

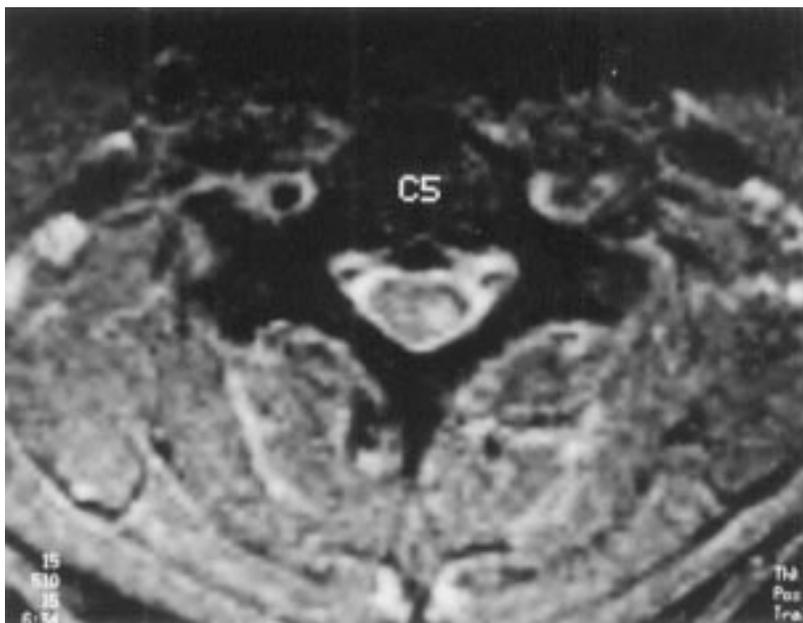
## LETTERS TO THE EDITOR

### A single focus of multiple sclerosis in the cervical spinal cord mimicking a radiculopathy

A 46 year old man was first examined in January 1996 for an impairment in the fine movements of his right hand. His history showed an optic retrobulbar neuritis, four years before, with a residual decrease of visual acuity to 6/10 and a pale disc on the left. Neurological examination disclosed only a disturbed stereognosis on his right hand. Visual evoked potentials (EPs) were very abnormal in the left, normal in the right eye. Brainstem auditory EPs and somatosensory EPs were normal. Both MRI of the brain and of the cervical spinal cord failed to show any aspect suggesting plaques. Cervical MRI showed extreme degenerative changes at the C5-C6 and C6-C7 level with a C6-C7 bulging disc. A cross section at the C5-C6 level showed a posterior osteophyte impressing the subarachnoid space but no areas of abnormal signal intensity within the spinal cord. Analysis of CSF showed a protein concentration of 310 mg/l with gammaglobulins at 21% and oligoclonal banding. Investigation of blood and CSF for infectious and immunological diseases was negative. The diagnosis at discharge was cervical discopathy and possible multiple sclerosis. Two months later the patient complained of a sharp throbbing, burning pain in the first and second finger of his left hand and on the outer side of his left arm, with an intense itching character. At examination scratch lesions drawn on the skin showed the C6 dermatome in its full extension. The bicipital reflex was reduced on the left. Sensory disturbance was limited to hyperalgesia in the C6 dermatome without a clear deficit of specific sensory modalities. Spinal MRI cross section at the C5-C6 level showed in T2 weighted images an area of abnormally high signal intensity within the cord, localised in the left posterolateral and posterior sections and extending to the central region (figure). The spondylosis was unchanged and there was no evidence of spinal or radicular compression.

A left pseudoradicular C6 syndrome, secondary to a fresh plaque of multiple sclerosis in the dorsal root entry zone and posterior horn was diagnosed. Treatment with 1000 mg methylprednisolone/day for three days led to partial improvement. Repetition of the treatment 20 days later led to remission of symptoms.

Pain in multiple sclerosis has been known since 1872, when Charcot referred to shoulder and pelvic girdle pain as symptoms of the disease.<sup>1</sup> However, its incidence is variously quoted in the literature, from "uncommon" to 82%.<sup>2</sup> Acute pain syndromes include trigeminal neuralgia, paroxysmal burning extremities, painful tonic seizures; chronic pain syndromes include dysaesthetic extremity pain, back pain, and painful leg spasms.<sup>3</sup> To our knowledge only two reports are expressly dedicated to radicular pain in multiple sclerosis. Ramirez-Lassepas *et al.*,<sup>4</sup> during a 15 year span, found 11 patients (3% of the newly diagnosed cases of multiple sclerosis in



MRI examination. The T2 weighted axial slice at the C5-C6 level shows an area of increased signal intensity in the spinal cord, mainly affecting the left posterolateral and posterior quadrants.

patients admitted to hospital) who presented with radicular pain and in whom radicular compression was ruled out by imaging techniques; eventually, multiple sclerosis was diagnosed when new neurological symptoms occurred, and was judged to be responsible for the acute radicular pain. In two cases demyelinating plaques within the spinal cord at MRI were thought to be in the appropriate location to explain the radicular (or more properly, pseudoradicular) symptoms. Uldry and Regli<sup>5</sup> reported four patients with a formerly diagnosed multiple sclerosis who complained of a radicular limb pain and in whom a relation between the location of one of the plaques shown at MRI and limb pain was postulated. In the present case the relation is unquestionable; in a patient with a possible multiple sclerosis but with previously non-contributory imaging, a single demyelinating plaque appeared within the spinal cord, in the appropriate location to explain the concomitant pain syndrome.

A further note of interest in this case concerns the physiopathology of the pain. The distribution of pain was strictly dermatomeric; however, intense itching, unusual in radicular pain syndromes, suggested a peculiar mechanism. Indeed, a plaque in the dorsal column may generate ectopic bidirectional sensory discharges with abnormal central and antidromic conduction to peripheral endings.<sup>6</sup> There is evidence that antidromic impulses cause the release of substance P at the peripheral terminals of primary afferents; substance P in turn has been shown to cause release of histamine from mast cells.<sup>7</sup> Antidromic conduction and release of histamine could explain the uncommon feature of pain in this case.

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### Production of endogenous interferon- $\alpha$ and $\beta$ in patients with multiple sclerosis

Multiple sclerosis is considered to be an autoimmune disorder affecting the CNS, and several lines of evidence have supported the role of immunological mechanisms in its pathogenesis.<sup>1,2</sup> The clinical finding that viral infections are often associated with or followed by acute multiple sclerosis relapses also suggests that an activation of the peripheral immune compartment may contribute to an acceleration of disease progression. Interferons (IFNs)—known as cytokines with antiviral, antiproliferative and immunomodulatory properties—have become part of the treatment of the disease as IFN $\beta$ -1b has been shown to alter the natural course of relapsing-remitting multiple sclerosis.<sup>3</sup> The interferon system forms an integral part of the defence system against infections. In response to viral stimulation, whole blood leucocytes of healthy people mainly produce IFN- $\alpha$  and a small proportion of IFN- $\beta$ . IFN- $\alpha$  and  $\beta$  are

structurally and functionally related and classified as type I interferons.<sup>4</sup> However, studies on the role of endogenous type I interferons in the disease process of multiple sclerosis are rare and the results have been largely inconclusive, so that the exact mechanisms by which IFN $\beta$ -1b lessens the frequency of attacks of multiple sclerosis still remain open to speculation.<sup>5</sup>

We investigated the ability of whole-blood leucocytes of 15 patients with multiple sclerosis to produce endogenous IFN- $\alpha$  and  $\beta$  in response to stimulation with Newcastle disease virus. The whole-blood assay is an effective method for analysing the production of interferons and provides an appropriate model of the in vivo situation.<sup>6</sup> Briefly, 100  $\mu$ l heparinised blood were mixed with culture medium at a ratio of 1:10 and stimulated with Newcastle disease virus in a final concentration of 0.8 haemagglutinating units/ml. Unstimulated assays served as controls. Concentrations of IFN- $\alpha$  and  $\beta$  in the supernatants of cell cultures were determined after 48 hours of stimulation by means of quantitative enzyme linked immunosorbent assay (ELISA). All patients had clinically definite multiple sclerosis of the relapsing-remitting subtype and had been in remission for at least three months. None of the patients had received immunosuppressive treatment or steroids during the three months before blood sampling and plasma concentrations of C reactive protein were normal in all patients. As a control group, we examined 20 age matched, healthy blood donors.

We found that patients with multiple sclerosis produced significantly lower amounts of IFN- $\alpha$  and  $\beta$  than the control group (figure). There was no spontaneous release of IFNs in either group. Previous studies on cytokine production in patients with multiple sclerosis have mainly focused on alterations during acute attacks and disclosed an upregulation of proinflammatory cytokines—for example, TNF- $\alpha$ —and an impaired production of immunosuppressive cytokines—for example, TGF- $\beta$ —in active disease.<sup>2,7</sup> Our findings imply a deficit in the ability to produce type I interferons in patients with stable multiple sclerosis, which may be a predisposing factor for susceptibility to disease. The finding seems to be specific to multiple sclerosis, as type I interferon responsiveness has been shown to be normal in patients with idiopathic Parkinson's disease

and in schizophrenic patients by our laboratory recently.<sup>8,9</sup> The mechanisms by which treatment with IFN $\beta$ -1b exerts its positive effects on the disease process might be explained by substitution of type-I interferon in patients with multiple sclerosis. Certainly, many different explanations may also be found.

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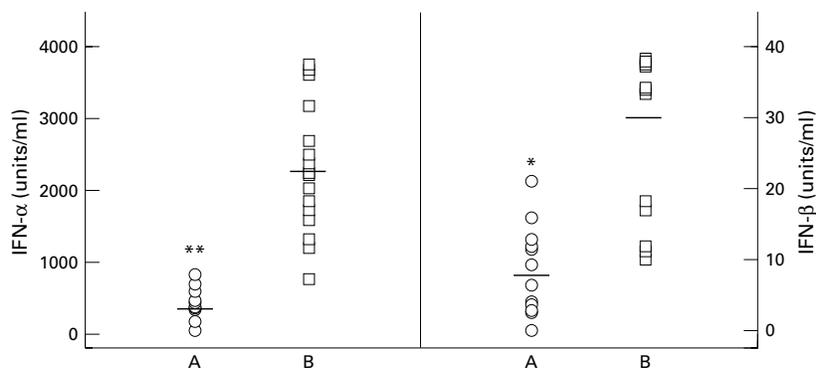
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Secretion of endogenous IFN- $\alpha$  and  $\beta$  in response to viral stimulation in patients with multiple sclerosis and controls. Each open figure represents the average of duplicate determination of IFN in the supernatants of cell cultures from (A) patients with multiple sclerosis and (B) controls. The horizontal bars represent mean IFN concentrations in each group. Values are given in Units/ml. \* $p < 0.001$ ; \*\* $p < 0.0001$  (Mann-Whitney U test). Interferon production was stimulated by Newcastle disease virus (Kumarov strain, inactivated by UV irradiation at 366 nm for 90 minutes) in a final concentration of 0.8 haemagglutinating units/ml. Cell cultures consisted of heparinised blood mixed at a ratio of 1:10 with RPMI 1640 culture medium supplemented with 100 U penicillin and 100  $\mu$ l streptomycin/ml.

## Repeated syncopes and extended paediatric hydrosyringomyelia/Chiari I malformation: relation or coincidence?

Syringomyelia is defined as a condition of tubular cavitations within the spinal cord, lined by glial tissue. In theory it differs from hydromyelia, a dilatation of the central canal of the spinal cord, which is lined with ependyma. However, in practice the distinction between the conditions is often difficult to make; thus the term hydrosyringomyelia for all intraspinal cavities of a non-tumorous nature has been proposed. Hydrosyringomyelia is often associated with anomalies of the posterior fossa, the most common of which is Chiari type I malformation. In a few cases, an association of hydrosyringomyelia with isolated syncopal events has been described. These syncopes occurred especially in adult patients with associated Chiari type I malformation and were typically, but not in all cases, preceded by an increase in intrathoracic pressure caused by coughing, sneezing, or other exertion such as a Valsalva manoeuvre.<sup>1–3</sup> Here, we report the case of a child with repeated syncopes, associated with hydrosyringomyelia/Chiari I malformation.

This 10 year old boy from Zaire was admitted for evaluation of syncope. This was the first episode; the syncope occurred while at rest at school. About one minute before the syncope, the patient experienced numbness of the left arm, occipital headache, and double vision, but no coughing, straining, or sneezing. Pallor of mucous membranes accompanying the syncope was not seen. Loss of consciousness lasted about five seconds, after which numbness of the arm as well as the double vision had disappeared. Except for the occipital headache, the patient then felt well.

Thus far psychomotoric development had been normal with excellent school performance in primary school. Family history showed no cases of epilepsy or other neurological affections.

On examination the child was alert and oriented and had fluent speech and intact comprehension. General physical examination was unremarkable with normal findings especially for the cardiovascular system. On neurological examination his mental as well as cranial nerve status was normal. Muscle tendon reflexes, muscle tone, and strength were normal. Testing of the sensory system disclosed no abnormalities; thermal, vibratory, and pinprick sensations were symmetric. Fine and gross motor proficiency were normal. No pyramidal signs, spasticity, or rigidity were evident.

During the follow up of 24 months, four further syncopes occurred with the same symptomatology as described for the first episode, but without the preceding numbness of the left arm or headache. Again there was no preceding coughing or sneezing. Three of these five syncopal events were preceded by movements and mild changes of body position such as bending to his schoolbag. Subsequent to all these syncopal events the patient's neurological status was normal.

The patient's cardiological investigation, including repeated Schellong tests, Valsalva manoeuvres, ECG, echocardiographies and 24 hour ECGs, was normal. Under clinical observation changes of body position imitating everyday movements (such as bending to the floor) were repeatedly performed, but did not lead to syncope. Several resting EEG records with photostimulation/hyperventila-



Figure 1 T1 weighted spin echo midsagittal MRI (TR: 404 ms, TE: 15 ms) showing Chiari I malformation with herniated cerebellar tonsils (arrow) and spindle shaped hydroxyringomyelia from C5 to T4 (arrow), with further smaller cavitations to T7 (arrow).

tion as well as two sleeping EEG records and 24 hour EEG records showed normal activity. Due to the unexplained nature of the repeated syncopes, a cerebral MRI was performed. This showed type I Chiari malformation with herniated cerebellar tonsils and compression of the foramen magnum. A subsequent MRI of the spine showed hydroxyringomyelia from C5 to T4, with further smaller cavitations to T7, with no evidence of cavitation above C4. No associated tumour could be found (figure). After consultation with our neurosurgeons we decided against neurosurgical intervention for the time being in view of the completely normal neurological status of the patient. A cerebral and spinal control MRI one and two years later showed no progression of the syrinx.

After diagnosing the extended hydroxyringomyelia and Chiari type I malformation, the question arose whether there is a relation between this and the repeated syncopal events. Considering the normal results of repeated cardiological investigations and EEG records (including resting, sleeping, and 24 hour EEGs) a cardiogenic or epileptogenic aetiology of the described syncopes seems unlikely.

There are various pathophysiological models of syncopes in patients with hydroxyringomyelia. According to the model of Williams, an increase of intrathoracic pressure caused, for example, by coughing, leads to a shift of CSF from the spinal to the cranial compartment. During the subsequent relaxation period a flow back to the spinal compartment due to a "sucking effect" may lead to hindbrain herniation with impaction of the cerebellar tonsils and to interference with the medullary baroreceptor reflex or dysfunction of the midbrain reticular activating system,

thus leading to syncope.<sup>4</sup> In our patient, with syncopes occurring with no evidence of preceding symptoms such as coughing to cause consecutively cerebral or spinal pressure changes, this explanation seems unlikely. The fact that autonomic disturbances occur even in subjects without foramen magnum anomaly indicates that anomalies of the posterior fossa may be not the only factor in the pathogenesis of autonomic disturbances associated with syringomyelia. In this context Noguez *et al* found some subclinical autonomic disturbances in patients with syringomyelia, especially in those with brainstem involvement. However, in some patients with no signs of such involvement, a fall of more than 2 SD in mean arterial pressure in response to standing was still found. Therefore for some patients the authors assume an underlying sympathetic defect (for example, produced by destruction of the lateral horns of grey matter), which is incomplete and not extensive enough to cause permanent orthostatic hypotension.<sup>5</sup> This would suggest that cavitation in the medulla with involvement of sympathetic structures could be another factor responsible for consecutive autonomic disturbances in patients with hydroxyringomyelia. This defect could result in temporary interruption of the spinal vegetative reflex arc with temporary postural hypotension. Considering the pattern of syringomyelic areas affected in our patient, damage to sympathetic structures neighbouring the syrinx may have led to temporary dysfunction of the sympathetic system with subsequent syncope. The assumption of a merely temporary interruption of the spinal vegetative reflex might explain the repeated normal results of clinical examination and Schellong tests, and that several changes of body position did not lead to a syncopal event in our patient. Furthermore it may be that pathophysiology of syncopes in patients with hydroxyringomyelia/Chiari I malformations is more complex—for example, due to synergistic neuropsychological influences such as increased attention while studying at school.

Despite the theoretical models outlined, the relation between isolated syncopal events in patients with hydroxyringomyelia and anomalies of the posterior fossa generally remains speculative. Furthermore the association of isolated syncopes and hydroxyringomyelia represents a very small fraction of all patients presenting with syncopes. Thus the decision to perform cerebral MRI in patients with unexplained syncopes must be considered on a case by case basis, although our case report shows that some patients may profit by performance of cerebral and cervical MRI to rule out hydroxyringomyelia and anomalies of the posterior fossa.

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### Magnetic resonance imaging of acute infarction of the anterior spinal cord

Infarction in the territory supplied by the cervical anterior spinal artery occurs infrequently, especially in young people. The anterior spinal artery supplies the ventral two thirds of the spinal cord and provides its major blood supply. In the cervical cord, the anterior spinal artery is supplied by anterior radicular arteries arising from the cervical branches of the vertebral arteries and the ascending cervical arteries.<sup>1</sup> There have been few reports of MRI in the first hours after the start of an anterior spinal artery syndrome. We describe a case of an acute anterior spinal cord syndrome appearing after two suppressed sneezes that was studied with MRI only four hours after the onset of symptoms.

A 37 year old previously healthy woman suddenly experienced severe anterior thoracic pain after two consecutive suppressed sneezes. Five minutes later, the pain irradiated to the arms and was followed by paresthesiae and weakness in both upper limbs. One hour later the weakness and paresthesiae had extended to the legs. On admission neurological examination showed tetraparesis, with a predominantly distal motor deficit in the arms (0/5 power distal and 3/5 proximal). There was an overall reduction in power to 3/5 in the legs. The deep tendon reflexes were diminished in the arms and absent in the legs. Plantar responses were indifferent. There was a loss of sensation for pain and temperature below the T2 dermatome. Light touch and vibratory and position sensitivity were preserved. The patient also developed a neurogenic bladder.

With these the clinical features, an infarction in the territory of the anterior spinal artery was suspected and an emergency MRI of the cervical spine was performed four hours after the onset of symptoms. This initial MRI, using fast spin echo sequences, failed to show any spinal cord signal abnormality (figure, A); immediately afterwards, a conventional sagittal dual echo long TR spin echo sequence showed a linear high signal intensity lesion affecting the anterior part of the cervical spinal cord between C3 and C7 (figure, B and C). No cord swelling was identified. All the findings were consistent with the clinical diagnosis of infarction of the anterior spinal artery.

Chest radiography, ECG, and routine laboratory examinations were normal. Chest CT performed to rule out aortic dissection was also normal. The patient was treated initially with intravenous methylprednisolone (1 g daily for three days).

Over the next 12 hours she developed flaccid paralysis of the lower and distal upper limbs, with continued diminished muscle power of the deltoid and biceps muscles. Deep tendon reflexes were abolished except for the biceps reflexes. The sensorial level was unchanged. An ECG failed to disclose thrombi. Somatosensory evoked potentials in the arms and legs showed no conduction blocks. Blood coagulation tests were normal.

Antinuclear and antiphospholipid antibodies analysis were negative. Serological tests for HIV, Epstein-Barr virus, lues, *Borrelia burgdorferi*, varicella zoster virus, and herpes simplex virus were negative. Four days later a follow up cervical spine MRI, including angiographic sequences of the vertebrobasilar system, was performed. Vertebral artery dissection could be ruled out, but the spinal cord showed pronounced swelling and on the long TR conventional spin echo sequences a diffuse high intensity signal covering almost the entire diameter of the cervical spine was identified that spared only its posterolateral borders (figure, D). The inferior extension of the signal abnormality reached the T1 level. Spinal angiography was not performed, as it was not considered to be clinically justified. A third MRI performed two months later showed an extensive area of atrophic myelomalacia of the cervical cord between C3 and T1.

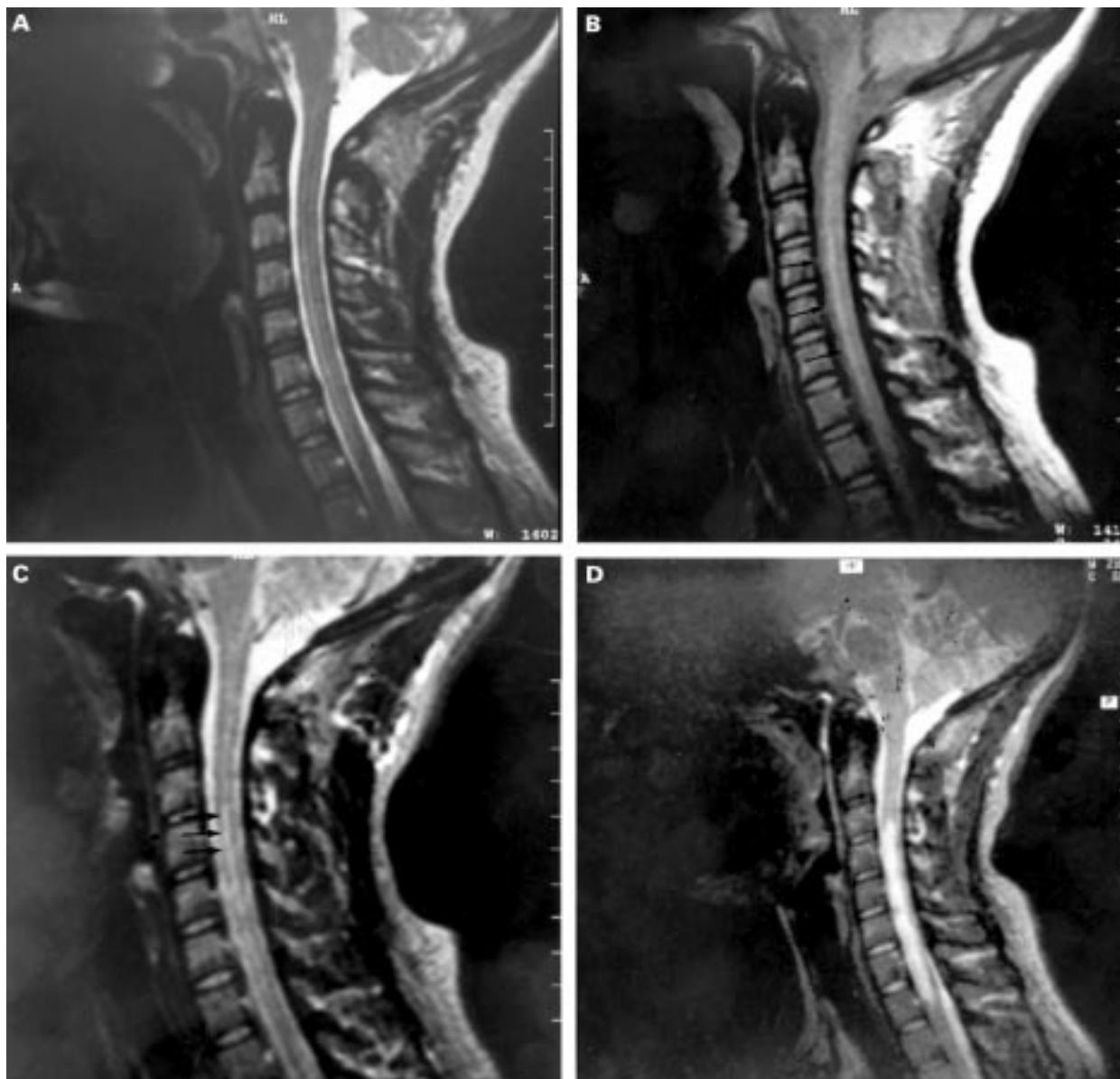
The patient made a slow clinical recovery, and four months later appreciable tetraparesis persisted.

Infarction of the cervical spine cord is rare, especially in young people. We think that the patient presented with infarction of the anterior spinal cord because of the sudden onset and rapid development of typical clinical features after two violent sneezes, with no posterior column involvement (dissociated sensory impairment), absence of cord compression, and exclusion of other known neurological diseases, all of which point to anterior spinal artery syndrome as a result of infarction in the territory supplied by this artery.

Different causes of anterior spinal cord infarction have been described in young people—namely, arteriovenous fistula, spinal surgery, cardiac surgery, arteriography, fibrocatilagenous embolism, polyarteritis nodosa, and carotid or vertebral artery dissection. However, the final cause is not identified in

half of the cases.<sup>2,3</sup> Spinal cord or brainstem infarctions have been reported in association with chiropractic manipulation<sup>1</sup> and hyperextension of the neck. Dissection of the vertebral artery was found in all these cases. In our patient this second diagnosis was ruled out with the combination of conventional MRI and MR angiography. Gutowski *et al*<sup>4</sup> reported another case of cervical posterior spinal artery infarction after sneezing. In our patient, the spinal cord infarction could have been caused by abnormal neck movements in association with the suppressed sneezes. The relation of extreme flexions of the neck (violent sneeze) with the abrupt onset of symptoms suggests vascular compression or obstruction of the vertebrobasilar system without arterial dissection.

Most cases of spinal cord infarction are associated with arteriovenous fistulas<sup>5</sup> that are not always identified on MRI, and it has been suggested that spinal angiograms should



(A) Sagittal fast spin echo T2 weighted image (5000/112) performed four hours after the clinical event showing no remarkable abnormalities. (B) Sagittal conventional spin echo proton density weighted image (2200/20) performed immediately after the sequence shown in (A) clearly shows a linear high signal intensity lesion affecting the anterior portion of the cervical spinal cord (arrows). (C) Sagittal conventional spin echo T2 weighted image (2200/80) confirms the high signal intensity lesion affecting the anterior portion of the cervical spinal cord (arrows). (D) A follow up MRI study performed four days later, using a conventional spin echo T2 weighted image (2200/80) shows a swollen and hyperintense cervical spinal cord.

be performed, at least in young patients, when no obvious cause is known. However, a more recent report shows a higher sensitivity of MRI in detecting this kind of malformation. In the presented case vertebral angiography was not considered clinically justified. The clinical contribution of angiography in those cases of anterior spinal infarction with an obvious traumatic event and in which a high quality cervical spine MRI has ruled out spinal vascular malformations and vascular dissection, may be limited and should not be considered mandatory.

MRI is a sensitive modality in the evaluation of the spinal cord for infarction. It rules out extradural compression, vascular malformations, and space occupying lesions. The differential diagnosis includes infectious or parainfectious myelitis, multiple sclerosis, and vasculitis. In inflammatory or demyelinating lesions, it is well known that T2 weighted images show lesions some time before the clinical onset, whereas with ischaemic lesions a normal or almost normal MRI is usually seen in the first few hours. The sudden onset of clinical symptoms after a rapid movement of the neck is very suggestive of infarction, but not of myelitis. In the acute phase after infarction the diameter of the spinal cord remains normal and diagnosis is based on signal abnormalities on the long TR sequences, which reflect the presence of cytotoxic oedema. However in the subacute phase, with the appearance of extensive vasogenic oedema, the high signal abnormalities are more evident and associated with cord swelling. In our case the anterior location and the temporal MRI changes, together with the sudden onset and rapid development of typical clinical symptoms, should help in differentiating spine infarction from other spinal cord lesions such as multiple sclerosis and neoplastic conditions.

We have not found any reported case of spinal cord infarction in which MRI was performed in the first four hours after the clinical event. In this acute phase only a subtle anterior linear hyperintensity was identified on the T2 weighted images. This abnormal intensity was not clearly seen on the fast spin echo sequence; however, we were able to identify it with a conventional spin echo sequence. Despite the fact that fast spin echo sequences have been accepted for routine use in the examination of spinal cord lesions, replacing conventional spin echo sequences, the second are more sensitive and should be used in selected cases, when obvious clinical lesions have not been clearly shown on the fast spin echo sequences. Fast spin echo imaging of the spine is in most ways similar to conventional spin echo imaging. However, there may be difficulties in detecting very small intramedullary lesions.<sup>6</sup>

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### Myoclonus induced by tacrine

Several adverse effects of tetrahydroaminoacridine, or tacrine, have been reported since 1986, when Summers and colleagues described that its use could lead to an improvement in cognitive defects in patients with Alzheimer's disease. The most common of them are hepatic toxicity, which makes liver function monitoring necessary, and cholinergic effects. Convulsions have also been described.<sup>1</sup> We report on a patient with moderate Alzheimer's disease who presented with non-epileptic myoclonus during treatment with tacrine.

The patient was a 68 year old woman who had been diagnosed with dementia of probable Alzheimer's type four years previously. A mini mental test examination score was 12 points. She had no other disease and was treated with clometiazole. She had no history of epilepsy or myoclonus related to dementia. Four days before admission she had started treatment with 40 mg tacrine daily and 24 hours later she progressively developed generalised uncontrolled abnormal movements, affecting all her limbs and her mouth. These abnormal movements were non-rhythmic, with a spontaneous presentation, although they could be brought on by touch and sound. They were suggestive of myoclonus and were reduced after treatment with clonazepam. Blood analyses were normal. Brain MRI showed a moderate degree of cortical and subcortical atrophy and EEG showed mild and diffuse neuronal dysfunction with an absence of spikes. Myoclonus disappeared 24 hours after withdrawal of tacrine. A few months later, tacrine was restarted to confirm the causative relation. She developed generalised myoclonus during the next 48 hours.

To our knowledge, non-epileptic myoclonus may appear in 20%-30% of patients with very advanced Alzheimer's disease, but non-epileptic myoclonus in association with tacrine in humans has not been previously reported. Tacrine is a centrally active non-competitive reversible acetylcholinesterase inhibitor and its action results in a prolongation of cholinergic activity.<sup>2</sup> Svejdova et al reported that non-epileptic myoclonus was induced in baboons (*Papio papio*) by 7-MEOTA (7-methoxytacrine, a tacrine derivative).<sup>3</sup> They speculated about a possible anticholinergic effect of 7-MEOTA by an antagonistic action on the muscarinic acetylcholine receptors. This effect has also been suggested by other authors.

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### Primary HIV-1 infection presenting with transient neurological deficit

An association between cerebrovascular disease (causing transient neurological deficit, transient ischaemic attacks, or cerebral infarction) and advanced HIV disease or AIDS is recognised.<sup>1-3</sup> There is also one report of ischaemic stroke as the first manifestation of HIV infection.<sup>4</sup> We report a patient with primary HIV-1 infection who presented with a transient neurological deficit. A previously healthy 33 year old right handed male homosexual presented as an emergency with sudden onset of right sided weakness, dysarthria, and dysphasia. He had been unwell for 10 days with fever, pharyngitis, malaise, myalgia, transient non-pruritic macular rash on the upper chest, and transient paraesthesiae affecting the hands. On admission to hospital the neurological features were improving but mild weakness of the right lower limb and expressive dysphasia were present. The neurological deficit resolved completely within 24 hours. Fever (>39°C), a petechial enanthem on the hard palate, and cervical lymphadenopathy were also noted. There were no features of endocarditis or meningeal irritation. Atypical lymphocytes were present in a blood film with normal full blood count. The erythrocyte sedimentation rate was raised at 45 mm/h; serum C reactive protein concentration was 14 mg/l (normal <10 mg/l). A chest radiograph, echocardiogram, cerebral MRI, urinalysis, blood and urine bacterial cultures, and serological tests for syphilis were negative. An examination of CSF showed a lymphocytic pleocytosis (70 lymphocytes/mm<sup>3</sup>) and increased CSF protein (1.62 g/l; normal <0.45 g/l); HIV RNA gag and pol sequences were detected in the CSF by polymerase chain reaction. Antibody studies indicated recent HIV-1 seroconversion, with rising anti-HIV IgG (enzyme linked immunosorbent assay (ELISA)) and falling anti-HIV IgM (ELISA). Serology for Epstein-Barr virus, cytomegalovirus, and toxoplasma was negative. Serum anticardiolipin antibodies were detected at a low concentration (18 GPL U/ml, normal <10 U/ml); lupus anticoagulant was not detected. Fever and leg pains persisted for three weeks. He was treated with zidovudine, lamivudine, saquinavir, and low dose aspirin, and made a complete symptomatic recovery within one month. No explanation other than HIV infection was identified to account for the neurological features, which were assumed to have an ischaemic cause. Antiviral triple therapy was continued for six months. The most common neurological manifestations of primary HIV infection are lymphocytic meningitis, reversible acute encephalitis, and peripheral mononeuritis; these have previously been found to be associated with accelerated progression of HIV disease. Focal neurological events would seem to occur

rarely during primary HIV illness but they may be underreported; we were unable to identify other reports of transient neurological deficit in this setting. In patients with advanced HIV disease, transient neurological deficit, and cerebrovascular events including cerebral infarction may be associated with non-bacterial endocarditis, CNS infections (including *Cryptococcus* and *Toxoplasma*), and CNS tumours, but they may also occur in the absence of an identifiable underlying cause.<sup>1-3</sup> In these patients the mechanism for transient neurological deficit and cerebrovascular events in HIV disease is unknown; anticardiolipin antibodies, which may predispose to cerebrovascular disorders,<sup>5</sup> were detected in 70% of patients with HIV-related transient neurological deficits in a controlled study.<sup>2</sup> In our patient, the cause of the transient neurological deficit is unknown; the possibilities include localised ischaemia caused by vascular obstruction or spasm, or a focal inflammatory lesion developing at the time of seroconversion. The preponderance of transient neurological deficit in late stage HIV disease and its occurrence during primary infection in our patient suggest a possible association with high HIV viral load. Primary HIV infection should be considered in at risk patients presenting with unexplained focal neurological symptoms.

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### The pallidoreticular pattern of brain damage on MRI in a patient with carbon monoxide poisoning

Neuropathological changes of carbon monoxide (CO) poisoning include the pallidoreticular pattern of brain damage<sup>1</sup> consisting of bilateral necrosis of the globus pallidus and substantia nigra. We here report brain MRI of a CO poisoning victim that showed bilateral lesions of the globus pallidus and substantia nigra. This is the first neuroimaging demonstration of the pallidoreticular pattern of brain damage in a patient with CO poisoning.

A 17 year old previously healthy man was found unconscious in a bathroom. He was transferred to an emergency room and diagnosed as having CO poisoning due to faulty ventilation. Hyperbaric oxygen therapy improved his consciousness from coma to being fully alert. However, he had parkinsonism. Severe akinesia was noted although there was no tremor or rigidity of the limbs. Additional hyperbaric oxygen therapy for six months did not improve his neurological deficit. Brain MRI, a year after CO exposure, disclosed bilateral pallidal lesions: the globus pallidus appeared streaked with a decreased signal intensity on T1 weighted images and an increased signal intensity on T2 weighted images (figure A). Also noted was an increased signal intensity of the substantia nigra on T2 weighted images (figure B). There was otherwise no alteration on brain MRI. A CSF examination showed a decrease in homovanillic acid concentration to 5.9 ng/ml (normal range 28.83-54.28 ng/ml) with normal values of CSF protein and sugar concentrations and normal cell counts.

Auer and Benveniste<sup>1</sup> described the pallidoreticular pattern of brain damage in necropsied cases of CO poisoning. They speculated that the iron rich regions could be affected by binding of CO to iron molecules. In our patient, bilateral pallidal lesions on MRI were consistent with necrosis because of MR signal features. A decreased concentration of homovanillic acid in the CSF<sup>2</sup> and an increased signal intensity of the substantia nigra on T2 weighted images seem to be due to neuronal loss and gliosis in the substantia nigra.

The pallidoreticular pattern of brain damage<sup>1</sup> to our knowledge has not been reported on MRI in patients with CO poisoning. We emphasise the possible involvement of the substantia nigra in some

victims of CO poisoning. In those patients, parkinsonism would be explained partly by neuronal loss in the substantia nigra in addition to the bilateral pallidal necrosis.<sup>3</sup>

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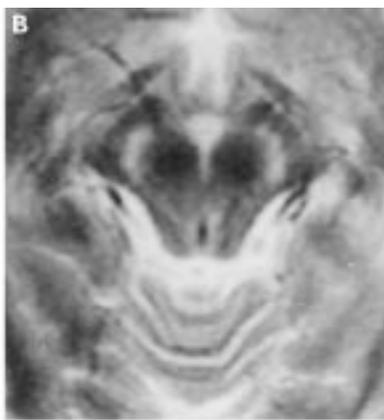
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### Information searching for multiple sclerosis

The acquisition of information is an important part of scientific work. In recent years, available information sources have multiplied exponentially, and as a result, we have come to find ourselves immersed in an "information overload". Although we feel committed to keeping up to date with the advances in neurology by using our information seeking skills, paradoxically the new, widely expanded information technologies have made it more and more difficult to gain knowledge about relevant literature sources and to retrieve information. Under the pressure of this situation, many of us have resorted to the passiveness of searching only the most commonly used databases such as Medline and Current Contents to acquire the information we need.

In the frequent practice of retrieving information needed for patient assistance, it is accepted that the use of Medline gives good results for European and North American countries. However, in searches directed towards investigation, we suspected that other, perhaps less accessible databases, could provide valuable additional information. To determine to what extent this might be true, we performed a literature search in the field of multiple sclerosis.

The analysis began by connecting to the 179 Science and Technology databases included in the host Dialog (Knight-Ridder Inc), using the commands for multiple database searching. To avoid classification problems due to variations in the internal structure of the databases, we requested that the search term "multiple sclerosis" appear in any part of the document. As the databases cover different periods and have different indexing policies, we restricted the search to the complete year of 1995 and, at the beginning, to the title field. However, we realised that using only the title would lead to poor results (for example, 613 titles in Biosis instead of the 1100 we used later), so we used the entire reference fields instead. Finally, we excluded databases devoted to medical Industries and ones that are contained in more general information sources (for exam-



(A) Axial T2 weighted MRI at the level of the basal ganglia. The globus pallidus shows an increased signal intensity. (B) Axial T2 weighted MRI of the midbrain. The substantia nigra shows an abnormally high signal intensity.

ple, the New England Journal Full Text Database). The first search yielded 24 usable databases with a total of 5350 references.

It was found that most references retrieved (4615) were concentrated within the following databases: Current Contents (1239), Biosis (1100), Embase (892), Medline (739), Pascal (406), and IAC Health and Wellness (378). The titles of the articles recovered were extracted and two main points were developed: duplication of references among the databases and the suitability of the databases for each information requirement. To determine suitability, the documents were classified according to their titles into four groups, representing the major headings in *McAlpine's multiple sclerosis handbook*<sup>1</sup>: (1) epidemiology, (2) clinical aspects (signs and symptoms, course, and prognosis, natural history, neuropsychology, diagnosis, laboratory diagnosis, and therapy), (3) pathogenesis (including genetics, immunology, and animal models), and (4) pathology. After carrying out the classification, we found that an important subset of documents did not correspond to any of the groups; these were then categorised into: (5) health promotion (including quality of life and social aspects), (6) general aspects (particularly review articles dealing with several of the former topics), and, (7) noise (documents with no apparent relation with multiple sclerosis). All the documents retrieved were classified by members of the multiple sclerosis unit (clinicians and basic researchers) after training sessions to establish the classification criteria, and the final review was performed by a neurologist expert in multiple sclerosis.

A high percentage of duplication of references was found in five of the databases studied (average overlap 22.4%). Health and Wellness showed no overlapping and, moreover, indexed most of the articles on Social Aspects. Considering only Medline, Embase, and Current Contents, average overlap was 26.6%.

The table shows the number of references retrieved and the percentage of references in relation to the total for each aspect of multiple sclerosis on each database.

For our purposes, quantity was more valuable than percentage, as the larger the number of references obtained the more the information that was gathered.

Thus according to the categories established, we found that the most suitable database for epidemiology, clinical aspects, and pathogenesis was Biosis, whereas the most appropriate for health promotion was Health and Wellness; pathology was best covered by Current Contents, and general aspects by Embase. The highest rate of noise was found in Current Contents.

These results evidence that use of Medline alone for multiple sclerosis information searches will not provide optimum returns and can have economic implications resulting from duplication of scientific efforts.

However, Medline is the best known and most available database around the world and it is unusual to find other information sources integrated within institutional information systems.

A way out of this problem is the use of On-line Search Services, a common element of library services. They can provide access to a wide range of databases and are managed by specialised information professionals.

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#### Lack of association between hepatitis G virus and multiple sclerosis

The aetiology of multiple sclerosis is still not fully understood. Infectious agents have been postulated as causes of the disease for over a century. A theory proposes that an exogenous stimulus initiates an immune response against endogenous CNS proteins. Supporting this hypothesis, some epidemiological studies strongly implicate an environmental factor in the development of multiple sclerosis.<sup>1</sup> Several common human viruses have been implicated in the pathogenesis of multiple sclerosis. However, despite data obtained from epidemiological, serological, and animal studies, no virus has been consistently isolated, or viral material uniquely identified, from patients with multiple sclerosis.<sup>2</sup> Hepatitis G virus (HGV), a novel potentially hepatotropic flavivirus, has recently been identified but little is known about the relation of this virus to chronic viral hepatitis and other chronic diseases.<sup>3,4</sup>

To investigate the relation between multiple sclerosis and HGV, we have studied the presence of HGV RNA, a marker of ongoing infection, and anti-E2 HGV antibodies, a marker of exposure and recovery of infection, in serum of patients with multiple sclerosis.<sup>5</sup>

We tested serum from 99 consecutive patients (68 females, mean age 35.2 (SD 11.9) years) with definite multiple sclerosis seen at our hospital. Fifty five patients had a relapsing-remitting, 17 a secondary progres-

#### Number of patients and controls positive for HGV RNA and anti-E2 antibodies

Group	HGV RNA (%)	anti-E2 (%)
RRMS (n=55)	0	8
SPMS (n=17)	0	2
PPMS (n=27)	2	8
Total MS (n=99)	2(2)	18(18)
Blood donors (n=1000)	19(1.9)	140(14)

RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; PPMS=primary progressive multiple sclerosis.

sive, and 27 a primary progressive disease. As controls, we included 1000 consecutive blood donors who had tested negative for HCV, HBV, and HIV markers. HGV RNA was determined by reverse transcription/polymerase chain reaction with specific primers of the 5' and NS5 regions (Boehringer Mannheim) and anti-E2 antibodies were detected from 10µl serum by µPLATE anti-HGenv (Boehringer Mannheim).

Results in patients with multiple sclerosis did not differ significantly from those in healthy blood donors (table). Two patients with multiple sclerosis had ongoing HGV infection, normal liver tests, and were negative for anti-E2 antibodies. None of the patients with HGV exposure (RNA or anti-E2 positive) had received blood transfusions and were not intravenous drug users or healthcare workers. No differences in age, sex, duration of disease, and clinical forms were found among patients with multiple sclerosis. Although the only two patients positive for HGV RNA were primary progressive patients, this finding must be interpreted with caution.

In conclusion, the prevalence of HGV infection is not higher in our population of patients with multiple sclerosis than in our controls. Our results do not therefore support any causative role for HGV in the pathogenesis of multiple sclerosis.

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Number (%) of references for each group and database

	Biosis	Embase	Pascal	Health and Wellness	Medline	Current Contents	Total
Epidemiology	52 (29.2)	31 (17.4)	19 (10.6)	4 (2.2)	36 (20.2)	36 (20.2)	178
Clinical aspects	399 (22.9)	372 (21.3)	192 (11)	116 (6.6)	321 (18.4)	341 (19.5)	1741
Pathogenesis	509 (31.1)	319 (19.5)	116 (7)	26 (1.5)	265 (16.2)	400 (24.4)	1635
Pathology	35 (23.8)	26 (17.6)	17 (11.5)	2 (1.3)	31 (2.1)	36 (24.4)	147
Health promotion	20 (11.2)	24 (13.4)	11 (6.1)	82 (46)	21 (11.7)	20 (1.2)	178
General aspects	16 (5.8)	23 (22.7)	8 (7.9)	19 (18.8)	15 (14.8)	20 (19.8)	101
Noise	92 (14.4)	126 (19.8)	49 (7.7)	104 (16.3)	74 (11.6)	190 (29.9)	635
Total	1123	921	412	353	763	1043	4615

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2 Cook SD, Rohowsky-Kochan, Bansil S, et al. Evidence for a viral etiology of multiple sclerosis. In: Cook SD, ed. *Handbook of multiple sclerosis*. New York: Marcel Dekker, 1996:97-118.

3 Linnen J, Wages J, Zhang-Keck Z, et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. *Science* 1996;271:505-8.

4 Tacke M, Kiyosawa K, Stark K, et al. Detection of antibodies to a putative hepatitis G envelope protein. *Lancet* 1997;349:318-20.

5 Schlueter V, Schmolke S, Stark K, et al. Reverse transcription-PCR detection of hepatitis G virus. *J Clin Microbiol* 1996;34:2660-4.

## BOOK REVIEWS

**A History of Neurosurgery.** Edited by SAMUEL H GREENBLATT. (Pp 623; £72.00). Illinois: The American Association of Neurological Surgeons, 1997. ISBN 1-879284-17-0.

Reviewing this book has given me considerable pleasure and as one who knew little of the historical development of neurosurgery this has been a real voyage of discovery. I cannot help but admire the remarkable achievements of our predecessors which have led to the evolution of a surgical discipline the scope and effectiveness of which could never have been contemplated even 50 years ago.

The long history of surgery of the head and brain before the late 19th century is of some interest, but it was really the major advances made in bacteriology, cerebral localisation, and anaesthesia at the end of the last century which allowed the birth of neurosurgery. The early development of the specialty relied very heavily on cross fertilisation of ideas from doctors and physiologists working in different centres in Europe and the United States. The importance and sheer excitement of the early scientific meetings is well described. The heady mix of important clinical discoveries together with a dramatic personae of eminent and innovative people could not be reproduced today.

In the early days it is amazing that any patient survived an operation on their head. Picture an operating theatre in which a neurologist is directing the surgeon to look elsewhere when the initial exposure has not uncovered the lesion. This is what Gowers did for Horsley in 1887, computerised image guidance—who needs it? Imagine controlling scalp haemorrhage without artery forceps, clips, or diathermy and, although Horsley introduced bone wax at a relatively early date, once the surgeons entered the brain there was no effective or safe means of achieving haemostasis. They relied on the use of galvanic cautery, just a hot wire loop and both brain damage and reactive swelling were frequent complications. Attempts were made to tie off bleeding vessels in the brain with heavy silk or linen suture and the result was that satisfactory haemostasis was rarely achieved and operations would be abandoned as a result of uncontrollable haemorrhage and many patients had postoperative haematomas. Control of intracranial pressure during surgery was rudimentary to say the least. Coughing and straining associated with open drop ether and an uncertain airway often led to sudden deaths and there were no reliable methods for monitoring the depth of anaes-

thesia. Many surgeons tried one or two brain cases before deciding that there was little to be gained in this field of surgery.

In this rather unpromising environment it is remarkable that Cushing announced his intention to specialise in neurosurgery in 1901 and although his name remains pre-eminent in the subject, it is perhaps William McKewen of Glasgow and Sir Victor Horsley of Queen Square who should be recognised as the fathers of modern neurosurgery. Cushing's remarkable contribution to neurological surgery was both to expand neurosurgical knowledge and techniques and at the same time to synthesise what knowledge was already available. He managed to do all this despite a very heavy clinical workload and without the benefit of modern research tools and methods. After an address by Cushing to the American College of Surgeons in 1919 the chairman of the session Dr William Mayo rose and solemnly announced "Gentlemen, we have this day witnessed the birth of a new specialty neurological surgery." However, Cushing was not admired by all and was in many ways a difficult colleague. Amongst others Dandy thought that his approach to research was flawed, in that he was inclined to have a theory and then use all of his efforts and ingenuity to prove the validity of it. Although this can be an effective approach to scientific advance it can also lead to serious errors. This book contains a very thorough account of the historical development of the specialty, much of it written by neurosurgeons who are able to appreciate the importance of the individual contributions and technical advances. The text also succeeds in giving the reader a feel for the intellectual milieu in which these developments took place. The Editor, Dr Greenblatt, initially trained as a historian, but his opening chapter was disappointing. The reader should not be discouraged by his rather ponderous and quasiscientific analysis of the historical developments of neurosurgery. Although his use of English may be off putting, especially to a British audience, his achievement in editing this splendid book should not go unrecognised. Overall this is an interesting and well written book and I am sure many neurosurgeons would wish to have their own personal copy. Among other reasons for buying it is that the illustrations are a rich source of material for slides which may enliven even the most tedious lecture.

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**Syringomyelia and the Chiari Malformations. Neurosurgical Topics Series.** Edited by JOHN A ANSON, EDWARD C BENZEL, AND ISSAM A AWAD. (Pp 202; \$95). The Illinois: American Association of Neurological Surgeons, 1997. ISBN 1-879284-42-1.

Syringomyelia is one of the many challenging conditions that neurosurgeons encounter and I was very pleased to be given this neurosurgical topic from the American Association of Neurological Surgeons to review. I was further pleased to see that the book has been dedicated to Bernard Williams whom I was privileged to know. He was kind enough to allow me to spend a day with him in his operating theatre shortly before he died. He concentrated his powerful and original intellect on syringomyelia and made an outstanding contribution to the understanding and management of this condition. He began with some well designed and conducted physiological studies on patients and then recorded his clinical data both prospectively and with complete honesty. The best chapter in this volume has been written by Bernard and one needs to read no further than this to gain a working understanding of the condition and a pragmatic approach to its treatment. However, Bernard would be the first to admit that he did not have all the answers and I enjoyed reading contributions from other eminent surgeons, many of whom have published extensively about syringomyelia. This book reinforces my opinion that authors who contribute chapters to books should have a wide personal experience of the conditions that they write about, which goes far beyond a review of the literature.

There are two particularly challenging situations which arise in the management of syringomyelia. One is patients with an associated hind brain hernia who do not improve after adequate craniocervical decompression in whom postoperative MRI shows adequate CSF at the cervicomedullary junction and no hydrocephalus. Many of the contributors (including Bernard) advocate shunting the syrinx but it seems to me no more logical to shunt the syrinx cavity in this situation than to shunt it initially. There is no rationale for the use of a shunt and the effect of shunting is unpredictable and may be associated with deterioration. Equally, patients with an idiopathic syrinx are by no means uncommon and attempts to demonstrate meningeal fibrosis are often unsuccessful. Sadly the book has not contributed to my understanding of the pathophysiology of either of these problems; nor has it helped me to treat this group of patients.

Readers familiar with these neurosurgical topics will know that there is a list of CME questions at the end. These are a very useful exercise as it is all too easy to read, and merely remember those tracts of the text which reinforce one's pre-existing prejudices.

Overall I thought that this was an excellent contribution and I am sure all surgeons who treat syringomyelia will wish to buy a copy for themselves and all departmental libraries should have one on their shelves.

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