Pulsed electromagnetic field therapy in the management of knee OA

It seems most unusual that in a review of “all currently available treatments” for knee osteoarthritis (OA) by 21 authorities and “two experts in the field of guidelines methodology”, pulsed electromagnetic field therapy was not mentioned in the text or the 51 references. This is particularly troubling because over 2800 publications between 1966 and 1998 were retrieved. An identical search for efficacy of magnetic field therapy during this period listed 31 studies with at least one control group, including two double blind trials citing benefits in knee OA from a peer reviewed arthritis journal.1 In 1999 over 50 000 patients received pulsed signal therapy (PST) prescribed by over 1000 doctors at more than 300 clinics and hospitals in 16 countries, where it is usually reimbursed by fiscal intermediaries because of its proven record of cost effectiveness and safety. A summary of PST double blind and randomised study results in over 50 000 patients has been published,1 and findings in 100 000 patients (the vast majority with knee OA) have also been reported at recent international conferences. Although “alternative” treatments ranging from minerals, vitamins, nutritional supplements, and capsicain and diclofenac gels to sex hormones were discussed, in contrast with PST, none satisfied the criteria the panel established to determine strong recommendation. Nor do any have the solid basic science studies that PST provides with its in vitro support for mechanisms of action to explain efficacy based on proteoglycan synthesis and chondrocyte regulation results.

Pulsed signal therapy is the result of three decades of research designed to characterise the piezoelectric signal that normally stimulates chondrocyte activity by creating a streaming potential in the extracellular matrix when bone is subjected to pressure. Although the transmission of this signal is impaired in OA, PST can reproduce this stream of potential in the extracellular matrix of human chondrocytes in culture. Proceedings of the International Conference on Bioelectromagnetics and Medicine, 1998; 429–434.

Although I am certified in cardiology and gastroenterology, a significant portion of my practice is now devoted to exploring how PST achieves its benefits.2 I have treated 1000 patients, most of whom had knee OA, with very gratifying results similar to those reported in the literature. The panel cited two prior efforts to establish guidelines for treating knee OA, emphasising that these “primarily represent consensus statements from expert panels”3 and “the type and strength of evidence to support such guidelines remain unclear.” Their stated objective, therefore, was “to develop guidelines relating to clinical issues in OA management, and to indicate clearly the level of evidence to support individual statements.”4 However, electromagnetic therapy approaches were again omitted, though at least one of the members is quite familiar with PST. The reason for this exclusion is not clear and I believe that your readership deserves to be aware of this extremely safe and effective option.

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Authors’ reply

We thank Dr Pfeiffer for raising this point. The EULAR recommendations for the management of knee osteoarthritis combined an evidence based approach and a consensus approach. The evidence based approach—that is, the literature research, was only applied for the treatment modalities selected by the experts at the first meeting of the committee (see table 1 of the paper).

Pulsed electromagnetic field therapy, with other less commonly used interventions, was not included in this list, and its evidence for efficacy was therefore not assessed. However, as emphasised by Dr Pfeiffer, evidence based evaluation of all other interventions would be of interest and could be considered for inclusion in the next round of evidence based guidelines.

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I read with much interest the article of Derksen et al in the January issue of the Annals of the Rheumatic Diseases.1 The authors gave a detailed introduction to the result of treatment of pregnant patients with antiphospholipid syndrome (APS). Despite the presence of only a limited amount of data from controlled studies the authors gave helpful recommendations for the daily management of these patients.

However, there is a major concern with which I would like to deal. As we know the success of treatment of APS with oral anticoagulants very much depends on the strictness with which the dose is adjusted to the international normalised ratio. The authors rightly suggest changing from oral anticoagulants to subcutaneous low molecular weight heparin in pregnant patients with APS. However, I believe that the dose of low molecular weight heparin has to be adjusted in individual patients.

The measurement of anti-factor Xa activity in plasma enables us to calculate the dose of low molecular weight heparin which is needed to achieve optimal inhibition of the coagulation cascade. Values of 0.6–1.0 U/ml are believed to give maximum protection against thromboembolic events.

From my experience the optimal dose of low molecular weight heparin may be different in different patients. Moreover, a second injection has to be applied to achieve optimal effect. Therefore, as long as controlled data are missing I would suggest the measurement of anti-factor Xa activity in pregnant patients with APS should be used to adjust the dose of low molecular weight heparin. This may result in better protection of mother and fetus in this disease.

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Authors’ reply

We thank Dr Fiehn for his interest and comments on our recent leader in the *Annals.* At present, there are insufficient data from randomised trials to give evidence based guidelines for optimal (prophylactic) treatment of many of the clinical manifestations of the antiphospholipid syndrome (APS). This not only holds for prevention of pregnancy related complications, the topic of our leader, but also for treatment of thrombosis related to antiphospholipid antibodies.

The major issue raised by Dr Fiehn is that he believes that in patients with APS one should use adjusted, not fixed, doses of low molecular weight heparin (LMWH). It is well known that anti-Xa activity relates to anti-thrombotic effects of LMWHs, and that the amount of LMWH needed to achieve and maintain a certain range of anti-Xa activity increases during the course of pregnancy. In most patients dose adjustment is needed in the second to third trimester (mean 20.5 (8.2) weeks), but individual patients vary widely in the time when the dose of LMWH needs to be adjusted from from twice to twice daily. Despite this, there is so far no clinical proof that for thrombophrophylaxis in pregnancy or prevention of poor pregnancy outcome an adjusted dose LMWH (with cumbersome and costly monitoring of pre- and post-injection anti-Xa activity) is better than a fixed dose based on body weight. Therefore, we do not share Dr Fiehn’s view that one should adjust doses of LMWH in all pregnant patients with APS.

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Interleukin 1 gene polymorphisms

I read with interest the recent article by Grilly and colleagues on the potential use of interleukin 1 (IL1) gene polymorphisms in predicting the need for joint surgery in patients with rheumatoid arthritis. Although the authors’ findings are certainly encouraging and worthy of further investigation, I would like to raise a couple of points as to how these were arrived at in the first place.

When adopting the “candidate gene” approach in any disease association study, it pays to consider carefully the physiological context of a hypothesis. In this case the authors worked on the premise that one of the IL1 gene family polymorphisms might correlate with disease outcome. These included polymorphisms both in the IL1 genes and the IL1 receptor antagonist (IL1ra) locus. The IL1ra is unique in being the only known endogenous competitive receptor antagonist. The genes encoding IL1α, β

Cauld epidural injections

Price et al recommend that caudal epidural injections should be carried out with x ray screening. In practice the technique of performed in the outpatient clinic, where screening facilities are not usually available. I have reviewed the outcome of 44 unscreened caudal epidural injections given to 34 patients in my outpatient clinic in the 12 months from July 1999 to June 2000. Patient selection was based on the basis of unilateral nerve root pain in the leg in the presence of symmetrical straight leg raising. However, nine patients had asymmetrically reduced straight leg raising and four of those with full straight leg raising had pain in the L4 dermatome, mostly with a positive femoral nerve stretch test on the affected side. Spinal mobility and the presence or absence of a neurological deficit did not influence the decision to offer an epidural injection.

The procedure was carried out with the patient lying prone on the examination couch. After thorough skin preparation and a local injection of 2 ml lidocaine (lignocaine) 2%, 40 mg triamcinolone hexacetonide mixed with 10 ml lidocaine 0.5% and 10 ml normal saline was injected into the epidural space through the sacral hiatus with a 20G spinal needle. The patient was subsequently kept prone for 30 minutes and remained horizontal for a total of 60 minutes before being allowed home.

Six of the patients were subsequently given a second epidural injection and two of them received three. In the 12 month period. The procedure was repeated only if there was a satisfactory response to the original injection.

For the purpose of this audit, outcomes were graded as:

1 Complete or substantial relief of root symptoms for a minimum of three months.
2 Temporary relief for between one week and three months.
3 A sustained partial response (up to 50% reduction in pain).
4 No response (negligible pain relief or pain reduced for less than one week).

For the first epidural injection, 13 patients were cured of their root pain or obtained relief for three months or more, six derived temporary relief, four partial relief, and 10 showed no response. One of the non-responders was subsequently deemed to have Achilles tendinitis rather than S1 root pain. The outcome in the remaining case is unknown as the patient defaulted from follow up.

Of the eight patients who received a second epidural injection, three were cured or had sustained relief, three partial relief, and two did not respond (despite previous satisfactory responses for four and nine months, respectively). Of the two patients who were given a third epidural injection, one enjoyed sustained relief of pain while the other had temporary relief for six to eight weeks.

In brief, 23/34 (68%) of patients experienced at least a temporary or partial response to the initial unscreened caudal epidural injection and of the eight patients who were given either two or three epidural injections, four obtained sustained relief from their leg pain. There were no complications from the procedure.

On further analysis of the results, 68% of patients with full straight leg raising showed at least a temporary response to the first epidural injection compared with 44% of those with asymmetrically reduced straight leg raising. Of patients with a neurological deficit, 85% experienced at least temporary pain relief.

Sixteen patients (47%) were ultimately referred to the clinic for pain management services for nerve root blocks and three (9%) for a surgical opinion on the basis of the results of a magnetic resonance imaging scan of their lumbar spine.

Although x ray guidance theoretically might improve the accuracy of placement of the spinal needle, these results show that caudal epidural injections can be carried out safely and effectively in an outpatient setting without radiological screening. This also ensures prompter treatment for the patient.

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Authors’ reply

Dr Sheehan’s letter describes an audit of the efficacy of caudal epidural injections. His audit clearly describes outpatient use of caudal epidural injections as being well tolerated and safe.

The main issue of our paper was not safety, however, rather that a high proportion of caudal epidural injections are incorrectly placed and therefore unlikely to be of any therapeutic benefit. Effectiveness is less clearly shown by Dr Sheehan’s audit as he has no control group. It is well known from the epidemiological studies of sciatica, that most patients will improve spontaneously with time alone. The degree of improvements in the audit is not dissimilar to that expected from the natural history of the condition. It is therefore difficult to state that the caudal epi- dural injections were effective. Certainly it is not possible from this audit to state that screened epidural injections would not be more effective.

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and the IL1ra have co-evolved as a cytokine control mechanism:\' agents eliciting IL1 production generally induce IL1ra gene transcription as well, either directly or through a feedback loop triggered by IL1 itself. IL1ra competes with IL1 for binding to the cognate receptor but produces no known signalling events upon binding. Additionally, one of the two IL1 receptors, type II, also lacks any known signalling capability and is thought to function as a decoy binding site. If it is assumed that polymorphisms found in various members of the IL1 gene family modify gene function then the implication is that they should be studied collectively, not individually. In support of this argument comes recent experimental evidence showing that a IL1-1ra levels are determined free from allelic combinations within the IL1 gene family, as well as evidence for linkage disequilibrium between polymorphic markers spread across the IL1 gene family locus. It is fair to say that Crilly and colleagues did allude in their paper to the possible existence of an extended IL1 gene family haplotype. However, there is already sufficient published evidence to justify examination of haplotype combinations of the investigated alleles in population studies.

On a different note, although the authors' argument about the validity of surgery as a study end point is convincing, their selection of a 15 year disease duration free from surgery as the study end point is convincing, their selection of this study was not to differentiate between patients that will or will not require surgery but, rather, to differentiate between rapid (<15 years) versus delayed (>15 years to surgery) disease progression. Even so, a more valid statistical approach might have been to analyse all patients as a single group and try to correlate genotype (or haplotype) with disease duration to surgery.

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**Author’s reply**

I thank Dr Vamvakopoulos for his interest in our article and would like to make the following response.

We agree that testing for haplotype combinations of the interleukin 1 (IL1) gene family allele would be useful. However, for a large number of alleles to be tested a considerable sample size would be needed to correct for multiple allele testing. This would require a multicentre study; this is limited by funding constraints.

Secondly, for the statistical analysis we predefined early and late surgery. Analysis was undertaken after discussion with a qualified medical statistician. Should the corresponding wish to analyse our data, we would be happy to allow access if guarantees can be provided.

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**LETTERS TO THE EDITOR**

**A case of shingles mimicking carpal tunnel syndrome**

A 59 year old woman with an eight year history of seropositive erosive rheumatoid arthritis (RA) receiving sulfasalazine and penicillamine presented with severe sudden onset pain radiating from the left elbow to the left thumb, index and middle fingers. Examination disclosed synovitis of the left wrist, which might have caused median nerve compression. The wrist joint was injected with 20 mg of triamcinolone acetate with 1% lidocaine (lignocaine). She returned the following morning complaining of worsening pain. She was clinically well with no fever. White cell count was normal, but the erythrocyte sedimentation rate (ESR) was raised at 73 mm/1st h. A transcutaneous nerve-stimulating (TENS) machine was applied and she was prescribed amitriptyline 25 mg at night. The following day she had improved significantly but had developed a vesicular rash in the C6 dermatome consistent with herpes zoster infection (fig 1). Viral titres were consistent with current varicella zoster infection.

**DISCUSSION**

Establishing the cause of pain in patients with RA can be notoriously difficult. In addition to the psychological factors that influence pain perception, wrist and hand pain may result from rheumatoid synovitis, soft tissue inflammation, or mechanical nerve compression at wrist, elbow, and cervical spine. Herpes zoster infection is heralded by burning discomfort in a dermatomal distribution, which may occur for up to five days before the onset of the typical rash. Cervical dermatomes are affected in up to 15% of patients and may result in diaphragmatic paralysis and lower motor neurone paresis. In this case the occurrence of prodromal symptoms of herpes zoster mimicked the symptoms of carpal tunnel syndrome, presumed secondary to RA synovitis.

RA increases the risk of herpes zoster infection. In one series the use of low dose methotrexate, long duration of disease, and seropositivity were risk factors for subsequent infection. Gold treatment may also increase the likelihood of shingles.

Immunocompromised patients should receive acyclovir early to avoid viral dissemination. In patients with RA the complexity of the differential diagnosis may delay diagnosis unless the possibility of herpes zoster infection is kept in mind.

Conflict of interest: none.

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fevers, gastrointestinal disturbances of nausea and vomiting, granulocytopenia, and hepato-cellular injury. More rarely, hypersensitivity can present with features of severe systemic infection and end organ dysfunction. Azathioprine is a commonly used immunosuppressive drug and is used in many medical specialties. Therefore recognising azathioprine hypersensitivity is important for all doctors. We report a case in which we suspect such an azathioprine hypersensitivity reaction.

A 32 year old Asian woman with mixed connective tissue disorder presented with a one day history of general malaise, fevers, and painful digits. Fourteen days earlier treatment had been started with azathioprine 50 mg daily, and her prednisolone increased from 5 mg to 15 mg daily owing to the development of proteinuria (1.5 g on 24 hour urine collection) and urticarial vasculitis on her lower legs.

On examination she was shocked, with a blood pressure of 70/30 mm Hg and had marked acrocyanosis (fig 1). The differential diagnosis included a lupus crisis or septic shock. She was treated in the intensive care unit with intravenous ceftriaxone, metronidazole, and prostacyclin for digital ischaemia after serial cultures were taken from all major sites. Staphylococcal toxic shock was excluded, with no growth on vaginal swabs and a negative staphylococcal toxin test. After negative cultures 1 g methylprednisolone was given for a possible flare up of her connective tissue disease. The azathioprine was discontinued. She improved despite concomitant intravascular coagulation. Multiple cultures from all sites did not identify any source of sepsis.

We suspected azathioprine hypersensitivity owing to:
- The timing of the patient’s illness in relation to the initiation of azathioprine
- The presence of recognised features of hypersensitivity—fever, chills, diarrhoea, hypotension, and hepatic dysfunction
- The effect of rechallenge. Three weeks after the presenting episode, one dose of azathioprine 25 mg was given for steroid-sparing effect (the initial illness was attributed to disease flare up); the patient had a more severe and rapid hypersensitivity response requiring treatment with intravenous colistin and haemofiltration in intensive care.

She improved after treatment with high dose corticosteroids. No cultures ever isolated an infective source.

This case shows the importance of recognising azathioprine hypersensitivity. Approximately 50 cases have been reported in patients with immune mediated diseases such as inflammatory bowel disease, multiple sclerosis, and immune thrombocytopenias, where the initial illness is often ascribed to sepsis or reactivation of underlying disease. Most reactions occur in the first four weeks of drug initiation. Hypersensitivity should always be included in the differential of fever, hypotension, and renal failure. The case was reported to the Committee on Safety of Medicines (United Kingdom).

The mechanism of the reaction is unclear. Azathioprine is composed of a nitroimidazole attached to 6-mercaptopurine. It is proposed that the imidazole component causes hypersensitivity, while the 6-mercaptopurine may cause haematological side effects. However, there are conflicting reports about the component of the drug to which the hypersensitivity reaction can be attributed. Fields reviewed 49 cases, where the reaction occurred equally in men and women, aged 16–76 years, and there was a wide variation in azathioprine doses. All patients who developed shock were also taking corticosteroids.

Support for an allergic reaction is that it occurs in only a small percentage of patients, and the event recurs with drug rechallenge, as occurred inadvertently in our patient. Rechallenge with azathioprine is therefore dangerous and should be done under careful observation. A hapten from the imidazole component may bind to a protein molecule to elicit type 1 hypersensitivity. Reactions mimicking sepsis may result from increased production of mediators such as tumour necrosis factor.

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Immunosuppressive treatment for vasculitis associated with Lyme borreliosis

Vasculitis of the central nervous system is a rare complication of Lyme borreliosis.1 We now report a case of early onset borrelia associated encephalitis followed by systemic vasculitis. Antibiotics failed to improve the clinical course and remission was only reached after extensive immunosuppressive treatment.

A 52 year old man was admitted because of fever, headache, tinnitus, and painful joints. He reported a tick bite on his left arm, which had occurred three weeks earlier and which was followed by a reddish skin erosion. His general practitioner started treatment with doxycycline, but the patient’s condition worsened. The patient had a fever of 39.9°C, further physical examination showed no other abnormalities. Except for an erythrocyte sedimentation rate of 51 mm/1st h and a leucocyte count of 16.1×10^9/l, routine blood analysis was normal. Cultures (blood, urine, stool) were negative. Enzyme linked immunosorbent assays (ELISAs) showed an increased anti-borrelia-IgM titre of 322.5 EU/ml (normal <30) with normal IgG levels, suggestive of early stage Lyme borreliosis. This was supported by western immunoblotting, with reactivity towards anti-borrelia-IgM. An ELISA was repeated after four weeks: the anti-borrelia-IgM was then raised to 800 EU/ml; the IgG level was also above normal. The number of splinter haemorrhages increased and a non-oliguric renal insufficiency developed, resembling a glomerulonephritis with microscopic haematuria, granular casts, and proteinuria (0.9 g/24 h). Screening markers of autoimmune diseases (antineutrophil cytoplasmic antibodies, antinuclear antibodies, cryoglobulins) were negative. A skin-fascia-muscle biopsy sample taken from the right leg showed vasculitis of medium sized arteries (fig 1). No spirochaetes were detected in this sample. Treatment with prednisolone (1 mg/kg/day) did not improve the condition of the patient within one week; therefore, cyclophosphamide (2 mg/kg/day) was added. Within two days the patient regained normal neurological functions. Renal function improved within four weeks (serum creatinine decreasing from 249 to 130 µmol/l, blood urea nitrogen decreasing from 56.4 to 24.4 mmol/l of urea) and the patient was weaned from the ventilator. Follow up was uneventful.

Vasculitis may develop within weeks after infection and complicate the clinical course of Lyme borreliosis. To our knowledge, this is the first description of a systemic vasculitis including cerebral and renal disease after Borrelia burgdorferi infection in a human being. Histological proof for vasculitis was assessed in a skin-fascia-muscle sample; the absence of spirochaetes therein suggests an autoimmune based pathogenesis.2 As in this case, laboratory support for acute B burgdorferi infection is an important issue, especially in endemic areas like the Netherlands.3 Whether elicited directly by the micro-organism or by secondary autoimmune mechanisms, vasculitis occurs in association with disseminated organ failure. Cyclophosphamide, successful in the case of B burgdorferi induced cerebral vasculitis,4 was effective for this case of systemic vasculitis as well.

In conclusion, persisting vasculitic activity should be suspected whenever antibiotic treatment does not improve the clinical course in Lyme borreliosis. When borrelia associated vasculitis has been histologically established, and does not respond to corticosteroid treatment alone, we suggest the combined use of prednisolone and cyclophosphamide.

Figure 1  Skin-fascia-muscle biopsy sample showing vasculitis of a medium sized artery and some necrosis of the vessel wall.

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Bilateral transient osteoporosis of the knee in pregnancy

Transient osteoporosis of pregnancy involving the hips has been reported widely. The knee is much less commonly affected and only isolated cases have been reported. We report the case of a woman in the third trimester of pregnancy with bilateral transient osteoporosis of the knees.
A 36 year old woman presented with a one month history of pain in the left knee followed a week later by pain in the right. The right knee deteriorated over one to two weeks until she was unable to weight bear. There was no pain at rest. At the time of presentation she was 30 weeks pregnant with her first child conceived through in vitro fertilisation. There was no constitutional symptoms. She walked with two crutches. Joint examination showed a slightly warm right knee with no clinical evidence of an effusion. Both knees were non-tender to palpation but painful at maximal flexion.

Investigations showed an erythrocyte sedimentation rate of 53 mm/1st h, C reactive protein slightly raised at 10 mg/l (normal <3), and globulins at 36 g/l (25–35) with a normal protein slightly raised at 10 mg/l (normal <3), with no evidence of anemia. The full blood count, and protein electrophoresis. Full blood count, and globulins at 36 g/l (25–35) with a normal protein slightly raised at 10 mg/l (normal <3), non-tender to palpation but painful at maximal flexion.

Figure 1 Magnetic resonance imaging at presentation. The T1 weighted sagittal image of the right knee shows diffuse low signal in the posterior aspect of the lateral femoral condyle. Note the low signal fluid in the knee joint cavity.

Transient osteoporosis is an uncommon condition affecting middle aged men or women in the third trimester of pregnancy. The hip joints are most commonly affected, being reported in 76% of cases. Antibodies against nuclear components are the hallmark of (a)typical cases and a review of the literature. Antinuclear antibodies, rheumatoid factor, and HLA-B27 were negative. Plain radiographs of the knees were normal. Magnetic resonance imaging (MRI) showed extensive oedema in the medial and lateral femoral condyles and some oedema in the surrounding soft tissues of the right knee (fig 1). There was an effusion in the suprapatellar bursa and some synovial proliferation. In the left knee there was a moderate amount of oedema in the medial femoral condyle and a trace of oedema in the medial tibial condyle.

A diagnosis of transient osteoporosis of pregnancy was entertained and the patient was treated with simple analgesics and followed up closely throughout the remainder of her pregnancy. She presented to the delivery suite in labour at 39 weeks’ gestation and successfully delivered a healthy 4500 g male infant by fast normal vaginal delivery. By three weeks post partum the pain had begun to resolve and she could walk without any aids. At three months post partum there was only residual discomfort in the right knee walking up and down stairs. Repeat MRI of the knees showed dramatic improvement in the bone marrow oedema. In the right knee there was only minor patchy oedema in the distal femur and proximal tibia. In the left knee there was some residual spotty marrow inhomogeneity in the lateral tibial plateau.

Anticholesterol antibody levels in patients with systemic lupus erythematosus

Systemic lupus erythematosus (SLE)—the prototype of immune complex diseases—is characterised by disturbances of the cellular and humoral immune systems. Antibodies against nuclear components are the hallmark of SLE, but a number of antibodies against proteins, glycoproteins, and carbohydrates have also been reported. Dyslipoproteinemia and accelerated athero-sclerosis, that commonly lead to coronary artery disease and other complications are recognised sequelae. The role of autoimmunity in the aetiology of atherosclerosis has recently been highlighted. Increased levels of antibodies against oxidised low density lipoprotein, lypo-phosphatidylcholine, and apolipoprotein A1 were found in patients with SLE. As reported earlier, we have shown marked alterations of anticholesterol antibody levels in patients with SLE.
(ACHA) levels in patients with various atherosclerotic vascular disorders. ACHA levels in patients with systemic lupus erythematosus (SLE) (55 women, five men), aged 42.6 (8.12), were enrolled into the study. The SLEDAI (SLE Disease Activity Index) score was used to measure disease activity. Patients were considered to have active lupus if they scored at least 2 on the modified SLEDAI scale (calculated by omitting anti-dsDNA and complement C3 and C4) and prompt antiphospholipid antibodies (APA) were obviously indicated to control their symptoms.

The level of cholesterol-specific antibodies was measured by a solid phase enzyme immunoassay described earlier. Polystyrene plates (Greiner, Frickenhausen, Germany) were coated with 5 µg/well cholesterol dissolved in 100 µl absolute ethanol and incubated at 4°C for 24 hours. After washing with PBS, washed and blocked with 0.1% casein (Reanal, Budapest, Hungary) in PBS, the wells were incubated with 100 µl samples of serum diluted 1:800 in PBS containing 0.1% casein. The binding of ACHA was detected by affinity-purified rabbit antibodies to human horseradish peroxidase conjugated γ-chain-specific rabbit antibodies (DAKO, Glostrup, Denmark), and with o-phenylenediamine (Sigma, St Louis, USA) using H2O2 as substrate. Optical density was measured at 492 nm (reference at 620 nm), and the mean of duplicates was calculated. Serial dilutions of purified immunoglobulin were used as standards in all experiments. Data obtained as optical density values were expressed in arbitrary units per millilitre (AU/ml), related to the standard curve. Our previous observations, in accordance with those of others, demonstrated the specificity of ACHA to cholesterol. The inter- and intra-assay variations of this method were 18.7% and 9.5%, respectively.

Differences between the parameters measured in controls and patients with SLE, between patients with active and inactive SLE, and those between patients with and without previous vascular events were calculated with the Mann-Whitney test. The χ2 test was used to estimate the discriminative power of ACHA between patients with SLE and healthy donors. The correlation of individual parameters with each other and with the SLEDAI score was calculated using Spearman’s rank correlation test.

Twelve samples (18%) were classified as having been obtained from patients with active SLE and 56/68 (82%) from patients with inactive disease. Three of the 12 “active” samples were from patients with SLE active in more than one organ system and nine were from patients with disease activity in one organ system only (mucocutaneous, joint, central nervous system, renal, or cutaneous). The difference between ACHA levels measured in the control group and in patients with SLE was significant (p<0.001) (fig 1). High ACHA activity in the upper quartile occurred in 29/68 (43%) patients with SLE and 13/60 (22%) controls (p=0.012). ACHA levels (mean (SD)) of patients with active (97 (81) AU/ml) or inactive (64 (38) AU/ml) SLE did not differ significantly (p=0.21) and did not correlate with the SLEDAI score (r=0.22, p=0.066). No correlation was found between the ACHA level and other parameters (such as anti-dsDNA, CH50, C3, and C4, data not shown). No significant differences were found between patients treated with corticosteroids for inactive disease or those with inactive disease and not receiving corticosteroid treatment (p=0.174). The latter group had not received corticosteroids for at least one year before blood samples were obtained. The difference between the ACHA levels of patients who had or had not experienced vascular events was not significant.

The observed increases of ACHA levels may be related to underlying chronic inflammatory disease. A number of conditions such as dyslipoproteinemia, nephrotic syndrome, and changes in cholesterol membrane domains might have elicited the increase of ACHA levels. Corticosteroid treatment might have stimulated ACHA production, though according to our observations this was obviously indicated to control their symptoms.

Intravenous immunoglobulin for treatment of gastrointestinal haemorrhage in dermatomyositis

Polyomysitis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting skeletal muscles and other organs, especially the digestive tract. Oesophageal motor disturbances are common, occurring in as many as 25–60% of patients with PM/DM. Gastrointestinal disease is less recognised in PM/DM, though it may be responsible for life threatening complications—for example, dramatic haemorrhage, perforation, pseudo-obstruction, and oxidized LDL in patients with SLE. Atherosclerosis (in press). The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). Arthritis Rheum 1982;25:1271-7.

the lungs, echocardiography, and abdominal ultrasound were normal. Treatment with prednisone was started at a dose of 1 mg/kg daily. As both the clinical and biochemical status continued to deteriorate gradually, the steroid regimen was increased to a dose of 1.5 mg/kg by the end of 1999.

In July 1999 the patient presented with a two week history of dysphagia and malaena evolving from one day. On admission, his general condition was poor and abdominal palpation was tender. Physical examination also showed cutaneous manifestations of DM and muscle weakness affecting both arms and legs. Muscle power of the patient was 65 points. Laboratory findings were as follows: C-reactive protein 30 mg/l, haemoglobin 6.6 mmol/l, mean corpuscular volume 90 fl, reticulocytes 150 x 10^9/l, white blood cell count 10 x 10^9/l, platelet count 490 x 10^9/l, CK 3000 U/l, and aldolase 13.5 U/l. Findings of renal and liver tests, total protein, and albumin levels were normal. Autoantibody screening was positive for ANA 1/1000 with a speckled pattern; other tests, particularly for anti Jo-1, rheumatoid factor, anti-cardiolipin and antiphospholipid antibodies, lupus-like anticoagulant, antineutrophil cytoplasmic antibodies, and cryoglobulin, were negative. Oesophageal manometry showed decreased peristalsis in the upper third of the oesophageal body and normal pressure in both upper and lower oesophageal sphincters. Gastroscopy demonstrated multiple small ulcerations affecting the stomach and the duodenum, with histology showing vasculitis of the small sized vessels. A diagnosis of gastrointestinal haemorrhage related to vasculitis and oesophageal impairment due to DM was made. The patient was given intravenous immunoglobulin at a dose of 1 g/kg for two consecutive days monthly for six months. Prednisone was simultaneously decreased gradually to 5 mg every 15 days. The patient had no gastrointestinal haemorrhage recurrence, swallowing disorders and muscle strength improved rapidly, and the dermatological signs cleared.

In November 1999 methotrexate treatment was started at a dose of 30 mg weekly. At one year follow up, the patient remains free of digestive, cutaneous, and muscle symptoms with methotrexate at a dose of 30 mg weekly and 12 mg prednisone daily.

Gastrointestinal motor abnormalities predominate in patients with PM/DM and have been extensively described, involvement of the gastrointestinal tract is considered to be less common.1 In a review of 96 patients with DM, Downey et al found that only four patients had gastrointestinal manifestations.2 Our findings confirm that gastrointestinal impairment is a major cause of morbidity in PM/DM, as our patient presented with life threatening gastrointestinal haemorrhage. A diagnosis of gastrointestinal vasculitis related to DM could reasonably be made for our patient because the onset of DM clinical deterioration and gastrointestinal impairment received intravenous immunoglobulin treatment, resulting in accurate diagnosis and management, and therefore decreasing both morbidity and mortality. The pathological mechanisms of gastrointestinal involvement are still not clearly understood in PM/DM, though it may be related to vasculitis of small sized vessels, leading to ischaemia, haemorrhage, and perforation of the gastrointestinal wall.3–5 Moreover, the present case is original, as our patient with DM and life threatening digestive impairment received intravenous immunoglobulin treatment, which prevented gastrointestinal haemorrhage recurring and produced dramatic and rapid remission of swallowing disorders. Authors have also mentioned a favourable outcome with intravenous immunoglobulin treatment in patients with systemic vasculitis—for example, Churg-Strauss vasculitis, microscopic polyangiitis, and lupus erythematosus.6–9 In this instance, a limitation was the concomitant continuation of steroids during the entire period of intravenous immunoglobulin treatment. However, the improvement of all gastrointestinal symptoms may reasonably be related to intravenous immunoglobulin treatment in our patient with DM because the gastrointestinal manifestations deteriorated persistently despite high doses of prednisone as a single treatment. The beneficial effect of the accompanying methotrexate treatment might also be excluded, as this later drug was started at the fifth month follow up of the patient.

Finally, our findings indicate that intravenous immunoglobulin should be considered the best treatment in both gastrointestinal and oesophageal haemorrhage related to vasculitis and oesophageal dysfunction due to steroid re-fractory DM, such a treatment offering the advantages of efficacy and good toleration. However, no definite conclusion can be drawn and further controlled trials with a large number of patients with PM/DM are required to establish optimal doses and effective management.

The most common form of facial paralysis is idiopathic—that is, Bell’s palsy. Sjögren’s syndrome (SS), a chronic inflammatory disorder characterised by lymphocytic infiltration of exocrine glands resulting in the so called “sicca complex”, is a rare secondary cause of this self limiting illness. Primary SS includes mostly peripheral, and to a lesser extent central, autonomic neuropathy and central nervous system involvement.1 A patient with unilateral facial palsy, autoimmune hypothyroidism, and Sjögren’s syndrome is presented.

A 41 year old woman developed right sided facial numbness, described as “dentist anaesthesia for tooth extraction”. One day later she had a reduced sense of taste and right facial weakness. General physical examination was not remarkable. Neurological examination showed anisocoria, peripheral right sided facial paresis, reduced sense of taste on the right half of the tongue, and dysaesthesia in the distribution of the second segment of the right trigeminal nerve. Although the erythrocyte sedimentation rate (ESR) was 30 mm/1st h, routine laboratory investigations were normal. Antinuclear antibody test, including IgG, IgG index, and oligoclonal or extra bands on electrophoresis, was not abnormal. Screening tests for herpes simplex and varicella virus, syphilis, and borrelia in the serum and in the liquor were negative. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Nerve conduction studies showed peripheral facial paresis. She recovered spontaneously from her symptoms within six months, during follow up the raised ESR persisted. Review of her medical history uncovered complaints of burning eyes and dry mouth, slight weight gain, and cold intolerance. There was a history of arthralgias and oral ulcers.

She denied using any drugs previously. A strongly positive anti-extracellular antigen (ENA)/SS-A antibodies test was shown on further investigation, with negative tests for antinuclear factor and anti-DNA antibodies/ rheumatoid factor and RNP/SS-B/Sm antibodies. Rose-Bengal staining showed corneal punctate lesions (van Bjiستerveld score 6). Lower labial biopsy showed histopathological findings matching the diagnosis of SS with a
focus score of one lymphocyte focus for 4 mm² salivary gland tissue. Additionally, thyroid function tests showed a raised thyroid stimulating hormone (11 mU/L), low free thyroxine (13.0 pmol/L) with positive antithyroid microsomal antibodies and negative antithyroglobulin antibodies.

The clinical, serological, and histopathological manifestations fulfilled the European study group criteria for the diagnosis of SS. The patient was treated with artificial tears and thyroxine supplements that returned her thyroid function tests to normal.

Prevalence of neuropathy in patients with SS ranges from 10 to 50%. Polynuropathy can be the first clinical manifestation of SS, and may even precede sicca symptoms in 40% of patients. However, less frequently, cranial neuropathy can occur with a predisposition to involvement of the trigeminal nerve. The vasculitic damage to vaso nervorum documented by pathologic studies is associated with a higher incidence of serum anti-SS-A (Ro) antibodies. The association of SS with autoimmune thyroid disease (AITD) is well recognized. AITD and SS share similarities in the immunopathology in addition to their genetic linkage to the HLA-DR3/DR4 alleles. Only nine cases of facial nerve involvement associated with SS have been described previously.

This case illustrates how facial palsy disclosed the primary SS as an underlying systemic disorder. To our knowledge the combination Bell’s palsy as presenting feature in a patient with SS, and hypothyroidism secondary to AITD has not been reported hitherto.

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### Table 1: Antitrypsin phenotypes in ANCA* (anti-PR3* or anti-MPO*) positive patients

<table>
<thead>
<tr>
<th>Phenoypes</th>
<th>ANCA+</th>
<th>Anti-PR3+</th>
<th>Anti-MPO+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous M</td>
<td>99 (63)</td>
<td>36 (60)</td>
<td>63 (65)</td>
</tr>
<tr>
<td>M1 M1</td>
<td>99 (63)</td>
<td>36 (60)</td>
<td>63 (65)</td>
</tr>
<tr>
<td>M2 M2</td>
<td>4 (3)</td>
<td>2 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>M3 M3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M4 M4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Heterozygous M</td>
<td>15 (31)</td>
<td>20 (33)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>M1 M2</td>
<td>48 (31)</td>
<td>20 (33)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>M1 M3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M1 M4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M2 M3</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other heterozygous</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M1 S</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>M2 S</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M1 other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>M2 other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>157 (100)</td>
<td>60 (100)</td>
<td>97 (100)</td>
</tr>
</tbody>
</table>

*ANCA = antineutrophil cytoplasmatic antibody; PR3 = proteinase 3; MPO = myeloperoxidase.

### Table 2: Antitrypsin alleles in ANCA* (anti-PR3* or anti-MPO*) positive patients

<table>
<thead>
<tr>
<th>Allele</th>
<th>ANCA+</th>
<th>Anti-PR3+</th>
<th>Anti-MPO+</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>250 (80)</td>
<td>94 (78)</td>
<td>156 (80)</td>
</tr>
<tr>
<td>M2</td>
<td>58 (18)</td>
<td>24 (20)</td>
<td>34 (16)</td>
</tr>
<tr>
<td>M3</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>M4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>S</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Z</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Total 314 (100) 120 (100) 194 (100)

*ANCA = antineutrophil cytoplasmatic antibody; PR3 = proteinase 3; MPO = myeloperoxidase.

Establish the distribution of α1AT in patients with the two main forms of ANCA (anti-PR3 positive and anti-MPO positive). Blood samples of patients with vasculitis received at the immunology department of the Section of Pathology, Queen Mary Hospital, Hong Kong, were tested for ANCA by indirect immunofluorescence, followed by enzyme linked immunosorbent assays (ELISA) for anti-PR3 and anti-MPO. α1AT phenotypes were determined by isoelectrofocusing, the results of which were compared with those of healthy Chinese adults.

A total of 137 samples from ANCA+ patients (either anti-MPO or anti-PR3 positive by ELISA) were evaluated, along with 64 (38%) of Chinese patients which were positive for anti-PR3 and 97 (62%) for anti-MPO by ELISA. All were Chinese patients with a clinical diagnosis of vasculitis. The total female ratio was 0.76 (0.04 for anti-PR3 positive and 0.67 for anti-MPO positive patients). The mean age of the two groups was 52.4 and 59.4 years, respectively. A total of 103 (66%) were homozgyous M, 50% (32%) heterozygous Z (for example, M1 M2), and 4% (3%) heterozygous M and a variant allele. Tables 1 and 2 show the allelic and phenotypic frequencies. In the female controls (n=1085), 717 (66.2%) were homozgyous M. Allelic variants were rare, accounting for only 0.7% of all alleles. The α1AT deficiency variant PiZ was absent in both the study group and the healthy control group. There was no significant difference in the proportion of homozgyous and heterozygous M phenotypes between the normal and the ANCA+ group (exact χ² test, p=0.10) and between α1AT deficient M (M1 M2) and 4% (3%) heterozygous M and a variant allele. This did not reach significance (1.26% vs 0.70%; exact χ² test, p=0.10).

The rarity of the PiZ allele in oriental and black populations has been previously reported, a finding which is confirmed for Chinese patients in this study. We found no association of α1AT variant phenotypes with ANCA in Chinese patients. It is interesting to note the large number of anti-MPO positive patients in the study group. In a separate study the anti-MPO to anti-PR3 ratio in Chinese patients diagnosed over a defined period was 1.4:1 (the reverse of the situation in white populations, where PR3-ANCA positive Wegener’s granulomatosis is much more common). Even for the Chinese patients who tested positive for PR3-ANCA, the positive predictive value for Wegener’s granulomatosis was less than 25%. The low prevalence of α1AT variant phenotypes may be one factor behind the uncommon presence of anti-PR3 in Chinese people. We conclude that α1AT does not have a significant role in ANCA.
associated diseases in southern Chinese among whom anti-MPO predominated.

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A case of cholesterol embolism with ANCA treated with corticosteroid and cyclophosphamide

We report a case of a patient with cholesterol embolism who showed positive for both myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) and who was treated with prednisolone (PSL) and cyclophosphamide.

A 50 year old man underwent cardiac catheterisation for back pain. The examination disclosed 90% stenosis of the right coronary artery and a saccular aneurysm in the thoracic aorta. The patient underwent percutaneous transluminal coronary angioplasty and the aneurysm was wrapped with an artificial blood vessel. Postoperatively, the patient had a fever, pleural effusion, abdominal pain, and increased white blood cell (WBC) count, CRP reactive protein, (CRP), and serum creatinine. The levels of blood and pleural effusion fluid were negative. PSL 15 mg/day was started. However, acute progression of renal failure required haemodialysis.

The patient was transferred to our hospital. Physical examination showed a temperature of 38.0°C and blood pressure of 178/98 mmHg. Cyanosis was noted in both heels and all toes with necrosis and ulcers at the tips of the fifth toes. He had an increased erythrocyte sedimentation rate (ESR) of 82 mm/1st h. Anaemia was noted with a red blood cell count of 2500×10⁹/l, while the patient’s WBC count was high at 12×10⁹/l. His platelet count (304×10⁹/l) was within the normal range. Biochemistry showed high levels of blood urea nitrogen (10.0 mmol/l of urea), creatinine (710 mmol/l), and CRP (11.3 mg/l).

Complements components were within normal ranges. PR3-ANCA and MPO-ANCA were high at 82E and 29E, respectively. After admission to hospital, circulatory disturbance in his toes worsened. A diagnosis of ANCA associated vasculitis was made based on systemic inflammatory findings and high levels of WBC, CRP, PR3-ANCA, and MPO-ANCA. High dose steroid treatment was started. Biopsies of the right heel skin and thigh quadriceps showed cholesterol embolism (fig 1). However, PSL treatment was continued together with three courses of cyclophosphamide pulse treatment because of persistent fever and high ANCA values. The treatment reduced the fever and toe necrosis, and the ulcers improved. ANCA gradually decreased to normal. The PSL dosage was reduced to 15 mg/day and the patient was discharged.

Cholesterol embolism predominantly affects elderly men with a history of hypertension, atherosclerotic vascular diseases, and renal insufficiency at the time of diagnosis. At least 31% of patients had a preceding history of anticoagulant use or the antecedent performance of a vascular procedure affecting the arterial circulation. The presence of these cholesterol embolisms within the vascular lumen triggers a characterised localised inflammatory and endothelial vascular reaction. The inflammatory changes resulting from cholesterol embolism may be responsible for many of the systemic manifestations such as fever, weight loss, myalgias, leukocytosis, eosinophilia, and a raised ESR. Thus cholesterol embolism is referred to as both vasculitis look-alikes and pseudovasculitis syndrome. The prognosis is poor, particularly in the presence of acute renal failure. Three ANCA positive cases of cholesterol embolism have been described. Peat and Mathieson reported an ANCA positive patient with dyspnoea and haemoptysis after acute deterioration of renal function. Cyclophosphamide and PSL improved the symptoms, but cyclophosphamide was discontinued and the PSL dose was reduced because renal and skin biopsies showed cholesterol embolisms. Subsequently, the patient died of intractable cardiac failure.

Kaplan-Pavlovic et al reported two cases of renal failure with positive MPO-ANCA.

The details are unknown for one patient. The other patient was treated with corticosteroid alone. This patient required haemodialysis and amputation of the toes. Although their treatment did not result in the improvement of vasculitis, the combination of PSL and cyclophosphamide was effective in our patient with ANCA.

This result suggests that active treatment with corticosteroid and cyclophosphamide should be considered in ANCA positive cases of cholesterol embolism.

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HLA-DRB1*0301 and DQA1*0501 in RA

Auranofin is an oral gold preparation used in the treatment of rheumatoid arthritis (RA). During treatment, proteinuria has been reported in approximately 3% of patients. In a few cases in which renal biopsies were performed, a membranous nephropathy was shown to have developed. Several anti-rheumatic agents have been reported to induce renal manifestations or drug induced lupus reactions, or both, in patients with RA. In these subjects a genetic predisposition for HLA has been previously suggested.

To determine whether similar genetic factors might be operative in auranofin induced nephropathy, we analysed the HLA-DRB1*, DQA1*, and DQB1* alleles in patients with development of renal manifestations or drug induced SLE reaction. Furthermore, we investigated if the renal side effects were associated with serological findings in accordance with systemic lupus erythematosus (SLE), thus indicating the development of a drug induced lupus reaction.

Six patients (three female, three male) who developed biopsy proven membranous nephropathy or significant proteinuria (>0.5 g/day) during treatment with auranofin are reported. All patients met the American College of Rheumatology criteria for RA. The median age before onset of auranofin treatment was 72 (52–83) years, 4/6 patients were rheumatoid factor positive and 2/5 patients were antinuclear antibody (ANA) positive. The median duration of auranofin treatment before the onset of proteinuria was 5 (4–10) months.

During auranofin treatment, two patients developed an increased ANA titre (1/200 and 1/1600) but no antibodies against anti-dsDNA, SSA/SSB, Sm, or RNP were detected. None of the patients developed an increased serum creatinine level. After withdrawal of auranofin, proteinuria decreased significantly or disappeared in all cases. Table 1 presents the HLA alleles. A high frequency of the alleles associated with SLE—namely, DRB1*0301 (DR3), DQA1*0501, and DQB1*0201, was recorded in the patients developing membranous nephropathy or proteinuria during auranofin treatment. Of these, DRB1*0301 and DQA1*0501 occurred in 4/6 of the patients, and 5/6 patients carried at least one of these alleles.

The importance of DR3 or DQA1*0501 in drug induced renal manifestations has previously been suggested in patients with penicillamine and sodium aurothiomalate induced renal side effects. Also, in accordance with these findings, the DQA1*0501 and DRB1*0301 alleles have been recorded in a high frequency in patients developing sulfasalazine induced nephritis.

In two cases the development of membranous nephropathy was accompanied by a simultaneous increase in the ANA titre, thus indicating development of a drug induced SLE reaction. However, both patients had previously presented some sign of an autoimmune reactivity pattern, which may confer a risk factor in the treatment with certain anti-rheumatic drugs in RA.

Simultaneous treatment with sulfasalazine had been given in two cases, but as the sulfasalazine treatment period was either limited, or lacked any time relation with the onset of proteinuria, it seems unlikely that the patients developed a drug reaction against sulfasalazine. Further arguments rejecting the possibility of a sulfasalazine induced drug reaction are the lack of anti-dsDNA antibodies and the rapid onset of proteinuria among the patients, thus contrasting with the findings reported in sulfasalazine induced SLE.

The mechanism for induction of membranous nephropathy during auranofin treatment is unknown. Interestingly, it has been suggested that gold can bind to and alter major histocompatibility complex-peptide complexes, thus giving a possible explanation of both beneficial effects as well as side effects during treatment. Another possibility is that auranofin may alter the cytokine pattern towards an SLE-like phenotype and thus facilitate the development of SLE associated manifestations in genetically susceptible subjects. In accordance with this hypothesis, auranofin or other gold preparations have been reported to inhibit the production of interleukin 1 (IL1), tumour necrosis factor α, and IL2. The effects on IL10, a cytokine reported to be increased in both patients with idiopathic SLE and their healthy relatives as well as in patients developing sulfasalazine induced SLE-like reactions, is unknown, however.

In conclusion, the data suggest that SLE related HLA alleles, with special focus on DRB1*0301 and DQA1*0501, may predispose to development of renal side effects or drug induced lupus reactions during treatment with auranofin, as also previously recorded during treatment with other anti-rheumatic agents. Development of drug induced SLE, here reported for the first time, may occur during auranofin treatment.