Antibodies to Mycobacterium paratuberculosis

EDITORS—The recent paper by Stainsby et al concerning Mycobacterium paratuberculosis is a reminder of the generally held suspicion that Crohn’s disease is caused by a transmissible agent (Gut 1993; 34: 371-4). No such transmissible agent, however, has been identified. The agency of microorganisms in inflammatory bowel disease has been questioned, and the characteristics of Crohn’s disease seem to be inadequately degraded by macrophages. This leads to an inflammatory change characterised by a granuloma. This suggests either an organism, which by its nature is resistant to macrophage action or alternatively that the macrophage population is somehow impaired and unable to cope with an otherwise innocent organism. It is not unreasonable to look for the cause of this disease among those organisms which have cell walls resistant to macrophage activity and that are not readily grown on conventional bacterial growth media. An anaerobic fungi saprophytic in ruminant digesta has recently been discovered and distinct species have been described including Neocallimastix frontalis, N pateriicum, Sphaeromona communis, and other as yet unidentified strains. These organisms occur in the rumen fluid, are present in the colon, and cause inflammation of the mucosa. We consider that Crohn’s disease may result from a disturbance of the rumen ecosystem caused by these fungi. If one or more of these species of fungi could be grown, they might be compared with the fungi cultured by others.

References

Reply

EDITORS—I found Dr Eastwood and colleagues’ report of a negative search for anaerobic fungi in Crohn’s disease of particular interest. The criteria justifying such a search, based on characteristics required of any putative agent responsible for the inflammation of Crohn’s disease, are, perhaps, as valid for fungi as mycobacteria. Despite our main negative report, however, on the association between mycobacteria and Crohn’s disease, quoted by Dr Eastwood, we feel that the evidence for a mycobacterial cause for Crohn’s disease is stronger now than it has been before. In his recent review,1 Dr Ciclitira also quoted our study as negative evidence of a role for mycobacteria in Crohn’s disease and was critical of the more positive study of Elsaghier et al.1 I believe, however, the two papers highlight the requirements of a successful study of humoral immunity directed at Mycobacterium paratuberculosis. In our report, in which we failed to show raised antibody titres to this organism in patients with Crohn’s disease, we commented on the high degree of cross-reactivity between M paratuberculosis and environmental species of mycobacteria, such as M avium, and the necessity to identify M paratuberculosis specific antigens to improve such studies. This has now been successfully achieved by Elsaghier and colleagues, who found raised antibodies to at least one of three antigenic preparations, each with a high degree of specificity to M paratuberculosis, in 84% of patients with Crohn’s disease, with 18% positive for all three. This study represents an important advance, showing that antibody levels to well characterised M paratuberculosis specific antigens are raised in Crohn’s disease. The criticism of inadequate use of controls is currently being considered in a collaboration between our two groups using a different population of patients with Crohn’s disease and an extended range of controls.

In addition to these developments in immunological approaches for examining the role of mycobacteria in Crohn’s disease, the other important advance has been in the identification of highly specific and sensitive techniques, such as the polymerase chain reaction, to the detection of M paratuberculosis. Culture of the organism from clinical samples has proved notoriously difficult. Amplification by polymerase chain reaction of DNA specific to M paratuberculosis has provided a rapid, highly specific, and far more sensitive alternative to culture. Indeed, previous attempts in either clinical and laboratory techniques. In the study reported by Sanderson et al,1’ M paratuberculosis DNA was identified in gut wall tissues from 65% of Crohn’s disease, 4-3% of ulcerative colitis, and 12-5% of control patients, providing further evidence of an association between M paratuberculosis and Crohn’s disease.

In our own preliminary studies, we have used several pairs of primers for the detection by polymerase chain reaction of DNA from a wide range of mycobacterial species. In addition, we are using mesenteric lymph node tissues as an alternative to gut wall tissues which may have been exposed to environmental strains of mycobacteria. In the small number of samples so far analysed, we have successfully detected M paratuberculosis or M avium in a proportion of tissues from patients with Crohn’s disease but not in tissues from controls (unpublished data). While not providing conclusive evidence, these various findings suggest that M paratuberculosis is still the most promising candidate for a role in the pathogenesis of Crohn’s disease. The application of these improved immunological and molecular biological approaches can only assist in determining the relevance of the clear association between M paratuberculosis and Crohn’s disease.

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Extracorporeal shock wave lithotripsy and gall bladder stones

EDITOR—We were interested in the paper by Elewaut et al on the results of extracorporeal shock wave lithotripsy of gall bladder stones (Gut 1993; 34: 274-8). Our figures exactly parallel theirs for we can get 98% clearance of solitary stones, less than 20 mm in diameter, in one year but not such good clearance in larger stones.
stones or more than one stone. The paper fails to make any comment on symptom relief, however, and the surprising result of our lithotripsy trial was that the symptoms were relieved, just as much as after cholecystectomy, within the first month of treatment, well before any stones had disappeared; and the pain relief for the whole year and the relief of many other symptoms did not depend on stone clearance: so we have to distinguish between success in terms of stone clearance and success in terms of symptom relief. Lithotripsy, for whatever reason seems a very cost effective way of doing the second, at least in the short term. We are at present following up our patients for longer periods to see if this symptom improvement is maintained.

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Reply

EDITOR,—We fully agree with Johnson and Ross that during a lithotripsy trial most patients feel extremely comfortable. This is not because of the lithotripsy itself, however, but a result of the well known effect of bile acids on gall bladder contraction. Although, the effect on gall bladder motility is still somewhat controversial,


Barrett’s oesophagus and development of dysplasia and adenocarcinoma

EDITOR,—Ifikhar et al (Gut 1992; 33: 1155–8) present results from a 15 year prospective study of endoscopic surveillance of 102 patients with columnar lined epithelium (for example, Barrett’s oesophagus). The aim of the study was to identify any significant risk factors for the subsequent development of adenocarcinoma. Data are presented suggesting that the length of columnar lined oesophagus was considerably longer in patients with dysplasia. None of the patients with dysplasia had a columnar lined oesophagus of less than 8 cm. The authors conclude that the length of Barrett’s oesophagus is a significant risk factor in the development of dysphasia and subsequent carcinoma and recommend intensive follow up of patients with Barrett’s oesophagus greater than 8 cm in length.

The results and conclusions of the study are inappropriate given the exclusion of patients with less than 5 cm of circumferential Barrett’s oesophagus. Adenocarcinoma has been reported in tongues or short segments of Barrett’s oesophagus. At least 52 per cent of a series of 28 resected specimens with adenocarcinomas centred in the oesophagus had a length of Barrett’s less than 5 cm. Additionally, adenocarcinomas occurring near the gastro-oesophageal junction may arise from small areas of specialised epithelium, which may be obliterated without the oesophagus being removed.

It would be inappropriate to ignore patients with the potential for dysplastic change when short segment Barrett’s oesophagus is found at endoscopy. Systematic biopsies should be taken and surveillance follow up should not differ from those patients with longer segment Barrett’s oesophagus unless appropriately conducted studies show a lesser risk of cancer.

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Screening and management of familial adenomatous polyposis

EDITOR,—Tait et al advocate annual colonoscopy as the ideal screening method for first degree relatives who carry the gene for familial adenomatous polyposis (FAP). (Correspondence on Letter to the Editor and reply Gut 1993; 34: 576.) Bradburn and Rhodes on the other hand make the case for the selective use of colonoscopy, recommending it only for those at high risk for FAP but without obvious polyps (or microadenomas) by their late teens, and in those in whom prophylactic colectomy has been delayed. This selective approach is suggested to minimise the morbidity and mortality associated with colonoscopy.

We report on two cases of colonoscopic morbidity, which, though anecdotal, add ‘meat to the bones’ of the present discussion.

Case 1: A 12 year old son of a patient with FAP was found to have polyps at sigmoidoscopy. Histological examination showed these to be adenomas. At colonoscopy at 16 years, the bowel was perforated. A laparotomy was performed for perforation and a defunctioning colostomy was created; this was closed six months after laparotomy. He was referred to St Mark’s Hospital after his father died from an upper gastrointestinal malignancy, but refused to attend for further hospital appointments or to have surgery, and is now under psychiatric counselling.

Case 2: A 15 year old son of a patient with FAP was found to have colonic adenomas. Annual colonoscopies were then performed, and at the age of 19 years, 20 polyps (size 2 mm) were removed. After this procedure the patient became unwell. A laparotomy was performed and a prolapsed sigmoid colon was drained. He was referred six months later to St Mark’s Hospital for definitive surgery. At laparotomy a large mesenteric desmoid tumour (not apparent at the first operation) was found. Neither the colon nor the desmoid tumour was able to be removed.

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