RHEUMATOID ARTHRITIS AND THE GUT

The association of joint disease with a variety of bowel disorders is well documented [1-5]. This has inevitably led to much speculation as to a possible aetiopathogenetic role for the gut in rheumatoid arthritis (RA) [6]. The evidence for a direct relationship between dietary antigens and the development of RA, remains controversial as does the role of diet in its treatment [7-11].

The concept that the development of arthritis could be an indirect consequence of alterations in bacterial flora is not new. Olhagen and Mansson [12] found evidence of abnormal flora in the form of high counts of *Clostridium perfringens* in 67% of 186 patients with RA, and increased alpha-antitoxin titres in 78%.

An animal model of arthritis closely resembling human RA is that induced in pigs after feeding them a diet high in fish protein. It was observed that increased numbers of *C. perfringens* appeared in the faeces prior to the development of arthritis [13].

Furthermore, the faecal microflora was examined in 25 patients with active RA and 25 healthy controls [14]. It was found that *C. perfringens* was carried by significantly more patients than controls, and there was a trend towards more frequent carriage of *C. perfringens* by patients with active disease. In a further sequential study of patients receiving penicillamine or sulphasalazine, carriage rates did not alter.

In a recent communication, Ebringer and his colleagues [15] reported high titres to *Proteus mirabilis* in 30 RA patients being treated with gold, compared with ankylosing spondylitis patients and healthy controls. They suggested that further studies with other groups of RA patients were required before Proteus micro-organisms could be implicated.

Another line of investigation has been to examine whether the intestinal mucosa may be abnormally permeable in RA, the implication being that the absorption of antigenic material may provoke a humoral or cell-mediated response resulting in joint injury.

Techniques that have been developed to investigate intestinal permeability include the differential sugar absorption tests, the *51*Cr-edetic acid (EDTA) absorption test, and the absorption of different polyethylene glycol polymers [16]. However, interpretation of these tests in patients with RA may be difficult as they may be influenced by drug therapy. A study of 41 patients with RA on standard nonsteroidal anti-inflammatory drugs (NSAIDs) and second-line agents, and 40 controls, failed to show increased small-bowel permeability using a differential sugar absorption test [17]. However, in a smaller study of 31 patients on mfenamic acid, abnormal permeability was found in nine patients, five with rheumatoid arthritis and four with osteoarthritis (OA), also using a differential sugar absorption test [18].

Bjarnason and his colleagues [19] used the *51*Cr-EDTA absorption test in 24 patients with RA, 18 with OA and 34 controls. They demonstrated that intestinal permeability was normal in untreated patients, but abnormal in patients treated with NSAIDs. They concluded that the intestinal abnormality was the consequence of treatment with NSAIDs and suggested that prostaglandins may play a role in maintaining intestinal integrity.

It has been shown that *111*indium-labelled autologous leukocyte scans show increased uptake over inflamed bowel in Crohn's disease and ulcerative colitis [20]. In Bjarnason's paper, a parallel study of 10 patients was reported with *111*In imaging and faecal excretion as described by Saverymuttu *et al.* [21, 22] to determine whether the abnormal permeability was associated with intestinal inflammation. It was concluded that the scan results suggested an inflammatory process in the ileocaecal region in many patients on NSAIDs. Doubt has been cast, however, on the role of NSAIDs in this respect, as ileocolonoscopies in 20 patients
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with RA on NSAIDs failed to demonstrate a macroscopic or microscopic inflammatory lesion [23].

The chance finding that some patients with RA who were having 111In-labelled leucocyte studies to look for isotope uptake by the joints also showed localized radioactivity in the gut led Segal and his colleagues [24] to study 26 patients with RA and 10 controls receiving NSAIDs. An abnormal localization of radioactivity was observed in 12 patients (46%) and in none of the controls. The distribution of the isotopes was over the ileocaecal area and lower ascending colon. In one patient the isotope localization was in the distal bowel, and subsequent investigation showed previously undiagnosed, asymptomatic ulcerative colitis. The authors pointed out that approximately equal numbers of patients with and without abnormal scans were on NSAIDs. Two untreated patients with RA had abnormal scans, and 10 patients on NSAIDs for other reasons did not have abnormal scans. They conclude that their results indicate that drugs are not the cause of the accumulation of leucocytes in the gut.

Similar findings are reported in a smaller study by Rooney and colleagues [25] in four out of six patients with RA. Extensive investigation of their index patient failed to reveal any significant bowel pathology.

What do these important observations suggest? Can we be certain that there is no inflammatory disease of the ileocaecal junction, particularly in those patients with abnormal accumulation of 111In-labelled leucocytes in the early (4 hour) scan? Are we to believe that the abnormal localization of the isotope is not a feature of increased permeability induced by NSAIDs? If these observations do not represent a secondary phenomenon, and are related to the pathogenesis of the arthritis, what is the role played by lymphoid tissue in Peyser’s patches? Clearly, further detailed examination is needed of those areas of the bowel exhibiting abnormal localization of labelled leucocytes. With regard to the role of drugs in intestinal permeability, further studies are needed with RA and OA patients, both on and off NSAIDs, compared with normal controls. However, are the available tests of intestinal permeability capable of demonstrating the abnormal passage of antigenic material through the intestinal wall, without the use of molecules resembling such material [17]?

Although incontrovertible proof of a primary role for the gut in the pathogenesis of RA is still lacking, promising and exciting new lines of investigation are being pursued. As Segal and his colleagues [24] suggest, if the link between a primary lesion in the gut, and the pathogenesis of the arthritis is substantiated, the therapeutic implications would be very considerable. The search must simply go on!

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REFERENCES


NOTICES

BRITISH ARTHROSCOPY SYMPOSIUM

Venue: The Old Swan Hotel, Harrogate, N. Yorks.
Information: P.O. Box, HP171, Shire Oak Street, Leeds LS6 2DP, UK. Telephone: Leeds (0532) 744711.

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