LETTERS TO THE EDITOR

Overexpression and Dysregulation of bcl-2 in Lymphocyte Subpopulations of Synovial Membrane

Sir—In agreement with Liang et al. [1], we also found a very strong bcl-2 mRNA expression in the synovial lining cells of synovial membranes (SMs) derived from patients with chronic rheumatic disorders, but we did not find a corresponding protein expression. This finding was comparable to the expression pattern in tonsillar epithelium, where no strongly stained cells for bcl-2 protein were present, but the in situ hybridization (ISH) staining was strong in epithelial cells except for superficial layers [2]. We conclude that the expression of bcl-2 mRNA and bcl-2 protein in the synovial lining layer reflects bcl-2 expression in epithelium, while it may be dysregulated in the follicular aggregates of lymphocytes in the SM (Figs 1 and 3).

By its function of preventing cells from apoptosis [3, 4], the bcl-2 protein plays an important role in B-cell differentiation in germinal centres [5, 6]. Some investigations have shown that the protein and mRNA expression of bcl-2 do not necessarily correlate. In germinal centre cells, the bcl-2 mRNA is highly expressed, whereas the bcl-2 protein expression is strong in the follicular mantle zone [2, 7].

In rheumatoid arthritis (RA), the transformation of the SM to immunologically active tissue with infiltration of B and T lymphocytes [8] and macrophages, which in some cases form follicular aggregates [9], is a characteristic feature besides the proliferation of synoviocytes. Recent investigations characterized these aggregates in some cases as germinal centres comparable to those in lymph nodes or spleen [10].

In an earlier study [8], we showed that bcl-2 protein is overexpressed in lymphocyte subpopulations of SM of patients with RA. So we also investigated the bcl-2 mRNA pattern in RA-SM by ISH on paraffin-embedded tissues. Therefore, a 26-mer oligonucleotide probe labelled with digoxigenin (DiG) was used in its sense (negative control) (Figs 2 and 4) and antisense form. Hybridizations were detected by alkaline phosphatase (AP)-conjugated...
anti-DiG antibody and enzymatic colour reaction with nitro blue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP) as substrate. We examined the SMs from 14 patients who were undergoing synovectomy or reconstructive joint replacement: 12 patients with definite or classical RA, one patient with ankylosing spondylitis (AS) and one patient with psoriatic arthritis (PA). The expression of bcl-2 mRNA in the follicular aggregates of RA-SM ranged from a few to nearly all the cells positively stained (Fig. 3). In one RA-SM and in the PA-SM, all cells were positive for bcl-2 mRNA. The AS-SM showed strong bcl-2 mRNA expression in its follicular aggregates, whereas in the lining layer the expression was balanced between positive and negative cells.

We conclude from our investigations concerning bcl-2 protein [8] and mRNA in follicular aggregates of RA-SM, that they result from a dysregulation of bcl-2, which is comparable to the distribution pattern in neoplastic follicles of a malignant lymphoma [2]. Because of the known anti-apoptotic impact of bcl-2 [1, 11, 12], we suggest that these infiltrates will not go into the pathway of programmed cell death (PCD) and as a result sustain the inflammation. This is supported by recent studies which have shown that the overexpression of bcl-2 did not directly induce a tumorigenic phenotype, but provides a survival advantage to cells by inhibiting cell death [13].

C. SCHORPP, A. GAUSE
Internal Medicine I, Saarland Medical School, D-66421 Homburg/Saar, Germany
Accepted 8 April 1997

polymerase chain reaction by sequence-specific primer (PCR-SSP); unfortunately, how consistent the results of the different techniques are, is currently unknown.

The aim of this work was to re-evaluate the expression of HLA-B27 by FC and PCR-SSP (which we define as the ‘gold standard’) in patients with ankylosing spondylitis (AS), which is considered to be the prototype for SpA.

In Spain, 12.8% [7] of AS patients have been shown to be HLA-B27 negative; this proportion is similar to that found by other authors in different populations. The present study was conducted on two groups of 13 patients each, diagnosed as having AS according to the New York modified criteria. The first group was typed as HLA-B27 negative and the second as HLA-B27 positive, both by the CTx technique.

Both positive and negative B27 patients had been studied at least twice by using the lymphocytotoxicity technique (polyclonal antibodies) prior to 1990. All patients were retyped for HLA-B27 by flow cytometry, using monoclonal antibodies from Beckton Dickinson. The reagent contains fluorescein isothiocyanate (FITC)-labelled anti-HLA-B27, clone GS145.2 (IgG1, kappa) [8]. They were also typed by PCR (Dynal for PCR-SSP) with primers that amplified all B27 subtypes. For statistical analysis, the kappa statistic [9] and test for significance were used.

The results obtained for the various types using the different techniques are given in Table I. The analysis for B27 by PCR-SSP confirmed that all 13 patients previously typed as B27 positive by CTx were in fact positive. However, only six of the 13 B27-negative patients were confirmed, the other seven being found to be B27 positive (kappa = 0.462, \( P = 0.008 \)) (not significant). The FC technique gives results that are 100% consistent with those obtained using PCR-SSP (kappa = 1, \( P = 0.000 \)).

Analysis by FC of 20 healthy donors routinely typed for complete HLA-B (B27 negatives) exhibited no reactivity to this monoclonal antibody.

The clinical features of the B27-positive and -negative patients are also summarized in Table I. No significant differences between the two groups in terms of severity or course of the disease were found.

The main argument against assigning to the HLA-B27 molecule the central role in the pathogenesis of SpA is the absence of the antigen in some individuals; while much evidence suggests ignoring this argument, its persistence is a serious hindrance to the development of pathogenic hypotheses involving B27 as a necessary factor for the disease to develop [10]. Our results, which require further support by wider studies of, preferably, the epidemiological–clinical type, suggest that whenever gene typing for HLA-B27 is not feasible, FC is to be preferred to the cytotoxicity technique.

Supported by a grant of the Junta de Andalucía (PAI).

E. COLLANTES-ESTÉVEZ, R. GONZÁLEZ FERNANDEZ,* E. MUÑOZ GOMARIZ, R. SOLANA LARA,* J. PEAÑA*
Unit of Rheumatology, University Hospital ‘Reina Sofia’ and Department of Medicine, University of Córdoba and *Service of Immunology, University

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Evolution</th>
<th>Setting</th>
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</table>

S, severe; M, moderate; B, benign; A, axial; P, peripheral; Mx, mixed.

TABLE I
Results of typing for HLA-B27 by lymphocytotoxicity, flow cytometry and PCR, and clinical and demographic features of patients.
Hospital 'Reina Sofia' and Department of Physiology, University of Cordoba, Cordoba, Spain
Accepted 4 April 1997
Correspondence to: E. Collantes Estévez, Facultad de Medicina, Departamento de Medicina, Avenida Menéndez Pidal s/n, E-14004 Cordoba, Spain.


Digital Sympathectomy for Ischaemia in Scleroderma

Sir—Scleroderma patients suffer a severe form of Raynaud’s phenomenon and may develop critical digital ischaemia with ulceration and gangrene [1, 2]. These features are often refractory to conventional therapy with calcium channel antagonists or hand-warming devices. Proximal surgical sympathectomy leads to poor long-term results, as sympathetic nerves supplying the digital arteries do not derive entirely from the cervical sympathetic trunk [3, 4]. By a novel technique, the digital vessels may be denervated under direct observation. Using the operating microscope, nerve fibres surrounding the proximal 2 cm of artery are dissected away [5]. A number of small series and case reports provide encouraging results for this technique [6–9]. Digital sympathectomy may be the only alternative to amputation when medical therapy has failed. Here we present a retrospective study of patients with scleroderma who underwent digital sympathectomy. The aims of the study are to examine the effect of digital sympathectomy on digital ulceration, severity of ischaemic pain and severity of Raynaud’s phenomenon. Thermography pre- and post-sympathectomy has been used to quantify any change in digital circulation [10].

Sixteen patients with scleroderma who had undergone digital sympathectomy were asked to complete a questionnaire. They scored digital pain pre- and post-surgery, the presence of digital ulceration pre- and post-surgery, the presence of pitting scars pre- and post-surgery, the complications of surgery and the overall impact of surgery.

Thermography was performed before and after surgery. Skin temperature was measured by infrared camera at 6 mm intervals from wrist crease to finger tip, and the gradient between finger tip and wrist crease recorded in degrees centigrade. Measurements were made at baseline, and 5 and 10 min after cold challenge.

There were 13 respondents. The mean follow-up period was 19.3 months. Mean pain score (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = worst pain ever experienced) fell from 3.9 before surgery to 3.2 after surgery (P < 0.022, 95% CI 0.12–1.3). The mean ulcer score fell from 0.92 per patient before surgery to 0.54 per patient after surgery (P < 0.018, 95% CI 0.079–0.69). The number of pitting scars rose from 0.58 before surgery to 0.83 post-surgery [not significant (ns)] (Table I).

The mean baseline wrist to finger tip temperature gradient was −3.5°C (s.e. 1.1) before surgery and −4.1°C (s.e. 0.43) post-surgery (ns). Five minutes after cold challenge, the relative finger tip temperature fell by a mean of 1.5°C (s.e. 1.9) in pre-operative fingers and by 1.6°C (s.e. 0.50) in post-operative fingers (ns). Ten minutes after cold challenge, the relative finger tip temperature fell by a mean of 3.3°C (s.e. 0.90) in the pre-operative fingers and by 1.0°C (s.e. 0.49) in post-operative fingers (P < 0.06) (Table II).

Two patients suffered minor wound sepsis. Both responded to oral antibiotics. One patient complained...

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**Table I**

<table>
<thead>
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<th>Clinical features before and after digital sympathectomy</th>
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<td>Pitting scars</td>
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**Table II**

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<th>Thermography before and after digital sympathectomy</th>
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<td><strong>Before</strong></td>
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<tr>
<td>Mean baseline temperature gradient in °C (S.E.M.)</td>
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<tr>
<td>Wrist crease to fingertip</td>
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<tr>
<td>Mean change in gradient 5 min post-cold</td>
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<tr>
<td>Challenge in °C (S.E.M.)</td>
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<tr>
<td>Mean change in gradient 10 min post-cold</td>
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Jaccoud’s Arthropathy Secondary to Severe Chronic Eczema of the Palms

Str—In 1869, Jaccoud [1] first described ulnar deviation and subluxation of the metacarpophalangeal (MCP) joints resulting from chronic inflammation of the articular capsule in rheumatic fever. The radiological features are classical with non-erosive ulnar deviation at the MCP joints with occasional characteristic hook-like osteophytes [2]. Histopathological examination demonstrates Aschoff bodies and focal lymphocyte collections in the articular capsule with normal articular cartilage. Jaccoud’s arthropathy has also been described in the feet and other joints [3, 4]. It has also been described in association with systemic lupus erythematosus (SLE), mixed connective tissue disease, Sjögren’s syndrome and rheumatoid arthritis [5, 6]. SLE is the commonest cause of Jaccoud’s arthropathy in North America and Europe at present.

A 21-yr-old Caucasian male presented with progressive, painless ulnar deviation and volar subluxation of the MCP joints of both hands over a 5 yr period. These deformities developed in association with palmar flexion contractures which were secondary to severe chronic eczema of the palms. Eczema had been present on the palms, cubital area, popliteal area and neck since the age of 6 months. Treatment with topical corticosteroid preparations had been prescribed, but the patient did not return for review and there was no history of rheumatic fever.

Clinical examination did not demonstrate signs of inflammatory arthritis or connective tissue disease. Full blood count, C-reactive protein and erythrocyte sedimentation rate were normal. Rheumatoid factor and antinuclear antibody were negative. Plain radiography of the hands confirmed bilateral ulnar deviation and volar subluxation of MCP joints without erosive arthropathy, typical of Jaccoud’s arthropathy (Fig. 1).

This is the first case to describe the features of Jaccoud’s arthropathy secondary to chronic eczema and in the absence of rheumatic fever, connective tissue disease, Sjögren’s syndrome or rheumatoid arthritis. The radiological findings are characteristic of Jaccoud’s arthropathy and satisfy the established diagnostic criteria [7]. The characteristic deformities of Jaccoud’s arthropathy are believed to be secondary to inflammatory capsular fibrosis, perhaps assisted by muscle imbalance. Histopathological features are similar to synovitis without pannus formation [6]. Eczema has similar histopathological features with a lymphohistiocytic infiltrate around the upper dermal blood vessels [8]. However, eczema is not associated

![Fig. 1.—Plain radiograph of hands demonstrating non-erosive deforming arthropathy with ulnar subluxation at the metacarpophalangeal joints: Jaccoud type.](image-url)
with inflammatory joint disease and our patient did not have evidence of an inflammatory arthropathy. Therefore, we conclude that features simulating Jaccoud’s arthropathy developed as a result of extra-articular disease. This has not been previously described and we conclude that the features of Jaccoud’s arthropathy can occur in the absence of articular capsular inflammation.

D. KANE, B. BRESNIHAN
Department of Rheumatology, St Vincent’s Hospital, Dublin 4, Ireland


Pelvic Arteriovenous Malformation as a Rare Cause of Sciatica

Sir—Pelvic arteriovenous malformations (AVMs) are rare lesions of uncertain aetiology, which may incidentally produce a variety of symptoms, including sciatica [1–8]. We describe a patient with a large pelvic AVM presenting with low back pain and sciatalgia.

A 78-yr-old man with no significant past medical history was referred with a 5 yr history of low back pain. Initially, he noticed the pain only when standing and walking; however, over the preceding 6 months, pain increased and became lancinating, irradiating along the posterior thigh and calf of his left leg, with numbness and tingling. The pain woke him from sleep without relief despite rest. He denied any constitutional symptoms or motor deficits.

Examination upon admission demonstrated decreased spinal motion in all planes. Straight-leg raising tests were markedly positive in the left leg. Neurological examination was normal, except for diminished left Achilles tendon reflex. Laboratory data were unremarkable.

Plain films of the lumbosacral spine revealed signs of extensive degenerative disc disease with marginal osteophytes, and an osteolytic lesion sharply outlined, without perilisional sclerosis, in the left superior hemisacrum. Magnetic resonance imaging (MRI) revealed a serpiginous tubular lesion, with flow signal void, corresponding to a vascular lesion (Fig. 1). This lesion eroded and destroyed completely the posterior-lateral portion of the left superior hemisacrum, occupying the sacral canal and, partially, the left S1–S2 ventral foramina. A saccular component of this lesion destroys the posterior-lateral portion of the left superior hemisacrum (white arrow). Note the normal right S1 nerve root (small white arrow).

and destroyed completely the posterior-lateral portion of the left superior hemisacrum, occupying the sacral canal and, partially, the left S1–S2 ventral foramina causing displacement and deformity of the S1 nerve root. Distal aortogram and selective left internal iliac arteriography confirmed the vascular aetiology of the lesion, showing signs consistent with an AVM supplied by the left lateral sacral artery (Fig. 2); endovascular embolization of the main feeders with steel coils was performed. The post-embolization course was unremarkable, and after the procedure the patient improved significantly. Follow-up angiography and computed tomography 6 months later revealed a residual lesion without evidence of radicular compression.
AVMs are uncommon vascular lesions formed by multiple abnormal communications between the arterial and venous systems without an intervening normal capillary network. The aetiology of these lesions has been a subject of controversy, although it is generally agreed that the greater part of these lesions are congenital, with a few that are acquired after trauma or surgery [1–3].

AVMs can involve any area of the body, although the extremities, head and neck are more commonly affected. Pelvic AVMs are extremely rare, especially in male patients; in this location, the lesions are more frequently acquired, resulting from neoplasms, pelvic trauma or surgical procedures. The lesions usually develop slowly over a long period of time before becoming symptomatic; however, rapid growth may occur, often in response to hormonal influence (such as occurs in puberty or during pregnancy) or trauma [1–3].

Symptoms of pelvic AVM include abdominal or pelvic discomfort and pain, rectal pain and tenesmus, genitourinary complaints including haematuria, hydronephrosis, unusual vaginal bleeding or impotence, and rarely low back pain and sciatica. In malformations with large arteriovenous shunts, congestive heart failure may ensue [2–8]. Sciatica as a symptom of a pelvic AVM is uncommon, with only two reported cases in the English literature [7, 8]. In these two cases, the condition was secondary to nerve root compression by the vascular malformation, as was seen in our patient.

Both enhanced CT and MRI are helpful to demonstrate the vascular aetiology of the lesion, and to evaluate its extension and involvement of adjacent structures [4, 7]. The diagnosis is confirmed by angiography which also allows the endovascular embolization.

Whereas asymptomatic or mildly symptomatic lesions should not be treated [1], the management of symptomatic AVMs presents a dilemma, regardless of whether surgical or radiological techniques are used [9, 10]. Surgical treatment includes ligation of feeding vessels that lead to the AVM or resection of the affected area. Most authors agree that simple ligation of feeding arteries has no value, since new collaterals develop rapidly to bypass the ligated vessels. Surgical excision should be limited to those malformations which can be completely resected.

Intra-arterial embolization has become an accepted and widely used therapy for AVMs. It is highly effective in providing symptomatic relief for varying periods of time, but recurrence of the lesion occurs in most cases due to recanalization and neovascular recruitment, and its long-term results are poor. However, despite intra-arterial embolization not being free of risks, it is a relatively minor procedure that can be repeated if symptoms recur, and currently is considered the palliative treatment of choice. It is also indicated as a preoperative procedure in the few patients who have reasonably localized malformations that are considered resectable. In these patients, embolization before excision can decrease operative mortality and complications by decreasing intraoperative bleeding.

In summary, our patient’s case shows that pelvic AVM, due to its space-occupying effect, may be an unusual cause of sciatica.


Department of Rheumatology, Hospital Príncipes de España and *Department of Magnetic Resonance Imaging (ID1), Hospital Duran i Reynals, Ciudad Sanitaria y Universitaria de Bellvitge, Hospital de Llobregat, Barcelona, Spain

Accepted 4 April 1997

Correspondence to: F. J. Narváez García, Department of Rheumatology, Hospital Príncipes de España, Ciudad Sanitaria y Universitaria de Bellvitge, C/ Feixa Llarga s/n, 08907, Hospital de Llobregat, Barcelona, Spain


Speed of Onset of the Response to Sulphasalazine

SIR—One of the difficulties patients have when starting disease-modifying anti-rheumatic drugs is the delay before they become effective. We were surprised by the study by van Gestel et al. [1] which suggested that the onset of response to sulphasalazine was quicker than that to methotrexate. However, we discovered that the speed with which the authors escalated the dose was much more rapid than our normal practice. We therefore substituted for our previous regime of escalating the dose to 2 g daily in 1 month, a regime of 500 mg bd for 1 week then 1 g bd.

Eight patients were reviewed by telephone 1 week after reaching their 1 g bd dose, and were reviewed in the out-patient clinic after 2 months on treatment.
Four other patients had out-patient reviews only. Of these 12, only one patient suffered significant side-effects, developing nausea at 500 mg bd which increased to an unacceptable level when he increased the dose to 1 g bd. All the other patients found this regime acceptable.

We have not undertaken a comparative study of the speed of onset of effect of the drug, although subjectively this seems a little quicker, but we do now feel that this more rapid introduction of sulphasalazine carries no additional risk of side-effects and at least offers the prospect of more prompt relief of symptoms. We intend using it as our routine in the future.

I. HASLOCK, J. STAMP
Department of Rheumatology, South Cleveland Hospital, Marton Road, Middlesbrough, Cleveland TS4 3BW
Accepted 16 April 1997


Reply
In our study, patients started sulphasalazine with a dose of 500 mg bd and added 500 mg every 5 days until (after 10 days) a dose of 1000 mg bd was reached. The new regime described by Dr Haslock and Mrs Stamp is the same as the one we use in daily clinical practice without additional risk of side-effects.

A. VAN GESTEL
Department of Rheumatology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands

Accuracy of History, Examination, Pulmonary Function Tests and Chest Radiographs in Predicting High-Resolution Computed Tomography-Diagnosed Interstitial Lung Disease

Stir—It was interesting to read the discussion between Jobanputra and Beyeler and colleagues on determining the presence of lung disease in RA patients prior to methotrexate treatment [1, 2]. We are currently investigating RA patients attending St Helens and Knowsley Trust Hospitals’ rheumatology out-patient departments for the presence of lung disease, regardless of respiratory symptoms, with clinical examination, chest X-ray (CXR), full pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT). Preliminary results from the first 60 patients investigated [3] may be of interest to the two groups: 33% were current smokers, 38% reformed smokers and 72% seropositive for rheumatoid factor. A single consultant radiologist (JK) interpreted the CXR and HRCT scans, blinded to clinical details.

Thirteen patients (22%) were found to have HRCT scan-diagnosed interstitial lung disease (ILD). Table I shows the accuracy of history, examination, PFT and CXR in predicting ILD.

A reduced DLCO detected the most patients with ILD, but was also found to be reduced in over 50% of patients without ILD due to other factors, e.g. cardiorespiratory disease other than ILD, anaemia and due to RA disease activity [4]. Examination of the patient remains a most useful screening test for ILD in terms of relative sensitivity and specificity, as well as cost.

It is also evident that RA patients can have ILD without symptoms or signs and the chest X-ray, with only 23% sensitivity, conveys no further useful information as regards excluding the diagnosis of ILD.

It is interesting that the only controlled trial to associate methotrexate pneumonitis with rheumatoid lung disease is based on findings of interstitial infiltrates on CXR [5].

Supported by a grant from the British Lung Foundation.

J. K. DAWSON,* D. R. GRAHAM† J. KENNY,† M. P. LYNCH
Department of Rheumatology, St Helens Hospital, Marshalls Cross Road, St Helens, Merseyside, Departments of *Respiratory Medicine and †Radiology, Whiston Hospital, Merseyside
Accepted 19 May 1997


| TABLE I |
|-----------------|-----------------|-----------------|-----------------|
| Shortness of breath with severe exertion only | 4 | 18 | 31 |
| Shortness of breath with climbing stairs | 3 | 27 | 24 |
| Shortness of breath walking on flat | 6 | 2 | 46 |
| Dry cough | 3 | 5 | 23 |
| Productive cough | 5 | 12 | 38 |
| Bilateral basal fine crackles | 7 | 11 | 54 |
| Restrictive PFT pattern | 5 | 2 | 38 |
| Reduced DLCO (< 75% predicted) | 9 | 25 | 47 |
| CXR asymmetrical basal infiltrates | 1 | 3 | 7 |
| CXR fibrosing alveolitis | 3 | 3 | 23 |
Anti-MPO in Adult- and Childhood-onset SLE

Sir—Circulating autoantibodies to myeloperoxidase (MPO) have been described in various forms of vasculitis, but seem to be relatively uncommon in adult-onset systemic lupus erythematosus (SLE) [1, 2]. In a recent review of adult- and childhood-onset SLE [3], it was demonstrated that disease onset was generally more severe in the childhood-onset cases and that major haematological manifestations and antibodies to DNA, Sm and RNP were more frequently found in this group. Adult-onset cases were more likely to have cardiopulmonary disease.

We wished to determine whether differences between adult- and childhood-onset SLE extended to the prevalence of anti-MPO antibodies. Sera from 44 patients with SLE whose disease commenced before 16 yr of age were studied. In this group, there were four males and 40 females. Antibodies to MPO were measured by direct-binding ELISA described elsewhere [4]. The upper limit of normal in the assays which detected both IgG and IgM autoantibodies was set at 20%, this figure representing a percentage binding >3 S.D. above the mean five normal sera included on every plate. The results were compared with those obtained from 58 adult-onset lupus patients, 43 of whom have been previously reported [4]. Two out of the 44 sera from childhood-onset cases had raised IgM levels (63%, 73%) compared with seven of the adult-onset cases, and one of the childhood-onset cases had a raised IgG level (93%) compared with eight of the adult-onset cases. By $\chi^2$ analysis, there was no statistically significant difference between these different groups with respect to the IgM anti-MPO antibodies, but there was a statistically significant difference ($P < 0.05$) for the IgG isotype. We conclude that although the numbers of sera from both adult- and childhood-onset lupus with anti-MPO antibodies are small, patients with adult-onset SLE are more likely to have IgG antibodies, but not IgM.

D. A. Isenberg, L. B. Tucker, *G. Cambridge Centre for Rheumatology, Bloomsbury Rheumatology Unit, Department of Medicine, Middlesex Hospital, London W1P 9PG and *Paediatric Rheumatology, Floating Hospital for Infants & Children, New England Medical Center Hospital, Boston, MA 02111, USA

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