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### Glycolytic enzymes in the CSF as tumour markers

Sir: In agreement with Twijnstra and colleagues<sup>1</sup> I find measurements of glycolytic enzymes in cerebrospinal fluid (CSF) such as lactate dehydrogenase (LDH) or phosphoglucoseisomerase (PHI) easy to perform, readily available and economical. A drawback in the detection of meningeal metastases is their limited specificity. The following suggestions may help to reach a greater specificity.

Although the authors have considered the possible influence of age and sex on enzyme activity in the CSF, they have apparently not taken into account the state of the blood brain barrier (BBB) and the enzyme levels in the blood. In evaluating plasma protein concentrations in CSF such as IgG, it is common practice nowadays to correct the CSF value for the serum derived fraction. A similar approach was recently undertaken for the estimation of another tumour marker, carcinoembryonic antigen in CSF.<sup>2</sup>

CSF/serum ratios range from 1/230 for albumin to 1/500 for IgG. The permeability of the BBB for these plasma proteins is governed by their molecular radii.<sup>2</sup> By analogy, for LDH, an enzyme with 140 000 D molecular weight, one would expect a quotient of about 1/360. With a serum value of 240 U/l (the upper limit of normal with standardised methods) one then arrives at  $240/360 = 0.7$  U/l for the LDH activity in the CSF. However, the normal value given by Twijnstra *et al*<sup>1</sup> lies at 10 U/l. Therefore, in great contrast to plasma proteins, only approximately 7% of the LDH activity in CSF originates from the blood under normal conditions. Accordingly corrections for serum LDH may appear unnecessary. While this is probably true for controls with normal LDH and intact BBB, it is different for cancer patients. Meningeal affection often causes considerable impairment of the BBB and in the

presence of systemic metastases LDH serum activity may be elevated several fold. Erroneously high CSF values may result especially when both conditions coincide. For PHI a correction formula analogous to Tourtellotte's calculation of the IgG synthesis rate has been proposed.<sup>3</sup>

It would be interesting to know if the three control persons with pathological CSF values above 26 U/l in Twijnstra's patients<sup>1</sup> displayed elevated serum LDH and/or BBB disturbances. Likewise the observed augmentation of CSF LDH in older subjects may be connected to the greater permeability of the BBB for people aged over 60 years. In addition, simultaneous measurement of CSF and serum enzyme activities often reveal a beneficial effect of the CNS-directed therapy, when at the same time the systemic cancer cannot be controlled.<sup>3</sup>

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### Shoulder abduction fatiguability

Sir: I read with considerable interest the recent article by Nicklin *et al* entitled *Shoulder abduction fatiguability*.<sup>1</sup> Having previously read and admired the work of two of the authors, I was encouraged to observe that their work continues in the application of hand-held dynamometry to assess the neurological patient. I have, nevertheless, several concerns with what the authors have recently presented in this journal.

My chief concern is their apparent failure

to take into account the influence of gravity during testing. By either testing shoulder abduction against gravity and not correcting for its influence or mixing the results of tests performed against gravity (in sitting) with those of tests performed with gravity eliminated (when supine) a potential source of error was introduced. Winter *et al* calculated that a failure to correct for gravity effects resulted in an absolute percentage difference of 2.4 (range -6.5 to 26.0) for knee extension.<sup>2</sup> The potential error associated with a failure to take gravity into account can be illustrated as follows: Suppose a subject's arm places 15 Newtons of force on a dynamometer, at its point of application. That is, with the arm abducted to 90° and the elbow flexed to 90° but resting on the dynamometer, a force of 15 Newtons is registered because of gravity. Next, suppose that the seated subject generates 140 Newtons of abduction force when tested as suggested by the authors. A 6.0% decline in this force over a series of 10 contractions would be 8.4 Newtons. This value, 8.4 Newtons, is only 5.4% of 155 Newtons, the actual force produced (140 Newtons + 15 Newtons to hold the arm against gravity). Thus, the fatigue index is decreased by  $(6.0 - 5.4)/6.0 = 10\%$  by including the weight of the arm. Now let us assume that the same subject is affected with a disorder that renders her weak. Gravity still results in 15 Newtons of force from the arm. The subject now generates 30 Newtons of force while seated. A 6.0% decline in this force equals 1.8 Newtons, which is 4.0% of 45 Newtons (30 Newtons + 15 Newtons to hold the arm against gravity). Thus, the fatigue index is decreased by  $(6.0 - 4.0)/6.0 = 33.3\%$  by including the weight of the arm. Granting that this is a highly hypothetical situation; the error resulting from a failure to correct for gravity, particularly in a weak arm, could be quite serious.

My second concern is with the muscle group selected by the authors for their study. Although good reasons probably exist for the authors' choice of the shoulder abductors, these muscles are probably more difficult than some others to test accurately. In a study in which I tested supine subjects, I found that forces obtained during repeated tests of shoulder abduction, unlike forces obtained during most other actions, differed significantly from one another.<sup>3</sup> I have observed that subjects tend to flex the trunk toward the contralateral side during shoulder abduction testing. This tendency, which is particularly apparent when subjects are tested in sitting, magnifies actual force production. Even the subject in the authors' fig 1 seems to be flexed to the right during testing

## Matters arising

of left shoulder abduction.

My third concern with the study is that the authors' results differ from those I have obtained and reported elsewhere.<sup>4</sup> Although the authors' work is, in many more ways, more comprehensive than my own, the two issues addressed above (correction for gravity and prevention of substitution) were controlled in my paper. The result of my study of knee extension was that relative endurance, which the authors seem also to be testing, was better in patients than in normal subjects. As the patients were weaker than the normal subjects, I suggested that force production in the patients decreased to some threshold level in less time or in fewer contractions. This, I proposed, was because the patients were closer to the threshold level to start with, not because their rate of decline in force production (Fatigue index) was any greater.

Whether the issues I have addressed are truly critical, when using hand-held dynamometers, to test fatigue, awaits verification. In the mean time the authors and other readers of their work may wish to exercise caution in inferring too much from the authors' findings.

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## Nicklin et al reply

We are grateful to Dr Bohannon for his helpful comments. We have in fact previously used the method which he illustrates to estimate the force required to maintain a limb part against gravity as a fraction of maximum voluntary force against gravity plus the effect of gravity: in seven muscle groups measured in each of two subjects the fraction varied from about 0.03 (for example, in elbow flexion) to in excess of 0.3 (for neck flexion) (unpublished data). We agree that it would be more accurate to estimate the effect of gravity particularly when different muscle groups are to be compared or when large changes in strength over time are in prospect. The results in the cases illustrated in our paper would scarcely be influenced by these considerations however.

It is true that shoulder abduction is more difficult to test with a hand held dynamometer than several other groups. The supine position with gravity eliminated seems particularly unsatisfactory in strong subjects compared with the sitting position using this technique. Shoulder abduction was chosen for our test because it is an action commonly examined clinically for

fatiguability. In addition we have an impression, notably in the myasthenias, of a selective response of certain muscle groups to treatment; hence it should not be assumed that similar results would necessarily be obtained with other (more "easily testable") groups. Further work comparing fatigability of different muscle groups in the same patient responding to treatment may be illuminating. We do not think that a minor truncal tilt would have significantly influenced our results particularly since we found no real difference in fatigue index between 90° and 60° abduction but particular attention needs to be paid by the tester to careful fixation proximal to the shoulder joint.

We have not found improved endurance in patients except in the notable case of hypothyroidism<sup>1</sup> provided that the initial contractions are not tentative due to lack of practice or discomfort. On the contrary we found no simple correlation between fatigue and muscle weakness in this test. Of course fatigue index depends critically on the forces of the first two contractions in the series and as may be seen from our fig 2 the pattern of these differs slightly (but significantly) for males and females. We have not as yet studied whether a similar trend occurs in patients.

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## Book reviews

**Neurological Skills: A Guide to Examination and Management in Neurology.** By MJG Harrison. (Pp 132; £15.00.) Guildford: Butterworth Scientific Ltd, 1986.

The student or young postgraduate in training has today an abundant choice of textbooks and sections in textbooks devoted to history taking, examination and the appraisal of common presenting symptoms of nervous disease.

That such texts are even more important than they were a generation ago is evident in

the obvious decline in their clinical skills and diagnostic discernment, not only in neurology but in internal medicine. This reflects on their mentors and the low priority accorded to neurological teaching by certain professors of medicine who determine curricula. And yet, how often we see patients with grave, acute neurological illness in whom there is no diagnostic abnormality of EEG, CSF, evoked potentials and scanning who performance are managed by the application of clinical techniques. How often do we see NHS funds squandered on useless "routine" tests in uncritical, ill-directed investigations of blackouts, spastic paraparesis or polyneuropathy? The failure to apply clinical

skills to narrow the investigation of organic nervous disease into the correct channel, with correspondingly richer dividends is sadly commonplace, justifying further attempts—such as Dr Michael Harrison's book—to rectify it.

This text in paperback covers is remarkably succinct (125 pages), yet is more than adequate for the undergraduate. It is divided into three sections: first, history and examination; second, common problems—which include headache, attacks of unconsciousness, memory loss, visual symptoms, vertigo, deafness, pain, muscle weakness; and third, "conditions". This section includes concise, possibly too concise