

MS *in focus*

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● Research in MS



multiple sclerosis
international federation

Editorial Board

Multiple Sclerosis International Federation (MSIF)

MSIF's mission is to lead the global MS movement to improve the quality of life of people affected by MS and to support better understanding and treatment of MS by facilitating international cooperation between MS societies, the international research community and other stakeholders.

Our objectives are to:

- Support the development of effective national MS societies
- Communicate knowledge, experience and information about MS
- Advocate globally for the international MS community
- Stimulate and facilitate international cooperation and collaboration in research into the understanding, treatment and cure of MS

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Cambridge
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Editor and Project Leader

Michele Messmer Uccelli, MA, MSCS, Department of Social and Health Research, Italian Multiple Sclerosis Society, Genoa, Italy.

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Lucy Summers, BA, MRRP, Publications Manager, Multiple Sclerosis International Federation.

Editorial Assistant

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Letter from the Editor



Many people with MS, healthcare professionals and researchers can remember a time when the only treatments available for MS were symptomatic therapies. Progress in MS research has made big leaps in the past 20-25 years. Today the MS community has better diagnostic tools and disease monitoring capabilities, a more complete picture of the disease process, more refined approaches to rehabilitation and, perhaps most encouraging, particularly for people with MS, medications that can actually slow the disease process and significantly reduce the number of exacerbations. All of the advances in our knowledge of MS are thanks to scientific research.

In the 21st century, people with MS in most parts of the world have access to an incredible amount of information on research through the internet, a potentially excellent resource. At the same time it is not always easy to sort through all of the claims that circulate from reliable and not so reliable sources. In order to evaluate research claims it is important to have an understanding of how research is designed, from the inception of an idea or hypothesis through to the practical application with people with MS.

In this issue of *MS in focus*, our aim is to provide a comprehensive presentation of how scientifically valid research is conceptualised and carried out. We have attempted to answer questions such as why so many subjects are often required in a quantitative research study, why studies that do not involve humans are so important in the evolution of new therapies, and how other types of research using qualitative methods help to complete the picture of MS. These questions and more have been answered thanks to contributions from scientists from different parts of the world. We hope you will find this issue informative and that you find answers to your questions about research in MS.

We look forward to receiving your comments.

Michele Messmer Uccelli, Editor

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The next issue of *MS in focus* will be on pharmacological treatments for MS. Please send questions and letters to michele@aism.it or marked for the attention of Michele Messmer Uccelli at the Italian MS Society, Via Operai 40, Genoa, Italy 16149.

Editorial statement

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Introduction to research in MS

Mark Freedman, Director of the MS Unit, University of Ottawa, Canada

The scientific method has long been held as the accepted way for organising a research project. It starts with an observation or a curiosity and follows with several plausible explanations (right or wrong). A researcher must choose one of these, or at least a top three, and then lay the framework for how to prove or disprove that any of these plausible explanations are correct. This is called outlining the hypothesis. Usually, the question is posed in the negative since it is easier to prove something is “not” than to prove that it “is”. So if someone thinks something is bigger, better or stronger than something else, they hypothesize that both are equal. If it is proved that they are not, then the hypothesis is rejected. This is why scientific method includes checks and balances to ensure that if a hypothesis is rejected, it is for the right reason.

MS research

So how does this apply to the cause or treatment of MS? How would a scientist go about proving causation? This would require several major steps, since many things might, by chance, be associated with MS but have nothing to do with the cause. To use an example, what if more people with MS have

freckles? It is already known that MS is predominantly seen in Caucasians, and since having freckles associates more with Caucasians, does that mean that freckles cause MS? Only once an association is clear, and there is a plausible way in which the association might actually cause the damage, would it be ethical to consider an intervention to correct the “abnormalities”. Can you imagine removing freckles because of an association to MS? It is hard to understand how freckles might have something to do with MS. As far-fetched though as it seems, pigment cells in the skin are closely related to brain cells and it may well be that whatever factor stimulates pigment cells to form freckles, also stimulates the immune system to attack myelin.

Phases of a clinical trial

Proposed treatments or drugs for MS must go through phases of testing. In phase I, the proposed drug or treatment is given to people without MS to find doses that are tolerable and relatively free of side-effects, then given to people with MS to ensure that they are not prone to different problems. Once a tolerable dose or procedure is agreed upon, there has to be some suggestion that the drug or treatment will do something for MS prior to giving it to thousands of people. This is phase II. For instance, there has never been a treatment to reduce attacks that has not been able to reduce disease activity measured on an MRI scan. For this reason, scientists often do smaller studies where the primary outcome is not attacks, which take time and a large number of people with MS to verify, but the results of an MRI. If it can be shown that the drug or treatment reduces MRI activity, then there is a good chance it will also reduce attacks.

In a phase III clinical trial, one group will receive the treatment and the other a “sham” treatment or placebo. It is key that neither knows which treatment they are getting, so subjects are randomised into two groups. Both are then followed carefully to insure that the ‘blind’ is maintained. Because the investigator can often tell who is getting the drug (due to abnormal blood tests,



or hearing the side-effects), the person who decides whether or not there has been an attack should have no other knowledge about that individual. The study then proceeds until there are enough attacks to distinguish whether or not the treatment has made a difference.

The ability to show a treatment effect when it is really there is called the “power” of the experiment. What if too few people are studied, or there were many people but few attacks? Such a study would be said to be “under-powered”, in that the chances of rejecting the hypothesis (that there is no difference) are low, even though it is likely that there should have been a treatment effect. Usually researchers determine the numbers based on what they think the treatment effect will be, or how much better the treated group would be relative to the placebo. Typically, if it is thought that the treatment leads to a 50 percent improvement, then the experiment should be able to demonstrate such a difference with a probability of at least 80 percent. Stated another way, if there are enough participants and attacks, then the chances of finding a difference of at least 50 percent, if it is really there, would be better than 80 percent.

The final phase of research (phase IV) involves studying what happens when a drug treatment is approved, released and used by doctors. This phase makes sure there are no surprises found in clinical practice. Some gather safety data, while other studies gather information about which individuals are better served with a particular drug compared to others.

Ethical considerations

It is imperative that throughout this investigative process the conduct of clinical trials respects the dignity of the participants. A well conducted study has a good chance of resulting in something important while not depriving individuals of another treatment, and minimising side effects or complications. Ethics boards must review protocols and approve them based on “ equipoise”, meaning that those who take part in a study are not overly exposed to risk for a return of minimal benefit. They review the informed consent process and ensure that the study is well explained and that any potential benefit is not overly stated. But most importantly, that any exposure to potential risk is clearly stated.

In much of the world now, in addition to the roles of ethics boards, physician researchers and staff involved in clinical research must undergo training in good clinical practice. This ensures that all involved understand what is required to protect the rights of people taking part, and deal with any adverse events that arise in the course of the study.

Progress in MS research

The field of MS research has flourished over the past couple of decades. New treatments are being trialed in rapid fashion owing to a well-defined research process. An understanding of MRI has moved from the research arena to everyday practice in the diagnosis of MS, allowing early identification. Other investigative tools are making their way now into clinical trials and probably soon to clinical practice. For example, optical coherence tomography may offer a less invasive method for assessing the amount of nerve damage taking place in the central nervous system by looking at the eye and the fibres entering the optic nerve. Advanced imaging, together with correlative pathological studies, has shown us that our concept of inflammation may not be correct; rather than simply going away or burning out with advancing disease, it just changes and becomes more diffuse with a different type of immune response. This means that measures aimed at curbing inflammation in the earlier phases of disease must change in order to deal with the inflammation of progressive disease.

We have also moved away from MS being primarily a “white matter (myelinated axons) disease”, with the discovery that grey matter (neuronal cell bodies and glial cells) is very much involved and may well be the most important determinant of disability. The next important development will be a “biomarker”, which would create a simple test that will tell us whether the disease is improving or worsening and will help direct treatment.

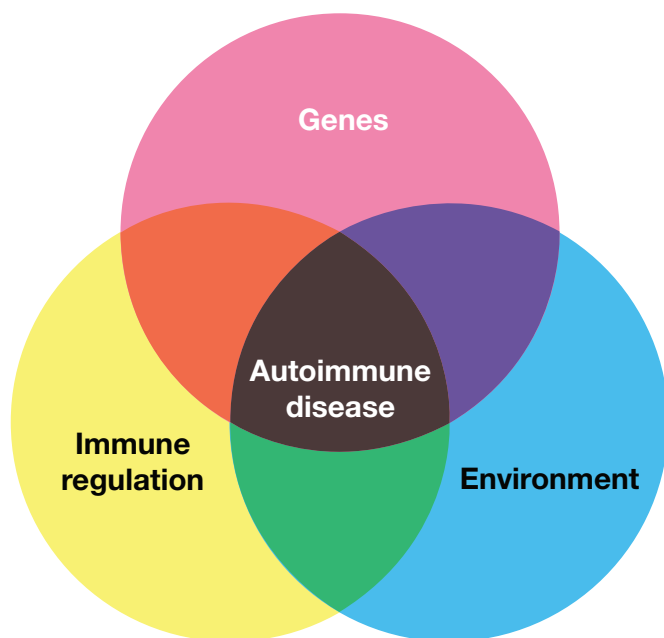
The articles in this edition of *MS in focus* look at the main areas of MS research currently being explored, the importance of qualitative research, research on diagnosis and monitoring, the latest developments in rehabilitative research, as well as how to understand research results.

Basic science studies in MS: an explanation of the main branches

Amit Bar-Or, MD, FRCPC, Montreal Neurological Institute, Canada

Basic science research in MS involves several main branches including the fields of genetics, environmental sciences, neuroimmunology and neurobiology. The ultimate goals of these areas of research are to understand how to halt and reverse injury in people living with MS, and to prevent those who are at risk of developing MS from getting it in the first place.

Our ability to achieve these important goals, including the development of new and more effective treatments for all aspects of MS, is dependent on identifying the different factors associated with the risk of developing MS, understanding the processes that contribute to injury in the central nervous system (CNS) of people with MS, as well as elucidating the mechanisms relevant to protection and repair in the CNS.



Genetics and the environment both contribute to the risk of developing MS

Genetics

While the cause of MS remains only partially understood, there is a lot of evidence pointing to roles of both genes and environment. One of the simplest ways of asking whether a condition is genetic or not, is looking at what is called the concordance rate of the condition in family members. The concordance rate for any condition essentially represents the likelihood that a particular family member will be diagnosed with that condition, if another family member already has the same condition.

In a purely genetic condition, the concordance rate is 100 percent among identical twins, since they essentially share the same genes. In MS, the concordance rate for identical twins is about 30 percent. This means that in spite of sharing essentially the same genes, if one of the identical twins has MS, the risk of the other identical twin ever developing MS is only 30 percent. This concordance rate is much higher than the risk of MS in a brother or sister who is not an identical twin (usually around 3 percent), indicating that genetics do contribute to the risk of developing MS. However, genetics cannot be the whole story. There must be other epigenetic



(processes by which heritable modifications in gene function occur without a change in the sequence of the DNA) and/or environmental factors that also make important contributions to the risk of developing MS.

Let us first consider what we have learned about the genetic contribution in MS. Recent developments in genetics have included the establishment of the human 'whole genome map' which means that, at least in terms of the sequence or structure of genetic material, the full genetic map of an individual can be defined. Researchers are still quite far away from knowing what the actual functions of all these genes are – partly because each gene may have more than one function, and the function of a particular gene may be very different, depending on when or how the gene gets activated. Even without fully knowing the function, it is possible to implicate certain genes in an illness by comparing the genetic map of many people with the condition to many people without the condition. These are called genetic association studies.

Thanks to international collaboration, several recent, large studies have resulted in the discovery of a number of genes that are likely to contribute to MS biology. There are several interesting lessons to take away from the discovery of these MS genes. The first is that each of these genes contributes very little to the overall risk of developing MS. This means that there are probably many more genes to be discovered, perhaps 100-200, that can each contribute a little to the risk. To make things more complicated, there are likely to be other genes that can contribute a little to protection from MS. It is the balance between the MS risk genes and the MS protective genes which ultimately defines the overall genetic contribution in a given person. This means that even having multiple risk genes does not necessarily mean that the person is genetically very pre-disposed to MS, because the same person may also have multiple protective genes that counter-balance the risk genes. This also means that the particular combination of genes contributing to the risk and protection in one person with MS is not necessarily the same combination

contributing to risk in another person with MS. Another issue relates to subtle but potentially important ways in which genes are regulated, so that the same genes may be expressed differently in different individuals (a field of study sometimes referred to as 'epigenetics'). These differences across individuals provide some of the reasons why it has been challenging to find a simple pattern of genes contributing to all of the genetic risk of MS. It may also help explain why the illness can be so different in different people with MS.

The other interesting lesson from these MS genetic studies is that the great majority of genes identified as being involved in the risk of developing MS, are also known to participate in immune responses – an observation that seems to support the view that abnormal immune responses are important contributors to the development of MS. For example, several of the genes implicated in MS are thought to be involved in how immune cells get activated, while other genes are involved in how the immune system tries to regulate itself. As we will see below, problems with either too much immune activation or not enough immune regulation, are probably both important contributors to the development of MS as well as to ongoing MS activity.

Environmental sciences

What about environmental factors contributing to the risk of developing MS? It is quite possible that just as with genetics, multiple environmental factors can contribute to the risk of, and possibly protection from, MS, and that these may differ in different people who develop MS. While the exact environmental factors involved in MS risk are not known, a few have been repeatedly implicated, such as a history of particular infections in early life, deficient levels of vitamin D and smoking.

For example, epidemiology studies (population studies) have indicated that people with MS are more likely to have been exposed to the Epstein Barr Virus (EBV) than people without MS. Low levels of vitamin D are also implicated in the risk of developing MS, which may contribute to the



Low levels of vitamin D can be caused by a lack of exposure to sunshine.

observation that MS is more common in certain parts of the world than others. It is worth noting that factors that may increase the risk of developing MS do not necessarily also contribute to the degree of MS activity once someone already has the diagnosis of MS. For example, it is possible for a particular virus (such as EBV) to be involved in the risk of developing MS, but once someone has MS, further exposure to EBV (or preventing such exposure) may not have any effect on established MS biology.

To date, research in the fields of MS genetics and environmental sciences have helped to identify some, but not all, of the risk factors that are likely to contribute to MS risk, and the search continues. It is interesting to note that, like the implicated genes described above, all of the identified environmental risk factors for MS (EBV infection, low levels of Vitamin D and smoking), are also known to influence activation and regulation of immune system responses and their interaction with the CNS. This explains the interest in the science of neuroimmunology, described below.

Neuroimmunology of MS

For a long time, MS has been considered to be a condition in which unregulated immune responses make an important contribution to CNS injury. Even without fully understanding the initiating triggers in MS, there are several lines of evidence that strongly support the view that immune abnormalities

are important in ongoing MS activity, especially relapses. Starting with the very first descriptions of the injury seen in MS, scientists acknowledged the presence of abnormal collections of immune cells that appeared in the CNS. These infiltrating immune cells are found around blood vessels at the sites of injury, which includes loss of the protective myelin insulation, or demyelination, around nerve fibres, and damage to the cells that make myelin (the oligodendrocytes). In these same sites of injury, also called lesions, there can also be considerable damage to the fibres of nerve cells or neurons. The pattern of immune cell infiltration around vessels is referred to as peri-vascular inflammation and suggests that immune cells from the circulation somehow get across the vessels and into the CNS, where they presumably cause damage to the oligodendrocytes, axons and neurons.

Perhaps the strongest evidence for this neuro-immune view of MS biology comes from clinical trials of approved therapies for MS. All the approved therapies, including beta-interferon, glatiramer acetate, mitoxantrone and natalizumab, were developed based on their ability to modify immune responses, and have been shown to decrease MS relapses. These therapies either decrease the ability of immune cells to invade from the circulation and into the CNS, or change the way the immune cells respond, so that they no longer cause damage even if they do get into the CNS. While these treatments certainly do not provide all the answers, their success in reducing MS relapses strongly suggests that the ability of immune cells from the periphery to get across the vessels and into the CNS, is one important component of the biology of new MS relapses.

It is worth noting that the ability of immune cells to get across the vessel and into the tissue, a process known as trafficking, is not in itself abnormal. Immunology scientists have shown that trafficking represents an important function of the normal immune system: indeed, we need to have immune cells traffic through different tissues in order to detect and, if necessary, respond to anything that should not be there, such as a virus or bacteria.

Normally, this process of trafficking is very well regulated, so that cells only get activated to the proper level, in the correct location, and leave that location once they are no longer needed. In MS, it is thought that the different steps involved in immune activation and trafficking are not properly controlled, resulting in overly activated immune cells that get to the CNS where they can cause damage.

A great deal has been learned recently about the many subtypes of immune cells that exist, how they interact with and influence each other, and how these complex interactions can contribute to both normal and abnormal immune responses. While the complexity of the immune system has been challenging, it has also provided scientists with opportunities to identify many additional targets for new therapies that continue to be actively pursued in clinical trials for MS and other immune-mediated conditions. Thanks to the ongoing research in the field of immunology, there is considerable excitement about oral immune medications for MS, such as fingolimod, that will be a welcome addition to the current injectables, as well as the promise of more new immune therapies on the near horizon that we hope will be able to completely stop new MS relapses, while being safe and easy to tolerate.

Neurobiology of MS

The branch of MS research known as neurobiology holds some of the greatest challenges but also some of the greatest promise. While preventing relapses remains an important goal, it is clearly not enough, as many persons with MS experience continued progression of neurological problems, even without obvious relapses. Studies of the neurobiology of MS are particularly important when it comes to understanding what causes progressive disease in persons with MS, and how we may be able to protect and eventually repair the different types of cells and their connections in the CNS.

The currently approved immune therapies that have been effective at decreasing relapses by targeting immune responses outside the CNS, do not appear to consistently prevent the ongoing progressive deterioration that many people with MS experience.

This means that there must be some other biological process contributing to CNS injury in people with established MS, in addition to the immune abnormalities outside the CNS that are responsible for relapses. The field of MS neurobiology focuses on what happens inside the CNS.

Similar to the field of MS neuroimmunology, scientists in the field of MS neurobiology are interested in understanding both the normal and the abnormal states of the CNS. Learning, for example, how different cells of the CNS develop normally, how neurons and their axons connect and interact with each other to enable normal transmission of information in the nervous system, how the oligodendrocytes make myelin that wraps around the axons and enables more efficient transmission – all provide the necessary background knowledge for better understanding which of these basic functions are compromised, or not working properly, in the CNS of people with MS.



CNS nerve cells (green) and glial cells (orange)

In addition to the oligodendrocytes, other supporting cells, known as glial cells, help maintain the normal state in the CNS. These include astrocytes and microglia. Astrocytes provide both nutrition and protection to neurons and their connections, and microglial cells have a particular ability to monitor the state of the CNS environment and have interesting immune properties that may be particularly relevant when considering interactions between CNS cells and invading immune cells. In addition to studying how the neurons and the different glial cells of the CNS develop and interact normally, neurobiologists in the MS field study how these elements respond to different types of injury, including immune-mediated injury.

An important question facing neurobiologists in the MS field is whether an initial immune-mediated injury to CNS cells can result in a subsequent ongoing process of degeneration of the CNS cells, even without continued immune insult. If true, this may provide insights into the biology of progressive disease in MS, and could also explain why approved immune therapies do not seem to help the progressive aspect of MS in individuals who have already sustained enough CNS injury.

Neurobiologists in the MS field study both normal CNS processes and responses to injury, at different levels and using a variety of methods. These include studies of individual cells and their internal functions, using, for example, techniques of molecular and cellular biology; studies of interactions between different types of CNS cells; studies of transmission of nerve signals (neurophysiology); studies of intact tissues of the CNS in different animal models; as well as studies of overall function including motor performance, including walking and coordination, and cognitive function, for example maze testing of learning ability in animal models or neuropsychological studies to assess higher cognitive functions in people with MS.

Increasingly sophisticated imaging tools, using new generation microscopes and advanced magnetic resonance imaging (MRI) methods, are now making it possible to observe many biological processes from the single cell level all the way to whole brain

functions, in both animal models and in humans. Using these complementary approaches and new research tools, neurobiologists in the MS field are working to discover the biological processes that contribute to progressive disease in people with MS. Understanding these processes will lead to approaches designed to protect from, and eventually halt, any further injury to the oligodendrocytes, neurons and axons.

Perhaps the ultimate goal of both neuroimmunologists and neurobiologists in the MS field is to understand how to achieve repair of already existing injury in the CNS, in order to reverse neurological disability and restore functions. This raises several important questions: how does one help damaged axons to grow? How does one generate new myelin from young (progenitor) oligodendrocytes in order to achieve remyelination? How can such processes of repair be coordinated, so that the proper connections are restored? While these questions are particularly challenging, several encouraging recent discoveries include the identification of a number of new growth factors that can support survival and function of particular brain cells, as well as various types of stem cells and progenitor cells that can theoretically help to restore injured or lost cells.

The different branches of basic research currently being pursued in the MS field emphasise the importance of tackling MS from different perspectives. There are real challenges but also real opportunities for advances that will eventually lead to treatments that halt and reverse injury in people with MS, and perhaps some day prevent MS in those at risk. It is worth noting that while MS research can be divided, as above, into several branches, there is an increasing recognition among scientists and clinicians of the importance of a coordinated effort. More and more, one sees scientific meetings and research symposia designed to bring together experts as well as trainees from across the disciplines of MS genetics, epidemiology, neuroimmunology and neurobiology. Fostering such exciting interactions and sharing of knowledge, perspectives and techniques is undoubtedly a recipe for greater and faster success in improving the lives of people with MS and their families.

Qualitative research

Deborah Payne, BA, MA, PhD, RN,
Director, Centre for Midwifery and
Women's Health Research, Faculty of
Health and Environmental Sciences,
AUT University, Auckland, New Zealand

What is qualitative research?

Qualitative research refers to research that endeavours to capture the meanings, interpretations and descriptions that people give in relation to a particular phenomena or event such as MS. Qualitative research gives an insider's view into the experiences of MS, thus allowing for valuable insights to be collected and gained.

Qualitative research can be of use when little knowledge exists about a topic. Researchers can gather information that can produce new knowledge that in turn contributes to the development of theory. Qualitative research can also be used to test quantitative findings or to complement a quantitative research project and add depth to its findings. It can bring to the surface the hidden voices and silenced issues within the healthcare system for people living with MS and their families.

Qualitative versus quantitative

As many authors on research point out, the definition of qualitative research is often based on its contrasts to quantitative research. One such contrast is that quantitative research distances its participants or subjects in the type of data that it collects and its data analysis, whereas qualitative research recognises the richness of people's experiences and insights. Their descriptions, recollections or perspectives are the data. Their words are not converted into numbers or percentages but are presented as part of the findings.

Whereas quantitative research aims to test and establish the causal relationship between variables so that this knowledge can be used to predict and control

phenomena, qualitative research has more to do with generating new knowledge about phenomena. It does not aim to foretell and direct, rather to understand. Quantitative researchers impose a theory or meaning on to their participants. Researchers transform a theory, for example, about MS and fatigue, into sets of measures and/or structured questionnaires with predetermined responses for participants to answer. The measures and responses are then analysed using statistics to either confirm or disprove the theory.

In comparison, qualitative research sets out to answer a question, such as: what is the meaning of fatigue for people experiencing MS? While qualitative researchers may use different ways of collecting data such as participant observation, or gathering various forms of documentation, one of the most common forms of data collection is face-to-face interviews. The interviews are carried out in a semi-structured way where, although there are open questions and specific topics to be addressed, there is a degree of flexibility that allows interviewees to talk about their experiences as they come to mind. Participants are given the opportunity to relate to the researcher in their own words their beliefs, values, views and experiences. In this way participants are not constrained as they are in quantitative research to just ticking a box or circling a number on a scale of one to five.

The interviews are then analysed. One of the most common ways of analysing the data is to identify the common themes articulated by the participants. However, researchers may also draw on a particular methodology, for example, phenomenology, discourse analysis, narrative or grounded theory (see box on page 12) to give a deeper, more philosophical interpretation of their findings. Which theory the researcher chooses is determined by the question that s/he wants answered. So a phenomenologist will ask what is the meaning or lived experience of fatigue? A discourse analyst may ask what discourses (communication of thought by words) are there in relation to fatigue?



Focus groups are an important way to collect qualitative data.

Another contrast is that qualitative researchers do not aim to generalise that their findings will apply to the wider population. This is based on the assumption that knowledge and behaviours are contextual. However, by being descriptive and transparent in their account of the research process, and showing excerpts from interviews, qualitative researchers provide the opportunity for their audience to decide how applicable their findings are.

Process

Just as quantitative researchers must ensure that their study is valid and reliable so must qualitative researchers ensure that they exercise rigour throughout the research process. They follow guidelines and principles to make certain that their research findings are credible and trustworthy.

Qualitative research in its breadth of methodologies allows for the study of MS from multiple angles and levels. It can examine the social relations between healthcare professionals or between healthcare professionals and people with MS. It can explore

Qualitative methodologies:

Case study is based on an in-depth investigation of a single individual or group.

Discourse analysis analyses written, spoken and/or signed language use.

Grounded theory generates a theory from data collected as opposed to beginning with a theory and collecting data to support or refute the theory.

Interpretive descriptive thematic analysis is an approach to dealing with data that involves the creation and application of 'codes' applied to data.

Narrative is a story that is recounted by a subject that describes an event or sequence of events through speech or writing or other creative form.

Phenomenology studies conscious experience as experienced from the subjective or first person point of view.

Qualitative data collection methods:

Semi-structured interviews have a framework of themes to be explored but are flexible, allowing new questions to be brought up during the interview as a result of what the interviewee says.

Open-ended questions are designed to encourage a full, meaningful answer using the subject's own knowledge and/or feelings.

Focus groups involve encouraging an invited group of participants to share their thoughts, feelings, attitudes and ideas on a certain subject.

how certain discourses shape policy and practice in relation to MS. It may be that researchers want to investigate the meaning of MS for the children of adults living with MS.

Conclusion

Qualitative research has the potential to add to the understanding of MS: for the people who live with MS, their families, their friends, their colleagues and the health professionals and community groups who support them. It can add to the general community's and policy makers' appreciation of MS, which in turn may enhance the quality of care and assistance available for people with MS and their families.

Rehabilitative research in MS

Fary Khan, MD, Principal Fellow,
Department of Medicine,
University of Melbourne and
The Royal Melbourne Hospital, Australia

Challenges in rehabilitative research

Rehabilitation is a complex intervention that poses a number of challenges for traditional research designs. Unlike simple pharmacological intervention, rehabilitation may include a number of different components, for example different therapies, which are interdependent, involving varied populations and contexts, and the impacts are therefore less straightforward to measure. Rehabilitation treatments are multifaceted and multilayered, and involve an organisational restructure as well as individual intervention. There are also ethical considerations.

Qualitative data may capture evidence about how people react and behave.

Wherever feasible, randomised controlled trials (RCTs) are accepted as providing the highest grade of evidence. The subjects are randomly allocated to receive or not to receive an experimental, therapeutic, preventative or diagnostic procedure, and are followed up to determine the effect. However, methodological requirements for robust RCTs in rehabilitation can be challenging. For instance, subject drop-out, or those who do not complete the study, in the control arm is often high, and can raise ethical considerations if treatment is withheld. It is also difficult to ensure subjects are “blinded” since rehabilitation requires active participation by the person with MS. At times this design may not be feasible in rehabilitation and needs to be supplemented by qualitative and quantitative approaches to capture the full range of experiences in the real life context.

Qualitative research (also see pages 11-12) may be better suited to answer questions about human interaction and how people interpret interaction.

Research in MS rehabilitation may include:

Randomised controlled trial For example to test the effectiveness of multidisciplinary rehabilitation for a group of people with MS compared with a group of people who are on a waiting list for rehabilitation.

Systematic reviews For example, reviewing whether multidisciplinary rehabilitation works in different settings.

Qualitative research techniques to model intervention in the context For example, looking at the disability profile of people with MS, or the impact of MS on caregivers.

Outcome development to capture a person’s perspective For example, the use of the International Classification of Functioning, Disability and Health to develop core sets for MS.

Cohort or open label studies to test out intervention protocols For example, the use of goal attainment scaling, where the person with MS and their healthcare professionals agree rehabilitation goals.

Evaluation of outcomes to be used to generate data to determine effect size For example, looking at the impact of bladder rehabilitation to determine if there is an improvement in a group receiving treatment compared with a control group.

In particular, qualitative data may capture evidence about how people react and behave and what they mean by their experiences, attitudes and behaviours. Quantitative methods aim for reliability (consistency on retesting) usually using standardised tools.

Alternative approaches to gathering evidence

People with MS form a diverse group with a wide range of clinical presentations and varied levels of disability, and therefore require an individualised approach to rehabilitation. Despite the guidance laid down in the UK Medical Research Council

framework for evaluation of complex intervention, RCTs cannot answer all the questions that need to be answered. An alternative approach to gathering evidence is through the use of clinical practice trials that acquire prospective and retrospective data without disrupting the natural course of treatment.

People with MS require an individualised approach to rehabilitation.

This routine data collection provides additional information about the nature of services provided, the outcomes of rehabilitative care and implications for clinical practice. Further it can provide answers as to which models of care work best for which type of MS, the intensity of rehabilitation required

and an assessment of care management processes. More recently this approach has been used in the MS population to quantify the intensity of rehabilitation required in inpatient rehabilitation programmes and to determine the complexity and need for therapy for people with MS.

As people with MS are very different, clinicians may not always agree with one another or incorporate the person's perspective into care. The clinical decision making process can be subjective and biased. In addition, if only standardised instruments are used to assess functional status there can also be bias. One approach to this problem is the use of goal attainment scales as an individualised person-centred outcome measure. This method has been used to demonstrate change following rehabilitation for people with MS and has been shown to give added value over standardised measures in evaluating outcomes that are meaningful to individuals and their families.

Potential solutions to specific issues in study design

Research design issues for complex interventions are standard for all RCTs. These address internal validity (to what extent are differences between study and control interventions real rather than the result of bias) or external validity (to what extent are the results of a trial generalisable). The rehabilitation research should address these two problems through a number of key methodological issues:

- Randomisation should be used to eliminate bias on selecting subjects. The results of subject selection should be concealed. Potential factors that might be unevenly distributed between the trial groups and thus confuse the results should be identified prior to trial design. Lack of differences in baseline data in study arms should show adequate randomisation. The trial arms should be comparable and participants' characteristics adequately similar.
- "Blinding" the therapist who is treating the subject and assessing the outcomes should eliminate bias resulting from the expectations of

Italian MS Society



the individual or the provider regarding results.

- The outcome should test the key hypothesis of the trial, for example the effectiveness of rehabilitation for people with MS. Secondary outcomes and intermediate measures should be used sparingly.

- Analysis of data should be performed for all participants, with complete data for both time points in an RCT.

From the perspective of organising health services

The implementation of rehabilitation as an intervention in the context of health services research also needs to be considered in the broader context. One approach, explained in the

table below, proposes three levels for defining a complex intervention in health services research to address issues of the health services organisation for optimal delivery of care. Although this approach is not a model in itself, the three levels are relevant to implementing research in MS.

Conclusion

MS rehabilitation research should reduce gaps in knowledge by improving the integration of evidence into practice to improve the outcomes for people with MS. Research of important clinical questions needs to be evaluated, it needs to translate locally, and it should use a synthesis of research evidence, individual studies and reports, and theoretical and methodological innovations.

Defining a complex intervention at three levels for health services research: case of provision of rehabilitation for persons with MS (adapted from Bradley et al., 1999)

Levels for defining intervention			
Key issue	Level 1 Theory and evidence	Level 2 Essential tasks and processes	Level 3 People and context
1. Target population	Focus on people with definite MS	Identify disability in people with definite MS Recruitment of subjects to intervention	Subjects assessed in tertiary care for MS related disability
2. Service provision	Lack of co-ordinated multidisciplinary MS rehabilitation Gaps in provision of secondary preventative care for people with MS	Deliver organised rehabilitation programme for people with MS	Limited local provision of care for MS related disability
3. Change behaviour	Self efficacy Guideline development	Provide individualised self-management plan Provide guidance for nurses and general practitioners, sent with the individual	Local expert group to identify key area for MS care

Research on diagnosing and monitoring MS

Georgina Arrambide, MD, and Xavier Montalban, MD, Clinical Neuroimmunology Unit, Multiple Sclerosis Centre of Catalonia, Vall d'Hebron University Hospital, Barcelona, Spain

MS is a chronic disease, often affecting young people, which leads to different degrees of disability over time. Although it is still controversial, there is therefore a tendency to start an early disease-modifying treatment, based on evidence that clinical and radiological measures in the first few years of the disease will impact on its long-term evolution. In order to start an early treatment, an early, accurate diagnosis should be made.

For this reason, studies have focused on people with clinically isolated syndromes (CIS), which are first episodes of demyelination of the type seen in MS, searching for possible biological markers of diagnosis and prognosis. A biological marker is a surrogate that can be measured objectively as an indicator of normal biological processes, pathological processes, or responses to treatment. To date, the most reliable marker for diagnosis and, to a lesser extent for prognosis in MS, is magnetic resonance imaging (MRI). Another surrogate of proven diagnostic value is the presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF).

Magnetic resonance imaging

MRI research has been one of the most active fields in MS in the last two decades and probably has changed our view of the disease itself. The most significant change in MS diagnosis came with the McDonald Criteria as, in comparison to previous criteria, it was no longer required to wait for a second

clinical attack to diagnose MS, which may take years to occur. MRI parameters were included that allowed an earlier diagnosis to be made. So, a diagnosis of MS in people with CIS can be established if the MRI demonstrates characteristic lesions with dissemination in space (DIS) and dissemination in time (DIT). To demonstrate DIS the brain MRI must have a certain number of lesions in different locations of the central nervous system (CNS). DIT requires the demonstration of new lesions compared with the baseline MRI or an asymptomatic gadolinium-enhancing lesion (a lesion that appears active on MRI, but apparently is not causing any specific symptoms) on a second MRI. When a lesion is enhanced by contrast, it means that the barrier that separates the CNS from the rest of the body is broken, allowing

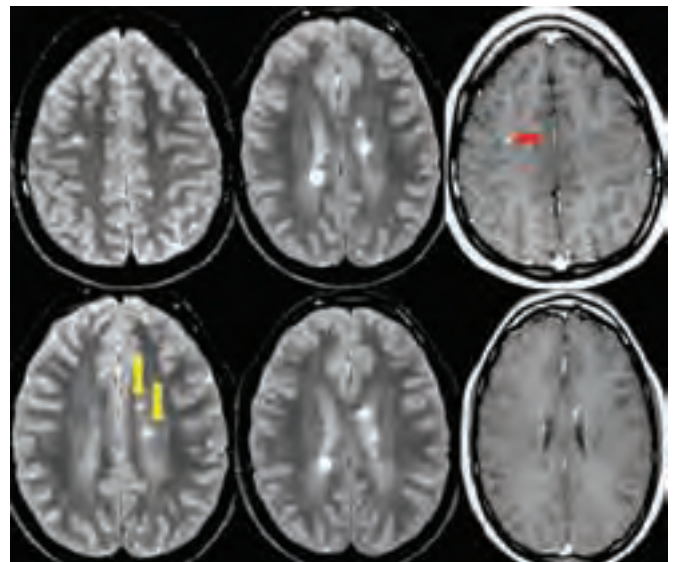


Image courtesy of Dr Alex Rovira

Brain MRI showing dissemination in space and time. The baseline MRI (top row) shows lesions appearing in deep and superficial areas of the brain, whereas the follow-up scan (bottom row) shows the presence of new lesions (yellow arrows). The red arrow shows a gadolinium-enhanced lesion.

immune components to penetrate into the CNS and is thus a measure of inflammation and disease activity.

Other MRI criteria have also been proposed. As two different MRI scans are still necessary to demonstrate DIT, a study group has recently proposed that a single brain MRI that shows DIS and simultaneous enhancing and non-enhancing lesions suggestive of DIT is very specific for predicting conversion to MS in people with CIS. The possibility of misdiagnosis at this stage, especially in some specific populations of people, for instance children, does exist. So, this new proposal for diagnosis of MS in people with CIS using MRI is still awaiting further evaluation.

MRI has also been used to evaluate response to treatment. A recent study demonstrated that the combination of clinical disease activity and the presence of new active lesions on MRI may be useful for identifying those individuals who appear to be not responding to a treatment.

Regarding disability, the location of lesions is relevant. The presence of lesions in the brainstem, cerebellum, and spinal cord as initial finding on MRI helps identify individuals who may be at higher risk of developing disability.

There are also non-conventional MRI studies, using special techniques not readily available everywhere, that have proved to be useful in measuring atrophy in relation to disease activity and response to treatment. Such studies have shown that irreversible tissue damage can already be detected in people with CIS. Besides, patients with CIS and a higher number of lesions are more prone to develop long-term disability.

Oligoclonal bands

One of the immunological mechanisms involved in MS is the presence of antibodies produced by a few cell lines during inflammation. Each cell line produces a specific kind of immunoglobulin and, when these are measured, each one of them will be demonstrated as a different band, hence the name oligoclonal bands (OCB). They represent the production of antibodies within the CNS and have also been included in the McDonald criteria.

The presence of OCB is an independent factor for developing MS in people with CIS. Besides, the combination of at least two lesions on MRI consistent with those seen in MS and the presence of OCB is used as an alternative method to demonstrate DIS in the current diagnostic criteria.

One research group has also studied a subtype of immunoglobulin in OCB, called IgM, observing that the probability of conversion to MS in CIS patients presenting with this subtype is very high one year after the first clinical attack. They have also observed that such a subtype can predict disability progression and that it is related to MRI lesion number. These observations remain to be validated in further studies.

Other biological markers

Despite these findings, MS remains an unpredictable disease. This is the reason why new biological markers for conversion to MS, disability progression and response to treatment are currently being studied. The aim of such studies is to find a marker that is more reliable, less expensive and easier to obtain than the current methods. With the advent of new techniques, many different proteins that can be measured in serum or in CSF are being studied. It is important to note, however, that none of them has proved superior to MRI and OCB so far and that their usefulness in the clinical setting remains to be elucidated.

Conclusions

The search for new biological markers to diagnose and monitor MS is a very promising field which is constantly evolving. To this date, MRI and OCB remain the main markers neurologists rely on when evaluating a person presenting with a CIS. MRI is also useful when monitoring a response to treatment. It is also important to remember that the pathological processes involved are not uniformly present among people with CIS or MS, thus contributing to the heterogeneity of MS regarding clinical course and response to different therapies. In the end, the decision-making process should be made jointly by both the person with MS and the neurologist based on the existing evidence and what can be applied to each individual case.

Understanding research results

Maria Pia Sormani, Department of Health Sciences - DISSAL, Genoa, Italy

Modern medicine is an evidence based medicine: this means that the assessment of risks and benefits of treatments and diagnostic tests must be obtained from the best available evidence gained from the scientific method. The scientific experiment in drug development is the clinical trial, that is, a research study in human beings that follows a pre-defined protocol.

The randomised controlled trial

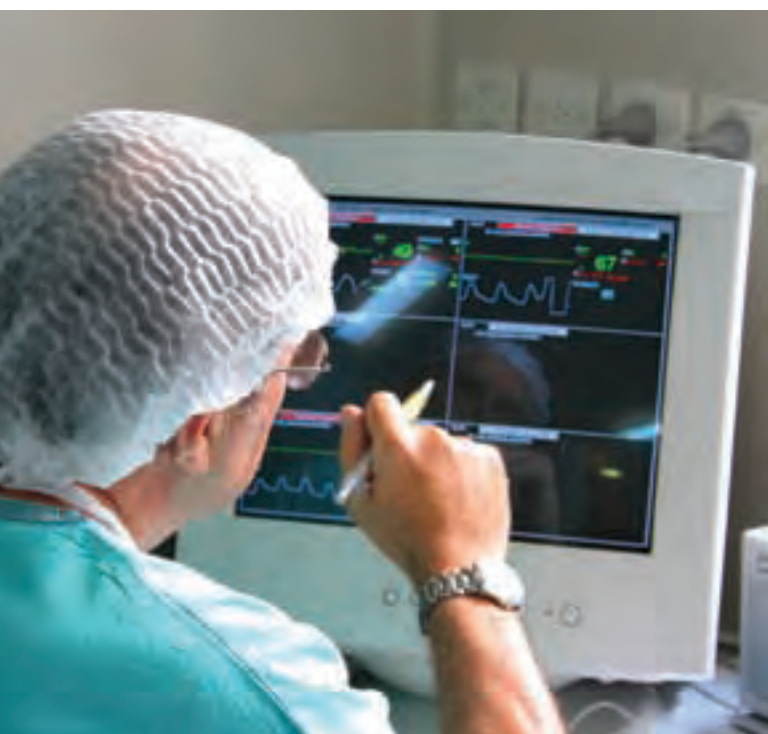
Researchers develop a plan for a clinical trial after laboratory studies indicate the promise of a new drug or procedure. The best designed trial is the controlled trial in which the group of people treated with the new medical intervention is compared with a “control” group, a group of people treated with the standard treatment for that disease. The decision whether a person in a

clinical trial is assigned to the experimental or the control arm is carried out through randomisation. Randomisation is a process that assigns people participating in a trial by chance, rather than by choice, to either the experimental group or the control group. The goal of randomisation is to produce comparable groups in terms of general participant characteristics and to avoid a selection bias, a systematic difference between the two groups that is influenced by the prognosis or responsiveness to treatment. The most reliable and impartial method of determining what medical interventions work the best is therefore the randomised controlled trial (RCT), that is the core of experimental research in medicine.

The primary endpoint

The result of a clinical trial is the comparison of the disease evolution between the two randomised groups (the experimental and the control group). The primary endpoint of a study is the variable measured at the end of the study that quantifies the disease evolution.

When planning a study different endpoints can be chosen depending on the scientific and clinical aims of the trial. For example, in MS, the primary endpoint of a study can be the total number of lesions counted by MRI that people with MS develop over the course of the study. In this case, the main result of the study will be the comparison of the mean number of MRI lesions between the two treatment groups to assess whether the experimental treatment is able to decrease their appearance. Otherwise, the primary endpoint can be the number of relapses counted over the duration of the study; again, the main result of the



study will be the comparison of the relapse rate between the two treatment groups, to detect if this is lower in the experimental group. Finally, a trial can have a disability endpoint, for example comparing the number of individuals with disability progression in the two groups.

The endpoint, that is, the aim of the study, is strictly linked to the phase of the clinical research. As mentioned in the introductory article of this edition of *MS in focus* (see page 3), phase I studies are those intended to evaluate the safety and the tolerability of the new drug. They may be uncontrolled, open-label studies as well as small controlled studies. Usually a small cohort of subjects is started on an experimental therapy at a low dose. Subjects can be healthy volunteers, people with the disease with no other or limited therapeutic options (in MS, for example, they could be people with primary progressive MS) or people with similar diseases, for example, other autoimmune diseases. Subsequently, the dose is increased in the same or in an independent group of subjects until a certain endpoint is reached or some adverse events are observed. Often, pharmacokinetics (the branch of pharmacology concerned with the way drugs are taken into, move around, and are eliminated from, the body) are performed after single and multiple dosing to understand drug metabolism.

Phase II studies are also called proof of concept studies, since their aim is to assess whether the new drug has any activity; so the primary endpoint for these studies will be an instrumental or laboratory marker able to give a first indication of the action of the drug. A phase III study assesses the efficacy of the new drug, that is, is designed to understand whether the treatment will be able to improve the quality of life or to prolong survival (for lethal diseases) of people. In MS, phase III studies will have endpoints related to the quality of life of subjects, typically number of relapses and disability progression risk.

Measures of treatment effect

Once the endpoint is established and defined,

a measure of treatment effect must be decided to quantify how much the treatment has worked. Estimates of the treatment effect can be grouped in two main categories: absolute and relative measures. To understand their meaning, it is helpful to take as an example the results of the five pivotal placebo controlled clinical trials in MS that led to the registration of natalizumab, interferon beta-1 a (intramuscular and subcutaneous), glatiramer acetate and interferon beta-1 b as shown in the table (see page 20).

The Absolute Risk Reduction (ARR) is an absolute measure of treatment effect: it represents simply the difference between the relapse rate in the control group and the relapse rate in the treated group. The advantage of an ARR-measured treatment effect is that it is easy to compute and interpret, providing a clear reflection of both the underlying risk of no treatment and the risk reduction associated with drug treatment. The main limitation of this method for estimating a treatment effect is that it strongly depends on the value of the reference group: if the relapse or progression rate in the reference group is low the ARR is bound to be low as well.

The Number Needed to Treat (NNT) is a second absolute measure of treatment effect: it is numerically defined as the reciprocal of the ARR, and can be expressed as the number of people that need to be treated with a drug instead of the control treatment to prevent 1 negative event (e.g. a relapse or a progression). As an example, in the natalizumab trial (first column), the annualised risk reduction after two years of treatment with natalizumab was 0.50 relapses/person/year; the NNT is therefore $1/0.50 = 2$. This indicates that, on average, for every two individuals treated with natalizumab for two years a relapse is prevented.

The relative measures – the relative risk and the relative risk reduction – are the most widely used measures for quantifying a treatment effect. The relative risk of relapses is expressed as the ratio of the relapse rate in the treatment and the control group. Similarly, the relative risk reduction

is calculated by subtracting the relative risk from 1. Relative risk and relative risk reduction are easy to compute and interpret, and are included in standard statistical software. These relative measures are also less dependent on the rate of events for a measured endpoint in the placebo group and, unlike the ARR, provide a single estimate of treatment effect that remains stable across MS populations with varying baseline risk.

It must be kept in mind that is very difficult to compare results across different clinical trials and that these comparisons can lead to different conclusions depending on how they are presented. For example, the natalizumab effect does not seem to be very different from the interferon beta-1 b if the absolute

difference of relapse rates is considered: the absolute decrease of relapse rate (ARR) is 0.50 and 0.43 for the natalizumab- and the interferon beta-1 b-treated subjects respectively. On the other hand, considering relative reduction instead, the natalizumab effect is twice the interferon beta-1 b effect (relapse rate reduction 68 percent as compared to 34 percent).

Conclusion

To have a complete picture of the results of a clinical trial it is important to understand the differences between relative and absolute measures; comparisons of results across trials can be dangerous and must always be conducted by exploring all the possible ways of expressing the treatment effect.

Annualised relapse rate measured over two years in five pivotal placebo controlled clinical trials and different measures of treatment effects

Trial	Natalizumab	Interferon Beta-1 a (30 micrograms)	Glatiramer Acetate	Interferon Beta-1 a (22 micrograms)	Interferon Beta-1 a (44 micrograms)	Interferon Beta-1 b (250 micrograms)
Frequency	n/a	Once weekly	Once daily	Three times weekly	Three times weekly	Once daily
Annualised relapse rate over two years - placebo	0.73	0.90	0.84	1.28	1.28	1.27
Annualised relapse rate over two years - disease-modifying drug	0.23	0.61	0.59	0.91	0.87	0.84
Absolute risk reduction	0.50	0.29	0.25	0.37	0.41	0.43
Number needed to treat	2	4	4	3	3	3
Risk reduction	0.32	0.68	0.70	0.71	0.68	0.66
Relative risk reduction	0.68	0.32	0.30	0.29	0.32	0.34
Reference	Polman, O'Connor et al. 2006	Jacobs, Cookfair et al. 1996	Johnson, Brooks et al. 1995	"The PRISMS Study Group" 1998	"The PRISMS Study Group" 1998	"The IFNB Multiple Sclerosis Study Group" 1993

Your questions answered

By Pablo Villoslada, Neurologist, Hospital Clinic of Barcelona, Spain

Q. I want to take part in a clinical trial for any new treatments. How do I find a good quality trial to take part in?

A. If you are followed for your MS by a neurologist affiliated with a specialised MS centre or clinic, the first option is to approach your physician or clinical coordinator at your MS centre. Many MS centres are involved in studies testing new therapies for MS and they can inform you about the best options for you.

If you do not attend an MS centre or clinic, your primary healthcare professional may be able to help you find information about MS trials in your area. Otherwise, your MS society may be able to provide the information you need.

You can also visit the website of other MS organisations, including MSIF (<http://www.msif.org/en/research/index.html>) or the US National MS Society (<http://www.nationalmssociety.org/research/clinical-trials/index.aspx>), that provide information about new therapies being tested. The latter offers an updated list of all new therapies under development.

The official website for clinical trials of any kind is <http://www.clinicaltrials.gov/>. This is a resource provided by the US government and it is mandatory to register any clinical trials on this site. There you can find studies by searching by a particular drug or centre, etc. You can contact the coordinator asking for a centre from your country participating in the study of your interest. For a review of this website, see page 27.

Q. I read about the latest research all the time but find very little on primary progressive MS, which is what I have. Why is this?

A. In the last few years, knowledge about the inflammatory aspects of MS has increased

significantly, leading to the development of many new therapies aimed at stopping inflammation. However, the biological basis of the progressive phase of MS is poorly understood, and for this reason there are few opportunities for developing new therapies for this group of patients, including people with primary progressive MS. Another difficulty is that proving the efficacy of a drug in relapsing MS is complex but possible using hundreds of patients followed for two years and using MRI for monitoring drug efficacy. However, the progressive phase of MS is very slow and heterogeneous, and there are not good MRI markers for measuring how it evolves over time. Even a two-year follow-up is a short period. This limitation also hampers the testing of new drugs for primary progressive MS. This last point is being studied through the potential development of biomarkers, namely new blood tests or new MRI techniques that allow physicians to monitor disease course and response to therapy. Finally, even with these difficulties there is interest in developing new therapies for primary progressive MS and hopefully, there will be some advances in the near future.

Q. Is it realistic to hope for a cure for MS?

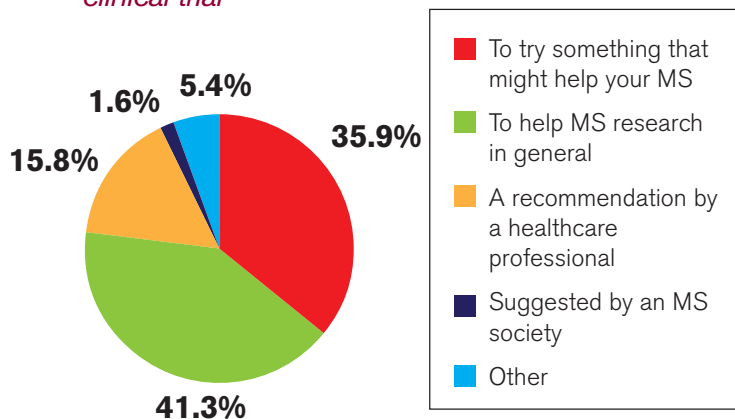
A. The cure for MS is going to require a thorough understanding of the biological basis of the disease, and after that, identifying which predisposing factor or factors can be modified. This is going to take some time, but research is moving in this direction. But the more realistic option instead of curing MS is stopping MS. Now, in many complex diseases such as cancer, AIDS and rheumatoid arthritis, the disease is not cured but it is very efficiently controlled and the accumulation of disability can be halted. With the new drugs for MS, a significant percentage of people are going to be stable for very long periods of time. Further, decreasing the uncertainty about whether the disease is going to progress or not is likely to have a significant impact on the quality of life of people with MS.

Research in MS survey

More than 1,180 people took part in MSIF's online survey about MS research. When asked if they had taken part in a clinical trial, the majority said no (82%), while 14% had taken part in a clinical trial and 4% had taken part in a rehabilitation trial.

For those that had taken part in a trial, 41% said their main motivation was to help MS research in general. One third took part because they wanted to try something that might help their MS.

Graph 1: Main motivation to take part in a clinical trial



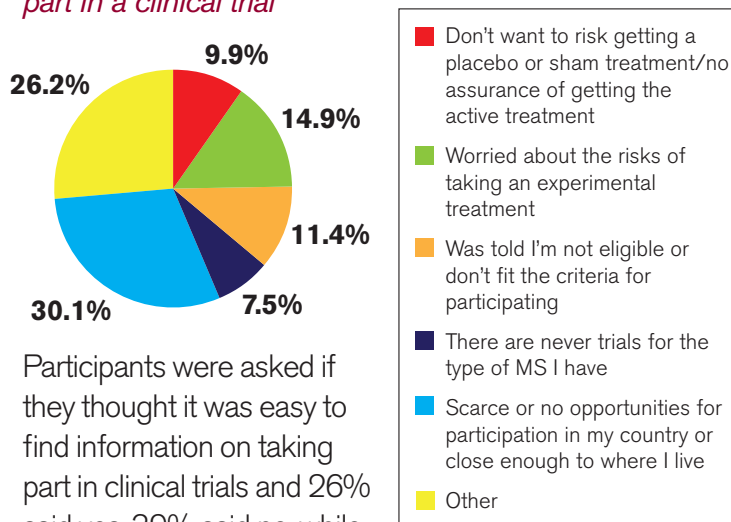
The majority (85%) felt adequately informed about what the study entailed before they signed the consent form, but more than half (52%) of those who took part in a trial said the researcher did not share the results of the study.

When asked whether they felt that taking part had helped their MS, 53% said yes, and 47% said no. Those who answered yes were asked how it helped. Some said the trial had helped their symptoms or had reduced the severity of relapses. Other interesting replies included:

- "It gave me more information on my disease course and ways to help handle stress."*
- "It made me acknowledge and accept the importance of exercise."*
- "It made me feel that I'm not alone."*
- "I developed a better understanding of the effect of MS on cognition"*

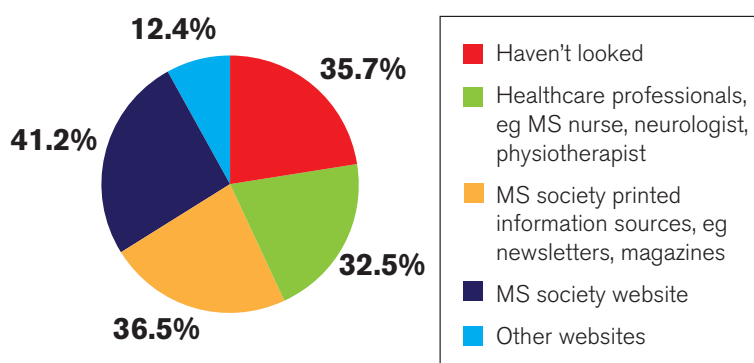
The main reason given for those who had not taken part in a clinical or rehabilitation trial was "scarce or no opportunities for participation in my country or close enough to where I live" (30%). Other reasons are outlined in the graph 2.

Graph 2: Reasons why participants had not taken part in a clinical trial



Participants were asked if they thought it was easy to find information on taking part in clinical trials and 26% said yes, 39% said no, while 35% hadn't looked. When asked where they had looked for information, 41% stated their MS society website but other sources were also similarly useful (as shown in graph 3 below).

Graph 3 – Where participants looked for information on clinical trials



Research priorities

Participants were asked to choose their top three priorities for MS research. The three that were supported the most were finding a cure (72%), new drug treatments or therapies (60%) and research into the cause of MS (58%).

Banking brains for science

Djordje Gveric, PhD and Richard Reynolds,
PhD, MS Society Tissue Bank,
Centre for Neuroscience,
Imperial College London, UK

Why do we need brain banks?

The brain is the most complex organ in the body and every one of its parts is vital for our normal functioning and wellbeing. Although a living brain can be studied using a number of imaging techniques, such as magnetic resonance (MRI), scientists rarely get a chance to study actual brain tissue. Surgical procedures and brain biopsies yield very small amounts of tissue, which is primarily used for diagnosis.

During the last couple of decades we have seen an ever-increasing need to access a number of specific brain areas in order to unravel different disease mechanisms in the neurological conditions that affect people. This in turn gave impetus to a systematic collection and preservation of post-mortem human brains, and modern brain banking was born. The use of post-mortem human brain tissue has already been instrumental in helping understand the pathology of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, and to develop new treatments.



Brain banking involves the systematic collection and preservation of postmortem human brains for research purposes.

In MS this approach has led to the development of some of the latest treatments, for example natalizumab, and is helping to answer questions such as why MS lesions appear in a random manner or what is the relationship between the location of MS lesions in the brain and the level of disability experienced by people with MS.

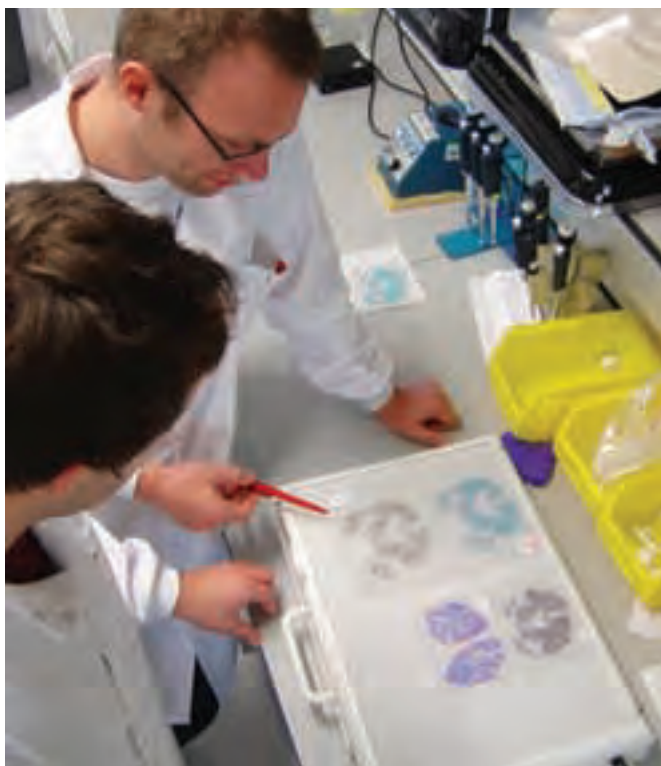
Resource for research

Over the years scientists have advanced knowledge of MS using different experimental approaches, ranging from looking at isolated proteins and cells to establishing animal models of MS. Whichever way they generate their conclusions, at some point scientists have to relate what they find back to the human tissue to make sure they are on the right track. This approach, termed validation and translation, represents the most important process in modern science and speeds up the delivery of scientific solutions from a laboratory to the individual.

MS Society Tissue Bank

This worldwide resource of brain and spinal cord tissue is one of the few brain banks specifically supporting scientific efforts to find a cure or better treatment for MS. The tissue bank has been part of Imperial College London since 1998. A major goal of the tissue bank is to make high quality brain and spinal cord tissue available to research groups investigating different aspects of MS.

Overall the tissue bank functions as a coordinating body between tissue donors, the scientific community, healthcare professionals and charitable organisations supporting MS research. All tissue bank activities are regulated by very precise ethical guidelines and laws, such as the Human Tissue Act. So far, more than 500 human brains and spinal cords have been collected, each one giving approximately 250 individual specimens. A large percentage of these specimens have already been used to supply more than 200 research studies whose experimental work has changed the way we think about MS and has opened new avenues for treatment.



Donating tissue is vital for MS research

Donating tissue for research is a lasting legacy and tissue banks exist only because of the foresight and generosity of people who have agreed to donate their organs. The MS Society Tissue Bank operates a UK-wide donor scheme and so far more than 5,000 potential donors, with and without MS, have joined the scheme. The whole scheme is community based, thus closely reflecting what is going on in the real world and allowing the tissue bank to collect sufficient numbers of different types of MS cases.

In order to retrieve and preserve tissue in the shortest possible time following a donor's death, ideally within 12-24 hours, the tissue bank is organised in a similar way to organ transplant units with bank co-ordinators on-call 24-hours a day, 365 days of the year. The quality of collected tissue is ensured by a thorough neuropathological examination of the tissues and a study of the clinical history of the individual, followed by production of a full report on each case. Both the report and collected clinical data are available to researchers and accompany every tissue sample supplied to a research project.

The need for brain tissue is constantly on the increase as scientists are developing new techniques and

coming up with new ways to find out what is going wrong in MS. It is not only that scientific experiments are consuming higher amounts of brain tissue but also, with recent advances in the field of genetics, there is a need to study a large number of different specimens.

The brain is a large structure but pathological changes are often confined to a very specific part of the brain which can be small in size. Furthermore, each brain that is retrieved from someone with MS has a limited number of lesions that show differences in size and distribution from one case to another. These are only some of the reasons why we need a constant flow of tissue into the tissue bank.

The tissue bank's open access policy ensures that no research group is refused access to tissue. The ethical, legal and scientific merits of tissue requests are carefully scrutinised by an independent body consisting of MS scientists, neuropathologists and people with MS. All requests receive equal treatment regardless of whether they come from academia or industry or whether they are part of an established research programme or a small pilot study.

Brain banking is an important part of science infrastructure and is rapidly establishing itself into a scientific discipline looking to find novel ways of preserving human brain tissue and of developing new uses for its tissue collections. Maintaining archival collections of tissue and data will allow scientists of the future to conduct retrospective studies on the influence of environment, lifestyle or the increasing number of drugs on both clinical and pathological aspects of MS. Most importantly, brain banking provides quality assurance to scientists and encourages the use of human tissue in research into causes and treatment of brain conditions. With such concerted efforts the MS puzzle might finally be solved.

Anyone interested in brain banks and their work should contact their national MS society, their neurologist or their MS nurse to see if there is a brain bank in their region or country.

MSIF research programmes

International Pediatric MS Study group

MSIF stimulates and facilitates international cooperation and collaboration in research through a number of important international programmes.

Children with MS represent only 2-5% of the MS population. Due to small numbers, there is a lack of research studies and treatments have not been systematically tested or approved for children. MSIF plays a key role facilitating the work of the International Pediatric Multiple Sclerosis Study Group (IPMSSG www.ipmssg.org), a group of 150 pediatric neurologists, scientists and healthcare professionals, whose aim is to optimise worldwide care, education and research in childhood MS.

Two flagship research projects have been identified by IPMSSG: the development of a clinical database based on a defined minimal dataset, and a multinational study on environmental exposures and MS in children. This study will be carried out over two years in diverse countries following 800 children with a first demyelinating event to examine the relationship between environmental risk factors (such as vitamin D insufficiency, host responses to microbial infection and pollutants) and the risk of developing MS.

With the emergence of several new drugs for MS in the pipeline, and the lack of a large enough pediatric MS population to participate in all the studies, careful planning is critical to ensure safety and efficacy of studies while avoiding delay of approval of new drugs that could greatly benefit children and adolescents with MS. In September 2010, MSIF facilitated a meeting to develop a global consensus statement from the IPMSSG regarding the current knowledge about treatments in pediatric MS and recommendations for future studies and clinical trials. This statement will inform and guide clinicians, pharmaceutical companies and regulatory agencies, such as the Food and Drug Administration of the USA and the European Medicines Agency.

Research coordination

In 2009, MSIF convened a Research Coordination Meeting, bringing together key players in the global MS medical and scientific community to review global MS research spending, set global research priorities and anticipate and prepare for future challenges, trends and opportunities. Nine current research priority areas were identified by the group and a further six emerging priorities were agreed for the future.

Current:

- neuroprotection and repair
- stem cell therapy
- genetics
- immunopathology of MS
- environmental factors
- patient registers
- clinical trials
- pediatric MS
- symptom relief, rehabilitation and palliative care

Future:

- environmental factors (including Vitamin D)
- pathology – gliosis (repair), axonal damage/grey matter involvement
- biomarkers – MRI, CSF and blood
- new treatments (including stem cell therapy)
- longitudinal studies of at-risk groups for developing MS – looking for risk factors and environmental triggers
- progression – risk factors and mechanisms

Research grants and fellowships

MSIF's McDonald Fellowships (www.msif.org/mcdonald) enable young and talented researchers from emerging countries to carry out a two-year research project in an MS centre of excellence. We also offer Du Pré Grants (www.msif.org/dupre) to enable researchers to undertake short-term visits to established MS research centres.

Interview with Paola Zarin, PhD

Head of Scientific Research, Italian MS Society, Genoa, Italy



What are the Italian MS Society's research priorities?

We have two main goals to achieve – tomorrow, a world free of MS and today, a world free from the fear of MS. The success in reaching these important goals is in the hands of MS scientists. People with more advanced MS and those who face symptoms

that impact their quality of life seek hope in scientific research today in order to live life to its fullest potential.

How does the MS Society decide to allocate funds to various areas?

At present extramural funds (funding given to researchers who are not directly part of the MS Society) are assigned through an annual call for proposals. The proposals are subjected to a stringent peer review process followed by an evaluation of the MS Society's Scientific Committee. In the last three years, the peer review process resulted in funding priority research projects in the areas of genetics, neuroimmunology and stem cell research. Although the MS Society's extramural research portfolio today covers major areas of research, with our 2011-2013 strategic plan we aim to strengthen our efforts towards translating basic research into improvements in medical and comprehensive care through special projects and theme-specific calls for proposals.

What are the different phases of research in which the MS Society invests?

The MS Society promotes and funds extramural research of excellence through its annual call for proposals. Moreover, in order to facilitate the translation of fundamental research into real benefits for people with MS, the MS Society calls for special projects in the areas of:

- preclinical research to evaluate new candidate neuroprotective molecules (e.g. Fast Forward Programme)

- translational research to improve the diagnosis of the disease (e.g. MRI research centres)
- clinical research to validate disease modifying and symptomatic therapies (e.g. stem cell research, Neurological Centre of Experimental Therapies – CENTERS programme)
- clinical research to validate new emerging therapeutic hypotheses.

In addition, intramural rehabilitation research is conducted through our Rehabilitation Research Unit, a centre of excellence in MS rehabilitation and socio-health research, which is part of our Social and Health Services department.

In the last 20 years, the MS Society has invested 27 million euro in MS research. In 2009, 36 research projects, 8 fellowship grants and 5 special projects were financed. In the last three years, research projects promoted by the MS Society resulted in 233 original papers published in international peer-reviewed journals.

What are the current research highlights for the MS Society?

- Special projects on stem cell research in collaboration with other organisations.
- Identifying new treatment relatively quickly and cost-effectively through non-profit clinical trials or treatment approved for use in other diseases.
- Studying the validity of the chronic cerebrospinal venous insufficiency hypothesis in MS by funding controlled clinical trials and with an epidemiological study to evaluate its prevalence in MS and other neurodegenerative diseases.
- Contributing to the Fast Forward Programme, founded by the US National MS Society, which focuses on speeding up the drug development process, bridging the gap between promising discoveries and the commercial expertise and funding to move them forward.

Reviews



Stem cell therapies in MS

Download free from
www.msif.org/stemcells

This booklet was produced through an international collaboration of stem cell experts, people with MS and MS organisations.

Stem cell science holds great promise for MS, and we are regularly tantalised by media reports and scientific claims, as well as being confronted by emotive ethical arguments. While there is good research being done, there is still a great deal of mythology around treatments, so clear incisive information is important to people with MS to improve levels of understanding about the science. Stem cell tourism is becoming a vexed issue across the world, and so this publication is very timely.

Stem cell therapies in MS provides this basic information and gives a clear sense of where science currently stands for each type of treatment. It lays out a realistic assessment of the various treatments and avenues of research, and does not promote stem cell treatment as a cure for this debilitating illness.

By explaining the various types of stem cells, from embryonic stem cells to engineered induced pluripotent stem cells, the booklet puts the science in context and will enable readers to better make sense of the stem cell debate.

As a person living with MS with a keen interest in stem cell science I found this booklet made complex science easy to understand. The question and answer section is particularly useful.

The debates around stem cells are hotly contested, and at times ill-informed, but we must encourage more research to be funded and completed across the world. Better information is an essential ingredient to progress, and this booklet, with its collaboration

of scientific and consumer perspectives, makes an excellent contribution.

Reviewed by Robert Pask, Australia

Review www.clinicaltrials.gov

Scientific research is especially important for a disease like MS, as the cause is unknown and there is no cure. If you are a person with MS, you want researchers to find that cure. One way to support this research is to participate in clinical trials. You can wait until your hospital invites you to participate in such a trial or you can find one yourself. The website **www.clinicaltrials.gov** has a database containing the details of many clinical trials worldwide and signals if they need any participants. It provides patients, their families, healthcare professionals, and members of the public easy access to information on clinical trials for a wide range of diseases and conditions.

The site originates in the USA but there are also many trials from other parts of the world. Currently, there are 96,000 clinical trials in the database.

For every clinical study the site provides a summary of the purpose of the study, the recruiting status, the criteria for participation, the location of the trial and specific contact information. Other useful additional information that may help someone decide whether to consider participating includes the research study design, the phase of the trial, the disease or condition and drug or therapy under study.

The site is easy to understand and navigate and there is a lot of information on the trials. There is even background information about what clinical trials are and different phases of research. As a person with MS you could call yourself a doctor after visiting this site!

The site focuses on information and not on layout or visuals – for example, there are no pictures. It is a website that does not pretend to be something it is not. It is a database for clinical trials. It is not very sexy, but it is very informative.

Reviewed by Reni de Boer, The Netherlands

MS *in focus*



multiple sclerosis
international federation

Skyline House
200 Union Street
London
SE1 0LX
UK

Tel: +44 (0) 20 7620 1911
Fax: +44 (0) 20 7620 1922
www.msif.org
info@msif.org

MSIF is a charity and company limited
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Registered Charity No: 1105321.

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