LETTERS TO THE EDITOR

Tetraparesis after posterior fossa surgery

We are interested in reaching surgeons who have witnessed patients exhibiting any degree of tetraparesis in the sitting, semisitting, or horizontal position after posterior fossa surgery. We have been collecting such patients for nearly 15 years and are interested in evaluating further case histories, surgical and anaesthetic records, postmortem data, and radiological studies when possible. Complete patient and surgeon anonymity will be maintained. We plan on testing our hypothesis for the cause of this devastating complication by compiling case data and identifying similarities.

Please forward appropriate case information to us.

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HIV related vasculitic mononeuropathy multiplex: A role for IVIg?

Necrotising vasculitis is one of the pathological findings of mononeuropathy multiplex in patients infected with HIV. It is an infrequent complication that can occur at different stages of immunosuppression and with a prognosis correlating with the degree of immunocompetence.¹⁻⁴ We report a patient with AIDS affected by necrotising vasculitis, who was successfully treated and followed up for 19 months.

A 35 year old woman with AIDS presented in February 1995 with a two week history of progressive weakness and pain of her right hand and a left foot drop. The patient had been followed up neurologically since March 1994 for a distal sensory neuropathy, confirmed by electrophysiological studies. Her distal sensory neuropathy involved the lower limbs and was thought to be a result of HIV infection but exacerbated by zalcitabine and didanosine.

Her medical history included recurrent pneumonia, syphilis, gonorrhoea, oral candidiasis, and *Clostridium difficile* colitis. Severe headaches had been evaluated in May 1994 with a normal MRI and lumbar puncture (venereal disease research laboratory test negative). Her CD4 count had dropped significantly from 392 to 94/mm³ between February and December 1994.

In February 1995, her neurological examination showed normal cognition, language, and intact cranial nerves. Motor examination disclosed normal tone, intrinsic muscle weakness of the right hand involving muscles supplied by both median and ulnar nerve, and trace movement with attempted

dorsiflexion of the left foot. Muscle stretch reflexes were symmetrically brisk but ankle jerks were absent. Plantar responses were flexor bilaterally. Skin evaluation indicated the presence of livedo reticularis. Electrophysiological studies showed a generalised axonal sensorimotor polyneuropathy with a superimposed mononeuropathy of the right median nerve.

Her packed cell volume was 29%, white cell count 2400/mm³, normal platelet count, CD4 cell count 103/mm³, sedimentation rate 15, positive antinuclear antibody 1:320 in a speckled pattern, cANCA 1:640 with negative antiproteinase-3, pANCA, rheumatoid factor, antidouble stranded DNA, cryoglobulins, and hepatitis B screening. Electrolytes and urinalysis were within normal limits. Cerebrospinal fluid showed 11 nucleated cells/ml (89% lymphocytes), glucose 50 mg/dl, protein 36 mg/dl. Chest radiography, CT of the sinuses, and renal function tests were all normal. Cytomegalovirus antibodies were present in the serum, but a polymerase chain reaction in blood was negative.

A combined biopsy of the left superficial peroneal nerve and peroneus brevis muscle was performed. The peroneus muscle showed evidence of moderate acute and chronic degeneration. Intramural as well as perivascular mononuclear cell infiltrates and fibrinoid necrosis with thrombosis of the perimysial blood vessels were noted. The superficial peroneal nerve showed severe reduction in the number of large myelinated fibres with evidence of frank fibre degeneration on teased nerve preparation. Several epineurial blood vessels were thrombosed and recanalised. No cytomegalovirus inclusions were noted and cytomegalovirus immunostaining was negative.

After her biopsy results, 1g prednisolone was given intravenously for three days, followed by oral prednisone at 60 mg/day. The pain improved significantly after the second day of intravenous steroids without any change in her strength. Two months after initial treatment, her strength was improved; however, she had developed a cushingoid appearance and hypertension. Prednisone was slowly tapered to 20 mg/day but more symptoms developed in the right hand. In June 1995, the patient presented with pneumococcal pneumonia and pneumococcaemia. High dose steroids were restarted and 2 g/kg intravenous immunoglobulin (IVIg) monthly, was added. The patient's strength improved further, and IVIg infusions were stopped after four consecutive months, while steroids were tapered slowly.

In October 1995, she was diagnosed with cytomegalovirus retinitis in the left eye and was treated with intravenous ganciclovir. Despite this intercurrent illness, the patient's strength continued to improve, and she regained full abduction of her right fingers and left foot dorsiflexion. In May 1996, a protease inhibitor was added to her double nucleoside analogue antiretroviral regimen, and as of September 1996, the patient continues to be neurologically stable, off steroids for the past seven months.

Our patient's nerve and muscle biopsy showed evidence of vasculitis with histological features similar to polyarteritis nodosa, as previously described in HIV infection.¹⁻⁴ The mechanism(s) responsible for necrotising vasculitis is not well understood. It is possible that the presence of HIV antigens may trigger an immune reaction with activation of complement.¹ On the other hand HIV may

play a more direct part given that HIV replication has been found in the proximity of the vasa nervorum.⁵

Cytomegalovirus infection is a common opportunistic condition in HIV infected patients with low CD4 cell count, and it has been associated with mononeuropathy multiplex.⁶ We concluded that cytomegalovirus was not responsible for mononeuropathy multiplex in this patient because at the time of presentation, there were no systemic manifestations of cytomegalovirus infection and the nerve and muscle biopsies were negative for either cytomegalovirus inclusions or specific cytomegalovirus immunostaining. In addition, we were unable to isolate cytomegalovirus from blood by using a polymerase chain reaction.

The therapeutic approach to necrotising vasculitis in patients with AIDS is problematic. The few available reports suggest that patients with high CD4 cell count (>200 per mm³) have a good prognosis and respond well to steroids.^{1,4} Patients with more severe immunosuppression have, in general, a poorer prognosis.^{2,3} The prolonged use of steroids alone, or in combination with a cytotoxic drug such as cyclophosphamide, can increase the risk of opportunistic infections in severely immunocompromised patients. Furthermore, the combination of steroids and cyclophosphamide has not been reported to be beneficial in patients with AIDS and necrotising vasculitis.^{2,3} On the other hand, IVIg has been reported to be useful in HIV seropositive patients with other inflammatory conditions such as polymyositis⁷ and in a few HIV seronegative patients with systemic vasculitis,⁸ even permitting tapering of the standard treatment—that is, prednisone and cyclophosphamide. IVIg may be also valuable in severely immunosuppressed HIV infected patients for decreasing the risk of bacterial infections,⁹ therefore allowing a safer administration of immunosuppressive treatment.

The patient we describe improved and has remained stable 19 months since the onset of necrotising vasculitis, after treatment with a combination of steroids and IVIg. We can only speculate on the contribution of IVIg in the successful treatment of this one patient. We suggest that steroids remain the drug of choice in patients with AIDS and necrotising vasculitis. Nevertheless, IVIg may be a useful adjunctive therapy allowing the reduction of the dosage of steroids and thereby reducing the risk of bacterial or other opportunistic infections.

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eyebrow lifting test: a novel bedside test for narrowing of the palpebral fissure associated with peripheral facial nerve palsy

A widened palpebral fissure has been regarded as one of the hallmarks of peripheral facial nerve palsy.¹ Contrary to this textbook description, however, peripheral facial nerve palsy often causes narrowing of the palpebral fissure on the affected side.² This narrowing probably results from drooping of the upper eyelid because of weakness of the frontal muscle, but the anatomical basis has not been clear. We report here a bedside test which is very helpful in differentiating two types of palpebral narrowing—that is, one caused by weakness of the frontal muscle and the other by weakness of the levator palpebrae superioris.

Ptosis—palpebral narrowing—in the present communication was defined as drooping of the upper eyelid to cover one third or more of the cornea, according to the criteria described by Caplan.³ Its severity was classified into three grades: (1) mild ptosis if the upper eyelid covered more than one third of the cornea, (2) moderate ptosis if it

covered more than one half of the cornea, and (3) severe ptosis if the palpebral fissure was nearly closed.

The subjects were six patients with peripheral facial nerve palsy with palpebral narrowing but with no abnormality of the pupils and eye movements (five men, one woman; age range, 33 to 72 years; mean age 60.3 years) and five patients with oculomotor nerve palsy having ptosis but without facial palsy (two men, three women; range 45 to 64 years; mean age 59.5 years). In all subjects peripheral facial nerve palsy or oculomotor nerve palsy developed acutely or suddenly. The palpebral narrowing was confirmed by the patient or family by comparison with the previous state. The aetiologies of peripheral facial nerve palsy consisted of peripheral facial nerve injury at craniotomy (one patient), sarcoidosis (one patient), and Bell's palsy (four patients), and those of oculomotor nerve palsy consisted of oculomotor nerve injury due to aneurysmal surgery at the top of the basilar artery (two patients), cavernous sinus syndrome (one patient), IC-PC aneurysm (one patient), and midbrain infarction (one patient). The patient with peripheral facial nerve palsy and sarcoidosis and the patient with oculomotor nerve palsy and midbrain infarction had bilateral palsy.

On neurological examination at their acute stage all were alert and cooperative. All showed drooping of the upper eyelid. No patient showed excessive contraction of the orbicularis oculi muscles as occurs in blepharospasm. All of the peripheral facial nerve palsy group were unable to close their eye tightly. All of the oculomotor nerve palsy group had either a dilated or normal sized pupil, but no weakness of the upper face on the affected side. With the patient looking straight ahead, the following items were evaluated: (1) severity of palpebral narrowing (ptosis), (2) position of the eyebrow on the affected side, and (3) change of palpebral narrowing when the eyebrow on the affected side was lifted manually by the examiner ("eyebrow lifting test").

Of the patients with unilateral peripheral facial nerve palsy, two showed severe, two moderate, and one mild palpebral narrowing. One patient with bilateral peripheral facial nerve palsy showed severe palpebral narrow-

ing on one side and moderate narrowing on the other side. Of the patients with unilateral oculomotor nerve palsy, three showed severe and one mild palpebral narrowing. One patient with bilateral oculomotor nerve palsy showed severe narrowing on both sides.

In four patients with peripheral facial nerve palsy and unilateral palsy, the position of the eyebrow on the affected side was much lower than the non-affected side, whereas in two patients with unilateral oculomotor nerve palsy, it was much higher. In the remaining three patients with unilateral peripheral facial nerve palsy or oculomotor nerve palsy and two with bilateral palsy, there was no remarkable laterality of the position of the eyebrows. However, on closer inspection the eyebrow on the narrower side of the palpebral fissure in two patients with peripheral facial nerve palsy (one unilateral and one bilateral) was definitely lower although the degree was slight.

In all of the peripheral facial nerve palsy group palpebral narrowing disappeared when the eyebrow on the affected side was lifted slightly, whereas in all of the oculomotor nerve palsy group palpebral narrowing remained unchanged, even when the eyebrow was lifted to its maximal extent (figure). In two of the patients with unilateral or bilateral peripheral facial nerve palsy, and in two of the patients with unilateral oculomotor nerve palsy, lifting of the eyebrow on the affected side led to drooping of the contralateral eyelid, although this phenomenon was not found in the others (figure).

Elevation of the upper eyelid is served chiefly by the levator palpebrae superioris innervated by the oculomotor nerve, and accessorially by Müller's muscle via the oculosympathetic pathway and by the frontal muscle via the facial nerve.⁴ The frontal muscle participates in eyelid elevation indirectly through the attachments into the eyebrow.⁴ Therefore, the palpebral narrowing due to frontal muscle weakness occurs as a result of drooping of the eyebrow, and is essentially different from palpebral narrowing caused by weakness of the eyelid muscles.²

We applied this difference to an "eyebrow lifting test". As was described, the result of this test was clear cut. All the palpebral narrowing due to peripheral facial nerve palsy disappeared, and all the narrowing caused by oculomotor nerve palsy remained unchanged. This implied that the peripheral facial nerve palsy related narrowing was attributable to weakness of the frontal muscle but not of the levator palpebrae superioris.

In patients with drooping of the contralateral eyelid elicited by lifting of the eyebrow, their attempts to overcome palpebral narrowing may have induced an increase in innervation in both levator palpebrae superioris muscles resulting in elevation of the contralateral eyelid, because Hering's law of equal innervation to agonist muscles applies to the levator palpebrae superioris as well as to the extraocular muscles.⁵ Therefore, it is plausible that in the two patients with peripheral facial nerve palsy resolution of palpebral narrowing on one side led to a decrease in levator palpebrae superioris innervation with resultant drooping of the contralateral eyelid. It remained to be determined, however, why this phenomenon occurred in some patients with peripheral facial nerve palsy and not in others, and why it also did in the two patients with oculomotor nerve palsy without resolution of palpebral narrowing.

(A) Bilateral peripheral facial nerve palsy. Top: primary position. Narrowing of the palpebral fissure is severe on the right side, and moderate on the left side. There is no remarkable laterality of the position of the eyebrows. Bottom: during eyebrow lifting test. The narrowing of the palpebral fissure is abolished on the right side, but is worsened on the left side. (B) Left oculomotor nerve palsy. Top: primary position. The narrowing of the palpebral fissure on the left side is severe, and the position of the eyebrow is much higher on that side. Bottom: during the eyebrow lifting test. The size of the palpebral fissure remains unchanged on the left side, but is narrowed on the right side.

Palpebral narrowing associated with peripheral facial nerve palsy showed a varying degree of drooping of the eyebrow. There were patients with a severe degree of narrowing. This indicates that the frontal muscle which has been considered as an accessory muscle, occasionally plays a very important part in eyelid elevation. We suspect that this is closely related to the skin condition of the upper face. Some Japanese people, especially elderly ones, have excessively loose skin of the upper eyelid or forehead, resulting in "masked" palpebral narrowing. In such a situation, occurrence of frontal muscle weakness can produce severe palpebral narrowing. In conclusion, the "eyebrow lifting test" is simple but very helpful in differentiating between two types of palpebral narrowing due to weakness of the frontal muscle and levator palpebrae superioris.

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Generalised motor neuron disease as an unusual manifestation of *Borrelia burgdorferi* infection

Lyme borreliosis is a well known multisystem disease caused by the spirochete *Borrelia burgdorferi* and can produce a wide array of neurological abnormalities in humans. The most frequent are meningitis, cranial neuritis, and painful radiculoneuritis.¹ Other clinical manifestations include chronic encephalomyelitis, spastic paraplegia, and axonal polyneuropathy. Our report concerns what we think to be the first case of a patient with upper and lower motor neuron disease and *Borrelia burgdorferi* infection of the CNS. A causal relation is strongly supported by an evaluation of the *Borrelia burgdorferi* specific antibody index and the patient's favourable response to medical treatment.

Fifteen months before admission a 33 year old patient noticed weakness in his right hand followed by weakness of the left hand and a progressive gait disturbance. Although he had no pain or sensory disturbance and no history of a tick bite, an erythema migrans, or

Severe atrophy of hand muscles.

arthralgias, his physician tested him for *Borrelia burgdorferi* specific antibodies in the serum because he lived in an endemic region. The test disclosed high concentrations of specific IgG antibodies (1:1200, cut off <1:200). The patient was treated with doxycycline for two weeks. A control examination performed in a different laboratory still disclosed high concentrations of specific IgG antibodies (1:160, cut off 1:40). Treatment was started again with cefotaxime (2g intravenously for five days). Six months later he was admitted to our hospital because of persisting paresis and muscle atrophy.

On admission, clinical examination disclosed hyperactive deep tendon reflexes with a clonus in both ankles. The muscles of both hands and forearms showed atrophy and severe paresis (figure). His gait was clumsy and stiff, and there was mild spastic paraparesis. There was no sensory loss, and cerebellar function was normal.

Needle EMG disclosed severe active denervation in the small hand muscles bilaterally. Mild to moderate signs of axonal damage were seen in the right anterior tibial muscle and in the left masseter muscle. Motor and sensory nerve conduction velocities were normal. No conduction block could be detected. F waves were abolished. Visual and sensory evoked potentials were normal. Motor evoked potentials disclosed prolonged central conduction times to both anterior tibial muscles and to the left abductor digiti minimi muscle.

Summary of antibody tests

Examination	Normal	Initial study	Follow up*
Serum:			
<i>B burgdorferi</i> IgG antibodies	<1:16	1:64	<1:16
<i>B burgdorferi</i> IgM antibodies	<1:48	1:12	<1:12
CSF:			
Total cell count (/μl)	<5	5	3
CSF/serum albumin ratio (10 ⁻³)	<7.5	4.7	3.5
IgG-local (%)	0	75	65
IgA-local (%)	0	20	10
<i>B burgdorferi</i> IgG antibodies	<1:16	1:16	1:2
<i>B burgdorferi</i> IgM antibodies	<1:48	<1:2	<1:2
<i>B burgdorferi</i> IgG antibody index	<1.5	24.0	18.0
<i>B burgdorferi</i> IgA antibody index	<1.5	2.2	7.2
14 kDa fragment IgG antibody index	<1.5	35.6	Negative

*Five months after treatment.

Routine blood chemistry was normal. Serum *Treponema pallidum* and GM1-specific antibodies were not detected. *Borrelia* serology tests showed slightly raised concentrations of *Borrelia burgdorferi* specific IgG antibodies in serum and clearly raised concentrations in the CSF. At the time of the first lumbar puncture (after antibiotic treatment), CSF contained five white blood cells/μl and a total protein concentration of 410 mg/l. Reiber-formula analysis² indicated an intrathecal synthesis of IgG and IgA. Employing a sensitive affinity blotting technique most of the oligoclonal IgG bands in the CSF were shown to be specific for *Borrelia burgdorferi*. This finding was confirmed by western blotting using identical concentrations of IgG in the CSF and serum. A higher number of *Borrelia burgdorferi* specific antibody bands were found in the CSF than in serum. Calculation of the *Borrelia burgdorferi* specific antibody index from enzyme linked immunosorbent assay (ELISA) studies disclosed raised values for IgG and IgA. Specificity of intrathecally produced IgG antibodies for *Borrelia burgdorferi* was confirmed by employing a highly specific 14 kDa fragment of the flagellin as antigen in enzyme linked immunosorbent assay (ELISA).³ The table shows the detailed data of the antibody tests on admission and on follow up examination five months later. MRI of the cervical spinal cord and the brain disclosed no abnormalities.

The patient was treated with ceftriaxone intravenously for two weeks, followed by oral

prednisone for 10 weeks. After this treatment the patient's condition improved slowly but continuously. At the time of the last clinical control examination 18 months after hospital discharge the patient was able to work without physical impairment.

Clinical and electrophysiological findings met all the criteria for the diagnosis of motor neuron disease. Clinical signs of lower motor neuron involvement were present in both arms. Electromyographic studies disclosed axonal loss at three different levels—namely, lumbar (anterior tibial muscle), cervical (hand muscles), and supraspinal (masseter muscle). Clear signs of damage to the upper motor neuron were also present. Although the symptoms of the patient could be explained by cervical myelitis the EMG findings with evidence of axonal damage in the anterior tibial and masseter muscle as well as the lack of any sensory abnormalities argue strongly against this possibility.

In addition, signs of inflammation in the CSF were not consistent with a diagnosis of amyotrophic lateral sclerosis. We identified a *Borrelia burgdorferi* infection of the CNS as the cause of the inflammation. Evidence included a raised specific IgG and IgA antibody index, the demonstration of *Borrelia burgdorferi* specific oligoclonal IgG bands in the CSF and the predominance of individual *Borrelia burgdorferi* specific antibody bands in CSF (as indicated by western blotting). The absence of a high white cell count and protein in the CSF could be attributed to prior antibiotic treatment. Optimising dose and duration, antibiotic treatment was renewed and combined with a long term steroid therapy. Four months later a CSF examination showed a considerable decrease in specific antibody concentrations, and the patient's condition continued to improve.

In the light of the evidence, it seems safe to conclude that the patient's symptoms were due to a CNS *Borrelia burgdorferi* infection which merely mimicked amyotrophic lateral sclerosis. Several reports have been published on spirochetal diseases leading to isolated damage to the motor system. Spinal meningovascular lues has been reported to cause a clinical syndrome mimicking motor neuron disease.⁴ Fredrikson and Link published a case report of a patient with isolated upper motor neuron symptoms due to CNS borreliosis who responded favourably to antibiotic treatment.⁵ Cases of painful motor neuropathy due to *Borrelia burgdorferi* specific infection have also been reported.¹ Halperin *et al*⁶ found serological evidence of exposure to *Borrelia burgdorferi* in nine of 19 patients with motor neuron disease. However, none of them showed signs of *Borrelia burgdorferi* specific immunoreactivity in the CSF or favourable response to treatment.

It can be speculated that the spirochete *Borrelia burgdorferi* has the ability to induce an immune reaction that specifically affects motor neurons. This reaction may mimic different, non-curable diseases, such as spastic spinal paralysis, spinal muscle atrophy, and amyotrophic lateral sclerosis. Therefore, we suggest that patients diagnosed as having progressive motor neuron disease, who live in endemic areas, should be tested for *Borrelia burgdorferi* specific antibodies in serum and in CSF. The test could reliably detect a rare, but treatable disease mimicking motor neuron disease.

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Severe but transient parkinsonism after tetanus vaccination

A 38 year old metal worker with a history of hypertension and hyperthyroidism presented with fluctuating fever and sweating, palpitations, tremor of the upper parts of both legs, and diplopia. These symptoms had been present for five days and had started within hours after he had received the last of three vaccinations for tetanus (TE anatoxal berna, contents: 20 LF tetanus toxoid, 2 mg aluminium phosphate, and 0.1 mg thiomersal, Primm BV, Almere, The Netherlands). These vaccinations were given because of an injury to his right index finger one month before. There was no family history of movement disorders. Physical examination showed profuse sweating, normal consciousness, a temperature of 37.3°C, symmetric rigidity of all four limbs, and a painful tremor in the upper parts of his legs. Muscle strength, tendon reflexes, and sensation were normal.

Within a week he progressed to severe hypokinetic dysarthria, a mask-like face, and a resting tremor of both hands, and he had bradykinesia and generalised rigidity, together with a cogwheel phenomenon in the arms.

Laboratory examination showed a creatine phosphokinase activity of 2682 U/l (normal <190 U/l) and normal blood concentrations of manganese, copper, ceruloplasmin, and carbon monoxide. His CSF showed 50 lymphocytes (normal range 0–3), slightly raised total protein (0.54 g/l; normal range 0.15–0.45 g/l), normal IgG index (0.43; normal <0.66), and negative serological tests on Epstein-Barr virus, herpes zoster virus, herpes simplex virus, syphilis, *Borrelia burgdorferi*, and *Mycoplasma pneumoniae*. Brain MRI was normal. Single photon emission computed tomography (SPECT) with ¹²³I-iodobenzamide (IBZM), specifically binding to the cerebral dopamine receptor (D2), showed a decreased ganglia:cortex ratio, indicating a postsynaptic disorder. Nevertheless, biperidine, levodopa and carbidopa, and pergolide were prescribed, result-

ing in gradual but impressive clinical improvement within several weeks.

The clinical syndrome was unclear during the first few days after admission, but gradually developed into a hypokinetic rigid syndrome with resting tremor, generalised bradykinesia, and rigidity. This responded well to treatment with levodopa/carbidopa and a dopamine agonist.

Possible causes of a rapidly progressive form of parkinsonism are encephalitis, intoxication, head trauma, tumour, ischaemia, or hydrocephalus.¹ Imaging studies showed no abnormalities, thereby excluding the last three possible causes. Repeated history taking failed to disclose head trauma. The profession of the patient might suggest poisoning, but blood concentrations of manganese and copper were normal. The CSF showed mild pleiocytosis, but serological testing for various specific microorganisms did not show any recent infection. Radionuclide imaging showed a pattern similar to that seen in progressive supranuclear palsy or multiple system atrophy.²

The sequence of events strongly suggests a relation between the vaccination and the neurological syndrome, although the causal nature is difficult to prove.³ To our knowledge, there are no reports of parkinsonism after tetanus immunisation. Alves *et al* reported a 5 year old boy who developed a postencephalitic rigid akinetic syndrome 15 days after vaccination for measles with live attenuated virus. Again, cause and effect remained open for debate.^{4,5}

The tetanus vaccine used in our patient does not contain any living microorganisms. However, repeated injections with the tetanus toxoid might have caused hypersensitivity, and also an immunological cross reaction of antibodies with neuronal tissue directly after the last injection. This might also explain the pleiocytosis and raised protein and IgG content in CSF. The alternative explanation is that one of the substances in the vaccine vehicle, thiomersal or aluminiumphosphate, had a neurotoxic effect.

Although we are aware that a causal relation between the vaccine and the hypokinetic rigid syndrome is far from established, we have no better explanation. We wish to record the patient history as a reference, in case analogous patients might be seen in the future.

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Cardiogenic syncope in temporal lobe epileptic seizures

Cardiac arrhythmias may cause syncopal attacks masquerading as epilepsy. Conversely, epileptic seizures can induce tachyarrhythmias or bradyarrhythmias (and rarely, as a result, fainting). Differentiating between these two possibilities may prove difficult without concomitant ECG and EEG recording.

A 39 year old male lorry driver, without cardiac and neurological disorders and not taking medication, was admitted to a coronary care unit after a cluster of episodes of loss of consciousness preceded by epigastric warm sensation and a bitter taste in the mouth, and followed by pallor, sweating, muscle jerking, and rigidity with arrest of the pulse. The episodes occurred both in orthostatism and clinostatism. Clinical investigation, laboratory tests, clinostatic and orthostatic blood pressures, echocardiography, and ECG at rest, during exercise, and during carotid sinus massage were normal.

He experienced another attack while on continuous ECG monitoring. A nurse stated that the patient complained, while standing, of epigastric discomfort, followed by a fleeting phase of unresponsiveness and purposeless arm and mouth movements. A few seconds later he fell and showed a generalised tonic convulsion. The pulse, apparently normal during the initial phase of the episode, abruptly ceased when the patient collapsed. The ECG recording (fig 1) showed a progressive decrease of heart rate, culminating in a sinus arrest of 9.5 seconds, preceding the fall. Another four episodes of sinus arrest of 4-5 seconds, without tonic convulsions, were recorded on the next day.

A permanent demand ventricular pacemaker programmed to trigger at 40 beats per minute (bpm) was applied, but episodes of epigastric discomfort with lack of responsiveness and automatisms, not followed by syncope or convulsions, recurred on the next day and prompted his transfer to a neurological unit. A standard EEG showed focal spike and wave with delta slowing on the right centroparietal region (C4-T4). A Medilog 9000 ambulatory EEG-ECG recording captured a seizure (fig 2) beginning with right centroparietal recruiting sharp waves, followed by a progressive sinus bradycardia and culminating in a junctional escape rhythm at 47 bpm. The sinus rhythm was recaptured by a transient sinus tachycardia. Other episodes of psychomotor type occurred in subsequent days, but there were no falls or tonic convulsions. The epileptic seizures were secondary to a right anterior temporal low grade astrocytoma, and subsided after treatment with carbamazepine and removal of the mass. The pacemaker was left in place, and the patient has been free of seizures, without anticonvulsants, for three years.

Epileptic seizures often cause disturbances in cardiac rhythm, generally consisting of mild changes in heart rate such as sinus tachycardia. The possibility of life threatening cardiac arrhythmias has been suggested by the higher incidence of sudden unexpected deaths among patients with epilepsy than in the normal population.¹ Males, young adults with anatomical causes of seizure disorder, patients not receiving or receiving subtherapeutic levels of antiepileptic medication, with concomitant heart disease, and with alcohol misuse present the major risks.¹ Generalised tonic-clonic seizures, alone or in combination

Figure 1 Two lead Holter recording of a syncopal attack (three uninterrupted minutes). During nausea and epigastric discomfort (minute 11.30) the sinus rhythm, superimposed by sweating and movement artifacts, progressively slows down. The syncope (minute 11.31) coincides with a sinus arrest of 9.5 seconds, intermingled with sporadic junctional escape beats and followed by a sinus rhythm (end of minute 11.31), that progressively accelerates up to 110 bpm (minute 11.32). Muscle artifact at the end of asystole indicates the occurrence of a tonic spell. CM1 = V1, CM5 = V5.

with partial complex seizures, are usually involved, and among proposed mechanisms is an intense sympathetic discharge to the heart, possibly time locked with vagal impulses and resulting in disordered cardiac rate, rhythm, or output.¹ There are only a few proved observations of epileptic bradycardia and asystole, and only in isolated cases²⁻⁴ has the cardioinhibitory effect of a seizure been documented by simultaneous EEG and ECG.

In animals, neuromediated bradycardia has been elicited by electrical stimulation of various regions of the limbic system. In humans, repeated observations pioneered by Van Buren⁵ have shown that seizure related bradyarrhythmias accompany electrical discharges originating from the temporal lobe, strengthening the hypothesis that neural structures within or adjacent to this lobe mediate cardioinhibition. A right-left hemispheric asymmetry for heart innervation has been suggested, but in the reported cases of ictal cardiac arrest right sided, left sided, and bilateral epileptic foci can be found.

Our case resembles that described by Smaje *et al*,⁶ in which temporal lobe seizures secondary to a right hemispheric intracranial

tumour induced recurrent episodes of sinus arrest, followed by syncope and muscle jerking; in this patient as well, surgical removal of the tumour reversed the epileptic seizures and the secondary cardiac involvement. Patients 1 and 2 of Constantin *et al* are similar.⁷ In these patients, monitoring led to the false diagnosis of primary cardiac arrest and to the implantation of a permanent pacemaker.

In our patient, the presence of epigastric sensations and purposeless arm and mouth movements preceding the fall should have suggested the diagnosis of partial complex seizures, but clinical clues were disregarded in the face of a repeated documentation of sinus arrest. Actually, only simultaneous EEG and ECG recording makes it possible to recognise the concurrence and the timing of cerebral and cardiac disturbances, and this examination should be recommended in patients with episodes of loss of consciousness of an unclear nature. Finally, it is likely that falling and tonic convulsions after sinus arrest were anoxic rather than epileptic in origin, as they did not show when sinus arrest was shorter than nine seconds, nor after

Figure 2 Simultaneous 15 lead EEG and one lead ECG recording of a partial complex seizure. A paroxysmal right temporal discharge (horizontal arrow), preceded by interictal spikes and sharp waves, is followed five seconds later by progressive bradycardia (vertical arrow). Thirteen seconds afterwards a junctional escape rhythm occurs (tract between stars, enlarged in the bottom tracing) at a mean rate of 47 bpm. Recapturing by the sinus rhythm (first beat after right star) takes place 34 seconds from the onset of the EEG discharge, and culminates in a sinus tachycardia at 120 bpm, which rapidly subsides after the cessation of the EEG paroxysm. The entire seizure lasted 54 seconds.

F=frontal, C=central, P=parietal, O=occipital, T=temporal EEG; even numbers=right; odd numbers=left; calibration: major time divisions 10 s.

pacemaker implantation. Besides, in the episode shown in fig 1 the fall and tonic spell occurred at the end of the period of asystole, whereas in the episode reported in fig 2 there was no EEG generalisation of the paroxysmal activity. However, simultaneous ECG-EEG recording of a tonic seizure could not be obtained.

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Recurrent coital amnesia

Transient global amnesia (TGA) is a well defined and not uncommon clinical entity, comprising the sudden development of a dense anterograde amnesia, usually accompanied by repetitive questioning, without alteration in consciousness or other epileptic phenomena, or the development of focal neurological features. Behaviour during the episode may otherwise appear normal and recovery is complete within 24 hours, except for an amnesic gap for the duration of the attack together with a short and variable period of retrograde amnesia.¹ The cause of TGA is not known, but it seems to be strongly associated with migraine, although other causes, including transient cerebral ischaemic attacks and epilepsy, have been reported. Attacks of TGA have apparently been precipitated by various physical and emotional stresses, including sexual intercourse.¹

The wife of a 64 year old man complained that on five separate occasions between March 1977 and October 1995, her husband had exhibited stereotyped attacks of amnesia after intercourse. During these events he would repeatedly ask questions such as "What are we doing?", "What time of year is it?", and "What time of day is it?", but readily recognised his wife and subsequently other people during the amnesic period. He seemed aware that he was experiencing difficulties but there was no alteration in conscious level, and his activities during intercourse and afterwards were otherwise unremarkable. The amnesic state lasted about 30-60 minutes on each occasion and he then recovered completely, except that he had no memory for the period of intercourse and only a very hazy recollection of foreplay. He had no associated headache with these

episodes, but gave a 20 year history of migraine without aura, and he had also experienced previous episodes of coital cephalalgia, with severe occipitonal headache at climax lasting some 20 minutes. He had never experienced TGA attacks under other circumstances, and had had intercourse without developing neurological symptoms on many other occasions.

His cardiovascular and neurological examinations were normal, and brain CT and extracranial ultrasound studies were normal. His EEG showed some sharply contoured theta activity in the right frontotemporal area.

The history of recurrent TGA attacks, together with the EEG abnormalities, raises the possibility of an epileptic aetiology in this patient, but this seems unlikely. Patients with epileptic TGA nearly always develop typical complex partial seizures within a year of the first TGA attack.¹ Pure amnesic seizures are characterised by similar selective memory impairment with preservation of other cognitive abilities, but are much briefer, not accompanied by retrograde amnesia, and patients are unaware that there is anything wrong during attacks.² Also, such attacks almost invariably occur in patients who have other, more typical complex partial seizures.² TGA in this patient therefore seems likely to be a manifestation of migraine.

The fact that a person can repeatedly experience selective amnesia for sexual intercourse, but otherwise function normally during the amnesic period, raises interesting social and medicolegal considerations!

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Severe sensorimotor polyradiculoneuropathy after ingestion of ethylene glycol

Ethylene glycol is the principal constituent in most motor vehicle "antifreeze" solutions. Reports of its potentially lethal effects if ingested first appeared soon after its widespread introduction in the 1930s. The principal toxic effect of ethylene glycol is renal failure due to deposition of oxalate crystals within tubules.¹ This, together with metabolic acidosis and cardiopulmonary collapse, accounts for the high mortality. The lethal dose is estimated to be 100 ml. Although rare, neurological complications are well recognised.² Cranial nerve palsies and optic atrophy are the most often reported. The mechanism of neuronal damage is unknown. Deposition of oxalate crystals in cranial nerves has been reported at necropsy and animal studies have shown evidence for a direct toxic effect of ethylene glycol on acetylcholinesterase positive neurons.³ We describe a case in which the ingestion of ethylene glycol led to a severe sensorimotor polyradiculoneuropathy.

A 43 year old man was transferred to the regional renal unit after presenting to a local casualty department in acute renal failure. Six days before admission he had deliberately ingested 250 ml antifreeze. There was a history of hypertension, acute myocardial infarction, atrial fibrillation, and a stroke, resulting in a left hemiparesis two years previously. He was taking digoxin, warfarin, and an ACE inhibitor.

On admission the pulse was 80 beats/min and blood pressure 150/60 mm Hg with a respiratory rate of 18/min. Examination of the chest disclosed bilateral basal crackles. A longstanding mild left hemiparesis with an extensor plantar response on the left was noted. Power in the right limbs was normal and the right plantar response was flexor. All reflexes were present. Serum biochemistry showed 61 mmol/l urea and 1461 µmol/l serum creatinine, with 130 mmol/l sodium and 5.7 mmol/l potassium. Full blood count showed a mild leucocytosis but was otherwise normal. The INR was greater than 10. Arterial blood gases were pH 7.063, pCO₂ 3.63 kPa, pO₂ 15.0 kPa, and HCO₃ 12 mmol/l. As would be expected at this late stage, no ethylene glycol band could be detected on serum chromatography and oxalate crystals were not seen on urine microscopy. Initial treatment consisted of haemodialysis, intravenous 1.4% bicarbonate, and intravenous vitamin K. Warfarin and digoxin were discontinued. The patient improved, was self caring, and fully mobile.

Two days after admission the patient complained of hearing loss and unsteadiness. Audiometry confirmed bilateral sensorineural loss of 40-60 dB. Bilateral facial

weakness and bilateral horizontal gaze nystagmus were also noted. Deep tendon reflexes were present and the left hemiparesis was unchanged. On the next day the patient suddenly deteriorated due to neuromuscular respiratory failure with a tachycardia of 100 b/min and normal blood pressure. Arterial gases at this time were pH 7.19, pCO₂ 6.35 kPa, and pO₂ 7.8 kPa. The patient was intubated and ventilated with immediate resolution of arterial blood gases. Except for intubation, full consciousness was maintained throughout. Chest radiography showed minor collapse at the right base. Sputum cultures were negative.

There was a global flaccid paralysis of the limbs except for some movement of the distal flexors of the right upper limb. He was areflexic and the plantars were unreactive. There was complete internal and external ophthalmoplegia. Corneal reflexes were absent and there were bilateral seventh nerve palsies. Tongue and palatal movements were restricted and the gag reflex absent. There was pronounced respiratory weakness with vital capacity being unrecordable. Communication via a simple yes or no code of squeezes in the right hand suggested some reduction of pain and pin prick sensation in the feet and fingers bilaterally.

The concentration of protein in CSF was 2.88 g/l. Nerve conduction studies were consistent with a diffuse axonal sensorimotor polyradiculoneuropathy. Electromyography showed evidence of denervation with reduced interference patterns seen in abductor pollicis brevis, first dorsal interossei, and tibialis anterior on the right. Fibrillations and fasciculations were seen in the right anterior tibialis and extensor digitorum brevis. Visual evoked responses were absent at the occiput whereas electroretinograms were normal. Brain CT and subsequent MRI showed evidence of old right hemispheric infarction. Muscle enzymes were normal. Stool culture and serology for *Campylobacter* were negative. Serum concentrations of lead, arsenic, and thallium were undetectable. A sural nerve biopsy performed during the third month of admission showed depletion of myelinated fibres with active Wallerian and axonal degeneration. Oxalate crystals were not seen.

Treatment with intravenous 0.4 mg/kg Sandoglobulin for five days was given without discernible improvement. Prednisolone (100 mg daily) had no obvious effect. At two months there was some improvement in limb power and the ophthalmoplegia had largely resolved. The patient was extubated and was able to take an oral diet. He became independent of dialysis but was left with stable renal impairment. Persistent nausea and vomiting was successfully treated with cisapride after demonstration of delayed transit by barium follow through. Troublesome peripheral paraesthesiae responded to car-

bamazepine. At five months the patient was walking with a Zimmer frame. There was bilateral optic atrophy with no perception of light in either eye. The patient was discharged to his own home.

In summary, a 43 year old man presented with a rapid onset of cranial nerve palsies, sensorimotor polyradiculoneuropathy, and neuromuscular respiratory failure over a 72 hour period, nine days after ingestion of ethylene glycol. Although cranial nerve palsies and even areflexia and a raised CSF protein have been reported after ethylene glycol ingestion, a widespread sensorimotor polyradiculoneuropathy giving rise to severe flaccid paresis of the limbs and respiratory muscles has not been previously described. The onset of symptoms at around seven to 10 days in our case correlates well with other previously described neurological complications of ethylene glycol intoxication.⁴ The possibility of this having been a critical illness neuropathy has been considered. However, the typical features of multisystem failure, sepsis, and normal F wave latencies described in that condition⁵ were not evident here.

It is possible that some instances of respiratory collapse and subsequent failure to wean off ventilation previously described after ethylene glycol poisoning may be attributable to unrecognised polyradiculoneuropathy. We would conclude that there is a case for monitoring all patients admitted with ethylene glycol poisoning with respect to their neurological status and respiratory function, including measurement of forced vital capacity and electrophysiological studies.

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PROCEEDINGS

Proceedings of the Association of British Neurologists, University of Leicester, 3-4 April 1997

ABN medal

Peter Kynaston Thomas CBE

Professor PK Thomas, a past President of the Association of British Neurologists, has made outstanding contributions to neurology, as investigator, clinician, author, educator, and editor.

"PK", as he is universally and affectionately known, trained with JZ Young in the Anatomy Department at University College. After working at the Middlesex, the National, and Montreal General hospitals, he was appointed consultant at the Royal Free Hospital in 1962, and soon afterwards at the National and Royal National Orthopaedic Hospitals. In 1974 he became Professor of Neurology at the Royal Free Hospital School of Medicine and the Institute of Neurology. His research output has continued unchecked after the conferment of his emeritus title in 1991. His formidable publication record includes, so far, 211 original articles, 61 review articles, 100 book chapters, and 13 books. He pioneered the study of cutaneous nerve biopsy and illuminated many aspects of peripheral nerve structure and function. His research has improved our understanding and management of nerve injury and inherited, metabolic, and inflammatory neuropathies. His publications are models of scholarship, written with the meticulous care which he generously shares with authors who submit articles to the books and journals which he edits.

"PK" has already earned the respect of the international neurological community and been honoured by his country as Commander of the British Empire. Last year the Association of British Neurologists took solace from awarding one of its first medals to "PK's" greatly loved wife, Anita Harding. This year the Association is proud to award its medal to "PK" himself, in admiration of his science, his scholarship, his unflagging energy, and his unflinching fortitude.

Platform presentations

PREGNANCY AND MULTIPLE SCLEROSIS (PRIMS): A EUROPEAN MULTICENTRE STUDY, PRELIMINARY RESULTS

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The aim of the PRIMS study was to ascertain in a prospective manner the effect of pregnancy and the postpartum period on the course of multiple sclerosis by the measurement of relapses and progression of the residual disability. From 12 European countries 232 pregnancies resulted in the delivery of a live infant and after excluding 12 second pregnancies, 220 pregnancies were analysed. Relapse rates (RRs) were assessed for each quarter of the year before the pregnancy, each trimester of pregnancy, and for the six months postpartum; annualised RRs per person were calculated. The RR remained constant in the year before pregnancy but fell in the first two trimesters of pregnancy ($P < 0.05$) with a further fall in the third trimester ($P < 0.001$). There was an increase in the RR in the first three months postpartum ($P < 0.05$) in comparison with the pre-pregnancy rate. The RR for the second postpartum period was non-significantly higher ($P = 0.13$). The RR for the nine months of pregnancy was significantly reduced ($P = 0.05$) but when the pregnancy year (pregnancy and three months postpartum) is considered the RR was not significantly different from that of the pre-pregnancy year.

A LINKAGE GENOME SCREEN IN MULTIPLE SCLEROSIS

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There is now overwhelming evidence that susceptibility to multiple sclerosis involves genetic factors. In the light of this the entire human genome has been screened for evidence of linkage and several potentially linked regions have been identified. In the first stage of this screen 311 microsatellite markers were typed in 129 families. Twenty regions showing some evidence of linkage to disease were identified. In the second stage 69 markers from 16 of these regions were typed in a further 98 families. The evidence for linkage increased in four regions. The analysis was performed using the multipoint sib pair linkage program MAPMAKER/SIBS and the significance of the results was established using computer simulations. The strongest evidence for linkage was found on chromosomes 17q22-24 and 6p21 (the major histocompatibility complex). In addition, linkage disequilibrium at the TNF α marker from the 6p21 region was also detected. On the X chromosome evidence for linkage in male-male pairs suggests a possible X linked dominant component to the disease.

This is the first genome screen to be completed in any neurological polygenic disease.

A LONGITUDINAL STUDY OF COGNITIVE, NEUROLOGICAL, AND MAGNETIC RESONANCE IMAGING CHANGES IN EARLY MULTIPLE SCLEROSIS

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Thirty six patients with recently diagnosed, clinically definite multiple sclerosis (MS) were included in a neuropsychological and MRI follow up study. The test/retest interval was two years. Patients were individually matched, on a range of demographic variables, with healthy controls who completed the psychometric battery at the same time intervals.

With the exception of verbal intelligence, the MS group was impaired on all areas of cognition assessed at baseline testing. Stepwise multiple regression analyses indicated that total lesion area (TLA) and physical disability (by self report), but not other clinical variables, were robust predictors of cognitive dysfunction.

At follow up, 10 patients had entered the secondary progressive phase of the disease and 18 had deteriorated by EDSS. Changes in disease status were mirrored by parallel changes in self reported disability but were relatively independent of increased lesion load. For the MS group as a whole, there was no evidence of significant change in cognitive ability over time. However, further analysis of the cognitive data showed changes dependent on the change in MRI lesion load. Patients in the MRI unchanged group maintained stable scores or improved slightly whereas those in the MRI changed group failed to show improvement or deteriorated slightly.

A SYSTEMATIC REVIEW OF BRAIN MRI IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

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Although there are many published studies of the use of brain MRI in the diagnosis of multiple sclerosis (MS), most report data on a very few cases, many of which were highly selected. As a consequence, there is considerable variation in the reported sensitivity of MRI. Moreover, it is unclear to what extent sensitivity is determined by factors such as field strength, the clinical presentation of the patient, and the clinical diagnostic criteria. The largest study to date of the sensitivity of brain MRI at clinical presentation is reported (509 patients with possible, probable, or definite MS in Edinburgh between 1990 and 1995). In addition, using Medline (1980-96) and reference lists, a further 80 published studies from 32 journals were identified. Of these, 36 studies failed to meet

basic criteria for inclusion, leaving 44 studies with data on 2780 patients. A total of 15 different criteria were used to categorise the MRI appearance as suggestive of MS. Data from both the Edinburgh study and the systematic review were combined, and the 95% confidence intervals (95% CIs) of the overall estimates of MRI abnormality were calculated allowing for extrabinomial variation. In patients with clinically definite MS, 95% (95% CI=92-97) of scans performed on 0.5 T or >1.0 T scanners were suggestive of MS, compared with 83% (76-90) on <0.5 T scanners. In clinically probable MS the rates were: >1.0 T, 84% (81-86); 0.5 T, 85% (75-94); <0.5 T, 62% (47-78). In possible MS the rates were: >1.0 T, 54% (45-63); 0.5 T, 62% (54-70); <0.5 T, 57% (48-65). There was no difference between the rates in patients with isolated optic neuritis and patients with isolated brainstem or spinal cord syndromes. In conclusion, the prevalence of MRI changes suggestive of MS is dependent on field strength, but is unrelated to the site of the lesion in patients with isolated syndromes.

CROSS SECTIONAL RESULTS OF A CLINICAL AND MRI STUDY OF PATIENTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Patients with primary progressive multiple sclerosis (MS) constitute less than 10% of the MS population. They have a different clinical course and pathological and MRI findings than secondary progressive patients and because of these differences have been excluded from therapeutic trials. Before such trials can commence it is necessary to characterise the clinical, demographic, and MRI features of a representative number of patients.

As part of a large European project which is studying two hundred patients with primary progressive or transitional MS (progressive disability with a relapse at the onset or a single relapse or remission during the course of the disease) over two years, 77 patients have been studied. Of these patients (40 male and 37 female) 59 of the patients were primary progressive and 18 transitional. There were no significant differences between the two groups with regard to onset age, disease duration, and disability as measured by the Kurtzke expanded disability status scale (EDSS). Similarly on MRI, T2 weighted lesion and T1 (black hole) lesion volumes, although both low, were not significantly different between the two groups.

For all patients there was no correlation between MRI findings and EDSS (T2 lesion volume: Spearman correlation coefficient 0.09, $P=0.43$ and T1 lesion volume: 0.14, $P=0.23$). 57 of the patients presented with spinal cord disease (52 with spastic paraparesis and five with progressive hemiparesis) whereas the other 20 presented with progressive cerebral involvement (visual failure, ataxia or brainstem syndromes). Although there was no difference in duration of disease or EDSS between these two groups, the mean T2 and T1 lesion loads were significantly lower if the presentation was of cord origin compared with the other clinical presentations ($P<0.001$).

This study underlines the uniqueness of this patient group, highlighting the differences between primary progressive MS and the more extensively studied secondary progressive group. The large cohort studied gives the potential to gain further insights into the pathogenesis of progressive disability in multiple sclerosis.

IDENTIFICATION AND SIZING OF THE GAA TRINUCLEOTIDE REPEAT EXPANSION OF FRIEDREICH'S ATAXIA IN 56 PATIENTS: CLINICAL AND GENETIC CORRELATES

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Fifty six patients with a clinical diagnosis of Friedreich's ataxia (FA) were investigated for the trinucleotide (GAA) repeat expansion recently found within the gene X25 on chromosome 9. All 56 were found to be homozygous for the expansion, with all but two patients having alleles of differing sizes. The expansion size ranged from 2 to 5 kb, with normal alleles around 1.5 kb. Sizing of the single copy of the expansion in eight sets of parents disclosed pronounced instability in the transmission of the expansion, with both increases and decreases in allele size. In patients with FA there was a significant inverse correlation between the average of the two expansion sizes and age of onset of symptoms. The GAA repeat expansion was found in the homozygous state in atypical cases of FA, such as older age of onset, preservation of lower limb reflexes, and cardiac presentations. In three families the father had the onset of a spinocerebellar ataxia as an adult, and in two the possibility of partial expression of heterozygote carrier fathers has been raised. More importantly, the history of an ataxic syndrome in a parent does not exclude the diagnosis of FA in the offspring.

THE TRINUCLEOTIDE REPEAT EXPANSION ON CHROMOSOME 12 (SCA2) IN AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS

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Affected members of 59 families with various autosomal dominant late onset cerebellar ataxias (ADCAs) and 40 patients with a similar phenotype but no family history, were investigated for the trinucleotide (CAG) repeat expansion which has been found in pedigrees showing linkage to the SCA2 locus on chromosome 12. The SCA2 mutation was found in 10 of 13 families with ADCA

Type I. Five of the 10 were British: the others originated from Italy, Denmark, West Indies, and India. The SCA2 trinucleotide expansion was not found in 11 families with ADCA and maculopathy (ADCA II) or in 35 with the pure type of ADCA (ADCA III). It was also not found in the 40 patients with idiopathic ADCA. DNA analysis for the SCA2 mutation is useful for diagnosis in single patients or small families with an ataxic syndrome and can be used for presymptomatic testing.

A GENETIC STUDY OF PAROXYSMAL DYSTONIC CHOREOATHETOSIS IN A BRITISH FAMILY

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Paroxysmal dystonic choreoathetosis (PDC) is an unusual dominantly inherited disorder characterised by attacks of involuntary dystonic and choreoathetoid movements. Typical attacks start as hemidystonia and progress to become generalised affecting all limbs, trunk, and neck muscles as well as speech. Attacks last several hours and can be precipitated by stress, excitement, alcohol, or caffeine. Clear consciousness is preserved throughout and patients are normal between attacks. The gene for PDC has recently been mapped to the long arm of chromosome 2. A six generation British family with PDC is described with the results of fine genetic mapping and candidate gene linkage analysis.

Positive lod scores were obtained for six genetic markers on 2q including a lod score of 5.08 at a recombination fraction of 0.0 for the marker D2S163. Construction of haplotypes allowed definition of a disease interval of 4 centimorgans (cM) of genetic distance between flanking markers.

The findings confirm the assignment of the gene for PDC to a locus on the long arm of chromosome 2 and provide evidence for locus homogeneity in PDC. The disease interval has been narrowed to 4cM and the findings provide support for the involvement of the gene for a chloride/bicarbonate exchanger as a candidate gene for PDC.

GENETIC COUNSELLING FOR MITOCHONDRIAL DNA DEFECTS

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In the absence of an effective treatment for mitochondrial DNA (mtDNA) disease, genetic counselling is of the utmost importance. However, extreme genetic and phenotypic diversity has prevented the identification of maternal risk factors for having an affected offspring. As a consequence genetic counselling has been limited to a discussion of maternal inheritance for most mtDNA mutations, and advice about the male predominance of Leber's hereditary optic neuropathy (LHON).

264 mother/child pairs were studied involving the transmission of the more common heteroplasmic mtDNA point mutations (A3243G MELAS, A8344G MERRF, and G3460A, G11778A, and T14484C LHON) in the hope of improving the counselling to patients with mitochondrial disease.

The results show:

(1) The risk of having affected offspring is different for mothers carrying the A3243G and A8344G mutations.

(2) Higher levels of the A3243G and A8344G mutations were associated with an increased frequency of affected offspring.

(3) For LHON, providing a mother had >20% mutant mtDNA in her blood, higher levels of mutation were not associated with a greater chance of having an affected son.

It is concluded that the analysis of mutant mtDNA can be used to predict the risk that a mother will have an affected child.

PHENOTYPIC MANIFESTATIONS OF CHROMOSOME 17P11.2 DUPLICATION

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Findings on 61 patients with a chromosome 17p11.2 duplication (HMSN 1a) showed a Charcot-Marie-Tooth (CMT) phenotype in 50 and a Roussy-Lévy phenotype in eight. Of the patients with a CMT phenotype, three had associated pyramidal signs, one of whom also had cerebellar and bulbar involvement. Diaphragmatic weakness was present in three severely affected cases. One case presented in middle life with incapacitating muscle cramps associated with calf hypertrophy and only mild signs of neuropathy. Prominent sensory loss was a consistent feature in one family, resulting in acrodystrophic changes. Concurrent focal peripheral nerve lesions were seen in seven patients, both with the CMT and Roussy-Lévy phenotypes. By contrast with the findings in younger patients, in this series of older patients with more advanced disease, in nerve biopsies myelin thickness tended to be relatively reduced for axon size, indicating remyelination and/or hypomyelination, and there was regression of the onion bulbs. The possession of two copies of the PMP22 gene within the duplicated region on chromosome 17p therefore gives rise to a range of phenotypes and not solely to a CMT syndrome, and the pattern of histological change in the peripheral nerves alters with advance of the disease.

CAN THE RESULTS OF PEER REVIEW IN CLINICAL NEUROSCIENCE BE ACCOUNTED FOR BY CHANCE ALONE?

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The initial selection of scientific work for funding, and subsequent acceptance of results for presentation and publication are based, often solely, on the process of independent peer review. However, there have been few attempts to assess its validity. In particular, there is very little published data on interobserver agreement. Is agreement between independent reviewers on the merits of scientific work any greater than would be expected by chance alone? We studied agreement between reviewers in their recommendations about papers submitted for publication to two neurology journals, and in the scoring of abstracts submitted for presentation at a neurology conference. Both journals routinely sent papers to two independent reviewers whose recommendations were recorded on a structured questionnaire. Journal "A" had 179 consecutive papers reviewed over a 12 month period. Agreement between the reviewers as to whether the papers should be accepted, revised, or rejected was no greater than that expected by chance ($\kappa = 0.08$, 95% CI 0.05 to 0.21). Journal "B" obtained recommendations from two reviewers on 116 of 200 consecutive papers. Agreement on whether to accept, reject, or revise the papers was poor ($\kappa = 0.28$, 95% CI 0.12 to 0.40). For papers in which both reviewers recommended acceptance, there was little or no agreement as to

the priority (low, medium, or high) for publication (Journal "A": $\kappa = 0.12$, 95% CI 0.29 to 0.05. Journal "B": $\kappa = 0.27$, 95% CI 0.01 to 0.53). Abstracts submitted for presentation at a neurology conference were given a score of 1 (poor) to 6 (excellent) by 16 independent reviewers. An analysis of variance (ANOVA) of the scores of abstracts submitted to three consecutive conferences revealed that differences between individual abstracts accounted for only 10-20% of the total variance of the scores on each occasion.

It is concluded that agreement between independent reviewers as to the overall worth of submissions to neurology journals and meetings could be accounted for by chance alone.

INVESTIGATING INDIVIDUALS FOR ASYMPTOMATIC CAROTID STENOSIS CAN BE HARMFUL

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Trials suggesting that endarterectomy reduces stroke risk in asymptomatic carotid stenosis have led to calls for ultrasound screening. A simple model was used to determine who might benefit or be harmed by three screening strategies: carotid ultrasound followed by catheter angiography, or by magnetic resonance angiography (MRA), or ultrasound alone. Estimates from the literature were used for sensitivity and specificity of ultrasound and MRA, risks of angiography and endarterectomy, and risk reduction after surgery for severe stenosis. Overall risks and benefits of screening were calculated for different levels of prevalence of severe asymptomatic stenosis in the screened population.

In the general population (<1% prevalence) screening would lead to more strokes than it prevents. Even using the most optimistic published figures, significant benefits are not seen until prevalences of around 20% are reached. With more realistic assumptions the prevalence would have to be even higher. The public health impact of screening such high prevalence groups would be very limited, and they cannot be reliably identified at present anyway. A person presenting with a positive ultrasound test should only be considered for surgery if their risk of truly having severe asymptomatic stenosis is high, and then the safest referral route is via MRA.

VERTEBROBASILAR INSUFFICIENCY: IS IT DIAGNOSABLE BY TRANSCRANIAL DOPPLER?

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The term "vertebrobasilar insufficiency" is often used inappropriately, but a group of patients in whom recurrent hindbrain dysfunction is due to ischaemia, possibly related to local hypoperfusion, exist, and recognition can be difficult. Hypoperfusion is often on the background of exhaustion of the cerebrovascular reserve, which can be measured using the transcranial Doppler to assess the response of cerebral arteries to changes in carbon dioxide (CO_2 reactivity). This technique

was applied to the basilar artery to assess its diagnostic utility.

Eighty nine patients with hindbrain ischaemia, 28 healthy controls, 23 with labyrinthine disorders, and 28 with amaurosis fugax, underwent basilar artery CO_2 reactivity testing. Changes in blood flow velocity to hypercapnia (vasodilatory reserve) and hyperventilation (vasoconstrictory reserve) were measured.

Testing was well tolerated. There was a significant reduction in mean basilar reactivity in patients with hindbrain ischaemia compared with each separate control group ($P < 0.02$). The difference was entirely due to loss of vasodilatory reserve.

It is concluded that hypoperfusion on the background of exhausted basilar reserve may be important in hindbrain ischaemia and can be practically measured by CO_2 reactivity. This may be useful to distinguish those patients with an ischaemic basis for recurrent hindbrain dysfunction from those with symptoms of other causes.

VERTEBRAL ANGIOGRAPHY TO INVESTIGATE POSTERIOR CIRCULATION ISCHAEMIA: IS IT WORTHWHILE?

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Angiography after a posterior circulation ischaemic event is often not considered because of the perception that the findings do not alter patient management. However, percutaneous transluminal angioplasty (PTA) is now available for the treatment of vertebral stenosis and anticoagulation may be indicated for dissection and occlusion.

All summaries of patients discharged from consultant neurologists at Atkinson Morley's Hospital between 1991 and 1996 were reviewed. Fifty three patients with posterior circulation ischaemia studied by vertebral angiography were identified and all angiograms were reviewed. Vertebral angiography was significantly abnormal in 32 patients (60%). Five (9%) had vertebral dissections, nine (17%) had unilateral occlusion of one artery, one had a basilar artery aneurysm with thrombus in the wall, and one had basilar artery stenosis. Sixteen (30%) had vertebral artery stenosis. The severity of the stenoses was 50%-69% in five patients (9%) and 70% or greater in 11 patients (21%). Twelve stenoses were considered suitable for PTA (23%). Eleven patients were anticoagulated (21%). The presence of carotid atheroma did not predict significant findings in the posterior circulation.

The natural history of vertebral artery disease is unknown but the results indicate that angiography after posterior circulation ischaemia will identify a significant number of potentially treatable lesions.

DISAPPEARING CEREBRAL INFARCTS ON MRI

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Brain MRI will become increasingly important in the diagnosis and follow up of stroke patients. However, the time course of changes

that occur in maturing cerebral infarcts is not well documented. The surprising finding is reported that on T2 weighted images, the infarct "disappears" at 12 days.

Cerebral infarcts in three patients were studied on several occasions, from within 72 hours of the onset of symptoms up to three months. T2 and proton density (PD) weighted images were obtained with a 1.5T whole body system (Signa, GE) and routine clinical imaging sequence. Imaging parameters were TE=17-19 ms and 95-102 ms, TR=3500 ms. The apparent T2 and a PD ratio (infarct/contralateral) was calculated for each infarct.

In each patient, the infarct was clearly visible as an area of high signal intensity on the admission scan. On day 12, large regions of the infarct became almost invisible. After day 12, the infarct became clearly visible again. These image changes corresponded to variations in the apparent T2 of the infarct. The PD ratio of the infarct, although raised, remained fairly constant throughout.

This report shows that the visibility of an infarct varies with time. Large cerebral infarcts may be missed if the MRI is performed around 12 days.

IS A RANDOMISED, PLACEBO CONTROLLED TRIAL OF LOCAL THROMBOLYSIS IN CEREBRAL VENOUS SINUS THROMBOSIS FEASIBLE?

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Cerebral venous sinus thrombosis (CVST) is an uncommon disorder with variable outcome. Treatment remains controversial, and the results of a double blinded, placebo controlled trial of low molecular weight heparin are awaiting publication. We report two patients with deteriorating Glasgow coma score in whom local thrombolysis was delivered during transfemoral venous angiography. Both made excellent recoveries, as assessed by the Glasgow outcome scale (GOS). These two patients are contrasted with 15 patients admitted over a four year period with a similar diagnosis in whom the management has been variable. Their clinical presentation, neuroimaging, management, and GOS are reviewed. Seven patients had papilloedema at presentation, and would not have been eligible for inclusion in the aforementioned trial.

There is uncontrolled data to support the aggressive management of CVST with thrombolysis. There is, however, no randomised clinical trial data to support such an approach. The current CVST trial addresses a heterogeneous group of patients in whom, in our experience, good outcome has occurred, in most irrespective of therapeutic approach. Whether trials of thrombolysis in life threatening CVST can be conducted, what methodology should be adopted, and whether such trials should be placebo controlled is discussed. This presentation might lead to a United Kingdom wide, multicentre trial of local thrombolysis in CVST.

SERONEGATIVE MYASTHENIA GRAVIS PLASMAS TRANSIENTLY INHIBIT ACETYLCHOLINE RECEPTOR FUNCTION

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Antibodies to the muscle acetylcholine receptor (AChR) are detected by immunoprecipitation of 125I- α -bungarotoxin labelled AChR in myasthenia gravis (MG), but about 15% of patients are "seronegative" (SNMG). However, it has been previously shown that plasma fractions from SNMG patients show inhibition of the function of the AChR in a muscle cell line TE671 that expresses the fetal form of the AChR.

A subclone of TE671, TE671- ϵ , that expresses the adult human AChR rather than the fetal form has now been used, and the plasma effects confirmed. Interestingly, the inhibition found (five of seven SNMG plasmas) was greatest (>60%) within 15 minutes of application of the plasma, but partially reversed in the continued presence of the plasma. Acute transient effects (up to 40% inhibition) were also seen on miniature endplate potentials at the mouse neuromuscular junction with four of five SNMG plasmas. Control plasmas showed <10% inhibition.

These results confirm that SNMG plasmas contain a factor that can interfere with the function of adult human AChR, and that is active at the neuromuscular junction. As we suggested previously, the effect may be due to modulation of AChR function via second messengers rather than to direct binding to the AChR.

PROGNOSTIC FACTORS IN GUILLAIN-BARRÉ SYNDROME

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To determine prognostic factors in Guillain-Barré syndrome, data were analysed from 376 patients randomised in a controlled trial of plasma exchange, intravenous immunoglobulin, or both treatments. The patients were divided into five groups according to motor nerve conduction studies: demyelinating, axonal, inexcitable, normal, or equivocal. Significantly more patients whose nerves were initially inexcitable (six of 12 (50%; 95% confidence interval (95% CI) 21-79%)) were unable to walk unaided 48 weeks after disease onset, compared with the demyelinating (44 of 258 (17%; 95% CI 13-22%)), axonal (1 of 10 (10%; 95% CI 0-44%)), normal (1 of 9 (11%; 95% CI 0-48%)), and equivocal (6 of 87 (7%; 95% CI 3-14%)) groups. Median number of days until ability to walk again was longer for the inexcitable group (>336 days; 95% CI 65->336 days) than for the normal (17 days; 95% CI 8-65 days), equivocal (23 days; 95% CI 19-31 days), demyelinating (51 days; 95% CI 41-63 days), and axonal (41 days; 95% CI 21-234 days) groups. Regression analysis was used to derive an equation predicting disability grade on a seven point scale at 48 weeks after onset. Disability was worse with older age, weaker arms at onset, recent gastrointestinal infection, and smaller motor action potential amplitudes. There was no significant predictive effect from sex, absence of sensory symptoms and signs, or delay until randomisation.

TRANSVERSE MYELITIS AS THE FIRST PRESENTATION OF CONNECTIVE TISSUE DISEASE AND GOOD OUTCOME AFTER EARLY IMMUNOSUPPRESSION WITH CYCLOPHOSPHAMIDE AND AZATHIOPRINE

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Transverse myelitis is a well described but rare complication of systemic lupus erythematosus (SLE) and has occasionally been seen in association with other connective tissue diseases. It can occur as the first manifestation of SLE although it is more often the first presentation of a demyelinating disorder. Establishing the cause in patients without any preceding infective illness or relevant history remains challenging, making the early introduction of potentially therapeutic but toxic treatments difficult. However, reports of early use of high dose steroids in SLE associated transverse myelitis suggest that early intervention is beneficial although not curative. And, most recently, case reports have described a great improvement after cyclophosphamide in patients with established SLE who subsequently develop transverse myelitis.

Five female patients (ages 26-68, mean 38.8 years) presented with transverse myelitis and histories, clinical signs, laboratory tests, and MRI were suggestive of underlying connective tissue disease. Two patients, who had a poor or unsustained response to high dose methyl prednisolone, showed a dramatic improvement after pulsed cyclophosphamide at low doses without complication. A third responded quickly to azathioprine and oral prednisolone. All remain well with minimal residual deficit (follow up five months to three years). It is suggested that an underlying connective tissue disease should be sought in all female patients with transverse myelitis.

ATTEMPTED INDUCTION OF EXPERIMENTAL AUTOIMMUNE NEURITIS WITH PMP22

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Experimental autoimmune neuritis (EAN) is an accurate animal model of the commonest form of Guillain-Barré syndrome—acute inflammatory demyelinating polyradiculoneuropathy. It has previously been shown that two myelin proteins, P2 basic protein and P₀ glycoprotein are capable of inducing EAN. It was investigated whether the 22 kDa peripheral nerve myelin protein PMP22, the product of the CMT1a (Charcot-Marie-Tooth disease type 1a) gene, will induce EAN. PMP22 cDNA produced by the reverse transcriptase polymerase chain reaction was expressed in *E. coli* as a fusion protein with glutathione-S-transferase. Lewis rats were immunised with 50 μ g purified PMP22 fusion protein and controls were immunised with the same amount of glutathione-S-transferase. Immunised animals developed antibodies to PMP22 and five of 10 developed limp tails whereas controls did not. The mean (SD) distally evoked sciatic nerve CMAPs after 20 days were 4 (1.6) mV in the PMP22 group and 7.3 (2.8) mV in the control group ($P < 0.05$). There was sparse infiltration, oedema, and

Table 1

Outcome	Series		Review	
	Medical (%)	Surgical (%)	Medical (%)	Surgical (%)
Asymptomatic	33 (5)	43.8 (7)	23.1 (3)	54.1 (72)
Improved	20 (3)	37.5 (6)	61.5 (8)	22.4 (50)
Total	53 (8)	81.3 (13)	84.6 (11)	76.5 (122)

demyelination in some spinal roots from the group of animals immunised with PMP22. Therefore PMP22 is another potential autoantigen in human inflammatory demyelinating neuropathy.

CAVERNOUS ANGIOMAS AND EPILEPSY: A CASE SERIES AND LITERATURE REVIEW

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A retrospective series and literature review are presented of epilepsy associated with cavernous angioma (CA) diagnosed by histology or MRI. The series consists of 31 patients seen at the National Hospital for Neurology and Neurosurgery over the past five years and includes 15 males and 16 females with age range at seizure onset 1.5–48, mean 24 years. 48.4% (15) patients were treated medically, 51.6% (16) surgically. Follow up was similar in each group.

The literature review includes 550 cases, 39% (215) with epileptic seizures (100 males, 80 females, not specified 35; age range 0.25–64, mean 30 years). Treatment was medical in 19.5% (42), surgical in 78.1% (168), and unspecified or radiotherapy in 2.3% (5). Outcome was specified in only 13 (30.6%) of the medically treated and 133 (79.2%) of the surgically treated group. In the surgical group follow up was 0.33–228, mean 37 months; in the medical group 0.25–36, mean 8.65 months.

In both the series and literature review surgery results in a greater proportion of asymptomatic outcomes than medical treatment (table). However, this requires interpretation in the light of selection criteria for surgery and severe limitations in the literature particularly that reporting CA treated medically.

AUDIT OF LUMBAR PUNCTURE PRACTICE IN UNITED KINGDOM NEUROLOGY CENTRES

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Thirty per cent of patients develop postlumbar puncture headache (PLPH) after lumbar puncture (LP) with a 20 g spinal needle. One third of these are severe and may require admission to hospital. PLPH is attributed to reduced CSF pressure resulting from leakage of CSF through the dural puncture site.

Traditionally bed rest has been advocated to reduce the risk of PLPH. However, this practice has not been shown to be of benefit in randomised clinical trials. By contrast, randomised studies have established that smaller gauge spinal needles and alignment of bevelled needles parallel to the spine lowers the incidence of PLPH (18% with a 22 g bevelled needle). Recent evidence from the anaesthetic literature indicates that the use of

newer “blunt” tipped spinal needles reduces the incidence of PLPH even further (7% with 22 g).

In the light of this published evidence, a postal and telephone survey was undertaken to determine current practice, with regard to the use of bed rest and the type of spinal needles routinely used for LP in United Kingdom neurology centres.

Practice varied considerably. The period of advised recumbency ranged from zero to 24 hours (median two hours). Most centres used more than one gauge of needle. The commonest was 20 g (76%), then 22 g (52%) and 18 g (30%), with one centre each using 19, 23, and 25 gauge needles. No centre reported using the newer “blunt” tipped needles.

Switching to 22 g “blunt” tipped needles would significantly reduce the morbidity associated with LP. In addition, the reduced need for inpatient services could save an average of £3680 per centre per year.

MYELOPATHIES IN HIV DISEASE

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The incidence and nature of myelopathies in HIV disease and the role of macrophages and tumour necrosis factor α (TNF- α) in the pathogenesis of vacuolar myelopathy (VM) was investigated.

Fifty one HIV seropositive patients with myelopathies were seen over a period of 26 months in a population of 1875 HIV seropositives (AIDS = 442). Clinically, there were 26 vacuolar myelopathies (13 definite, 13 suspected) and 25 non-vacuolar myelopathies (seven acute, 11 acute/subacute myelodysplastic, and seven chronic myelodysplastic). The diagnosis was confirmed at postmortem in 14 cases (five definite and two suspected vacuolar myelopathies, herpes zoster myelitis, CMV myelodysplastic, lymphomatous myelodysplastic, cervical spondylitis). Survival analysis showed no difference between patients with myelopathy and AIDS controls. HIV and nutritional parameters, serum B12, and folate were not different in VM, other myelopathies, sequential HIV seropositive admissions (n=51), and neurologically asymptomatic controls (n=30).

Pathologically the changes in 20 cords with VM started in the mid-low thoracic cord and increased rostrally as the disease progressed. Activated macrophages were prominent in mild to moderate lesions. Immunocytochemistry in 15 spinal cords with VM showed TNF- α in macrophages, microglia, and endothelial cells. Levels of TNF- α in the CSF of patients with VM (n=17) were not different from HIV seropositive (n=48) and negative (n=7) normal and disease controls.

The annual incidence of myelopathies was 1.1% of the HIV seropositives. Various non-vacuolar myelopathies were as frequent as VM in HIV infection. The pathogenesis of VM may involve a combination of immune mediated myelin and oligodendrocyte injury, impairment of repair mechanisms due to depletion of S-adenosyl methionine, and HIV augmentation of macrophage activation.

DOES SEROTONIN HAVE A CNS ACTION IN MIGRAINE?

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The development of serotonin (5HT₁)-like agonists as treatments for the acute attack of migraine has led to considerable interest in their mechanism of action and, to some extent, renewed interest in the role of 5HT in the disorder. The initial synthesis of this class of compounds was predicated on the clinical finding that intravenous 5HT terminated acute attacks of migraine. In this study electrophysiological methods have been used to characterise possible CNS actions of serotonin in migraine. The superior sagittal sinus was isolated in the α -chloralose (60 mg/kg, intraperitoneally and 20 mg/kg intravenous supplement two hourly) anaesthetised cat. The sinus was stimulated electrically (100 V, 250 μ s duration, 0.3 Hz) and neurons in the dorsal C2 spinal cord were monitored by electrophysiological methods. After baseline recordings in each animal 5HT (15 μ g/kg/min) was infused for five minutes in the presence of either vehicle (group A) or the 5HT_{1B/D} antagonist GR127935 (100 μ g/kg, intravenously; group B). The baseline probability of cell firing after sagittal sinus stimulation was 0.61 (0.1) at a latency to the fastest peak of 11.1 (0.4) ms. In group A 5HT infusion alone had a small effect of increasing mean blood pressure (12 (3) mm Hg) which in itself did not alter cell firing. In group A 5HT alone had an inhibitory effect on evoked trigeminal activity which developed 15–20 minutes after commencement of the infusion. The inhibition of cell firing lasted for 20 minutes after which the activity returned to baseline. In group B the combination of 5HT and GR127935 had no effect on trigeminal cell firing although the small hypertensive effect was still present.

These data indicate that 5HT inhibits evoked trigeminal nucleus firing via a receptor at which GR127935 is an antagonist, such as 5HT_{1B/D}. It is likely that some part of the effect of 5HT in migraine relates to inhibition of the trigeminal nucleus activity although these data do not absolutely exclude non-neuronal actions.

HOW LONG IS THE INTERVAL NEEDED TO DETECT ATROPHY DUE TO ALZHEIMER'S DISEASE FROM MRI?

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The measurement of brain atrophy by positional matching (registration) and subtraction of serial MRI has been shown to distinguish Alzheimer's disease (AD) from normal aging when the atrophy is measured over a year. The utility of such assessments would be greatly increased if it was possible to identify atrophy due to AD from scans performed

over a shorter interval. Twenty four normal controls had two MR scans separated by intervals of six to 30 months (mean 15 months). Six patients with probable AD had scans with intervals of three to seven months (mean five months). Atrophy calculated from the registered scan pairs was expressed as a percentage of brain volume lost.

For the control group the mean (SD) brain loss was 0.14% (0.4%); only one control had a loss greater than 0.7%—this patient had been started on diuretics in the interval. For the AD group the mean (SD) loss was 1.4% (0.6%)—10 times the control loss despite the shorter intervals. Only one patient in the AD group had brain atrophy of less than 1% (with a gap of only three months).

These results suggest that an interval of four months may be enough to identify atrophy due to AD from registered MRI.

IDIOPATHIC ATAXIA OF LATE ONSET: GLUTEN SENSITIVITY IS PART OF THE ANSWER

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More than 85% of patients with coeliac disease (CD) have no gastrointestinal symptoms. Definition of CD based solely on small bowel morphology has been replaced by the more inclusive term “gluten sensitivity”, a state of heightened immunological responsiveness (reflected by circulating antigliadin antibodies) to ingested gluten in genetically susceptible subjects. Ataxia is the commonest neurological complication of CD. Among Harding’s exclusion criteria for diagnosis of idiopathic late onset cerebellar ataxia is the presence of chronic diarrhoea, acknowledging that CD is associated with cerebellar ataxia.

Using antigliadin antibodies we have identified 22 patients with idiopathic ataxia and gluten sensitivity (mean age (range) 59 years (20–85), 17 male, 5 female). 85% of them have HLA genotype of CD (A1, B8, DR3, DR7, DR4, DQ2, DQ8). The commonest presenting symptom was gait ataxia. Three patients had extrapyramidal signs. Neurophysiological examination in 19 patients showed coexistent neuropathy in 15 (sensorimotor axonal neuropathy in eight, motor axonal neuropathy in five, mixed demyelinating/axonal in one, mononeuropathy multiplex in one). Necropsy in one patient showed Purkinje cell loss and lymphocytic infiltration of the cerebellum and posterior columns.

Gluten sensitivity may be present in many patients with idiopathic cerebellar ataxia. This has important aetiological and therapeutic implications.

CNS TISSUE SOD₁ MUTATIONS IN MOTOR NEURON DISEASE: CORRELATIONS WITH CLINICAL AND MOLECULAR PATHOLOGICAL FEATURES

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Point mutations in the gene encoding Cu/Zn superoxide dismutase (SOD₁) underlie 20% of familial motor neuron disease (MND)

cases. It is unknown whether somatic SOD₁ mutations in CNS tissue could underlie some cases of sporadic MND. There are few published reports of the pathology of MND in cases with defined SOD₁ mutations and it is unknown whether specific mutations are associated with particular molecular pathological findings.

The aims of this study were to: (1) Determine whether somatic mutations of the SOD₁ gene are associated with sporadic MND. (2) Correlate the genetic mutations identified with clinical and molecular pathological features.

Eighty cases of MND from the Newcastle Brain Tissue Bank have been screened for SOD₁ mutations using simultaneous SSCP (single strand conformation polymorphism) and heteroduplex analysis of genomic DNA (extracted from cerebral cortex, as well as an alternative source), followed by direct sequencing of PCR products. Molecular pathology of the neuronal lesions was examined using antibodies to ubiquitin and neurofilament proteins.

Abnormalities in the SOD₁ gene were found in six of 80 cases. These comprised point mutations in exon 4 (E100G, one case; I113T, two cases). Two cases had previously undescribed deletions in the 3 untranslated region of the gene, which were not found in 200 control samples. In one case there was a point mutation in the intronic sequence preceding exon 2.

There was no evidence that somatic mutations of the SOD₁ gene are a common cause of sporadic MND. The molecular pathology associated with different SOD₁ mutations showed distinct patterns: in particular, the I113T cases showed dramatic ubiquitin positive neurofilamentous inclusion bodies within motor neurons.

A UNITED KINGDOM GENETIC STUDY OF PARKINSON’S DISEASE

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The recent finding of linkage to markers on chromosome 4q 21–23 in one multigenerational family suggests that some cases of Parkinson’s disease (PD) have a genetic aetiology. Family studies provide conflicting evidence regarding frequency of familial PD but have relied on family history and have not included physical examination of relatives.

Ninety four probands (mean age 63.0) with clinically typical idiopathic PD were recruited from 93 families. We have examined as many living first and second degree relatives as possible. Four relatives were found to be mildly affected when the family history had suggested that they would be normal. A sibling of one proband was said to be affected but was found to be normal on examination.

Twenty five of 94 probands had affected first or second degree relatives. The segregation ratio (SR) in sibs was 0.05 in all families and 0.21 in 25 familial cases. In parents the SR was 0.04 in all families and 0.16 in familial cases. The age at onset in probands was significantly less than in ancestors (mean difference 17.9 years, 95% CI 9.7 to 26.1) suggesting anticipation. There was no difference in paternal age compared with population in familial (mean difference 0.53, 95% CI –2.46 to 3.53) or sporadic cases (mean difference 0.69, 95% CI –0.87 to 2.25).

The study is continuing but it has been shown that failing to examine available relatives will miss some secondary cases. Similar SR in sibs and parents, and anticipation suggest that autosomal dominant inheritance with reduced penetrance could be responsible for a proportion of cases. The absence of paternal age effects suggests that sporadic cases are not due to new dominant mutations.

A CONTROLLED COMPARISON OF THE EFFECT OF PERGOLIDE AND BROMOCRIPTINE ON MOTOR CONTROL IN PARKINSON’S DISEASE

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Pergolide and bromocriptine are both effective dopamine agonists used in Parkinson’s disease (PD). Pergolide has theoretical advantages in motor control because of a dual action on D1 and D2 receptors, compared with bromocriptine, which acts as an agonist on D2 only. The dose equivalence of the two drugs is important in clinical practice but has not been formally evaluated.

Twenty two patients with Parkinson’s disease whose symptoms were inadequately controlled on combination therapy with levodopa and either bromocriptine (n=9) or pergolide (n=13) were recruited. After crossover, the dosage was adjusted at weekly intervals to achieve the same degree of motor disability as at trial entry. The dose was then adjusted further to optimise motor response.

The dose equivalence of pergolide and bromocriptine after crossover was 16:1 whereas after optimisation it was 27:1. Both drugs significantly improved the overall unified Parkinson’s disease rating scale (UPDRS) score (P<0.0001) especially subscores of orientation (P<0.0001), daily living activity (P<0.0002), motor examination (P<0.0001), and dyskinesia (P<0.004).

This study shows that careful dose adjustment improves apparently refractory motor disability in PD, but pergolide has no superiority over bromocriptine.

Poster presentations

RECURRENT SACRAL RADICULOMYELOPATHY CAUSED BY HERPES SIMPLEX TYPE II: A CASE REPORT

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The most common neurological causes of acute urinary retention in young adults are lumbosacral disc herniation, spinal cord compression, spinal demyelination, or myelitis. However, para or postinfectious sacral radiculopathy is well recognised and the specific association of urinary retention with genital herpes simplex virus (HSV) infection is referred to as Elsberg syndrome. Whereas many women being treated for genital herpes simplex infections experience some minor urinary symptoms, rarely a more severe necrotising myelitis may occur. Recurrent neurological problems with recurrent episodes of genital herpes can occur and the use of prophylactic acyclovir to avoid these has been suggested.

A patient is reported with lumbosacral radiculomyelopathy who presented with constipation, stiff legs, and urinary voiding difficulty and a history of recent perineal lesions. There was no definite history of recent exposure to HSVII nor history suggestive of demyelination, but initial investigation showed a pronounced CSF lymphocytosis with raised protein and IgG and weakly positive oligoclonal banding. Neither CSF culture, electron microscopic nor PCR studies yielded evidence of viral infection. No evidence of demyelinating or connective tissue disease was found on further laboratory or radiological investigation. Acyclovir was given and sphincter control and walking returned to normal within five days. The diagnosis of postherpetic radiculomyelopathy was supported by further assay of the original CSF and of serial serum samples which showed raised HSV II IgM. This diagnosis was only confirmed later when a recurrence of sacral numbness was accompanied by the reappearance of genital lesions: herpes simplex type II virus particles were seen in culture of lesion material after six days.

A CASE OF GENETICALLY CONFIRMED FRIEDREICH'S ATAXIA PRESENTING WITH CHOREA

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Friedreich's ataxia (FA) is an autosomal recessive disorder characterised by progressive limb and gait ataxia. Recently, a trinucleotide repeat expansion in intron 1 of the X25 gene on chromosome 9 has been shown to be the genetic defect in FA. Direct mutation analysis is now possible allowing delineation of the range of phenotypes associated with this genotype.

This 21 year old man was previously well other than surgery for thoracic scoliosis at the age of 14. He presented with a two year history of involuntary movements of all four limbs, an inability to sit still, and difficulty running. There was no family history. Examination showed generalised chorea. There were no cerebellar signs. He was areflexic with no other sensory abnormalities. Plantar responses were flexor. His gait was abnormal because of choreiform intrusion and was not broad based. Neurophysiology showed a mild axonal neuropathy. Genetic analysis confirmed that he was homozygous for the FA intron I expansion.

Chorea is a rare manifestation of FA which has previously been controversial. This is the first report of chorea in a patient confirmed to have the FA genetic abnormality.

It is suggested that molecular genetic testing for the FA expansion should be considered in cases of chorea of unknown cause. (A video of this case was presented.)

T CELL RESPONSES TO THE ϵ -SUBUNIT OF THE ACETYLCHOLINE RECEPTOR (AChR) IN MYASTHENIA GRAVIS

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The generation of pathogenic anti-AChR antibodies in myasthenia gravis (MG) is thought to be a T cell dependent process. Such T cells recognise a small fragment (epitope) of the protein presented by an HLA class II molecule. The AChR is composed of the subunits, $\alpha_1\beta\gamma\delta$ in foetal and denervated muscles; in adult endplates ϵ replaces the γ -subunit. Identification and characterisation of autoreactive T cells in MG is vital if specific immunotherapy is to be developed. Despite intensive efforts by several groups very few clones have been isolated, and these are specific for natural AChR a subunit epitopes. Recently three CD3+CD4+ T cell clones recognising an epitope on the human recombinant ϵ -subunit have been isolated; two from patients with young onset MG and one from a patient with penicillamine induced myasthenia. Peripheral blood lymphocytes responding to human recombinant ϵ -polypeptide were expanded with the cytokine interleukin-2, and then cloned by limiting dilution. In each case the epitope is mapped to an extracellular domain, ϵ residues 190-229, but the clones will also respond to whole AChR delivered to antigen presenting cells by adsorption on to immunomagnetic beads. These findings implicate for the first time the ϵ -subunit as a potentially important autoantigen in MG.

RELAPSING POLYNEUROPATHY AND BRAINSTEM ENCEPHALITIS: A CLINICAL AND PATHOLOGICAL CASE REPORT

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Coexistent brainstem encephalitis and peripheral neuropathy have previously been described. This is the first pathological report of such a case.

A 75 year old man is reported who had a subacute onset of bilateral ophthalmoplegia, facial palsies, bulbar palsy, limb ataxia, extensor plantar responses and an areflexic tetraparesis. Brain MRI showed enhancing abnormalities intrinsic to the brainstem along the floor of the fourth ventricle. A CSF lymphocytosis was present. Nerve conduction disclosed a demyelinating polyneuropathy. The patient initially responded to cyclophosphamide but over the course of four years had three further relapses each of which responded to intravenous immunoglobulin. He died four years after his initial presentation during a relapse. The postmortem examination found severe active encephalitis involving tectal and tegmental regions of the midbrain, pons, and medulla. There was also evidence of a demyelinating neuropathy.

This patient showed evidence of both a brainstem encephalitis and a polyneuropathy which were relapsing and responsive to immunosuppression.

5-HT_{2C} RECEPTOR STIMULATION IN THE TREATMENT OF LEVODOPA INDUCED DYSKINESIAS

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Dyskinesias are among the most debilitating side effects encountered after long term levodopa treatment of Parkinson's disease (PD).

The neural mechanisms underlying PD involve overactivity of the output regions of the basal ganglia—that is, substantia nigra pars reticulata (SNR) and medial segment of the globus pallidus (GPM). By contrast, levodopa induced dyskinesia is characterised by underactivity of these regions. 5-HT_{2C} receptors are concentrated in the SNR and GPM and are excitatory. Thus in untreated PD, 5-HT_{2C} receptor activation may be contributing to overactivity of GPM/SNR. 5-HT_{2C} receptor antagonists reduce the activity of the SNR in parkinsonism. However, further reduction in 5-HT_{2C} transmission may further reduce the activity of these regions, thus leading to dyskinesia.

6-Hydroxydopamine lesioned rats were treated with levodopa (6.5 mg/kg plus benserazide, 1.5 mg/kg twice daily) for 21 days. This resulted in an enhanced behavioural response to levodopa which modelled the pharmacology, neurochemistry, and molecular changes of levodopa induced dyskinesias in PD. When given with levodopa, the selective 5-HT_{2C} receptor antagonist, SB 206553 (20 mg/kg) caused a pronounced increase in this hyperkinesia to 267% compared with vehicle. The serotonin selective reuptake inhibitor clomipramine significantly reduced levodopa induced hyperkinesia by 68% (10 mg/kg) and 82% (20 mg/kg), compared with vehicle. The effect of clomipramine was completely blocked by SB 206553 suggesting an involvement of 5-HT_{2C} receptors. Thus 5-HT_{2C} receptor agonists may be useful adjuncts to levodopa in the treatment of PD. Indeed, such effects may underlie the finding that fluoxetine has some benefit in reducing apomorphine induced chorea.

TUMOUR NECROSIS FACTOR MICROSATELLITES SHOW SIMILAR ASSOCIATIONS IN PRIMARY PROGRESSIVE AND RELAPSING-REMITTING/SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Previous allelic association studies with microsatellite markers within a 20 kb region around the tumour necrosis factor (TNF) genes showed significantly different allele distributions for TNF- α and β markers in relapsing-remitting/secondary progressive MS (RR/SPMS) v normal controls. Considering the suspected immunogenetic heterogeneity in MS, these associations have been tested in primary progressive MS.

Association studies incorporated 206 normal controls, 178 RR/SPMS patients, and 100 PPMS patients (all Northern Irish origin) using polymorphic dinucleotide repeat markers TNF- α , TNF- β , and TNF- δ . Forward primers were 5'-end labelled with 6-Fam, polymerase chain reaction products were analysed on an Applied Biosystems 373A fluorescent fragment analyser, and Genescan 672 software was used for allele sizing. Statistical analysis involved a c2 test for multiple independent variables.

TNF- α marker allele distributions differed significantly between PPMS patients and controls ($P=0.025$, $df=8$) but were similar in PPMS and RR/SPMS patients ($P=0.902$, $df=8$). For the TNF- β marker, alleles 127

and 128 showed association with both patient categories (PPMS v controls, $P=0.03$, $df=2$: RR/SPMS v controls, $P=0.005$, $df=2$). No association occurred with the TNF- δ marker in either patient group (PPMS v controls, $P=0.92$, $df=4$: RR/SPMS v controls, $P=0.76$, $df=4$).

These data indicate that the TNF contribution to MS genetic susceptibility is similar across its full clinical range.

TOXIC EFFECTS OF FREE RADICALS IN AN IN VITRO MODEL OF MOTOR NEURON CELL DEATH

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There is evidence that free radicals contribute to cellular damage in motor neuron disease (MND). Free radical mediated cell damage has been examined in a hybrid neuroblastoma-motor neuron cell line, NSC34. The aims were to produce a model of motor neuron toxicity which replicates the biochemistry of MND, to look at the mechanisms of cell death, and to investigate different ways of preventing cell death.

Millimolar concentrations of ascorbate in the presence of Fe^{2+} can generate free radicals. Addition of 5 mM ascorbate to the culture medium caused a significant reduction in heavy neurofilament protein whereas actin and tubulin were unaffected. The distribution of phosphorylated neurofilaments was altered, forming clumps in the perinuclear region of the cells reminiscent of changes in MND.

The responses of these NSC34 cells to oxygen and nitrogen free radicals were also studied. Brief exposure to hydrogen peroxide or peroxynitrite (0.1 to 1.0 mM) caused delayed cell death. Chromatin degradation was shown by the presence of DNA-histone complexes in the cytoplasm of treated cells, which preceded cell lysis. Cytotoxicity was reduced by actinomycin D, which inhibits RNA synthesis, or with benzamide, which inhibits poly(ADP-ribose) polymerase. This suggests that the induced cell death is apoptotic.

In conclusion, this work represents the initial characterisation of a cell culture model which is relevant to MND. Some morphological and biochemical features of cell death have been described and some potential inhibitory compounds identified. These cells are currently being transfected with plasmids expressing mutant Cu,Zn superoxide dismutase found in familial MND to determine the effect on cellular sensitivity to free radical damage.

REGIONAL BRAIN ATROPHY, CAG REPEAT NUMBER, AND CLINICAL PHENOTYPE IN HUNTINGTON'S DISEASE

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CAG repeat numbers in the Huntington gene were correlated with the regional brain atrophy and clinical phenotype in 23 adult onset (range 17-63; mean 44.6 (SD 13.2) years) necropsy cases of Huntington's disease. All had chorea and dementia during life.

CAG repeat number (39-56; mean 45.4 (SD 4.6)) correlated inversely with age at onset of chorea ($r=-0.81$, $P<0.0001$), dementia ($r=-0.77$, $P<0.0001$), and death ($r=-0.85$, $P<0.0001$), but not with disease duration or initial symptoms.

Cross sectional areas of the affected brain regions were measured morphometrically from the coronal brain slices at four levels (genu of the corpus callosum, amygdala, accumbens, hippocampus). These included the caudate, putamen, pallidum, thalamus, amygdala, hippocampus, and the cerebral cortex and white matter within the frontal, temporal, and parietal lobes.

None of these morphometric variables correlated with number of CAG repeats.

The frontal cortical, but not striatal, atrophy was related to age of onset of chorea ($r=0.48$; $P=0.03$) and dementia ($r=-0.50$; $P=0.03$). The second also correlated with the temporal cortex atrophy ($r=-0.48$; $P=0.04$), but not with age at death. This may suggest greater cortical involvement in younger cases.

Thus tissue atrophy in advanced Huntington's disease seems unrelated to the underlying genetic defect, and may be, at this stage, affected by other (secondary?) pathogenetic factors. However, a correlation between earlier clinical onset and CAG expansion suggests a proportionally accelerated neurodegeneration in preclinical Huntington's disease.

ABNORMALITY IN VISUOSPATIAL FUNCTION OF PATIENTS WITH PARKINSON'S DISEASE

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The purpose was to evaluate the pathophysiology of visuospatial impairment in Parkinson's disease (PD) and its progression as a function of disease duration.

Using an automated CRT based test, the achromatic contrast sensitivity, orientational contrast sensitivity, and chromatic-discrimination thresholds of 31 patients with PD and 29 age matched controls were assessed. The achromatic and orientational contrast sensitivity (vertical and horizontal gratings) were measured using sinusoidal gratings of various spatial frequencies. Chromatic-discrimination thresholds were measured along the red/green and tritan confusion axes. Patients with PD were categorised using Hoehn and Yahr stages of stability. Data were analysed using a paired Student's t test and Scheffe's multiple comparison test.

The achromatic contrast sensitivity of patients with PD was significantly lower at all spatial frequencies compared with controls ($P<0.0001$). On an individual basis, 14 of the 31 patients with PD had significant horizontal contrast sensitivity deficit. Chromatic discrimination thresholds (tritan: $P>0.001$, Red/green: $P<0.05$) were significantly raised in patients with PD.

The findings are consistent with the theory that visuospatial impairment in PD could be due to changes not only in the retina but also in the visual cortex.

DO T2 AND GADOLINIUM ENHANCING T1 LESIONS REFLECT SEPARATE UNDERLYING PATHOLOGICAL PROCESSES IN MULTIPLE SCLEROSIS?

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Not all hyperintense T2 signal may arise from previous gadolinium enhancing T1 lesion. Thus under some conditions, changes in T2 weighted lesion volume and gadolinium enhancing T1 lesion frequency may reflect fundamentally different pathological processes. To test this lesion frequency maps in a population of 20 patients with multiple sclerosis were compared.

The MRI images were registered in standard stereotaxic space and lesions segmented out. The data for all patients were then averaged to yield separate lesion frequency distribution maps for the T2 or the gadolinium enhancing T1 lesions. These maps suggest significant discrepancies between gadolinium enhancing T1 and T2 lesion distribution. The brain was then divided into periventricular and peripheral regions. For the periventricular region the ratio of T2 lesion inside to outside was 1.7:1 whereas for T1 enhancing lesions the ratio was 0.7:1. The differences between the distribution ratios were highly significant ($P=0.0009$).

These results raise three possibilities: (1) T2 lesion is not critically dependent on previous T1 enhancement. (2) The periventricular white matter may be more susceptible to developing T2 weighted signal change. (3) There is selective burnout of the periventricular region with disease progression.

These findings suggest that T2 hyperintensive and gadolinium enhancing T1 lesions may provide quantitatively different information concerning disease progression.

TRANSCRIPTIONAL CONTROL OF THE HUMAN MUSCLE ACETYLCHOLINE RECEPTOR GENES

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A critical step in neuromuscular junction development is the switch of acetylcholine receptor (AChR) expression from fetal subtype ($\alpha_2\beta\delta\gamma$) to adult subtype ($\alpha_2\beta\delta\epsilon$). Animal studies show that the mechanism of regulation involves the binding of trans activating factors to AChR gene promoter regions. Two important elements identified are E and N boxes, implicated in tissue specific and synapse specific expression respectively. This study investigates the human γ and ϵ promoter regions, searching for homology with animal models.

The promoter regions of human genomic γ and ϵ subunit genes were subcloned, sequenced to nucleotides -943 and -1574, and compared with transcriptional control elements of other species.

E boxes and contiguous areas present in the γ subunit promoter show over 80% sequence identity between human and rat/mouse consistent with their role in tissue specific transcriptional regulation. By contrast, E box sequences in ϵ promoters are not highly conserved between species, suggesting a

lesser role in transcriptional control of the ϵ subunit. A highly conserved N box region is located in the ϵ promoter between nucleotides -92 and -97, but not in the γ . This further implicates the N box in the regulation of synapse specific expression and is supporting evidence for a differential mechanism of synaptic versus extrasynaptic AChR expression.

MANAGEMENT OF PATIENTS WITH SINGLE SEIZURES

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This prospective study was designed to analyse the local management of single seizures. The protocol involved referral by accident and emergency physicians to an epilepsy nurse specialist, a neurologist, and a neuroradiologist.

The first 100 referrals were received within a 28 month period. The male to female ratio was 51:49 and 84% of referrals were between the ages of 16 and 50. Over 80% of all single seizure referrals were seen by the epilepsy nurse specialist and neurologist in less than four and 28 weeks respectively. Brain CT was abnormal in 21% of cases. Abnormalities included seven malignancies, eight patients with cerebrovascular disease, and two patients with previous brain surgery.

Of 100 cases, 56 had a seizure disorder of which 14 were classified as provoked seizures, 13 unprovoked, and 29 were recurrent unprovoked. The recurrence rate in this group was 52%. Of the 14 provoked seizures five were alcohol related, seven were considered reflex anoxic seizures, one patient had herpes encephalitis, and one patient had had a significant head injury.

Only 75% of referrals had clear documentation of driving advice from accident and emergency. One patient had been initiated on antiepileptic drugs, which was contrary to the agreed protocol.

ABDOMINAL MYOCLONUS AND MYORHYTHMIA IN NEOPLASIA

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Paraneoplastic syndromes with abnormal movement are rare. Two cases are described in which movement disorder was a major feature.

A 70 year old man developed intractable hiccups and non-obstructive sleep apnoea in May 1996. Four months later he gradually developed paraplegia with a sensory level at T8 and abdominal myoclonus. These were continual rhythmic myoclonic jerks of anterior abdominal muscles at about 60/minute, not interfering with breathing and present during sleep. There was no paraspinal rigidity. Lumbar puncture showed raised protein (1.43 g/l) with normal cell morphology. MRI of the spine and brain stem was repeatedly normal and so was a radioisotope bone scan. Electromyography showed pronounced denervation in lower limbs, absent F responses, but normal nerve conduction. Prostatic biopsy confirmed adenocarcinoma. Purkinje cell antibodies were negative.

The diagnosis was paraneoplastic encephalomyelitis secondary to prostatic adenocarcinoma.

A 61 year old woman developed progressive cerebellar ataxia in 1989. One year later

she developed non-Hodgkin's lymphoma treated by chemotherapy. In 1995 she was bedbound because of severe ataxia and had developed a 2 Hz tremor of the mouth, neck, and limbs both at rest and on movement (myorhythmia). Jerky eye movements were noted, suggestive of opsoclonus. Lumbar puncture disclosed raised protein (3.7 g/l). MRI showed advanced cerebellar, brain stem, and central cerebral atrophy but no lymphoma. Purkinje cell antibodies were not detected.

The diagnosis was paraneoplastic myorhythmia and opsoclonus secondary to non-Hodgkin lymphoma.

A videotape of the involuntary movements was shown.

UNUSUAL PRESENTATION OF ALCAPTONURIA WITH NEUROPATHY AND MYELOPATHY: A CASE REPORT

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Alcaptonuria is a rare autosomal recessive disorder characterised by complete deficiency of homogentisic acid oxidase and inability to metabolise homogentisic acid. Affected persons excrete homogentisic acid in the urine which becomes dark when alkalinised or oxidised. Older alcaptonuric patients have intensely pigmented connective tissues—ochronosis—particularly involving cartilaginous joint surfaces of the large weight bearing joints.

A 55 year old Egyptian patient presented with neuropathy and myelopathy after injury to the right leg. There was no history of any disease. Radiological changes in the spine, hips, and knees suggested the diagnosis of alcaptonuria, which was confirmed by clinical and laboratory data. MRI detected cervical cord compression at the C3/C4 level by alcaptonuric affection of the spine. He also had axonal neuropathy evidenced by electrophysiological studies and nerve biopsy. Myelopathy secondary to alcaptonuria has been reported in a few patients, but there seems to be no report of an association between alcaptonuria and peripheral neuropathy.

A STUDY OF THE GLUTATHIONE S-TRANSFERASE M1 GENE IN PARKINSON'S DISEASE

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There has been considerable interest in the role of oxidative stress and free radicals in the pathogenesis of Parkinson's disease (PD). Glutathione serves as a major antioxidant defence against reactive species derived from hydrogen peroxide. The glutathione S-transferases (GST) are a family of enzymes that catalyse glutathione conjugation with electrophilic compounds. Thus the GST enzyme family serve as an intracellular defence mechanism via detoxification of potential mutagens, carcinogens, and xenobiotic compounds. Of the GST enzymes, much work has already been published concerning the association of null homozygotes of the GSTM1 gene and susceptibility to several forms of malignancy. More recently, a single report has suggested a significantly increased frequency of the GSTM1 gene

deletion in PD compared with controls (67% v 51%). As part of a study of several candidate xenobiotic genes, this hypothesis was explored further by studying a larger group of patients with PD.

Genomic DNA was analysed by the polymerase chain reaction (PCR) in 187 patients with PD and 392 controls, and the PCR products were studied after gel electrophoresis for the presence or absence of the GSTM1 gene. All subjects were white and unrelated. The diagnosis of PD was made using the United Kingdom PDS Brain Bank criteria.

The frequency of the GSTM1 deletion was no different in the patients with PD (97/187; 52%) compared with controls (203/392) (52%).

In conclusion, the study looked at a larger group of patients with PD and controls than the initial report. Therefore, it would seem that deletions of the GSTM1 gene do not play a significant part in the aetiology of PD, and further work should be directed towards the study of other genes.

INCREASED PROTEIN DEGRADATION IN A MITOCHONDRIAL DISEASE AND ITS MODULATION BY DICHLOROACETATE

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Pyruvate dehydrogenase deficiency is one of the best characterised childhood inherited metabolic disorders associated with early neurodegeneration and developmental brain abnormalities. Most cases are genetic defects to the critical X linked a subunit of the E1 α -keto acid decarboxylase polypeptide (E1 α). A patient cell line with an E1 α missense mutation (R302C) which results in reduced immunoreactive protein concentrations (~20% of normal) was utilised. E1 α mRNA levels seem normal but the mutant polypeptide is degraded abnormally rapidly (wild type $K_d=0.027$, mutant $K_d=0.06$). The working hypothesis is that alterations in the conformation or phosphorylation state of the mutant E1 α protein may modulate the stability and catalytic capacity of the pyruvate dehydrogenase complex.

Dichloroacetate (DCA) is a simple organic compound utilised clinically in the treatment of a variety of mitochondrial disorders. It acts primarily by modulating the activity regulating phosphorylation of the E1 α subunit through the inhibition of the E1 α -specific kinase. However, chronic DCA treatment of cell lines causes a 2 to 2.5-fold reduction of the rate of E1 α degradation. This effect is fully reversible. Rates of cytoplasmic and mitochondrial protein turnover seem unaltered during DCA treatment, suggesting that it is having a specific effect on the E1 α subunit turnover.

HUMAN EMBRYO KINASE 2 (HEK2) IN A GLIOMA SUBGROUP: THE O-2A LINEAGE AND NERVOUS SYSTEM DEVELOPMENT

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A cell line of the human oligodendrocyte-type 2 astrocyte (O-2A) lineage has been grown from a human glioblastoma multiforme (the Hu-O-2A/Gb1 cell line). Hu-O-2A/Gb1 cells

have a similar antigenic phenotype, growth factor response profile, and proton nuclear magnetic resonance spectra to that of rodent O-2A progenitor cells. As part of this characterisation Hy-O-2A/Gb1 ribonucleic acid yielded HEK2 receptor tyrosine kinase fragments. Of 19 low passage malignant human glioma cell populations examined, high HEK2 messenger ribonucleic acid expression was limited to those having strong glial characteristics. In situ hybridisation confirmed high HEK2 expression in the three original glioblastoma multiforme tumour samples from which the strongly positive HEK2 cell populations were derived. Therefore a distinct subset of gliomas show high HEK2 expression. Differential in vitro HEK2 expression was found in both the Hu-O-2A/Gb1 cell line and the rodent O-2A lineage depending on cell phenotype.

During human nervous system development in situ hybridisation showed HEK2 expression in the ventricular and subventricular layers of the rhombencephalon, cerebellum, and spinal cord where developing glial lineage cells might be found, but also in areas where neurons predominate.

HEREDITARY SPASTIC PARAPLEGIA WITH LATE ONSET DEMENTIA: LINKAGE TO CHROMOSOME 2 (SPG4 LOCUS)

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Hereditary spastic paraplegia (HSP) may have autosomal dominant (AD), autosomal recessive, or X linked inheritance in pure or complicated forms. Pure AD-HSP has been linked to loci on chromosomes 2, 14, and 15. The locus at chromosome 2p21-24 (SPG4) accounts for 45% of pure AD-HSP. 43 members of an Irish family with AD HSP and dementia had neurological and neuropsychological examinations. Genetic linkage was carried out using microsatellite markers spanning the candidate regions for pure HSP on chromosomes 2, 14, and 15.

Twelve members were considered definitely affected with HSP. Five affected members over the age of 50 years and one of 12 sibling controls showed a similar pattern of cognitive impairment on assessment, which was unlike that seen in Alzheimer's disease. Genetic linkage was established to the candidate region for pure HSP on chromosome 2 (SPG4) by linkage to the marker D2S2374 (two point lod score=3.34, theta=0.05, assuming 90% penetrance).

This is the first report of linkage of AD-HSP with late onset dementia to the SPG-4 locus for pure AD-HSP and suggests either close proximity of two genes for HSP, allelic heterogeneity, or variable phenotypic expression.

OPTIMISATION OF CONTRAST ENHANCED MRI AS A MEASURE OF MULTIPLE SCLEROSIS DISEASE ACTIVITY

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Gadolinium (Gd-DTPA) increases the sensitivity and reliability of MRI for detection of active multiple sclerosis (MS) lesions. Three potential methods were studied for further improving sensitivity: 0.3 mmol/kg (triple dose) Gd-DTPA, magnetisation transfer (MT) contrast imaging, and the introduction of a delay between contrast injection and imaging. Fifty patients were studied on two occasions, 24-72 hours apart, with triple and single dose Gd-DTPA. Pairs of postcontrast T1 weighted images with and without MT were obtained for three time periods (early: 0-20 minutes, early delay: 20-40 minutes, and late delay: 40-60 minutes).

Overall, triple dose Gd-DTPA resulted in the detection of 75% more enhancing lesions than single dose ($P<0.002$). In isolation, MT or delay alone failed to significantly increase sensitivity whereas a combination of MT and early delayed imaging significantly increased sensitivity (single dose: 47% increase, $P<0.05$; triple dose: 27% increase, $P<0.01$). The most sensitive imaging modality (MT, late delay, and triple dose Gd-DTPA) resulted in 126% more enhancing lesions than standard single dose imaging ($P<0.005$). In primary progressive MS, no approach improved sensitivity over standard single dose imaging, supporting previous evidence that progression to disability may be related to other factors besides inflammation. In conclusion, a combination of MT, delay, and triple dose Gd-DTPA may prove beneficial in treatment trials for relapsing-remitting and secondary progressive MS.

T1 HYPOINTENSITY, DISABILITY, AND ATROPHY OF THE SPINAL CORD IN MULTIPLE SCLEROSIS

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There is a strong relation between atrophy of the spinal cord assessed with MRI and disability in multiple sclerosis (MS). A similar relation has been shown in the cerebrum where atrophy evolves independently of blood-brain barrier breakdown, as assessed with gadolinium enhanced MRI. This may suggest a distinct pathogenesis for the development of disability in progressive MS. The pathological process that underpins atrophy is unclear but the question has been addressed by studying the relation between atrophy, disability, and intrinsic change within the cord. Sixty patients with MS and 30 normal controls underwent spinal cord imaging using a T1 sequence to acquire axial sections of the cord at the C2 level. These sections were histogram matched to allow comparison of image intensity and a manual outlining technique was applied from which mean cord image intensity over 10 axial slices was calculated. Within the patient group there was a significant relation between atrophy and T1 hypointensity ($r=0.36$, $P<0.005$). T1 hypointensity also correlated with disability as measured with the EDSS ($r=-0.39$, $P<0.005$). This study shows that atrophy is associated with a generalised reduction in signal on T1 weighted images. It is possible that this change may represent diffuse gliosis.

CORRELATION OF CLINICAL SUBTYPES OF MULTIPLE SCLEROSIS WITH CRANIAL AND CERVICAL PLAQUE DISTRIBUTION IN MRI

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The purpose was to compare lesion site and extent on craniocervical MRI with clinical subtypes in multiple sclerosis (MS).

One hundred and twenty nine patients with clinically definite MS underwent craniocervical MRI. Number, clinical site of attacks, and neurological dysfunction were documented. Plaque number, size, and position were measured from cranial MRI. Cervical cord lesions were documented and cord diameter at C5 measured.

One hundred and twenty nine patients (relapsing-remitting (RR) 70; secondary progressive (SP) 31; benign MS (BMS) 20, and primary progressive (PP) 8) were studied; 64.5% had cervical cord plaques (PP 100%, SP 65%; RR 64.2%; BMS 50%). Of these, motor sensory attacks were the significant initial presentation (PP 100%; RR 78%; SP 60%; BMS 60%) and weakness was common (PP and SP 100%; RR and BMS 60%). In patients without cervical cord lesions polysymptomatic brainstem and cerebellar attacks were significant at initial presentation and pyramidal signs without weakness was common (BMS 50%; RR 47%; 30% of SP and 25% of PP had plaques involving > 50% cross sectional area of the cord compared with RR (4.5%) and BMS (10%). Cranial lesion load was highest in BMS (BMS 43.1 (1.8); SP 37.08 (2.4); PP 29 (2.4); RR 21.96 (1.6)). Patients without cord lesions had higher mean cranial lesion load, particularly the SP group (40.21 (2.1) v 33.95 (1.4)). Infratentorial lesions were high in SP (SP 13.4%; PP 6.8%; RR 6.5%; BMS 6.1%). Periventricular lesion load was high in BMS without cord lesions (12.2 (2.4) v 6.2 (1.2)).

In conclusion, differences in lesion site and extent correlated with different MS subtypes.

THE DIAGNOSIS OF MARFAN'S SYNDROME

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One hundred years ago Marfan presented a five year old girl whose limbs were unduly long and slender and the muscles thin; the fingers and toes showed pronounced arachnodactyly. Knee joint movement was impeded by tendon shortening. Long term follow up disclosed an improvement in physical status.

Subsequent reports of the syndrome added other sites of connective tissue disorder, cardiovascular and ocular; autosomal dominant inheritance was established. Tissue culture showed that the collagen produced in the syndrome was abnormally soluble. More recently, muscle biopsies on affected patients have shown one or other form of congenital myopathyrod body, concentric laminated body, undifferentiated muscle tissue.

The patient reported here was an 8 year old boy with long, thin limbs, hyperextensible joints, and arachnodactyly. A motor point muscle biopsy displayed large numbers of small mitochondria in both main fibre types (pleoconial myopathy); in places muscle tissue was malformed and contained remnants of adipose tissue. A peripheral neuropathy was also demonstrated in which neuromuscular junctions showed impaired

axonic flow. It seems that the concept of Marfan's syndrome should now be extended to include genetic association with other congenital disorders; the possible deleterious effect of abnormal collagen on adjacent tissues should also be borne in mind.

IS THE DIAGNOSIS OF THE HYPERVENTILATION SYNDROME USEFUL?

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The hyperventilation syndrome is a diagnosis which provokes much controversy. There is disagreement over whether the

patients are hyperventilating, and if they are, whether this is causative or an epiphenomenon.

A total of 105 patients with the hyperventilation syndrome seen during a 23 month period, out of 2597 new outpatients (4% of new patients) were reviewed. Patients were noted to either have hyperventilation syndrome alone (54), or associated with another diagnosis (23), or after another diagnosis (28). Treatment involved a detailed description of the hyperventilation syndrome and referral to physiotherapy for breathing retraining.

Follow up in 101 patients (median 4.5 months) found a good or excellent response

in 79 of the 91 who attended physiotherapy, with a resolution of symptoms in a further eight who did not attend physiotherapy. The remainder had little or no response, none deteriorated.

Whereas the diagnosis of hyperventilation may not reflect the correct pathophysiological causation for the symptoms in these patients, this study suggests that using the diagnosis, which allows the patient to understand their symptoms on the basis of a simple physical model and leads to a logical course of breathing control therapy, results in a high rate of recovery. This suggests that the diagnosis is useful in clinical practice.

MATTERS ARISING

Dostoevsky's epilepsy induced by television

I refer to the letter written by Cabrera-Valdivia *et al*¹ in which they describe a 25 year old woman with "ecstatic epilepsy" evoked by sitting near the television. This compulsive pleasure seeking behaviour, which is called self induced epilepsy, is often described in patients who are photosensitive and television sensitive.

The first cases of self induced television epilepsy were described by Andermann² in 1971 and by Jeavons and Harding³ in 1975. Some 150 self inducing patients are described in the literature between 1932 and 1995. Two thirds of these patients are females, which is according to the sex distribution in photosensitive patients in general. The onset of the self inducing behaviour is at a mean of 6 years of age (range 1-15). Treatment is difficult as many do not want to get rid of this phenomenon.⁴ Over the past 15 years some 50 self inducing patients have been investigated in the Epilepsy Centre, Meer and Bosch, Heemstede, The Netherlands.

One of these patients, who had a history similar to the 25 year old woman was described in 1989.⁵ This female was compulsively attracted to the television set and to a fluorescent lamp, sunlight, and venetian blinds since childhood. She was often found with her nose pressed up against the television set. Sometimes her head was nodding and she seemed to be in a trance. At the age of 17 she now admits to self induction only if she is upset. In normal circumstances she feels too ashamed to use this manner of self induction.

It is very likely that the Spanish woman, as described in this letter, is photosensitive. There is no mention of a negative response to photic stimulation. Furthermore, it can well be that a false negative response is found as it is of the utmost importance to perform photic stimulation with an appropriate stimulator and to stimulate at different eye conditions. No television sensitive patients have been seen or described who are not photosensitive or pattern sensitive as well.

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- 1 Cabrera-Valdivia F, Jiménez-Jiménez FJ, Tejero J, Ayuso-Peralta L, Vaquero A, García-Albea E. Dostoevsky's epilepsy induced by television. *J Neurol Neurosurg Psychiatry* 1996;61:653.
- 2 Andermann F. Self-induced television epilepsy. *Epilepsia* 1971;12:269-75.
- 3 Jeavons PM, Harding GFA. *Photosensitive epilepsy*. London: Heinemann, 1975.
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Ecstatic seizures induced by television

As Cabrera-Valdivia *et al*¹ suggest, ecstatic experiences during spontaneous epileptic seizures are exceedingly rare. Intensely pleasurable experiences are, however, common in self induced seizures, as in the patient whom they describe. Of those 5% of people with epilepsy who are photosensitive some 30% can be shown by prolonged EEG telemetry with video recording in a well lit environment to induce epileptiform discharges by various means, either waving the outstretched fingers of one hand in front of the eyes or carrying out a manoeuvre involving upward deviation of the eyes with the fluttering of the eyelids.^{2,3} Patients are usually reluctant to discuss their habit but some 50% can be persuaded to do so and commonly describe pleasurable sensations ranging from release of stress to ecstasy. Some may induce orgasm.⁴ Patients who described similar experiences self induced by approaching closely to a television set have been reported previously.^{5,6}

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Cabrera-Valdivia *et al* reply:

We appreciate the interest of Binnie and Wilkins and Kasteleijn-Nolst Trenité regarding our report on Dostoevsky's epilepsy.¹ We agree in part with their comments. However, the cases that they quote as having similar experiences self induced are not described under the term "ecstatic" or "Dostoevsky's" epilepsy. The patient reported by Andermann² had typical absence attacks with a pattern of generalised spike and wave at 3-3.5 Hz during hyperventilation, and elicited by intermittent photic stimulation; the patient described this as a "trance-like" or "hypnotic" feeling without any reference to the affective state.

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- 1 Cabrera-Valdivia F, Jiménez-Jiménez FJ, Tejero J, Ayuso-Peralta L, Vaquero A, García-Albea E. Dostoevsky's epilepsy induced by television. *J Neurol Neurosurg Psychiatry* 1996; 61:653.
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Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease

Holmes *et al*¹ presented interesting data suggesting that the presence of an apolipoprotein E (ApoE) $\epsilon 4$ allele did not effect the rate of progression of cognitive impairment. They also examined various non-cognitive symptoms, finding a positive association between depression and ApoE $\epsilon 2$ genotype.

We followed up 51 patients with DSMIII-R dementia, representative of those with dementia in contact with psychiatric services in the United Kingdom for one year. Standardised clinical diagnosis were made according to the NINCDS ADRDA, DSMIII-R, Hachinski scale, and the criteria of McKeith *et al* for senile dementia of Lewy body type. Cognitive function was assessed at baseline and one year of follow up with the cognitive section of the Cambridge assessment for mental disorders in the elderly (CAMCOG). Psychiatric symptoms were also evaluated. Depression was examined using the Cornell depression scale and psychotic symptoms using the Burns symptom checklist. These were diagnosed according to RDC criteria and the criteria of Burns *et al*. Psychiatric symptoms were evaluated at monthly intervals for one year. A detailed description of the methodology is given elsewhere.² ApoE genotyping was performed on genomic DNA extracted from whole blood samples according to established procedures.³

The mean age of the patients was 79; 38 (75%) were women and they had mean CAMCOG scores of 48. Thirty six patients had possible or probable Alzheimer's disease, 10 had a diagnosis of vascular dementia, and three received a diagnosis of senile dementia of Lewy body type. Two patients had DSMIII-R dementia which could not be further classified. Five patients were homozygous for $\epsilon 4$ and 23 were heterozygous.

Patients with one or more $\epsilon 4$ alleles had a mean deterioration of 12.8 points on the CAMCOG score over one year compared with a mean of 11.4 in patients without any alleles, a non-significant difference (Mann-Whitney U test $z=0.67$, $P=0.50$), supporting the findings of Holmes *et al*. Patients with one or more ApoE $\epsilon 4$ alleles were, however, significantly less likely to develop RDC major depression (odds ratio 0.31, 95% confidence interval 0.09-0.99) and were significantly more likely to experience at least one psychotic symptom over the year of follow up (Fisher's exact test $P=0.006$). The last association was more impressive as all 28 patients with one or more $\epsilon 4$ alleles experienced psychotic symptoms. Too few patients had the apolipoprotein $\epsilon 2$ genotype to permit meaningful statistical analysis.

This is clearly just a small pilot study, but it does offer some provisional evidence that $\epsilon 4$ positive people may have a different non-cognitive phenotype. This is supported by other recent work,⁴ also reporting that patients with $\epsilon 4$ genotype were significantly more likely to experience psychosis. Although the multiple comparisons made in the study of Holmes *et al*¹ necessitate caution, it would have been valuable to report the actual P values, particularly as other work does suggest a possible association between $\epsilon 4$ genotype and psychotic symptoms.

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- 1 Holmes C, Levy R, McLoughlin DM, Powell JF, Lovestone S. Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1996;**61**:580-3.
- 2 Ballard CG, Saad K, Patel A, *et al.* The prevalence and phenomenology of psychotic symptoms in dementia sufferers. *Int J Geriatr Psychiatry* 1995;**10**:1-9.
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- 4 Ramachandran G, Marder K, Tang M, *et al.* A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease. *Neurology* 1996;**47**:256-9.

Holmes *et al* reply:

In reply to the comments by Ballard *et al* we have extended our original study¹ by ApoE genotyping an additional 68 Alzheimer's disease cases from the Camberwell Dementia Case Register² bringing the total to 232 cases fulfilling NINCDS-ADRDA criteria (154 probable and 78 possible, mean age 82.4 (SEM 0.4) years, 178 (77%) women). In all other respects the patient selection and assessment were identical to that previously reported and gave rise to frequencies of 0.03, 0.66, and 0.30 for the ApoE ϵ 2, ϵ 3, and ϵ 4 alleles respectively. In this extended study in accord with our previous findings the only significant association was between the presence of the ApoE ϵ 2 allele and the Cornell score (Mann-Whitney *U* test, *P* = 0.03) and with the presence of depressive symptomatology (Mann-Whitney *U* test, *P* = 0.01) after Bonferroni correction. However, we welcome the opportunity to present the full data set before Bonferroni correction (table) as it concurs with the findings of Ballard *et al* and other studies³ which suggest an association of the ApoE ϵ 4 allele with psychotic phenomena as well as suggesting a possible association with wandering behaviours and eating disturbance. Unlike Ballard *et al* we did not, however, find a negative (or positive) association between depressive symptomatology and the presence of the ApoE ϵ 4 allele suggesting that it is the presence of the ApoE

ϵ 2 allele rather than the absence of the ApoE ϵ 4 allele that is associated with depressive symptomatology in Alzheimer's disease.

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BOOK REVIEWS

Pocket Companion to Neurology in Clinical Practice. Second Edition. Edited by BRADLEY, DAROFF, FENICHEL, AND MARSDEN (Pp758; price £35.00). Oxford: Butterworth Heinemann, 1996. ISBN 0 7506 9787 3.

What is the point of these pocket companions in neurology? There are certainly plenty of them: either distillations of authoritative textbooks (such as this and the companion to Victor and Adams) or culled from residency teaching programmes (for example, *The Little Black Book of Neurology* produced from Robert Daroff's department). The "salient points of clinical diagnosis and management—those most useful at the bedside" have been extracted from Bradley, Daroff, Fenichel, and Marsden's two volume textbook. Does this mean we get earthy advice from

grizzled neurological veterans? Well, not really. Emergency treatments are reasonably covered. But this book will not transform your difficult clinics. If you wondered about treating insomnia, all you will learn is that management should be "individually designed dependent on the causative factors". As much space is devoted to the treatment of the Lambert-Eaton myasthenic syndrome as to the symptomatic management of multiple sclerosis; more to Lesch-Nyhan disease than to tension headache. Here is a clue to the real purpose of these little books. They are to be pulled out in those quiet moments to indulge in that most neurological of activities, the pursuit of the arcane. There are excellent chapters on the neurocutaneous disorders and inborn errors of metabolism. There are three good pages on the mucopolysaccharidoses and a cracking appendix on neurogenetics. What does it matter that not one clinical trial in the management of stroke, carotid stenosis, Guillain-Barré syndrome, or CIDP is mentioned?

ALASDAIR COLES

Survey of Functional Neuroanatomy. Third Edition. By BILL GAROUTTE (Pp 224; price \$15.00). California: Mill Valley Medical Publishers, 1994. ISBN 0-9643644-0-9.

It is not uncommon to find neuroanatomy books that bewilder the uninitiated undergraduate, or clinician for that matter. It is therefore refreshing to find that this book by Garoutte confronts this issue and makes it an understandable text. The key to all learning lies in starting from the basics and dealing with concepts, which makes hanging details on a lot easier. This book assumes a negligible background in neuroscience and starts from the fundamentals of descriptive neuroanatomy of the human nervous system through to its embryology and some aspects of its pathology. Importantly, it does not deal with the anatomy in isolation and makes enough reference to physiology to put the topic into perspective making it more functionally relevant than most of its contemporaries.

The use of enormous numbers of diagrams has meant that the text is a bare minimum with most of the information in illustrated form making it easier to assimilate. In using this idea it seems that one or two diagrams have become rather *too* complicated and they are very difficult to interpret. The clinical cases are a little uninspiring and could have been used to create a lot more enthusiasm. However, the questions at the end of the topics are a useful adjunct to test ones understanding of the subject and could be exploited usefully by those teaching neuroanatomy.

Overall the beauty of this book is to make it simple enough for the most ignorant of students but yet enough detail is present in it for it to be an ideal crammer for undergraduates coming up to examinations. The price makes it very affordable and I recommend it highly.

OMAR MALIK

Association between the presence of non-cognitive symptoms and the presence of the ApoE ϵ 2 and ϵ 4 alleles by Mann Whitney *U* test (*n*=232)

Symptom group	Subjects with one or more symptoms (<i>n</i> (%))	Association with presence of ApoE ϵ 2 allele (<i>P</i> values)	Association with presence of ApoE ϵ 4 allele (<i>P</i> values)
Persecutory delusions	105 (50)	0.45	0.02*
Other delusions	31 (13)	0.37	0.05*
Auditory hallucinations	30 (13)	0.11	0.83
Visual hallucinations	53 (23)	0.25	0.98
Other hallucinations	18 (8)	0.09	0.15
Misidentifications	49 (21)	0.12	0.20
Depression	115 (50)	0.0009***	0.11
Aggression	121 (52)	0.38	0.18
Wandering	131 (56)	0.98	0.04*
Stereotypes	182 (78)	0.09	0.23
Sleep disturbance	166 (91)	0.73	0.58
Eating disturbance	88 (38)	0.35	0.04*

P*<0.05; **P*<0.001.