Serum proteins in ulcerative colitis: electrophoretic patterns in the inferior mesenteric artery and vein

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EDITORIAL COMMENT. These studies suggest that there is a local production or release of alpha 2 globulins and a fixation or destruction of gamma globulin by the diseased colon.

Previous studies have indicated that in patients with severe attacks of ulcerative colitis, changes occur in the levels of the serum proteins. These changes consist principally of a fall in the serum albumin level, and a rise in the level of the alpha 2 globulins (Bicks, Kirsner, and Palmer, 1959; Brooke, Dykes, and Walker 1961; Soergel and Ingelfinger, 1961). Furthermore attacks of ulcerative colitis which fail to respond to conservative treatment are almost invariably accompanied by a low level of serum gamma globulin (de Dombal, 1967).

However, these studies have done nothing to indicate the mechanisms responsible for the observed serum protein changes. In further investigations, therefore, the electrophoretic patterns have been compared in samples of blood removed at operation from the inferior mesenteric artery and the inferior mesenteric vein. Nineteen patients have been thus studied: a group of 10 patients with severe ulcerative colitis and a control group of nine patients with rectal or colonic cancer.

A further group of nine control patients with colonic carcinoma were studied; in seven of these patients blood was removed from the inferior mesenteric artery and vein and analysed by the same method. In the remaining two patients with a right-sided carcinoma of the colon, blood was removed from the appropriate right colic artery and vein and was again analysed in an identical manner.

FINDINGS

The overall findings of this study are shown in Figure 1. This figure compares the arterial and venous concentrations of each protein fraction, both in the case of the control patients with colonic cancer, and in the case of the patients with ulcerative colitis. It will be seen that the arterial and venous concentrations of the various protein fractions are virtually identical in each of the nine patients with carcinoma. However, in each of the 10 patients with ulcerative colitis a well-marked rise in the venous sample in the level of the alpha 2 globulin

CLINICAL MATERIAL AND METHODS

Between 1 March and 31 August 1966, a group of 10 patients were brought to radical surgery because of severe attacks of ulcerative colitis which were unresponsive to conservative treatment. At operation, immediately after the abdomen was opened, the inferior mesenteric vessels were identified and isolated. A sample of blood was then removed from the inferior mesenteric artery and a further sample from the inferior mesenteric vein. Both of these vessels were then ligated and divided in the usual manner.

The samples of blood were then centrifuged and the serum was pipetted off. Total protein and albumin levels were determined using a routine Biuret method; and electrophoresis was carried out for each of the two samples using cellulose acetate membrane. Results have been expressed as g. % and each result is the mean of two entirely separate estimations which were performed on each individual sample.

FIG. 1. Comparison of serum protein levels in the inferior mesenteric artery and vein in 10 patients with ulcerative colitis (white circles) and nine patients with colonic cancer (black dots).
fraction was shown. It is noticeable also that in each of the 10 patients with colitis, less gamma globulin was found in the venous sample than in the arterial sample.

Figures 2 and 3 indicate that these arteriovenous differences are almost certainly significant. Figure 2 deals with the alpha 2 globulins and shows the standard error of estimation of this fraction (worked out on the basis of the nine control cases with colonic cancer) to be in the region of ±0.01 g.%. It can be seen that in all 10 of the colitis patients the venous alpha 2 globulin concentration exceeds the arterial concentration by on average around 10 times the standard error of estimation. It may be concluded from Fig. 2, therefore, that the rise in the venous alpha 2 globulin concentration in patients with ulcerative colitis is highly significant.

Figure 3 deals with the gamma globulins. The standard error of estimation in calculating this fraction in the nine control colon cancer patients is in the region of ±0.02g.%. A glance at Fig. 3 indicates that all 10 colitic patients had an arterial concentration which exceeded the venous concentration, on average by four or five times the standard error of estimation of this fraction. It may be concluded, therefore, from Fig. 3 that the fall in the venous gamma globulin level is also highly significant.

FIG. 2. Comparison of arterial and venous concentrations of alpha 2 globulins in 10 colitic patients (white circles) and nine patients with colonic cancer (black dots). (Regression line for control cancer patients approximates to 45° line: x = 1.022y + 0.019; r = 0.998; s.e.e. = ±0.01 g. %.)

FIG. 3. Comparison of arterial and venous concentrations of gamma globulins in 10 colitic patients (white circles) and nine patients with colonic cancer (black dots). (Regression line for control cancer patients again approximates to the 45° line: x = 1.036y + 0.021; r = 0.997; s.e.e. = ±0.02g. %.)

DISCUSSION

As a result of several surveys over the past decade, it is now widely accepted that serum protein changes occur in patients with ulcerative colitis. The changes which are noted in the systemic serum proteins during severe attacks are principally threefold: a fall in the serum albumin level, a rise in the alpha 2 globulin fraction, and a fall in the level of gamma globulin (Bicks et al., 1959; Brooke et al., 1961; Soergel and Ingelfinger, 1961; de Dombal, 1967).

The nature of the mechanisms which are responsible for bringing about these serum protein changes has previously been far from clear. Nevertheless, data from the present study provide some indication of the mechanism by which two of the observed changes are brought about, namely, the rise in the systemic alpha 2 globulin level, and the concomitant fall in the gamma globulin level.

**ALPHA 2 GLOBULINS** The data from the present study indicate a significant rise in the alpha 2 globulin concentration in the venous return from the inflamed colon, and such a rise was not observed in any of the nine control cases of carcinoma. If the concentration of alpha 2 globulins is higher in the venous return from the colon than in the arterial blood supplying it, then several possibilities are immediately apparent.

It could possibly be argued that the rise in the venous sample of the alpha 2 globulins was due merely to haemoconcentration. This seems extremely unlikely, since the other globulin fractions, and the albumin level, do not show a similar rise in the venous sample. In addition, concomitant studies showed virtually no difference in the haemoglobin and P.V.C. level in the inferior mesenteric artery.
and vein of these patients, indicating that no haemo-
concentration was taking place.

Recent studies by Millar and Brooke (1966) have
indicated that in patients with ulcerative colitis
absorption of macromolecules takes place across
the damaged colonic mucosa; and it could also be
argued that this absorption of macromolecules
was responsible for the rise in the venous alpha 2
concentration. Such absorption of macromolecules
may well be taking place; but clearly this cannot
explain the selective rise in the alpha 2 globulin
concentration in the vein. Therefore, some additional
mechanism must be at work, and it is difficult to avoid
the conclusion that in patients with ulcerative colitis,
the systemic alpha 2 globulin concentration rises
because of the local production or release of these
globulins.

The inflamed colon of ulcerative colitis is perhaps
a unique organ for study, since it possesses the
important advantage of being a single widely
inflamed organ situated at the end of a long vas-
cular pedicle. However, this does not mean to say
that the local production of alpha 2 globulins is
necessarily restricted to patients with ulcerative
colitis. A rise in the systemic alpha 2 globulin
concentration has been noted in many other in-
flammatory and neoplastic diseases (Hoch-Ligeti,
Irvine, and Spinkle, 1953; Neumayer Perger,
Schinko, and Tschabitscher, 1956; Peterman, 1960;
Heim and Lane, 1964; Atwell, Duthie, and Goligher,
1965; McCathie, Owen, and Macpherson, 1966).
Glycoproteins form an important fraction of the
alpha 2 globulins, and it is of interest to note that
a similar rise in these proteins has also been widely
noted (Catchpole, 1950; Almquist and Lausing,
1957; Burnett, McAllister, and Shields 1963; Shields,
McAllister, and Burnett 1963).

In view of the data from these previous studies,
it now seems reasonable to argue that the observed
rise in the systemic alpha 2 globulins in many other
conditions may also be due to the local production
or release of these proteins and not to any general-
ized response on the part of the body.

It is interesting that in the present series of patients,
a high venous alpha 2 globulin level was not found
in any of the nine patients with colonic cancer.
In most cases this was undoubtedly due to a dilu-
tional effect, since blood was removed from the
inferior mesenteric vein at a considerable distance
from the colonic cancer. In the two patients with
right-sided colonic cancer, however, blood was
removed from a vein close to the lesion. No large
rise was noted in the venous alpha 2 globulin level
in either of these samples but is interesting that both
showed a rise in the alpha 1 globulin concentration
in the venous sample.

GAMMA GLOBULINS If part of the serum gamma
globulin is entering the colon and not leaving it,
two possibilities are immediately apparent. First
there could be a selective loss of gamma globulin
in the faeces of patients with ulcerative colitis.
This seems unlikely, for preliminary observations
on a small series of patients would appear to con-
firm the findings of Soergel and Ingelfinger (1964),
who have indicated that the rectal mucus of patients
with ulcerative colitis is little different from the
rectal mucus of control patients. Certainly no select-
ive loss of gamma globulin seems to be taking place.

The second intriguing possibility is that gamma
globulin is being bound or destroyed in the colon.
Such a possibility has already been suggested by ex-
periments in vitro (Broberger and Perlmann, 1959),
and the present study would appear to provide
confirmatory in vivo evidence in favour of the find-
ings of these workers in this respect.

Broberger and Perlmann were, however, unable
to demonstrate any cytotoxic effect of the antibody
which was bound to the colon in the in vitro studies
which they reported. Indeed, further recent studies
have shown a complete lack of correlation between
the prevalence of autoantibody and the clinical
pattern of ulcerative colitis, and have suggested
that the tissue damage may well be caused by
sensitive white blood cells rather than by circulating
antibodies (Perlmann and Broberger, 1963; Harrison,
1965; Wright and Truelove, 1966).

The present series of studies again appears to
confirm these findings, in that the response of the
patient to conservative therapy appears to be directly
related to the amount of gamma globulin available
in the serum (de Dombal, 1967). It does seem more
likely, therefore, that the gamma globulin fixation
in the colon takes place as part of a defence mechani-
sm, and may well be the result of the initial attack
rather than its immediate cause.

MECHANISMS RESPONSIBLE FOR PROTEIN CHANGES
Thus the present study enables a tentative scheme
to be put forward to explain the observed serum
protein changes in patients with ulcerative
colitis. The data from the present study suggest
that the sequence of events which takes place in
patients with an attack of ulcerative colitis is as
follows:

1 During the course of a localized attack upon
the colonic mucosa, alpha 2 globulins are released
locally, and pass into the systemic circulation via
the inferior mesenteric vein.

2 As a sequel to this attack upon the colonic
mucosa, there is a reaction by the immune systems
of the body, which results in an increased production
of gamma globulin.
3 The gamma globulin thus produced is liberated into the systemic circulation where some of it passes via the inferior mesenteric artery to the colon.

4 The gamma globulin having reached the colon is either destroyed or is fixed there.

Such a tentative scheme may well be open to severe criticism because many of the details by which these mechanisms are brought about are as yet unknown. However, on the basis of the present data, this scheme does seem to be the mechanism most likely to be responsible for the observed serum protein changes in severe attacks of ulcerative colitis.

SUMMARY

The serum protein levels in the inferior mesenteric artery and the inferior mesenteric vein have been compared in 19 patients who came to operation, 10 patients with severe ulcerative colitis, and nine control patients with colonic cancer.

In all 10 of the patients with ulcerative colitis there was a significant rise in the level of the alpha 2 globulins in the inferior mesenteric vein and a concomitant significant fall in the venous gamma globulin concentration. No such changes were observed in the control patients with colonic cancer.

It is suggested that these observations are the result of two specific mechanisms in patients with ulcerative colitis, namely, the local production or release of alpha 2 globulins, and the fixation or destruction of gamma globulins in the inflamed colon.

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