LETTERS TO THE EDITOR

Re: Prolactin and Systemic Lupus Erythematosus

Sir—We read with interest the article by Mok et al. [1]. In this paper, as well as in the previous report, the authors did not find any correlation between prolactin (PRL) and lupus activity in systemic lupus erythematosus (SLE) patients, in spite of the fact that experimental studies using animal models have shown sufficient evidence that PRL plays a role in autoimmune rheumatic disease [2]. In contrast, the clinical trials carried out in humans, including the article by Mok et al., have shown contradictory data concerning the participation of PRL in SLE and its relationship with disease activity. The debate has not yet yielded a satisfactory conclusion. Recently, we carried out an analysis using the results from the English language literature concerning the correlation between PRL and lupus activity in SLE patients [3]. Briefly, we found five papers on this topic; the same articles alluded to in the references in Mok’s article. In only three of those papers was enough information found to perform an analysis of the power of the study. Of these three papers, only one found a correlation between hyperprolactinemia (HPRL) and disease activity; the other two articles did not find statistically significant differences between HPRL and disease activity. However, the power of those studies was <31%, with the risk of committing an error of type II or β, which means that the authors could conclude that there were no differences when it is possible that differences did exist. In our analysis, which took into consideration all the results from those papers, we found an association between HPRL and lupus activity ($\chi^2; P = 0.03$), concluding that the inconsistency in the clinical trials concerning HPRL and lupus activity could be explained in part by the low power of the studies. In the same manner, Mok et al. did not find a correlation between PRL and lupus activity using SLEDAI. However, Mok, as well as the previous papers on this topic with negative results, does not show a formal analysis of the power of the study, and also does not show enough data for the reader to carry out the calculation of the power of the study. Moreover, Mok et al. display a dispersion graph between PRL and SLEDAI using 153 matches in only 72 patients; the graph does not show a linear correlation (scatter), and it is not correct to effect the correlation using the Pearson coefficient in this case. They should be transforming the data in order to have a normal distribution, or they must use the Spearman coefficient. We do not find any justification or reason to analyse 150 matches as a transverse study when 80 of those matches were from the same patients at a different time; these data must be analysed in a different way because repeated samples are from the same SLE patients.

Finally, in the discussion, Mok et al. did not mention the possibility that the anti-PRL autoantibody could be the cause of HPRL in SLE patients. Moreover, the interpretation is different from the finding by Hattori et al. [4] in idiopathic HPRL patients with anti-PRL autoantibody without autoimmune rheumatic disease. Hattori et al. found that the autoantibodies to PRL interfere with the real values of serum PRL using the radioimmunoassay (RIA) technique, showing that the measured levels of this hormone are lower than the real values, i.e. false low levels. In contrast, the immunoradiometric assay (IRMA) technique expressed more confident results.

We are running a transverse design study with a large number of SLE patients. At this time, we have studied 260 SLE patients; of those, 42 have shown HPRL (16.2%, 95% CI = 11.7–20.7%). We consider the values >20 ng/ml (520 mU/ml) as HPRL. Moreover, we have found 14 females with autoantibodies against PRL; this autoantibody is an IgG detected by affinity chromatography (Sepharose coated with Protein A and G), and none of the SLE patients with anti-PRL autoantibody have displayed normal values of PRL. Our results, as well as those shown by Hattori et al., show that the presence of antibodies to PRL could interfere with the real values of PRL when the technique used is RIA (double antibody). In contrast, the IRMA technique appears to be more specific and confident. In our study, the range of direct PRL using RIA was 17.8–69.4 ng/ml; using IRMA it was 31.1–229.7 ng/ml. The proportions of direct PRL to total serum PRL using the RIA in the presence of anti-PRL autoantibody were 64.3 ± 38.1% and, without anti-PRL autoantibody, 106.4 ± 12.5% (P = 0.0003). In contrast, when using IRMA, the proportions were the same with or without autoantibodies to PRL (116.2 ± 23.3 vs 120.6 ± 17.7%, P = 0.55). We also found a positive correlation between the titres of anti-PRL autoantibody and the serum levels of PRL ($r_e = 0.98$, P = 0.0001). Our explanation of these phenomena is similar to that discussed in previous papers by Hattori et al. using PRL [4] and Schneider and Pervos [5] using the thyroglobulin assay. There appears to be enough evidence that in some SLE patients with HPRL, the anti-PRL autoantibody could be the cause of HPRL. However, it is necessary to carry out more experimental studies in order to know more about the role of the anti-PRL autoantibody in autoimmune rheumatic disease.

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Angiographic findings of Takayasu’s Arteritis in Lebanon

Sir—We report herein the angiographic findings in Takayasu’s arteritis in 15 patients seen at the American University of Beirut–Medical Center (AUB-MC) over a 12 yr period. All patients fulfilled the American College of Rheumatology (ACR) classification criteria for the disease [1]. This classification necessitates the presence of at least three of the following six criteria to diagnose the disease: (1) age at disease onset of ≤ 40 yr; (2) claudication of extremities; (3) decreased brachial artery pulse; (4) systolic blood pressure difference of > 10 mmHg between the arms; (5) audible bruit on auscultation over one or both subclavian arteries or abdominal aorta; (6) arteriogram abnormality (narrowing or occlusion of the aorta or one of its branches).

There were 11 females (73%) and four males, the mean age at diagnosis was 29.5 yr (range 12–64 yr) and 12 patients (80%) were below the age of 40 yr. Twelve patients (80%) had claudication of an extremity on presentation, also 12 (80%) patients had a decreased brachial artery pulse. Ten patients (67%) had a > 10 mmHg difference between the arms, and nine patients (60%) had a bruit over the subclavian arteries or the aorta. Total aortography was performed in all patients and the results were classified according to the new classification of Hata et al. [2] as follows: five patients (33%) had involvement of the branches of the aortic arch only (type I), one patient (7%) had involvement of the ascending aorta, aortic arch and its branches only (type IIA), three patients (20%) had involvement of the ascending aorta, aortic arch with its branches and thoracic descending aorta (type IIB), one patient (7%) had involvement of the thoracic descending aorta, abdominal aorta and/or renal arteries (type III), two patients (13%) had involvement of the abdominal aorta and/or renal arteries only (type IV), and finally three patients (20%) had the combined features of both type IIB and IV (type V).

Table I shows a comparison of the angiographic findings between our patients and a group of Japanese and Indian patients. Types I and II were significantly more common in the Japanese compared to the Indian population [2, 3]. In addition, Indian patients had a rather higher frequency of type IV disease [2, 3]. Similarly to the Japanese patients, Lebanese patients showed (using a $\chi^2$ analysis) a significantly higher frequency of type I and II involvement compared to the Indian patients ($P < 0.001$).

Our data suggest that the vascular lesions of Takayasu’s arteritis in the Lebanese patients occur primarily in the ascending aorta, aortic arch and/or its branches, and extend into the abdominal aorta.

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Spondylodiscitis Caused by Streptococcus equisimilis

Sir—Infectious non-tuberculous spondylodiscitis may be caused by a wide variety of micro-organisms. Gram-positive microbes are responsible for the majority of cases, with staphylococci accounting for about one-half to three-quarters of these cases [1]. Group C streptococci are rare pathogens and include the large colony of Voges–Proskauer-negative bacteria (S. equi, S. equisimilis, S. zooepidemicus and S. dysgalactiae), as well as the minute colony of Voges–Proskauer-positive S. anginosus (‘S. milleri’). Streptococcus equisimilis is the strain most frequently isolated in human infections and has been identified as an aetiological agent of meningitis, brain abscess, endocarditis, pneumonia, cellulitis, neutropenic sepsis, puerperal sepsis, septic arthritis and osteomyelitis [2].
We present the case of an 83-yr-old man with infectious spondylodiscitis due to *S. equisimilis* with apparent primary focus in the oral cavity. To our knowledge, no previous cases of *S. equisimilis* spondylodiscitis have been described.

An 83-yr-old Caucasian man with a medical history of non-insulin-dependent diabetes mellitus and moderate aortic insufficiency was hospitalized with complaints of fever and back pain of 6 weeks duration. On physical examination at admission, the patient had a temperature of 38°C, a blood pressure of 150/60 mmHg, diffuse gingivitis and localized midline tenderness over the lower thoracic spine. No rash or lymphadenopathy were found. Neurological examination revealed only mildly hypoactive patellar and Achilles reflex.

Investigations revealed: WBC (6.9 × 10^9/l), normocytic normochromic anaemia (Hb: 102 g/l), platelets (127 × 10^9/l), ESR (58 mm/h), C-reactive protein (52 mg/l) and glucose (115 mg/dl). Alkaline and acid phosphatase, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactic dehydrogenase, bilirubin, calcium, phosphorus and urea nitrogen were normal. A tuberculin test (2 UI-RT 23) was negative. X-ray films of the thoracic spine disclosed narrowing T8–T9 disc space. Magnetic resonance imaging (MRI) was performed. The disc space and the vertebral bodies showed a decreased signal in T1-weighted images and an abnormal increased signal intensity in the T2-weighted images (Fig. 1). These findings were consistent with infectious spondylodiscitis. Three of six blood cultures performed at admission yielded a group C *Streptococcus* later identified as *S. equisimilis*. Culture of the urine, as well as agglutination tests for *Brucella* and *Salmonella* microorganisms were negative.

A CT-guided needle aspiration of the T8–T9 disc space was performed. Microscopic examination of stained specimens disclosed a moderate number of Gram-positive cocci, but cultures were negative. The hospitalization period was uneventful and after 16 days of satisfactory ceftriaxone therapy (2 g once daily), the patient was discharged and continued this therapy on an ambulatory basis for three more weeks. On 4 month follow-up, ESR and C-reactive protein returned to normal, and the patient did not suffer from any thoracic pain.

There is agreement that vertebral osteomyelitis is a process involving bacterial seeding; there is less agreement as to whether the route is arterial or venous. Haematogenous vertebral osteomyelitis is usually associated with a single organism as the aetiological agent. In the absence of bacteraemia, the diagnostic procedure of choice is a bone biopsy, performed with a cutting needle, and guided by fluoroscopy or CT scanning. MRI is extremely sensitive in detecting and delineating infective lesions, regardless of their spinal location. Osteomyelitis is associated with oedema of the bone marrow, and is therefore seen as bright-intensity imaging on T2-weighted scans and as low-intensity imaging on T1-weighted scans. In our patient, MRI was consistent with infectious spondylodiscitis and three blood cultures yielded *S. equisimilis*, but subsequent cultures of specimens from the disc space were sterile. We suggest that the infection originated by a haematogenous route due to a primary bacteraemic event where the probable source of the organism was the oral cavity.

The Lancefield group C streptococci are serologically identified by the group-specific carbohydrate rhamnose-N-acetylgalactosamine, located on the cell wall. The large-colony group C streptococci also demonstrate differences in their pathogenicity in humans and animals. They are common inhabitants of many animal species. In humans, they may be isolated from healthy skin, as well as the nasopharynx and oropharynx, intestinal tract and vagina [2]. In most cases, these organisms are sensitive to penicillin, although individual cases of penicillin and erythromycin resistance have been reported [3].

There have been several reports of septic arthritis due to group C streptococci [2–5]. This microorganism appears to affect joints with pre-existing rheumatological conditions, but no underlying

*Fig. 1.—*Sagittal T2-weighted magnetic resonance image demonstrates narrowing and high-intensity signal in the disc space at T8–T9 with spread to the adjacent vertebral end plates.*
malignancy has been described. To our knowledge, no previous cases of S. equisimilis spondylodiscitis have been published.

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Joint Physiology and Synovial Cell Proliferation

Sir—We read with interest the articles by Edwards and Morris [1] and Čeponis et al. [2]. The latter have contributed importantly to the now extensive evidence that rheumatoid arthritis is associated with increased synovial cell proliferation. Proliferation indices, using cell cycle antigens or nucleotide incorporation, indicate rates of synovial cell proliferation comparable with some cancers [2–6]. We agree that more recently developed antibodies to Ki67 antigen label proportions of synovial cells which are similar to other markers of proliferation, such as proliferating cell nuclear antigen, and that low labelling indices observed in some earlier studies may represent technical difficulties [6, 7]. Synovial cell proliferation may continue for many years in rheumatoid arthritis, with only limited expansion of the synovium. This apparent paradox can be explained by concurrent synovial cell death [6, 8, 9]. A picture is emerging of rapid turnover both of synovial fibroblasts and of endothelial cells, far in excess of the rate of change in total cell number. This increased cell turnover is associated with the synovium acquiring an immature phenotype. Vascular structures in rheumatoid synovitis express antigens such as integrin αβ3, which would be downregulated in mature tissues [6].

We suggest that vascular immaturity is a likely explanation of the deficient innervation of synovium in rheumatoid arthritis which is noted by Edwards and Morris. Innervation of the neovascularure begins only several weeks after the initiation of angiogenesis [10]. Increased release of neuropeptides such as substance P remains a plausible hypothesis, but cannot explain the observed depletion in inflamed synovium of non-secreted neuronal proteins such as protein gene product 9.5 [11, 12]. Substance P–like immunoreactivity has frequently been detected in synovial fluids, but more stringent attempts to identify this with intact substance P using high-performance liquid chromatography have had little success [13]. This is not surprising considering the abundance of membrane peptidases within the inflamed synovium which would be expected rapidly to degrade peptides such as substance P [14, 15]. Immunoreactivity in synovial fluid is likely to be a very imprecise measure of the release of metabolically unstable peptides.

The synovium in rheumatoid arthritis should be viewed as a highly dynamic tissue, in which stroma, blood vessels and nerves continue to grow over long periods, and where there is concurrent cell death and neuronal damage. The histological snapshot reflects a balance in which nerves and vessels have immature phenotypes and abnormal distributions, being deficient in the superficial synovial layers, but present in the deeper synovium [11, 16, 17]. The physiology of the normal joint differs importantly from the pathophysiology of the persistently inflamed joint.

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17. Čeponis A, Konttinen Y, Mackevicius Z, Solovieva SA, Hukkanen M, Tamulaitien M et al. Aberrant vascularity and Oxpentifylline (OXP), a non-specific PDE inhibitor, has been shown to reduce significantly the onset of mercucr chloride-induced arthritis in rats [4], and to have a significant ameliorative effect on severe RA in humans [5, 6]. Unfortunately, OXP is poorly tolerated in patients with long-standing RA [5, 6], possibly because severe systemic disease confers poor tolerance of drugs in general. We hypothesize that patients with either early or relatively mild RA might be more tolerant and therefore an ideal group for OXP treatment.

We have conducted an open prospective study of OXP, 400 mg three times daily, over 12 weeks in 20 patients (median age 59 yr, range 26–75 yr, 16 female) fulfilling the 1987 ARA revised criteria for RA. The median disease duration was 2 yr (range 1–17 yr), seven had erosions and all were rheumatoid factor positive. At enrolment, all patients had three or more of the following disease activity criteria on two consecutive occasions (at least 1 week apart): early morning stiffness (EMS) > 45 min (median 75, range 15–210), three or more tender or swollen joints (median tender 10, range 0–17; swollen 10, range 2–20), ESR > 25 mm/h (median 56, range 26–87), CRP > 20 mg/l (median 31, range 0–105). Five patients had had mild RA for > 5 yr with a median swollen joint count of 10/28 (range 7–17), EMS of 60 min (range 20–60) and CRP of 46 mg/l (range 4–90). All patients were taking a non-steroidal anti-inflammatory drug (NSAID) and two were taking a steady dose (< 10 mg/day) of oral prednisolone. Fifteen patients had never received a DMARD and the remainder had not taken a DMARD for at least 4 weeks.

### An Open Study of Oxpentifylline in Early Rheumatoid Arthritis

Sir—The phosphodiesterase (PDE) inhibitors are a family of drugs with many anti-inflammatory properties, including inhibition of TNF transcription [1–3]. Oxpentifylline (OXP), a non-specific PDE inhibitor, has been shown to reduce significantly the onset of mercucr chloride-induced arthritis in rats [4], and to have a significant ameliorative effect on severe RA in humans [5, 6]. Unfortunately, OXP is poorly tolerated in patients with long-standing RA [5, 6], possibly because severe systemic disease confers poor tolerance of drugs in general. We hypothesize that patients with either early or relatively mild RA might be more tolerant and therefore an ideal group for OXP treatment.

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<table>
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<tr>
<th>Table I</th>
<th>Numbers of patients remaining on oxpentifylline treatment and Paulus response rates throughout the trial</th>
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<td>Trial week</td>
<td>Baseline</td>
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<td>No. remaining</td>
<td>20</td>
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<td>No. withdrawn due to inefficacy</td>
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<td>No. withdrawn due to adverse event</td>
<td>4</td>
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<tr>
<td>Paulus response rates</td>
<td>No. Paulus 20%</td>
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<td>Paulus 50%</td>
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Outcome data were collected twice at baseline and every 2 weeks for 12 weeks during treatment: EMS, pain score (10 cm visual analogue scale), tender and swollen joint counts (total 28), grip strength (mean of right and left hands, mmHg), Stanford Health Assessment Questionnaire (HAQ, modified for UK patients), patient’s and assessor’s global assessment (five-point scale), ESR, CRP, full blood count, urea, electrolytes and liver enzymes. Compliance was assessed by performing a tablet count at each assessment. No change in NSAID or other treatment was permitted. Responders were classified according to the 20% and 50% Paulus response criteria [7]. A comparison of mean baseline and end of the trial (the time a patient withdrew or the 12 week assessment) outcome measures was performed with the Wilcoxon signed rank test.

The number of patients remaining in the trial, withdrawals and Paulus responses at fortnightly intervals during the trial are shown in Table I. Ten patients (50%) completed 12 weeks of OXP treatment and seven (35%) opted to continue with OXP after the study. Adverse events were reported by nine patients (45%), most frequently neck or occipital pain (n = 5), which resolved in four cases whilst OXP was continued. The five patients who withdrew early due to adverse events (mainly gastrointestinal) were significantly older than the remaining 15 patients (median age 71.5 vs 56.5 yr, respectively; \( P = 0.007 \), Mann–Whitney \( U \)) and had a higher tender joint count (median count 13.5 vs 8, respectively; \( P = 0.01 \), Mann–Whitney \( U \)). There were no other significant differences in baseline demographic, clinical or laboratory scores between patients who completed the trial and those withdrawn due to inefficacy or adverse events.

On Paulus criteria, there was a 20% improvement in 7/20 patients (35%) and a 50% improvement in 3/20 patients (15%). Comparison of individual baseline and end of trial outcome measures (see Table II) revealed a significant improvement in EMS and HAQ in the whole study group. In contrast, a more substantial clinical response was seen in the patients who remained on OXP treatment for >9 weeks (n = 11). In this group, the 20 and 50% Paulus response rate was 64 and 27%, respectively, and there were significant improvements in 5/6 clinical scores, but not in ESR or CRP (see Table II).

In conclusion, OXP treatment was not associated with any serious adverse events; however, tolerability was poor despite the selection of patients with early or mild RA.

On an intention-to-treat basis, efficacy was disappointing, but there was an impressive clinical response, particularly in the HAQ, in those patients who remained on OXP for >9 weeks (including four with side-effects). However, other than by age, the responders could not be distinguished at baseline from those destined to withdraw due to adverse events or inefficacy.

The problem of poor tolerability may be overcome by the next generation of isozyme-specific PDE inhibitors. Lymphocytes and macrophages preferentially express the type III and IV isozymes of PDEs [8, 9], and Rolipram, a type IV inhibitor, is reported to ameliorate established collagen II-induced arthritis in rats both clinically and radiologically [10]. Our findings in humans lend clinical support to the theoretical rationale to develop PDE inhibitors as a safe means of targeting the immune response in the inflamed joint.

We thank Dr O. Duke for helpful discussions and access to patients, Mrs J. Dunwoody for help with data collection and Hoechst Marion Roussel for the supply of oxpentifylline.

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Depression in Rheumatoid Arthritis

Sir—I read, with great interest, the study of depression in rheumatoid arthritis [1]. With the availability of newer diagnostic tools, depression can be more accurately measured and characterized. Nonetheless, that it played a part in RA symptoms has long been assumed; the depressive aspects seem to parallel the degree of chronic pain, as profiles in tests are similar to those seen in other chronic pain syndromes, not rheumatological in nature. The respected authors of this paper state that further research is needed to determine whether RA is accompanied by more depression than osteoarthritis. That study was performed some time ago [2] and is referred to in a later paper [3]. I think that is because RA patients characterize their symptoms as coming from a disease (RA), whilst osteoarthritis patients personalize the pain (my knee hurts). That distinction probably sets up a different diagnostic algorithm for the sufferer.

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