MS Convention
Lay Paper (24/10/2003)
http://www.mssociety.org.uk

Multiple Sclerosis Society

50 years on – are we closer to unlocking the mystery of MS?

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The 50 years since formation of the MS Society has seen a vast accumulation of knowledge about multiple sclerosis. In 1953, it was thought that 1 in 1300 people develop the disease. Now the number is more like 1 in 400. This is probably not because multiple sclerosis is getting more common but the result of there being more people at risk, increased awareness and earlier recognition. In the 1950s, the symptoms and signs of multiple sclerosis were well recognised. Neurologists could describe accurately the appearance of plaques in the brain and spinal cord. There were no scans. The only test was a lumbar puncture and without very good use being made of the sample. No one had more than the most general ideas about the cause of multiple sclerosis or how parts of the brain and spinal cord were actually damaged. Treatment was chosen largely by guesswork and without very precise ways of sorting out whether it was actually any good - other than by asking patients and doctors what they thought. At least the danger of confusing multiple sclerosis with hysteria, commonplace in the 19th century, had been scotched and the condition was recognised as an important physical disorder of the central nervous system, in need of some good research and a few lucky breaks. In 2003 there is no shortage of new information and opinion relating to the cause, mechanisms, natural history and treatment of multiple sclerosis.

But is it possible to sort the fact from the fiction, and are we nearer a solution to this difficult disease?

Building on the pioneering work of John Kurtzke, reasons for the geography of multiple sclerosis are keenly argued - the rival theories being that the illness tracks the distribution of Northern European genes (sometimes dressed up as the Viking hypothesis) or, based on evidence for epidemics and from migrant groups, that multiple sclerosis is acquired because of exposure to a germ. Clearly multiple sclerosis is a moving target. For some epidemiologists, the factors being distributed are genes, for others they are germs. Both are probably right - multiple sclerosis resulting both from nature and nurture through the interplay of genetic and environmental factors. A great deal of work has gone into unravelling the genetics of multiple sclerosis. Real progress has been made although the genes are still undiscovered. The problem is like trying to find an unknown number of needles in one or more of twenty-three haystacks. But as a result of candidate and whole genome screens, and the application of knowledge gained through the Human Genome Project, some of the needles are definitely glinting and the search is down to a few bales not the whole farmyard. Finding the germ is proving even more difficult. The current best guesses include *human herpes virus 6*, *Epstein Barr virus* or *Chlamydia pneumoniae*. Importantly, it may not be the fact that one particular germ can cause multiple sclerosis but, rather, to whom this happens and when. Perhaps everyone is exposed at some point but the process is triggered only in those at increased risk for genetic reasons, and at a particular time of life.

Medical scientists working in the 19th century devoted their efforts to descriptions of multiple sclerosis. These included a full account of the symptoms and signs, and the appearance of affected tissue – to the naked eye and under the microscope. The pioneers were Robert Caswell, Jean Cruvielhier, Jean-Martin Charcot and James Dawson, and later Russell Brain

and Douglas McAlpine and colleagues. Their work was completed 50 years ago but there has since been a systematic update in knowledge on the natural history seeking to illustrate the complete experience of multiple sclerosis in the population. No longer is this knowledge coloured by the experiences of a few or dominated by descriptions of those who got interested in one particular feature of the illness – losing sight of the wood through over preoccupation with the trees. Now, the series of natural history studies from London (Ontario: George Ebers and colleagues), Gothenberg (Sweden: Oluf Andersen and colleagues) and Lyon (France: Christian Confavreux and colleagues) tell the whole story of what it is to have multiple sclerosis, and for the entire spectrum of affected persons. In parallel, the natural history of the lesions in multiple sclerosis has been revealed through the use of magnetic resonance imaging and spectroscopy (acknowledged through award to the inventors, Paul Lauterbur and Sir Peter Mansfield, of the 2003 Nobel prize for Medicine). Its application to multiple sclerosis is to the credit of Ian McDonald and the MS Society (especially John Walford and the late Dr Reginald Kelly). The team at the Institute of Neurology (especially David Miller and Alan Thompson) and Paul Matthews (Oxford) have since charted the natural history of individual lesions in multiple sclerosis – the large but submerged part of the disease iceberg – and in many clinical settings. Other laboratory methods were introduced, also primarily to advance, make more accurate and predict the diagnosis of multiple sclerosis in people with suspicious symptoms. But knowledge gained from these laboratory tests – spinal fluid analysis (by Ed Thompson and the late John Whitaker, in the modern era) evoked potentials (George Dawson, Martin Halliday and Ian McDonald) and magnetic resonance imaging – served the double purpose of shoring up the inflammatory doctrine of tissue injury (oligoclonal bands in the cerebrospinal fluid) and the effect of demyelination on normal workings of the brain and spinal cord (evoked potentials).

Doctors and people with multiple sclerosis now have plenty to think about when trying to see the big picture on how things go wrong - the pathogenesis - and suggesting ways of putting a spanner in the works. The headlines of where we were 50 years ago is that multiple sclerosis is due to patches of demyelination disseminated throughout the brain and spinal cord (but nowhere else) each interfering with the normal electrical workings of the nervous system and ending up as hard scars due to overgrowth of astrocytes – the underlying nerve fibres remaining intact, and everything driven by the process of inflammation following the arrival of immune cells from the bloodstream. A few old lessons had been forgotten but the gist of the story seemed right. As much through a sense of frustration that more rapid progress has not subsequently been made, and with insights gained from new knowledge, that story has intermittently been challenged but, for most informed commentators, not replaced. What have been the milestones that mark the consolidation of knowledge over the last 50 years?

First, a series of landmark studies (from John Prineas, Cedric Raine, Hans Lassmann, Hugh Perry, Margaret Esiri, Bruce Trapp and Claudia Luchinetti, amongst others) have used new methods to describe the core features and variations of the pathological process. They have shown that the inflammatory process is invariable; that, in addition to loss of myelin, nerve fibres are caught up in the acute phase of tissue injury; that remyelination is a routine feature of injury and repair in multiple sclerosis but it seems not to last; and that a rather different sequence of events may occur in some people – in short, that there is disease heterogeneity. Second, the consequences of injury to axons and myelin have been described starting with the

original experimental and applied work of Ian McDonald and Tom Sears, and with major contributions by many of their students, notably Ken Smith. They

have helped us to understand the mechanism of many previously mysterious symptoms of the illness and to understand the clinical course – typically a phase of episodes with full recovery, then relapses with persistent symptoms and signs, and finally slow progression. Here, the message is that the inflammatory process can interfere with the workings (function) of the nervous system without at first necessarily damaging the structure. But if that inflammation does not immediately settle, the window of safety is lost and a cascade of further events then inevitably follows which interferes with salutatory conduction in the central nervous system and increasingly damages axons. Third, has been the increase in understanding of how the nervous system is built and might be re-constructed after injury of the type that occurs in multiple sclerosis. With the definitive description of axon-glial arrangements by Richard and Mary Bunge in the 1960s, building on the earlier descriptions of glial subtypes by del Rio Hortega, a new era in experimental neurobiology began with description of the glial progenitor by Martin Raff in 1983. This allowed an exponential increase in knowledge relating to the cellular architecture and catastrophes of tissue destruction in multiple sclerosis, and provided a framework for thinking about repair. Now that work is widely distributed – especially in the laboratories of Richard Reynolds, Robin Franklin and Neil Scolding. Once, remyelination was seen as a nice addition to treatment - perhaps contributing something to the restoration of function - but very much a luxury. Now, current ideas on the pathogenesis put the neuroprotective role of remyelination centre-stage making this an essential component of any comprehensive strategy for stabilising tissue injury and limiting the accumulation of disability and progression in multiple sclerosis. And at a time when individuals and society question the need and dividend from animal experiments, it is appropriate to confirm the extent to which knowledge on how different cells and structures interact has been assembled through the work (in this country) of Bill Blakemore, Robin Franklin and Ken Smith using animal models to explain one

aspect or another of the complex processes that make for tissue injury and repair in multiple sclerosis.

In 1953, the treatment of multiple sclerosis included artificial pyrexia, arsenic and drugs that dilate blood vessels. Corticosteroids had been introduced in the previous year for the treatment of relapse. Although general measures aimed at improving health were available and recommended, the principles of clinical trials had only just been described and none yet carried out in the context of multiple sclerosis. Although the therapeutic era had begun, the story to date was of clinical charisma and the exploitation of vulnerable patients littering the historical highways and by-ways of therapeutic endeavour in multiple sclerosis. It had not been an altogether golden road. Now, the issue of treatment dominates the clinical research field although, through the initiatives of Alan Thompson and Jeremy Hobart (amongst others), the important contribution of rehabilitation is not neglected. Things started to change with the pioneering work of the late Larry Jacobs and the last ten years has seen the completion of clinical trials leading to identification of drugs that modestly influence the natural history of multiple sclerosis, leading to drug licences in many parts of the world. Everyone recognises that these advances in treatment represent only a start in improving prospects for the individual with multiple sclerosis. It is significant that only one treatment that may help people with multiple sclerosis has been developed in the United Kingdom (by Herman Waldmann, Greg Winter and Geoff Hale). The rest come from elsewhere. But it is important to remember that treatments can do more than make people with multiple sclerosis better. For example, the work of Alasdair Coles has indicated why results to date have been disappointing and how strategies might be improved by selecting treatment on the basis of the process that drives tissue injury at each step in the cascade, and timing these in the individual patient to the most appropriate stage of his/her natural history.

Uncertainty breeds speculation and multiple sclerosis has attracted more than its fair share of wacky ideas. Not all can be dismissed as the idle thoughts of ill-informed amateurs. Several come from the mouths and pens of qualified medical scientists. This is no less true in 2003 than it was in 1953. Those who develop these hypotheses exercise the luxury of picking from the entire corpus of knowledge on multiple sclerosis, facts which decorate their particular interpretation without necessarily having to stir from the theoretical armchair and test their ideas experimentally. Although often a harmless enough exercise, occasionally the ideas have caused distress, undermined mainstream doctrines on the aetiology and mechanisms of tissue injury in multiple sclerosis, required time spent dealing with spurious media interest provoked by the more provocative claims, and distracted from serious research.

So what have we learned? Multiple sclerosis results from the interplay of genetic and environmental factors. Thus, the aetiology depends on race and place, on nature and nurture. The genes are several exerting independent and interacting effects. The germs are enigmatic – probably several and unavoidable. The problem is not “if” but “who” and “when” the infection occurs. They trigger an immunological response in the body as a whole that settles on the brain and spinal cord. Inflammation drives that process. It causes acute injury of axons and myelin. Remyelination happens but is not tough enough to put right all the problems. And it is undermined by successive waves of inflammation and more tissue injury. In some people and in some lesions, there is more inflammation, in others less; in some more antibody formation and complement deposition, in others less; in some more oligodendrocyte damage, in others less. In short, there is pathological heterogeneity. But whatever the route, the consequence is persistent demyelination, axonal loss and failure of sustained remyelination. Then, the permanent loss of myelin begins to tell and nerve fibres start to disappear from loss of the myelin that normally coats their surface and evidently keeps

them healthy. With the loss of myelin and axons, the permanently injured tissue scars by overgrowth of astrocytes and the hard – sclerotic – plaque is formed. Treatment modestly reduces the frequency of inflammatory episodes in the relapsing-remitting phase. It does rather little to reverse existing disabilities or halt progression. But if this sounds gloomy, the insight provides hope and a way forward. Rather than treat people with drugs that cannot re-write neurological history and put back together tissue that is irretrievably injured, we need to target treatments to that stage of the illness when they can do most. If disability and progression cannot easily be treated, they should be prevented so as to head off the trouble that might otherwise lie ahead. It is, to use a nursery metaphor, the difference between putting Humpty Dumpty back on the wall *versus* stopping him from falling off in the first place.

Ahead lies more research based on an improved understanding of the cause and mechanisms of tissue injury in multiple sclerosis, building on these achievements and providing treatments that limit and repair the damage - reliably, predictably and safely for the affected individual facing an otherwise uncertain neurological future. In 50 years from now, we will not be holding conferences with lectures entitled “are we closer to unlocking the mystery of MS?”