MEDICAL PRACTICE

Clinical Progress

Ulcerative Colitis

Epidemiology and Aetiology, Course and Prognosis

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Ulcerative colitis is an inflammatory disease of unknown origin, characterized clinically by recurrent attacks of bloody diarrhoea and pathologically by a diffuse inflammation of the wall of the large bowel. The changes spread proximally from the rectum, and are confined to (or most severe in) the colonic and rectal mucosa.¹ The disease was first mentioned by name in 1859 by Sir Samuel Wilks² (though similar non-contagious forms of diarrhoea have been recorded for almost 2,000 years, dating back to a description in A.D. 117 by Soranus of Ephesus³). Nonetheless, the last decade has seen a considerable surge of interest in the disease.

Epidemiology

Ulcerative colitis is often alleged to be a disease of industrialized Western countries. Certainly it is most commonly found in Britain, where the incidence is roughly 5 per 100,000 of the population at risk, and the prevalence roughly 80 per 100,000.⁴ In North America, over the northern half of Europe, and in Australia and New Zealand the corresponding prevalence figures are roughly half those found in Britain, though both the incidence and prevalence of ulcerative colitis in Europe are probably on the increase.⁵⁻⁸ Nevertheless, it is now accepted that ulcerative colitis has a world-wide geographical distribution, cases having been reported from as far

afield as South and Central America,⁹⁻¹¹ the Middle East,¹²⁻¹⁴ Africa,¹⁵ India,¹⁶ and Japan¹⁷ in the last 10 or 15 years.

The female-male sex ratio in several large series^{4, 5, 18-20} has been remarkably consistent at around 1.5:1, as has the age distribution, a fact which has aroused comment from an aetiological standpoint.²¹ Generally speaking, ulcerative colitis first affects the patient between adolescence and the early thirties; but, there is another, smaller group of patients who first suffer from ulcerative colitis in their sixties or seventies. Between 5 and 10% of patients have a family history of ulcerative colitis or Crohn's disease, about ten times the figure which would be expected by chance.^{22, 23}

The disease affects many races—Europeans, Africans, Jews, Arabs, Indians, Japanese, and even the North American Indian.²⁴ Of particular interest are situations in which the different races inhabit the same area of the world together. Thus in North America the disease is said to be more common in whites than in non-whites, and most common of all in Jews⁶ (though it is doubtful if this is so in Britain and the incidence of ulcerative colitis in Israel itself is not particularly high¹⁴). In Switzerland ulcerative colitis is quite common in most parts of the country, but is almost unheard of in the Italianate Ticino.²⁵ In New Zealand among Europeans the incidence and prevalence are comparable to those already discussed, yet ulcerative colitis is almost unknown in Maoris.²⁶ The reasons for these differences remain unexplained, as does the aetiology of the disease itself.

Aetiology

Though the aetiology of ulcerative colitis remains unknown, there have recently been substantial shifts of emphasis among

the various possible causes. Thus it is no longer regarded as an infectious disease (though possibly bacteria are in some way involved in the colon's immunological response^{27 28}). Moreover, it is now widely felt that any abnormal psychological findings in colitis patients are more usually the result of this debilitating disease than its cause. Several careful studies have failed to define any significant differences between the psychological make-up of patients with ulcerative colitis and control subjects taken from the general population.^{29 30} Finally, despite much careful work in the early 1960s which seemed to implicate foodstuffs such as milk as possible aetiological agents,³¹ the proportion of patients who gain any long-term relief from dietary restriction alone seems depressingly small.

IMMUNOLOGICAL FACTORS

In contrast, there now seems little doubt that immunological factors are important in ulcerative colitis, even if their precise role remains obscure. Thus though the discovery of autoantibodies to colonic tissue³² has been widely confirmed,³³⁻³⁵ it is still far from clear what causes their development,²⁷ and there is little relationship between antibody titre and the course of the patient's disease.³⁴ Also, though cytotoxicity in the lymphocytes of colitic patients has been widely noted,³⁶⁻³⁸ it is equally doubtful whether this is a disease-specific effect.

However, recently R. G. Shorter and his associates³⁹⁻⁴¹ have shown, firstly, that cytotoxicity can be induced in healthy adults by preincubation with a lipopolysaccharide extract from *Escherichia coli* 0119:B14; secondly, and conversely, that sensitized lymphocytes from colitic patients showed diminished cytotoxicity after preincubation with the *E. coli* extract. They suggest that the extract may contain a specific antigen (so that its preincubation with sensitized lymphocytes results in their desensitization) and that cytotoxicity may be an *in vitro* expression of delayed hypersensitivity. Hence it seems reasonable to hope that this work will go some way towards solving the puzzling aetiology of ulcerative colitis, as well as telling us a lot about the normal immunological mechanisms in the gut.³⁹

Two other studies obliquely concern the aetiology of ulcerative colitis. Firstly, P. R. J. Burch and his colleagues⁴² have found an astonishingly similar age-specific distribution, which is world wide. They argue that the primary cause of ulcerative colitis is intrinsic rather than extrinsic, a finding which would favour the view that ulcerative colitis is an autoaggressive disease. Finally, a recent and on-going study from St. Mark's Hospital⁴³ has provided perhaps the most important evidence of all—namely that ulcerative colitis probably is a disease entity. These workers employed numerical taxonomic or "clustering" techniques (such as those widely used in biology for classification of species) and were able to show that a group of patients tentatively labelled as suffering from ulcerative colitis formed a small homogeneous "cluster." This indicates that we are probably justified in alluding to ulcerative colitis as a single disease entity—(definite contradiction to the situation vis-à-vis Crohn's disease, where no such clustering was possible).

Course and Prognosis

In the past ten years several large-scale studies of the course and prognosis have appeared from Oxford,¹⁸ Leeds,¹⁹ and from Edinburgh.^{44 45} Perhaps the most remarkable aspect of these studies—apart from their virtually complete follow-up—is their agreement on several of the major issues (though there are naturally numerous differences between the series in points of detail).

COURSE OF DISEASE

Ulcerative colitis may pursue various forms, but the most common is a chronic relapsing disease, with symptomatic attacks lasting from one week to several months alternating with periods of remission sometimes lasting for several years. Roughly each patient has somewhat less than a fifty-fifty chance of experiencing symptoms from ulcerative colitis in a given year and this risk is unaffected by the patient's age, sex, duration of symptoms, or extent of diseased bowel. Nevertheless, some patients may even suffer from chronic continuous disease, though this seems to have become rarer recently.

The severity of disease is influenced by several factors, of which three are the most important. The first is the duration of symptoms; the first attack is often the most severe and carries the greatest risk (though once this is over the duration of disease seems to have little effect on its severity, and "burnt-out" colitis is hardly a valid term). Secondly, the age of the patient; the very young and the very old are far more likely to suffer from severe attacks than those in intermediate age groups. Last and most important, is the extent of disease; since patients with extensive or total colitis are more likely to suffer from severe attacks of disease than those with proctitis or distal colitis. (In the Leeds series the risk of an attack being a severe one was increased five-fold by the presence of extensive disease.)

Incidentally, though the classification of severity put forward by S. C. Truelove and L. J. Witts⁴⁶ 15 years ago is often criticised, no superior classification has yet been put forward, and in practice it is extremely useful. On the other hand, the word "fulminating" has been the subject of several mutually incompatible definitions and should be dropped.

PROGNOSIS

The prognosis of any patient suffering from ulcerative colitis depends on a combination of three factors: age; the extent of bowel affected; and, if the disease is active, the severity of attack. The mortality is highest in patients over the age of 60, those who suffer from severe attacks, and those with extensive disease, involving all or nearly all of the colon and rectum. Combinations of these poor prognostic factors are particularly lethal. This knowledge has enabled us to propose a much more rational system of management and to define more precisely the respective roles of conservative and operative therapy. Equally important has been the realization that many of the complications of ulcerative colitis—local, like perforation, stricture, or perianal sepsis, and "systemic" such as uveitis, arthritis, or skin lesions—are also somewhat influenced by the extent and particularly the activity of the patient's colitis. Indeed, many of these complications disappear entirely after removal of the bowel.

Finally cancer of the large bowel is found almost exclusively in patients with extensive colitis, among whom the cancer risk varies according to their duration of symptoms. In the Leeds series the cumulative cancer risk in patients with extensive colitis was around 5% after 10 years and no less than 41.8% after 25 years. This has led to the suggestion that prophylactic surgery on the grounds of cancer prevention may be justifiable if the patient has extensive colitis and a ten-year history; but this is a major step for the patient, especially if there are no symptoms at the time.

B. C. Morson and L. S. C. Pang⁴⁶ have suggested that precancerous changes can be detected on rectal biopsy. If this finding can be widely confirmed the test might be exceedingly valuable—though great caution is necessary, since the consequences of false-negative results would be considerable.