MATTERS ARISING

Small intestinal bacterial overgrowth in patients with rheumatoid arthritis

I read with interest the paper by Henriksson *et al*,[1] in which the authors demonstrated an altered character in the small bowel's bacterial flora in patients with rheumatoid arthritis. However, the authors did not demonstrate the presence of bacterial overgrowth. The syndrome of bacterial overgrowth is characterised by diarrhoea with malabsorption. The mechanism by which the bacterial overgrowth causes symptoms is not known. These symptoms are related to an increase in the luminal bacterial flora and the presence of obligate anaerobes (colonic luminal flora) as judged by jejunal fluid culture or breath tests. The patients in the study did not have any evidence of malabsorption or diarrhoea.

The investigations used, apart from the bile acid deconjugation test, had not been previously validated in patients with bacterial overgrowth. Quantative bacterial culture was not done; the bacterial flora was of oral type, not colonic. The presence of enterobacteriacae (a facultative anaerobe), tryptic activity, gas production (both not specific to obligate anaerobes) and the use of jejunal biopsy culture (biopsies culture produces different flora than fluid culture) are not proven features of bacterial overgrowth of the small bowel. The controls used did not have the syndrome of bacterial overgrowth as they were clinically well (achlorhydria, whilst associated with an altered and increased bacterial flora, does not necessarily cause symptomatic bacterial overgrowth). Thus only the three patients with positive bile acid deconjugation tests could be considered to have investigational evidence of bacterial overgrowth. In view of previously reported changes seen in the small bowel's bacterial flora of elderly and infirm people,[2] perhaps the findings were not surprising considering the multi-system involvement of rheumatoid arthritis. To confirm their hypothesis that disease activity is due to and not causing the bacterial flora changes, the authors could have studied the influence of either proton pump inhibitors or antibiotics on disease activity.

S J LEWIS
Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW, United Kingdom

1 Henriksson A E K, Blomquist L, Nord C-E, Midtvedt T, Uribe A. Small intestinal bacterial overgrowth in patients with rheumatoid arthritis. *Ann Rheum Dis* 1993; **52:** 503–10.
2 Haboubi N Y, Montgomery R D. Small bowel bacterial overgrowth in elderly people: Clinical significance and response to treatment. *Age and Ageing* 1992; **21:** 13–9.

AUTHORS' REPLY: We appreciate the remarks made by Dr S J Lewis about the small bowel microflora in patients with rheumatoid arthritis (RA) and would like to give the following comments.

We feel that the two concepts *bacterial overgrowth* and *bacterial overgrowth syndrome* are sometimes confused. We used the concept *bacterial overgrowth* to designate an altered microflora in the upper small intestine in patients with RA, and the criteria were clearly stated in the article. The *bacterial overgrowth syndrome*, also known as blind loop or stagnant loop syndrome, is characterised by steatorrhea and other signs of malabsorption. We agree that our patients with RA did not have the bacterial overgrowth syndrome.

Dr Lewis, however, seems to presume that only an altered small intestinal microflora complicated by the bacterial overgrowth syndrome is of interest in patients with RA. This view has to be questioned as we still do not know what types or quantities of microbes demonstrated in the upper small intestine are of interest in these patients.

The aim of our study was not to describe a bacterial overgrowth syndrome in patients with RA, but rather to denote an altered small intestinal microflora. A combination of techniques was preferred to get a comprehensive picture of small intestinal microflora, as it has been shown that different tests may be necessary to detect bacterial overgrowth in the upper small intestine.[1] It has been suggested that a qualitative change may be more important than a quantitative change;[2 3] hence we used the growth of Enterobacteriaceae (*Escherichia coli* or *Klebsiella*) without counting the microorganisms as one of the criteria of bacterial overgrowth. These species originate from the colonic and not from the oral microflora.

The clinical significance of our findings is still uncertain. The RA patients with signs of bacterial overgrowth had significantly higher rheumatic disease activity as well as rheumatoid factor titre. Dr Lewis's suggestion that the changes in the small bowel bacterial flora may be secondary to multi-system involvement of RA certainly cannot be excluded. As for his contention that treatment with proton pump inhibitors or antibiotics would confirm our hypothesis, it should be noted that the small intestinal bacterial overgrowth in these patients was not only related to lack of gastric acid and that we know very little about the types of microorganisms involved; severe flare ups after treatment with antibiotics have been observed in patients with RA,[4] possibly by changing the intestinal microflora in the 'wrong' direction.

Å E K HENRIKSSON
Department of Rheumatology, Karolinska Hospital, S-104 01 Stockholm, Sweden

L BLOMQUIST
Gastroenterological Unit, Department of Internal Medicine, Karolinska Hospital, Sweden

A URIBE
Section of Gastroenterology and Hepatology, Department of Internal Medicine, Uppsala University Hospital, S-751 85 Uppsala, Sweden

1 Suhr O, Danielsson Å, Hörstedt P, Stenling R. Bacterial contamination of the small bowel evaluated by breath tests, ^{75}Se-labelled homocholic-tauro acid, and scanning electron microscopy. *Scand J Gastroenterol* 1990; **25:** 841–52.
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4 Henriksson Å E K. Unpublished observations.

Correspondence to: Dr Henriksson.

Relapsing polychondritis as a secondary phenomenon of primary systemic vasculitis

Papo *et al* recently reported[1] that in 33 patients with relapsing polychondritis (RP) low titres of (c/p)ANCA occurred in 24% of the cases. They concluded that low titres of cANCA therefore are not specific for Wegener's granulomatosis (WG). We do not think that this line of reasoning is correct. We and others have earlier reported that cANCA is a highly specific and sensitive marker for WG.[2 3] Thus we conclude that the presence of ANCA in RP, may instead indicate, that polychondritis occurs in the course of a primary systemic vasculitis (PSV), for example, WG.

We have seen such an association of PSV with polychondritis in six of seven patients with RP (three women, four men).[4] The diagnosis of RP was either made histologically or according to the diagnostic criteria established by McAdam *et al*.[5] In six patients, RP presented as a secondary phenomenon during an acute phase of a primary vasculitic entity. Autoantibody screening revealed cANCA (PR3 ANCA +) in two patients, pANCA in one patient and autoantibodies to native collagen type II in four. According to the Chapel-Hill-Definitions 1993[6] and the ACR-Classification-Criteria for PSV 1990,[7] the underlying PSV in these six patients was: histologically proven WG (PR3 ANCA +) in two cases, microscopic polyangiitis in three cases (one pANCA +), classic polyarteritis nodosa in one case (table).

We think that polychondritis can be diagnosed more often as a secondary phenomenon in PSV than has previously been recognised. The diagnosis of PSV has been considerably improved by the detection of ANCA and the establishment of ACR-Classification-Criteria and Chapel-Hill-Definitions for PSV. Subsequently, PSV with secondary polychondritis seems to be recognised more often. Although there are only very few case reports on the association of RP with recognised, classified PSV,[8 9] the coincidence of RP with unclassified vasculitic symptoms is said to be about 10%.[10] The occurrence of glomerulonephritis in RP seems to be even more frequent (29 of 112 patients).[11] These vasculitic symptoms may be attributed to an underlying PSV, that has not previously been recognised as such. We conclude that the occurrence of ANCA in RP should encourage thorough investigation for the presence of PSV, in which the polychondritis may be a secondary phenomenon. This is important, as the vasculitis determines the therapy and prognosis of the disease.

K HANDROCK
W L GROSS
University of Lübeck, Rheumaklinik Bad Bramstedt GmbH, Oskar-Alexander-Str 26, 24572 Bad Bramstedt, Germany

Table Vasculitic organ involvement and immunological features in patients with primary or secondary RP

Patient	*Organ involvement*	*cANCA*	*pANCA*	*Coll II Ab*	*Disease*
1	—			+	RP
2	B, (K), N, E, Ey, H, S	+			WG + Rp
3	B, E, (K)	+			WG + RP
4	B, (K), N, Ey, H, S			+	mPA + RP
5	B, E, (K)		+	+	mPA + RP
6	B, N, Ey			+	mPA + RP
7	B, N, H				cPAN + RP

Extended ELK-Classification (Nölle *et al* 1989): B = constitutional symptoms, E = ENT, Ey = eye, H = heart, (K) = kidney (non dialysis dependant), S = skin, N = nervous system, WG = Wegener's granulomatosis, mPA = microscopic polyangiitis, cPAN = classic panarteritis nodosa, RP = relapsing polychondritis

1 Papo T, Piette J C, Le Thi Huong Du *et al.* Antineutrophil cytoplasmic antibodies in polychondritis. *Ann Rheum Dis* 1993; **52:** 384–5.
2 Nölle B, Specks U, Lüdemann J, Rohrbach M S, DeRemee R A, Gross W L. Anticytoplasmic Autoantibodies: Their Immunodiagnostic Value in Wegener Granulomatosis. *Ann Intern Med* 1989; **111:** 28–40.
3 Cohen Tervaert J W, Huitema M G, Hene R J, *et al.* Prevention of relapses in Wegener's granulomatosis by treatment based on anti-neutrophil cytoplasmic antibody titre. *Lancet* 1990; **336:** 709–11.
4 Handrock K, Schwarz-Eywill M, Kekow J, Gross W L. Rezidivierende Polychondritis: Eine eigene Entität oder Symptom einer systemischen Vaskulitis? *Medizinische Klinik* 1993; **88**(2): 3.
5 McAdam L P, O'Hanlan M A, Bluestone R, Pearson C M. Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. *Medicine* 1976; **55:** 193.
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11 Chang-Miller A, Okamura M, Torres V, *et al.* Renal Involvement in Relapsing Polychondritis. *Medicine* 1987; **66:** 202–17.

AUTHORS' REPLY: In their series of seven patients with relapsing polychondritis (RP), Handrock and Gross could detect ANCA in six patients, two with Wegener's granulomatosis (WG), three with microscopic polyangiitis and one with classical polyarteritis nodosa. They conclude that the presence of ANCA in RP indicates that polychondritis occurs as a secondary event of a primary systemic vasculitis.

Our experience is very different. Among our eight ANCA-positive RP patients, three only had vasculitis.[1] Among these three, WG could be diagnosed in only one with low titre (1/20) P-ANCA. The two others, one with C-ANCA and one with P-ANCA, had minor cutaneous vasculitis and no visceral involvement. Among our 25 ANCA-negative patients, nine had vasculitis (cutaneous in seven, quiescent WG in one, mononeuritis multiplex in one). These data indicate that ANCA may be detected in RP without defined systemic vasculitis, including microscopic polyangiitis. In the Mayo Clinic experience, eight of 22 patients with RP had ANCA with perinuclear or nuclear pattern.[2] Such discrepancies might result from recruitment bias and/or differences in the size of the studied groups, but also from the major problem of diagnostic procedures which requires further discussion.

Obviously, vascular involvement is frequent in RP and can affect vessels of any size, from aorta to capillaries. Its frequency has been said to be as high as 56% in McAdam's series.[3] In RP, microscopic angiitis has proved to represent the anatomical basis responsible for dermatological and renal manifestations, and is suspected to cause neuropathies, audiovestibular disturbances and episcleritis.[3 4]

RP is frequently associated with various inflammatory or autoimmune disorders, ranging from ulcerative colitis and rheumatoid arthritis, two ANCA-associated diseases,[5 6] to thyroiditis, spondylarthropathies and primary systemic vasculitides, including Behcet's syndrome.[7–9] Some of these diseases are clearly distinct from RP but *associated* with, while others *share*, many manifestations with RP which results in obscure nosological considerations and difficult differential diagnosis. The main problem is trying to distinguish RP from WG,[10] since both diseases frequently have striking similarities, mainly saddle nose deformity and laryngotracheal involvement (although resulting from different processes), arthritis, episcleritis and skin vasculitis. Necrotising glomerulonephritis, otitis, sinusitis, nasal septal perforation and proptosis, which are more suggestive of WG, also occur in a small percentage of patients with RP.[8 10] Unfortunately, tests for ANCA are not available in reports for those patients with 'atypical' manifestations of RP. Last but not least, auricular chondritis, which is supposed to be the hallmark of RP, has been described in a few patients with WG.[11 12] Facing this critical problem, physicians can get help from histological data and from some more specific clinical manifestations such as lung cavitary infiltrates or peculiar dermatological involvement for WG,[13] and conversely for RP diffuse tracheobroncheal dynamic collapse, ascending aorta aneurysm or dysmyeolopoietic syndrome in the absence of previous immunosuppressive treatment.[4 14] These features may diagnose some intriguing patients as probably having auricular chondritis in the course of an otherwise unremarkable WG.[11 12] In the absence of clearly discriminating data, an overlap between RP and WG is the only conclusion, as described in a case we recently reported.[15] Such puzzling problems, however, are restricted to less than 5% of cases in our experience of 100 RP and 75 WG. Extending the question to the whole spectrum of systemic vasculitis encountered in RP increases the ratio of patients concerned to 11 of 112 in Michet's series,[7] which remains far less frequent than suggested by Handrock and Gross.

Nevertheless, we agree with these authors that chondritis can probably occur as an epiphenomenon in the course of some definite inflammatory disorders. This is true not only for primary systemic vasculitides, but also for systemic lupus erythematosus,[16] possibly for other rheumatic diseases, and even for lepromatous leprosy.[17] Under such circumstances, cartilage involvement frequently differs from the typical features of RP, regarding the usual sparing of the respiratory tree and the lack of a relapsing/remitting course which defines RP. Histological data on auricular chondritis is rare.

A clear-cut categorisation of patients with vasculitic manifestations and chondritis seems impossible. Definitions of RP, WG and other vasculitides are inherited and remain purely descriptive of clinical symptoms and pathological data that sometimes overlap, in the absence of a comprehensive view of their pathophysiology and aetiology. Recent studies on ANCA have provided new and promising insights into the processes involved, but their application to diagnosis is mainly restricted to the close association of WG with ANCA specific for proteinase 3, which were constantly negative in our patients with RP.[1] Computer-derived criteria for the classification of vasculitides, such as those developed by the American College of Rheumatology are important for large studies but not particularly relevant for individual patients, especially in the discussion of overlaps between diseases sharing many manifestations. For example, a patient with a typical history of RP complicated by renal involvement switches to the diagnosis of WG in case of epistaxis,[18] a symptom only occurring occasionally in RP.[3] Conversely, a patient with a history of WG, including arthritis and episcleritis, can be classified as RP if auricular chondritis occurs, according to the empirical criteria used by Michet.[7]

Finally, some practical conclusions can be drawn for clinicians. In most cases RP is a primary disease, even in the presence of vascular manifestations. It should not be considered or treated as a vasculitis on the sole basis of ANCA positivity. However, in some rare cases patients share manifestations of RP and WG. Due to the poor response of WG to steroids alone, first-line regimes used in such patients with RP/WG overlap should probably include additional cyclophosphamide.[15]

J C PIETTE
T PAPO
LE THI HUONG DU
Service de Médecine Interne,
Groupe Hospitalier Pitié-Salpêtrière,
75651 Paris Cedex 13,
France

O MEYER
Service de Rhumatologie
Hôpital Bichat,
75018 Paris,
France

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