

arthritis involving *I belli* and *Cryptosporidium* infestation in patients with AIDS are not yet well known. Further studies should help clarify these questions. We are not aware of any previous report of reactive arthritis after enteric infection due to *I belli* and we believe this to be the first such report.

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urinary monoclonal free light chains. These are now best detected using the more sensitive techniques of immunoelectrophoresis or immunofixation. As this interesting case demonstrates, serum immunoglobulin levels can remain normal in a few cases, even in the terminal stages of disease. It is therefore imperative that paired serum and urine samples are sent for immunochemical analysis.

We feel it is potentially misleading to say that "... Traces of urinary BJP in isolation can prove to be benign ...". It is generally agreed that their detection is highly suggestive of underlying lymphoproliferative disease in the majority of cases and it is unwise to dismiss such findings as benign.² In addition the definition of "a trace" will depend heavily on the detection system employed in individual laboratories – accurate quantitation of the free light chains should routinely be undertaken; measurement of total urine protein is less informative. These are the important lessons we must appreciate if patients with occult myeloma are to be detected and successfully treated.

We would emphasise that in patients presenting in this manner, a more aggressive investigational approach is indicated, including early bone marrow examination and radioisotope scanning of bone. Only when negative results from these investigations are available would it be advisable to monitor the patient over time remembering that a repeat bone marrow examination is always an option at a later date.

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AUTHORS' REPLY We are pleased that the first article in *Lesson of the month* has attracted interest and correspondence.

In reply to Dr Edgar *et al*, we feel that the use of Bence-Jones protein (BJP) as a descriptive term for urinary monoclonal free light chains is in such standard usage as to be fully acceptable; few clinicians or laboratory scientists would be in any doubt as to the meaning of this term.¹

The agarose gel electrophoretic assay used for the detection of urinary BJP in our laboratory has a sensitivity of 0.08 g/l, which after concentration of urine ×200 gives a lower limit of detection of approximately 0.001 g/l of monoclonal BJP (Sheldon J, personal communication). In this case BJP was not quantified but was expressed as two faint bands of Kappa protein at initial testing. The laboratory routinely expresses BJP calculated as a 'percentage of total urinary protein'.

It is our experience, and that of our colleagues in the laboratory, that the term 'benign' can be applied to the presence of a monoclonal protein in persons with no evidence of myeloma, Waldenstroms macroglobulinaemia, amyloidosis or other related B cell malignancy. We suggest that the term can only be applied once the condition is shown to be stable with time – five years for IgG and IgA and 10 years for IgM paraprotein. An

alternative term monoclonal gammopathy of unknown significance (MGU) is better used when any doubt exists.

We agree with Dr Edgar *et al*, and hope that *Lesson of the month* highlights the need to follow up the findings of even a faint band of BJP with serial BJP measurements. It was this omission which led to the difficulties encountered in this case. However, we appreciate the concern expressed by Dr Edgar that early bone marrow examination be undertaken if any BJP is detected and there is general agreement that this decision should be based on clinical judgement. Most clinicians would find it impossible, for reasons of resource limitation and clinical acceptability, to perform bone marrow examination on every patient with any detectable BJP, although this is a moot point. Certainly levels of >0.01 mg/l are more suggestive of malignancy and should be investigated with bone marrow examination. As far as other investigations are concerned plain radiographs are generally regarded as a more sensitive indicator of the presence of myeloma. Isotope bone scans can often be normal in myeloma even with significant bony deposits. Interpretation of the finding of BJP may be aided also by assay of β₂ microglobulin. β₂ microglobulin may be elevated either with deterioration in renal function or with myeloma tumour mass; interpretation of elevated levels may be difficult.

If *Lesson of the month* continues to draw attention to important clinical issues and to open areas of controversy then it will surely achieve its intended purpose.

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Antiphospholipid antibodies (aPL) in systemic lupus erythematosus. Are they specific tools for the diagnosis of aPL syndrome?

We read with interest the paper by Ghirardello *et al*¹ on antiphospholipid antibodies (aPL) in systemic lupus erythematosus (SLE) but would suggest that their conclusion, "lupus anticoagulant (LA) but not anticardiolipin antibody (aCL) positivity is a specific tool for the diagnosis of thrombotic complications... in SLE", is interpreted with caution.

There are a number of methodological problems in setting up a study of this kind which should be highlighted:

- This study was retrospective and it cannot be assumed that because a patient is aPL +ve at the time of study, they were also aPL +ve at the time of diagnosis of SLE. In fact, the authors do not specifically state in reference to the 47 patients who had experienced pregnancy, whether they were diagnosed as having SLE at that time. It is therefore likely that the recording of aPL complications using

MATTERS ARISING

Bence-Jones protein and vertebral osteoporosis

We welcome the introduction of *Lesson of the Month* and read with interest the case report submitted by Hughes *et al*¹ regarding the investigation of patients presenting with back pain. As the authors rightly point out, the exclusion of occult lymphoproliferative disorders in this group of patients is of the utmost importance. There are, however, several points of concern arising from the case particularly in relation to the clinical interpretation of monoclonal urinary free light chains.

The use of the term Bence-Jones protein (BJP) can cause confusion as it refers to the original heating test for the detection of

this approach will be inaccurate. Ideally, a prospective study is needed with the enrolment of SLE patients at the time of aPL detection and close observation over a long follow up time.

2) The lack of standardisation of both lupus anticoagulant and anti-cardiolipin tests continues to be a major problem in interpreting clinical data published on antiphospholipid antibodies.² However, better interlaboratory agreement was achieved when IgG and IgM aCLs were recorded in a semi-quantitative fashion (that is, negative, or low, medium, high positive).³ Ghirardello *et al* do not specifically comment on such standardisation for their own laboratory.

3) The ELISA assay for aCL is clearly a more sensitive assay for detecting aPLs than the Russell viper venom time.⁴ Interestingly, in this study LA positivity was only found in those patients who were aCL positive. Furthermore, a significant association between high titres of IgG aCL and arterial thrombosis suggests that the aCL titre may be more important than the presence of aCL in SLE patients. Previous reports have suggested that aCL, rather than LA, is a better predictor of fetal death in SLE pregnancy,⁵ and that high titre aCL carries a worse prognosis.⁶ In this regard, Ghirardello *et al* have not studied aPL complications at different titres of aCL. Furthermore, patients in 'risk pregnancies' were treated with aspirin which could influence the frequency of complications observed.

In summary, larger prospective studies of SLE patients with aPL, better standardisation of aPL assays, and analysis of differing titres of aCL in respect of aPL complications are needed.

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AUTHORS' REPLY Dr Hopkinson *et al* suggest caution in interpreting the conclusion of our study regarding the specificity of antiphospholipid antibodies (aPL) for aPL complications in systemic lupus erythematosus (SLE). However, it seems they did not take into account the second part of our conclusion; that is, "the measurement of IgG anticardiolipin antibody (aCL) level seems to be a valuable requirement before attributing clinical value to aCL positivity". We believe therefore that our conclusion summarised our results regarding LA and both aCL positivity and level.

Dr Hopkinson also comments adversely about some of the methodological approaches we used.

1) Our study was a cross-sectional rather than a retrospective study. In fact, individuals were concurrently classified as 'SLE with aPL complications' or 'SLE without aPL complications' and as 'aPL positive' or 'aPL negative' at a single point in time.¹ Nevertheless, we decided to include some anamnestic manifestations which occurred after SLE diagnosis to define individuals as 'SLE with aPL complications' and to be able to evaluate possible relationships between aPL and some low prevalence aPL complications. Such a study design, that has been widely used to investigate the clinical significance of aPL,²⁻⁴ has both well known advantages and disadvantages. As Dr Hopkinson and colleagues pointed out that the time that elapsed between the occurrence of anamnestic manifestations and the aPL determination may be a bias in our study. However, the relevance of this bias depends on some variables, particularly on the total amount of anamnestic data recorded and the length of time elapsed from their occurrence and the aPL determination.

Although the prospective study may be considered 'ideal' for this purpose, some ethical considerations should be taken into account by authors who are interested in research as well as in patient care. In performing such studies antithrombotic and anticoagulant treatment should also be avoided in patients considered at risk of thromboembolic complications on the basis of previous studies, including cross-sectional ones (for example, patients with LA and/or high IgG aCL level). This methodological requirement seems to be particularly unethical in setting up studies on SLE pregnancy outcome, since aspirin is now largely and effectively administered to pregnant women who are at risk for preeclampsia,⁵ a complication frequently observed in pregnant patients with SLE.

2) We currently record aCL positivity in a semi-quantitative manner, according to the KAPS group international guide-lines on aCL test standardisation.⁶ Otherwise, in our study we expressed aCL results by calculating a cut-off point and testing its specificity for aPL complications in SLE by ROC curve analysis.⁷ We considered as optimum cut-off aCL mean levels +4 standard deviations (SD) of 100 healthy subjects and found that, by increasing the number of SD (for example,

to 6 SD), the specificity improved although to a lesser extent than the sensitivity loss.

3) We agree with Dr Hopkinson regarding higher sensitivity of ELISA assay in respect to the Russell viper venom time for aPL detection, as well as a better value of high IgG aCL titre rather than the only aCL presence in SLE, as it stated in our paper. Conversely, we agree with other reports^{2,8,9} that LA rather than aCL positivity is a predictor of aPL complications in SLE, since we assessed specificity using an original approach, that is, the evaluation of aPL profile only in aPL positive patients with and without aPL-related manifestations; patients with complications of aPL syndrome definitely due to factors different from aPL were thus excluded.

Finally, Dr Hopkinson's reference 5 seems inappropriate in this context since Lockshin's patients "do not represent a random cross-section of pregnant patients with SLE" as they were specifically referred to him because of prior fetal death.¹⁰

In conclusion, a cross-sectional study seems to be a suitable design to reach a goal like ours. A large prospective study, but with some ethical reservations, could provide more striking results.

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