the Bank Statement

News from

The UK Multiple Sclerosis Tissue Bank

ISSUE 2 - 2004

A newsletter for you

In this issue, find out …

Welcome to the second issue of the Tissue Bank's newsletter. Some of you will have already registered as donors, while others will be in the process of deciding whether it is right for you; or may be, you are the relative or friend of someone who has donated tissue. We hope that our **Bank Statement** will keep **all of you** up to date with what is going on here at the Tissue Bank.

- how the work of the Tissue Bank was reviewed
- what the Bank has achieved over the last six years
- about 6 research projects being supported by the Tissue Bank
- who makes-up the Tissue Bank Team
- what things we would like you to tell us

How it all started?

In 1998, the Multiple Sclerosis Society awarded a 5-year grant to Imperial College London at Charing Cross Hospital to enable the setting-up of a national Tissue Bank for research on multiple sclerosis (MS). The aim of this centralised facility is:

➔ to co-ordinate the collection of tissue donated for MS research, and
➔ to distribute the donated material to scientists conducting research on MS.

Reviewing our work

The progress that the Tissue Bank had made over the first 5-year grant period was assessed by an Independent Review Panel appointed by the MS Society. The Panel was chaired by **Professor James Underwood** (President, Royal College of Pathologists; Chairman, Working Committee on Organ Retention) and comprised of experts in neuropathology, neurology and MS research. The panel also included a relative (**Mrs Sharon Rowsell**) of a person who had donated tissue, a person living with MS (**Ms Bryony Jones**) and representatives from the MS Society.

"…one of the best in the UK and Europe."

The diligence with which the members of the Panel examined the work of the Tissue Bank has meant that we have been able to draw on their report to further improve our work. We are delighted that upon the recommendation of the Review Panel, the Board of Trustees of the MS Society decided to fund the Tissue Bank for another five years (March 2003 to February 2008). The overall conclusion reached by the Independent Review Panel was that the UK Multiple Sclerosis Tissue Bank was "**one of the best in the UK and Europe**".

Recruiting individuals on the Tissue Bank's Donor Scheme

Progress in the work of the Tissue Bank

We have continued to raise the profile of the Tissue Bank as a facility for those who want to donate tissue to research after their death. Over the last five years, Professor Richard Reynolds (Scientific Director) and Dr Abhi Vora (Manager) have given **over 100 talks** on the importance of the availability of tissue for research. As well as these face-to-face interactions, we have written articles for magazines including MS Matters and TeaMSpirit. We have also promoted our work amongst neurologists and nurses, so that they are also able to pass-on information about tissue donation. We have used these promotional exercises to get in touch with as many people as possible who want to find out about donating tissue to research on the cause and treatment of MS.

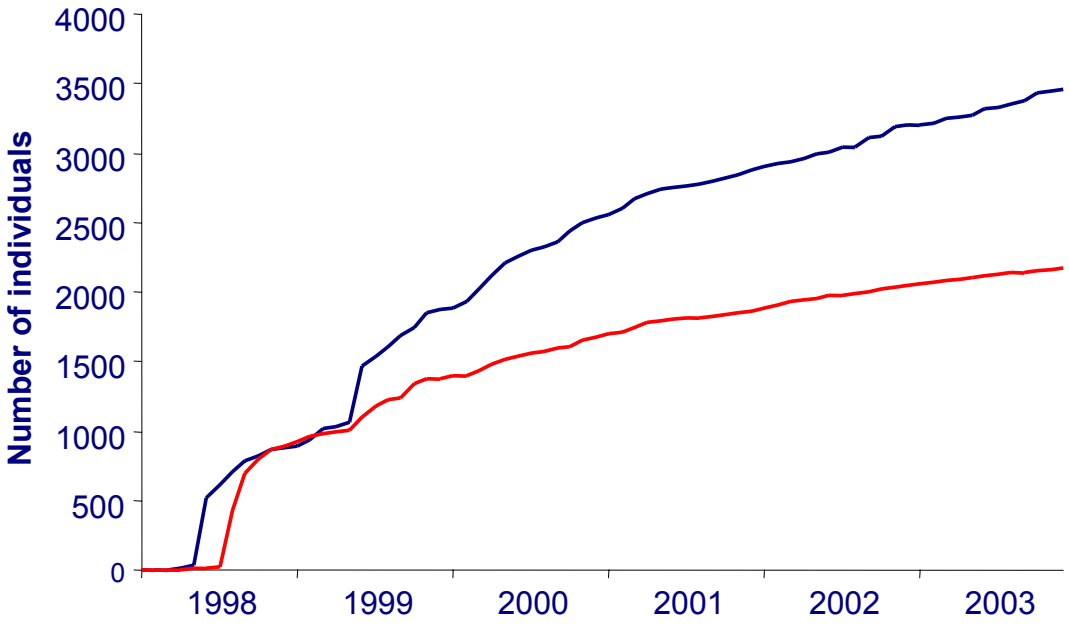
Over 2000 registered donors…

…but we need more

The graph below shows how the number of people requesting an Information Pack (blue line) and registering as donors (red line) has continued to rise over the last 6years. At the end of six years, we had supplied over **3,452 Information Packs** and **2,186 individuals had registered** on the Tissue Bank's Donor Scheme. We will continue raising our profile because **we need even more people to register.**

Accumulation of enquiries and registered donors

- **blue** line information requests
- **red** line registered donors



Need for tissue from people that did not have MS

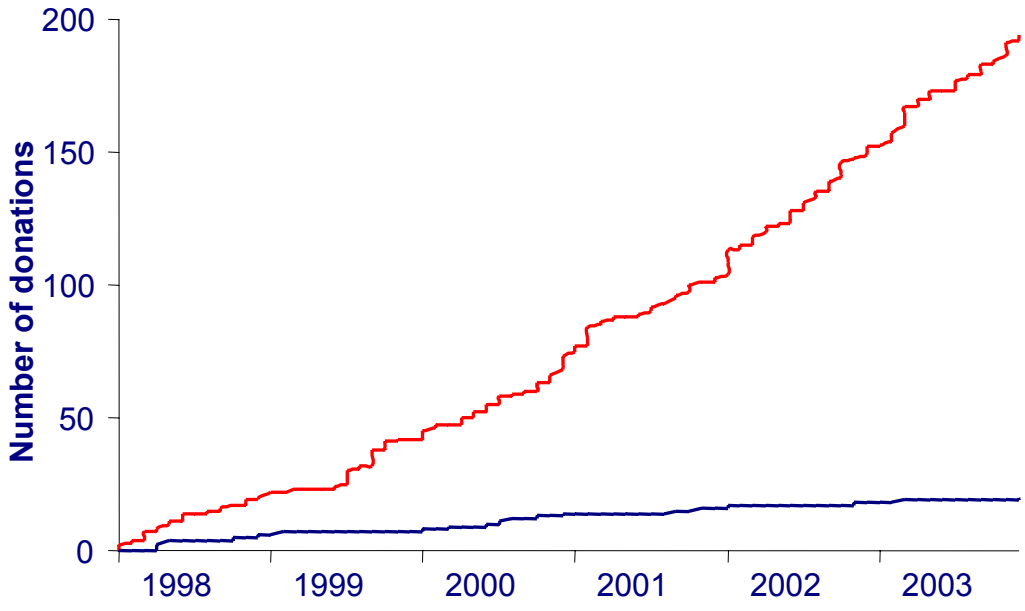
Scientists need to study tissue from MS patients side-by-side with tissue from people who did not have MS ("normal controls") and tissue from people who had conditions other than MS ("disease controls"). Only by making these comparisons can they identify the changes that are caused by MS. Up to now, we have concentrated on recruiting people with MS on to our donor scheme, with the result that **only 22%** of the 2,186 people registered on the scheme do not have MS. So, we **need more people without MS to register** as donors to help research on MS.

Fulfilling last wishes

Over the last six years, we have been in the privileged position of fulfilling the last wishes of **194 people who had lived with MS** and **20 individuals who did not have the condition**. This graph shows how, over the six years, we have accrued tissue from these 214 donors – all of whom wanted to help find even better treatments for MS.

Accrual of 214 tissue samples

- **red** line MS donors
- **blue** line non-MS donors



We have been overwhelmed by the willingness of a range of professionals to help us with this task – including doctors, nurses, coroner's officers and pathology technicians; all working together to retrieve donated tissue as soon as possible after death. Their

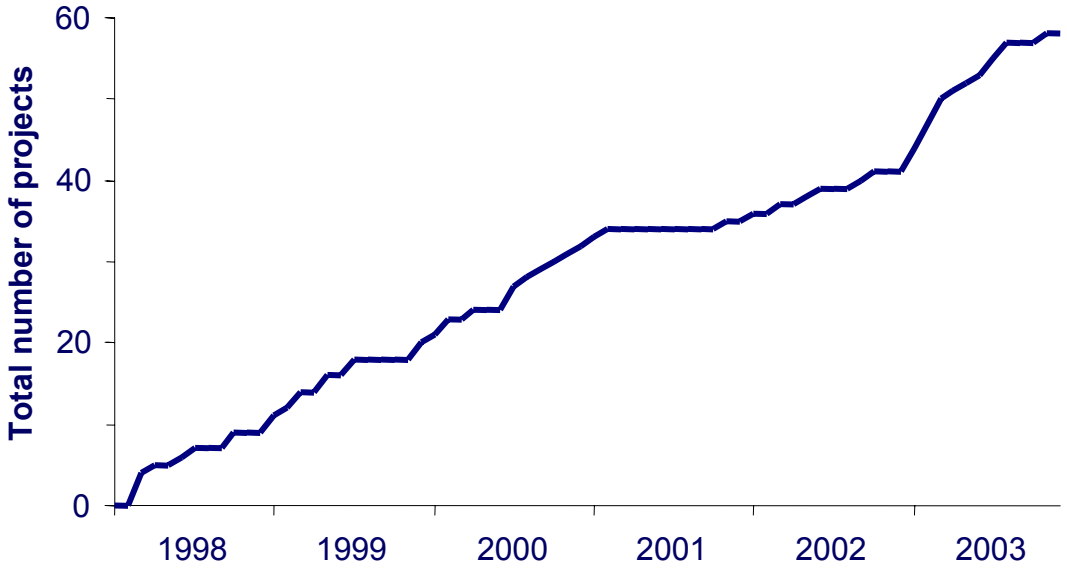
70% already used in research

goodwill and the effectiveness of our collection procedure has allowed us to process tissue from **70% of our donors within 24hours of death**; quite a feat considering our donors are drawn from across the whole of the UK. What is more, **tissue from 70% of all our donors has already been used in research**.

A Resource for Research

As well as raising the awareness of the MS community to our work, we have also been promoting the Tissue Bank as a **"Resource for Research"** in the scientific community. As a result of these promotional exercises and the high quality of service that we offer to researchers, the number of studies that the Tissue Bank supports has steady grown as seen in the graph below. We are now providing tissue and/or cerebrospinal fluid samples to **57 different projects**.

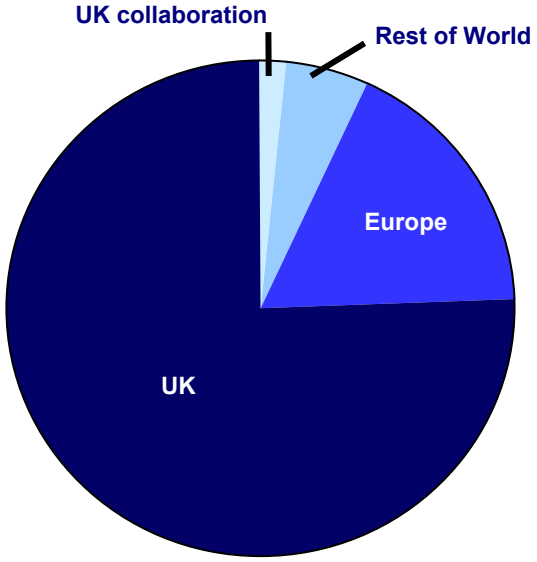
57 projects supported over 6years



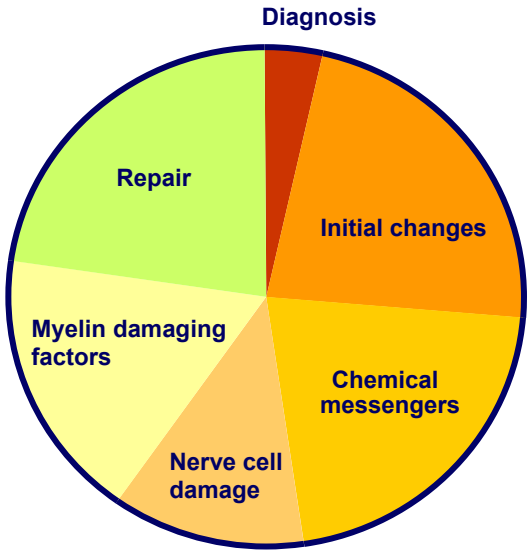
obligation to donors

Although the Tissue Bank has been set-up to help us gain a better understanding of MS irrespective of where the studies are being carried out, we believe we have an obligation to support research in the country where our donors were resident. The pie chart on the left below shows that three quarters of the 57 projects supported by the Tissue Bank are being carried out in the UK.

majority of projects are UK-based



57 studies in 6 areas of essential research



Supporting the whole spectrum of MS research

The 57 projects cover the whole spectrum of research on multiple sclerosis: including diagnosis; earliest changes within a lesion; chemical messengers that drive the immune system; factors that damage myelin and nerve fibres (axons); and, remyelination. The pie chart on the right above shows how the 57 projects are on the whole evenly distributed into these 6 categories. We have selected a project from each of the six areas to give you an idea of the type of research that the Tissue Bank is supporting.

1 Diagnosis

Using magnetic resonance imaging (MRI) to find out what is happening within MS lesions

Professor David Miller - MS Nuclear Magnetic Resonance (NMR) Research Unit at Queen Square, London.

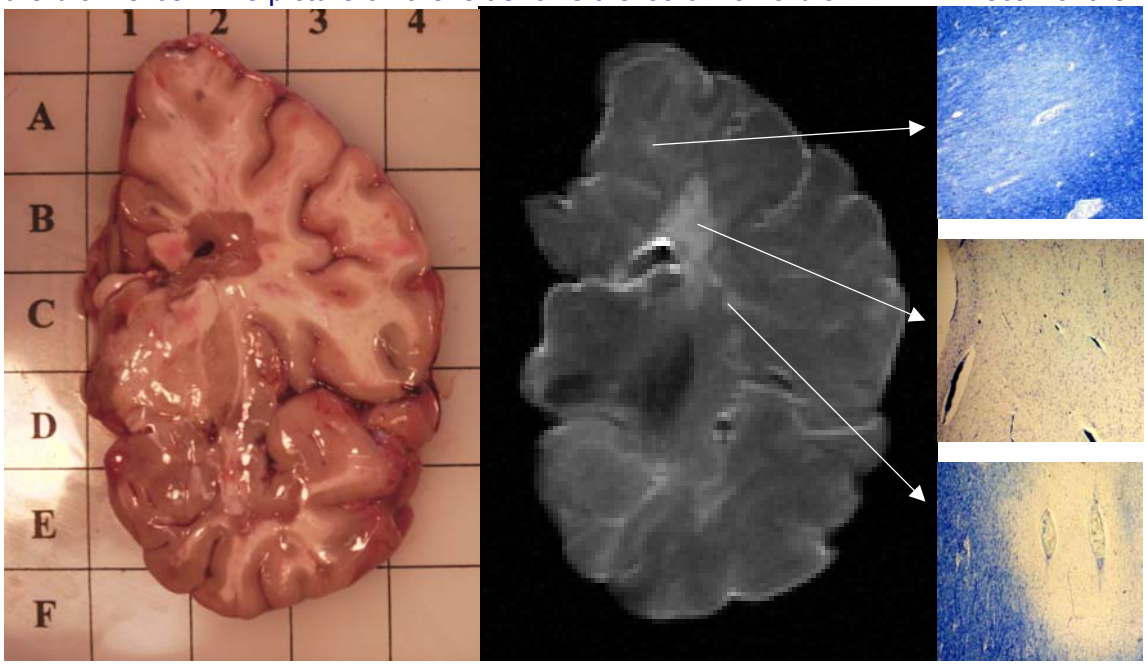
Typical aspects of the typical MS lesion

Lesions within the brain and spinal cord (central nervous system – CNS) of people living with MS have one or a number of features, for example: myelin destruction (demyelination), new myelin formation (remyelination) or a loss of the nerve fibres that are normally enveloped by the myelin (axonal loss). These different facets of the lesion can be clearly seen in tissue samples removed from the brain after death; but, is it possible to detect them in a person living with the condition? The NMR Research Unit is trying to find a magnetic resonance imaging (MRI) technique that will do just that.

Can MRI tell us what is happening within lesions?

Over the last six years the NMR Unit has been supplied with brain slices from over 50 MS patients and 2 individuals without MS. The brain slices are scanned using a number of MRI techniques and areas that have "lit up" on the scan are dissected out, stained and examined under a microscope. The microscopic features (demyelination, remyelination, axonal loss) of the lesion are then related to the MR images obtained of the brain slice. The picture on the left shows a slice of half a brain. An MR scan of the

Compare the image with the tissue



slice (lesions appear as white patches) is shown in the second panel. The three arrows indicate lesions that were later dissected out; their appearance under a microscope is shown in the three smaller pictures on the far right.

What happens with each brain slice supplied to the project

→ scan
→ dissect out
→ stain
→ compare

This project aims to extend the use of MRI beyond diagnosis by finding out which imaging techniques are best for studying the effect that MS therapies have upon lesions in a person living with MS. A number of techniques in this ongoing study are already showing promise including "magnetisation transfer (MT)" MRI. This technique has already been used to show that β-Interferon promotes lesion recovery in people with relapsing-remitting MS.

Why is this research important?

2 Earliest changes

How normal is normal?

Dr Nicole Schaeren-Wiemers, University Hospital Basel, Switzerland and Professor Richard Reynolds, Imperial College London

Multiple sclerosis is characterised by the presence of discrete areas of demyelination scattered throughout the CNS; with these islands of damage surrounded by normal tissue. Since new lesions would have to appear in this normal area, could examining these areas reveal the earliest changes in the development of MS lesions? The two research groups lead by Dr Schaeren-Wiemers and Professor Reynolds are using a very sensitive technique called "microarray analysis" to look for these changes in so called "normal appearing white matter" in tissue from MS donors.

Are very subtle changes in "normal" tissue the start of a new lesion?

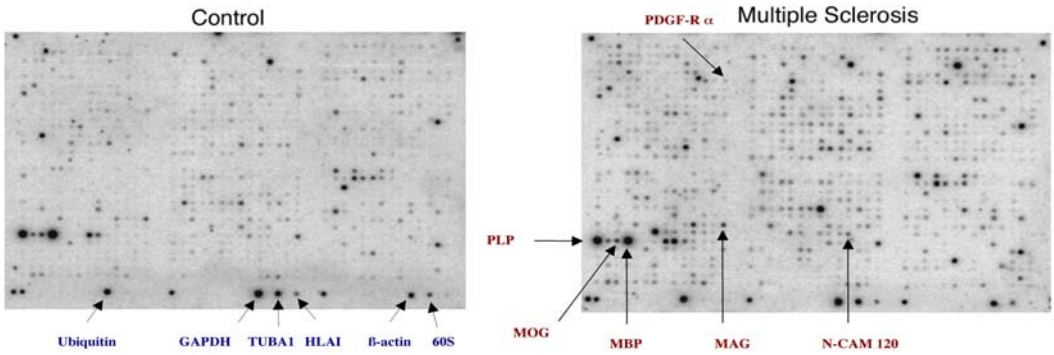
The experiment…

Tissue samples were selected from 10 MS tissue donors and 7 patients that did not have MS. These samples were first examined under a microscope to ensure that the MS tissue did not contain a lesion and that it appeared essentially "normal"; all 17 samples were then introduced into the microarray system. The system can **test 3,000 genes in a single experiment**! It allows the researcher to identify which of the 3,000 genes have been switched on and which ones turned off in the tissue.

Testing 3,000 genes

This is what microarray looks like…

…the spots show which genes have been switched on



These pictures show two microarray slides; the left one received tissue from a control and the right, a sample from an MS donor. Each dot represents one gene; and the darkness of the dot indicates how activated the gene was. When the researchers compared the intensity of dots obtained using the control tissue samples with the normal appearing MS tissue, they found that the activity of **334 genes** had changed – in particular, one group of genes that directs the response of cells to stress; and a second group regulating the response of tissue trying to protect itself against damage.

334 genes changed in "normal" MS tissue

These research groups suggest that in the brains of people living with MS, there is a balance between "damage" on the one hand and "defence against damage" on the other. It is when the balance tips to "damage" that a site becomes susceptible to developing a lesion. This work gives rise to a new area of research with the focus on why lesions fail to develop in some areas of normal appearing tissue in MS. Could new therapies look at tipping the balance to help the brain tissue protect itself against damage?

A new avenue for research on therapies?

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3 Chemical messengers

How do white blood cells breach the blood-brain barrier?

Professor Nicola Woodroofe, Sheffield Hallam University, Sheffield

Components of the immune system, the white blood cells and antibodies, are thought to be responsible for damaging the myelin and oligodendrocytes (cells that make the myelin) in lesions seen within the CNS of individuals living with MS. An early event in the formation of an MS lesion is one of white blood cells moving from the circulation into the brain tissue. The dissection of this seemingly simple, but actually complex series of events is the task that Professor Woodroofe and her group have set themselves. They are looking at a potent chemical messenger used by the immune system called TNF (the letters stand for **t**umour **n**ecrosis **f**actor - a name that has more to do with how it was discovered than what it actually does). One of the actions of TNF is to act on blood vessel walls in the brain (blood-brain barrier - BBB) to allow the passage of white blood cells across the BBB and into the tissue. The secretion of TNF is caused by the action an enzyme called – ADAM17. In the first series of experiments, Professor Woodroofe's group have been setting-up a system with which they can accurately detect and locate ADAM17 within the brain.

It all starts with white blood cells crossing the BBB

TNF – a potent messenger

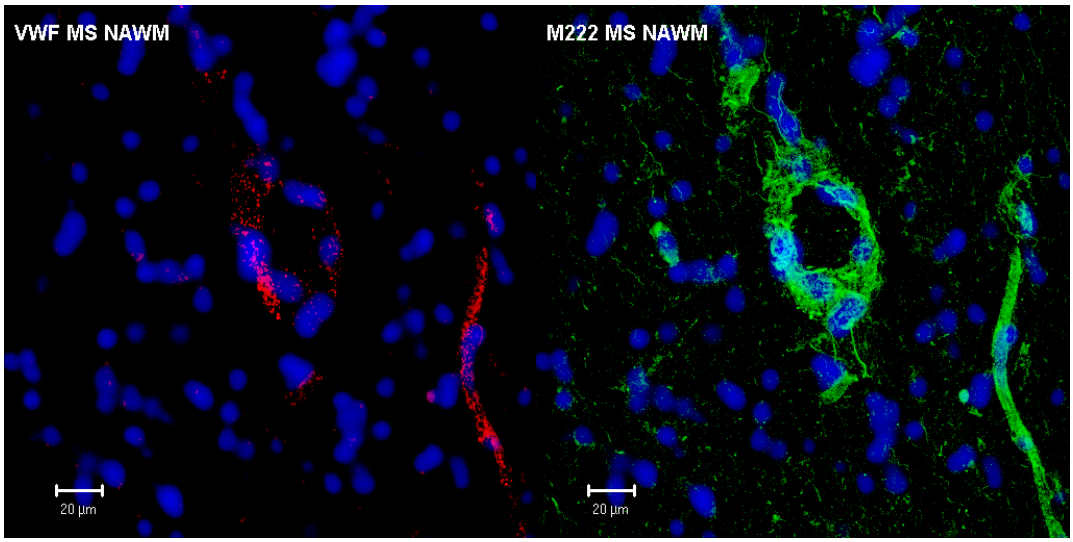
…released by ADAM17

The images below show what is seen when looking down a microscope at tissue slices from an MS patient. The slices have been treated with three different dyes that fluoresce –the wisps of red on the background of purple dots in the picture on the left show the presence of two blood vessels in the tissue slice; and, the one on the right shows that these blood vessels are expressing large amounts of the enzyme ADAM17.

ADAM17 present on blood vessels in MS tissue

TNF is a potent chemical that plays a number of different roles - as well as its effects on the BBB, TNF may also be responsible for demyelination. One way of stopping the

Visualising the players…



purple = all cells
red = BBB
green = ADAM17

Why are these studies important?

detrimental actions of TNF is to prevent its release by inactivating ADAM17. As a first step Professor Woodroofe's group is learning more about the presence of ADAM17 within MS lesions.

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4 Damage to nerve cells

How is grey matter affected in MS?

Professor Margaret Esiri, University of Oxford, Radcliffe Infirmary

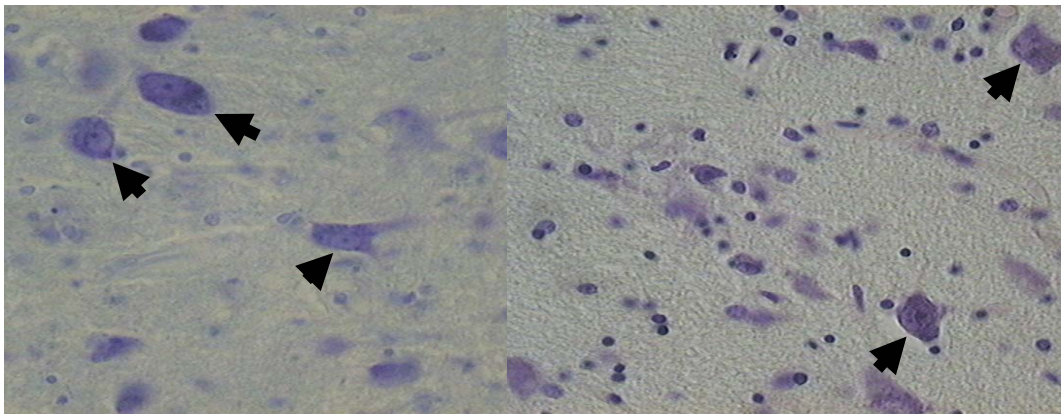
grey and white areas

The varied symptoms experienced by people living with MS arise because of the development of discrete areas of damage (lesions) within the CNS. The CNS can be divided into two areas according to the relative proportions of myelin (wrapped around axons) and nerve cell bodies (an axon is a single outgrowth from a nerve cell body along which nerve impulses travel).

Why is "grey" grey, and "white" white?

Areas that have more nerve cell bodies than myelin appear grey (grey matter) and regions that are richer in myelin look white (white matter). Since some of the symptoms associated with MS, especially disturbances in the so-called "higher" functions (such as memory and concentration) may be caused by damage to nerve cell bodies, the group in Oxford have been looking to see how grey matter is affected in MS. One study looked closely at one grey matter area - the thalamus (the brain's "telephone exchange") in tissue donated by eight MS patients and two patients that did not have MS (control subjects).

Nerve cell bodies in the thalamus from a control and MS subject



35% reduction in the number of nerve cells

These are images of the thalamus from a control (left) and an MS donor (right) seen under a microscope. Fewer nerve cell bodies (arrows) are present in the MS sample; there was an overall 35% reduction in the thalamus from the eight MS patients.

Implications for therapy

Since the loss of nerve cells in the grey matter may contribute to some of the symptoms experienced by individuals living with MS, new therapies need to not only tackle demyelination but also ensure that nerve cell bodies are protected from harm.

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5 Myelin damage

This is what oligoclonal bands look like…

…bands = antibodies

Could these antibodies be destroying myelin?

Myelin is a complex compound…

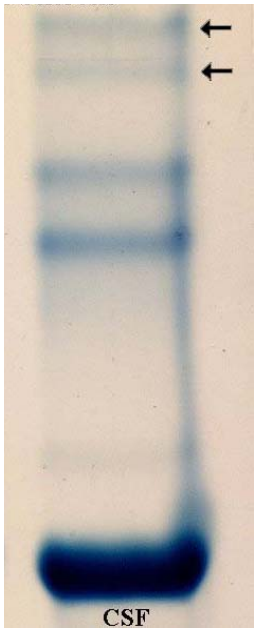
…one of its constituents is MOG

Implications for therapy…

Antibodies in oligoclonal bands might attack myelin

Dr Sandra Amor, BPRC, Rijswijk, The Netherlands

An important test used in the diagnosis of multiple sclerosis is the detection of oligoclonal bands in the **c**erebro**s**pinal **f**luid (CSF) that is sampled from a lumbar puncture. The bands are there because antibodies (molecular anchors that are very choosy in what they attach to) are being manufactured in the brain. These are washed away by the fluid that bathes the brain - the CSF. Ever since these bands were discovered, scientists have been striving to identify the compound to which the antibodies are trying to attach. Could the compound be myelin? If yes, then these antibodies could be playing a role in damaging the myelin within MS lesions. Myelin is a complex material made up of many different proteins, fatty molecules and sugars; and so the question is really - are antibodies in oligoclonal bands binding to any "bit" of myelin? The first task for Dr Amor is to prepare myelin from brain tissue and then separate out one particular component – **MOG** (myelin oligodendrocyte glycoprotein). There are a number of reasons why MOG holds a particular interest for Dr Amor. If a laboratory animal is made to manufacture antibodies to MOG as part of an immune response, then these antibodies attack myelin in the CNS resulting in a disease that is similar to MS. Also, MOG is present on the surface of myelin sheaths where it would be easily reached by antibodies. The only problem is that MOG is present in very small quantities. So currently, Dr Amor is purifying MOG from brain tissue donated by MS patients and from people that did not have MS. Why is it important to identify the exact component of myelin to which the antibodies are binding? Because there are now ways available of switching off the immune system from making antibodies; but remember that antibodies play a vital role in protecting our bodies against invading micro-organisms, so, the trick is only to switch off making those antibodies that may be attacking the myelin.



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6 Repair

…darkness of blue staining = amount of myelin

…a completely remyelinated lesion millimetres away from a partially remyelinated one

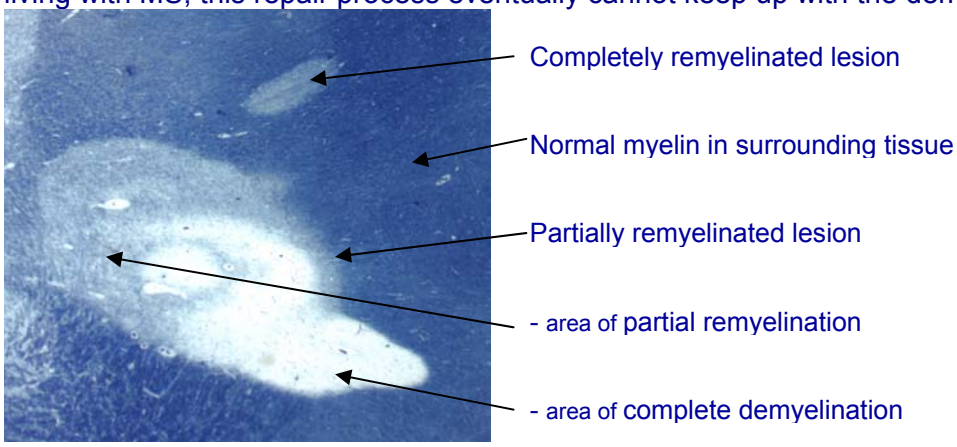
How do axons control myelination?

…they use PSA-NCAM

Why does remyelination fail?

Professor Catherine Lubetzki, Hôpital de la Salpêtrière, Paris

Although remyelination is a process that occurs naturally within the CNS of people living with MS; this repair process eventually cannot keep up with the demyelination.



In order to understand this group's approach to answering the question "Why does remyelination fail?" we first have to know that when axons are developing during childhood, they stop myelin formation occurring until the time is right by coating themselves in a layer of a "non-stick" molecule called **PSA- NCAM** (**p**oly**s**i**a**lylated-**n**eural **c**ell **a**dhesion **m**olecule). Myelin sheaths can only wrap themselves around the naked axons once they have stopped expressing PSA-NCAM. Could the failure of remyelination in MS lesions be due to the demyelinated axons coating themselves with PSA-NCAM? To answer this, the group looked at the presence of PSA-NCAM on

Could PSA-NCAM be preventing remyelination in MS?

Implications for therapy…

myelinated, demyelinated and remyelinated axons in tissue samples from 24 MS donors and 5 donors that had not had MS (the control subjects). They found that the myelinated axons in normal tissue from MS and control donors did not have PSA-NCAM; nor did the axons in completely remyelinated lesions. However, axons in completely demyelinated lesions were coated with PSA-NCAM. These observations have led the group to suggest that in demyelinated MS lesions, the presence of PSA-NCAM on axons prevents them from being remyelinated. They are now trying to find ways of stopping this molecule from being produced, since this could help the process of myelin repair.

The Tissue Bank Team…

…working to fulfil the wishes of people wanting to find better treatments for multiple sclerosis.

The Full Timers

Dr Abhi Vora (manager)
Miss Nirali Patel (research assistant)
Mrs Sue Fordham (secretary)
Mr Iyob Ghebrenegus (research technician)

The On-call Assistants

Miss Anne Palser, Miss Bella Polito, Dr Owain Howell, Miss Lynne Christian and Iyob and Nirali

The Neuropathology Team

Prof Manuel Graeber,
Dr Federico Roncaroli
and Dr Steve Gentleman

Directors and Neurology Team

Dr Richard Nicholas,
Prof Richard Reynolds (scientific director)
and Dr Omar Malik (clinical director)

And finally…

…please let us know…

we value your feedback, please contact us by…

- of any changes that we need to make to our copy of your consent forms, (eg change of address, next-of-kin or general practitioner)
- how we could improve what we do at the Tissue Bank
- your suggestions for items to include in our next newsletter
- if you do not wish to receive another newsletter

Telephone:---020 8846 7324
Email:----------ukmstissuebank@imperial.ac.uk
Website:-------www.ukmstissuebank.imperial.uk
Post:----------The UK Multiple Sclerosis Tissue Bank
Division of Neuroscience and Psychological Medicine
Imperial College London
Charing Cross Campus
Fulham Palace Road
London W6 8RF

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