

Multiple Sclerosis in its European Matrix: Some Aspects of History, Mechanisms and Treatment

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ABSTRACT: Susceptibility to multiple sclerosis is influenced by several genes which are relatively common in populations of European origin. Their precise identification is currently being intensively investigated. The pathophysiology of the main clinical features is better understood. *Relapse* results from abnormalities of conduction to which both demyelination and inflammation contribute. At the membrane level, *remission* depends on the formation of new sodium channels which restore conduction even in persistently demyelinated axons. Remyelination presumably contributes and synaptic re-organisation may also do so. Axonal degeneration contributes to irrecoverable deficit and *progression* of disability. These observations suggest new therapeutic strategies. The management of multiple sclerosis needs to be improved. Progress requires an ethically based partnership between patients, whose needs are paramount, the research and caring communities and the pharmaceutical industry.

RÉSUMÉ: La sclérose en plaques dans sa Matrice Européenne: observations sur l'histoire, les mécanismes et le traitement. La susceptibilité à la sclérose en plaques (SEP) est influencée par plusieurs gènes dont la fréquence est relativement élevée dans les populations d'origine européenne. L'identification de ces gènes fait l'objet de recherches intensives. La physiopathologie des principales manifestations cliniques est mieux connue. Les récurrences résultent d'anomalies de conduction aux quelles la démyélinisation et l'inflammation. Au niveau de la membrane, la rémission dépend de la formation de nouveaux canaux sodiques qui restaurent la conduction même dans les axones qui demeurent démyélinisés. On présume que la remyélinisation et la réorganisation synaptique y contribuent. La dégénérescence axonale contribue au déficit irrémédiable et à la progression de l'invalidité. Ces observations suggèrent de nouvelles stratégies thérapeutiques. Le traitement de la SEP doit être amélioré. Le progrès repose sur une alliance, basée sur des principes éthiques, entre les patients, dont les besoins sont primordiaux, les chercheurs, les soignants et l'industrie pharmaceutique.

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Beyond reasonable doubt, multiple sclerosis (MS) is in its origin a European disease. The case, more specifically, that it may be connected with the Vikings has been made by Charles Poser¹ and Sten Fredrickson.² Understanding how the disease came to emerge in Europe remains a problem. Nevertheless, part of the story is becoming clearer. As you will see, understanding the European origin of MS has been helped by knowing about its prevalence elsewhere in the world, and we must gratefully acknowledge at the outset that our present understanding of the disease has depended to an important extent on scientific contributions made beyond the changing boundaries of Europe, in particular, from the United States and Canada and around the Pacific rim from West to East and from South to North, where indigenous populations have prevalences 20 times less than in Europeans sharing these environments or living elsewhere at similar latitudes³.

However, as physicians, our primary concern is with

individuals, not populations. A recent development in the attitude of neurologists towards MS has been the long overdue placement of the person with it at the centre of discussions about it. This is part of a welcome general change of attitude in medicine. For too long, doctors thought – knew – that they knew best what was good for the patient. They do not, and they cannot because, for the most part, they do not know what it is like to suffer from any particular disease.

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Central to any effective partnership between patient and doctor in identifying the relevant problems of a disease and in prioritising research to solve them, is an appreciation of how the disease changes the life of the person with it. Fortunately, in MS, we have several sources we can tap. Arguably, the most comprehensive is the case of Augustus d'Este. In this review I plan to use his case to illustrate the experience of MS, and as a starting point for a consideration of some aspects of the disease in which I have been interested over the past 40 years: susceptibility to it, its pathophysiology, and how to assess the effectiveness of treatment. The progress in our understanding has been real but important questions remain unanswered in almost every facet of this complex disorder.

AUGUSTUS D'ESTE

The story of Augustus d'Este is told in his own words in two manuscripts in the archives of the Royal College of Physicians in London. The first is entitled "The Case of Augustus d'Este". It was edited and published by Douglas Firth in 1948.⁴ The second is an unpublished personal diary beginning about two years before d'Este's death. Together, they provide a moving account of the tragedy – as it so often is – of MS.

It is all too easy to lose sight of the central fact that the individual who manifests the symptoms and signs of MS has a life beyond our clinics, and that much of the drain on the emotional and physical resources of the person with MS derives from accommodating the restrictions imposed by the illness within the framework of her – or his – personal and family life. d'Este's diaries reflect this imperative and although his life was, in many respects, a privileged one, his trials resonate with those of all who have MS. For this reason, I shall spend some time describing the social context of the diary, which has wide connections with the history and geography of Europe.

Who was Augustus d'Este and when did he live? The apparently simple answer to both questions is provided by the statement that he was a grandson of King George III of England, the mad King George. But, as with the disease from which he came to suffer, little is straightforward about this man – neither his status, his name nor his life. Helpful accounts of his life and family are provided by Firth⁴ and Gillen.⁵

The prelude to the story begins in London in February 1772 when King George III forced through Parliament a law which made it illegal for a member of the royal family to marry without the permission of the monarch. The Act was deeply unpopular with press and Parliament because the potential for injustice was built in: the King could, if he chose, alter the succession to the throne by capricious timing of approval amongst his offspring. Nevertheless it was passed.

We now move ahead some 20 years. In November 1792, the King's 6th son, Prince Augustus Frederick (later Duke of Sussex) arrived in Rome. He very much wanted a useful job there, but his father ignored his pleas. There was little else to do but to enjoy the social life of the expatriot community. He soon met the aristocratic Lady Augusta Murray, who was descended on her mother's side from King James II of Scotland and Edward IV of England and on her father's from Charles VII of France. The Prince mentioned her in a letter to his eldest brother in March 1793 and within a month thereafter they were married. They can

have had little idea of the trouble they were letting themselves in for, though two facts make it clear that they knew they were doing wrong. First, the clergyman, the Reverend William Gunn, was very reluctant to perform the ceremony, probably because he knew the penalty for anyone doing so was "total forfeiture of all goods and estates, imprisonment at the will of the King, and not to be relieved, even if starving".⁵

Secondly, when they returned to England later that year, they took the unusual step of being married a second time, in St. George's Church, Hanover Square. The following month, their son, our Augustus, was born. News of this event soon reached the ears of the King. His Queen (Queen Charlotte) recorded in her diary

*"To Day the Kg told me that the Ld Chancellor had acquainted Him Yesterday after the Levé with the disagreeable News of Augustus's marriage with Ldy Augusta Murray eldest Daughter to Earl Dunmore on Thursday the 5th December 1793 at St. Georges Hanover Square, that the Register was found, & that He had given Orders to the Chancellor the Archbishop of Canterbury & the other Ministers to proceed in this Unpleasant business as the Law directs..."*⁵

The marriage was annulled in August. Thus, though the boy was biologically the grandson of King George III, the provision of the unpopular Act of Parliament of 1772 enabled him to disown the lad.

There was further trouble to come. A second child was born in 1801. Prince Augustus believed – wrongly as it turned out – that because of his travels he could not have been the father. Their relationship broke down and Lady Augusta took custody of the children.

To Prince Augustus's increasing exasperation, Lady Augusta brought the children up to expect royal privileges which, of course, were not forthcoming. She changed their place of residence frequently, and from time to time, their names. Finally, the Prince became fed up and wrote to the boy who was now at Harrow School ...

*"My dear Son,... it is best that you should at once take the Name by which you are to be known hereafter. Not being able to give you that most congenial to my Wishes and Feelings, I have selected one of the Names of My Family, which is Este. By this I shall in future call you: it is one you need in no way regret and which marks whom you are, to whom you belong and with whom you are connected..."*⁴

But how does it come about that the Prince who was of a German family that had been in England for two generations, should have the name of the great family of Ferrara, a name which appears in Dante's Divine Comedy, a name that we associate with the Villa d'Este and its fountains and their musical evocation by Liszt? The villa had been built for Cardinal Hippolito d'Este as a reward for his support in the election of Pope Julian III. This Hippolito is of interest to our story. The great eighteenth century historian, Edward Gibbon explains part of the connection between the d'Estes and the Hanoverians.⁶ Gibbon has it that "the primitive stem divided into two branches" in the eleventh century; the elder migrated to the banks of the Danube and the Elbe and gave rise to the Dukes of Brunswick and the Kings of Great Britain; and the younger stayed in Este and nearby Ferrara. Research on the genealogy of the present

Prince of Wales⁷ reveals that there is a second line of descent from the Italian branch of the family, from Alberto I d'Este, who founded the University of Ferrara in 1391, now the site of important work on the epidemiology of MS, to which I shall return.

Gibbon tells, in his characteristically majestic prose, a story about Hippolito d'Este which has a certain resonance with the one I have just told, a story of illicit love and its consequences:

"The Cardinal Hippolito was enamoured of a fair maiden of his own family: but her heart was engaged by his natural brother; and she imprudently confessed to a rival, that the beauteous eyes of Don Julio were his most powerful attraction. The deliberate cruelty of the Cardinal measured the provocation and the revenge: under a pretence of hunting, he drew the unhappy youth to a distance from the city, and there compelling him to dismount, his eyes, those hated eyes, were extinguished by the command, and in the presence of an amorous priest,



Figure 1: Augustus d'Este, aged about 18. Painting believed to be by Sir William Beechey. By courtesy of Mr Hugh Murray.

who viewed with delight the agonies of a brother. It may, however, be suspected that the work was slightly performed by the less savage executioners, since the skill of his physicians restored Don Julio to an imperfect sight."

This disagreeable tale also resonates with the next part of my story which begins with loss of sight and recovery. We come now to Augustus d'Este himself (Figure 1), his diaries, and his illness.

THE ILLNESS OF AUGUSTUS D'ESTE

It is inescapable that d'Este suffered from MS. His illness began before the pathology was first depicted by Carswell in 1838⁸ and ended with death 20 years before the definitive description by Charcot in 1868.⁹ It was thus not diagnosed in life. The following extracts from his diaries are representative, and illustrate the basis for the retrospective diagnosis. They also highlight certain features of the disease, which I wish to discuss, and how it interfered with his life.

"In the month of December 1822 I travelled from Ramsgate to the Highlands of Scotland for the purpose of passing some days with a Relation for whom I had the affection of a Son. On my arrival I found him dead. I attended his funeral:- there being many persons present I struggled violently not to weep, I was, however, unable to prevent myself from so doing:- Shortly after the funeral I was obliged to have my letters read to me, and their answers written for me as my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence:- Until I attempted to read, or to cut my pen, I was not aware of my Eyes being in the least attacked. Soon after, I went to Ireland and without anything having been done to my Eyes, they completely recovered their strength and distinctness of vision..."

"In the month of January 1826... My Eyes were again attacked in the same manner as they had been in Scotland... my Eyes again recovered."

"October 17th, 1827. To my surprise I there [in Venice] one day found a torpor or indistinctness of feeling about the Temple of my left Eye. At Florence I began to suffer from a confusion of sight:- about the 6th of November the malady increased to the extent of my seeing all objects double. Each eye had its separate vision... The Malady of my Eyes abated, I again saw all objects naturally in their single state... Now a new disease began to show itself: every day I found gradually (by slow degrees) my strength leaving me... At length about the 4th of December my strength of legs had quite left me, and twice in one day I fell down upon the floor... I remained in this extreme state of weakness for about 21 days..."

"... on the 21st January [1828] I was strong enough to begin a journey from Florence... to Rome... On the journey I was able to walk up some steep Hills... I rode out on horseback most days, and my strength gradually returned. I never was able to run so fast as formerly, nor could I venture to dance."

Thus on this occasion recovery, or remission, which had been complete following the first two episodes, was only partial.

Further relapses occurred, some with incomplete remission. There were episodes of incontinence and impotence. By 1843 he recorded that:

"When standing or walking I cannot keep my balance without a Stick... About the 16th of December I returned to London from Brighton in consequence of again considering, that, from the searching quality of the Sea Air, I was gradually becoming less capable of taking exercise."

It is clear that by this stage, after an initially relapsing and remitting course, he was entering the secondary progressive phase of the disease. By January 20th 1846 he recorded that:

"... I have regained some of my Strength ... but then ... I suffer very much indeed from sharp Spasmodic pains in my Feet and Legs ... my Sensations seem to be awful Indicators that some very sad Change has taken place, or is taking place in my System ... For the last 12 months ... my Hands have become slight sufferers from my Disease..."

In 1847, d'Esté recorded meticulously in a Gentleman's Almanac his determined efforts to keep mobile. His deficit was accumulating. On the 18th August he noted:

"Alas! only walk in my Room 14¼ minutes"

and on the 22nd

"Alas! Alas! during this Week I only walk for 2 Hours & 33 Minutes".

But as all such patients notice, there were variations from day to day. On September 1st he walked for 22¼ minutes, and on the 2nd for 65 minutes and did not have to lie down at all during the day. On the 4th, however, he walked for only six minutes. On 15th September, he recorded "I walk in my Room 46¼ mins"

A possible hint of cognitive impairment comes in December that year when he records on December 12th:

"I go to My Sister's Church. A Stranger does Everything - Alas! I cannot follow him. I believe that there was Good in his Sermon".

By this time his handwriting had deteriorated, as can be seen by comparing his working copy of his Case of February 1846 (Figure 2) with an entry in January 1848 (Figure 3). The last entry was in February and he died in December.

Figure 2: Augustus d'Esté's handwriting in 1846. By courtesy of the Royal College of Physicians, London.

1848.
January. Monthly Abstract. Ramsgate -

RECEIVED.	My Days Walking	PAID.
Monday - January 19	I walk in my Room for	44 - 1/4
Tuesday - Jan. 20	I walk in my Room for	43 - 3/4
Wednesday - January 21	I walk in my Room (Thanks to) One Hour & 18 - 1/4 minutes	78 - 1/4
Thursday - January 22	I walk in my Room for -	44 - 3/4
Friday - January 23	I walk in my Room for -	45 - 1/4
Saturday - January 24	I walk in my Room for -	19 - 3/4
Sunday - January 25	I walk in my Room for -	66 - 1/4
During this Week I walk 6 Hours & 41 - 3/4 Minutes -		341 - 3/4
Monday - January 27	I walk in my Room for -	45 - 3/4
Tuesday - January 28	I walk in my Room for -	54 - 1/4
		100 - 1/4

Figure 3: Page from the Gentleman's Almanac in which Augustus d'Esté recorded his walking. January 24-31, 1848. By courtesy of the Royal College of Physicians, London.

I have spent some time on one person with MS to emphasize the importance of placing individuals at the centre of our concerns. I wish now to turn to three topics raised by d'Esté's illness: why he developed it; what the mechanism of his relapses, remissions and progression were; and how it was treated then and how we should approach the problem of treatment now.

WHY DID D'ESTE DEVELOP MULTIPLE SCLEROSIS?

It is obvious from what I have said that d'Esté's genetic background relates to much of Europe: Italy, Germany, France and Scotland with its Viking connections, to mention only those elements to which I have referred already.

The mass of evidence indicating that there are both genetic and environmental factors involved in the causation of MS is well-known. Let me remind you of just one piece which makes the point particularly cogently. It is the conclusion from large twin studies carried out in Canada¹⁰ and the UK¹¹ (with which the smaller French study¹² is not necessarily at odds) that the concordance rate for dizygotic twins is about 3%, whereas as for

monozygotic twins it is about 25%. Clearly a genetic factor is involved.

But turn the figures round the other way, and the conclusion is inescapable that the genetic factor is not enough: three quarters of the causative influence must come from elsewhere, that is, the environment. What the environmental factors are still elude us despite fifty years of investigation, though a planned investigation in Australia where there is a seven-fold difference in prevalence rate between tropical Queensland in the north and the high latitude temperate Tasmania in the south^{13,14} has the potential to take us further.

Fortunately, we are better placed in relation to the genetic factors. The generally accepted statement that the prevalence of MS increases with increasing latitude in northern Europe and in migratory populations derived from it, conceals the fact that within Europe there are pockets of unexpectedly high or low prevalence compared with adjacent regions. A good example is provided by Sardinia where the prevalence is 152 per 100,000¹⁵ compared with 32 – 69 per 100,000 in mainland Italy.¹³ These and other marked local variations in prevalence within Europe, where individual populations have been relatively stable for the past 1000 years, offer a special opportunity to help elucidate the nature of the genetic component in MS. This opportunity has been seized by the Cambridge group led by Alistair Compston. The project, Genetic Analysis of Multiple Sclerosis in Europeans, is a remarkable instance of pan-European collaboration. The starting position was the observations reported in *Nature Genetics* in 1996 derived from three separate genome surveys of MS.¹⁶⁻¹⁸ These surveys utilised DNA from populations in Canada, France and USA, and UK. All found several areas of interest and it was reassuring that all identified the HLA region of the sixth chromosome as potentially linked to MS. This is not surprising, given that it was well-established that in each of these populations the disease is associated with what is now known as DR-15 (formerly DR-2).

These studies were looking for linkage – that is for genes which were inherited through the family in the same way as the disease is. The failure to identify regions where linkage was statistically unequivocal was a disappointment, a disappointment shared with investigators working on other complex traits such as inflammatory bowel disease and asthma. There was, accordingly, a move away from linkage studies to association studies, that is to studies which aimed to identify genetic differences between those who do and those who do not have the disease. Such studies are more powerful and for modest effects more efficient, even though they require the typing of many more markers.

In the Genetic Analysis of Multiple Sclerosis in Europeans project there are 23 collaborating centres in 18 countries within Europe. They are in areas of varying prevalence; Australia with its transported European population and wide range of prevalences is also participating. DNA has been collected from 2670 individuals, 961 affected and 1709 unaffected, and has been pooled in each centre for analysis using 6000 micro-satellite markers, more than 10 times as many as in the 1996 studies.

The analyses are being performed by young investigators from each centre who bring their material to the laboratory in Cambridge or to the Decode Laboratory in Iceland which is

collaborating on the project. Here they learn the appropriate molecular genetic techniques, obtain their results; and return to their own laboratories with the new skills which will facilitate further analysis of their local material in the future.

The outcome is not yet known but the analysis is almost complete. Optimism about success is increased by the recent identification of a susceptibility locus in inflammatory bowel disease using the same approach.^{19,20}

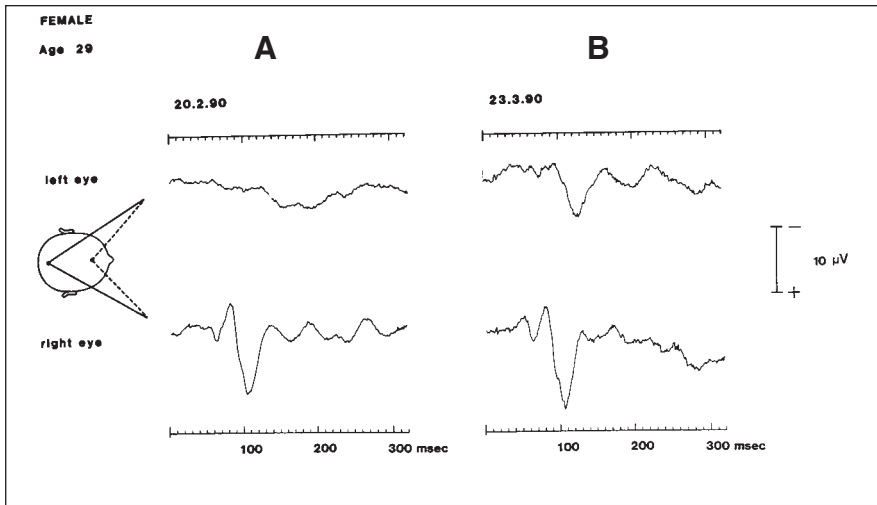
MECHANISMS OF RELAPSE, REMISSION AND INSIDIOUS PROGRESSION

Let us turn now to the second question raised by d'Este's illness: what are the mechanisms of relapse, remission and progression?

My interest in these issues goes back more than forty years to the time when my Professor of Physiology at the University of Otago, A.K. McIntyre, suggested that I look at the effects of experimental demyelination on conduction, about which little was then known. It was easier to study the peripheral nervous system than the central, so that is what I did. The results of the next three years of work can be summarised by saying that at a focal experimental demyelinating lesion in a nerve, the size of the compound action potential is reduced indicating that conduction is blocked in many fibres; surviving conduction is delayed because, as recording from single fibres showed, it is slowed in the demyelinated area.²¹

Later, Sears and I showed that the same is true for demyelination in the spinal cord.²² Martin Halliday and I then applied these principles to man using the visual evoked potential and showed that the same phenomena occur in MS.^{23,24} I shall return to this in a moment. The problem in 1973 was that there was no way of correlating directly the pathology in patients with the physiological changes. The situation changed a decade later with the introduction of MRI. Paty and his colleagues²⁵ showed that the abnormalities seen in the brain of MS patients correspond with plaques at postmortem, and Kermode et al²⁶ showed that the earliest detectable event using gadolinium enhancement and standard MRI is, in most (but not all)²⁷ new lesions, a breakdown in the blood brain barrier. When a patient at the National Institute of Health, Bethesda, died some ten days after an enhanced MRI, it was found that there was inflammation in the enhancing lesions but not in the nonenhancing, leading to the conclusion that in this context, enhancement indicates the presence of inflammation.²⁸ Johnson et al, in 1987,²⁹ developed a method for imaging the enhanced optic nerve. It was now possible to make a direct correlation of the characteristics of an MRI – visible lesion with electrical conduction and clinical function. Youl et al³⁰ studied patients with optic neuritis. They were scanned at presentation (within two weeks of onset) and again a month later. The occurrence of symptoms correlated with the inflammatory phase of the lesion. Of special interest were the visual evoked potential findings.

Figure 4 shows that, in addition to a delay, there is a decrease in the amplitude of the visual evoked potential from the affected eye (largely attributable to conduction block) during the acute phase when vision is poor. One month later, the amplitude of the evoked potential has returned towards normal, indicating that conduction block has partially resolved: the vision has also

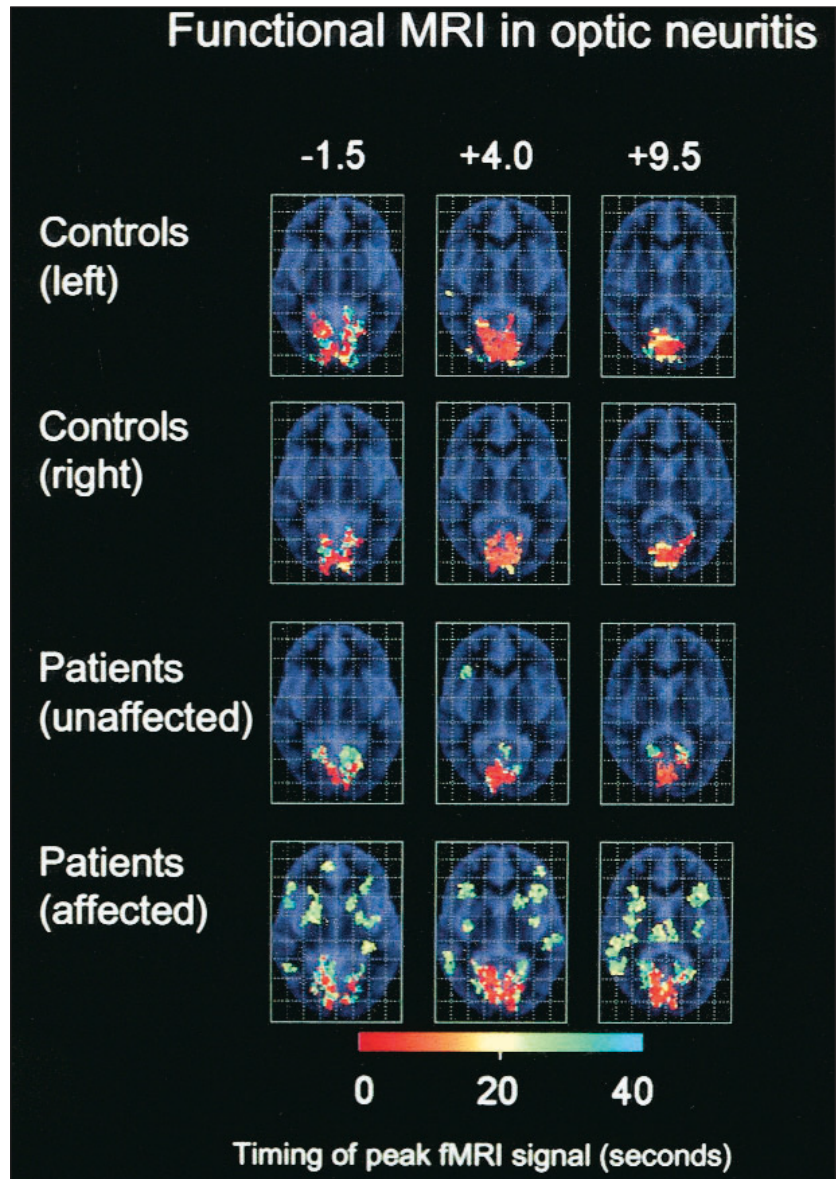


Left:
Figure 4: Visual evoked potentials from a 29-year old female patient with acute left optic neuritis recorded (on 20 February 1990) (A) within two weeks of onset of symptoms and (B) 31 days later. There is a small, delayed response from the left eye at the first recording which has recovered in amplitude at the second. Data provided by Youl et al.³⁰

Right:
Figure 5: Generic brain activation maps from seven control subjects and seven patients showing areas of significant response to monocular photic stimulation compared with binocular darkness. The one tailed probability of false positive activation is $p < 0.0001$ for each voxel; activated voxels are colour coded according to the delay (in seconds) of the periodic response relative to the onset of photic stimulation. The left side of each map represents the right side of the brain; z coordinates in standard space are given for each slice in mm. In the control subject group (left eye) there is activation only in the visual cortex bilaterally, with a larger area of activation in the right compared with the left visual cortex. The right eye response showed a similar pattern but with greater activation of the left visual cortex. In the patient group (unaffected eye) there is a single additional focus of activation in the right insula-claustrum. In the patient group (affected eye) there is additional activation of a network of multimodal processing areas including bilateral insula-claustrum, lateral temporal cortex, posterior parietal cortex, thalamus, and corpus striatum. Note that the periodic response in extraoccipital areas is considerably delayed relative to the response in the visual cortex.

Reproduced from Werring DJ, Bullmore ET, Toosy AT, et al. Recovery from optic neuritis is associated with a change in the distribution of cerebral response to visual stimulation: a functional magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* 2000; 68: 441-449 with permission from the BMJ Publishing Group.

returned to normal. These changes correlate with the cessation of enhancement, presumably signalling a decline in the intensity of inflammation. Demyelination persisted, given that there was a persistent delay in the evoked potential. From these observations we may conclude that there is something about the inflammation itself which is contributing to conduction block. Ken Smith and his colleagues have argued from convincing experimental evidence that nitric oxide (NO) (production of which is increased in MS³¹) is one of the inflammatory products which is contributing it.³²



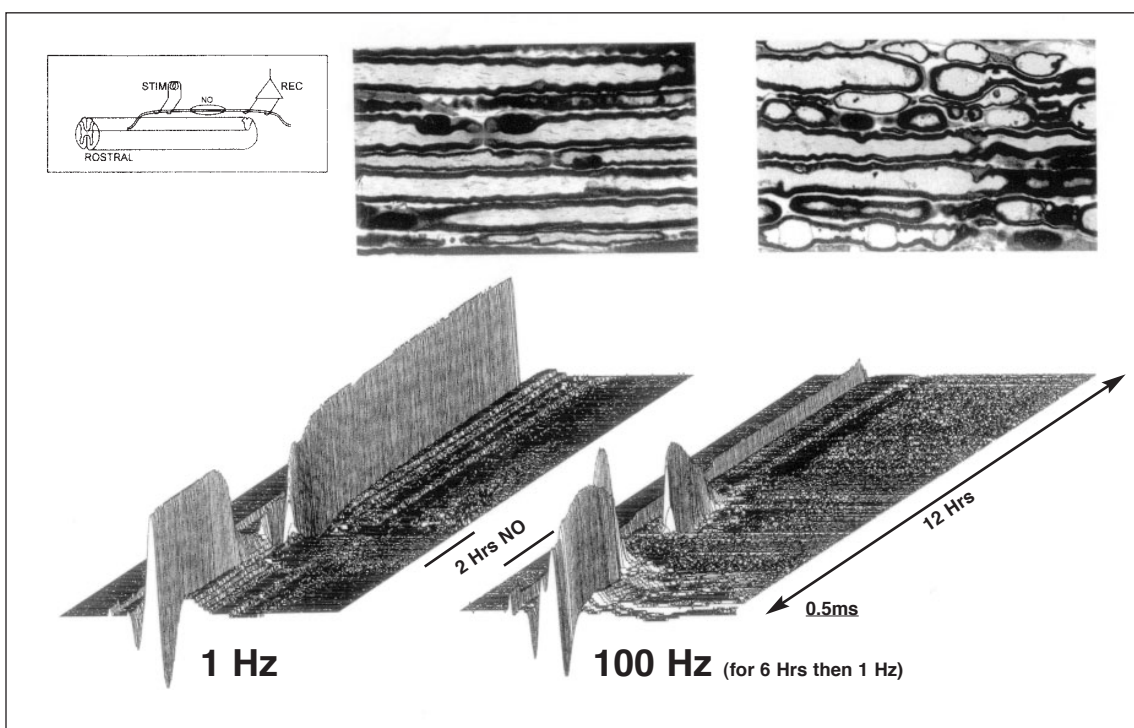


Figure 6: Lower plots: two series of compound action potentials recorded in parallel from two separate dorsal roots using the arrangement indicated (top left). The earliest records are shown at the front, and each plot shows approximately 12 hours of recorded data. The left plot shows records obtained with continuous 1 Hz stimulation, whereas 100 Hz stimulation was employed for the first six hours on the right. Exposure of both roots to nitric oxide for two hours (indicated) resulted in almost total conduction block, but whereas conduction was restored to the axons on the left upon washing, the restoration on the right was only partial and temporary. Upper illustrations: histological examination of the roots at the end of the recording period revealed that the axons in the root on the left were normal in appearance, whereas those stimulated at 100 Hz during exposure to NO were degenerating. For a more detailed description, see reference 32.

Reprinted from Smith KJ, Kapoor R, Hall SM, Davies M. Electrically active axons degenerate when exposed to nitric oxide. *Ann Neurol* 2001; 49: 470-476. Copyright © American Neurological Association. Reproduced with permission of John Wiley & Sons, Inc.

Another conclusion from Figure 4 is that because conduction is still delayed, the demyelinated fibres must have acquired the ability to conduct. In experimental demyelinating lesions, restoration of conduction is achieved by the insertion of new sodium channels into the denuded axon membrane.³¹ Does this happen in MS? Yes. Moll et al³³ have shown in postmortem material that there is increased saxitoxin binding, i.e. increased numbers of sodium channels, in demyelinated areas where axons survive but not where the axons have degenerated. This is clearly an important mechanism in the early stages of recovery from an acute relapse. But there remains something of a problem.

Normal function in the nervous system requires orderly and precise timing of arrival of impulses at synapses. However, after recovery, unequal slowing in different fibres persists. This is a problem which has interested me since those first experiments on demyelination in peripheral nerve I have described. Another observation made at that time was that recovery of motor function could occur while conduction in motor (and sensory) fibres was still very abnormal.²¹ What this observation and the experience of optic neuritis suggest is that somehow the nervous system is able to adapt to deal with the distorted information it receives.

The advent of functional MRI has enabled us to take a first

step towards testing this hypothesis. Werring and his colleagues³⁴ studied seven cases of isolated optic neuritis who had recovered normal acuity and who at the time of functional imaging had no additional cerebral lesions at MRI. They asked the question: "Is there a difference in the pattern of activation in the brain following a simple visual stimulus between normal individuals and those who have recovered from optic neuritis?" The results are shown in Figure 5.

The top row shows the response from normal subjects. There is activation in the occipital cortex. The response from the normal eye in patients was similar (middle row), but the response after stimulating the affected eye was quite different (bottom row). Multiple additional areas, all with extensive visual connections, were activated. Similar changes have been observed in the motor system.^{35,36} When Werring et al³⁴ looked separately at those in whom the latency had, exceptionally, returned to normal, presumably as a result of re-myelination (which occurs in MS), the extent of activation was much less. These observations, of course do not establish that adaptive mechanisms are a necessary part of the recovery process. Their relevance should emerge from the current studies charting the evolution of the changes from the acute stages and comparison with non-demyelinating optic neuropathy.

To return to the second question raised by d'Este's illness, we can now answer that *relapse* results from acute inflammation and demyelination, both elements making a direct contribution to conduction block. *Remission* occurs as the inflammation subsides and the new sodium channels become active. Remyelination, to the extent that it occurs will contribute and adaptive changes may play a part.

What about the *progression* of disability so noticeable in d'Este's account of his illness? It has become clear over the past five years or so that the axonal degeneration which has long been known to occur in MS may occur early, as Lassmann,^{37,38} Perry,³⁹ Trapp⁴⁰ and their colleagues have shown. Of special interest to us as clinicians, is that it is an important determinant of irrecoverable disability, as Losseff and Davie and their colleagues have shown.^{41,42} There are several hints that continuous progression may result from continuing axonal degeneration³¹ but we still await a definitive serial clinical and MRI study.

If we are to intervene beneficially in the disease process, we need to understand the factors determining axonal degeneration. We know a little about it. There is experimental evidence that both demyelination itself and inflammation can damage axons.³¹ The recent experiments of Smith et al³² have revealed a possible mechanism for the effect of inflammation. What they did first was to induce an experimental demyelinating lesion in the spinal cord of the rat. When NO in concentrations of the order likely to exist in MS lesions was introduced, conduction was blocked. Washing out the NO led to restoration of conduction.

The same thing happened when the experiment was done with normal roots; the histology afterwards was normal. When Smith et al³² combined the same concentration of NO over the same period with impulse activity in the roots at 100 Hz (frequencies which are seen, for example, in normal walking) conduction block was irreversible, and the roots showed evidence of degeneration (Figure 6).

What was the mechanism? Their hypothesis is that axonal degeneration is precipitated by the accumulation of Ca⁺⁺ (and perhaps Na⁺) as a result of the known toxic effect of NO on mitochondria.⁴³ The nerve impulse depends on the inward flux of Na⁺. Ca⁺⁺ enters with the Na⁺. The Na⁺ and Ca⁺⁺ must be pumped out, a process which consumes energy provided by adenosine triphosphate which is synthesised in the mitochondria. In the demyelinated nerve, mitochondrial function will be impaired by NO. There is an additional problem which I think is relevant: in the demyelinated axon there is an enormous increase in inward current, i.e. in Na⁺ (and therefore Ca⁺⁺) influx during continuous conduction.⁴⁴ This must be pumped out. The combination of an increased demand for energy, and a diminished capacity to provide it, leads to an accumulation of Ca⁺⁺ which triggers the mechanisms which lead to degeneration.⁴⁵

This hypothesis is supported by Kapoor, Smith and colleagues' very recent observations that Flecainide,⁴⁶ which reduces Na⁺ and Ca⁺⁺ entry into the axon, and blocking the Na⁺/Ca⁺⁺ exchanger⁴⁷ can protect against axonal degeneration in their experiments. We are just at the beginning of our understanding of the mechanisms of axonal degeneration, but this start with its therapeutic implications is a propitious one.

TREATMENT

This brings me to my last topic: treatment. We know what d'Este's physicians used because he meticulously recorded their prescriptions in his diary. In keeping with the contemporary theories of disease, they included various metallic salts, Strychnine and plant extracts. For the episode of diplopia, he "was twice bled from the temples by leeches", purged, induced to vomit, and twice bled from the arm. He was treated with diets, baths and galvanism, and records that having his weak legs "rubbed with brushes and the torpid part of my back rubbed ... with a Liniment ... succeeded completely". I do not doubt that his physicians too thought that their ministrations were beneficial when he had a remission. But as Dr Samuel Johnson said, reviewing a book on spas in the mid-eighteenth century ...

*"It is incident to physicians, I am afraid, beyond all other men, to mistake subsequence for consequence..."*⁴⁸

This lesson, preached more than 200 years ago, not by a physician but by a literary man, has been a hard one for us in our field to learn, even though it has been a matter for repeated comment for a century now, that one of the problems in MS is distinguishing therapeutic effect from the natural history of the disease.

The unfinished story of how we have moved towards the goal of determining whether a treatment is useful or not has been told by J. Rosser Matthews in his admirable book *Quantification and the Quest for Medical Certainty*.⁴⁹ The story began about the time of onset of d'Este's illness. The problem, in essence, was how to measure effectiveness in the face of individual variation. The first step was taken by Pierre-Charles-Alexandre Louis (Figure 7) who, in 1825, wrote a monograph on tuberculosis based on his observations of patients at *la Charité* in Paris.⁵⁰ He argued for numerical comparison based on Laplace's theory of probability. Laplace himself had anticipated that his calculus of

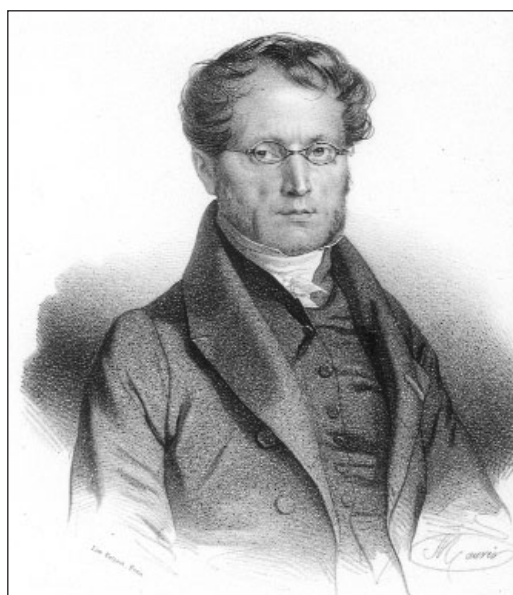


Figure 7: Pierre-Charles-Alexandre Louis. Engraving by A Maurin. By courtesy of the Royal College of Physicians of London.

probabilities could be applied to the evaluation of treatment.⁴⁹ Louis' ideas resulted in an intense debate in the Academies of Science and Medicine over the next decade. Prominent physicians, such as Cruveilhier and Risueño d'Amador, held that certainty in medicine could only be reached on the basis of induction based on observations on individual patients. This view accorded with that of the physiologists, exemplified by Claude Bernard, who asserted that proof emerged only by a process of induction from experimental results derived from the study of individual animals.

In the late 1850s, the debate was taken up in Germany, where it was conducted largely in the journals. The controversy was precipitated by the mathematician and physicist, Gustav Radicke, who turned his interests to the application of statistics to medicine.⁵¹ Again, he was opposed by physiologists.

The next phase was centred on London at around the turn of the century. There had, by this time, been some acceptance of a role for numerical comparison in medicine, and Sir Almroth Wright (who in the figure of Sir Colenso Ridgeon was criticised by George Bernard Shaw in his play *Doctor's Dilemma*) used statistics in his assessment of the effectiveness of a typhoid vaccine for the British Army. The statistician Karl Pearson, however, pointed out that the method used was not decisive. The chief confrontation came a little later (1911) over something Wright called the opsonic index, which he believed could determine whether a specific bacterial infection was present in a given patient. The statistical inadequacies of the work were pointed out by Major Greenwood (Major was his forename, not a military rank), a protégé of Pearson's. Greenwood tackled Wright in a forthright manner. The title of his paper gives something of the flavour of the debate: *On methods of research available in the study of medical problems. With special reference to Sir Almroth Wright's recent utterances*.⁵² In the following decade, the statistical arguments found increasing favour, including among Sir Almroth Wright's colleagues, who privately referred to him as Sir Almost Wright or as Sir Always Wrong.⁵³

Greenwood and his American colleague Raymond Pearl continued to promote vigorously the application of statistics to medicine. The crucial next step came in 1935 with the publication of R.A. Fisher's *The Design of Experiments*⁵⁴ in which he stressed the central importance of randomisation in the controlled experiment. The idea was originally developed in the context of agricultural research. Greenwood recognised its 'epoch-making' importance, not least for medical research.

The triumphant vindication of the clinical trial based on a statistical approach and the principle of randomisation came in 1948 with the publication of the trial of treatment of tuberculosis with streptomycin.⁵⁵ It had been devised by Austin Bradford Hill (Figure 8), a pupil of Greenwood's. Of it, a commentary in the *Bulletin of the Johns Hopkins Hospital* commented, 'the report [of the trial] merits study not only for the results but for the way the experiment was conducted ... The result is that a rather limited number of cases, only 107 all told, have served to give definitive results which one can interpret with confidence'.⁵⁶

The application of these principles to the problems of treatment in MS was still two decades away. The first published attempt related to the trial of ACTH in the treatment of relapse.⁵⁷ In 1983, a workshop organised by the National Multiple

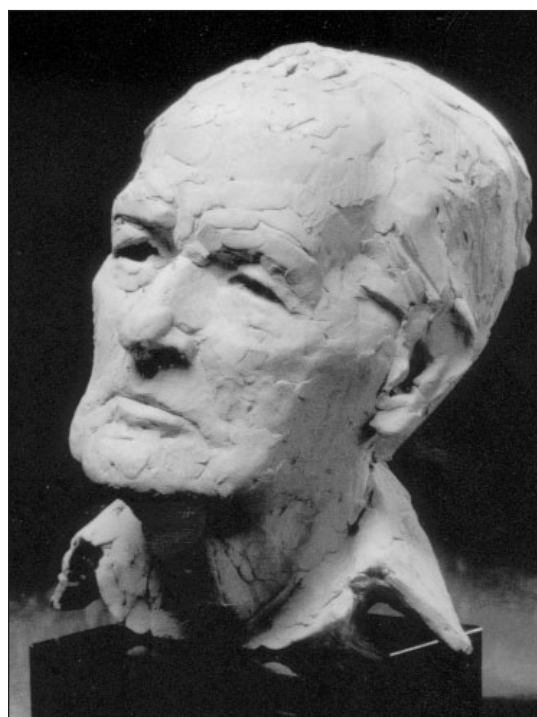


Figure 8: Austin Bradford Hill. Photograph of head in biscuit-fired clay, by Neil French. By courtesy of the Royal College of Physicians of London.

Sclerosis Society of the USA concluded that the best way of determining the effectiveness of treatment designed to modify the course of MS was the randomised, double blind, placebo controlled trial.⁵⁸ This led to the full scale application of the principle in the trials of beta-interferon and glatiramer acetate, published a decade or so later.⁵⁹⁻⁶¹ These clinical trials have consistently shown that the beta-interferons and glatiramer acetate reduce relapse rate by about a third – a really significant step forward – but when it comes to the question of slowing the rate of progression of disability, the evidence is not consistent. Some trials suggest that progression may be delayed; others (sometimes even with the same preparation given in the same way) that it is not; and even the positive trials provide evidence for, at best, a modest effect.

It is a matter for regret that the discussions of data from clinical trials sometimes lack the objectivity which we are entitled to expect in clinical science. In this otherwise encouraging decade, we have witnessed the deplorable spectacle of physicians presenting highly partial accounts of evidence for the beneficial effects of treatment, and we have seen a pharmaceutical company swell an audience with several hundred individuals for a single paper favouring its product, then taking them away to a social engagement before the discussion of the paper was finished. Advancing our understanding of MS and how best to treat it is ill-served but such practices, practices which, sadly, may emerge when we forget that at the centre of all our efforts must be the person with MS.

Now it would be ridiculous to imply that such actions are the norm. They are not. Pharmaceutical companies have made

important innovative contributions, not only to research, but to patient welfare as well and most physicians work tirelessly to achieve the best for their patients. There is a pressing need for industry and the profession to agree to a basis for constructive collaboration in the design, conduct, analysis and reporting of clinical trials. Industry needs us and we need industry. People with MS need us both, and have the right to expect us to work together first and foremost for their benefit.

Even with optimal collaboration we are still faced with a practical difficulty which paradoxically derives from the very successes of the 1990s. Given that we do have licensed treatments (albeit modest in their effects), it is no longer ethically justified in most circumstances to assess new agents using the large placebo controlled trials which have hitherto been necessary to demonstrate effectiveness. What is to be done?

Henry McFarland and John Noseworthy pointed out to me in 1998 that there is a mass of serial MRI and clinical data from untreated individuals which has been accumulated in the last decade or so in the placebo arms of clinical trials and in population based epidemiological studies over a rather longer period. There is a considerable degree of homogeneity in this data, in part as a result of the efforts in the 1990s to standardise methods of measurement and collection of data; in this the pharmaceutical industry played a crucial role. The Multiple Sclerosis International Federation, therefore, undertook to set up a centre which could amass this data in a secure way and use it to model mathematically the course of the disease. The overall aim is to identify combinations of clinical and MRI markers which will be more reliably predictive of the future than those so far identified. New treatments will be assessed in groups of patients defined by the markers, thus, it is hoped, avoiding the use of placebo groups. The centre, named in honour of Sylvia Lawry, the founder of the first Multiple Sclerosis Society and the International Federation, has been established in Munich. The major holders of placebo and natural history data are collaborating. The Centre now has 44 data sets derived from more than 14,000 patients and representing more than 60,000 patient-years. The analysis has begun and the first paper is nearing completion. This is an excellent example of what can be done when industry and the profession work together.

It is to be hoped that this venture signals a new commitment by both industry and the profession to develop further an ethical relationship in the service of patients, so that a girl, or a boy like Augustus d'Este, who has the European susceptibility genes and later develops MS, might be saved from the almost inevitable collapse of the quality of his/her life as he/she becomes increasingly disabled.

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