LETTERS TO THE EDITOR


SIR—We have concerns about this paper relating to the methodology, to certain statements relating to key results and the potential for these statements to imply exaggerated safety of meloxicam over other NSAIDs.

Our main concern is with statements such as ‘With respect to ... the most serious of NSAID associated side effects, meloxicam was better tolerated than the comparators ...’ (Summary, line 8). This constitutes a major safety claim for this product and, if valid, an important therapeutic advance. As such, the data must be unequivocal. We do not believe this to be the case for reasons detailed below.

Independent expert opinion has confirmed that a standard subcategorization of ‘serious gastrointestinal (GI) complications’ would comprise: (i) melaena or haematemesis; (ii) perforated upper GI ulcer; (iii) haemorrhagic upper GI ulcer. The references in the Discussion (p. 76, para. 6) also consider serious GI complications in terms of ‘upper GI bleeding and/or perforation’ (but do not include ulcers).

The three subcategories of serious GI complications defined above are shown individually in Table IV of the paper and appear to equate to the ‘Serious PUB’ category in this table. We regard this category as the key data in the paper pertaining to serious GI complications because it is also stated in the text (p. 74, para. 2) that ‘the majority of GI adverse events defined as serious fell into the category of a PUB’. This is the only mention of serious GI events in the paper and they are not listed in either table; however, they can be derived by subtraction of ‘non-serious’ from ‘total’ events in Table III. The absolute numbers of serious GI complications (according to accepted criteria) derived from Tables III and IV are shown in our Table I. There are minor differences in these numbers dependent on the data source (which we cannot explain on the basis of the data provided in the paper). It is clear that there are no differences in serious GI adverse events (or serious PUB) between treatment groups.

The advantage claimed in the Summary and elsewhere in terms of a reduction in ‘most serious’ NSAID side-effects is only achieved by pooling ulcer rates with what are usually regarded as serious GI complications (as defined above). Ulcers are not regarded as serious complications until they bleed or perforate, and thus the category of ‘PUB %’ in Table IV is a clinically inappropriate grouping of data.

This is, however, the category on which claims are based for meloxicam’s advantage (in terms of ‘most serious’ side-effects) despite the statement in the text (p. 70, para. 3) that this classification includes non-serious events. There are also no differences in ulcer rates in the data provided for duodenal and gastric ulcer incidence.

This analysis has a number of major flaws which we believe have introduced serious bias into the treatment comparisons, including the following.

(a) The method of analysis (‘global analysis’) indicated in the title is misleading, because the analysis of GI adverse events excludes many patients treated with meloxicam. Neither is this a formal meta-analysis using methodology designed to avoid bias due to confounding. Most notably, the analysis excludes patients on meloxicam 30 or 60 mg because these doses ‘...did not show advantages in their benefit/risk ratios ...’ (p. 68, para. 4). This implies that the risks are dose related and, if so, a credible safety analysis should show the number of serious GI adverse events at higher doses.

It is well recognized that serious GI adverse events on NSAIDs are dose related, and a similar dose-related increase in side-effects, particularly GI, has been reported for meloxicam [1].

Other patient groups excluded from the analysis of GI adverse events are certain patients receiving meloxicam 7.5 or 15 mg, all Phase 1, open label or single-blind studies, and patients with indications other than OA or RA. As a result, more than half (52%) of patients on meloxicam 15 mg do not contribute to the event rates quoted for this dose. Since three ‘PUB’ are reported in Table IV for this dose of meloxicam, it would be pertinent to know how many such events occurred in the 1692 patients who have been excluded.

The consequences of restricting a ‘global’ analysis to what is, in fact, a highly selected subset of patients exposed to meloxicam are not discussed, nor are any sensitivity analyses reported to confirm retrospectively the robustness of the conclusions.

(b) The risk of GI complications is proportional to the duration of exposure to NSAIDs. Because duration of exposure has not been taken into account in this analysis, this potentially invalidates most of the comparisons of event rates between treatments. For example, the event rates presented do not take account

<table>
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<th>TABLE I</th>
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<td>Serious GI adverse events (n) (derived from Table III)</td>
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<td>--------------------------------------------------------</td>
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<tr>
<td>Meloxicam 7.5 mg</td>
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<td>Meloxicam 15.0 mg</td>
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<td>Piroxicam 20 mg</td>
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<td>Diclofenac 100 mg</td>
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<td>Naproxen (750–1000 mg)</td>
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of the fact that exposure to naproxen was 75% longer than exposure to piroxicam and 67% longer than exposure to meloxicam 7.5 mg. Furthermore, since only 48% of the patients exposed to meloxicam 15 mg for an average of 128 days (Table I) contribute to the event rates quoted in Table III, it is impossible for the reader to gauge the extent of the confounding in this group of patients.

(c) Pooling patients who receive the same dose of the same drug across a heterogeneous set of studies has introduced bias into the treatment comparisons. For example, a diclofenac group consisting exclusively of patients with OA is compared with a pool of meloxicam 7.5 mg patients consisting of only 35% OA patients. The other 65% are RA patients who are, as the authors themselves point out, generally younger, for which reason they have a lower risk of NSAID-induced complications.

(d) None of the individual studies included in this analysis were designed to assess serious GI complication rates, and even collectively their power to do so is low. The fact that there are no statistically significant differences in serious PUB rates (Table IV) or serious adverse event rates (not presented in the paper, but shown above) is not sufficient even to claim equivalent safety for meloxicam.

We have described several major concerns about the methodology used and the way that certain results are presented (or excluded). These issues raise significant concerns about the quality of the data and how far they should be used to support claims for the safety of meloxicam. In particular, the results do not show that meloxicam is associated with fewer ‘serious GI complications’ (as defined by accepted criteria) than comparator NSAIDs.

‘Non-serious GI adverse events’ [most commonly dyspepsia, nausea, abdominal pain, diarrhoea (p. 71)] are significantly lower in both meloxicam groups when all of these events are combined; however, this is not consistent when individual events (e.g. dyspepsia) are considered and it may be due to the confounding effects discussed above.

These conclusions are confirmed by a recent bulletin (monograph) on meloxicam issued by the Swedish Regulatory Authorities, which states that ‘No statistically significant difference in either GI or other adverse events could be detected’ (between meloxicam and comparator NSAIDs) [1].

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Accepted 4 December 1996


Reply
We wish to respond to Dr Fenn’s and Dr Morant’s letter. The correspondents from Searle have criticized a number of the features and conclusions of our recent global analysis of the safety of meloxicam [1]. In doing so, they imply that some of the study strengths are indeed weaknesses, arbitrarily discard data which they do not like, and refer to anonymous ‘independent expert opinion’. They have implied that NSAID gastropathy is more common in OA than in RA, and that data from open label studies may safely be combined with those from randomized double-blind clinical trials.

We sought rigorously to analyse and conservatively interpret a large randomized double-blind experience with meloxicam and comparator drugs. It should also be noted that all our prospective double-blind studies in RA and OA have been included in the evaluation. We restricted the analysis to patients with RA and OA to avoid confounding indication bias, and excluded patients receiving 30 or 60 mg of meloxicam since these doses do not have advantages in their benefit/risk ratios over established NSAIDs and thus are neither therapeutically recommended nor approved.

Far from exaggerating the safety of meloxicam over other NSAIDs, we conclude conservatively that meloxicam was better tolerated than the comparator drugs piroxicam, naproxen and diclofenac, and have noted that these were well-established comparator drugs. We attribute the favourable meloxicam safety profile to its preferential inhibition of inducible cyclooxygenase-2 relative to constitutive cyclooxygenase-1. We use the definition of serious GI toxicity of NSAIDs (symptomatic upper GI ulcers, gross bleeding or perforation) established by the FDA Arthritis Advisory Committee [2] and standard statistical methodology including Kaplan–Meier estimation and Cox proportional hazards modelling.

An asterisk indicating statistical significance was erroneously omitted from our Table IV, indicating that the difference in serious upper GI perforations, ulcerations and bleeds (PUBs) between 7.5 mg meloxicam and 100 mg diclofenac SR was statistically significant ($P < 0.05$; log rank test).

None of the multiple, confusing and contradictory arguments of the correspondents directly attack any major portion of the methodology or the conclusions of our paper. With regard to the several criticisms, we (and our consultants) believe that it is not appropriate to combine open label studies with double-blind studies and that open studies without controls cannot be used for valid comparative evaluation. We believe that the trials should be limited in indication so as more accurately to ensure comparability, that pooling of gastric and duodenal ulcers (as in our evaluation) is appropriate, that studies of healthy volunteers should not be confused with the treatment of illness, that patients with OA, despite being older, do not have a higher incidence of GI side-effects than those with RA [3, 4] and that our methods and conclusions are valid.

We are pleased to report that the results of two large prospective double-blind studies, each of which included more than 9000 patients, comparing meloxicam 7.5 mg to 100 mg of diclofenac SR and piroxicam
20 mg, respectively, over 4 weeks in patients with OA (Boehringer Ingelheim, paper in preparation) have been presented and confirm in every major respect the global analyses and conclusions presented in our paper.

M. DISTEL, E. BLUHMKI,* C. MÜLLER, † J. F. FRIESE‡
Medical Department, *Department of Biostatistics and †Department of Data Management, Boehringer Ingelheim and ‡Department of Immunology and Rheumatology, Stanford University School of Medicine, 1000 Welch Road, Suite 203, Palo Alto, CA 94304-1808, USA

2. Paulus HE. FDA Arthritis Advisory Committee meeting: serious gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs; drug-containing renal and biliary stones; diclofenac and carprofen approved.

Middle Colic Artery Rupture: An Unusual Presentation of Polyarteritis Nodosa

Sir—A 59-yr-old woman was admitted complaining of colicky lower abdominal pain of 7 days duration. Previously she had been well with no significant past medical or surgical history, and was not taking any medication.

Initial assessment demonstrated anaemia (Hb 7 g/dl; normochromic, normocytic) and impaired renal function (urea 13, creat 151). Two days previously, she had had a nose bleed of ~50 ml, but no haematemesis or melena (clotting studies were within normal limits). Over the subsequent 3 days, the abdominal pain increased in severity, and the anaemia and renal failure continued to deteriorate (urea 56, creat 862). She was transferred to the regional intensive therapy unit for continuous veno–veno haemofiltration renal support and cardiovascular stabilization. Ultrasound investigation demonstrated normal kidneys, but a large volume of free fluid in the abdominal cavity. Paracentesis showed this to be frank blood with a high polymorphonucleophil count. Gram stain and culture were negative. After further resuscitation, a laparotomy was performed revealing 6 l of bloody fluid in the abdomen and rupture of the middle colic artery. The ascending colon to distal transverse colon was resected and a primary anastomosis performed. Concurrent investigations showed a positive P-ANCA and ESR 118 mm/h. Histological examination confirmed polyarteritis nodosa (PAN) with rupture of the middle colic artery (Fig. 1). Four days later, a renal biopsy was performed showing focal and segmental necrotizing and proliferative glomerulonephritis, concomitant with PAN. Intravenous steroids were commenced (hydrocortisone 100 mg/tds) and 10 days later cyclophosphamide was added for persistent pulmonary haemorrhages. Her recovery was complicated by a series of infections (originating from the chest and i.v. lines) and an ischaemic infarction of the left internal capsule manifest as a right-sided hemiparesis. After a total of 4 weeks of intensive therapy, she was transferred to the renal wards for dialysis, physiotherapy and further cyclophosphamide. Two weeks later, she was discharged home on oral steroids and continued intermittent dialysis for a further 2 months. The hemiparesis improved such that she is now able to live independently.

PAN is a rare condition occurring predominantly in middle-aged men. Fibrinoid necrosis of small and medium-sized vessels leads to microaneurysm formation—most commonly involving the renal, coronary and cerebral vessels. Infarction, haemorrhage and progressive organ failure may follow.

Although spontaneous aneurysm rupture is rare, acute presentation of PAN secondary to haemorrhage has been noted involving renal [1], hepatic [2], tibial [3], suprarenal and gastric coronary arteries [4]. Pain and signs of haemorrhage are the usual presenting features. Bowel perforation [5], ischaemia [6], necrotizing vasculitis of the mesentery [7] or gastrointestinal haemorrhage [8] are other causes of abdominal symptoms.

Involvement of the gastrointestinal tract in PAN occurs in ~37% of individuals [4]. To our knowledge, this is the first report of PAN presenting with middle colic artery rupture. Although surgery is most commonly performed for aneurysm rupture, embolization with platinum coils [2] or gelfoam [1] has been shown to be effective.

R. HIXSON, F. CALDER, D. WATSON
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Accepted 12 September 1996


### Distinctive Ethnic Differences in the Incidence of Osteoarthritis

**Sir**—The interesting report by Hameed and Gibson [1] on the lower incidence of osteoarthritis (OA) in Pakistani patients as compared with English Caucasians should be supplemented by experience from Israel. The most important fact in our experience is that our patients are of variable ethnic extraction. In addition to patients of European extraction, many of our patients belong to families who came from North Africa, the Middle East or Yemen.

In a study on 327 OA patients published many years ago, we reported the definite higher incidence of Heberden’s nodes, but lower incidence of gonarthrosis and coxarthrosis in patients of European extraction (European patients: EurP) as compared with non-EurP. The respective incidence EurP: non-EurP for the above three types of OA was 2:1; 1:4 and 1:4 [2].

Recently, we have reviewed the incidence of different rheumatic diseases in a large sample of 2335 (out of >7000) patients seen by us over a period of 20 yr. The numbers of EurP and non-EurP were nearly equal.

OA was diagnosed at 1658 different sites (about 1.6 diagnoses per patient). There was a definite higher incidence of all types of OA in EurP. However, the probably much more interesting finding was the relatively very low incidence of OA among patients of Yemenite extraction as compared with other non-EurP (Table I).

It goes without saying that OA is much less frequent among patients of non-European (Oriental) extraction as compared with Europeans. However, the distinct lower incidence of OA among those of Yemenite origin calls for at least two important interpretations. One is a genetic determinant; the other seems to be the so-called ‘Western way of life’, including all environmental factors, nutritional habits, etc., which have ‘infiltrated’ the Middle East, but did not reach, at least until recently, certain distant corners of the world, as is the case here with immigrants from Yemen.

**I. Machtey**

**3. Brande Street, Petah-Tiqva, Israel**

**Accepted 13 December 1996**


**Reply**

We thank Dr Machtey for the interest in our paper. The supposition that susceptibility to OA may be influenced by some unspecified feature of life in the West seems improbable. The familial association of generalized OA is strong evidence for a genetic rather than an environmental factor. It is the concurrence of multiple affected joints which so characterizes the pattern of OA in Europeans. This accords with the observations made by both us and Dr Machtey. Our unpublished community survey of joint diseases amongst 2056 Pakistani adults living in England showed an increase of low back pain (standardized morbidity ratio 2.3, 95% CI 1.7–2.9) compared with residents of Pakistan, but other rheumatic problems were either similar or were increased to a lesser extent. OA was not obviously more common amongst the Pakistanis in England, all of whom had been born in the UK or had been living there for at least 10 yr. Knee pain prevalence was similar to that of affluent Pakistanis in Pakistan, but greater than that amongst poorer residents. This attests to the consistent association of body weight with knee OA. Our data do not support a pernicious influence of Western lifestyles on the development of OA beyond what can be achieved by a plentiful diet.

**T. Gibsons, K. Hameed**

Clinical Rheumatology Unit, Guy’s Hospital, London SE1 9RT and Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

**Clinical Improvement and Radiological Deterioration in Rheumatoid Arthritis**

**Sir**—Bresnihan and his colleagues [1] have once again produced a thought-provoking paper. However, in this...
age of ‘sound bites’, there is a danger that the article will be misinterpreted. The article reports on clinical improvement and radiological deterioration in rheumatoid arthritis. On the basis of these observations, they propose that the pathogenesis of synovial inflammation and articular erosion may differ. That may or may not be true. However, close perusal of their results shows that a large proportion of their patients still had active disease. Indeed, activity of disease correlated best with the degree of radiological progression. Thus, the interpretation which I place on their findings is that with inadequate control of synovial inflammation there is ongoing joint damage. Thus, we need to use existing drugs more effectively and develop newer and more effective therapies. In the meantime, we have no definitive evidence that we should discard our present measures of synovial inflammation in monitoring disease therapy.

G. S. Panayi
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Accepted 4 February 1997


Reply
We thank Prof. Panayi for his interest in our article. We agree that clinical and laboratory evidence of articular inflammation correlated with progressive articular destruction. However, we have suggested that the pathogenetic processes underlying articular erosion may continue independently in patients with apparently quiescent disease. Whilst our present measures of articular inflammation may identify patients at greater risk of progressive articular destruction, their absence should not lead to complacency, and there is a clear need to develop newer and more effective therapies for preventing articular erosion.

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Joint Inflammation and Erosion: Different Mechanisms?
Sir—In their paper, ‘Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that the pathogenesis of synovial inflammation and articular erosions may differ’ [1], Mulherin and colleagues claim that there is a paradox between clinical improvement and radiological deterioration in rheumatoid arthritis. They base this on their data which show continued radiological deterioration over a mean period of 6 yr despite an improvement in clinical and laboratory features of inflammation. The implication of this observation is that there may be mechanisms other than synovial inflammation responsible for the progression of erosive disease. No doubt the dichotomy between the inflammation and progression of erosions is true, but does it represent a true paradox and does it suggest alternative mechanisms for the deterioration in erosive disease?

There are a number of possible explanations, which I have outlined below, for the observed apparent discrepancy that would be consistent with the hypothesis that synovial inflammation is the cause of erosive disease.

1. Most of the parameters of inflammation measured are (or should be) reversible with treatment or with natural fluctuations in disease activity. Erosion scores, on the other hand, can only remain constant or deteriorate. As at least some of the patients studied continued to have active disease, then it would be expected that overall the group would continue to show deterioration on their radiographs. This possibility is highlighted by the authors’ findings that a correlation remained between change in Larsen Index and the absolute values for inflammatory parameters at review.

2. Inflammatory parameters were measured only at the beginning and the end of the study. If continued synovial inflammation is the mechanism for continued erosive damage, then progression of erosive disease would be better correlated with the area under the curve of inflammatory parameters over the study period, not a single measurement at the end of the study or the overall change over the 6 yr.

3. There is a ‘lag phase’ between starting a second-line drug and improvement in inflammatory parameters. Thus, patients with active disease, even when treated, are going to be at risk of erosions until treatment becomes effective.

It is always easier to criticize than to do, and the question probably cannot be answered definitively until we have more effective drugs which totally suppress inflammation. However, it should be possible at present to attempt to answer the question by studying serial radiographs in patients who continue to fulfill, over a prolonged period, strict criteria for remission.

In the meantime the evidence, including that from Mulherin et al. [1], continues to point towards the need for early aggressive control of disease activity.

T. Pullar
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Accepted 31 January 1997


Systemic Lupus Erythematosus Following Escherichia coli Sepsis in an Elderly Woman

Sir—We report the case of an elderly woman who presented in septic shock and who, during her hospitalization, developed typical dermatological and serological features of SLE.

A 72-yr-old woman was brought to the emergency unit in a state of shock after she had a tonic-clonic seizure at home; this followed a few days history of generalized fatigue and feverishness. Her past medical history was negative except for a history of diffuse arthralgias. Her shock was attributed to *Escherichia coli* sepsis. This organism was recovered from a urine specimen and two blood cultures taken on presentation. Her condition was stabilized with fluid hydration and inotropic agents, and she showed good improvement with antibiotic therapy, except for her mental state as she was always drowsy and disorientated. A lumbar puncture did not reveal any evidence of meningitis and MRI of the brain showed only diffuse cortical atrophy. Ten days after her admission, she developed an erythematous maculopapular rash over the face, anterior chest and upper back. The appearance of this rash raised the possibility of SLE; this coincided with a decrease in her white blood cell count from 20,400 cells/mm³ on presentation to 2400 cells/mm³ (polymorphs 63%; lymphocytes 33%; monocytes 4%), haemoglobin 9.8 mg/dl, haematocrit 29% and platelet count 177,000 cells/mm³. An ANA test on HEP-2 cells was positive with a uniform pattern, the anti-double-stranded DNA (dsDNA) level was 1100 IU/ml (normal < 100), anticardiolipin antibodies were positive, and the C3 level was 45.5 mg/dl (normal 80–180). Her renal function tests showed a creatinine clearance of 50 ml/min with 625 mg of protein in urine per 24 h. With these findings, SLE was diagnosed and the patient was started on prednisone 80 mg daily. One week after the initiation of prednisone, the patient had a massive pulmonary embolus documented by a ventilation perfusion lung scan, and soon after she had a cardiac arrest and died.

SLE is predominantly a disease of young females; however, in 12–17% of cases the diagnosis is made after the age of 50 yr [1, 2]. SLE in the elderly is
characterized by a more insidious onset of disease [1], several years delay in establishing the diagnosis [3], presenting symptoms mimicking primary Sjögren’s syndrome or polymyalgia rheumatica [1, 4], a higher frequency of serositis, interstitial pulmonary disease, positive anti-La [5] and antiphospholipid antibodies [1, 6], less female preponderance [1], lower anti-dsDNA titres [1, 4], and a lower frequency of alopecia, Raynaud’s phenomenon, fever, lymphadenopathy, hypocomplementaemia and neuropsychiatric illness [5]. One explanation for the less severe clinical and immunological expression of SLE in older patients is the senescence of the immune system [7].

The role of infection in the induction of autoantibody production and autoimmune diseases is not yet fully understood. In a study to explore the role of infection in the induction of anti-DNA antibodies, Robertson and Pisetsky [8] reported that 5/8 patients with *E. coli* bacteraemia demonstrated increased levels of antibodies to single-stranded (ss) DNA from *E. coli*. The sera of these patients also reacted with ssDNA from other bacterial and mammalian species, and showed an isotypic distribution similar to that seen in patients with SLE [8]. In another study, Gilkeson *et al.* [9] have shown that normal mice immunized with ssDNA derived from *E. coli* developed an immune-mediated proliferative glomerulonephritis secondary to renal deposition of anti-DNA antibodies as in lupus. Furthermore, *E. coli*, as well as microorganisms like *Mycobacterium* species and *Pseudomonas aeruginosa*, are known to produce heat shock protein (HSP); this protein may have a role in the pathogenesis of rheumatic diseases like SLE [10]. One theory on the role of these proteins in the induction of autoimmunity proposes that the host initially reacts to microbial infections with an enhanced cellular and humoral response to the microbial HSP, thereafter cross-reactivity may occur with the HSP of the stressed host because of structural similarities to the microbial HSP [10, 11].

The exact relationship between sepsis and the onset of SLE in our patient is difficult to define; however, this case may suggest a role for infective agents in the pathogenesis of certain rheumatic diseases, like SLE.

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Accepted 17 December 1996

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4. Wilson HA, Hamilton ME, Spyker DA *et al.* Age influences the


**Visual Loss and Giant Cell Arteritis**

**Sir—**In their excellent clinical study of polymyalgia rheumatica (PMR) and temporal arteritis, Myklebust and Gran [1] describe a very low incidence of ocular complications. I concur with their observation that the ‘development of important loss of vision’ in contemporary patients with giant cell arteritis (GCA) is ‘rather infrequent’, and agree that it is likely that selection bias — viz. the reporting of hospitalized patients — may have contributed to an overestimation of the frequency of visual catastrophes in GCA in older series.

However, another explanation for the infrequency of visual loss in GCA in recent studies may well be the prompt and appropriate use of corticosteroids in the management of both PMR and GCA. It is important to keep in mind that studies on GCA from the pre-steroid era contain extraordinary and sobering numbers of patients who developed blindness during the course of their disease. In 1947, for example, Andersen [2] reported that 24 of 56 patients with GCA developed ‘more or less severe ocular symptoms (sic)’. In 1959, Russell [3] reported that 15 of 25 patients treated without steroids incurred visual impairment, but that 10 of 10 subsequent patients treated with steroids had no visual impairment.

Recognition of PMR and GCA as clinical entities, and appropriate utilization of steroid therapy, remain important ingredients in minimizing the potential complications of these diseases.

W. P. DOCKEN

