smokers.[5 6] It is interesting to note that NPC is associated with the Epstein-Barr virus,[7] one of a number of viruses which have been implicated in the pathogenesis of RA.[8] Therefore, passive smoke might potentially predispose subjects to RA as a result of changes within the nasopharynx resulting in antigenic stimulus by a virus that triggers RA.

We agree with the authors that new information is urgently needed about any factor associated with the risk of RA. In view of emerging data highlighting smoking as an important environmental risk factor for the development of seropositive RA,[3 9] and also this study by Heliovaara *et al*, we propose that passive smoking should be considered as a potential candidate factor for the development of RA.

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Authors' reply

It is not easy to measure passive smoking. Nevertheless, determinations of serum cotinine and thiocyanate recommended for the detection of indirect exposure to tobacco smoke have been shown to indicate exposures of recent occurrence.[1 2]

To test the assumption put forward by Drs Hutchinson and Moots we studied coffee consumption for its associations with serum cotinine and thiocyanate concentrations in a sample of men who had participated in the Mini-Finland Health Survey and served as an age matched control group in a nested case-control study of lung cancer.[3] A modification of the Nicotine Metabolite RIA kit method (Diagnostic Products Corporation, Los Angeles, USA) was used to determine serum cotinine concentrations.[4] Serum thiocyanate was determined by the spectrophotometric ferric nitrate method.[5] Of the total of 158 men in the sample, 39 reported current smoking, and 10 others had serum cotinine ⩾200 mg/l or thiocyanate ⩾20 nmol/l, suggesting direct exposure to tobacco. Exclusion of these men left 109 non-smokers for the final analyses.

No significant association was seen between the number of daily cups of coffee and serum cotinine concentration (age adjusted r=0.08, p=0.38). Contrary to the assumption of Drs Hutchinson and Moots, there was a negative correlation between serum thiocyanate level and coffee consumption (age adjusted r=−0.21, p=0.03). The findings are in agreement with our impression that in Finland coffee is not consumed to any greater extent in notably smoky environments. Rather, coffee consumption is confined to breakfast at home and coffee breaks both during working hours and leisure time.

On the basis of these preliminary results it seems unlikely that passive smoking would have correlated strongly enough with coffee consumption to explain the close associations between coffee consumption and the occurrence of rheumatoid factor (RF) and the risk of rheumatoid arthritis (RA) in our study. Nevertheless, our results are far from being conclusive. Whatever the links between coffee consumption, RF, and RA, we agree with Drs Hutchinson and Moots that passive smoking should be considered a potential risk factor for RA.

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LETTERS TO THE EDITOR

Polyarteritis nodosa complicated by thrombotic thrombocytopenic purpura

A 56 year old woman was diagnosed with polyarteritis nodosa (PAN) in June 1998 based on the presence of fibrinoid necrosis and infiltration of polymorphonuclear cells into medium and small sized arteries on a skin biopsy specimen. She presented with erythema on her arms and legs, with fever and body weight loss. Tender masses were palpable on her right abdomen. Small erythematous lesions and livedo reticularis were seen on the arms and legs.

Laboratory investigation on admission disclosed anaemia (haemoglobin 73 g/l) and leucocytosis (22.5×10^9/l) consisting mainly of neutrophils (85%). Creatinine clearance was 39 ml/min. Serological examination showed raised levels of C reactive protein (88.6 mg/l). Serological tests for syphilis, hepatitis B virus antigen, and antibody for hepatitis C virus were negative. A high titre of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) (201 EU) was detected in her sera. An abdominal computed tomography scan showed bilateral perirenal haemorrhages.

The patient was treated with 1000 mg of methylprednisolone for three successive days, followed by 500 mg cyclophosphamide intravenously. Plasma exchange was performed, also. Within three days, treatment had reduced the body temperature to normal and lowered the C reactive protein concentration (<10 mg/l).

The patient rapidly developed thrombocytopenia on the fifth day after admission to hospital, and the lowest platelet count was 15.0×10^9/l on the eighth day after admission. She became unconscious, and showed features of haemolytic anaemia and renal failure. A provisional diagnosis of disseminated intravascular coagulation was made because of thrombocytopenia, a low concentration of fibrinogen (1.6 g/l), and a high fibrinogen and fibrin degradation product level (22.6 μg/ml). We treated her with nafamostat mesilate (200 mg/day) and infusion of fresh-frozen plasma. This treatment produced a marked increase in fibrinogen concentration but failed to improve the platelet count. Further laboratory tests showed fragmented red blood cells in peripheral blood. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was established based on these findings. The patient was treated with plasma exchange with 2700 ml fresh-frozen plasma.

Within one week of treatment the platelet count returned to normal and consciousness level improved dramatically. However, renal failure was irreversible and she continued to undergo dialysis. Unfortunately, the patient died from haemorrhage from a duodenal ulcer. Necropsy findings included small and medium sized polyarteritis in the kidney, uterus, pulmonary hilum, hepatic hilum,

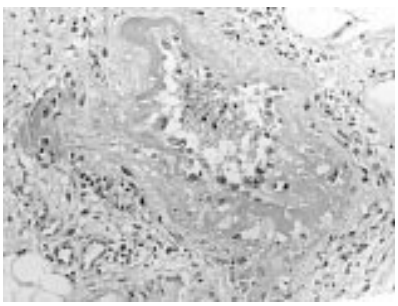

Figure 1 Necropsy finding of ileum end. Note fibrinoid necrosis of medium sized artery. Haematoxylin and eosin stain. Magnification ×400.

adrenal grand, ileum (fig 1), and ascending colon. Several stages of vasculitis existed, which was a typical finding of classic PAN. We failed to detect vasculitis affecting arterioles, venules, or capillaries. Duodenal bleeding was from peptic ulcers, which is not associated with arteritis.

A few reports have described TTP complicating certain forms of rheumatic diseases, including systemic lupus erythematosus and systemic sclerosis.[1 2] To our knowledge there are no reports published in English of PAN complicated by TTP.

The necropsy finding was classic PAN because vasculitis affected vessels larger than arterioles and there were no pathological findings of glomerulonephritis.[3] We failed to detect vasculitis affecting arterioles, venules, or capillaries. MPO-ANCA is usually a marker of microscopic polyarteritis or necrotising glomerulonephritis but does not distinguish it from classic PAN with certainty.[4]

Our case suggests the possibility of secondary TTP due to PAN. We speculate that endothelium damage by PAN may enhance the development of TTP, particularly in the presence of inflammatory processes. Our patient unfortunately died from massive bleeding from a duodenal ulcer. However, conventional treatment for TTP, including plasma infusion and plasma exchange, were effective in this case, too.[5] Our case emphasises the need to consider TTP when thrombocytopenia occurs with vascular disease, because early and correct treatment of TTP may improve morbidity and mortality in these patients.

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Placement of intra-articular injections verified by ultrasonography and injected air as contrast medium

Intra-articular injection of long acting corticosteroid is a corner stone in rheumatological treatment. The injected intra-articular corticoid is more effective when correctly placed.[1 2] Injection of radiographic contrast material has shown that fewer than half of the injections are correctly placed in the joint space after blind injection.[1]

Generally, the clinical application of ultrasonographic examinations can be enhanced by contrast agents.[3] The most commonly used technique is creation of microbubble contrast agents. Such agents, applied to the bloodstream, have been used for hepatic, nephrologic, cardiologic, and transcranial examinations.[4] Obviously, the risk of air embolism depends on the anatomical site of the injected air contrast. Transient ischaemic attacks are described after echocardiography with air contrast[5] and in animal models haemodynamic effects during venous air infusion can be measured.[6] Intra-articular injection of air and subsequent lateral and posterior radiographs have shown that this technique can enhance the precision of the procedure.[7] The disadvantage of this method is that the result can first be seen after the injection, and that a correction can only be made with a new injection. In the joint space the air is separated from the vascular system and when only small amounts of sterile air are used the risk of venous air embolism is negligible. Air is a very effective contrast medium in ultrasonography. Air sonography has been used for the diagnosis of meniscus lesions in knee joints[8] and for rotator cuff lesions in the shoulder[9].

We expand the applicability of this method to all joints, not only for diagnosis, but also for the correct placement of the needle before injection of medicine (steroid, osmium acid, viscosupplementation). The sterile air that is contained in the capped vial with lidocain or steroid is used as contrast medium. The needle is guided into the joint space of the distended capsule by ultrasonography.

When the steroid and lidocain are mixed in the syringe a small volume of air will be in the needle itself (~0.05 ml). The air in the needle is clearly seen when the injection is started and will secure the correct placement of the needle. With this technique, it is not necessary to use two separate syringes and the inclination of the syringe will not cause the air to move from the needle to the bottom of the syringe.

If the knee is injected, injection directly into the recess of the knee is recommended, which will make the small volume of air momentarily visible.

Figure 1 illustrates the ultrasonography of a metatarsophalangeal joint in a patient before and after injected air. The intra-articular air is clearly seen. We have made over 1000 ultrasonography guided intra-articular injections without any complications. This method is easy, inexpensive, without risk and radiation, and should be used routinely in rheumatology. Chemical synovectomy of the knee, especially, should always be guided by ultrasonography, and with this technique smaller joins can also be considered for chemical synovectomy.

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HLA class II alleles and synovial fluid cytology in RA

Rheumatoid arthritis (RA) is associated with HLA-DR4, which is encoded by the DRB1 gene. This genetic predisposition has been shown to lie within the sequence motif present in the third hypervariable region of the DRB1 gene.[1] This sequence of amino acids has been called the "disease epitope" and can be encoded by DR4 subtypes as well as non-DR4 alleles; DR1 subtypes, DR10 and DR14 subtypes .[1] Hence, it is also termed the shared epitope. In addition to imparting susceptibility to RA, HLA-DR4 has also been shown to be associated with the severity of the rheumatoid disease, including destructive erosive joint disease, rheumatoid factor positivity,[2] and extra-articular manifestations, such as rheumatoid nodules, vasculitis, and Felty's syndrome.[3 4] HLA-DQ genes are in linkage disequilibrium with HLA-DR and subjects who are DR4 positive may either be DQB1*0301 or *0302 positive; certain extra-articular features of RA have been shown to be associated with HLA-DQB1*0301.[4 5]

Synovial fluid cytology in RA is heterogeneous both with respect to total white cell