changes which impact patients' daily lives, remit before the end of a trial.

The problem of summing estimated disability changes at different levels of clinical rating scales as raised by Simonian and colleagues, is a different point altogether and hardly limited to an analysis by the AUC statistic. If data on changes at different levels of a rating scale are required, then stratification analysis according to baseline disability⁷ can be carried out using any outcome measure including "confirmed progression", overall EDSS change, or AUC.

Simonian and colleagues consider that AUC is appropriate for "growth data", which in terms of multiple sclerosis would apply to patients deteriorating steadily with chronic progressive disease. In fact, as stated by Matthews *et al.*,⁸ the AUC statistic is particularly relevant for summarising *peak data* such as the increase and decrease of disability associated with a relapse. However, it is also relevant and appropriate for the analysis of the complex mixture of peaked, multi-peaked, and growth data, which characterises the disability course of relapsing-remitting multiple sclerosis. If the functional form of the disability progression were known, we would of course be able to use parametric modelling (for example, exponential decay or linear decay). Our analysis is non-parametric and the only assumptions we make are that the events are stochastic and the measurements are serially correlated.

We did not imply that the AUC statistic "should be used in isolation" any more than a mean or median EDSS should be the only summary measure. The AUC clearly does not provide information about the direction of disability change and we pointed out that additional analyses would be necessary to determine time trends. Whereas we agree that theoretically, *irreversible disability progression* in multiple sclerosis is best assessed by time to events, in practice outcomes such as EDSS of 6.0, are not truly irreversible and subject to substantial measurement error. Event history analysis is more appropriate for truly irreversible events such as death or loss of virginity (!) rather than those we typically use in relapsing-remitting multiple sclerosis. Commonly employed disability end points, such as EDSS change from study entry to completion, and the so-called confirmed progression at 3 or 6 months, have major flaws as already discussed in our paper.

The relative merits of clinical rating scales such as the EDSS, Scripps neurologic rating scale, or the proposed multiple sclerosis functional composite should not be confused with the statistical methods used to analyse serial scores acquired from these scales. Whether the functional composite turns out to be better or worse than established scales remains to be seen, but this does not in any way impinge on the desirability of applying AUC analysis to serial data derived from any clinical rating scale (including the functional composite). We think that because this summary measure statistic (AUC) takes into account both transient and permanent disability, as well as the magnitude and duration of disability changes, and because it is simple to apply, sensitive and variance stabilising through its incorporation of all serial time points, it is both appropriate and clinically meaningful for outcome analysis of treatment trials of relapsing-remitting multiple sclerosis.

CLARENCE LIU
LANCE D BLUMHARDT
*Division of Clinical Neurology, Faculty of Medicine,
University Hospital Queen's Medical Centre,
Nottingham NG7 2UH, UK*
ALAIN LI WAN PO
*Department of Pharmaceutical Sciences, Aston
University, Birmingham B4 7ET, UK*

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Hypothesis on the pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS

We read with extreme interest the article by Tan and Guilloff.¹ The excellent review illustrates the current knowledge on transmethylation abnormalities in the pathogenesis of neurological complications of HIV infection. It is most convincing in its ability to bridge evidence of cytokine activation, myelinotoxic, and neurotoxic events, with abnormalities of methylation in the nervous system.

Our group has been working for years on the hypothesis that AIDS associated myelopathy and other HIV related neurological disorders are consequent to an induced metabolic abnormality of the transmethylation pathway. Our initial clinical studies with methionine supplementation suggest that signs and symptoms of myelopathy and cognitive function improve with methionine supplementation.²⁻⁵ Although still preliminary, these data offer further argument for a pathogenetic role of methylation in neurological complications of AIDS, and suggest that a therapeutic approach aimed at correcting this metabolic abnormality may be beneficial. We are now conducting a larger, controlled study to further assess treatment of neurological complications of AIDS with L-methionine.

ALESSANDRO DI ROCCO
PETER WERNER
*Department of Neurology, Beth Israel Medical Center
and Albert Einstein College of Medicine,
New York, USA*

Correspondence to: Dr A Di Rocco, Beth Israel Medical Center, PACC, 10 Union Square east, Department of Neurology, New York, NY 10003, USA.

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BOOK REVIEWS

Amyotrophic Lateral Sclerosis: A Synthesis of Research and Clinical Practice. Edited by ANDREW EISEN and CHARLES KRIEGER. (Pp303, £45.00). Published by Cambridge University Press, Cambridge, 1998. ISBN 0 521 58103 6.

From its very first sentence, this monograph on amyotrophic lateral sclerosis is anchored in its writers' personal experience. Its contents are, they tell us, "based on 664 patients"—"all examined by one of the authors". Professor Eisen and Dr Krieger have reviewed all aspects of the condition, from molecular mechanisms to bedside care. Their approach is essentially focused on clinical issues, but the book is also a useful introduction to the basic science. They review the diagnostic process from the standpoint of the clinic room, stressing both the rarity of conditions that mimic the disease and, in view of the gravity of the diagnosis, the vital need to seek out any potentially treatable disorder. The stamp of seasoned knowledge is particularly evident when the text turns to electrophysiology. Here, readers are offered precise advice and encouraged to perform techniques—such as recording corticomotoneuronal excitatory postsynaptic potentials—themselves.

The personal approach that underpins the book sometimes leads the argument in unexpected directions. On only the third page, studies of sex hormones are discussed to explain the male predominance in young onset cases. In this and other areas "not shared- by conventional dictum—" as the authors' preface has it, references are mainly to their own papers. In the chapter on therapy, which opens with a survey of trial methodology and reviews the underlying mechanisms of potential therapeutic agents, only four pages are spent on symptomatic treatment of the patient. This brief overview touches on, but hardly does justice to such topics as respiratory support and gastrostomy feeding—two interventions of established benefit. Moreover, it makes scant mention of the need for multidisciplinary care. For a summary of these issues, readers would find Mitsumoto's *Care and Management of the Patient with ALS* much more useful.

The superspecialist may quibble over the odd detail (there is no mention of the dual pattern of inheritance of the D90A superoxide dismutase mutation, a paradox apparently unique in inherited disease) and recent