

## EDITOR'S CHOICE

## PSYCHOIMMUNOLOGY

**Mind over macrophages**

One of the expanding areas of immunology nowadays, albeit with fringe elements, is "psycho-immunology": exploring the relationship between neural activity, behaviour and the immune system. This group from New York strayed into this territory by accident, when they made some surprising findings during pre-clinical testing of a novel drug in stroke. CNI-1493 is an inhibitor of macrophage activation by preventing the phosphorylation of p38 mitogen activated protein kinase. Curiously, when injected intraventricularly, CNI-1493 suppresses systemic TNF- $\alpha$  production in response to endotoxin. This paper describes the experiments that explore the mechanism of this effect. First, they showed that the dose of CNI-1493 required to reduce systemic TNF- $\alpha$  is 10,000 times less for intracerebral- as opposed to intravenous- administration. Then they demonstrated that the protective effect of CNI-1493 is mimicked by direct stimulation of the vagus nerve, and abolished if the vagus is surgically cut. The inescapable conclusion is that CNI-1493 acts centrally, via the vagus, to regulate peripheral inflammation, perhaps by vagal release of acetylcholine acting upon the nicotinic receptors found on resident macrophages. There are two important conclusions from this work. First, drugs may control systemic inflammation through an action on the brain and secondly, vagal stimulation may have an immunosuppressive effect. -AJC

**Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, Sudan S, Czura CJ, Ivanova SM, Tracey KJ.**

*Pharmacological stimulation of the cholinergic antiinflammatory pathway.*

**JOURNAL OF EXPERIMENTAL MEDICINE**  
2002 Mar 18;195(6):781-8.

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**Schizophrenia is an autoimmune disease**

So claims this paper from Argentina. It is based on the finding of an autoantibody in the sera of patients with schizophrenia that binds to frontal cortical cells. Many claims for autoimmunity in the past have been made on the finding of an autoantibody but we now recognise that this is simply not sufficient evidence. For healthy humans produce antibodies and T cells that react against self. Sterin-Borda's group have amassed, with a technological tour de force, comprehensive circumstantial evidence that the antibodies they have found are pathogenic. Their starting hypothesis is that patients with schizophrenia have antibodies against the particular acetylcholine receptor found in the frontal cortex (the M1 muscarinic receptor: M1mAChR). Happily for the investigators, the rat and human M1mAChR are closely homologous. They demonstrated, by both indirect immunofluorescence and flow cytometry, that sera from 21 patients with paranoid schizophrenia, but not controls, bound to rat frontal cortical cells. They then extracted, from both patient's and controls' sera, an IgG fraction that bound to a peptide representing the sequence of the second extracellular loop of the M1 mAChR. They ran this fraction, in an immunoblot, against a rat frontal cortex membrane and showed that patients' anti-M1 mAChR revealed a band of similar molecular mass to an established anti-M1 mAChR, which could be inhibited by excess peptide, demonstrating specificity. Patients' anti-M1mAChR showed a similar band of much lower intensity, making the point again that low affinity antibodies exist which bind to self in normal people. However, dot blot and ELISA studies showed that the patients' sera, but not controls', show a concentration dependent increase in binding. The next step in their analysis is to see if this binding has any functional effect. They show convincingly that patients' sera and their anti-M1 mAChR fraction act as an agonist at the mAChR and cause a rise in intracellular second messengers (phosphoinositide and cyclicGMP) when applied to rat frontal cortex slices. None of this shows that the autoantibody is pathogenic in patients. To do that would require the classic approaches of transfer of the autoantibody to laboratory animals to see if it causes schizophrenia-like problems (but how are these detected in rats?) and elimination of the antibody in patients (by plasma exchange or other immunosuppression) to see if the disease is modified. -AJC

**Borda T, Perez Rivera R, Joensen L, Gomez RM, Sterin-Borda L.**  
*Antibodies against cerebral m(1) cholinergic muscarinic receptor from schizophrenic patients: molecular interaction.*  
**JOURNAL OF IMMUNOLOGY**  
2002 Apr 1;168(7):3667-74.

## PERIPHERAL NEUROPATHY

**Anti-MAG antibodies and bad packing**

This study, from John Hopkins and involving peripheral neuropathy luminaries Jack Griffin and Richard Hughes, is a neat example of the usefulness of clinical material to the basic sciences. It concerns the packing of neurofilaments within axons. This controls axon calibre, which is so important to their function. It has been proposed that neurofilament packing may be modified at a local level by the phosphorylation of neurofilament sidearms: so increasing the distance between neurofilaments and thus axon calibre. One molecule that may be responsible is myelin-associated glycoprotein (MAG) found on Schwann cells. So the authors studied electron micrographs of sural nerve biopsies from patients with a paraproteinaemic neuropathy and anti-MAG antibody comparing them to other demyelinating neuropathies and normal nerves. The hypothesis was confirmed: the neurofilaments from patients with the anti-MAG antibody were more densely packed than either of the other groups. Neurofilament sidearm phosphorylation was not studied though. This work is useful in two ways. First, it adds to the evidence that the anti-MAG antibody is pathogenic in these patients (always a problem in autoantibodies associated with human disease). Secondly, it suggests a mechanism

whereby a Schwann cell molecule may influence axons and thus perhaps contribute to the axonal degeneration seen in demyelination of both the central and peripheral nervous systems. **-AJC**

**Lunn MP, Crawford TO, Hughes RA, Griffin JW, Sheikh KA.**

**Anti-myelin-associated glycoprotein antibodies alter neurofilament spacing.**

**BRAIN**

2002 Apr;125(Pt 4):904-911.

## NEURO-OPHTHALMOLOGY

### Extraocular muscle forever young?

The radically different disease susceptibility between extraocular muscle (EOM) and other skeletal muscle is both well recognised and diagnostically useful in clinical practice. The pathophysiological basis for this difference is poorly understood, but differences in surface antigens might account for selective EOM involvement in the autoimmune disorders myasthenia gravis and Graves disease while a high level of oxidative metabolic activity could explain its susceptibility to mitochondrial disorders. By contrast, EOM is spared in dystrophinopathies despite similar expression levels of dystrophin and related membrane support proteins. EOM is also spared in transgenic animals lacking dystrophin but not in animals lacking both utrophin and dystrophin, which suggests that EOM is uniquely able to successfully substitute utrophin when dystrophin is deficient.

The present study provides exciting new information indicating that mature uninjured EOM fibres continue to incorporate myonuclei from satellite cells at a rate that in other skeletal muscle is only seen following injury. The authors show that EOM satellite cells, unlike those of other skeletal muscles, are continually 'activated' in the healthy adult rabbit. Thus they continue to express the myogenic regulatory factor MyoD and rapidly start dividing following plating without requiring a prolonged activation period. It is particularly interesting to find that satellite cells in uninjured adult EOM muscle continue to incorporate bromodeoxyuridine (BrdU), a marker of cell division.

More compelling still, the presence of BrdU-labelled nuclei in EOM myofibres suggests that satellite cell nuclei are continually being incorporated into healthy fibres. This raises the possibility that active remodelling permits the rapid repair of the sarcolemmal damage associated with deficiency of dystrophin and other members of the dystrophin-glycoprotein complex. A better understanding of why EOM is spared despite sustaining apparently the same pathophysiological insult is likely to provide key insights into both disease mechanisms and potential therapeutic targets in the muscular dystrophies. **-WR**

**McLoon L, Wirtschafter J**

**Continuous myonuclear addition to single extraocular myofibres in uninjured adult rabbits.**

**MUSCLE AND NERVE**

2002; 25: 348-358

### Superior oblique myokymia: a neurovascular compression syndrome?

Superior oblique myokymia (SOM) is an ocular motility disorder characterised by paroxysmal unilateral oscillopsia. (In my practice it is a condition which, once missed, has never been forgotten.) As long ago as 1983 it was suggested that neurovascular compression of the trochlear nerve was the cause, a view supported by occasional reports of successful microvascular decompression surgery. However, neuroimaging studies have hitherto lent no support to the hypothesis. Now, using a specific magnetic resonance imaging protocol (3-D Fourier transform constructive interference in steady-state and 3-D time of flight magnetic resonance angiography +/- Gd-DTPA) which shows small structures surrounded by CSF, further claims for the neurovascular compression hypothesis have been made.

In six patients with SOM, imaging showed contact between branches of the superior cerebellar artery and the trochlear nerve close to or

at its point of exit from the midbrain, the root exit zone (REZ). On the contralateral, asymptomatic, side no such contacts were observed (i.e. sensitivity = 100%), although more distal contacts ( $\geq 3$  mm from REZ) were seen. It is argued that the REZ is the critical area since the transition here from PNS to CNS myelin renders the nerve electrophysiologically vulnerable (no epineurium or perineurium in CNS). Whether the patients responded to medical (carbamazepine) and/or surgical (microvascular decompression) therapy is not reported. The specificity of neurovascular contact is lower, since 15% of asymptomatic individuals scanned had this finding: hence it does not reliably predict symptoms.

The data are suggestive, although not compelling, that SOM be regarded as a neurovascular compression syndrome, along with some instances of trigeminal neuralgia and hemifacial spasm. Certainly patients failing carbamazepine might merit detailed neuroimaging to search for neurovascular contact which might potentially represent a surgically remediable cause. **-AJL**

**Yousry I, Dieterich M, Naidich TP, Schmid UD, Yousry TA.**

**Superior oblique myokymia: magnetic resonance imaging support for the neurovascular compression hypothesis.**

**ANNALS OF NEUROLOGY**

2002;51(3): 361-368

## NEUROPHYSIOLOGY

### Charging patients

Nerve conduction studies typically involve stimulation at one site and recording a response a few centimetres distant from the stimulation site either on the nerve or muscle. The idea that stimulating a finger and recording from a toe would generate anything diagnostically meaningful seems unlikely and even perhaps a little comical, but such techniques have been used to estimate intracellular and extracellular water volumes (whole body bioelectrical impedance analysis). This relies on a simplified body circuit model and a sizeable number of assumptions and has a somewhat limited application. A more promising avenue with bioimpedance, as a neurological tool, has been investigated by Rutkove and colleagues in which local bioimpedance analysis (LBA) studies of the thigh were performed. A number of electrodes are placed in series along the anterior surface of the thigh, one of which delivers alternating current, parameters defined from recordings of resistance and capacitance are then derived (phase curves). A similar arrangement can also be applied to the forearm. Comparing controls with an eclectic group of patients, with conditions such as inflammatory myopathy, polio and motor neuron disease, differences in these parameters were evident. Changes also paralleled both disease deterioration and improvement in follow up studies extending over 18 months and were not purely dependent on muscle bulk. Tantalising, phase curves appear to be different between these pathologies but this needs further clarification. It is certainly easy to imagine situations where this analysis may be helpful, such as investigating intensive care patients where EMG studies can sometimes be limited by a lack of muscle activation, or following up effectiveness of immunosuppressant treatments in inflammatory myopathies. If this technique is to have a future, then studies comparing age matched controls with a homogenous patient group will be a required and indeed further studies are envisaged. **-JR**

**Rutkove SB, Aaron R, and Shiffman CA.**

**Localised bioimpedance analysis in the evaluation of neuromuscular disease.**

**MUSCLE AND NERVE**

2002 25, 390-397.

### Realising the visual prosthesis

Bypassing the connections from the eye to visual cortex by stimulating the latter artificially may provide a limited degree of functional vision in cases of blindness. Research on this possibility began in the 1960s with intracortical microstimulation techniques. A less invasive

approach utilising painless transcranial magnetic stimulation is currently being investigated, but selecting which subjects may benefit from such an approach remains a problem. One unresolved question is whether long-standing visual deafferentation leads to irreversible impairment of visual cortex function that might impair such technical approaches. To try and address this, Gothe and colleagues have recently assessed different categories of visually impaired subjects with optic atrophy of various aetiologies including glaucoma, retinitis pigmentosa, cone cell dystrophy, and optic nerve meningioma without concomitant damage of post geniculate pathways. The 35 registered blind subjects were compared with 10 controls; the blind subjects were divided into 3 groups dependent on degree of residual vision. The partial or complete long-term deafferentation had been present for at least 10 years. By applying transcranial magnetic stimulation pulses over the occipital skull in normals, perception of brief flashes of white or coloured patches of light (phosphenes) can be achieved. A threshold from the intensity of stimulation and their distribution in the visual field can also be determined. Group 1 patients (visual acuity <20/400) had comparable responses to the control group. Of the group 2 (light or movement perception only) patients, 60% were able to perceive phosphenes in response to TMS. In group 3, only 2 out of 10 patients reported phosphenes. Surprisingly thresholds for phosphene responses did not significantly differ between controls and patients but active stimulation sites did differ, suggestive of some form of functional remodelling. In conclusion the degree and duration of visual deafferentation needs to be considered in any attempt to artificially revive the dormant visual cortex. -JR

**Gothe J, Brandt S, Irlbacher K, Sabel SRB, and Meyer B.**

***Changes in visual cortex excitability in blind subjects as demonstrated by transcranial magnetic stimulation.***

**BRAIN**

**2002 125: 479-490**

## STROKE

### ☆☆☆ RECOMMENDED

#### Chiropractic manipulation and stroke

There are many reports of posterior circulation stroke secondary to vertebral artery dissection seemingly provoked by chiropractic manipulation of the neck. However these are generally anecdotal cases or small series. Thus the true relationship of chiropractic manipulation as a cause of stroke is open to publication, selection and recall bias. This study seeks to determine whether, and if so with what risk, chiropractic manipulation of the neck really does lead to vertebral artery dissection.

Each of 582 patients with a posterior circulation infarct admitted to hospital in Ontario were identified retrospectively and matched to 4 controls from the local population. Public health billing records were used to identify all persons having chiropractic manipulation prior to the event date. Patients under the age of 45 were five times (95% CI 1.32-43.87) more likely to have undergone chiropractic manipulation than controls in the week before stroke onset and were five times as likely (95% CI 1.34-18.57) to have made 3 or more visits to a chiropractor for neck manipulation in the previous month. There was no association for patients over the age of 45 yrs.

This is the first population based control study to test the association between chiropractic manipulation and vertebral artery stroke and does demonstrate an association for young people. The results correspond to an incidence of 1.3 cases of stroke within 1 week of manipulation per 100,000 (greater than the 1 per million previously suggested). However, biases do exist – patients who may have had a subarachnoid haemorrhage from intracranial extension of the vertebral dissection and patients with carotid dissections were excluded. The vertebral artery strokes were not all proven dissections. The visit to the chiropractor may have been due to the initial neck pain of a spontaneous dissection and the manipulation was not actually the cause of

the dissection (although may have aggravated it). Clearly a large prospective population based case control study is the only way to eliminate such bias but this would require a long study period. Meantime the neurologist who sees a patient with a posterior circulation stroke needs to consider a dissection as a likely cause, patients who have had a previous spontaneous dissection should probably avoid chiropractors and chiropractors should refer on any patient who develops neurological symptoms between or after treatment sessions. Should they warn patients of the risk? Since it is 1:100 000 presumably not. -PJM

**Rothwell DM, Bondy SJ, Williams JL.**

***Chiropractic manipulation and stroke: a population based case control study.***

**STROKE**

**2001;32:1054-1059**

## MOVEMENT DISORDERS

### ☆☆☆ RECOMMENDED

#### Neural transplantation for Huntington's disease - the controversy continues

The notion that Huntington's disease (HD) can be cured by the grafting of embryonic striatal tissue has a long experimental history, but relies on the belief that the brunt of the pathology targets this structure. However, there is mounting evidence that the disease is diffuse at onset, although the contribution of these non-striatal pathologies to disease manifestations is not known. Thus much controversy exists as to whether the use of striatal transplants will ever be of value in halting the disease in affected patients, and tends to polarise researchers in those who support this approach and those who believe it is pointless. Proponents of this approach were supported by the successful French study of Peschanski and colleagues published in the Lancet at the end of 2000, but the opponents of the procedure have now been armed by this recent study from Tom Freeman and colleagues in South Florida. As a proponent for the procedure, it should be stated early on that no-one has ever believed that this approach is going to cure patients of HD in much the same way that embryonic nigral grafts do not cure all of the problems in PD (see ACNR 1.2). It has never been seen as an alternative to preventative therapies (see e.g. ACNR 1.5 p31), but may help with some of the core deficits, especially in those with established disease.

In this latest study patients with moderate HD were grafted with a part of the developing human embryonic striatum and then followed up for 12 months. The overall result was that there was no significant benefit from the procedure and that in a number of cases surgical complications were seen such as sub-dural haematomas. This study led Ira Shoulson and Tim Greenamyre to write an editorial in this same issue of Neurology, calling for a halt to this transplant practice in HD. So what conclusions should we draw from this study?

Well, not a lot primarily because not enough information is yet available on this procedure and this recent study does have some major problems with it, namely:

- the dissection of the developing striatal tissue adopted by the team has never been shown to produce functional benefits in animal models of disease, unlike the less selective dissection adopted by the more successful French team;
- the HD patients were followed up for relatively short periods of time, which may have been insufficient to see full clinical effects as evidenced by the earlier French study;
- patients were probably more advanced than those seen in the earlier studies and this may have led to the increased complication rate reported in this study;
- the benefits of transplantation in some patients may have been lost by analysing the group as a whole rather than by individual. It is well-known that neural grafting produces variability between patients often for reasons that are not apparent.

Therefore this negative study should be taken notice of, but it should not be interpreted as providing the final nail in the coffin for grafting in HD. It is still too early to know whether the procedure will be of benefit but premature claims of failure (and success) do more harm than good, and much more is needed before a line can be drawn under this type of therapeutic approach in HD - **RAB**

**Hauser R Furtado S, Cimino CR, Delgado H, Eichler S, Schwartz S, Scott D, Nauert GM, Soety E, Sossi V, Holt DA, Sanberg PR, Stoessl AJ, Freeman TB.**

***Bilateral human fetal striatal transplantation in Huntington's disease.***  
**NEUROLOGY**

**2002: 58: 687-695**

### **Wives as well as offspring at risk on Guam**

The Guamanian outpost of the National Institute of Neurological Disorders and Stroke has now been studying patients on the "largest land area between the Philippines and Hawaii" since the early '50s. In 1958 a prospective epidemiological study was initiated of the first-degree relatives and spouses of a 5-year cohort of Chamorros with ALS and parkinsonism-dementia complex (PDC) and individually matched controls. The latest analysis of the patient-control registries retains the earlier methodology but the 'ALS + PDC' classification has been abandoned and patients with both diseases have been classified according to the disease with the earlier onset.

Previous registry results already suggested strongly that Guamanian ALS and PDC are familial disorders since the two diseases are frequently seen in the same family as well as in the same individual, and neuronal degeneration in both conditions is characterised by Alzheimer-like neurofibrillary tangles in the brain and spinal cord. Furthermore, parents and siblings are at significantly increased risk of contracting either disease. This is the first follow-up at which sufficient time has elapsed to demonstrate a significantly higher risk for developing either disease among the offspring of patients with PDC but not, apparently, of individuals with ALS. The reasons for this difference are not clear but might be related to the younger age (about 6 years) of the offspring of ALS patients.

So are all cases of ALS and PDC on Guam hereditary? While confirming the familial nature of the disease, the results are against the involvement of simple Mendelian dominant or recessive genes in the aetiology of the disease(s). Indeed, two lines of evidence suggest the additional involvement of extraneous factors. First, there is an increased risk of developing the disease in spouses (wives only) of patients with ALS (but not PDC). Secondly, during the past 30 years, the age at onset for both ALS and PDC has increased by almost 10 years - an observation that has been attributed to the effects of "modernisation" on the island. -**WR**

**Plato CC, Galasko D, Garruto RM, Plato M, Gamst A, Craig U-K, Torres JM, Wiederholt W.**

***ALS and PDC of Guam: forty-year follow-up.***

**NEUROLOGY**

**2002: 58:765-773**

## **GLIOMA**

### **High-grade glioma adjuvant chemotherapy is beneficial**

There is no doubt that malignant gliomas carry a particularly bad prognosis, with a median survival of 9 months. Current management involves cytoreductive surgery followed by a course of radiotherapy. Over the last 30 years a number of randomised studies have been undertaken in an attempt to improve this survival by adjuvant chemotherapy (nitrosourea based agents, which are lipid soluble and therefore able to penetrate the blood brain barrier). Each of these studies has failed to provide a conclusive answer to whether or not adjuvant chemotherapy is beneficial or not in patients with high-grade gliomas because of small numbers. It is therefore timely that this meta-analysis has provided evidence that adjuvant chemotherapy provides a small but significant improvement in survival. With data from 12 randomised trials and 3004 patients a 15% relative decrease in the risk of death with adjuvant chemotherapy was calculated. This trans-

lates to an increase in survival at 1 year of 6% and a median survival time increase of two months. Subgroup analysis demonstrated no effect on the benefit by histology type, age or sex of patient, resection extent and performance status. Despite beneficial primary outcome measures as mentioned above, data on the quality of life during this extended survival time is essentially absent but the authors comment that nitrosoureas are easily administered and fairly well tolerated. None the less the two most important aspects of this meta-analysis are that high-grade gliomas are chemosensitive and that more work on novel agents should be a matter of priority if any further survival improvements are to be expected. -**TH**

**Glioma Meta-analysis Trialists (GMT) Group.**

***Chemotherapy In Adult High-Grade Glioma: A Systematic Review And Meta-Analysis Of Individual Patient Data From 12 Randomised Trials.***

**LANCET**

**2002: 359:1011-18**

## **MULTIPLE SCLEROSIS**

### **☆☆☆ RECOMMENDED**

### **Failure of remyelination in MS - Inhibition of oligodendrocytes not lack of oligodendrocytes**

Understanding why remyelination fails in some MS lesions will allow development of therapeutic strategies to undo the damage inflicted on the nervous system by this disease. If the failure of remyelination is as a result of no infiltrating oligodendrocytes, transplanting oligodendrocytes could be considered a rational therapeutic procedure. It goes without saying then that if the converse is true and oligodendrocytes are present but fail to remyelinate because of a prevailing inhibitory microenvironment then manipulation of this inhibitory environment to create a more permissive environment would be a better treatment option. By being able to define oligodendrocyte precursors, premyelinating oligodendrocytes and mature oligodendrocytes in chronic MS lesions from autopsies, Trapp's group has addressed this question. It is clear that chronic lesions (less than 15 years old) have numerous premyelinating oligodendrocytes, which are associated with axons but fail to remyelinate. This allows the authors to suggest that the machinery for remyelination is in place but there is some as yet undefined inhibition of the remyelination process. However if the lesions are older than 15 years they lose the ability to maintain or produce oligodendrocytes, as there is evidence that these oligodendrocyte precursors undergo apoptosis. It would appear therefore, that there is a window of opportunity for therapeutic intervention before a lesion is 15 years old. -**TH**

**Chang, A, Tourtelotte, W.W, Rudick, R, and Trapp, B.**

***Premyelinating Oligodendrocytes In Chronic Lesions Of Multiple Sclerosis.***

**NEW ENGLAND JOURNAL OF MEDICINE**

**2002: 346:165-73**

### **☆☆☆ RECOMMENDED**

### **Longitudinal correlation between MRI abnormality and disability from MS**

Using the well-studied group of patients from the Queen Square cohort who fifteen years ago presented with isolated syndromes suggestive of MS who underwent MRI, Brex and co-workers have studied the progression of the lesions and determined their predictive value. In this group of patients (n=71) 88% of those with abnormal MRI scans developed MS whilst only 19% of those with a normal scan developed MS.

In the earlier years the lesion load (number and extent of lesions) correlated with prognosis and this correlation continues at 14 years.

The 14 year EDSS score correlated moderately with MRI lesion volume at 5 years ( $r=0.6$ ) and also the increase in lesion volume over the first 5 years ( $r=0.61$ ). Although there is correlation between early MRI abnormalities and the disability this correlation is modest and the authors suggest early MRI lesion load could provide guidance but should be used with caution in individual decisions pertaining to disease modifying agents. **-TH**

**Brex, P.A, Ciccarelli, O, O'Riordan, J, I, Sailer, M, Thompson, A.J, and Miller, D.H.**

**A Longitudinal Study Of Abnormalities On MRI And Disability From Multiple Sclerosis.**

**NEW ENGLAND JOURNAL OF MEDICINE**

**2002: 346:158-64**

## Antibiotics for multiple sclerosis?

Already a patient with multiple sclerosis (MS) has asked me to prescribe antibiotics for her condition, flourishing a cutting from the *Daily Mail* provoked by this paper.

Rats with experimental allergic encephalomyelitis (EAE), an animal model of MS induced by immunisation with myelin-oligodendrocyte glycoprotein (MOG), were treated with minocycline, a second generation tetracycline. In addition to its antibiotic action, minocycline has anti-inflammatory properties, including inhibition of: microglial activation; synthesis of matrix metalloproteinases (MMP), inducible nitric oxide synthetase, and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ); and mRNA upregulation of caspases 1 and 3, thought to be involved in apoptosis. It has been reported to slow progression in a transgenic animal model of Huntington's disease (*Nature Medicine* 2000; 6: 797-801).

Rats with MOG-induced EAE treated with minocycline showed reduced disease severity and disease progression compared to sham-treated controls. Histological comparisons showed an absence of T-cell infiltration, reduced MMP expression and no microglial activation in the treated animals. Increased interleukin-10 and reduced IFN-g indicated deviation of the anti-MOG T-cell immune response away from Th1 phenotype (disease-associated) towards the Th2 (immunosuppressive) phenotype. However there was also a rise in TNF- $\alpha$  secretion by T cells, which would tend to promote EAE.

Clearly it is not possible to extrapolate from EAE to MS, but certainly these data suggest that a trial of minocycline in the latter would not be unreasonable. Minocycline is a safe drug, which has been used for extended periods in other conditions (rheumatoid arthritis, acne). Moreover, it is considerably cheaper than some of the drugs currently used in MS. However, its immune effects might have clinical consequences, perhaps leading to the emergence of other autoimmune disorders (as seen with CAMPATH-1H treatment). **-AJL**

**Popovic N, Schubart A, Goetz BD, Zhang S-C, Linington C, Duncan ID.**

**Inhibition of autoimmune encephalomyelitis by a tetracycline.**

**ANNALS OF NEUROLOGY**

**2002: 51(2): 215-223**

## Immunomodulatory effects of Glatiramer Acetate

Glatiramer Acetate (GA) is a random copolymer consisting of glutamic acid, lysine, alanine and tyrosine. It was originally developed, over 30 years ago, to mimic encephalogenic components of myelin basic protein for the induction of experimental autoimmune encephalomyelitis (EAE) in mice – an animal model of multiple sclerosis (MS). However, unexpectedly it inhibited the development of EAE, which resulted in GA being developed as a potential disease-modifying drug in the treatment of MS. Human trials later demonstrated a significant reduction in the relapse frequency when patients with relapsing-remitting multiple sclerosis are treated with GA. However, to date nobody has been able to explain these effects.

In investigating the mechanism of action of GA within both animal models and human trials, an antigen specific Th2 T cell proliferative response to GA has been identified. It was postulated that this might result in bystander suppression of aggressive Th1 cells that recognise 'self' antigens.

However, until now no group had satisfactorily assessed the effect of GA on the CD8+ T cell population, which requires direct immunophenotypic characterisation, due to their relatively low numbers. Karandikar *et al* took on this challenge. They used a combination of flow cytometry to assess the proliferation of T cells and the molecular characterisation of flow sorted T cells subtypes.

They demonstrated that untreated patients with relapsing remitting MS, when compared with healthy controls, have a deficient CD8+ T cell response when their lymphocytes were exposed to GA in vitro. Following the commencement of treatment with GA there is an up regulation of the CD8+ proliferation response, and only a brief statistically insignificant rise in the CD4+ cells. They confirmed that both the CD4+ and the CD8+ cell responses are HLA dependent. The functional profile of the CD8+ cells that were promoted by GA was inconclusive, although suggestive of a regulatory/suppressive nature with increased production of TGF $\beta$ . However both cell types produced TNF $\alpha$  that may be pro or anti inflammatory in different systems.

This paper therefore raises the possibility that the disease modifying effect of GA may be at least in part via its effects on promoting GA specific CD8+ cell proliferation. As several investigators have identified defective suppressive function in the CD8+ cell population in MS, the group postulate that up regulation of this cell population may explain the effects of GA, and reflect an important target for future disease modifying drugs. The group also raise the possibility of using CD8+ T cell monitoring as a marker for monitoring GA therapy. **-ALC**

**Nitin J. Karandikar et al.**

**Glatiramer Acetate (Copaxone) therapy induces CD8+ T cell responses in patients with multiple sclerosis.**

**THE JOURNAL OF CLINICAL INVESTIGATION**

**2002: 109(641-649)**

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