PostScript

LETTERS

Best evidence and the clinical decision making process

The articles by Helfenstein¹ and Newcombe² highlight the difficulties faced by clinicians in making a treatment decision for their patient when confronted by contradictory evidence. We are now faced with an ever increasing array of data of variable quality, which all need to be considered, for us to reach the best treatment decision for our patients. Systematic reviews, the cornerstone of evidence based medicine, are an important and increasingly utilised tool that use predefined objective criteria to aggregate data from trials, to provide evidence on which to base clinical decisions. However, systematic reviews have their own problems. Some, such as the finding of increased mortality with the use of intravenous albumin,³ have been controversial and heavily criticised.⁴ Dr Helfenstein highlights another problem with meta-analysis¹—that is, depending on the model chosen the interpretation of an individual trial within a meta-analysis can vary. Most clinicians, like myself, will not be familiar with the statistical techniques utilised in meta-analysis. Thus, the issues highlighted in these two articles^{1,2} will add further to the confusion felt by many.

Given these problems, what evidence should we rely on to make a clinical decision for our patients? Should the findings of a randomised controlled trial that are contrary to the findings of a meta-analysis take priority in our decision making process? Clearly, there are no simple answers to these questions. We should certainly not go back to the days when treatment was based solely on personal anecdotal experience and disregarded good trial evidence. A rigid hierarchy on which to base a clinical decision has been proposed: in this model, case reports are at the bottom end of the scale while randomised controlled trials and systematic reviews are at the top end of the scale.⁵ However, there may be situations where the rigid application of this hierarchy is inappropriate. For example, observational studies may provide evidence that is as good, if not better, than that provided by randomised controlled trials.⁶ Certainly, this is the current situation when one is focusing on the harms caused by medicines, where randomised controlled trial evidence is singularly absent or unreliable. Similarly, poorly conducted randomised controlled trials, which are then included in a systematic review, can produce erroneous and contradictory results.⁷ By contrast, a good single randomised controlled trial can over-turn many years of conventional "wisdom" that may have been based on observational data. For example, a meta-analysis of observational studies suggested that hormone replacement therapy (HRT) was associated with a 50% reduction in the relative risk of coronary events.⁸ Conversely, the single HERS randomised controlled trial found no benefit of HRT in secondary prevention of coronary events.⁹ The findings of HERS have been supported by angiographic studies,¹⁰ and the evidence taken together, has led the

American Heart Association to no longer recommend the use of HRT in secondary prevention of coronary artery disease.¹¹ Finally, it is also important to consider whether results from trials, where patient recruitment is often dependent on a long list of specific inclusion and exclusion criteria, are applicable to an individual patient in a real-world situation.¹² All these factors therefore have to be considered in making a clinical decision; thus, in my opinion, the answer to the problem highlighted by Helfenstein is not simple,¹ but crucially depends on a critical appraisal of the characteristics of the evidence that is available.

M Pirmohamed

Department of Pharmacology,
University of Liverpool, Ashton Street,
Liverpool L69 3GE, UK;
munirp@liv.ac.uk

References

- 1 Helfenstein U. Data and models determine treatment proposals—an illustration from meta-analysis. *Postgrad Med J* 2002;78:131-4.
- 2 Newcombe RG. Clinical applications of findings of clinical trials and systematic reviews. *Postgrad Med J* 2002;78:129-30.
- 3 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40.
- 4 Horsey P. Albumin and hypovolaemia: is the Cochrane evidence to be trusted? *Lancet* 2002;359:70-72.
- 5 Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000;321:255-6.
- 6 Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000;342:1878-86.
- 7 Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' guides to the medical literature: XXV. Evidence-based medicine: principles for applying the users' guides to patient care. Evidence-Based Medicine Working Group. *JAMA* 2000;284:1290-6.
- 8 Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
- 9 Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13.
- 10 Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9.
- 11 Mosca L, Collins P, Herrington DM, et al. Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;104:499-503.
- 12 Dans AL, Dans LF, Guyatt GH, et al. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. *JAMA* 1998;279:545-9.

Valproate encephalopathy and hyperammonaemia

In their excellent review of non-hepatic hyperammonaemia, Hawkes and colleagues acknowledge the diverse modes of presentation of, and the importance of a high index of suspicion for, encephalopathy secondary to raised blood ammonia concentration.¹ We would like to complement their review by reporting the case of a 78 year old woman with valproate encephalopathy associated with hyperammonaemia.

The patient presented to the accident and emergency department with a four week history of acute on chronic confusion, altered personality, and uncharacteristic aggressive behaviour. She had been taking sodium valproate (modified release) 500 mg twice daily and 300 mg at night, in addition to carbamazepine (modified release) 400 mg twice daily, for epilepsy diagnosed 20 years earlier.

On examination, her temperature was 37.5°C. The patient was confused, extremely agitated, and uncooperative. Asterixis was noted. The deep tendon reflexes were symmetrically depressed but present in all limbs and the plantar responses were extensor. There were no signs of meningism. Physical examination was otherwise unremarkable.

Full blood count, renal, liver and clotting profiles were normal on admission. In addition, the random blood level of carbamazepine was 8 mg/l (therapeutic range 4-10 mg/l) and of valproate was 80 mg/l (therapeutic range 60-100 mg/l). Computed tomography of the head did not reveal any intracranial space occupying lesion or haemorrhage. Examination of the cerebrospinal fluid was unremarkable. Nevertheless, the patient was started empirically on acyclovir treatment for presumed herpes simplex encephalitis.

Over the subsequent three days, the patient's level of agitation became extreme and a neurological opinion was requested. The diagnosis of valproate encephalopathy was suspected and a blood ammonia concentration confirmed hyperammonaemia (174 µmol/l, normal range 0-59 µmol/l). Within 24 hours of discontinuing the sodium valproate, the patient's aggression and agitation resolved and her level of confusion improved. The blood ammonia fell to 39 µmol/l 11 days after stopping the sodium valproate, and the patient was eventually discharged home on an increased dose of carbamazepine alone (600 mg twice daily) for treatment of her epilepsy.

Since 1979, there have been at least 30 cases of sodium valproate associated encephalopathy reported in the specialist neurological and pharmacological literature, however, only two reports have appeared in the general medical literature in English.^{2,3} Hyperammonaemia is an important and potentially reversible cause of encephalopathy, and should be suspected in any confused patient on sodium valproate therapy.

**M O'Neill, R W Dubrey,
R M Grocott-Mason**

Department of Cardiology, Hillingdon Hospital,
Uxbridge, Middlesex UB8 3NN, UK;
mdoneill@doctors.org.uk

References

- 1 **Hawkes ND**, Thomas GAO, Jurewicz A, *et al*. Non-hepatic hyperammonaemia: an important, potentially reversible cause of encephalopathy. *Postgrad Med J* 2001;**77**:717–22.
- 2 **Coulter DL**, Allen RJ. Secondary hyperammonaemia: a possible mechanism for valproate encephalopathy. *Lancet* 1980;i:1310–1.
- 3 **Jones GL**, Matsuo F, Baringer JR, *et al*. Valproic acid-associated encephalopathy. *West J Med* 1990;**153**:199–202.

Recurrent orogenital ulcers with papilloedema and headaches

I enjoyed reading the self assessment question by Abbas *et al* published recently.¹ It would be of great interest to know the ethnic background of this 33 year old man. In a study by Daif *et al*, from Saudi Arabia, Behçet's disease accounted for almost one fourth of their cases of cerebral venous thrombosis (CVT),² likely to be explained by the higher prevalence of Behçet's disease in the Middle East.³

It is imperative that all patients with CVT, even in the presence of a known aetiological factor, have a thorough diagnostic work-up, as multiple factors can be encountered in an individual patient.⁴ Also, the factor V gene mutation has been shown to be associated with a sixfold increase in venous thrombosis risk in Behçet's disease.⁵

Recombinant tissue plasminogen activator, rather than urokinase, can be used as a local thrombolytic agent, but must be restricted to patients without haemorrhage. It should be used after anticoagulation therapy alone has not provided sufficient clinical improvement, and after ruling out other causes of a patient's worsening condition.^{4,6}

Z Morcos

Department of Neurology,
University Hospitals of Cleveland,
11100 Euclid Avenue, Hanna House # 5,
Cleveland, OH 44106-5040, USA;
zeyad_m@hotmail.com

References

- 1 **Abbas MAM**, Cotta R, Rashid W. Recurrent orogenital ulcers with papilloedema and headaches. *Postgrad Med J* 2002;**78**:54, 57–8.
- 2 **Daif A**, Awada A, al-Rajeh S, *et al*. Cerebral venous thrombosis in adults: a study of 40 cases from Saudi Arabia. *Stroke* 1995;**26**:1193–5.
- 3 **Sakane T**, Takeno M, Suzuki S, *et al*. Behçet's disease. *N Engl J Med* 1999;**341**:1284–91.
- 4 **Biousse V**, Bousser MG. Cerebral venous thrombosis. *The Neurologist* 1999;**5**:326–49.
- 5 **Gul A**, Ozbec U, Ozturk C, *et al*. Coagulation factor V gene mutation increases the risk of venous thrombosis in Behçet's disease. *Br J Rheumatol* 1996;**35**:1178–80.
- 6 **Bousser MG**. Cerebral venous thrombosis. Nothing, heparin, or local thrombolysis? *Stroke* 1999;**30**:481–3.

A elderly lady with collapse

I enjoyed reading the anatomical discussion about the third cranial nerve presented by Huwez *et al* in a recent issue of the journal,¹ and I wish to make a few relevant anatomical and clinical points.

All the extraocular muscles are innervated by an ipsilaterally located subnucleus, with the exception of the superior rectus muscle, which is innervated by a contralateral subnucleus.²

The particular relationship between the third cranial nerve and posterior cerebral

artery (above), the superior cerebellar artery (below), and the posterior communicating artery (parallel) deserve further comments, especially when clinicians are faced by an acquired isolated third nerve palsy in adults. As the pupillary fibres in the third cranial nerve are located dorsally and peripherally, a dilated pupil is frequently an early sign of a compressive lesion. An aneurysm at the junction of the posterior communicating artery and internal carotid artery is a common cause.³ Actually, around 30% of all third nerve palsies are caused by aneurysms, especially posterior communicating aneurysms.⁴

Other causes include compression or infiltration by neoplasm, infections, large dolichoeccentric vessels, or shifted supratentorial structures. Occasionally it may be seen in generalised polyneuropathy (Miller-Fisher variant).⁵

Z Morcos

Department of Neurology,
University Hospitals of Cleveland,
11100 Euclid Avenue, Hanna House # 5,
Cleveland, OH 44106-5040, USA;
zeyad_m@hotmail.com

References

- 1 **Huwez FU**, Umasankar U, Aggarwal D. An elderly lady with collapse. *Postgrad Med J* 2002;**78**:105, 111–12.
- 2 **Balcer LJ**. Anatomic review and topographic diagnosis. *Neurosurg Clin N Am* 1999;**10**:541–561.
- 3 **Biousse V**, Newman N. Third nerve palsies. *Semin Neurol* 2000;**20**:55–74.
- 4 **Biousse V**, Newman N. Aneurysms and subarachnoid hemorrhage. *Neurosurg Clin N Am* 1999;**10**:631–51.

Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient

In a recent issue of the journal McNulty and Hardy published a very interesting case history on the failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient.¹ Their third self assessment question was "What may be the explanation for this profoundly unwell patient with type 1 diabetes and hyperglycaemia not to have developed diabetic ketoacidosis?" The authors' explanation is "because her insulinopenia was offset by her hypoadrenalism".

However, in patients with diabetic hyperglycaemic hyperosmolar syndrome (without ketoacidosis, as in the authors' patient) increased concentrations of adrenal hormones are usually found.² This makes the authors' explanation very improbable. On the other hand, Schade and Eaton pointed out in 1977 (their p 596) that "insulin deficiency per se may not alone cause ketoacidosis".³ An illustration of this problem is in the paper by Burge *et al*: they compared two groups of diabetic patients, with lower and higher hyperglycaemia. Ketone bodies were higher in the group with lower blood glucose. In decompensated diabetes mellitus, increased amounts of 34 organic acids have been identified⁴; it is not known whether they are insulin dependent or not. Nevertheless, they can cause severe acidosis, for example, a blood pH of 6.85 was found in the patient of Vernon and Postellon in absence of acetoacetic and β -hydroxybutyric acids.⁶

Therefore, the authors should also ask: What are the exact mechanisms and details of

development of both ketoacidosis and acidosis without ketone bodies in diabetic patients?

V Rosival

Department of Clinical Biochemistry,
Dérer's Hospital, Limbová 5,
SK-833 05 Bratislava, Slovakia

References

- 1 **McNulty SJ**, Hardy KJ. Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient. *Postgrad Med J* 2001;**77**:734, 739–40.
- 2 **Ennis ED**, Stahl ElvB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. *Diabetes Reviews* 1994;**2**:115–26.
- 3 **Schade DS**, Eaton RP. The controversy concerning counterregulatory hormone secretion. *Diabetes* 1977;**26**:596–9.
- 4 **Burge MR**, Hardy KJ, Schade DS. Short-term-fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. *J Clin Endocrinol Metab* 1993;**76**:1192–8.
- 5 **Niwa T**. Mass spectrometry in diabetes mellitus. *Clin Chim Acta* 1995;**241**–**242**:190–220.
- 6 **Vernon DD**, Postellon DC. Nonketotic hyperosmolar diabetic coma in a child: management with low-dose insulin infusion and intracranial pressure monitoring. *Pediatrics* 1986;**77**:770–2.

BOOK REVIEW

A Disease Once Sacred.

By M J Eadie and P F Bladin. (Pp 248; £24.) John Libbey, 2001. ISBN 0-86196-607-4.

Written by two Australian epileptologists this book follows the historical concepts of epilepsy, ranging from mythological early views of the supernatural to the modern concepts of pathophysiology and treatment. Part I is a short outline of the present understanding of epilepsy including definition and classification. Parts II, III, and IV cover the clinical manifestations of epilepsy, the nature of the epileptic process and remedies, each examined from an historical viewpoint.

Some ancients believed in the influence of bodily humours in triggering seizures, while others felt that sufferers from this malady had supernatural powers or were influenced by spirits or demons. Gradually, however, the concept of epilepsy as an illness with an underlying organic process began to be accepted along with a better comprehension of the origins and mechanisms of epileptic activity within the brain. The influence of Hughlings Jackson and the gradual acceptance of his views by his contemporaries makes particularly interesting reading.

With regard to treatments for epilepsy the early remedies are discussed; this is followed by reference to the discovery of the effectiveness of bromide, more recent drug treatments and, ultimately, the evolution of the "designer" drugs.

A major feature of the text is the liberal use of historical quotations supplemented by an extensive historical bibliography. Overall this

book provides a fascinating trip through history, following our understanding of this intriguing condition through to the present state of knowledge. It is recommended to anyone with an interest in the history of medicine and of epilepsy in particular.

R Abbott

Department of Neurology,
Leicester Royal Infirmary, UK

DIARY

Professional Updating in Epidemiology. Design of Vaccination Programmes: From Sero-Epidemiology to Cost-Effectiveness

8–12 July 2002, University of Warwick, Coventry, UK. The course intends to develop understanding of the epidemiological principles of vaccine programme design, including

serological surveys, parameter estimation, transmission dynamic models, and cost-effective analysis of different programmes. For further information contact Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK (tel: +44 (0)2476 523540, fax: +44 (0)2476 523701, email: s.j.hicks@warwick.ac.uk).

Falk Workshop: Bile Acids and Pregnancy

2 June 2002, Freiburg, Germany.

Falk Symposia

Bile Acids: From Genomics to Disease and Therapy

30 May–1 June 2002, Freiburg, Germany.

GI Inflammation and Disturbed Gut Function: The Challenge of New Concepts

4–6 October 2002, Freiburg, Germany.

Targets for Treatment of IBD

6–8 October 2002, Freiburg, Germany.

Disease Progression and Carcinogenesis in the Gastrointestinal Tract

9–10 October 2002, Freiburg, Germany.

For further information on the above contact the Falk Foundation eV, Congress Division, Leinenweberstr 5, PO Box 6529, D-79041 Freiburg, Germany (tel: +49 761 15140, fax: +49 761 1514359, email: symposia@falk foundation.de).