

**RESEARCH BULLETIN 35:
June 2004**



This bulletin provides a short summary of the research relating to MS and other neurological diseases in the following major scientific journals:

Multiple Sclerosis	June 2004
Current Opinion in Neurobiology	June 2004
Neurology	June 2004
Anaesthesia	May 2004
Disability and Rehabilitation	May 2004

The articles are organised according to topic as follows:

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DAMAGE IN MS

The relationship between inflammation and nerve fibre loss

Title: The pathogenesis of multiple sclerosis: is it really a primary inflammatory process?

Authors: F Maggs & J Palace.

Place of Report: Oxford, UK.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, pages 326-329.

Research Summary

In MS a number of events occur including inflammation, damage to myelin (the protective sheath surrounding nerve fibres) and nerve fibre loss. The specifics of how these events interact in MS is not fully understood and there is disagreement as to which process occurs first. Some researchers believe that inflammation occurs first, causing myelin damage and subsequently, nerve fibre loss. An alternative theory is that inflammation is secondary to nerve fibre loss. This report examines the evidence for this theory.

Nerve fibre loss in the brain and spinal cord (central nervous system – CNS) is linked to the progression of disability. Until recently it was thought that this only occurred with progressive forms of MS. However, more recent research has reported nerve fibre loss in areas of inflammation (through the study of post mortem and biopsy brain tissue), early in the disease course of MS. Individual studies have also shown that myelin damage does not appear to be related to nerve fibre loss. These findings suggest that nerve fibre damage and loss occurs early in MS, and might be a possible cause of inflammation.

Under normal conditions nerve fibres play a role in limiting inflammation - therefore it is likely that nerve fibre loss can lead to inflammation. Studies have shown that this inflammation may actually be protective, as a number of factors which protect nerve fibres from damage are released during this process. This may be reflected in a slower rate of disability progression for those with relapsing remitting MS, in which relapses are triggered by inflammation. Similarly, people with secondary progressive MS who still have

superimposed relapses appear to accumulate disability at a slower rate than those without.

Studies have shown that the relationship between inflammation and disability progression is complex, but that suppressing inflammation does not appear to slow nerve fibre loss. A long-term follow-up of people who have received beta interferon, which suppresses inflammation in MS, also supports this theory, as effects on disability progression are limited.

This report summarises that nerve fibre loss appears to occur early in MS and can lead to inflammation. Suppressing inflammation does not appear to significantly slow disability – inflammation may even be protective for nerves. The report concludes that new therapies should be targeted at protecting nerve fibres rather than limiting inflammation.

Key messages

- In MS a number of events occur including inflammation, damage to myelin and nerve fibre loss, although how these factors interact is not clear.
- An emerging theory is that inflammation is secondary to nerve fibre loss and is examined in this review.
- Nerve fibre loss has been shown early in MS and is a possible cause of inflammation.
- Inflammation (which can cause relapses) may actually be protective as a number of factors which protect nerves are released.
- Suppressing inflammation does not appear to significantly slow disability.
- New therapies should be targeted at protecting nerve fibres rather than limiting inflammation.

PRIMARY PROGRESSIVE MS

Characteristics of primary progressive MS

Title: Natural history of primary progressive multiple sclerosis.

Author: G Ebers.

Place of Report: Oxford, UK.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, supplement 1, pages S8-S15.

Research Summary

Primary progressive MS (PPMS) is estimated to affect between 10 and 15% of people with MS. It is characterised by a slow progression of disability, without any “attacks” (periods of relapse) or remission (recovery). Much less is known about PPMS, than other forms of MS. Part of the reason is due to the difficulty of conducting clinical trials in people with PPMS, because of the relatively long timescale which is needed to measure disability progression. This review summarises what is known about PPMS, through natural history studies, which monitored people with PPMS for an average of 25 years.

PPMS is most commonly diagnosed in men aged 30-35 and women aged 40-45 years, later than the majority of cases of relapsing remitting MS (RRMS). Unlike RRMS, it affects men and women equally. MRI (a non invasive technique which visualises damage in the brain and spinal cord) plays a major role in both the diagnosis and monitoring of people with RRMS. However, people with PPMS typically have fewer and smaller lesions (areas of damage) as visualised by MRI scans than people with RRMS (although MRI cannot be used to make a differential diagnosis between RRMS and PPMS). It has also been suggested that PPMS is extremely similar to secondary progressive MS, without the initial relapsing stage.

Although PPMS is progressive, it does advance at slightly different rates in different people. The most significant predictor of later disability is the rate of accumulation of disability early in the disease, with those having less disability early, taking longer to reach more significant levels later. The number of different “systems” involved is also identified as a prognostic factor - those

people with multiple affected areas of the body have a poorer prognosis. Age and gender have been shown to have no effect on the rate of progression.

Designing clinical trials for PPMS is difficult as people often have a higher level of disability at diagnosis, which can exclude people from trials where unaided walking is required. Longer follow up periods are needed to detect changes in disability.

In summary, this information on PPMS is useful in clarifying relationships between different types of MS and identifying factors associated with a better or worse outcome. Information from natural history studies could be used to design appropriate clinical trials in people with MS and may negate the need for a "no treatment" comparison in clinical trials.

Key messages

- Primary progressive MS affects 10-15% of people with MS and is characterised by a slow progression of disability.
- It is most commonly diagnosed later than relapsing remitting MS, affecting men and women equally.
- People with primary progressive MS have smaller and fewer areas of damage visualised by MRI scans.
- Early accumulation of disability early on in the disease and multiple affected areas of the body are poorer prognostic factors.
- Age and gender have been shown to have no effect on the rate of disability progression.
- Long follow-up periods in clinical trials involving people with primary progressive MS are needed to assess disability progression.
- Information on the natural history of primary progressive MS may negate the need for a "no treatment" comparison in trials of potential therapies for PPMS.

STEM CELLS

Can stem cells be used for remyelination?

Title: Cell-based remyelinating therapies in multiple sclerosis: evidence from experimental studies.

Authors: S Pluchino, R Furlan & G Martino.

Place of Report: Milan, Italy.

Journal Reference: Current Opinion in Neurobiology, 2004. Vol. 17, pages 247-255.

Research Summary

In MS a number of events occur including inflammation, damage to myelin (the protective sheath surrounding nerve fibres) and nerve fibre loss, which can lead to disability. Remyelination (myelin repair) can occur and restore function to nerves, but this process is limited and fails over time. Possible reasons for this include loss of oligodendrocytes, the cells that produce myelin and changes in the environment, which discourage remyelination. This review summarises some of the cell based strategies currently being developed to promote remyelination.

Transplanting cells which have the capacity to remyelinate nerve fibres, into areas of damage in the brain is a technique under development. The only study in humans so far has involved transplanting Schwann cells, which make myelin outside of the brain and spinal cord, into areas of damage in the brain. Three people with MS have received transplants but although there were no serious adverse effects, investigation showed no evidence that the transplanted cells survived. Other possible cells which are being investigated include olfactory ensheathing cells, which can be taken from behind the nose and stem cells, unspecialised cells which have the capacity to develop into different cell types. Both these cell types have shown promise in early animal studies, although further research is needed to evaluate their potential.

Limitations in using cell based therapies include the need for an unlimited source of the cells, and the need to access several different areas of damage

in the brain and spinal cord at the same time. MS in particular is characterised by multiple dispersed areas of damage.

The route of administration of cell based therapies is another key issue. However, recent experiments have shown that injecting stem cells into the bloodstream or the fluid surrounding the brain and spinal cord may be a possibility, as it appears that the cells can "find" areas of damage. However, the ability of cells to actually develop into myelin producing cells once in place is unclear.

There has been increased interest in the use of cell based remyelination strategies and a number of cell types which could play a role in remyelination are being explored. Despite some limitations, the authors highlight that further studies investigating whether stem cells can generate functional cells are needed.

Key messages

- MS is characterised by inflammation, damage to myelin and nerve fibre loss.
- Remyelination (myelin repair) can occur but this fails over time.
- A number of cell based therapies to promote remyelination are under development including the use of Schwann cells, olfactory ensheathing cells and stem cells.
- Schwann cells have been transplanted into humans with no serious adverse effects but also no beneficial effect.
- Issues include the need for an unlimited source of cells which are able to access multiple areas of damage.
- Further studies are needed to evaluate whether transplanted cells can make functional myelin, once in areas of damage.

CLINICAL RESEARCH

The future for clinical research

Title: The state of patient-oriented research in neurology.

Authors: R Sacco, B Malow & L Williams.

Place of Report: New York, USA

Journal Reference: Neurology, 2004. Vol. 62, pages 1051-1055.

Research Summary

Clinical or patient orientated research involves human volunteers, either directly, as in a clinical trial or, for example, through interviews. Both basic (laboratory based) and clinical research are major areas of work for many neurologists. However, despite major advances in basic research over the last 25 years there has been a lag in “translational research” (a major part of clinical research) to transform discoveries and progress in the laboratory into potential treatments for patients.

A major barrier to translational research is the lack of time available for clinical researchers to commit to research. A recent survey found that only 18% of clinical researchers had more than 50% of their time “ring fenced” for their research studies.

Similarly, there is an identified difficulty in recruiting trained clinical researchers and many doctors do not want to enter this field. Reasons given for this include high debts, the long duration of clinical training, high administration requirements and concerns about a lack of facilities for translational research.

This report highlights the need to increase the career opportunities for those involved in clinical research. This is already happening in the US through the development of new programmes aimed at improving the training of clinical researchers. This includes training in skills vital to clinical research not routinely taught in medical schools, such as statistics, ethics and scientific writing. The report goes on to suggest that more work is needed to increase opportunities for those already working in the field of clinical research so that

the quality and quantity of clinical research in neurology can keep pace with the basic science developments.

Key messages

- Clinical research (research which involves human volunteers) is declining, despite major advances in laboratory-based research.
- Translational research to transform discoveries in the laboratory into potential treatments for patients is also declining.
- A major barrier to this type of research is a lack of time "ring fenced" for research studies.
- Recruitment of clinical researchers is also a problem, due to long training periods, administration and a lack of translational research facilities.
- Increased career opportunities for both new and current clinical researchers are needed, to keep pace with laboratory developments.

CANNABIS

Is cannabis effective for pain treatment?

Title: Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies.

Authors: W Notcutt, M Price, R Miller, S Newport, C Phillips, S Simmons & C Sansom.

Journal Reference: Anaesthesia, 2004. Vol. 59, pages 440-452.

Research Summary

Pain affects approximately half of all people with MS and is also a common symptom in other conditions. A significant amount is as a direct result of MS damaging nerves, known as neuropathic pain. Unfortunately, this type of pain responds poorly to standard drugs and this, often long-term symptom, is difficult to treat effectively. There are anecdotal reports that cannabis is beneficial for a range of symptoms associated with MS, including pain, nausea and sleep problems, although research-based evidence to support this view is limited.

This study looked at the effectiveness and safety of two cannabis extracts, called tetrahydrocannabinol (THC) and cannabidiol (CBD), alone and in combination, in people with long-term pain. All results were compared to a placebo (a "control" substance known to cause no effect).

32 participants with long-term pain (as a result of different conditions, including MS) took part in the study. The most effective cannabis extract dose was determined in an initial phase of the study and each participant received THC alone, CBD alone, THC and CBD in combination and placebo for two separate one-week periods over the eight-week study period. All treatments were administered via a spray under the tongue. Each participant self-rated the severity of their two worst symptoms, their sleep pattern and any side effects, before administration of any treatments and on a daily basis for the duration of the study.

Results showed that both the combination treatment and THC alone significantly improved the two main pain-related symptoms nominated by the

participants. CBD alone was not found to have any effect. All cannabis extracts were found to significantly increase the number of “good” nights of sleep, although not lengthen the number of hours of sleep. The main side effects were dry mouth, drowsiness and feelings of euphoria (feeling “high”).

In summary, THC alone, and in combination with CBD, was effective in relieving pain and improving sleep in this small number of participants. The authors suggest that the next steps are to study cannabis extracts in a wider selection of specific pain problems in order to determine the full extent of potential benefits.

Key messages

- Pain is a common symptom of MS. Pain arising from damage to nerves is often difficult to treat effectively.
- There are anecdotal reports that cannabis can help reduce pain, although research-based evidence to support this is limited.
- The effectiveness of two cannabis based extracts, called tetrahydrocannabinol (THC) and cannabidiol (CBD), alone and in combination, were assessed in 32 people with long-term pain.
- Each participant assessed the impact of the extracts on two self-chosen pain-related symptoms.
- Results showed THC, alone and in combination with CBD significantly improved pain-related symptoms and improved sleep quality.
- The main side effects were dry mouth, drowsiness, and feelings of euphoria.
- The authors suggest that the effect of cannabis extracts for specific pain problems should be studied in a larger number of participants.

DAILY LIVING

Independence in MS

Title: Performance of activities of daily living in multiple sclerosis.

Authors: E Mansson & J Lexell.

Place of Report: Sweden.

Journal Reference: Disability and Rehabilitation, 2004. Vol. 26, no. 10, pages 576-585.

Research Summary

MS, particularly in the later stages of disability progression, can result in a reduced ability to perform daily activities. This in turn can impact significantly on a person's independence and quality of life. Daily activities can be broadly divided into those related to personal activities (e.g. dressing, eating, going to the toilet, washing and general mobility) and areas which can impact on independence such as shopping, housekeeping, cooking and communication. This study aimed to assess the impact of moderate to severe MS on these factors and explore the relationship between disease severity and ability to perform daily activities.

A total of 44 people with moderate to severe MS took part in the study. Levels of disability were assessed at the start of the study. Each participant was assessed by healthcare professionals, using a number of specialised measurement scales, for their ability to carry out both personal and independence-related tasks.

Results showed that participants had some limitations in personal care, mostly related to self-care, transferring and general mobility, with half the participants assessed as "dependant". The majority of participants did not have any significant cognitive or communication problems. Despite some participants being able to satisfactorily perform personal activities, they reported significantly reduced levels of independence, which meant their ability to live independently was affected.

In summary, moderate to severe MS reduces the ability to perform both personal and independence related daily activities, for some people. Assessments of both these areas is identified as important in order to fully evaluate people's needs and introduce programmes to manage them.

Key messages

- MS can impact on the ability to perform both personal and independence related daily activities.
- The impact of moderate to severe MS on performance of daily activities was assessed.
- Half the 44 participants were assessed as "dependant", although the majority did not have any significant cognitive or communication problems.
- Some participants reported reduced levels of independence.
- Assessment of peoples' ability to carry out daily activities is important in introducing programmes to manage them.

YOGA

Are exercise and yoga beneficial for MS?

Title: Randomised controlled trial of yoga and exercise in multiple sclerosis.

Authors: B Oken, S Kishiyama, D Zajdel, D Bourdette, J Carlsen, M Haas, C Hugos, D Kraemer, J Lawrence & M Mass.

Place of Report: Oregon, USA.

Journal Reference: Neurology, 2204. Vol. 62, pages 2058-2064.

Research Summary

Yoga is a commonly practised technique incorporating meditation, breathing and postures based around specific stretches. Iyenger yoga is the most common type practised in the US, in which participants use contraction and relaxation of different muscles to create specific stationary positions. This also comprises a relaxation component. Research has shown that exercise has a beneficial effect on quality of life, fatigue and mood, suggesting physical activity may be beneficial generally. This study aimed to assess the effect of yoga in comparison to general exercise, in people with MS.

69 participants with mild to moderate MS were randomly assigned to a six-month Iyenger yoga or exercise programme or a no intervention group (people on the waiting list for exercise or yoga). Yoga and exercise sessions were once per week and lasted 90 minutes, with daily home practise strongly encouraged. The exercise session consisted of cycling on an exercise bike. Participants filled out a diary of participation. Attention, alertness, mood and fatigue were assessed before the start of the trial and after the six-month period.

Results showed that there were no adverse events related to the yoga or exercise. Attendance rates at exercise and yoga weekly classes was 65 and 68% and home practice occurred on 45 and 51% of non class days, respectively. There was no effect of either intervention on attention or alertness. Both interventions produced improvements in fatigue to a similar level.

The authors note that as the yoga programme was significantly modified to take into account some of the limitations that people with MS may have, the results may not be generalisable to community based yoga programmes. However, this trial adds important information on the beneficial effects of physical activity in people with MS.

Key messages

- Yoga is a commonly practised technique incorporating meditation, breathing and postures based around specific stretches.
- This study assessed the effect of a weekly 90 minute yoga session, in comparison to exercise (cycling on an exercise bike) and no activity, in people with MS.
- 69 people with mild to moderate MS took part in the six-month study.
- Effects on attention, alertness mood and fatigue were assessed.
- Participants in both groups attended approximately two thirds of sessions.
- No adverse effects related to the yoga or exercise were reported.
- Both programmes improved fatigue levels, to a similar level.
- This study highlights the beneficial effects of physical activity in people with MS.

ANTEGREN

Antegren to treat relapses?

Title: Randomised multicentre trial of natalizumab in acute MS relapses: clinical and MRI effects.

Authors: P O'Connor, A Goodman, A Willmer-Hulme, M Libonati, L Metz, R Murray, W Sheremata, T Vollmer, L Stone and the Natalizumab Multiple Sclerosis Trial Group.

Place of Report: Toronto, Canada.

Journal Reference: Neurology, 2004. Vol. 62, pages 2038-2043.

Research Summary

Antegren (natalizumab) is a type of antibody which is currently undergoing a large controlled clinical trial to assess its affect on relapses and disability progression in relapsing remitting MS and secondary progressive MS with relapses. It acts to reduce the passage of immune cells into the central nervous system (CNS: brain and spinal cord) where they can cause inflammation and damage. Relapses are caused when a sufficient amount of immune cells pass into the CNS and cause damage in specific areas. This study assessed the effect of a single dose of Antegren (administered via intravenous infusion) in people who had just had a relapse, to see whether it would speed-up recovery.

180 people with mild to moderate relapsing remitting or secondary progressive MS with relapses, who were not taking any other disease modifying therapy took part in the study. Participants received either placebo (a control substance known to cause no effect), or a low or high dose of Antegren. MRI scans, a physical examination and a self-rated assessment of participants well-being were completed before receiving the drug and for 14 weeks afterwards.

Results showed that neither dose of Antegren significantly affected the recovery time from a relapse. Disability levels, neurological assessment and participants' perception of their well-being were not significantly different between the three groups. An improvement was seen in 50% of participants

two weeks after the start of the relapse, irrespective of which treatment they received. However, MRI scans showed a significant decrease in the size of new lesions, (specific areas of damage) compared with the control group, up to two weeks after administration of Antegren (both doses). There was also a trend towards a decrease in the number of new lesions at weeks one and three after administration.

These results indicate that recovery from relapses is quicker than previously thought, whether given Antegren or not. The MRI changes shown in this study also raise the possibility that long-term treatment with Antegren might be a future therapeutic option. An initial study has shown that Antegren has a significant impact on MRI scans and relapse rates in people with relapsing forms of MS. Results from the larger follow up trial are expected later this year.

Key messages

- Antegren is a type of antibody which reduces the movement of immune cells into the brain and spinal cord, which causes damage in MS.
- This study assessed the effect of a single dose of Antegren on the rate of recovery from a relapse.
- 180 people took part in the study, receiving either a low or high dose of Antegren or placebo.
- Neither dose of Antegren significantly affected the recovery time from a relapse - there was no difference in disability levels or well-being, compared to no treatment.
- MRI scans showed a significant decrease in the size of new lesions, compared to the placebo group, up to two weeks after administration.
- An initial study with Antegren has shown that Antegren has a significant effect on relapse rate and MRI visualised damage.
- Results from a larger follow-up trial are expected later this year.

TREMOR

A further look at 1-octanol for tremor

Title: Open-label dose escalation study of oral 1-octanol in patients with essential tremor.

Authors: H Shill, K Bushara, Z Mari, M Reich & M Hallett.

Place of Report: Minneapolis, USA.

Journal Reference: Neurology, 2004. Vol. 62, pages 2320-2322.

Research Summary

Tremor is a common symptom of MS. The most common form of this symptom in people with MS is called essential (or intention) tremor (ET), which occurs when people want to do or reach for something. This study follows on from a previous study which showed that 1-octanol (a type of alcohol) was effective in treating ET. Beneficial effects were seen over a three-hour period, with no significant side effects (refer to Research Bulletin 32). This study follows on from this and aims to find the maximum dose of 1-octanol which can be given without unacceptable side effects.

20 people with mild to moderate tremor (with a range of causes) participated in the study. Three people took the lowest dose of 1-octanol. In the absence of serious side effects further groups of three participants took progressively higher doses of 1-octanol over the study period. Measurements of effectiveness were completed before the study and hourly until 3 hours after administration. Tremor was assessed by handwriting and drawing tasks as well as through a sensor strapped to the participants' wrist, which objectively measured the degree of tremor.

All subjects completed the trial with no significant adverse effects. No participant showed overt signs of toxicity (drunkenness), although the highest dose appeared to produce some subjective reports of sedation. Four participants also reported an unusual (although not unpleasant) taste in the mouth after administration. Results from the drawing and handwriting tasks improved significantly from before treatment, with each dose. The major response was seen at two hours after administration, for both the manual

tasks and the sensor results. There was a suggestion of a more prolonged response at higher doses.

1-octanol appears to be well tolerated over a range of doses, with minimal side effects. The authors highlight that the small participant numbers prevent firm conclusions being drawn but suggest this drug may produce real benefit. Larger trials to monitor effectiveness are being considered.

Key messages

- Tremor is a common symptom of MS.
- Essential (or intention) tremor occurs when people want to do or reach for something, and is the most common form.
- 1-octanol, a type of alcohol, has previously been shown to effectively treat essential tremor over a three-hour period.
- 20 people with mild to moderate tremor took increasing doses of 1-octanol.
- Tremor was assessed by an objective sensor attached to the participants' wrist, and handwriting and drawing tasks.
- There were no serious adverse effects, although the highest dose produced sedation in some participants.
- The major beneficial effect was seen at two hours after administration - higher doses produced a more prolonged effect.
- This study only involved a small number of participants and larger trials to assess effectiveness further are being considered.

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