

LETTERS TO THE EDITOR

Is Gitelman's Syndrome an Acquired Disease?

SIR—In a recent case report, Casatta *et al.* [1] state the possibility of a 39-yr-old female with chronic sialoadenitis and acquired Gitelman's syndrome. The patient clearly complies with several criteria of Gitelman's syndrome, such as hypokalaemic alkalosis, hypomagnesaemia, hypermagnesuria and hypocalciuria, but the familial disease condition, which excludes the diagnostic possibility reported, is missing. Casatta *et al.* [1] did not carry out screening of family members and regard the clinical case as acquired Gitelman's syndrome. Autosomal recessive inheritance is usual in this syndrome, although families with autosomal dominant inheritance and differing clinical expression have been reported [2]. In recent years, different analyses of several families have confirmed the association of markers close to the thiazide-sensitive Na-Cl co-transporter gene on chromosome 16 [3, 4].

The patient described by Casatta *et al.* [1] provides features of distal and proximal tubular dysfunction. Hyperuricaemia and acute arthritis express proximal tubular failure and inadequate bidirectional transport of uric acid. The patient's daily urinary elimination of uric acid of 2.9 mmol excludes overproduction. On the other hand, affection of the distal tubule together with dissociation of transport of calcium and magnesium (hypermagnesuria and hypocalciuria) is evident [5]. Contrariwise, defective salt transport in the thick ascending limb of the loop of Henle with a high incidence of hypercalciuria is described in Bartter's syndrome. Furthermore, it is questionable that the first case suffers from Bartter's syndrome. She presented hypocalciuria (0.74 mmol daily) and this fact has been suggested to distinguish between both syndromes [6], as the authors indicate in their discussion. It must also be pointed out that, according to a recent report [7], the reabsorption capacity of Na⁺/Cl is poor at the level of the distal tubule in Gitelman's syndrome, a circumstance that has not been objectified in the case reported by Casatta *et al.* [1] with reduced amounts of urine Na⁺ (75.6 mmol daily) and urine Cl⁻ (70 mmol daily).

In our opinion, the diagnostic possibility of tubulointerstitial nephritis with features of proximal and distal tubular affection in patients with chronic sialoadenitis cannot be denied, contrary to what can be stated of acquired Gitelman's syndrome.

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- in tubular hypomagnesemia-hypokalemia with hypocalciuria (Gitelman's syndrome). *Kidney Int* 1995;47:547–51.
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Reply

We read with interest Gascón *et al.*'s comments on our paper describing two acquired tubular disorders associated with chronic sialoadenitis, i.e. Gitelman's and Bartter's syndrome.

We agree that most reported cases of Gitelman's syndrome are congenital; therefore, a familial scrutiny of the biochemical characteristics is crucial. This was not the case in our patient no. 2. She had a full remission of her biochemical abnormalities after courses of steroid and she is still doing well now after 3 yr of follow-up.

As far as patient no. 1 is concerned, we agree that she did not have hypercalciuria, a distinguishing feature between Gitelman's and Bartter's syndrome. When present, it certainly helps to distinguish between the two; unfortunately, it is not always present in Bartter's syndrome, which can be diagnosed anyway because of the hypokalaemic hyper-reninaemic/hyperaldosteronism without hypertension plus hypomagnesaemia and hypermagnesuria. In addition, as clearly reported in the paper, our patient had a high-turnover osteoporosis (with high PTH levels). It is well known that PTH reduces the overall clearance of calcium, showing an opposite effect at the proximal (decreased Ca reabsorption) vs distal (increased Ca reabsorption) tubule. This might explain the hypocalciuria in our patient with severe osteoporosis. In addition, data on uric acid should be treated with caution in patients taking large amounts of analgesics. In conclusion, we believe that the major biochemical characteristics fully satisfy the criteria of acquired Gitelman's and Bartter's syndrome in our patient. This is not very far from saying that the patients had a tubulointerstitial nephritis with a clinical expression limited to the derangement of specific nephron segments and functions, as Gascón claims.

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A Trial of Unfashionable Techniques (Texts and Prizes) in Undergraduate Rheumatology Education

SIR—Undergraduate rheumatology education is becoming a fashion victim. Bedside teachers suspicious of the value of special study modules, problem-based learning and the interactive CD-ROM can find little research by which to judge these usurpers of tradition [1]. We present data that support the continued use of the text and prize, orthodox techniques in a world of novelty.

Thirty-six Leeds University medical students, within 3 months of their final examinations in medicine, were studied whilst attached for 1 month, in groups of three, to a teaching unit. On arrival (Day 1), they completed a multiple-choice question (MCQ) paper which consisted of 10 multi-part questions on rheumatology clinical signs and 10 questions on rheumatology theory. The maximum possible score was +20 for both clinical (C) and theory (T) questions, points were subtracted for incorrect or omitted questions. The students were then given a text consisting of 18 A4 pages dealing with the interpretation of rheumatology physical signs. No corresponding file relating to the theory questions was supplied.

On a rotating basis, 12 students were told the following. Group (a): 'This leaflet contains details of important physical signs which you should be able to recognize and interpret before you leave this unit' (<24 h warning group). Group (b): As in (a), plus 'You will be retested with the MCQ that you have just completed before you finish your clerkship' (26 day warning group). Group (c): As in (a), plus 'You will be retested with the MCQ that you have just completed before you finish your clerkship—whichever performs best will receive 25 pounds' (prize group).

All groups were retested on Day 26, groups (b) and (c) by pre-arrangement. Group (a) was given <24 h notice of retesting. For each group, the C and T scores were examined using the Wilcoxon signed rank test to discover whether the scores on Day 1 and Day 26 differed.

On Day 26, C scores were significantly higher than on Day 1 in all three groups ($P = 0.005$). The only T score that rose significantly was found in group (c) offered the £25 prize ($P = 0.002$) (Table I).

The Kruskal–Wallis test was carried out on the changes in score (Day 26 – Day 1), but found no difference between the groups.

The usefulness of an information leaflet is confirmed by this study [2]; here the rheumatologist can concen-

trate on a scaffolding of important facts and principles. If no leaflet is available, short odds on winning £25 (index linked to 1992–6 rates) will produce an improvement in performance.

Rheumatologists have intuitively used texts and prizes in undergraduate teaching. They should not abandon these until the new professors of medical education produce research evidence of something better.

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Reply to J. R. Kerr [1]

In our study, a laboratory strain of *Pseudomonas aeruginosa*, a Gram-negative bacterium which colonizes the bowel and is involved in urinary tract infections, was used as a control when measuring antibodies in active rheumatoid arthritis patients (RA) following the detection of increased antibodies to *Proteus mirabilis*. Out of 77 573 sequences (PIR-Release-44), the susceptibility sequence was found in *Pseudomonas* species (isoamylase precursor). We assumed that *P. aeruginosa* would contain such a sequence. The search was carried out in 1995 and since that time new entries have been entered into the database such as the one indicated above. We thank the above author for clarifying the presence of the cross-reactive epitope in *Pseudomonas* species.

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TABLE I

Scores on Day 1 and Day 26 median (range); $n = 12$ (each group), and P values for C and T between Day 1 and 26 (Wilcoxon signed rank test)

| | Clinical (C) | | Theory (T) | |
|----------------------------|-----------------|------------------------|-----------------|------------------------------|
| | Day 1 | Day 26 | Day 1 | Day 26 |
| < 24 h notice (a) | -4.5 (-18 to 6) | 10 (4-16) $P = 0.003$ | -4.5 (-12 to 5) | 0.5 (13-10) $P = 0.158$ ns |
| 26 days notice (b) | -1.5 (-10 to 8) | 8.5 (1-17) $P = 0.004$ | -1 (-19 to 10) | 3 (-12 to 11) $P = 0.075$ ns |
| 26 days notice + prize (c) | -2 (-18 to 5) | 13 (0-19) $P = 0.002$ | -4.5 (-15 to 9) | 4 (-2 to 14) $P = 0.002$ |

Kienbock's Disease in Rheumatoid Arthritis

SIR—Kienbock's disease, or radiologic avascular necrosis (AVN) of the carpal lunate, is an uncommon disease of unknown aetiology. Most cases of Kienbock's disease are 'idiopathic' because no obvious aetiological factors can be identified. We describe a patient with seronegative rheumatoid arthritis (RA) who developed AVN of the left lunate during the course of her illness. The association of Kienbock's disease and RA has not been described before.

A 40-yr-old woman presented in March 1997 because of symmetrical polyarthritis involving the proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, knees and ankles for >2 yr, which was associated with marked morning stiffness. Physical examination revealed tenderness and swelling of both wrists and the small joints of the hands, but there were no rheumatoid nodules. Her ANA was positive at low titre, but the anti-dsDNA, anti-ENA and rheumatoid factor (RF) were negative. Initial radiology of the involved joints did not demonstrate any erosive changes or other abnormalities. Her erythrocyte sedimentation rate (ESR) was raised to 58 mm/h, but the C-reactive protein was within normal range. In view of the clinical synovitis, hydroxychloroquine (200 mg daily) and non-steroidal anti-inflammatory agents were initiated. Two months later, her joint symptoms improved, but she complained of persistent pain and tenderness in her left wrist. A repeat X-ray of the wrists revealed sclerosis of the left lunate bone, which was compatible with stage III Kienbock's disease (Lichtmann's classification) [1]. The relative length of the ulna and the radius was normal. A lateral X-ray of the left wrist (flexion and extension views) did not reveal any dislocation of the lunate bone. A magnetic resonance imaging (MRI) confirmed the presence of osteonecrosis of the left lunate and mild effusion of the wrist joint (Fig. 1).

The patient is right-handed and could not recall any previous trauma to the left wrist. There were no occupational risk factors for Kienbock's disease. She is a non-smoker and non-drinker, and her lipid profile was within normal limits. She had not been taking steroids, and her anticardiolipin antibodies and lupus anticoagulant were repeatedly negative. As she was reluctant to undergo surgery, a conservative approach with analgesics and splintage programmes was recommended.

The pathogenesis of Kienbock's disease is unclear. Anatomical risk factors, such as a shortened ulna relative to the radius (ulnar negative variance) and a smaller size of the lunate with more radical inclination, have been described [2, 3]. It is postulated that these anatomical variations result in an increased chronic shearing stress to the lunate bone, and lead to microfracture and subsequent AVN. This mechanical theory is supported by the occurrence of Kienbock's disease in patients with cerebral palsy in whom the increased muscle tone and involuntary movements augment the pressure between the radius and the lunate, and lead to stress microfracture of the bone [4]. Recently, Jensen [5] studied the intraosseous pressure in 10 patients with Kienbock's disease before surgery and demonstrated that venous stasis of the lunate might be a mechanism for the ischaemic process. Although avascularity is thought to be the chief pathogenetic mechanism, common predisposing factors for osteonecrosis, such as corticosteroid therapy, hypercoagulability states, haemoglobinopathies, alcoholism, trauma and vasculopathy, have rarely been described in association with Kienbock's disease [6–8].

AVN is a well-recognized feature of autoimmune diseases. Steroid usage, vasculitis and a thrombotic tendency or vasculopathy related to the presence of associated antiphospholipid antibodies are the major risk factors. Interestingly, extensive literature search

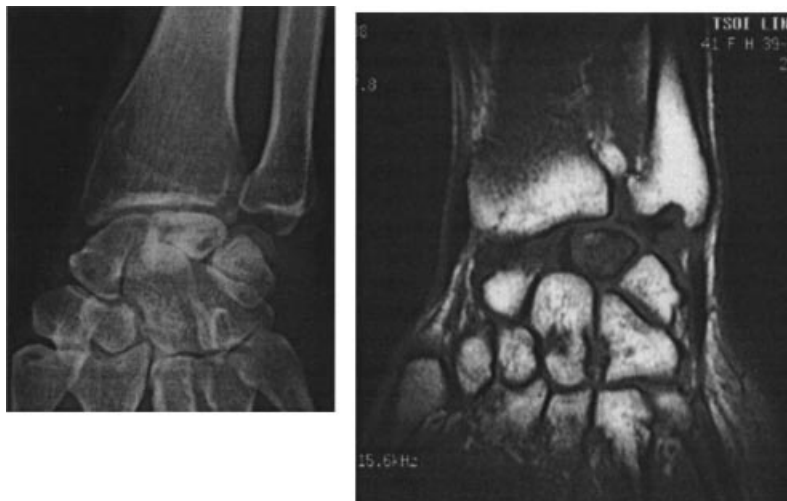


FIG. 1.—Plain radiograph of the left wrist showed increased density of the lunate with evidence of collapse. This was compatible with stage III Kienbock's disease (Lichtmann's classification). The T1-weighted spin-echo coronal MR image of the same region revealed collapse of the lunate bone. The normal bright marrow signals of the lunate were lost as compared to other carpal bones. A small effusion of the wrist joint was also present. No bony erosions were seen.

only revealed two reported cases of Kienbock's disease in autoimmune disorders [9, 10]. Our patient developed Kienbock's disease during the course of her RA, in the absence of steroid treatment. Chance co-existence of the two diseases is very unlikely as Kienbock's disease is rare in our locality and there was a clear temporal relationship between the RA and the avascular process. An increase in intra-articular pressure within the wrist compartment, causing impidence of venous return and consequent vascular insufficiency to the lunate, may be a possible triggering mechanism for the osteonecrosis. For any arthritic patients who complain of persistent pain at a single joint, local causes such as AVN should be excluded, even in the absence of obvious predisposing factors. MRI is a sensitive tool for the detection of early AVN so that intervention can be instituted promptly.

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Circulating Levels of IL-1 β , IL-6 and Soluble IL-2 Receptor in Polymyalgia Rheumatica and Giant Cell Arteritis and Rheumatoid Arthritis

STR—Polymyalgia rheumatica/giant cell arteritis (PMR/GCA) may be difficult to diagnose at onset. Unless a positive temporal artery biopsy is obtained, the diagnosis is a clinical one which may be supported by a raised ESR or CRP, but not always [1, 2]. Even in biopsy-proven GCA, the ESR may be normal [3, 4].

The diagnosis of relapse during treatment is often even more difficult, as the symptoms may be less florid

than at onset, and the ESR and CRP are usually not elevated [1, 2, 5]. Mason and Walport [6] have stressed the importance of not relying on the ESR and CRP to diagnose relapse in PMR/GCA, although Chakravarty *et al.* [7] have shown that many general practitioners and hospital physicians do just that. At present, there is no reliable laboratory indicator of disease activity in PMR/GCA. We have therefore studied whether measurement of cytokine levels is helpful in PMR/GCA.

Plasma levels of IL-1 β and IL-6, and serum levels of soluble IL-2 receptor (sIL2R), were measured using commercially available enzyme-linked immunosorbent assays (ELISAs). Samples were available from before treatment and during subsequent clinical remissions and relapses. Treatment consisted of prednisolone 40–60 mg for GCA and 10–20 mg for PMR, reducing according to clinical progress. Comparison was made with age- and sex-matched controls, and with patients suffering from rheumatoid arthritis (RA), trauma and febrile illness.

In 35 PMR/GCA patients before treatment, plasma IL-1 β levels were slightly, but significantly, raised (median 4 pg/ml) compared with controls (median 0 pg/ml) ($P = 0.0001$). By 10 days of prednisolone treatment, IL-1 β concentration had fallen to normal (median 0 pg/ml). In 21 relapses of PMR/GCA, plasma IL-1 β rose to 5 pg/ml ($P = 0.0016$ for the comparison with controls).

In 12 patients with active RA, the median IL-1 β level was 0 pg/ml, which was the same as in matched controls, whereas in 12 patients with pyrexia due to infection or malignancy IL-1 β was raised at 5 pg/ml ($P = 0.005$).

Plasma IL-6 was slightly, but not significantly, raised in 30 patients with PMR/GCA before treatment: at 8.5 pg/ml compared with controls 0 pg/ml ($P = 0.078$). In 18 clinical relapses on treatment, IL-6 was not increased.

In 12 patients with active RA, plasma IL-6 was 9 pg/ml, not significantly higher than controls. However, in eight trauma cases, the median IL-6 level was raised at 29 pg/ml ($P = 0.001$ for the comparison with matched controls), and in 14 patients with febrile illness plasma IL-6 was raised at 18.5 pg/ml ($P = 0.012$).

Serum sIL2R was elevated in 41 PMR/GCA patients before treatment, at 476 U/ml, compared with controls 366 U/ml ($P = 0.031$). In PMR/GCA suppressed on prednisolone, sIL2R levels were actually lower than controls (301 U/ml, $P = 0.0005$). In 33 relapses in 17 patients, there was a slight rise in sIL2R, but this was not a significant increase, and the levels were still significantly lower than controls. This suggests that prednisolone itself lowers circulating sIL2R. This was supported by the findings in a single volunteer taking prednisolone for 10 days. From day 3 of the prednisolone course until 3 days after the course, sIL2R levels were significantly lower than baseline values (median 181 U/ml compared with baseline median 207 U/ml, $P = 0.009$).

In 12 RA patients, serum sIL2R concentration was elevated at 687 U/ml compared with controls 366 U/ml ($P = 0.011$).

In the initial diagnosis of PMR/GCA, these three investigations had no advantage over the conventional investigations of ESR and CRP, but in relapses plasma IL-1 β was more likely to be raised than ESR or CRP. In the future, more sensitive IL-1 β assays may make this a useful investigation in confirming relapses of PMR/GCA.

It is interesting that in active RA this study did not find raised plasma levels of IL-1 β . Other studies have shown conflicting results. Eastgate *et al.* [8] did find high levels of IL-1 β , but others did not [9, 10]. Grassi *et al.* [11] found that rheumatoid factors interfered in IL-1 ELISAs, causing falsely high results. Interference due to IgM rheumatoid factors could be completely neutralized by dithiothreitol (DTT) which depolymerized the IgM. In our study, the plasma samples for IL-1 assay were treated with DTT, so this source of false-positive results was eliminated. Another possible reason for discrepancies between studies of RA is patient selection, in that perhaps only the most active rheumatoid disease requiring hospital admission results in raised plasma IL-1 β levels, while less florid disease in out-patients does not.

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Can the Routine Culture of Synovial Fluid be Justified?

SIR—Septic arthritis is a significant cause of mortality and morbidity [1]. In the general population, the annual incidence is 2–9.2/100 000 [2–4], but rises considerably in patients with rheumatoid arthritis or prosthetic joints [5]. *Staphylococcus aureus* is the most commonly implicated organism [6]. In many rheumatology centres, synovial fluid is sent for culture in the absence of clinical suspicion of infection, often as a 'baseline' in the unlikely event of iatrogenic joint sepsis, following intra-articular corticosteroid injection. Although rare, this is the most feared complication of the procedure, which is now performed in almost one in eight of all out-patient rheumatology consultations [7]. Despite this, there is no single agreed protocol for skin preparation [8] or subsequent intra-articular injection [9]. With ever-increasing pressure on limited resources, we set out to investigate whether the 'routine' culture of synovial fluid could be justified.

We undertook a retrospective study of all synovial fluid sent to the University Department of Microbiology at Glasgow Royal Infirmary over a 3 month period. Details of the clinical indications for joint aspiration, patient demography, risk factors for joint sepsis including any immunosuppressive drug therapy, co-existing medical conditions and underlying rheumatological diagnosis were recorded using a standard questionnaire. Synovial fluid was collected in sterile universal containers and cultured on the same day in 10% carbon dioxide, on chocolate agar and anaerobically for up to 24 h. The number of positive cultures and the organisms identified were determined.

A total of 108 joints were aspirated from 83 patients. The knee was the joint aspirated in all but one case. The female:male ratio was 3:1 and the median age was 60 yr (17–93).

It has been the practice in our department to send all synovial fluid for culture and the vast majority of

TABLE I
Potential risk factors for sepsis

| Risk factor | Number | Percentage of joints (%) |
|-------------------------------------|--------|--------------------------|
| Previous joint aspiration/injection | 19 | 18 |
| Age >75 yr | 8 | 7 |
| Skin sepsis | 7 | 6 |
| Chronic obstructive airways disease | 5 | 5 |
| Prosthetic joint | 4 | 4 |
| Urinary sepsis | 4 | 4 |
| Diabetes mellitus | 2 | 2 |
| Trauma | 2 | 2 |
| Pulmonary sepsis | 1 | 1 |

joints (81%) were aspirated by a rheumatologist. The commonest diagnosis by far was rheumatoid arthritis (76%). Almost one in five joints had previously been aspirated or injected (Table I). Twelve patients had co-existing infection; 38% of the total number of 83 patients were taking immunosuppressive therapy. The great majority were taking either methotrexate or corticosteroids. Overall, sepsis was clinically suspected in 31 joints (29%) and not in 77 (71%). Only one aspirate was positive for culture. This was synovial fluid obtained from an 80-yr-old man with a prosthetic knee joint for osteoarthritis. Pneumococcus was cultured from the knee following a proven pneumonia with the same organism. There was a high degree of clinical suspicion of joint sepsis in this case.

Thus, in most cases, the synovial fluid sent for culture was not expected to yield bacteria by the clinician. Only one culture-positive synovial fluid was identified in a 'high-risk' patient in whom sepsis was strongly suspected. There were no unexpectedly positive cultures and no cases of iatrogenic joint infection.

Synovial fluid culture is time consuming and costs £10.83 per sample at Glasgow Royal Infirmary. Approximately £3500 per annum would be saved at our hospital alone if synovial fluid was not sent 'routinely' for culture. This would represent an approximate annual cost saving of £2.0 million for the National Health Service as a whole. In view of the low yield of positive cultures, which confirms the findings of a previous study [10], we propose that synovial fluid should only be sent for culture if septic arthritis is considered a possibility or in cases of diagnostic doubt. This would not jeopardize patient care and would result in resources being used more appropriately.

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Cytophagic Histiocytic Panniculitis: A Rare Catastrophic Form of Systemic Panniculitis

SIR—We report here a rare catastrophic form of systemic panniculitis in a young man. Despite compelling clinical evidence, the diagnosis was made only on a post-mortem biopsy.

A 28-yr-old Kuwaiti man presented with a 1 week history of fever and chills associated with a few painful irregular erythematous nodular lesions on his left thigh that resembled firm abscesses. Attempted surgical drainage and penicillin for 7 days did not help, but left a non-healing gaping wound. Over the next 2 weeks, additional lesions appeared on the back and neck, the upper and lower limbs, abdominal wall and thighs, associated with increasing constitutional symptoms and hepatosplenomegaly. Investigations showed mild pancytopenia, mildly elevated erythrocyte sedimentation rate (ESR) and low serum albumin. Repeated microbial cultures from the various sites, the various serological tests, autoantibody screening and imaging procedures were non-contributory. Bone marrow examination showed hypocellularity consistent with a chronic inflammatory process. Acid-fast bacilli were not seen. Biopsy from the lesion showed lymphohistiocytic panniculitis. No granuloma was seen. Antibiotic treatment did not result in improvement.

At 3 months in the follow-up, a rheumatology consultation was requested. A diagnosis of 'systemic panniculitis consistent with Weber Christian disease' was suggested and indomethacin treatment was initiated. All clinical features showed improvement. However, the condition relapsed in a few weeks with repeated vomiting, fever and the appearance of fresh skin s.c. tissue lesions over the trunk and scrotum that were markedly inflamed. Investigations showed low haemoglobin, high platelet count and high ESR. Renal parameters were normal. Liver function tests showed low serum albumin, raised liver enzymes, mild jaundice and abnormal coagulation profile. Diagnosis of Stevens–Johnson syndrome due to indomethacin was considered, and he was treated with corticosteroids with various supportive therapies and antibiotics as guided by the reports from the microbiology laboratory. He showed slow improvement over the next 2 months, but relapsed again in 1 month with additional

features of increasing jaundice, exudative ascites with deteriorating liver functions and right-sided pleural effusion. Over the next 3 days, he was treated with antibiotics and salt-free albumin infusions with a provisional diagnosis of spontaneous bacterial peritonitis. Terminally, he developed features of disseminated intravascular coagulation and acute renal failure possibly due to septicæmia. Despite standard management he went into shock and died. A post-mortem biopsy of the inflammatory lesion on the abdominal wall showed lobular panniculitis with several histiocytes showing foamy cytoplasm, apoptotic bodies and necrotic debris giving the typical 'beanbag' appearance (Fig. 1) characteristic of cytophagic histiocytic panniculitis.

The patient described here demonstrates the difficulty in diagnosing severe systemic forms of panniculitides, uncommon conditions that invariably have a fatal outcome [1, 2]. However, analysis of the clinical features of this patient leave no doubt that the patient had an illness highly suggestive of severe systemic panniculitis.

Panniculitides are now classified histologically into 'septal', 'lobular', 'mixed forms' and those 'with vasculitis' [1, 2]. The majority of these conditions are secondary to some other underlying cause that may be infection, drug allergy, etc. [1, 2]. When there is no apparent cause, the label 'primary' is used. By themselves, panniculitides are benign self-limiting conditions with little systemic involvement except mild constitutional symptoms and minor musculoskeletal features [1, 2]. However, rarely systemic forms of panniculitides are seen that could be lethal. Two such forms of panniculitides include systemic forms of Weber-Christian disease and cytophagic histiocytic panniculitis (CHP) [3–7]. A generic term, 'Weber-Christian disease', has been suggested for all systemic forms of lobular panniculitides that also includes a severe systemic form which occasionally has a fatal outcome [3, 7]. Based on these considerations, this patient was

diagnosed as having the systemic form of Weber-Christian disease and managed accordingly. However, the histology of the lesion terminally showed a rather characteristic appearance of CHP [4–7].

Experience has shown that the lesions of non-suppurative panniculitis are often confused with suppurative panniculitis (i.e. cellulitis or abscess). Associated minor constitutional symptoms and arthralgias and myalgias are ignored. Patients receive antibiotics with an attempt to 'drain' the lesion. As most of these diseases are benign self-limiting conditions (i.e. erythema nodosum related to some transient infection) [1, 2], the lesions subside without any further problem. However, in those with recurrence of lesions, further efforts then lead to the diagnosis of 'panniculitis'. This patient demonstrated many of these features. His disease was correctly categorized as systemic panniculitis. However, he was considered to have Weber-Christian panniculitis which generally does not have a serious fatal outcome [1, 2]. Unfortunately, the patient turned out to have CHP, an extremely rare form of systemic panniculitis that resembles Weber-Christian disease (by itself an uncommon panniculitis). It is resistant to the usual forms of treatment and has high mortality of >70% [4–6]. However, a recent review recommends cyclosporin [8].

The experience with this patient emphasizes the need for accurate histological characterization as the essential first step in the diagnosis and management of any form of panniculitis.

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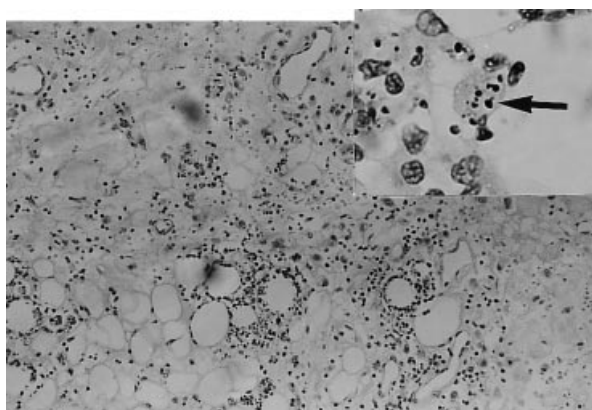


FIG. 1.—Lobular panniculitis in the periphery and in the centre of the fat lobule of the subcutis. The inflammatory cells are mostly histiocytes and lymphocytes. The inset shows apoptotic bodies and necrotic debris with large histiocytes giving a 'bean bag' appearance. H&E $\times 100$; inset, H&E $\times 400$.

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The Pharmacokinetics and Human Anti-mouse Antibody Response in Rheumatoid Arthritis Patients Treated with a Chimeric Anti-CD4 Monoclonal Antibody

SIR—CD4⁺ lymphocytes have been implicated in the pathogenesis of rheumatoid arthritis (RA). Consequently, they are attractive targets for therapy using monoclonal antibodies (mAbs). A number of murine anti-CD4 mAbs have been tested in refractory RA patients [1]. The initial results were encouraging, but the use of murine mAbs in human diseases has been hampered by the development of human anti-mouse antibody (HAMA) response. This is a major disadvantage since HAMA could lead to anaphylaxis and diminish efficacy on repeat treatments. This problem may be circumvented by using chimeric mAbs that are constructs of murine mAb variable domains and the constant region of human immunoglobulin; therefore, they should be less immunogenic. Furthermore, chimeric antibodies have a serum half-life 5–6 times that of murine antibodies. Therefore, the dose and treatment frequency may be reduced if chimeric mAbs are used. We have investigated the use of a chimeric depleting anti-CD4 mAb, cM-T412 (Centocor Inc., USA), in the treatment of RA [2, 3]. Some patients, particularly those who had a high percentage of synovial fluid lymphocytes coated with cM-T412, showed significant clinical improvement [3]. Here, we report the serum concentration of cM-T412 and the incidence of HAMA in these patients.

Twelve patients with American College of Rheumatology defined RA [4] and who had active disease as previously described [3] were recruited. All patients were treated with 50 mg of cM-T412 daily for five consecutive days as an induction course. Six patients (Group A) then received 50 mg of cM-T412 weekly for 5 weeks as maintenance treatment. Group B (six patients) was retreated with a second course of five daily 50 mg doses of cM-T412 5 weeks after the initial induction treatment course. Blood samples were taken at weeks 0, 2, 4, 6, 8, 10, 12 and 16. Serum cM-T412 [5] and HAMA [6] were measured by ELISA and sandwich enzyme immunoassay, respectively, as previously described.

After five daily 50 mg doses of cM-T412, at week 2 the median serum cM-T412 was 11.5 ng/ml (range 0–400 ng/ml). Even in the patient with the highest serum concentration of cM-T412, the value remained very low. Weekly treatment with 50 mg of cM-T412 in Group A patients had no cumulative effect on serum cM-T412 concentration. Group B patients showed a transient but a very small increase in serum cM-T412 after the second treatment course.

After the first course of treatment with cM-T412, only 2/6 and 5/6 of patients in Group A (Fig. 1a) and B (Fig. 1b), respectively, developed HAMA responses (titre > 1/20). However, the HAMA titres were low, except in four who had a titre > 1/40. This is much lower than expected when compared with murine mAbs. After all treatments, four patients (67%)

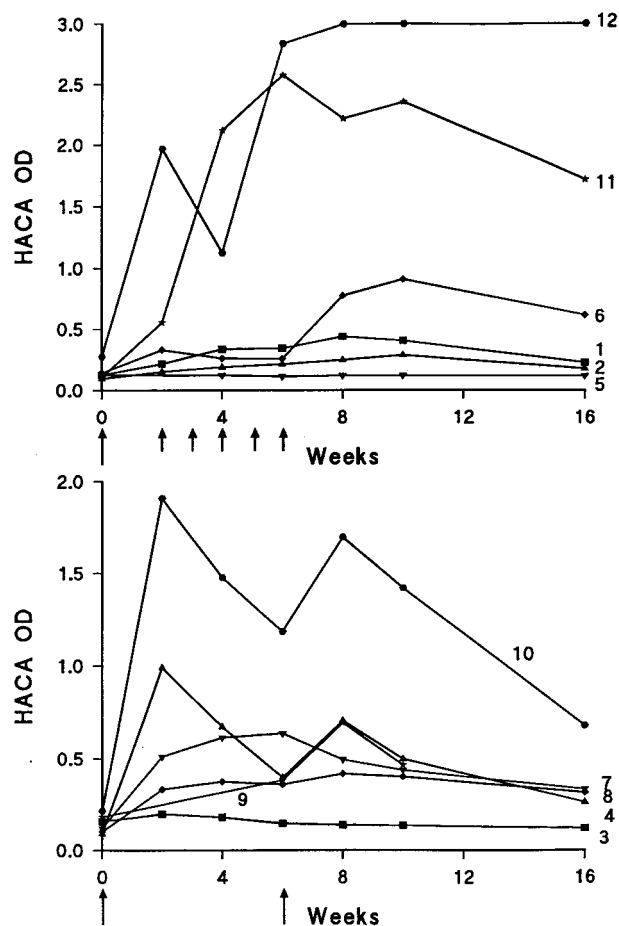


FIG. 1.—Human anti-mouse antibody (HAMA) response in Group A patients [upper panel, (a)] and Group B patients [lower panel, (b)]. Arrows indicate time points when treatments were administered. Lines are labelled by the patient number. The vertical axis shows the ELISA optical density readings for the HAMA.

in Group A produced HAMA responses with titres ranging from 1/40 to 1/20 400. Five patients (87%) were positive in Group B with titres ranging from 1/20 to 1/320. Peak HAMA titres attained by Group A patients (40, 80, 640, 20 400) were higher than those attained by group B (20, 40, 40, 40 and 320); however, these were not statistically significant. All HAMA responses were declining by week 16.

One patient developed a mild urticarial skin rash after the ninth dose of cM-T412 and treatment was stopped. Her skin rash resolved spontaneously. A moderate titre of HAMA (1/640) was found in her serum at week 6.

The use of murine mAbs in human diseases is usually associated with the development of HAMA. When murine anti-intercellular adhesion molecule-1 (ICAM-1) mAb was used in an open trial for treatment of RA, all the patients developed HAMA 2 weeks after treatment [7]. Re-treatments were less effective and some patients developed angioedema [8]. However, one might expect cM-T412 to be less immunogenic for two reasons. First, cM-T412 is a chimeric mAb and, second, it may induce tolerance to

itself. Indeed, the incidence of HAMA responses to murine anti-CD4 mAb was less than with other murine mAbs [9]. In our current study, we have shown that after five daily treatments with 50 mg of cM-T412, only 60% (7/12) of the patients developed HAMA response, suggesting that chimeric antibodies are indeed less immunogenic [9].

The serum concentrations of cM-T412 were extremely low. Ten days after the first treatment course, in most patients, the serum concentration of cM-T412 was undetectable whilst the highest concentration was only 400 ng/ml. This compared with the *in vitro* data showing that the concentration required to inhibit lymphocyte proliferation was 5 µg/ml [10]. This would suggest that higher doses of cM-T412 are necessary to inhibit inflammation, but this would have led to more profound CD4 lymphopenia.

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Pleural Effusion as a Form of Presentation of Temporal Arteritis

SIR—Giant cell arteritis (GCA) is a well-recognized multisystemic disease involving multiple organs [1]. Pulmonary symptoms are unusual and only in 4% of cases do they constitute the initial manifestation of the disease [1]. Pleural effusion is a very infrequent form of presentation, and to date only nine reports have been published [1–8]. We describe here a patient presenting with pleural effusion.

A 69-yr-old woman was admitted with a 6 month history of progressive fatigue and dry cough. She also complained of progressive weakness of her lower extremities and daily headache in the last 2 months. On physical examination, the patient appeared mildly ill. Her temperature was 37.3°C and her breath rate 24/min. Decreased breath sounds with diminished vocal fremitus were present at the base of the left lung. Heart examination was unremarkable, as were the abdominal and neurological examinations. A pulseless and slightly thickened left temporal artery was observed. Laboratory analyses showed a haemoglobin of 9.6 g/dl, haematocrit 34%, MCV 90, white cell count of $10.3 \times 10^9/l$ (neutrophils 85.5%, lymphocytes 5.5%, monocytes 6.9%, eosinophils 1.9%, basophils 0.2%), platelet count of $477 \times 10^9/l$, fibrinogen of 6.56 g/l and α -2 globulin of 20%. The erythrocyte sedimentation rate (ESR) was 98 mm at the first hour. A chest roentgenogram showed a massive left pleural effusion. Thoracentesis yielded serous fluid with great cellularity, containing mesothelial cells, polymorphonuclear cells and eosinophils. No malignant cells were present. Pleural fluid analysis showed glucose of 119 mg/dl, protein of 3.8 g/dl, lactate dehydrogenase of 447 U/l and adenosine deaminase of 14 IU/l (normal < 40 IU/l), with no antinuclear antibodies or rheumatoid factor. Sputum and pleural cultures for bacteria and *Mycobacterium tuberculosis* were negative. Blood cultures and serological studies for *Brucella*, Q fever, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, cytomegalovirus and Epstein–Barr virus were all negative. A chest CT scan showed a massive left pleural effusion. No adenopathies or pulmonary lesions were observed. Fiberoptic bronchoscopy was performed and revealed no abnormalities. With the suspicion of GCA a biopsy of the temporal artery was performed. The biopsy specimen showed an intimal fibrosis with lymphocytic and mononuclear infiltrates of the vessel wall, disruption of the internal elastic lamina and dense perivascular fibrosis with prolifera-

tion of capillaries, consistent with GCA. Treatment with prednisone (1 mg/kg/day) was started and the patient's condition improved rapidly, with complete clearance of pleural effusion and normalization of the ESR. Corticotherapy was tapered progressively with no recurrences. Two years later, the patient remains symptom free on 5 mg/day of prednisone.

GCA does not always present with the classic manifestations of headache, jaw claudication and blindness. In ~9% of patients, respiratory tract symptoms are present at the onset of the disease, and in ~4% of cases they constitute the first manifestation [2]. Dry cough is the most common respiratory symptom. Pleural effusions are rare in GCA and the histological findings in biopsy specimens are non-specific. To date, only nine cases of pleural effusion in GCA have been reported in the literature [1–8]. Pleuritic chest pain was referred in six cases. Biochemical fluid characteristics have been described in only five cases [5–8]. In all of them, pleural fluid was an exudate, as in our patient, with a predominance of polymorphonuclear cells in four patients [8]. In one case, an initial predominance of lymphocytes and, after numerous relapses, of eosinophils (which can be attributed to repeated thoracenteses) was reported [7]. A high mesothelial cell count, as in our patient, was also present in four of five cases reported previously and was not associated with any particular disease [8]. We did not perform a pleural biopsy, but the changes found in previous published cases were non-specific [8].

The pulmonary manifestations reported in the literature—nodular lesions, interstitial infiltration or pleural effusions [2, 8–10]—improved with corticosteroid therapy, as in our patient. The rapid response to corticosteroids with complete resolution of the pleural effusion after a few days, and the patient's follow-up, are arguments against other aetiological causes like infections or neoplasms. The mechanism of pleural affection is unclear, but since GCA is a multi-systemic disease involving many organs, we suggest that the respiratory symptoms in these patients are more likely due to primary vasculitis of the lungs.

We recommend that whenever respiratory symptoms accompany the classical symptoms of temporal arteritis, despite its rarity in GCA and even more so as an initial manifestation, primary vasculitis of the lungs should be considered.

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A Survey of Ehlers–Danlos Syndrome: Hearing, Voice, Speech and Swallowing Difficulties. Is There an Underlying Relationship?

SIR—We would like to report the results of a recent survey which, for the first time, has demonstrated hearing, speech, voice and language difficulties in a large cohort of patients with Ehlers–Danlos Syndrome (EDS). EDS is an inherited disorder of connective tissue that affects multiple organ systems. There is a classic triad of skin hyperextensibility, joint hyperlaxity and bruising [1]. Although the EDS is being increasingly studied, this is the first time that an assessment of speech-related problems has been sought.

The first author is a speech therapist who has become professionally involved with this group of patients and was struck by the absence of literature on the problems she encountered. A postal questionnaire was circulated to the 411 members of the nationwide EDS support group and EDS types I, II, III, IV and VI were represented amongst the returns. The questionnaire was specifically designed for this survey and included introductory questions such as 'Have you got/ever had difficulties with your voice?'. Further sub-questions were then asked according to the respondent's answer. There was a > 50% response rate from a single mailing. The mean age was 45.5 yr (range 1.5–80 yr), with more females than males.

The most commonly reported symptom was difficulty in swallowing. This occurred in 39% of responders. Of these, three-quarters had difficulty clearing their throat on one swallow and two-thirds reported a tightness or a lump in the throat during swallowing. They reported the need to swallow several times before the pharynx was cleared. Many subjects found that eating soft food helped, whereas others felt unable to eat alone for fear of choking. Difficulties in chewing occurred in 25%. Discrepancies between lower and upper jaw alignment were major components of their problems. Orthodontic and temporomandibular joint problems in EDS are well described [1, 2].

There was also a high rate of aurally related symptoms and 28% reported being unable to sustain a voice or shout. Delays in language development and premature degeneration of speech according to the prompt question of 'Have you ever had difficulties with understanding or using your own speech?' occurred in a higher frequency than in the general population. The incidence of dysphonia in the general population is 28 per 100 000 [3]. The current study identified dysphonia in 89 out of 327 (27%). Speech and language difficulties are estimated to occur at a rate of 1100 per 100 000 (1%) in pre- and school-age children [3], but EDS subjects reported difficulties at a rate of 157 out of 327 (48%) in this age range. Tiring and other age-related effects on voice, such as poor quality, limited range of pitch and maintenance of voice, etc. were reported from age 11 onwards. The mean age of onset was 36 yr (range 11–63 yr). The language difficulties were self-limiting in 46%, but remained persistent in 54% of subjects.

The high prevalence of speech and swallowing difficulties in EDS may suggest that some of these problems are secondary to the underlying connective tissue defect.

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Polymyalgia Rheumatica Presenting After Successful Treatment of Cushing's Disease

STR—A 55-yr-old woman was referred with poor wound healing and recurrent wound abscesses. She had been diabetic for 8 yr and on oral hypoglycaemic agents for the last 2 yr. On examination she was Cushingoid. Investigations confirmed Cushing's disease with a left-sided pituitary microadenoma which was excised at trans-sphenoidal hypophysectomy. Her post-operative 09:00 a.m. serum cortisol was 36 nmol/l with symptoms of hypoadrenalism, confirming remission of her Cushing's disease. She was commenced on hydrocortisone replacement with a routine maintenance dose of 10 mg/5 mg/5 mg (a.m./noon/p.m.) [1].

Two weeks after hypophysectomy, she complained of headaches and scalp tenderness. Plasma viscosity (PV) had risen from 1.67 to 2.17 pc (normal range 1.5–1.72 pc). Temporal arteritis was suspected and she was commenced on 40 mg of prednisolone with immediate symptomatic relief. Temporal artery biopsy was

normal and, to speed her recovery from the Cushing's, her prednisolone was gradually stopped. Her headaches and scalp tenderness recurred a month later, associated with blurred vision, PV 1.92 pc. Ophthalmological opinion suggested an ischaemic optic neuropathy secondary to diabetes mellitus. Headaches and scalp tenderness continued intermittently for 7 months. She subsequently complained of myalgia, morning stiffness and muscle weakness. Physical examination revealed proximal muscle tenderness and minimal (grade 4+/5) symmetrical proximal upper limb weakness only. Her hydrocortisone day curve to assess replacement levels was satisfactory and 24 h urinary free cortisol, serum potassium and muscle enzymes were within their respective reference ranges, with PV 1.78 pc, haemoglobin 11.5 g/dl. A diagnosis of polymyalgia rheumatica was made and she responded to a therapeutic trial of prednisolone, requiring a maintenance dose of 10–15 mg daily. After 9 months on prednisolone, her Cushing's disease symptoms recurred. Her 09:00 a.m. and midnight serum cortisol levels were undetectable off steroid therapy, confirming iatrogenic Cushing's syndrome. Prednisolone was stopped and hydrocortisone substituted initially at high dose and gradually reduced to her usual maintenance dose. She remains well as of March 1997.

This case illustrates the potent anti-inflammatory effects of natural glucocorticoids. The emergence of polymyalgia rheumatica coincided with the reduction of these glucocorticoids to physiological levels following the removal of the ACTH-secreting tumour. There are, to our knowledge, only three reported cases of conditions that were unmasked following treatment of Cushing's syndrome. Raccach *et al.* [2] described two cases of inflammatory arthropathy following surgical treatment of Cushing's disease. The first case was probably an exacerbation of rheumatoid arthritis. In the second case, an unlabelled inflammatory rheumatism appeared in a context of post-operative corticotrophic deficiency. In both cases, physiological replacement doses of hydrocortisone relieved their symptoms, whereas in our case symptoms persisted despite adequate hydrocortisone replacement. The symptomatic relief with prednisolone in our case is most likely to be related to the dose of glucocorticoid used. Akama *et al.* [3] reported an association of Carney's complex (adrenocortical nodular hyperplasia, cardiac myxomas, and spotty pigmentation of skin and mucous membranes) and sarcoidosis. The sarcoidosis became apparent 10 months post-adrenalectomy. The raised glucocorticoids could have suppressed the development of sarcoidosis. Interestingly, as far back as 1951, Caughey and McCoy [4] described a case of Addison's disease with a recurrent polyarthritis which was exacerbated by deoxycortisone and relieved by cortisone.

The present case presents two problems: (a) making the diagnosis of temporal arteritis/polymyalgia rheumatica following pituitary surgery and (b) future management. Although a raised plasma viscosity could have been a result of surgery, headaches, scalp tenderness and a rapid response to steroids were in favour

of temporal arteritis. Transsphenoidal hypophysectomy surgery rarely causes headaches as it is not an intracranial procedure due to the extracranial approach, unlike the transfrontal approach which is now rarely used. Polymyalgia rheumatica was diagnosed on symptoms, although there was minimal, but unexplained, proximal upper limb weakness.

The future management of our patient is problematic. Although we had no histological proof of temporal arteritis, we did have a high PV and symptoms of polymyalgia rheumatica in the presence of an adequate hydrocortisone replacement dose. Conversely, the steroids used to treat her polymyalgia rheumatica resulted in overall worsening of her clinical state.

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Detection and Follow-up of Wegener's Prostatitis by Transrectal Ultrasound

SIR—Prostatic involvement has been described in 2.3–7.4% of patients [1, 2] with Wegener's granulomatosis (WG), but presentation with prostatic symptoms is rare. We report a patient presenting with acute urinary retention secondary to WG of the prostate. Transrectal ultrasound (TRUS) detected prostatic involvement and demonstrated its regression with treatment. This is the first reported case in which TRUS has been used for this purpose.

A 52-yr-old man presented with acute urinary retention following a 4-week history of perineal pain, urinary frequency, nocturia, hesitancy and dysuria, and a 3-month history of arthralgias and mild weight loss. He had mild hypertension, was a non-smoker, and attributed an intermittent post-nasal drip to his occupation in a dusty builder's yard. On examination, he had a pyrexia (37.9°C), a distended bladder and, on rectal examination, a firm, asymmetrically enlarged (right lobe > left), tender prostate. Otherwise, systemic examination was unremarkable. Urinary catheterization yielded a residual 750 ml. Urinary microscopy

showed 600 red cells/cm² and 240 pus cells/cm². Casts were absent and culture was negative. Urea, electrolytes and creatinine clearance were normal. White cell count was 12.4 × 10³/μl (94% neutrophils), ESR 45 mm/h and CRP 210 U/l (<10). Prostatic specific antigen (PSA) was 6.5 μg/l (normal 0–4 μg/l, <20 μg/l in benign hypertrophy). Flexible cystoscopy confirmed an enlarged prostate. Infective prostatitis was diagnosed and ciprofloxacin commenced. A prostatic biopsy was not performed because of the potential infective risk and the low clinical suspicion of carcinoma.

Over the next week, he developed a persistent dry cough. Chest X-ray showed ill-defined shadowing along the left heart border. CT scan of the chest showed a 3 cm mass occluding the proximal lingular bronchus, without lymphadenopathy. Peroral fiberoptic bronchoscopy demonstrated stenosis of the lingular orifice by a friable haemorrhagic mass. Histology showed ill-defined but non-caseating granulomatous inflammation with foci of giant cells, histiocytes, polymorphs and lymphocytes. Neoplastic features were absent. Stains for fungus and alcohol-acid-fast bacilli (AAFB) were negative. cANCA was elevated at a titre of 1/640 and proteinase-3 antibody (PR3) at 223.1 U/ml (<2).

In view of these respiratory findings, a granulomatous aetiology for the prostatitis was suspected. Transabdominal ultrasound showed an enlarged prostate (4.7 × 5.1 cm), but no focal abnormality in the prostate or bladder. TRUS of prostate, however, demonstrated a focal echolucent 0.5-cm-diameter nodule with typical granulomatous appearance, adjacent to the periurethral zone and impinging on the urethra (Fig. 1). Colour flow imaging was normal. Prednisolone 60 mg, cyclophosphamide 100 mg and co-trimoxazole 400 mg daily were commenced. A trial without catheter, 3 weeks later, was successful. Symptomatic improvement occurred over 3 months. Mild haematuria and dysuria secondary to cyclophosphamide-induced haemorrhagic cystitis settled with dosage reduction to 50 mg. White cell count, ESR, CRP, cANCA, PR3 and PSA decreased to normal. Chest X-ray showed significant improvement. Follow-up TRUS of the prostate at 1 yr showed complete resolution of the periurethral nodule (Fig. 1).

Prostatic involvement in WG is an unusual but under-recognized finding. A Mayo Clinic series found prostatic involvement in 4/174 patients (2.3%) [1], whereas Walton's [2] classic literature review (1958) found prostatic involvement in 4/54 patients (7.4%). Clinical sequelae resulting from prostatic granulomata are unusual. A 1994 literature review found only 18 case reports of prostatic symptoms due to WG (five haematuria, eight chronic obstruction, five acute retention) and only 7/18 reported prostatic symptoms as the initial complaint [3]. Typical findings on rectal examination are an enlarged, firm, indurated prostate. Urinalysis may show microscopic or frank haematuria, sterile pyuria or proteinuria (from prostatic or co-existent renal pathology) [4]. Cystoscopy may show



FIG. 1.—Transrectal ultrasound of the prostate (sagittal-oblique view). A focal nodular thickening in the periurethral zone is seen at presentation, but is no longer present on the repeat scan at 1 yr follow-up.

an abnormal prostatic channel with friable or necrotic prostatic tissue [1]. Histopathology may show irregular granulomas with central necrosis, palisading histiocytes, giant cells and small-medium vessel vasculitis (contrasting with the well-defined granulomas of sarcoidosis, or central caseation in tuberculosis). As findings are non-specific, the diagnosis should be supported by positive cANCA and PR3 which have 98% specificity for WG [5], although sensitivity varies from 33 to 90% depending on the extent and degree of disease activity [6]. Our case describes how TRUS may non-invasively detect prostatic involvement in WG, and usefully demonstrate regression of lesions with successful treatment. Careful real-time gray-scale ultrasound is more useful than Doppler or colour-flow imaging [7]. Medical management comprises combination prednisolone and cyclophosphamide [8]. Surgical transurethral resection may satisfactorily re-establish prostatic channel patency [1], but as recurring obstruction may occur, surgery should be reserved for patients with severe presenting symptoms or failure of medical treatment [9].

Of note, although co-existent extra-prostatic involvement at presentation is likely (particularly upper or

lower respiratory tract: 73 and 50%, respectively [5]), a bronchostenotic lesion, as in our case, is unusual. Daum *et al.* [10] found that only 4/51 patients (7.8%) with respiratory symptoms, signs and biopsy-proven WG had tracheal or bronchial stenosis at bronchoscopy.

In summary, prostatitis is an under-recognized complication of WG. In patients with known WG and suspected genitourinary involvement, TRUS provides a non-invasive means of detecting prostatic involvement and monitoring the response to treatment.

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Re: Interaction Between Methotrexate and Trimethoprim

SIR—I was interested to read the letter by Steuer and Gumpel [1] on the interaction between methotrexate and trimethoprim. This drug interaction is more widely known than they are perhaps aware, and is listed in the British National Formulary (BNF) [2] even if not in the BSR guidelines.

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2. British National Formulary 1997;34:564.

Methotrexate and Penicillin Interaction

SIR—We read with interest the recent review of methotrexate therapy [1]. Although probenecid and NSAIDs were discussed in the alterations in clearance of methotrexate, we noted that penicillins were not. This is of particular interest to us as one of our local pharmacies is not dispensing penicillin to patients on methotrexate, after advice was given from methotrexate manufacturers (Maxtrex-Pharmacia and Upjohn).

Like probenecid and aspirin, penicillins are weak organic acids, which compete with the renal tubular secretion of methotrexate and decrease its clearance. In rhesus and cynomolgus monkeys, it has been shown *in vitro* and *in vivo* that methotrexate and penicillin share a common secretory system in the kidney, and penicillin blocks methotrexate secretion by inhibiting cellular uptake and stimulating efflux [2]. It has been reported where this potential interaction has manifested itself in a 16-yr-old patient on high-dose methotrexate [3]. The *Medical Journal of Australia* published a report of five patients on low-dose methotrexate who were admitted because of neutropenia. Four of the aplastic crises had been thought to be due to, or exacerbated by, concomitant penicillin antibiotic administration in patients with impaired renal clearance [4].

In view of these recognized interactions between methotrexate and penicillin, it would be safe clinical practice either to prescribe an antibiotic other than penicillin derivatives or omit methotrexate whilst the patient takes their penicillin. In particular, in patients who have methotrexate toxicity causing neutropenia, penicillins should be avoided.

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Discordance for Systemic Lupus Erythematosus and Hyper IgE Syndrome in a Pair of Monozygotic Twins

SIR—We read with interest the letter of North and colleagues [1] describing the case of a child suffering from hyper-IgE syndrome (HIE), complicated by systemic lupus erythematosus (SLE) [1].

We report here the cases of two 23-yr-old female monozygotic twins, M. and S., discordant for HIE and SLE. They are daughters of non-consanguineous par-

ents. Family history was negative for autoimmune and immunodeficiency disorders.

M. was considered to have HIE based on clinical and laboratory findings: she suffered from persistent dermatitis (papulo-pustular rash involving preferentially the face and buttocks), furunculosis, some episodes of *Staphylococcus aureus* cutaneous abscess formation and other infections (recurrent otitis, stomatitis and hydrosadenitis). Laboratory investigations showed high IgE levels [4640 IU/l; normal value (NV): <190], moderate eosinophilia (1430 cells/ μ l) and raised IgG (2260 mg/dl; NV: 670–1550). Anti-*Staphylococcus* IgE was not detected. Polymorphonuclear cell (PMN) function studies showed a defective chemotactic response both to normal human AB serum (NHS-AB) activated with zymosan (20%) and to *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (34%) (in healthy controls: >70%), whereas phagocytosis of *Candida albicans*, nitroblue tetrazolium reduction and chemiluminescence [spontaneous, and after activation with NHS-AB-zymosan or with phorbol myristate acetate (PMA)] tests were normal; chemotactic activity of patient serum activated with zymosan was also normal. Parasitological research was repeatedly negative. During follow-up, antinuclear and other autoantibodies were never detected. HLA serological typing showed A24 (9), Aw68 (28), B35, B44, Bw4, Bw6, Cw4, Cw7, DRw11 (5), DRw52, DQw7 (w3). Notably, in 1984, idiopathic thrombocytopenic purpura (ITP) was diagnosed and treated with a short-term course of corticosteroids with permanent complete remission.

S. has no history of atopic diseases or of susceptibility to infections. After some years of arthralgia and Raynaud's phenomenon, in 1994 she presented with chronic arthritis of the small joints of the hands. Laboratory tests showed mild lymphopenia (around 1000–1200/ μ l) ANA +, anti-dsDNA: 176 IU/ml (NV: <7), anti-Ro/SS-A +; CH50: 92%, C3: 100 mg/dl, C4: 10.5 mg/dl (NV: >14), polyclonal IgG hypergammaglobulinaemia (2130 mg/dl) and mild increase of total IgE (502 IU/l). Antiphospholipid antibodies were absent. Her HLA phenotype was identical to that of her sister. She was treated with hydroxychloroquine 200 mg/day with disappearance of arthritis. In the follow-up, she complained only of Raynaud's phenomenon and an episode of bilateral parotid gland swelling, whereas anti-dsDNA titre, complement and IgE levels did not show significant changes.

Discordance for HIE and SLE, respectively, in monozygotic twins is not unexpected; in fact, HIE is considered an autosomal dominant disease with incomplete penetrance [2], whereas concordance for SLE between monozygotic twins is reported as ranging from 24% [3] to 69% [4].

On the other hand, the presence of HIE and SLE in this pair of monozygotic twins follows other case reports of an association of these two diseases in single individuals [1, 5, 6]. Our observation reinforces the hypothesis of a common genetic background for these two disorders. This hypothesis is supported by the

TABLE I
In vitro cytokine production by activated peripheral blood mononuclear cells

| | M. | S. | Healthy controls |
|-----------------------|-------|-------|---------------------|
| IL-2 (ng/ml) | 206.0 | 456.2 | 162.7 (133.0–300.4) |
| IL-4 (pg/ml) | 25 | 16 | 13 (6–24) |
| IFN- γ (ng/ml) | 2.0 | 9.0 | 75.9 (39.6–143.4) |

Data on normal controls are expressed as the median (25th–75th percentile) observed in 20 individuals.

observations of a permanent rise in IgE levels also in the girl with SLE, and of an autoimmune disorder, albeit transient (ITP), in the girl with HIE, which suggest a reduced penetrance of genetic factors. The discordance for SLE and HIE might be accounted for by this variable penetrance and by the role of environmental triggers (e.g. infections) which could differ between the pair.

One possible mechanism by which this postulated common genetic background might contribute to the generation of HIE and SLE is abnormal T-cell cytokine production. It is well known that T lymphocytes can be classified according to the pattern of cytokine secretion into these two profiles [7]: type 1 helper T-cell (Th1) clones secrete IFN- γ , whereas type 2 (Th2) clones secrete IL-4 and IL-5; both secrete IL-3 and GM-CSF. In humans, IL-2 production is not restricted to Th1 cells; it can also be induced by stimulating 'naive' T cells which differentiate into precursors of Th1 and Th2 cells (so-called Th0 cells) [7, 8].

In HIE, defective production of the Th1 cytokine IFN- γ has been demonstrated [9].

SLE is also characterized by abnormalities of T-cell functions, including reduced T-cellular responses and increased T-cell help for humoral immunity. Data emerging from some murine models and from humans have led to the hypothesis that in SLE there is predominance of Th2 cytokines (reviewed in [10]). The increased prevalence of drug, skin and insect allergy in SLE patients [11], and the increased levels of serum IgE in children of mothers with SLE [12], support this hypothesis.

We have studied cytokine production by peripheral blood mononuclear cells stimulated for 72 h with

PMA (5 ng/ml) + ionomycin (500 ng/ml), observing a markedly reduced production of the Th1 type cytokine IFN- γ in both sisters, whereas IL-2 and IL-4 production was raised or preserved (Table I). This observation may support the hypothesis of defective Th1 cytokine production as a unifying factor in SLE and HIE.

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