Letters to the Editor

Compensated hypothyroidism

Sir,

In the evaluation of compensated hypothyroidism,¹ due cognisance should be taken of the fact that an identical thyroid function profile can characterise primary hypoadrenalism in the absence of intrinsic thyroid disease, hence its reversibility on correction of cortisol deficiency through the use of replacement therapy.² The issue is complicated further by the fact that secondary hypoadrenalism can co-exist with a variety of autoimmune disorders, including subclinical primary hypothyroidism.³ Finally, in occasional patients with pituitary or hypothalamic disorders, instead of the expected fall in serum thyroid stimulating hormone (TSH), when the thyrotropin-releasing hormone/TSH axis is affected, an increase may occur, even in those who are euthyroid on the basis of thyroid hormone levels, resulting in TSH levels of up to 9 mU/l.⁴ Failure to recognise coexisting hypoadrenalism in each of these instances, could result in a situation where thyroid replacement therapy precipitates adrenal crisis due to the fact that "the increase in metabolic rate after administration of thyroxine presumably necessitates increased secretion of adrenal steroid, without which the patient develops adrenocortical failure".⁵

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Accepted 14 January 1999

- 1 Benediktsson R, Toft AD. Management of the unexpected result: compensated hypothyroidism. *Postgrad Med J* 1998;74:729-32.
- 2 Topliss DJ, White EL, Stockit JR. Significance of thyrotropin excess in untreated primary adrenal insufficiency. *J Clin Endocrinol Metab* 1980;50:52-65.
- 3 Kasperlik-Zaluska AA, Czarnocka B, Czech W, et al. Secondary adrenal insufficiency associated with autoimmune disorders: a report of twenty five cases. *Clin Endocrinol* 1998;49:779-83.
- 4 Faglia G, Beck-Peccoz P, Ferrari C, et al. Plasma thyrotropin response to thyrotropin-releasing hormone in patients with pituitary and hypothalamic disorders. *J Clin Endocrinol Metab* 1973;37:595-601.
- 5 Fonesca V, Brown R, Hochhauser D, Ginsburg J, Havard CWH. Acute adrenal crisis precipitated by thyroxine. *BMJ* 1996;292:1185-6.

Sir,

The article by Benediktsson and Toft¹ made interesting reading. However, there are several points which need to be discussed, especially from a neuropsychiatric viewpoint. Although the exact cause-and-effect relationship between depression and thyroid hormones has not been established, the strength of association appears to be quiet high. There is mounting evidence that overt hypothyroidism is associated with a range of neuropsychiatric dysfunctions.² As far as subclinical hypothyroidism is concerned, it is increasingly being linked to lifetime risk of depression with rapid cycling bipolar disorder and other mood disorders.³ In fact, in the elderly depressed patient, laboratory assessment of thyroid functions is mandatory to avoid misdiagnosis.³ Taking into account the high prevalence of mild depressive disorders in the

community and its potential associated risks of suicide, disability, and impairment in work performance, a detailed assessment of these cases, including thyroid function testing, is required.⁴ Every case of depression, especially in the elderly, should therefore be biochemically assessed for subclinical hypothyroidism and considered for replacement therapy.

Another situation in which thyroid estimation has therapeutic relevance is the newborn infant. Prompt detection and management of hypothyroidism in the newborn is essential to prevent permanent cerebral damage and mental retardation, which may occur if timely replacement therapy is not instituted.⁵

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Accepted 20 January 1999

- 1 Benediktsson R, Toft AD. Management of unexpected result: compensated hypothyroidism. *Postgrad Med J* 1998;74:727-32.
- 2 Haggerty JJ Jr, Stern RA, Mason GA, et al. Subclinical hypothyroidism—a modifiable risk factor for depression? *Am J Psychiatry* 1993;150:508.
- 3 Stern RA, Prange AJ. Neuropsychiatric aspects of endocrine disorder. In: Kaplan HI, Sadock BJ, eds. *Comprehensive textbook of psychiatry*, 6th edn. Baltimore: William and Wilkins, 1995; pp 245-6.
- 4 Paykel ES. Milder depressive chronicity: an important clinical problem. In: Judd LL, Saeleu B, Filip V, eds. *Basic and clinical science of mental and addictive disorders*. Biological Psychiatry, vol 107. Basel: Karger, 1997; pp 39-43.

ACE inhibitors and insulin sensitivity

Sir,

I read with great interest the study by Piedrola et al.¹ An improvement in insulin sensitivity was found after 6 months in patients with coronary artery disease (CAD) treated with captopril and to a lesser extent diltiazem, compared to isosorbide mononitrate and atenolol. They subsequently concluded that captopril might be regarded as first choice therapy in the management of CAD, especially associated with metabolic abnormalities. This conclusion is misleading and there are major weaknesses in their study design.

Firstly, angiotensin-converting enzyme (ACE) inhibitors are only licensed for treatment of hypertension and heart failure. The use of this group of drugs in normotensive patients with stable CAD may lead to hypotension, resulting in worsening of myocardial ischaemia. This is more likely to occur with the co-administration of captopril (short half-life) and isosorbide mononitrate.

Secondly, Piedrola and colleagues excluded subjects with a previous history of hypertension in their study but made no reference to their blood pressure measured before and 6 months after treatment in various treatment groups. It has been shown that, in patients with non-obese and normoglycaemic essential hypertension, steady-state plasma glucose is higher than in normo-

tensive subjects during insulin sensitivity tests.² Hence, it is possible that the improved insulin sensitivity in the ACE inhibitor group could be related to a blood pressure lowering effect rather than a drug class effect.

Previous studies investigating the effect of ACE inhibitors on insulin sensitivity have produced conflicting results. The validity of these studies is often compromised by poor study design, lack of placebo data, and heterogeneous patient populations in which the biochemical mechanisms of insulin resistance and drug responses may differ. Overall, ACE inhibitors probably have a modest class effect by increasing muscle blood flow, inhibiting local renin-angiotensin system and increasing kinin levels, thereby enhancing insulin-mediated glucose disposal.² While the role of ACE inhibitors in improving insulin sensitivity (a surrogate marker of CAD) has not been fully established, they should only be used in the presence of a clear clinical indication.

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Accepted 26 January 1999

- 1 Piedrola G, Novo E, Serrano-Gotarredona J, et al. Evolution of insulin resistance in coronary artery disease patients on four different pharmacological therapies. *Postgrad Med J* 1999;75:27-31.
- 2 Suzuki M, Ikebuchi M, Shinozaki K, et al. Mechanism and clinical implication of insulin resistance syndrome. *Diabetes* 1996;45(suppl 3):S52-54.

This letter was shown to the authors who responded as follows:

Sir,

In our recently published study, we demonstrated that the use of captopril and, to a lesser extent, diltiazem in patients with coronary artery disease (CAD) was accompanied by an improvement in insulin sensitivity.¹ Dr Chan suggests that the use of angiotensin-converting enzyme (ACE) inhibitors in these patients may lead to hypotension and that the improvement in insulin sensitivity may be due to a decrease in blood pressure instead of a class effect of captopril.

We found no adverse effects with the combination of isosorbide mononitrate plus captopril in our CAD patients. There were no changes in blood pressure through the 6-month study in patients treated with captopril, as low doses were used (12.5 mg/12 h). In fact, other drugs which are conventional therapies for CAD, such as diltiazem and atenolol (also used in our work) may decrease blood pressure (they are also first line therapy for hypertension) and, at least in theory, worsen myocardial ischaemia. They have been shown to improve morbidity and mortality in CAD, however, and are now part of our current approach in these patients.

Arterial hypertension has been related to insulin resistance; non-obese non-diabetic hypertensive patients display a decrease in insulin sensitivity in comparison to adequately matched controls.³ These metabolic abnormalities have been shown to improve

with the use of ACE inhibitors but not with other antihypertensive drugs (such as thiazides), provided that the same reduction in blood pressure is achieved.⁴ This strongly suggests that it is not the blood pressure lowering effect of the drug which modifies insulin sensitivity but a drug effect. The use of an ACE inhibitor is thus a logical approach in patients with metabolic abnormalities and CAD, and an improvement in insulin sensitivity in such patients with these drugs was demonstrated in our study. This does not mean that all CAD patients should be treated with ACE inhibitors, as not all of them display metabolic abnormalities. Further, we realise that no definite conclusion on morbidity and mortality can be drawn from our study. But the results do suggest that ACE inhibitors may represent a coadjutant therapy in the management of patients with CAD and a deleterious metabolic profile.

G PIEDROLA

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Accepted 24 February 1999

- 1 Piédrola G, Novo E, Serrano-Gotarredona J, *et al.* Evolution of insulin resistance in coronary artery disease patients on four different pharmacological therapies. *Postgrad Med J* 1999;75:27–31.
- 2 The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–46.
- 3 Ferranini E, Buzzigoli G, Bonnadona R. Insulin resistance in essential hypertension. *N Engl J Med* 1987;317:350–7.
- 4 Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989;321:868–73.

Inhibition of advanced glycated end-products

Sir

Szalecsky and colleagues raise an interesting series of points on the enzymatic antioxidant defence system and its role in the pathogenesis of diabetic complications when its function of free-radical clearance is impaired.¹ It is conceivable that one of the ways in which the scavenging function of the antioxidant enzymes may be reduced is by glycation of their free amino terminals to produce the advanced glycated end-product (AGE) variants of these enzymes. High blood glucose is known to cause glucose to bind covalently and nonenzymatically to various proteins *in vivo* to generate AGEs. Glycation can alter the structure as well as the function of physiological proteins. Therefore, hyperglycaemia may modify the properties of the antioxidant enzymatic defence proteins and increase the susceptibility of the patient with diabetes mellitus to vascular damage from the resulting excess of free-radical species.

The levels of AGE are known to be elevated in the serum of patients with diabetes. AGEs have been linked with retinopathy, nephropathy and neuropathy, as well as being implicated in large vessel disease. The mechanisms leading to micro- and macro-angiopathy are thought to occur by an interaction of AGE with a receptor (known as RAGE) expressed on the cell surface membrane of vascular endothelial cells. The agonist-receptor interaction appears to be responsible for eliciting fundamental lesions in the vessel wall that promote atherosclerosis and diabetic microangiopathy in the animal model. In human retinae with non-

proliferative and proliferative diabetic retinopathy, AGEs have been closely associated with the expression of vascular endothelial growth factor,² which is known to induce new vessel formation and thus AGE may play a crucial role in the pathogenesis of retinopathy by elevating vascular endothelial growth factor levels in the microenvironment of the diabetic retina. Ultrastructural studies of human diabetic retinopathy have shown AGE to be localised in the nodular lesions of sclerosing glomeruli, where it is believed to disrupt the normal architecture of mesangial matrix proteins. In another set of experiments, elevated AGE levels in the sciatic nerve of diabetic rats were associated with a significantly reduced nerve conduction velocity when compared with age-matched control animals, suggesting a role of AGE in diabetic neuropathy.³

It is therefore interesting to speculate that an inhibition of AGE synthesis, or its antagonism at the level of the RAGE receptor, could be important in preventing the genesis of vascular diabetic complications. For example, it has been shown in a Type 2 diabetes animal model that decreasing serum AGE levels prevents the progression of diabetic glomerular sclerosis.⁴ Inhibition of AGE with aminoguanidine has been observed to prevent or improve retinopathy and neuropathy in animals. Furthermore, prevention of AGE synthesis with aminoguanidine in mice reduces the development of diabetes and in addition preserves pancreatic structure and function.⁵ In the quest for AGE-suppressing compounds, aspirin has also been found to prevent the formation of AGE by competing with glucose for selected amino terminal binding sites on proteins. With regard to large vessel disease, the use of particular compounds to degrade the AGE formed in connective tissue has been observed to decrease the accelerated arterial wall stiffness found in experimental diabetes. When the binding of AGE to its vascular endothelial receptor was prevented in diabetic mice by using a soluble moiety of the receptor, the process of atherosclerosis was suppressed completely.⁶

Since AGE species are chemically irreversible and correlate with the level of glycaemia, they may potentially serve as a biochemical marker of diabetes mellitus in a similar way to the use of glycated haemoglobin to monitor metabolic control, in addition to providing a direct index of the severity of micro- and macrovascular damage. Furthermore, a slowing of the progression of micro- and macrovascular disease by reducing the production or physiological effectiveness of AGEs by drug treatment may herald an intended intervention at a molecular level in diabetic therapeutics.

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Accepted 10 February 1999

- 1 Szalecsky E, Prechl J, Feher J, Somogyi A. Alterations in enzymatic oxidant defence in diabetes mellitus - a rational approach. *Postgrad Med J* 1999;75:13–7.
- 2 Lu M, Kuroki M, Amano S, *et al.* Advanced glycation endproducts increase retinal vascular endothelial growth factor expression. *J Clin Invest* 1988;15:101:1219–24.
- 3 Sensi M, Pricci F, Pugliese G, *et al.* Role of advanced glycation end-products (AGE) in late diabetic complications. *Diabetes Res Clin Pract* 1995;28:9–17.
- 4 Nakamura S, Makita Z, Ishikawa S, *et al.* Progression of nephropathy in spontaneous dia-

betic rats is prevented by OPB-9195, a novel inhibitor of advanced glycation. *Diabetes* 1997;46:895–9.

5 Piercy V, Toseland CD, Turner NC. Potential benefits of inhibitors of advanced glycation end products in the progression of type II diabetes: a study with aminoguanidine in C57/BLKsJ diabetic mice. *Metabolism* 1998;47:1477–80.

6 Park L, Raman KG, Lee KJ, *et al.* Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation end-products. *Nat Med* 1998;4:1025–31.

This letter was shown to the authors who responded as follows:

Sir,

Drs Gandhi and Patel, in their valuable letter related to our article, refer to the fact that research in recent years has proven that levels of the late products of non-enzymatic glycosylation, the so-called advanced glycated end products (AGEs), are elevated in the sera of diabetic patients. Moreover, it is also accepted that binding of these molecules to their receptors (RAGEs) expressed on vascular endothelial cells plays a basic role in the development of diabetic micro- and macro-angiopathy. Thus, AGE can play a role in diabetic retino-, nephro- and neuropathy.

These data lead to the possibility, as reviewed in Dr Gandhi's letter, that by inhibiting AGE production (eg, by aminoguanidine or aspirin) or blocking receptor binding, we may be able to reduce the risk of late diabetic complications and thereby improve life quality and expectancy in diabetic patients. Since AGE species are irreversibly modified and their concentrations are correlated with the severity of glycaemia, it has been suggested that they could be used as a diabetic marker, or as an index of micro- and macro-angiopathy.

Two stages of non-enzymatic protein glycosylation are known.^{1,2} Early glycation events are mainly detectable on short-lived proteins such as haemoglobin enzymes. In this case a Schiff base is produced via the reaction between glucose and free amino groups. In a few weeks time a more stable but still reversible Amadori product is formed, a molecule with a ketoamine bond. This process is directly correlated with the serum glucose concentration and is selective to protein structures, the latter being responsible for tissue selectivity. Amadori products go through further structural changes (dehydration, chemical cross-linkage, conformational change) to yield stable species of AGE, the late products of glycation. AGEs are capable of further reacting with other proteins. AGE-modified soluble and matrix proteins possess a chemotactic activity, inducing monocyte migration, they inactivate NO, and induce production of adhesion molecules. Monocytes phagocytose AGEs into molecules with lower molecular weight, which are more mobile and able to activate smooth muscle cells deeper in the vessel wall. The physico-chemical properties of the collagen matrix also suffer changes. Free radicals released during these processes promote degradation and polymerization of proteins. Taken together, glycation starts a cascade of pathophysiological reactions which form the basis of atherosclerosis.

AGEs are removed by the liver, by macrophages via scavenger receptors (the latter also take up glycated and modified lipids), and by RAGEs. RAGEs are expressed at higher levels in certain pathological states (diabetes, inflammation, etc) in some organs (eg, kidneys) and allow the uptake and integration

of AGE into the tissues and their excretion via the kidneys. Immunohistochemical studies can demonstrate these processes,⁴ but these techniques are not yet commonly available. AGEs can also be detected in body fluids by competitive ELISA and immunofluorescence.⁵

It would therefore seem reasonable that inhibition of the development of early and late glycation products may prevent the premature atherosclerosis of diabetic patients. The most potent and important means of preventing diabetic complications is the strict control of glucose metabolism, as demonstrated by the Diabetes Control and Complications Trial in 1993.⁵ The trial proved that good metabolic control, as assessed by HbA1c levels, not only prevents the development of complications but also stops further deterioration.

In summary, we conclude that there are, at least theoretically, several points and ways of intervening with the production, uptake and elimination of AGEs. As the formation of this species is a relatively long-term process influenced by numerous factors acting at different time points (actual glucose control, protein structures, diseases, exogenous factors such as smoking, etc), we think that the presence of AGEs is primarily a global marker of an individual's pathological history, thence micro- and macrovascular damage, and not only of the metabolic changes of diabetes.

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Accepted 22 March 1999

- 1 Kennedy L, Baynes JW. Non-enzymatic glycosylation and the chronic complications of diabetes: an overview. *Diabetologia* 1984;26:93-8.
- 2 Brownlee M, Vlassara H, Cerami A. Non-enzymatic glycosylation and the pathogenesis of diabetic complications. *Ann Intern Med* 1984;10:527-37.
- 3 Niwa T, Katsuzaki T, Miyazaki S, et al. Immunohistochemical detection of imidazolone, a novel advanced glycation end product, in kidneys and aortas of diabetic patients. *J Clin Invest* 1997;99:1272-80.
- 4 Mitsuhashi T, Vlassara H, Founds HW, Li MY. Standardizing the immunological measurement of advanced glycation endproducts using normal human serum. *J Immunol Meth* 1997;207:79-88.
- 5 Somogyi A, Korányi L, eds. *Metabolic and mineral metabolic diseases in practice*. Budapest: Medicina, 1998; p 97.

Book reviews

The reviewers have been asked to rate these books in terms of four items: readability, how up-to-date they are, accuracy and reliability, and value for money, using simple four-point scales. From their opinions, we have derived an overall 'star' rating:

★ = poor; ★★ = reasonable; ★★★ = good; ★★★★ = excellent

Data interpretation questions in paediatrics

Fiona Finlay, Liz Lambert, Simon Lenton, Jacqui Clinch, pp 256. Blackwell Science Ltd, 1998. £16.95, paperback. ★★★★★

This useful text will be valuable for all junior paediatricians preparing for the Membership College exams in paediatrics. It contains 115 questions of the range of conditions commonly covered in the data question section of the college exams. Clear explanations of the answers are given and all the questions are usefully referenced to appropriate sections of three standard text books of paediatrics and neonatology. When used together with this small book this will prove an efficient way to study and learn for the examination. The book is competitively priced and is easily transportable in the pocket.

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MCQs for the PLAB examination, Kavita Dutta, pp 160. Butterworth Heinemann, 1998. £15.99, paperback. ISBN 0 7506 4004 9. ★★

The success rate for the PLAB examination is about 30% and therefore any publication that can guide candidates to the standard required is to be welcomed. The author is able to bring a personal touch to the book as she herself had to sit the PLAB examination. The book consists of a compilation of MCQs from past PLAB tests, collected by her. These are presented in 15 papers which cover the major clinical subjects and basic sciences, and sensible advice given on MCQ technique such as the importance of timing, negative marking, and avoiding common errors. PLAB part one is held in several overseas centres and since the stem questions arise from previous papers, this book will be useful for candidates abroad who may have difficulty in getting examples of past

papers. There is a helpful index at the back of the book.

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Trauma care: beyond the resuscitation room, Peter Driscoll, David Skinner, eds, pp ix + 312. BMJ Books, 1998. £135 (£130 to BMA members), hardback. ISBN 0 7279 0933 9. ★★★

Trauma care is a new publication which attempts to fill a different niche from its predecessors. Although the first chapter deals with the initial assessment and management of the trauma patient, subsequent chapters attempt to bridge all treatment from initial assessment through to early definitive care, following a system-based approach. The book would make a good supplement to the Advanced Trauma Life Support manual and will be of interest to those working in Accident & Emergency Departments, to admitting doctors responsible for early inpatient care, and to specialists who wish to appraise themselves of current management in other specialties.

The balance between initial and later management varies from one chapter to another. In the section on spinal injury for example, 16 pages are devoted to initial care and only the last four pages to definitive management. For abdominal injuries, the principles of early care are covered in the first four pages and the remaining seven are mainly surgical in content. Despite the title, some of the content of books that deal with the initial care of traumatised patients has been duplicated. Intensive care and specialist management justifiably predominate in certain areas, such as the chapter on shock.

The editors state that the book "endeavours to be exhaustive in its scope from resuscitation to rehabilitation". This is an ambitious aim, even in 300 pages. I am not convinced that the book fully encompasses

rehabilitation, for example, in the chapter on limb injuries.

The text is well organised and presented with many high-quality colour plates, X-rays and illustrations, and tables on almost every page. This raises the price to £110 which will be too expensive for many. However, it is readable and useful and each chapter lists references or recommendations for further reading. Most of the contributors are well established Consultants who have contributed to in other books on trauma.

In summary, this book will appeal to those who are interested in or committed to the provision of care for patients suffering multiple trauma. The quality of reproduction is matched by the price and it certainly tries to encompass trauma care from resuscitation to rehabilitation, although that ambition has not been completely fulfilled in this first edition.

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Key topics in gastroenterology, SHC Anderson, G Davies, HR Dalton, pp x + 286. BIOS Scientific Publishers, 1999. £21.95, paperback. ISBN 1 8599 6281 5. ★★★★★

This text is a new member of a large series of books dealing with the various medical sub-specialties. The three authors include a London university hospital specialist registrar and two provincial district general hospital gastroenterologists. This is probably about the right sort of balance and the approach is factual and didactic without being overwhelmingly academic.

The layout is as an encyclopaedia with topics from abnormal liver function tests to Wilson's disease. To get the best out of the book it is probably best to consult the table of contents before the index.

Most of the chapters are quite readable short monographs on the topic, but some degenerate into rather off-putting lists, such as in jaundice and the classification of gastri-

tis. Chapters mainly address specific diseases though some relate to symptoms.

Candidates for the MRCP could be assured of being reasonably up to date having read through this book and this is clearly its principle aim. Physicians who are not specialists in gastroenterology may also find it useful. However, it was sad to see the solecism repeated in 1999, that gallstones are the prerogative of the middle aged.

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Randomised controlled trials, Alejandro Jadad, pp 128. BMJ Books, 1998. £12.95 (£11.95 to BMA members), paperback. ISBN 0 7279 1208 9. ★★

The issue of trial design is increasingly recognised as central to the evaluation of the benefit from any healthcare intervention. The author describes the book as an introductory guide aimed primarily at clinicians, young

researchers, research staff and trainees in any health profession.

My personal view, admittedly, in the author's own words (p 81) "idiosyncratic, ... informal and subjective", is that while I fully endorse all that is said, these are not quite the right contents to target at this readership. In particular, chapter 4 deals with assessing the quality of randomised controlled trials, an important issue for all readers, but perhaps not to such depth; the section on developing a formal instrument to assess trial quality will be of direct concern to few.

Conversely, there is much that has not been included, and that could profitably be enlarged upon. The author admits that the book is not meant to be a statistics text, and refers readers to Altman's excellent book, *Practical statistics for medical research* (Chapman & Hall, 1991). Nor should it be, but it would be worth enlarging a little on the key issues of sample size and power, and the preference for point and interval estimates of effect size rather than hypothesis tests, and cross-referencing another booklet published by

BMJ Books, *Statistics with confidence*, with accompanying software, second editions of which are to appear this year. The author refers to the recognised need to make the most of existing knowledge, leading to a strong evidence-based medicine emphasis, though the other consequence of this, health services research, is not elaborated on.

The book would be easier to assimilate with a few more examples. This is done very well in chapter 3, in which the issues are developed in the context of a new drug to delay disease progression in multiple sclerosis. This approach could also have been profitably applied elsewhere.

I will find this book very useful as a source of material for my teaching, refereeing and research collaboration. But it is not exactly what I would have written as an introduction to the subject for clinical researchers.

ROBERT NEWCOMBE

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International Postgraduate Diary

University of Warwick Short Courses

12–15 July 1999: Techniques and applications of molecular biology: a course for medical practitioners

Details: Dr Charlotte West, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK. Tel + 44 1203 523540; fax + 44 1203 523701; e-mail: ca@dna.bio.warwick.ac.uk

5th International Congress on the cell biology of reproduction

1–3 July 1999: St John's College, Cambridge, UK

Details: Congress Secretariat, PO Box 3219, Barnes, London SW13 9XR, UK. Tel + 44 181 741 1311; fax + 44 181 741 5172; e-mail: L.wilding@iop.bpmf.ac.uk

17th World Congress on sarcoidosis and other granulomatous disorders

8–13 November 1999: Kumamoto, Japan

Details: Prof Masayuki Ando, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860, Japan. Tel +81 96 373 5150; fax +81 96 371 0582

World Congress of Interventional Cardiology

14–16 October 1999: Mumbai, India

Details: Prof Dr Lekha Pathak, Secretary General, World Congress of Interventional Cardiology, Santacruz (West), Mumbai 400 054, India. Tel + 91 22 6490261; fax + 91 22 6494946

International Institute for Continuing Medical Education

1–4 July 1999: Musculoskeletal MR (Lake Buena Vista, FL, USA)

6–9 July 1999: Breast imaging in transition (Naples, FL, USA)

8–11 July 1999: State of the art ultrasound (Hamilton, Bermuda)

16–18 July 1999: Breast imaging: optimizing your practice and exceeding the standard of care (San Francisco, CA, USA)

2–5 August 1999: Breast imaging today and tomorrow (Santa Fe, NM, USA)

30 August–3 September 1999: Imaging in Tuscany (Tuscany, Italy)

3–5 September 1999: Advanced MRI (Montreal, Quebec, Canada)

24–26 September 1999: Internal derangements of joints: advanced and intensive MRI (Las Vegas, NV, USA)

27–30 September 1999: Mammography in Edinburgh (Edinburgh, UK)

30 September–3 October 1999: Breast imaging update (Hilton Head, SC, USA)

9–12 October 1999: Mt Sinai 1999 Body imaging update (New York, NY, USA)

13–17 October 1999: Mt Sinai 1999 Brain, spine, neurovascular and ENT imaging update (New York, NY, USA)

Details: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925, USA. Tel +1 770 641 9773; fax +1 770 552 9859

University of California School of Medicine at San Francisco/University of Cincinnati School of Medicine

4–6 November 1999: Otolaryngology update (San Francisco, CA, USA)

Details: University of California, Office of Continuing Medical Education, UCSF Box 0742, LH450, San Francisco, CA 94143-0742, USA. Tel +1 415 476 4251; fax +1 415 476 0318

International Skeletal Society and the University of California, San Diego

18–21 August 1999: International Skeletal Society annual meeting and course (Seattle, WA, USA)

Details: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925, USA. Tel +1 770 641 9773; fax +1 770 552 9859

Falk Symposia

10/11 September 1999: New concepts on etiopathogenesis and treatment of inflammatory bowel disease (Warsaw, Poland)

16–18 September 1999: Cytokines and cell homeostasis in the gastrointestinal tract (Regensburg, Germany)

20/21 October 1999: Immunology and liver (Basel, Switzerland)

22–24 October 1999: Liver cirrhosis and its development (Basel, Switzerland)

25 October 1999: Interventional endoscopy in hepatology (Basel, Switzerland)

Details: Falk Foundation V—Congress Division, Leinenweberstr 5, PO Box 6529, D-79041 Freiburg, Germany. Tel +49 761 130340; fax +49 761 1303459; email: symposia@falkfoundation.de