Mexiteline on segmental hyperhidrosis

Ishibashi et al reported the excellent efficacy of mexiteline for the treatment of segmental hyperhidrosis in two patients (who had syringomyelia and cavernous haemangioma of the spinal cord, respectively). They presented the decrement in the patients’ sweat rate by oral administration of mexiteline.1

Previously we performed a clinical study focusing on sweating and identified 10 patients with segmental hyperhidrosis among 30 patients with syringomyelia. We followed up the patients with hyperhidrosis for 1–10 (mean 5.0) years. The amount of sweating did not change in any of them during the follow up period, although we did not perform a quantitative analysis. Consequently, we speculated that hyperhidrosis persists for at least a year. It is possible that the course of the symptoms in the cases reported by Ishibashi et al were modified by the growth or activity of spinal cord lesions. We consider it imperative that these authors describe any spinal cord lesions and how they may have shifted. However, although they did not mention the duration and time courses of the improvement in their patients, we suppose that the duration of the follow up for each patient would not have exceeded several months, judging from how the authors described their experience. In addition, even though they did not test the effects of mexiteline on control subjects or on other parts of the body in the same patients, we can be assured that the improvement in hyperhidrosis was due to the oral administration of mexiteline, on the assumption that the spinal cord tumour could not have changed in such a short time. We consider that it would be informative for clinicians if Ishibashi et al were to disclose the drug dosage and the time course of its effects and to describe the features of the spinal cord lesions.

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References

Authors’ reply
We are grateful Sudo et al, as they allow us to clarify a point of our study that was not discussed in the paper recently published in this Journal.1 They asked about the possibility of natural remission and the non-specific effect of mexiteline on sweating.

We administered 200 mg/day mexiteline or 400 mg/day carbamazepine to our patients. Both patients noticed their hyperhidrosis was relieved within two days after administration. Although we did not perform a quantitative analysis several months after treatment, the clinical improvement of hyperhidrosis persisted. In addition, the magnetic resonance images of spinal cord lesions (syringomyelia and cavernous haemangioma) in both patients were followed up for two years. During the follow up period, the spinal cord lesions did not change their size, position, and intensity on magnetic resonance imaging. Therefore, the natural course of the spinal cord lesions could not explain the improvement of hyperhidrosis during the treatment and quantitative analysis in our patients.

The sweat rate of the area of observed hyperhidrosis was decreased without a difference of the sweat rate on the healthy side after oral administration of mexiteline. We calculated the ratio of the sweat rate on the affected side to that on the healthy side—the ratio was 2.13 before treatment and decreased to 0.97 on day 7 after the treatment. We therefore consider that the mexiteline had an excellent effect only on the area with hyperhidrosis. Although we did not test the effects of mexiteline on control subjects, we think that the result on a healthy area of each patient was an appropriate internal controls for the evaluation of the drug’s effect on hyperhidrosis.

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Patent foramen ovale, cerebrovascular risk, and complement

Nedeltchev et al report that the presence of a patent foramen ovale (PFO) is a significant risk factor for recurrent cerebrovascular events, the risk being higher in patients with more than one previous embolic event. They highlight the absence of a current proven medical treatment or prevention regimen. Cardiac right to left shunting is present in a quarter of the population. It is thus worth drawing attention to a particular subgroup of patients with PFO that may be at an even more increased risk than the authors report—sport divers, most of whom fall within the age range of the above study.

Neurological sequelae constitute 80% of decompression sickness. Not only has neuroimaging shown an increased frequent brain ischaemic events in divers, but also multiple such ischaemic lesions have been found specifically in sport divers with PFO.1 While PFO’s role in haemodynamic significance is a risk factor that necessitates habit modification, often the radiological lesions do not correspond well to the neurological deficits of experienced divers.

This point, coupled with the increased risk of arterialisation of venous bubbles and the paradoxical nature of bubble genesis, suggest that a PFO is a risk factor in this subgroup for the development of neurovascular disease.2 Unknown is the added risk with age that remains to former divers. A poorly understood mechanism of bubble induced complement involvement in the pathogenesis of the neurological sequelae in decompression sickness has been suggested.3 Similarity of such symptoms to the postcerebral bypass syn- drome lends support to the hypothesis of complement-based neuroprotective strategy options for the future.4

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References

Authors’ reply
We thank Dr Demetriades for his comments on our study. While the average person with a patent foramen ovale (PFO) may not be at increased risk for neurological events, there seem to be subgroups of patients at increased risk. PFOs with large diameters, right to left shunting at rest, or high membrane mobility and PFOs associated with atrial septal aneurysms have been identified as “dangerous PFOs” by several investigators.5,6 In addition, coagulation abnormalities may promote paradoxical emboli in patients with PFO.7 To this list, Dr Demetriades adds special occupations or sports that may be dangerous in people with PFOs, specifically divers. Playing wind instruments has also been mentioned previously.8 However, many problems related to PFO remain unresolved. Even in groups that are believed to be at high risk for neurological events, deciding whether and how to treat a PFO cannot be derived from evidence based medicine. Deciding how to proceed depends on the opinion of the attending physician and is not based on data from randomized trials.

The PICSS (PFO in cryptogenic stroke study) showed that secondary prevention of cryptogenic stroke in patients with PFO by using warfarin or aspirin does not result in any difference.9 The PC-trial is an ongoing randomized trial we initiated to compare
endoavascular PFO closure versus medical treatment alone. We hope that it will provide useful information on secondary stroke prevention in patients with presumed paradoxical embolism. It is also conceivable that divers who have ever had “the bends” would benefit from PFO closure.

Recently reported data suggest links between decompression illness, migraine with aura, and right to left shunts. These observations not only extend the clinical manifestations of PFO but also bring into discussion new pathophysiological aspects of migraine. If the association between complicated migraine and PFO can be corroborated, a randomised trial on PFO in such patients may be worthwhile.

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Demyleination in the brain as a paraneoplastic disorder: candidates include some cases of seminoma and central nervous system lymphoma

We read with interest the report of Ayuso-Peralta et al., which describes a 58 year old woman who presented with several neurological symptoms. Brain imaging was consistent with leukoencephalopathy, and analysis of blood and cerebral spinal fluid was unrevealing. A few months later the patient experienced further neurological deterioration and an open brain biopsy showed central nervous system (CNS) lymphoma, together with diffuse demyeletion.

The authors observed that the presentation of cerebral lymphoma as a diffuse leukoencephalopathy is not frequent and they discuss possible aetiologies of the predominant demyeletion in their case. They do not mention the possibility of a paraneoplastic aetiology.

The authors reference a similar case previously reported in the Journal. That report also does not acknowledge a possible paraneoplastic aetiology for diffuse brain demyeletion preceding the discovery of CNS lymphoma. Two other recent reports in the Journal described focal tumour-like lesions of brain demeyleination associated with lymphoma. Two other recent reports elsewhere described focal tumour-like lesions of brain demyeletion confined to cerebral white matter. Two other reports elsewhere have described biopsy confirmation of large focal demyeletion lesions in the brain associated with seminoma. Many questions concerning aetiology remain unanswered. Given the spatial association was distant.

The associations between brain demyeletion and CNS lymphoma have been close, both temporally and spatially, making considerations of aetiology more complex. Taken together, the seminoma reports and the CNS lymphoma reports have many similarities in their patterns of associated brain demyeletion, raising the possibility of similar mechanisms of demyeletion. Many questions concerning aetiology remain unanswered. Given the available information, we suspect a paraneoplastic aetiology in all of these cases. We feel that future reports of brain demyeletion associated with CNS lymphoma should consider this possibility in their data collection and in their discussion of results.

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References

Genotype predisposition to leukoaraiosis

Leukoaraiosis, which can cause symptoms ranging from a mild cognitive impairment to severe subcortical dementia, is a significant public health problem. One quarter of subjects aged 65 years or over are affected by some degree of leukoaraiosis. It has been proposed that the spatial association was distant.

These observations not only extend the clinical manifestations of PFO but also bring into discussion new pathophysiological aspects of migraine. If the association between complicated migraine and PFO can be corroborated, a randomised trial on PFO in such patients may be worthwhile. A number of genetic susceptibility factors for leukoaraiosis have been put forward, with the assumption of polygenic aetiological factors. We were pleased to read the article by Hassan et al in this journal. The authors stated that the angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism in the ACE D/D genotype was an independent predictor for leukoaraiosis in patients presenting with classic lacunar syndromes. We earlier conducted large prospective studies in which we also examined the importance of the ACE D allele and other common mutations in the development of small vessel infarction and leukoaraiosis. Our results were consistent with the findings of Hassan et al, and their results from several other aspects, (1) Our stroke study confirmed the genetic heterogeneity of ischaemic stroke in that the ACE D/D genotype proved a significant susceptibility genotype for small vessel brain infarction, as did the Leiden V mutation for large brain infarction. (2) In our leukoaraiosis study, the ACE D/D genotype was found to be a significant risk factor for leukoaraiosis in combination with brain infarction. (3) We also reported that clustering of the homozygous MTHFR 677 TT genotype in one person can mean a moderate (about fivefold risk), but highly significant (<0.0005) risk of leukoaraiosis without infarction. These data from our other approaches confirm the possible aetiological role of the ACE D/D genotype in leukoaraiosis relating to small vessel brain disease. The genotype differences may explain why some patients who are exposed to clinical risk factors such as hypertension, exhibit a much higher susceptibility to leukoaraiosis than other subjects with the same clinical risk factors. Besides the classic clinical risk factors, the consistently growing knowledge of the genetic background of leukoaraiosis may permit the recognition of a large population at high risk of a new type of brain damage, and hence this may lead to a more effective prevention.

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References
Neurochemistry of consciousness: neurotransmitters in mind


Consciousness is a portmanteau word, full of rich and different meanings: contrast Marxian, pre-Piouday, and anaesthesiologists’ use of the term. In recent years it has also become a fashionable hunting ground for neuroscientists, who are rarely troubled by such complexities. For them, consciousness is being awake rather than asleep, being reducible to awareness. Sweeping aside centuries of philosophical debate, they ponder over whether “it” “resides” in specific anatomical brain structures, in microtubules, in patterns of neurotransmitter release, or whatever. The present book is typical of this type of cheerfully unsophisticated empiricism: it hunt for what the editors call “NCNs”—neural correlates of consciousness—on neurotransmitters, hence the subtitle. However, the concern with “mind” ceases at that point; this elusive phenomenon finds no place in the book’s index. The central question for the editors is whether the acetylcholine on the dopaminergic system is the likely substrate for conscious awareness. This reductionism characterizes most of the chapters. That on memory, for instance, abandons even animal memory for a discussion of a physiological phenomenon called long term potentiation, and even the psychoanalyst Mark Solms, on dreams, who surely ought to have a broader perspective, confines himself to contrasting cholinergic and dopaminergic hypotheses. However, the authors are clearly writing to an editorial brief: each chapter, in a book ranging from discussions of attention and motivation through psychotropic drug mechanisms to mental retardation and autism, following a brief nod to marginally wider concerns, offers a neurotransmitter by neurotransmitter list of potential associations or correlations with “states of awareness.” Within these limitations many of the chapters provide competent friendely overviews of their themes. If the book’s pretensions weren’t so much larger this would be fine; as it is, those hoping for a more multilevel or theoretically informed discussion will be disappointed.

Steven Rose

Risk control and quality management in neurosurgery


This is an interesting and timely publication. The book contains a compilation of material presented at an international meeting held in October 2002. It has been divided into various sections that take the reader through grouped papers and finally a projection into the future. As would be expected, the material covers experience and lessons gained in other areas such as aviation and nuclear research. The authors, generally set in status, originate from Europe, the United States, and the United Kingdom and therefore offer a diverse collection of views, opinions, and experience relevant to a very wide readership. The increasing requirements for quality assessment and competency make this a very valuable reference book for both departmental and institutional libraries. However, it certainly will be of value to individual readers as well. It should be recommended reading for trainees to understand the principles and the ongoing thought behind many of the practices and control measures that they will encounter and will need to participate in as their experience and seniority advance. The quality of contributions and the outline of the information do vary, as would be expected in such a compilation, but overall very few pages or chapters do not prove insightful nor provide useful guidelines. It will be of value to all medical disciplines, since the principles are universal and the terms of reference or yardsticks used are convertible or transferable. It is highly recommended.

J Van Dellen

Primary progressive multiple sclerosis


The field of multiple sclerosis (MS) is awash with literature on every aspect of the disease ranging from epidemiology and genetics to pathology and treatments. It is unusual, therefore, to find a lacuna in this niche but this book seems to have found one.

Primary progressive multiple sclerosis is written to encapsulate the latest evidence on aspects of this condition, which until recently was not regarded as important in understanding demyelinating disease. Filippi and Comi have brought together all the important players in the study of primary progressive MS. Their contributions summarise the latest information on the epidemiology, genetics, immunology, pathology, imaging, and clinical trials and therapies in primary progressive MS. This book is meant to be a useful guide to the subject and does not prove to be an authoritative account. However, it occasionally is a little too brief in its explanations and definitely lacks pictures, tables, and diagrams in the early parts of the book. This makes it a rather bland and dry account initially. When the diagrams and scanned images do appear in the latter parts of the book, many of them lack definition and it is not always easy to see the details that are being referred to.

All in all this is a good up to date summary of the latest news in primary progressive MS and in particular the imaging aspects of the disease, as would be expected from the interests of the editors. It would be a useful adjunct to other literature for those working in the field of demyelinating disease.

Omar Molik

Multiple sclerosis: a guide for the newly diagnosed, 2nd edn


This book is an invaluable guide for patients with multiple sclerosis (MS), as well as their friends and families. The fact that a second edition has become necessary is extremely encouraging for those involved with MS and highlights the recent therapeutic advances for this still devastating diagnosis. Most people who develop MS are desperate for information about their new disease and many turn to the internet for answers. Unfortunately, they are then faced with misleading or simply incorrect information, which can leave patients confused or disillusioned.

The authors present detailed information in the first two chapters covering the pathological processes causing the symptoms of MS and the diagnostic tests and procedures. It is clear the lack of a cure for MS but discusses all the options including steroids for acute attacks, disease modifying drugs, and symptomatic treatments. The chapter focuses on the psychological impact of the disease ranging from epidemiology and genetics to pathology and treatments. There is a whole chapter on the importance of early diagnosis and gives information about current diagnostic tests and procedures. The book is an invaluable guide for patients with MS and their families. It is recommended for all those working in the field of demyelinating disease.
Disordered mind and brain: the neural basis of mental symptoms


The premise of this book is that the key to understanding the neural basis of the major mental disorders is an understanding of the origin of five symptom clusters or dimensions common to these disorders. These are reality distortion (hallucinations and delusions); disorganisation (of thought and behaviour); psychomotor poverty and excitation; depression and elation; and anxiety. Thus, there are five chapters each devoted to a description of a specific dimension and an exposition of how it is correlated with cognitive abnormalities derived from the dysfunction of specific neural processes.

These central chapters are preceded by five chapters describing the neuroscience of brain systems thought to be involved in generating the various symptom clusters. These are brief and the literature reviews are in no way comprehensive. Nevertheless, they serve the purpose of informing the reader of the basic neuroanatomical and neurophysiological concepts that underpin Professor Liddle’s approach to understanding mental illness.

The final four chapters summarise the current evidence regarding the neurobiology of schizophrenia, bipolar affective disorder, obsessive compulsive disorder, and psychopathy. Each ends with a synthesis that integrates this with the previous account of how the symptom clusters arise.

The explanatory power of Professor Liddle’s thesis concerning the neural basis of mental symptoms is stronger for some symptom dimensions, such as reality distortion, than others, such as distortion. But it is the general unifying approach that is the major strength of this book—the detail will certainly be honed over the next decade. Another strength is that this is a self contained book! It assumes no neuroscientific or medical knowledge other than the most basic. There are many excellent colour illustrations. Therefore, this book can be highly recommended to anybody interested in the disordered mind and brain.

Eileen Joyce

CORRECTIONS


Due to the style used in house for listing authors affiliations in the Letters section of the journal, the author’s names have been incorrectly listed. The correct order should read as follows:


This also applies to:


The correct order of the authors is: Lünenmann JD, Schwarzenberger B, Kassim N, Zschenderlein R, Zipp F.

Aarsland D et al. Donepezil for cognitive impairment in Parkinson’s disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 2002;72:708–12. An error occurred in the production process in which the codes of the two lines were erroneously interchanged. The correct figure appears below:

Figure 2 Change in mini mental state examination (MMSE) score from baseline over the two treatment sequences. Values are mean (SE).
CORRESPONDENCE

Measuring carotid stenosis

Comparing a new test with a standard involves measuring disagreement. In the case of measuring carotid artery stenosis, some of the disagreement between different tests is because of inherent differences in how the stenosis is demonstrated (test characteristics). This is what we are most interested in when assessing a new technology. However, some of the disagreement simply reflects variability in how we physically make the measurement with the standard technique. Choosing the point of maximum stenosis, choosing the point in the common carotid artery for use as a denominator, measuring from an eyepiece, or measuring from calipers all introduce variation when measuring carotid stenosis. The resulting observer variability in reporting contributes to disagreement between methods but to some extent is independent of the method used to generate the angiogram in the first place.

In the medical literature, disagreement between methods is often attributed entirely to test characteristics, with little appreciation of the role of observer variability in reporting. When one method is compared with another at the same films, it is not readily apparent how much of the disagreement is caused by the method used and how much by the process of measurement, unless observer variability data are also presented. In the recent paper from Patel et al, interobserver variability data are presented but their significance in relation to overall disagreement does not appear to have been appreciated.

Using the data from Patel et al (tables 2 and 4) for symptomatic carotid arteries, it is noted that when 34 carotid digital subtraction angiograms (DSA) are measured by one radiologist, there was disagreement in seven cases out of 34 carotid digital subtraction angiograms (DSA) are measured by one radiologist. This is not apparent how much of the disagreement is caused by the method used and how much by the process of measurement, unless observer variability data are also presented. In the recent paper from Patel et al, interobserver variability data are presented but their significance in relation to overall disagreement does not appear to have been appreciated.

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Cerebral metastasis after primary renal cell carcinoma

The article by Roser et al.1 in which it was shown that the treatment of intracranial metastases originating from renal cell carcinoma can on occasion be successful, was most interesting.

We have followed the clinical course of a patient with a renal cell carcinoma with a low mitotic index since 1989. In this patient the course was distinctly more malignant but the disease has also been successfully treated to date. In the last 13 years, this patient has had four metastases surgically removed and a further nine treated with stereotactically guided percutaneous single dose convergent beam irradiation (stereotactic modified linear accelerator, 6–15 MV photons, 18–20 Gy prescribed to the 80% isodose). Apart from slight mnemonic deficits, the patient is in good health.

The following factors which affect the prognosis1 were all met by our patient:

- The interval between the diagnosis of renal cell carcinoma and the first detected brain metastasis exceeds 17 months (our patient, 18 months; the patient described by Roser et al.1 36 months);
- Age below 60 years at the time of initial diagnosis;
- Primary tumour of the left kidney, initial nephrectomy;
- Diameter of primary metastasis < 2 cm;
- Not more than one brain metastasis at the time of initial treatment;
- Solely intracranial metastases;
- Karnofsky > 70%;
- No systemic symptoms such as fever or weight loss at the time of diagnosis;
- Blood sedimentation rate under 50 mm/h at diagnosis of renal cell carcinoma.

Patients in whom prognostic factors predict a good outcome should be treated with intent to cure.

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References
effects of drug therapy on cognitive and affective functioning because of the reduction in seizure activity are usually far greater than the negative effects”, more information would have been welcome in an otherwise very well balanced chapter. The book would well serve those for whom it is intended, namely, neuroimmunologists, neurologists, neurologists, psychiatrists, and other professionals who deal with patients with epilepsy. The editors rightly stress the “official line” that the majority of patients with epilepsy can achieve good control, with low associated risks.

Lina Nashef

Greenfield’s neuropathology, 7th edition


What can one say. The latest (7th) edition of Greenfield’s Neuropathology has hit the bookshops, and indeed what a resounding thud it makes! The present edition is bigger than ever, again running into two volumes, but now totalling some 2330 pages and ending an equally staggering £395. It comes equipped with a handy CD version of the illustrations, a mere snip at £145.

The 7th edition has undergone considerable changes in content, since the last edition five years ago, reflecting the ever expanding increase in knowledge of diseases of the nervous system and muscle that has come from the exponential growth in neuroscience research over the past decade. Areas of cellular and molecular neurobiology, and the contributions that genetics and neuroimaging have made towards improving our understanding of the causes of disease and our clinical investigative and diagnostic skills, are more strongly featured. Hence, while greater emphasis has been placed on the basic science of disease, the classic descriptive morphology for which Greenfield is renowned is well maintained. There are new chapters on “Metabolic and neurodegenerative diseases of childhood” and “Peripheral and mitochondrial diseases”. The chapter on “Pathology of schizophrenia” has been shrewdly expanded to cover “The pathology of psychiatric disorders”. Other chapters have been retained as such, but many have been rewritten with new authors reflecting the pre-eminence of each within their particular subspecialty. There is increased reliance on colour illustrations, line diagrams and tables to illuminate the text, and these are of excellent quality throughout. As to be expected, all chapters are written authoritatively with clarity and style, comprehensively illustrated, and lavishly referenced. Judging by the content of the chapters on ageing and dementia, prion disease, and movement disorders, it is my guess that if anything is not included in each chapter, it’s probably not worth including anyway. The accompanying CD rom is user friendly, and the images are downloadable—a boon to those wishing to produce a ready made lecture or presentation of distinction. The book is a must for practicing and trainee pathologists, but is equally compelling for workers in other clinical neuroscience disciplines and basic researchers interested in the roots of the dysfunctional nervous system. Possession of the 7th edition is guaranteed lasting quality and full value, but before lashing out make sure both your arms and shelves are strong enough to accommodate its presence.

David MA Mann

Smell and taste complaints


Despite the fact that problems with tasting and smelling are common in the general population, few physicians have the knowledge and training to authoritatively deal with them. Christopher Hawke’s Smell and Taste Complaints provides a straightforward guide to the understanding and management of chemosensory disturbances, reflecting the first clinically oriented book of its kind since Ellis Douce’s The Sense of Smell and its Abnormalities (Edinburgh: Churchill Livingstone, 1974). This 180 page pocket sized book provides a cogent overview of the anatomy and physiology of the olfactory and gustatory systems, practical approaches towards their assessment, and suggestions for therapy and management. Importantly, it provides the practitioner with the names and addresses of specialised taste and smell clinics throughout the world, aiding the referral process. Although there is little new in this guide, and much of the material seems to have been derived from second hand sources, it presents the available information in a well organised and easy to read manner. Moreover, it addresses basic clinical issues rarely addressed in a single publication. Its major drawback is the lack of reference backing for many of its statements, some of which are questionable. I found, for example, some of the “facts” unfamiliar, and would have welcomed knowledge of their source. Bits of the material are dated (for example, the role of IP, receptors in olfactory function, the nature of olfactory receptor cell regeneration) and several sections of the book seem lengthy, uncrtical, and of little practical value. Thus, nearly seven pages are devoted to the topic of odour memory, a topic with inherent theoretical issues and problems that are not addressed by the author. However, the book is not intended to be a research book and, despite such shortcomings, it accomplishes its goal of educating the practitioner and providing him or her with a practical roadmap for clinical assessment and treatment. Indeed, the clinical information provided is comprehensive and well illustrated. This inexpensive book is a must for any physician who has the occasion to see patients with chemosensory disturbances or has even a casual interest in chemosensation, and should serve to elevate the level of appreciation of these senses within the medical community at large.

Richard L Doty

CORRECTIONS

The following errors occurred in the short report by Merliniti L, Carbone I, Capanni C, et al. Familial isolated hyperCKaemia associated with a new mutation in the caveolin-3 (CAV-3) gene. J Neurol Neurosurg Psychiatry 2002;73:73–7. On page 66, left column, line 9, proline should replace leucine, line 12, protein should replace enzyme, and in table 1, line 8 Del-TTF (63–65) should replace TTF (63–65).

We regret that an editing error occurred in the correspondence from Jaster JH, Dohan FC, and O’Brien TF. Demyelination in the brain as a paraneoplastic disorder: candidates include some cases of seminoma and central nervous system lymphoma. J Neurol Neurosurg Psychiatry 2002;73:332. The description of a patient expanded altered, in the first line of the fourth paragraph the text should read “... patient who had a non-neurological malignancy, seminoma, and subsequently developed a paraneoplastic syndrome...”.

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