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Collagenous colitis: disease or diversion?

Unexplained chronic diarrhoea is common, and in 1976 a distinctive histological change of the large intestinal mucosa termed "collagenous colitis" was proposed by Lindstrom as a cause of chronic watery diarrhoea.¹ Ten years later more than 50 cases have been described.¹⁻¹⁵ The histological hallmark of collagenous colitis is a thick eosinophilic band in the superficial aspect of the colonic mucosa, immediately deep to the surface epithelium and sometimes extending around the uppermost part of the crypts. Examination by histochemistry,^{2,3} electron microscopy,^{3,14,16,17} and immunocytochemistry^{9,18} has confirmed that the band is collagenous and has shown that there may be subtle changes in the adjacent epithelium, capillary endothelium, and pericryptal fibroblasts.^{14,17} Subepithelial collagen in the colonic mucosa is not in itself pathological (its synthesis is a physiological function of the pericryptal fibroblast sheath related to epithelial cell turnover^{19,20}), but it is usually inconspicuous on routine examination by light microscopy.²¹ Most studies of its thickness in "control" samples show that the upper limit of normal can be taken as 7 μm ,^{3,5,9,11,22,23} whereas in collagenous colitis it usually exceeds 15 μm and in many cases reaches 60-70 μm .¹⁻¹⁵

The cause of the excessive collagen deposition is a mystery. Although the term collagenous colitis trips easily off the tongue, the colitis is often unimpressive on histological examination. In most cases inflammatory cells, usually lymphocytes and plasma cells,⁶ are only modestly increased in the mucosa, but sometimes eosinophils⁷ or mast cells⁹ are conspicuous. Nevertheless, the changes of collagenous colitis have occasionally followed a histologically proved acute, but non-specific, mucosal inflammation.^{10,12} A thickened collagen plate is not a feature of ulcerative colitis, Crohn's disease, or any hitherto recognised variety of inflammatory bowel disease.^{5,9,24}

Collagenous colitis occurs almost exclusively in women, and they may be almost any age (range 23 to 81 years).¹⁻¹⁸ Apart from the chronic watery diarrhoea, which may be present for weeks or many years, patients are remarkably well.¹² No firm association has been made with any other

medical condition, although polyarthritides or rheumatoid disease has featured in some reports.^{11,15,25,26} Routine haematological and biochemical measurements are usually normal, microbiological investigations are negative, barium studies are generally unremarkable, and endoscopic abnormalities of the large bowel mucosa are nearly always unimpressive, even if present. The term collagenous colitis was originally chosen by Lindstrom by analogy with collagenous sprue, a lesion of the small intestine in which villous atrophy and a sub-epithelial collagen band are associated with malabsorption,²⁷ but the two lesions are unrelated clinically and do not coexist. Collagenous colitis is confined to the colon and is usually diffuse,^{7,13,23} albeit with some variation in the collagen thickness. Usually the change is apparent in a rectal biopsy, although not always.²²

The course of the illness is variable: some patients have chronic persistent diarrhoea¹⁴; some have relapses and remissions^{10,13}; and a few have apparent spontaneous resolution either with⁸ or without^{10,28} disappearance of the abnormal collagen band. Conventional medical treatment is usually ineffective,¹² although there are reports of improvement with metronidazole,^{11,29} mepacrine,⁴ prednisolone,^{10,13} sulphasalazine,^{23,26} and loperamide¹¹ and also with the homoeopathic remedy Natrum Mur.¹² But even those people with persistent symptoms suffer little detriment to their general health.¹²

As chronic watery diarrhoea is common and the histological changes of collagenous colitis seem to be rare the relation between them must be questioned critically. Does the thickened collagenous band cause diarrhoea by forming a barrier to water absorption, as suggested by Lindstrom,¹ or is it a consequence of the diarrhoea? Or do the collagenous band and diarrhoea coexist by chance? Two perfusion studies have supported Lindstrom's hypothesis by showing net secretion of sodium chloride and water into the colonic lumen,^{18,30} but a third study gave conflicting results.¹⁵ That the thickened collagen plate is a mere consequence of diarrhoea is unlikely because it is not found in other diarrhoeas of known cause.

Some aspects of collagenous colitis make us sceptical of its clinical importance; sometimes the band is seen without the diarrhoea,²² and the band may persist after the symptoms have resolved.^{10,28} Nor do the absence of a recognised aetiological agent, the widely variable clinical course, and the lack of a uniform response to many treatments support a specific disease process. Most published reports are of small numbers of cases with varied emphasis, and many contain conflicting findings. What is now needed is a coordinated effort to collect details of many carefully investigated patients. Meanwhile we conclude that while chronic watery diarrhoea and substantial thickening of the collagen plate undoubtedly coexist in some patients there is insufficient evidence to accept collagenous colitis as a disease entity. The onus remains on the protagonists of collagenous colitis to show that it is more than a histological change of questionable importance.

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Doctors' ignorance of statistics

Many of us faced with someone who quotes statistics find it difficult to distinguish whether any consequent conclusion is correct or whether we have been bamboozled. If we do not understand the basics of statistics then we cannot question the statements and claims that are built on them. But the nature of medical science is to use an understanding of probability to interpret limited studies and thus move closer towards assertions of what might be "true" or "right." Yet, recent evidence suggests,² many doctors know little about statistics.

Wulff and colleagues sent a questionnaire to 250 Danish doctors (of whom 148 replied) to assess their knowledge of elementary statistical expressions (standard deviation, standard error, $p < 0.05$, $p > 0.05$, and the correlation coefficient r).¹ Although the study was itself imperfect (it had some ambiguous multiple choice questions and did not verify the answers against what statisticians might answer), it produced thought provoking evidence of ignorance. From nine multiple choice questions respondents produced a median correct response of 1.4. The authors concluded: "The statistical knowledge of most doctors is so limited that they cannot be expected to draw the right conclusions from those statistical analyses which are found in medical

journals." Note, however, even in this article critical of others' knowledge, the extrapolation from 148 replies to a statement about "most doctors"—an example of studying a sample and then drawing global conclusions.

Nevertheless, the Danish doctors who replied clearly knew little (and the 102 who did not reply may have known less). Are doctors in other countries more knowledgeable? The evidence suggests not. Other studies have reported defects in statistical skills^{2,3} and shown that they become worse with increasing time from graduation.² In one study the respondents showed a perceived need for other doctors to have a biostatistical training together with a lack of enthusiasm for their own education in the subject⁴—a dichotomy that has been noted before.⁵ But innumerate doctors cannot interpret scientific biological data.⁶ They are doomed to have to accept without reservation the statements made in summaries, discussions, or conclusions, and their clinical practice may thus be altered on the basis of flimsy or inconclusive evidence.

In Britain the General Medical Council has since 1967 recommended that the medical curriculum should include teaching in statistics,⁷ and each medical student is now exposed to between 11 and 48 teaching hours (median 24) and most are examined in this knowledge. This teaching is reviewed at a workshop of statisticians held annually at the University of Bristol.⁸ But the problem remains that if interpreting statistics is not a regular activity the knowledge will evaporate. All doctors will have known the first and second laws of thermodynamics at some stage, but few could now recite or use them. Statistics cannot be understood in a vacuum: knowing that a correlation coefficient can vary between 0 and +1 (or 0 and -1) is of little value unless one understands its dependence on the number of observations. Similarly values become highly significant when the number of observations is large even when the correlation coefficient is very small.

There are a variety of approaches to the problem, which are not mutually exclusive. Medical students must continue to be taught the basic technicalities of statistics, and some comprehension of p values, r values, and confidence intervals should be instilled into all. But the teaching also needs to encompass a sense of what data mean. The need is to teach how to obtain information from data and knowledge from information. Journals need to ensure that results are explained in terms that the statistically amblyopic can still comprehend. Confidence intervals should be more widely used,^{9,10} and diagrams should be encouraged, especially where correlations are concerned. Expansive statements claiming "fact" from probability should be discouraged, and, despite the policy of some editors, all medical journals should allow space in their letter columns for disagreements and informed counter opinions.

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