgA (mg/100 ml)	223	0.02	156	0.02	— 67	0.3
IgA (% total Ig)	4.6	0.05	2.4	0.2	— 2.2	0.3
IgM (mg/100 ml)	4	0.90	7	0.7	3	0.9
IgM (% total Ig)	— 0.9	0.3	— 0.8	0.2	0.1	0.9
IgG (mg/100 ml)	436	0.05	421	0.02	— 15	0.95
IgG (% total Ig)	— 3.6	0.2	— 1.7	0.4	1.9	0.4

Table III The difference between the mean serum protein and immunoglobulin concentrations in patients with ulcerative colitis, ulcerative proctitis, and in controls

β -Globulin (g/100 ml)	γ -Globulin (g/100 ml)	IgA		IgM		IgG	
		Mg/100 ml	% Total Ig	Mg/100 ml	% Total Ig	Mg/100 ml	% Total Ig
0.8 $\pm$ 0.1	0.9 $\pm$ 0.2	460 $\pm$ 251	14.5 $\pm$ 5.6	115 $\pm$ 73	3.8 $\pm$ 2.0	2,435 $\pm$ 537	81.7 $\pm$ 6.0
0.6 $\pm$ 0.1	0.6 $\pm$ 0.2	237 $\pm$ 157	9.9 $\pm$ 5.1	111 $\pm$ 40	4.7 $\pm$ 1.5	1,999 $\pm$ 435	85.3 $\pm$ 5.9
0.6 $\pm$ 0.1	0.7 $\pm$ 0.3	304 $\pm$ 185	12.1 $\pm$ 5.6	108 $\pm$ 48	4.6 $\pm$ 1.8	2,014 $\pm$ 564	83.4 $\pm$ 6.2

Table II continued

the patients in groups A or C. The latter group had the lowest α_2 -globulin concentrations of the whole ulcerative colitis group (Fig. 1).

β -Globulin

The mean β -globulin concentration of the ulcerative colitis patients was significantly greater than that of either the controls or the patients with ulcerative proctitis (Table III). The ulcerative colitis patients in group C had the highest β -globulin concentrations, while those in group B had the lowest concentrations of β -globulin (Fig. 1).

γ -Globulin

The mean absolute serum γ -globulin (g/100 ml) for the 15 patients with ulcerative colitis was significantly greater than the corresponding means

for both the 11 patients with ulcerative proctitis ($P = 0.005$) and for the 37 controls ($P = 0.05$) (Table III). The difference between the patients with ulcerative proctitis and the controls was not significant. The ulcerative colitis patients in group B had the highest γ -globulin concentrations, while those in group B had the lowest concentrations of γ -globulin (Fig. 1). However, the differences were not significant because of the wide scatter of results about the three means.

Immunoglobulin A

The immunoglobulin concentrations were determined independently of the γ -globulin by quantitative immunodiffusion. The mean absolute serum IgA concentration (mg/100 ml) for the 15 patients with ulcerative colitis was significantly greater than the corresponding means for 11

FIG. 1. Mean values $\pm$ standard error for the three groups of patients with ulcerative colitis. Group A (no operation, four patients); group B (at time of operation, six patients); group C (long-term postoperative, five patients). — — —, proctitis mean.

patients with ulcerative proctitis ($p = 0.02$) and for 37 controls ($p = 0.02$) (Table III). The difference between the patients with ulcerative proctitis and the controls was not significant. The mean relative serum IgA concentration (% total Ig) for the ulcerative colitis patients was significantly greater ($p = 0.05$) than that for patients with ulcerative proctitis (Table III). There were no significant differences between either the absolute or relative concentrations of IgA for the three groups of patients with ulcerative colitis (Fig. 1).

Immunoglobulin M

The mean absolute and relative concentrations of IgM for both ulcerative colitis patients and ulcerative proctitis patients were within normal limits. The patients with ulcerative colitis in group B had higher absolute and relative concentrations of IgM than the other ulcerative colitis patients.

Immunoglobulin G

The mean absolute serum IgG concentration

(mg/100 ml) for the 15 patients with ulcerative colitis was significantly greater than the corresponding means for both 11 patients with ulcerative proctitis ($p = 0.05$) and 37 controls ($p = 0.02$) (Table III). The difference between the patients with ulcerative proctitis and the controls was not significant. There were no significant differences between the mean relative IgG concentrations of the ulcerative colitis and ulcerative proctitis patients or the controls (Table III). Nor were there significant differences between either the absolute or relative IgG concentrations for the three ulcerative colitis groups (Fig. 1).

SERIAL DETERMINATIONS

Serial determinations of the serum γ -globulin and immunoglobulin concentrations were carried out in three of the patients with ulcerative colitis (nos. 38, 93, and 131) and in two of the patients with ulcerative proctitis (nos. 63 and 178). Results from one ulcerative colitis patient (no. 38) are shown in Figure 2. The two patients with ulcer-

FIG. 2. Serial determinations of γ -globulin and immunoglobulin concentrations following total colectomy and rectal resection in a patient with ulcerative colitis.
—●— Absolute concentration (mg/100 ml or g/100 ml).
---▲--- relative concentration (% of total Ig or globulin).

ative proctitis did not show any consistent change in the serum γ -globulin or immunoglobulin concentrations during the period of investigation. Two of the patients with ulcerative colitis were investigated after colectomy but before rectal resection. These patients and the third were subsequently studied following rectal resection. The immunoglobulin concentrations showed considerable variations in each patient, and it was difficult to relate changes to colectomy or rectal resection. After colectomy the IgG concentrations appeared to increase, while after rectal resection the absolute IgG concentration decreased in two of the three patients. Although the absolute concentration of IgG tended to decrease after rectal resection, the relative IgA concentration increased in all three patients following rectal resection, and was unchanged in the third two years after operation.

IMMUNOELECTROPHORESIS AND IMMUNOELECTROPHORECTIOPRECIPITATION USING TISSUE ANTIGENS

No positive reactions were demonstrated when sera from patients with ulcerative colitis or ulcerative proctitis were tested against phenolic or saline extracts of autologous, homologous, or heterologous human or rat, intestine, colon, or rectum.

Discussion

In this series, the patients with ulcerative colitis showed significant increases in the serum α_2 , β , and γ -globulin concentrations accompanied by similar increases in the IgA and IgG concentrations. The serum globulin and immunoglobulin concentrations of the patients with ulcerative proctitis were within normal limits.

Previous reports in the literature have suggested that autoimmune phenomena are involved in the aetiology of ulcerative colitis but the results from tests *in vitro* for serum antibodies against alimentary antigens have been inconclusive (Polcak and Vokurka, 1960; Edgar, 1961; Gray *et al*, 1961; Henriksen *et al*, 1962; Soergel and Ingelfinger, 1964; Broberger, 1964; Harrison, 1965; Lagercrantz *et al*, 1966; Wright and True-love, 1966; McGiven *et al*, 1967).

Bjørneboe (1943) demonstrated the considerable increase in the serum globulin concentration following immunization with polyvalent pneumococcus and salmonella vaccines. Immunoglobulins have already been associated with specific autoimmune factors, eg, reagins, rheumatoid factor, and LE factor (Heremans, Vaerman,

Carbonara, Rodhain, and Heremans, 1963; Mackay and Burnet, 1963; Glynn and Holborow, 1965). In the present study measurement of the concentrations of the three major immunoglobulins, IgA, IgM, and IgG, was used as a measure of increased immunological activity.

Since IgA predominates in the plasma cells of normal human intestinal mucosa (Crabbé, Carbonara, and Heremans, 1965; Crabbé and Heremans, 1966; Gelzayd, Kraft, and Fitch, 1967) a study of serum IgA concentrations was of particular interest in the present investigation. The presence of a consistently increased serum immunoglobulin concentration in patients with ulcerative colitis would provide further evidence of immunological disorder in this disease and would also be of potential diagnostic value. If changes in the serum immunoglobulin concentrations were directly related to the clinical severity or time course of the disease, this would suggest a direct relationship between the increased immunological activity and the development of clinical signs and symptoms. The effect of surgical removal of the diseased colon on the serum immunoglobulin concentrations is also of interest.

If the inflammatory reaction in the bowel wall were to be the sole cause of the rise in serum immunoglobulins it would be natural to expect higher concentrations where the inflammatory reaction was both more extensive and more severe. Comparison of the results from the three subgroups of patients with ulcerative colitis did not show any significant differences between their immunoglobulin concentrations.

Serial studies were carried out in three patients who had undergone colectomy followed by rectal resection. If the diseased colon and rectum were the primary source of autoantigen, the concentrations of the serum immunoglobulins containing the corresponding autoantibody would be expected to return eventually to within normal limits. However, the immunoglobulin concentrations showed considerable variations in each patient, and it was difficult to relate changes to colectomy or rectal resection. After colectomy the IgG concentrations appeared to increase while after rectal resection the absolute IgG concentrations decreased in two of the three patients. Although the absolute concentration of IgA tended to decrease after rectal resection, the relative IgA concentration increased in all three patients.

The apparent continuation of immunological disorder despite removal of the target organ and source of organ-specific autoantigens, could be explained thus. Clones of immunoglobulin-producing cells which have already been committed

to produce a specific autoantibody could continue antibody synthesis in the absence of the corresponding antigen. Circulating antibodies against infectious diseases are known to persist at low titres long after the removal of the original antigenic stimulus. Alternatively, the persistence of raised immunoglobulin concentrations could represent a systemic lesion of which the colitis was only one manifestation. Removal of the colon would have no effect on the fundamental systemic lesion. This view is supported by the persistence of nonspecific inflammatory changes in the eye and the joints of one patient. Further evidence for this hypothesis is the failure to demonstrate any precipitation reaction between the sera of patients with ulcerative colitis and extracts of rectal mucosa in the present study.

As we now look in retrospect at the patients with ulcerative colitis in group B, it is of interest to note that they had the highest titre of α_2 -globulin. These were the patients in whom it was deemed on clinical grounds that resection of the colon was necessary. It is of interest that De Dombal (1968) reported an increase in α_2 -globulin associated with clinical relapse, which itself is an indication for surgical treatment in patients with ulcerative colitis.

The prolonged clinical study of ulcerative proctitis suggests to us that this is not ulcerative colitis in a mild form. In every instance complete resolution took place and recurrence has not developed even without recognized treatment. The serum immunoglobulins in these patients in no way differed from those of normal controls. We would agree that the apparent inflammatory change in the rectum was of lesser degree than in ulcerative colitis. It could therefore be properly suggested that the immunological response might be less marked. The fact that it does not seem to have occurred suggests that the difference between the two conditions is not one of degree, an observation in keeping with the different clinical course of the two conditions. In this series the diagnosis was firmly made on the clinical findings before serum immunoglobulin data had been obtained. We suggest that an examination of the serum immunoglobulins may prove to be a useful additional test for distinguishing between ulcerative colitis and ulcerative proctitis.

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