Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled “Antiphospholipid antibodies and RA: presence of β2GP1 independent aCL” by Bonnet et al published in the *Annals* in March 2001. We believe that the letter needs additional clarification owing to inconsistencies in the terminology, methodology of antiphospholipid antibody (aPL) detection, and determination of positive values.

The use of the term “anticardiolipin antibodies” was somewhat misleading. The term was introduced and abbreviated as “aCL,” a group of antibodies detected in many conditions, but the β2 glycoprotein 1 (β2GP1) dependence of the aCL was not defined, even though the authors focused on β2GP1 independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines the antibodies detected by the classical aCL enzyme linked immunosorbent assay (ELISA).—that is, both β2GP1 dependent and β2GP1 independent antibodies.

There were some potential methodological errors in determining β2GP1 independent aCL. It was shown that antibodies against β2GP1 (anti-β2GP1) from patients with the antiphospholipid syndrome (APS) have the ability to bind β2GP1 in complexes with cardiolipin only if the β2GP1 concentration in solution is high enough. The threshold concentration of β2GP1 was found to be just about 2 μg/mL, because no binding of anti-β2GP1 was seen when serum samples were diluted 1:200 or more. As the physiological concentration of β2GP1 in human serum is approximately 200 μg/mL, the threshold binding concentration is reached at a serum dilution of 1:100. In the presence of a relatively high concentration of endogenous β2GP1, the statement that antibodies detected by this method are exclusively β2GP1 independent is unjustified, as the sera containing high titres of anti-β2GP1 might have yielded positive results by the method described in the letter.

The definition of antibody units in the letter is not clear and using Harris’s standards for β2GP1 independent aCL is not appropriate. With the use of Harris’s standards, the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined. However, Harris’s standards were designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominantly, β2GP1 independent aCL. β2GP1 independent aCL were not defined in those standards and they were not meant as standards for β2GP1 independent assays.

The interpretation of anti-β2GP1 ELISA as a method to detect β2GP1 dependent aCL may not be valid in all cases. It was shown that not all anti-β2GP1 binding β2GP1 adsorbed on polystyrene high binding plates also recognize β2GP1 associated with cardiolipin. We reported this binding pattern for anti-β2GP1 in children with atopic dermatitis, and the same was shown also for some patients with autoimmune diseases, including APS.

The method for purification of β2GP1 was not described. Because the authors focused on patients with rheumatoid arthritis (RA), it should be ensured that immunoglobulins were specifically removed from the β2GP1 preparation. If this purification step was not carried out, traces of immunoglobulins in the β2GP1 preparation might have yielded positive results for sera containing high titres of rheumatoid factor (RF). In fact, all sera containing IgM anti-β2GP1 also had RF and the authors already suspected that this might be due to non-specific binding involving RF.

The method for determining cut off values was not explained and the number of normal human sera (NHS) included in the study as negative controls was not given. From the data presented in the letter, one may conclude that the cut off values were arbitrarily set at 20 units both for IgG and IgM isotypes of β2GP1 independent aCL and for anti-β2GP1. We recently compared the sensitivity of anti-β2GP1 ELISA and classical aCL ELISA. The results showed great differences between their sensitivities and therefore also between the cut off values calibrated by the same standards. In addition, the authors did not report the proportion of NHS positive for each assay and the values of positive samples compared with patients with RA. Instead, they just referred to one study, which is only one of the several published estimations of aPL in healthy subjects.

We would like to support our criticism by adding some data about aPL in our patients with RA. We randomly selected 53 serum samples from patients fulfilling the ARA criteria for RA and 53 NHS as negative controls. The samples were tested for anti-β2GP1, β2GP1 dependent aCL, and β2GP1 independent aCL. The assays were calibrated with β2GP1 dependent monoclonal aCL (IgG and IgM anti-β2GP1 ELISA and β2GP1 dependent aCL ELISA) and positive in-house standards (all IgA assays and β2GP1 independent aCL). The cut off values for anti-β2GP1 were set as described by calculating the mean ± 2 SDs of logarithms of absorbance values for NHS and the 95th centile value of 32 NHS for both β2GP1 dependent and β2GP1 independent aCL. For the anti-β2GP1 determination, we used affinity purified β2GP1 adsorbed on Costar high binding plates as previously described. The β2GP1 preparation did not contain any immunoglobulins or β2GP1 independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously by both β2GP1 dependent aCL on the same plate by adding β2GP1 in parallel duplicate wells. The final concentration of β2GP1 was 10 μg/mL. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β2GP1. For the final determination of β2GP1 dependent binding, the values obtained in wells without β2GP1 were subtracted from the values measured in wells with added β2GP1. The patients’ histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the χ² test where appropriate.

Table 1 presents the frequency of positive sera in each group (NHS, RA, RA-RF positive, and RA-RF negative). The frequency of increased anti-β2GP1, β2GP1 dependent aCL, and β2GP1 independent aCL was higher in patients with RA than in controls, but the difference was significant only for anti-β2GP1. There were no differences in the frequency of β2GP1 independent aCL in patients with rheumatoid arthritis (positive or negative for RF) and normal controls.

<table>
<thead>
<tr>
<th>No of positive samples:</th>
<th>Anti-β2GP1</th>
<th>β2GP1 dependent aCL</th>
<th>β2GP1 independent aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgA</td>
</tr>
<tr>
<td></td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
</tr>
<tr>
<td>NHS (n=53, n=321)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RA (n=53)</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=30)</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=17)</td>
<td>1</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; β2GP1, β, glycoprotein 1; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.
any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2GPI and anti-β2GPI dependent aCL of IgA isotype. Interestingly, 9/11 RA sera which showed binding to β2GPI adsorbed on a high binding plate did not recognise β2GPI associated with cardiolipin, as already reported.2 In contrast, 3/9 RA sera binding to β2GPI complexed with cardiolipin did not recognise β2GPI adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2GPI in RA, which may differ in fine specificity from anti-β2GPI in APS.

The sera from our patients with RA exhibited an even higher frequency of β2GPI independent aCL than that reported in the letter. As expected from reported data, the presence of β2GPI independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GPI (10 µg/ml) lowered the binding of β2GPI independent aCL by about 50%, probably owing to the competition between β2GPI independent aCL and β2GPI for the same binding sites on cardiolipin.

Conclusion, patients with RA may have anti-β2GPI and β2GPI dependent aCL, which might be associated with the signs of APS. The importance of distinguishing β2GPI independent aCL and β2GPI for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2GPI and β2GPI dependent aCL than that reported in the letter. As expected from reported data, the presence of β2GPI independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GPI (10 µg/ml) lowered the binding of β2GPI independent aCL by about 50%, probably owing to the competition between β2GPI independent aCL and β2GPI for the same binding sites on cardiolipin.

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5 Harris EN. Specificity and sensitivity of antibodies to β2-glycoprotein I and anti-β2-glycoprotein 1, and antinucleosome antibodies in patients with rheumatic diseases. J Rheumatol 1997;24:2139–44.

Authors’ reply
In response to the comments of Ambrozic et al we would like to make a number of observations to the data published earlier in the Annals.3 The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera. The dependence of aCL on β2-glycoprotein 1 (ß2GPI) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous ß2GPI in block- ing buffer (containing fetal calf sera or bovine serum). In our previous study solution did not contain bovine or calf sera but only purified bovine serum albumin. So, this method was adapted to detect antibodies directed against cardiolipin antigen alone and not against the complexes of cardiolipin bound to exogenous β2GPI. This method justified the terminology of β2GPI independent aCL for sera containing aCL without anti-ß2GPI antibodies. The absence of anti-ß2GPI antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen sera. The concentration of exogenous β2GPI contained in human serum is not significant at a 1/100 dilution (the dilution employed to screen sera), in comparison with the 10% of calf sera added to the test as source of exogenous β2GPI in the assays used for the detection of β2GPI dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2GPI) did not react with β2GPI in the other ELISA test specifically designed to detect anti-ß2GPI autoantibodies, and therefore which could detect hypothetically high titres of anti-ß2GPI antibodies contained in these sera.

Harris’s standards were used after calibra- tion of our positive control sera from patients with proven antiphospholipid syndrome (APS), which were used to perform controls in every microtiter plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera.4 The antiphospholipid antibodies, including aCL, are directed against several anti- genic targets. Among them, some epitopes are located on the cardiolipin alone. These data were described by Harris when aCL were first characterised in systemic lupus erythemat- sus sera reacting in a VDRL test. By radioimmunoassay, he showed that antibodies contained in these sera were directed against cardiolipin contained in liposomes used as a reagent of the VDRL test.5 These reagents were constituted by lipids alone without any other cofactor such as ß2GPI. So, Harris’s standard can also be used to detect aCL directed only against phospholipid and not against the complex ß2GPI-cardiolipin. In addition, the use of Harris’s standards seems to be better adapted to the detection of polyclonal anti- phospholipid antibodies, than monoclonal human aCL used as internal controls. The β2GPI used in our assay was provided by Stago laboratories (Asnières, France) and was purified from human sera. We used sodium dodecyl sulphate-polyacrylamide gel electrophoresis and western blotting to en- sure that this purified protein was not contaminated.

For every antibody determination, aCL and anti-ß2GPI autoantibodies, normal levels were established from sera of a large number of normal subjects (blood donors) as previously described.6 In this study, 50 serum samples, provided by consenting healthy donors, were tested as controls.

Cut off values were determined as the mean and two standard deviations of the arbitrary units obtained by reference to positive and negative internal standards. For every serum, we defined the corrected optical density (OD) (that is, the mean OD obtained in three coated wells minus the OD corresponding to non- specific binding of each serum, obtained in three uncoated wells). The cut off values defined for anti-ß2GPI and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-ß2GPI test were purified from patients with APS and were used according to previous studies.7,8

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-ß2GPI antibodies in normal sera. The percentage of positive normal serum samples was <3%. These differences between our results and those of Ambrozic et al are probably associated with a differing sensitiv- ity and specificity of the methods between the two laboratories.

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References

Methotrexate and postoperative complications
Grennan et al report the safety of continued methotrexate in the perioperative period.7 Previous investigators have despaired of answering this question due mainly to the difficulty in recruiting subjects.8 It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of wound complications.

Despite this important finding, we believe that the results of this study should be regarded with some reservation: continuation of methotrexate throughout the perioperative period should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate related pancyclopenya.9,10 Indeed, in a community based, observational study of metho- trexate use in 460 patients we found the
periprocedural period to be especially hazardous for patients with renal impairment and sepsis.

Two subjects developed pancytopenia under these conditions, one of whom died.

Although all consecutive patients were included in the study by Grennan et al, it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made about the prevalence of this in the study group. It is important to note that this is a study of methotrexate use in elective surgery.

We suggest caution should be taken in patients with renal impairment (best assessed by creatinine clearance) and in the elderly with comorbid cardiovascular disease when approaching surgery. Sudden volume loss, bleeding, or dehydration will impair methotrexate excretion and increase the risk of bone marrow toxicity in this group. It may be prudent in those assessed as at high risk of this complication to stop methotrexate one week before the operation and restart treatment one or two weeks after the operation, depending on postoperative progress. This time period without methotrexate treatment will not compromise control in the vast majority of patients, although after four weeks without treatment, most will have a flare of the disease.

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References

Authors’ reply
Dr Wluka draws attention to the potential hazard of methotrexate prescribing in sub-

jects with chronic renal failure and sepsis, and we would not disagree with this point. The risk of surgery is increased by any coinciden-
tial medical disease including renal failure and sepsis as well as chronic vascular disease. We noted this in our study.

The role of the doctor/rheumatologist is to ensure that any such chronic medical prob-
lems are under optimal control before elective orthopaedic surgery. Methotrexate treatment should not be withdrawn from patients with rheumatoid arthritis if the disease is well con-
trolled before elective surgery. The comments of Dr Wluka do not invalidate this conclusion.

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LETTERS

Proximal myopathy and bone pain as the presenting features of coeliac disease

It is rare for coeliac disease to present only with symptoms of osteomalacia, without the classic symptoms of diarrhoea, steatorrhoea, and abdominal discomfort.1-3

A 22 year old woman presented with 18 months of a waddling gait disturbance, hip and back x rays were normal. She experienced bone pain when being hugged, when laugh-
ing, or coughing, and had difficulty standing up from a low chair and holding her arms up to blow-dry her hair. She had extreme tiredness and thought she might have lost some weight, but there were no gastro-

intestinal symptoms.

On examination, she was pale and had dif-
ficulty squatting and holding her arms above her head.

Investigations showed a mild anaemia sec-
ondary to β thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphatase of 1375 U/L (nor-
mal 30–120 U/L), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.0 mmol/l (0.81–1.4 mmol/l), 25-
hydroxy vitamin D <5 nmol/l (15–110 nmol/l), and raised parathyroid hormone 53.1 pmol/l (1.0–6.5 pmol/l).

Investigations were carried out for a malab-
sorption syndrome. Antigliadin, antienthymo-
sial, and antiglutaminase antibodies were strongly positive, and a small bowel biopsy showed almost total villous atrophy, confirm-
ing the diagnosis of coeliac disease.

A bone scan demonstrated increased activity

throughout the skeleton, consistent with secondary hyperparathyroidism. Osteoporosis was demonstrated by dual emission x ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm² (2.65 SD below the young adult female mean) and the neck of the femur 0.633 g/cm² (2.9 SD below the mean).

Treatment involved a gluten free diet, ergo-
calcirol 3000 IU daily, calcium carbonate 600 mg twice a day, slow release ferrous sulphate 350 mg daily, and folic acid 5 mg daily.

Within two months her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphatase re-
duced to 374 U/L. Bone mineral density had increased markedly after 12 months of treat-
ment, with the lumbar spine increasing by 37% to 1.204 g/cm² (mean level for young adult women), and the neck of the femur by 39% to 0.878 g/cm² (0.8 SD below the mean). She had also gained more than 7 kg in weight, and repeat gastroscopy and duodenal biopsy were normal.

Osteomalacia is now an uncommon dis-
case, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965,1 there have been several case reports of coeliac disease presenting with bone pain, proximal myop-
athy, radiographic findings of pseudoarthrosis and Looser’s zones, or secondary hyperpara-
thyroidism evident on bone scan.2-5 Most patients were middle aged or elderly, responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates.6 A recent case finding study of coeliac disease showed that many patients in fact present with non-
gastrointestinal symptoms, of which anaemia is the most common.

Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area, secondary hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.2

Secondary hyperparathyroidism can de-
velop if this is not in the context of a bone mass loss and bone turnover. Low bone mineral density is probably due to a combination of hypocalcaemia, impaired bone mineralisation, and re-
duced exercise because of skeletal pain and proximal weakness.7

Early diagnosis of coeliac disease is impor-
tant because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determin-
ation of antigliadin and antidendymosial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.6,8 There is a genetic influence on the susceptibility to coeliac disease, with a 10% prevalence rate among first degree relatives. On screening our patient’s relatives, one of two siblings was also found to have coeliac disease. A strong association has been found with HLA-DR3 and DR5/DR7.8

Treatment with a gluten-free diet with sub-
sequent villous restitution on repeat biopsy has been associated with rapid gains and even normalisation of bone mineral density; the greater the degree of osteopenia, the more rapid the gain.9 The change is due to improvement of calcium and vitamin D status, leading to remineralization of the large volume of unmineralised osteoid matrix.2

Introduction of hormone replacement therapy in women approaching the meno-
pause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.10

Osteomalacia presenting with muscle weakness and aches may be the only present-
ing features of coeliac disease. Prompt treat-
ment and diagnosis is important because treatment with a gluten-free diet and hormone replacement therapy including vitamin D may lead to rapid and effective recovery.11

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www.annrheumdis.com

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more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. Both plasma and lysed PBMC samples were read on atomic absorption spectrophotometer (Perkin Elmer, Norwalk, CT) at a wavelength of 213.8 nm for Zn and 324.7 nm for Cu. The atomic absorption spectrophotometer was calibrated with reference standards obtained from Sigma Chemicals Company (St Louis, MA).

Thirty nine patients (31 women) with RA had a mean (SD) age of 36.2 (8.3) years (range 18–52) and mean disease duration of 53.8 (36.6) months (range 6–168). Twenty patients had inactive and 19 patients active disease, respectively. Twenty two healthy controls (14 women), well matched for age (mean age 34.2 (6.2) years, range 20–56) with the two patient groups, were studied at the same time. Both patients and controls were of middle socioeconomic status. Table 1 shows the plasma and PBMC levels of Zn and Cu.

Our results are in agreement with earlier studies which showed that plasma Zn levels are significantly lower among patients than controls (p<0.05). Additionally, it is shown here that Zn levels are significantly higher in patients with active RA than those with inactive RA (p<0.01). There was overall a negative correlation between plasma and PBMC levels of Zn and Cu.

The plasma and PBMC copper (µg/l) levels were significantly higher in patients with active RA than those with inactive RA (p<0.01). There was overall a significant negative correlation between plasma and PBMC copper levels. The effect of concomitant drugs must be considered. The number of patients receiving non-steroidal anti-inflammatory drug and second line drugs was similar. None of the patients received corticosteroids in the preceding eight weeks.

It would be premature to speculate about a possible role for supplementation with Zn and Cu for patients with RA. From the results shown in this study, patients with inactive RA had similar levels of Zn and Cu as controls. If the diet of patients with active RA were deficient in Zn (as shown by plasma levels) it would be unlikely to contain an excess of Cu and vice versa for PBMC levels. The more plausible explanation would be that this represents a redistribution of trace elements between plasma and PBMCs, and a control of inflammation would lead to levels close to those seen in controls. Hence, further studies need to be carried out on paired samples in a cohort of patients, once the disease is active and again when it becomes inactive. If plasma and PBMC Zn levels decrease with the control of inflammation and attain the levels of controls then there would be no indication for dietary supplementation with these metals.

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Table 1 Copper and zinc levels in plasma and PBMCs of patients with RA. Results are given as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma copper</td>
<td>1646 (357)</td>
<td>1716 (296)</td>
<td>1696 (348)</td>
<td>1646 (348)</td>
</tr>
<tr>
<td>Plasma zinc</td>
<td>687 (467)</td>
<td>732 (526)</td>
<td>710 (498)</td>
<td>702 (492)</td>
</tr>
<tr>
<td>PBMC copper</td>
<td>580 (432)</td>
<td>620 (472)</td>
<td>600 (452)</td>
<td>590 (442)</td>
</tr>
<tr>
<td>PBMC zinc</td>
<td>135 (28.6)</td>
<td>140 (30.4)</td>
<td>138 (29.2)</td>
<td>130 (28.5)</td>
</tr>
</tbody>
</table>

PBMCs, peripheral blood mononuclear cells; there was no correlation between age, duration of disease, rheumatoid factor positivity, or any second line drug with plasma or PBMC levels of Zn and Cu.

*Overall levels were significantly lower among patients than controls (p<0.05) and patients with active RA had lower levels than those with inactive RA (p<0.05).†Overall levels were significantly (p<0.05) and patients with active RA had higher levels than controls (p<0.05) and patients with inactive RA (p<0.05).‡Overall levels were significantly different between plasma and PBMC copper levels (p<0.05).§Overall levels were significantly different between plasma and PBMC copper levels (p<0.05).∥Overall levels were significantly different between plasma and PBMC copper levels (p<0.05).

References


Essential cryoglobulinaemia (type 1) in three patients characterised by Raynaud’s phenomenon, arthralgia-arthritis, and skin lesions

The relevance of monoclonal gammapathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gammapathy or
paraproteins in adults is about 1%. This incidence increases in people over 70 years of age. When a paraprotein is detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance (MGUS). Among these patients, about 1% develop a malignancy (mainly multiple myeloma, and in different disease entities like amyloidosis, malignant proliferative disorders, and in different disease entities like amyloidosis, malignant proliferative disorders, associated with hepatitis C infections, and rheumatic diseases. The overall incidence of paraproteins in adults is about 1%. This incidence increases in people over 70 years of age. When a paraprotein is detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance (MGUS). Among these patients, about 1% develop a malignancy (mainly multiple myeloma, and in different disease entities like amyloidosis, malignant proliferative disorders, and in different disease entities like amyloidosis, malignant proliferative disorders, associated with hepatitis C infections, and rheumatic diseases.

Owing to their immunochromeproperties, paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the so-called cryoglobulins. When cryoglobulins are detected in the serum of a patient, this finding is usually associated with the coexistence of paraproteins. Recently, three patients with a clinical picture of a necrotising vasculitis associated with an essential cryoglobulinaemia (type 1) were admitted to our department. The causative relationship between the cryoglobulinaemia and the clinical symptoms was reduced by the reduced severity of the clinical signs when paraprotein levels were decreased.

Case reports

Patient A was a 69 year old man who, in May 1999, developed extremely painful purpura of the upper part of the third finger of his left hand. In the following days the upper part of his upper leg became necrotic. Angiography of the arteries showed normal vessels. Immune electrophoresis showed the presence of 8 g/l of an M component (IgG). An assay for the detection of cryoglobulinaemia was positive. Cryofibrinogen determination showed no evidence for antiphospholipid antibodies and/or cryoglobulins, are common presenting manifestations of underlying IE.

Seroimmunological alterations, including antibodies and/or cryoglobulins, are common manifestations of infective endocarditis (IE). However, specific autoimmune disorders, such as cryoglobulinaemic vasculitis (CV) associated with IE have seldom been described. CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and complement 1q", in 70–90% of patients with CV a triggering role of hepatitis C virus (HCV) has been suggested. We report the case of two patients who showed a typical CV with severe neurological involvement as the presenting manifestation of underlying IE.

Case 1

In November 1994 a 63 year old woman presented with fever, purpura, paraesthesias, and pseudoaxotic gait. Her past clinical history was unremarkable except for a prosthetic implant of the left hip four years previously. Table 1 shows the main clinico-urological features. Repeated blood cultures were negative. Neurological examination showed abnormal tactile sensation in the arms and legs; mild ideomotor slowing down; shabby movements; and unsteady gait. An electrophysiological study recorded a moderate sensorimotor peripheral neuropathy, while chest x ray examination, abdominal echography, and eco-carotography were normal.

Cutaneous purpura biopsy disclosed a leuco- cytoclastic vasculitis. Truncocephalic magnetic resonance imaging showed a weighted high signal intensity, punchiform lesions at the white matter consistent with brain vasculitis. Thus a central and peripheral neuroopathy complicating CV was established, and prednisone (50 mg) combined with cyclophosphamide (100 mg) was given daily. However, the patient's clinical status progressively worsened and, finally, she died owing to cardiorespiratory failure two weeks after the initiation of treatment. Necropsy disclosed coarse endocardial vegetations on the left sided valves infected by 

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References


as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the aetiology of prevalent CV symptoms is often due to a delay in the diagnosis of IE. Furthermore, the CV seen in our two patients was strongly associated with other less common, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinicomicrobiological evaluation, including transesophageal echocardiography.

In conclusion, CV may represent the premonitory phase of IE, as CV associated with peptidoglycan antibodies in mixed cryoglobulinemia. Arthritis Rheum 1999;42:2507–16.


ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hydralazine, penicillamine, allopurinol, and propylthiouracil.11

Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis,11 other antihypertensive drugs, such as carbimazole and thiamazole, have been linked.12 Furthermore, ANCA positivity has been described in the course of Graves’ disease without vasculitis.13

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease. Diagnosis of the disease was based on typical signs and symptoms of hyperthyroidism, raised serum triiodothyronine and thyroxine, very low or undetectable thyroid stimulating hormone, and increased thyroid radioactive iodine uptake. All patients had been receiving treatment with carbimazole for at least two months. None of the patients were treated with propylthiouracil or any drug affecting the immune function. ANCA antibodies were determined by indirect immunofluorescence (IF) on ethanol fixed granulocytes, as described elsewhere.14 Staining patterns were described as cANCA, when a diffuse granular cytoplasmic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed, and as ANCA when a distinct, homogeneous, non-granular cytoplasmic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere.15 Hospital Universitair Germans Trias I Pujol is a 533 bed hospital situated on the outskirts of Barce- lona. It is a referral hospital serving a population of 700 000 inhabitants. The immunology laboratory is a reference centre.

ANCA (IF) were detected in 21 (60%) of the serum samples. The titre ranged from 1/40 to 1/2560. The immunofluorescence staining pattern was as follows: nine (26%) pANCA, seven (20%) cANCA, and five (14%) pANCA. ELISA was positive in just one case (for MPO) in the patient with an IF titre of 1/2560.

Our results are very similar to those of Agellana et al, who reported ANCA positivity by IF in 21 (29%) patients with Graves’ disease.16 The IF staining pattern was cANCA in five cases and pANCA in one case. Anti-MPO antibodies were detected only in one (5%) of the patients. In our study ANCA were detected in 21 (60%) serum samples. The IF staining patterns were more heterogeneous, but the ELISA results were similar.


Human MPO and human thyroid peroxidase (TPO) share global similarities which indicate that MPO and TPO are members of the same gene family. Therefore, it seems conceivable that MPO autoantibodies may cross react with TPO. Findings suggesting such a relationship were reported by Haapala et al. who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and 16 with thyroid disorders. 

There is a need to determine the actio-pathogenetic role of ANCA antibodies in Graves’ disease, the precise relation between ANCA and antithyroid drugs and, lastly, the antigens which are responsible for the ANCA positivity.

ANCA positivity in Graves’ disease may be attributable to either antithyroid drugs (thi-azazole or propylthiouracil) or to the disease itself.

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Acknowledgment

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References


**Table 1**

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal PGE</strong></td>
<td><strong>Basal PGE</strong></td>
<td><strong>Basal PGE</strong></td>
</tr>
<tr>
<td>Control</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Patient</td>
<td>0.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

IL, interleukin; INFγ, interferon γ.

Whole blood was incubated with or without PGE, 10 μg/ml, for six hours in the presence of Brefeldin A. Cells were stained with FITC-anti-CD3 and, after erythrocyte lysis and permeabilization, with the phycoerythrin conjugated anticytokines. Samples were analysed by flow cytometry.

www.annrheumdis.com
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation.1 Synovial and serum osteocalcin correlate positively.1 In ankylosing spondylitis (AS) the serum concentration of osteocalcin has been reported to be low2 or normal.3 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.5

To answer the question whether serum osteocalcin is a useful marker of disease activity in AS, longitudinal studies may be more sensitive and specific. For this reason changes in serum osteocalcin were correlated with changes in ESR, which is probably still the best marker of inflammation in AS.4

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age range (11) years; disease duration (9) years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, electrotherapy, underwater exercises, and radon treatment as prescribed by the patient’s doctor. Patients were advised not to change their drug treatment. The ESR was determined according to Westergren, the result at one hour being considered to be low6 or normal.7 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.

The following laboratory values were obtained: haemoglobin 113 g/L packed cell volume 0.35, leucocyte count 8.3×10^9/L, platelet count 371×10^9/L, erythrocyte sedimentation rate 71 mm/1st h. Other test findings, including serum electrolytes, blood urea nitrogen, and creatinine, were all normal. Echocardiography showed a dilated cardiomyopathy associated with severe mitral and aortic insufficiency. The patient was treated for heart failure with inotropic agents and furosemide (frusemide) and improved greatly.

At the fourth month of follow up a physical examination showed hypertension and decreased left radial and brachial pulses. A systolic blood pressure difference greater than 10 mm Hg between both arms appeared (right arm, 140/100 mm Hg; left arm, 110/70 mm Hg). Laboratory findings showed increased blood urea nitrogen and creatinine levels. Urine analyses disclosed microscopic haematuria and mild proteinuria. Antinuclear antibodies were positive (1:20). Protein electrophoresis showed a decreased serum albumin level, hypergammaglobulinaemia, and increased IgG, IgA, and IgM.

Taking into account the patient’s medical history, a lymphocyte proliferation test was not carried out on the patient. Enzyme linked immunosorbent assay (ELISA) and polymerase chain reaction tests for HIV-1 and HIV-2 were repeatedly negative, but we did not look for HTLV-1 and HTLV-2. Echocardiography disclosed dilatation of the thoracic aorta and stenosis of the left subclavian artery. Magnetic resonance imaging showed dilatation and irregular contour of the innominate and descending aorta, and narrowing of the abdominal aorta (fig 1). The patient underwent cardiac catheterisation and angiography. Angiographic examination showed narrowing of the left subclavian artery, dilatation of the thoracic aorta, and occlusion of the superior mesenteric and renal arteries. Moreover, the patient’s left kidney could not be visualised.

The patient received prednisone treatment (2 mg/kg/day), but he died in the initial steroid treatment period owing to severe cardiac failure.

Takayasu arteritis may be the third most common form of childhood vasculitis after Kawasaki disease and polyarteritis nodosa.
CD4+ lymphopenia may cause dysgammaglobulinemia and autoimmunity syndromes such as Takayasu arteritis.

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References

Recurrent orbital pain and diplopia in a 12 year old boy

A previously healthy 12 year old boy was referred to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia. The first disease manifestation had started three years before, when the patient suddenly presented with diplopia and painful periorbital and eyelid oedema. Limited abduction of the right medial rectus muscles. Electromyography showed increased insertional activity, fibrillations, and positive sharp waves. Ocular myositis was diagnosed. The oral prednisone dose was raised to 30 mg/day and rapidly tapered after improvement of signs and symptoms. In November 2000, cyclosporin (3 mg/kg/day) was introduced; no relapse of the ocular findings has been seen so far, and prednisone has been progressively reduced to the current dose of 5 mg/day.

The group of idiopathic inflammatory myopathies encompasses a variety of common and uncommon syndromes. The uncommon variants of myositis include orbital myositis, a condition that is rare in adults and even rarer in children. Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, ScI, giant cell myocarditis, and Crohn’s disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease, ocular myopathies, such as mitochondrial disorders and oculor dystrophies; and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinus thrombosis are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extraocular muscles. The clinical features are those of orbitopathy with optic neuritis, diplopia, ptosis, and lid retraction. The disease shows a marked response to corticosteroid therapy. Recurrence is common. Orbital magnetic resonance imaging (MRI) may be helpful in showing thickening of the extraocular muscles. Orbital biopsy is occasionally necessary to establish the diagnosis.

Figure 1 Magnetic resonance imaging shows dilatation and irregular contour of the descending aorta and narrowing of the abdominal aorta.

Figure 1 Orbital MRI (T weighted image with contrast) that shows increased signal and size of the right rectus lateralis muscle.
Hodgkin’s lymphoma is rare. Sciatica or spinal lymphoma, involving peripheral eosinophilia rising from 1% to 22% in the past five years was detected. Two years before hospital admission an extensive urticarial erythema developed. An abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotopic scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes. An MRI scan showed extensive infiltration involving vertebral bodies and appendages throughout the lumbosacral spine, being most intense at the biconcave L5; the appearance was consistent with lymphoma or myeloma (fig 1).

During his stay in hospital, the patient’s pain resolved completely after treatment with non-steroidal anti-inflammatory drugs, analgesics, and physiotherapy. His haematologist started treatment of the patient with chlorambucil 10 mg/day for 10 days to be repeated every three weeks, these cycles to be continued for 12 months.

Eight months after the diagnosis of spinal lymphoma, the patient has remained well and active; his back pain is minimal.

In rheumatology, it is essential to differentiate between malignant disease and the more common causes of back pain. Our patient was in a good physical condition, which is unusual for someone with malignancy, his presentation with low back pain appeared to be a typical case of sciatica, and the pain settled down with conventional treatment. Clinically there was no evidence of recurrence of lymphoma—for example, enlarged lymph nodes, weight loss, or fever. However, because of his age at presentation and significant past history thorough investigations were mandatory.

**Sciatia or spinal lymphoma**

The involvement of the central nervous system and vertebrae by low grade non-Hodgkin’s lymphoma is rare. In a previous “lesson of the month” in this journal, it was implied that there is always a bad prognosis for patients with spinal lymphoma; however, milder cases may also occur.

A 71 year old man presented to us in January 2000 with a three month history of severe low back pain affecting mainly the left lumbar area and buttock, radiating to the outer aspect of the left thigh and calf. He did not have bladder symptoms or history of recent falls. On examination, he looked well; there was no lymphadenopathy. He had restricted back movement with tenderness of lower lumbar spinal processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and coordination. Knee jerks were reduced, ankle jerks were absent, both plantars were down going, and there was no sensory deficit.

He had a past history of epilepsy, which was controlled by phenytoin and phenobarbitone. In 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypersplenism. Splenectomy was performed in 1994, his blood count returned to normal, and repeated full blood counts were stable. In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis but no infiltration. Treatment was started with citrinonate and calcium.

Investigations showed normal serum biochemistry apart from a mild increase of alkaline phosphatase, which was 242 IU/l (normal 60–220). The total white cell count was 24.7×10⁹/l, differential count showed neutrophils 3.5×10¹⁰/l (14%), lymphocytes 17×10⁹/l (69%), monocytes 4.0×10⁹/l (16.0%), eosinophils 0.2×10⁹/l (1.0%), basophils 0.06×10⁹/l (0.0%), and occasional atypical lymphocytes were seen in blood film. The erythrocyte sedimentation rate was 4 mm/1st h, a myeloma screen was negative, and prostate specific antigen was normal.

A lumbosacral spine x ray examination showed biconcave L5 with diffuse osteopenia.
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 1×10⁹/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed a calcified cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right anexectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.89×10⁹/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal <80), and total IgE 769 IU/ml (normal <100), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antineutrophil cytoplasmic antibody values were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaline and hyaline-crystal casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 55 g/l, a leucocyte count of 1.05×10⁹/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovariun histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyps.

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, but the poor response to steroids and cyclophosphamide was noted. The patient underwent a second laparotomy after three weeks of treatment. Peripheral blood leucocytes were 18.1×10⁹/l with 3% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to 435 IU/l. Purulent fluid in the peritoneal cavity and two perforations in the ileal wall were found. Bowel histology showed wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophilic infiltrates. Granulomas were not found. E coli grew from the peritoneal fluid. Intravenous metronidazole and gentamicin were started. Four days later a new perforation was suspected and a third laparotomy was done, showing a perforated necrotic small bowel plaque. A broad bowel resection was performed but the patient’s evolution was complicated by high fever, ileus, and vomiting, and she died 48 hours later. A necropsy was not allowed.

Abdominal pain is reported in up to 29–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described, the last of these being responsible for up to 10% of the CSS deaths. Acalcific cholecystitis, although very rare, may be the first and sometimes the unique manifestation of the CSS. Its evolution is usually tied, and sometimes only diagnosed at necropsy. Abdominal ultrasonography should be included in the routine screening of patients with CSS.

The right oophoritis was due to vasculitis, with an eosinophilic infiltrate suggestive of CSS (fig 1). As far as we know, this is the first reported case of CSS with confirmed ovariun involvement.

The ascitic fluid, rich in eosinophils, the eosinophilic infiltration of major omentum and the clinical evolution suggest that the peritoneal involvement was due to the CSS, an extremely rare complication of this disease. Eosinophilic peritonitis was suggested by Lanham owing to serosal involvement in the CSS,5 but has only been confirmed in one case so far.6

The poor response to steroids and cyclophosphamide is striking. Despite the reduction of the peripheral eosinophilia and ESR there was widespread eosinophilic bowel infiltration and vascular fibrinoid necrosis in the laparotomy samples. The evolution of the disease in our patient was catastrophic, especially as she had only one of the five Guillevin CSS mortality associated factors—namely, gastrointestinal involvement.7

In summary, CSS abdominal complications should be promptly suspected and treated. In addition, CSS ovariun involvement, although rare, should be included in the differential diagnosis of ovariun vasculitis.

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References

NOTICE
Dr Barbara Ansell CBE
A service of thanksgiving for the life and work of Dr Barbara Ansell will be held on Saturday 16 February 2002 at 11.00 am at Southwark Cathedral, London Bridge. Tickets may be obtained by sending a stamped self-addressed envelope to: Memorial Service, British Society for Rheumatology, 41 Eagle Street, London WCIR 4AR. All are welcome to attend.

FORTHCOMING EVENTS
3rd International Congress on Autoimmunity
20–24 Feb 2002; Geneva, Switzerland
Contact: Professor Yehuda Shoenfeld, 3rd International Congress on Autoimmunity, PO Box 50006, Tel Aviv 61500, Israel
Tel: 9722 314 0018
Fax: 9722 517 5674
Email: autoimm02@kenes.com
22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
Contact: Professor F.C. Breedveld, Leiden University Medical Centre, Department of Rheumatology, PO Box 9600, 2300 RC Leiden, The Netherlands
Tel: +31 (0)71 526 3598
Fax: +31 (0)71 526 6752
Email: F.C.Breedveld@lumc.nl
Website: www.ewr.r.org

Tenth Intensive Applied Epidemiology Course for Rheumatologists
11–15 Mar 2002; Manchester, UK
No previous experience in epidemiology is needed. The course is residential and limited to 24 places.
Contact: Ms Lisa McClair, ARC Epidemiology Unit, University of Manchester, Oxford Road, Manchester M13 9PT, UK
Tel: +44 (0)161 275 5993
Fax: +44 (0)161 275 5043
Email: Lisa@fs1.ser.man.ac.uk

OMERACT VI
11–14 Apr 2002; Bali
Includes two modules: MRI and economics; and four workshops: patients’ perceptions, imaging (healing), progressive systemic sclerosis, minimally important clinical difference and osteoarthritis.
Contact: Conference Organisers Q2Q, 7 Swann Street, Old Isleworth, Middleshcire TW7 6RJ, UK; or Peter Brooks, Faculty of Health Sciences, Level 1, Edith Cavell Building, Royal Brisbane Hospital, Herston 4029, Australia
Fax: +61 208569 9553
Email: tony@q2q.co.uk or p.brooks@mailbox.uq.edu.au

British Society for Rheumatology
XXIXth AGM
23–26 Apr 2002; Brighton, UK
Contact: BSR, 41 Eagle Street, London WC1R 4TL, UK
Website: www.rheumatology.org.uk

4th EULAR Sonography Course
25–28 April 2002; Madrid, Spain
The course is entitled “Practical use of musculoskeletal ultrasonography”
Contact: Esperanzo Naredo
Email: enaredo@eresmas.com
Website: www.eular.org/courses and www.samerint.it/eular

10th International Vasculitis and ANCA Workshop
25–28 Apr 2002; Cleveland, Ohio, USA
Contact: Deborah J Bork, The Cleveland Clinic Foundation, Desk A50, Center for Vasculitis Care and Research, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: 216 445 8533
Fax: 216 445 7569
Email: borkd@ccf.org
Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

International Congress: New Trends in Osteoarthritis
9–11 May 2002; Milan, Italy
Contact: Organising Secretariat, O.I.C. S.R.L., Via Fatebenefratelli 19, 20121 Milan, Italy
Tel: +39 02 65 71 200
Fax: +39 02 65 71 270
Email: osteoarthritis@oic.it

10th World Congress on Osteoporosis
10–14 May 2002; Lisbon, Portugal
Contact: IOF Secretariat, 71 cours Albert Thomas, F-69003 Lyon, France
Tel: +33 4 722 91 41 77
Fax: +33 4 722 90 90 52
Email: info@ioflyon.org
Website: www.osteounited.org

5th European Conference on Systemic Lupus Erythematosus
26–30 May 2002; Athens, Greece
Chairman Professor HM Moutsopoulos Secretariat: Amphithirion Congress Organising Bureau
Email: hmoutsop@med.uoa.gr
Website: congress.amphitrion.gr

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wyss, Executive Secretary EULAR, Wilkokerstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: eular@bluewin.ch
Website: www.eular.org

10th International Congress on Behcet’s Disease
27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behcet’s Disease. Up to eight young investigator awards, each of $500, will be awarded on the basis of abstracts submitted.
Contact: Professor Ch C Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabeckstrasse 60–62, 14195 Berlin, Germany
Fax: 49 30 84456908
Email: zoubbere@zedat.fu-berlin.de
Website: www.userpages.fu-berlin.de/~zoubbere
ISBD website: www.behcet.ws

29th Scandinavian Congress of Rheumatology
15–18 Aug 2002; Tromso, Norway
Contact: Hans Nossent, Department of Rheumatology, University Hospital Tromso, Norway
Tel: 47 776 27294
Fax: 47 776 27258
Email: 29scr2002@rito.no or revhan@rito.no

Translational Research in Autoimmunity
21–22 Sep 2002; Pavia, Italy
Contact: Organising secretariat: eventi S.R.L., Corso Cavour, 18/20 - 27100 Pavia, Italy
Email: tra@e20pr.com
Website: www.e20pr.com
Congress website: www.medicine.ucsd.edu/albani/2001meeting

OsteoArthritis Research Society International (OARSI) World Congress
22–25 Sep 2002; Sydney, Australia
Contact: OsteoArthritis Research Society International (OARSI), 2025 M Street, NW, Suite 800, Washington DC 20036, USA
Tel: +1 202 367 1177
Fax: +1 202 367 2177
Email: oarsi@oarsi.org
Website: www.oarsi.org

10th International Congress on Antiphospholipid Antibodies
29 Sep–3 Oct 2002; Sicily, Italy
Deadline for abstracts 1 Apr 2002
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kenes International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 5140018/9
Fax: 972 3 5140077 or 972 3 5172484
Email: aps@kenes.com
Website: www.kenes.com/aps

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases
14–17 Oct 2002; Nashville, Tennessee, USA
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA
Tel: (615) 343 7329
Fax: (615) 343 7534
Website: www.eicosanoids.science.eayne.edu

66th American College of Rheumatology AGM
25–29 Oct 2002; New Orleans, USA
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 290, Atlanta, Georgia 30045-4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@rheumatology.org
Website: www.rheumatology.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis
7–9 November, 2002; Barcelona, Spain
Contact: Yolande Piette Communication, Boulevard Kleyer 108, 4000 Léige, Belgium
Tel: 32 4 254 12 25
Fax: 32 4 254 12 90
Email: ypc@compuserve.com

Certifying Examination in Pediatric Rheumatology
18 Nov 2002
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA
Tel: 919 929 0461
Fax: 919 929 0461
Email: ypc@compuserve.com

Future EULAR congresses
18–21 June 2003, EULAR 2003 Lisbon, Portugal
9–12 June 2004; EULAR 2004 Berlin, Germany
8–11 June 2005; EULAR 2005 Vienna, Austria
21–24 June 2006; EULAR 2006 Amsterdam, The Netherlands
Essential cryoglobulinaemia (type 1) in three patients characterised by Raynaud's phenomenon, arthralgia-arthritis, and skin lesions

J G den Hollander and A J G Swaak

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