Deficit, recovery and the *vis nervosa*

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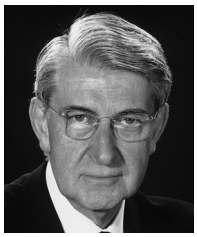

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ABSTRACT – Physicians have long sought to explain neurological deficit and recovery on the basis of alterations in the agent of nervous action. The ancient Greeks knew that the brain influences muscles and they showed experimentally that the effects were mediated by nerves. Galen believed that the agent of action was the animal spirits. Ideas began to change with a new approach to knowledge and the revival of experimentation that followed the arrival in Venice of ancient Greek manuscripts after the fall of Constantinople in 1453. In the mid-18th century the notion of animal spirits was replaced by that of the *vis nervosa* and speculation began that the agent might be electrical. This was established by the mid-19th century. The nature of conduction in nerve was clearly different from that in a wire but how it took place remained uncertain until Hodgkin and Huxley proved the ionic hypothesis in the mid-20th century. In the following decades the membrane mechanisms of conduction failure and restoration were elucidated, with practical consequences in the form of improved diagnostic methods and the potential for more rational approaches to treatment. The demonstration that adaptive cortical plasticity contributes to recovery raises the possibility of new strategies for neurological rehabilitation.

KEY WORDS: adaptive plasticity, axon, channels, conduction, demyelination, remyelination

Two very different cases seen while I was a medical student raised similar questions and provided the starting point for my interest in the mechanisms of neurological deficit and recovery, and for much of the research with which I have been involved over the past 50 years. In 1953, I saw my first patient with multiple sclerosis and I was struck by the degree of recovery possible from even a severe relapse. In 1957, I saw a youth who had been accidentally shot in the thigh. He was paralysed below the knee. But after a week or two, to the surprise of all, voluntary movement began to return at the ankle. It is obvious to us now that the deficits in these two patients and their recoveries must have been mediated by changes in the electrical properties of axons traversing the lesions. But this explanation was not always so apparent and, in the timescale of attempts to understand deficit and recovery, is very recent. In this lecture I shall describe the history of the growth in our understanding of these phenomena.

Ancient history

Hippocrates recorded in the 5th century BC that the brain influences muscles: he (or they, since the *Hippocratic corpus* is the work of more than one hand) noted that injury to one side of the head produces spasms in the opposite side of the body.[1] That the influence of the brain on muscles is mediated by nerves was demonstrated by Erasistratus in Alexandria in the 3rd century BC; in his dramatic public vivisections he would silence the squealing of a pig by pinching the recurrent laryngeal nerves.[2] Galen did the same in the 2nd century AD and extended his experiments to sectioning the spinal cord, showing that motor and sensory function below the lesion was lost, the pattern depending on the size and location of the cut. He concluded that the function of the nerves was mediated by what he called the 'animal spirits', formed in the brain by a complex process that goes beyond this article. These spirits passed through the nerves to the 'feeling and moving parts' but how they did so he could not decide.[3]

There matters rested for more than 1,000 years during which the Barbarian incursions destroyed the Roman Empire.[4,5] By the 5th century the ability to read Greek was lost in the Latin West and in the centuries that followed, the Greek masters were known only through increasingly and inevitably (given the difficulties of translation) corrupted Arabic versions of their writings. Ironically, it was a new threat to Graeco-Roman civilisation that led to new understanding as a result of a radically changed approach to knowledge.

New approach to knowledge

In the early 15th century, John VIII Palaeologus, Emperor of Byzantium, could see that the only hope for the survival of his Empire was to gain the support of the Western princes in resisting the Turkish invasions. This was impossible, however, so long as the Church was in schism (which it had been since the 11th century), the Western princes being Catholic and Byzantium Orthodox. In an attempt to secure

reunion, the emperor attended a Council of the Church held at Ferrara and Florence in 1438. He was accompanied by the great scholar John Bessarion, Archbishop of Nicea. Union was agreed but the Greek citizenry would not accept it.[6] The Turks invaded and within 15 years Constantinople had fallen and the Byzantine Empire was destroyed. Bessarion, who abided by the decree of union and was appointed Cardinal, saw this coming and decided to stay in the West. Venice had impressed him by its political stability and the Cathedral Church of St Mark was particularly welcoming. Accordingly, he made two great gifts to the Republic. One was a relic of the True Cross in a reliquary in front of which Bessarion was depicted by Gentile Bellini (Fig 1). The second, of particular interest to us, was his collection of 746 manuscripts of which 482 were Greek.[7] He pledged these manuscripts to St Marks where they formed the nucleus of the Marciana Library and became available to the scholars of Venice's university at Padua. For the first time in many centuries they had access to uncorrupted Greek manuscripts.[8] The result was a rebirth of classical learning, which led to the scientific renaissance and, over the next century, a profound change in the method of inquiry in philosophy and natural science, including medicine. Authority was questioned, and careful observation of the phenomena of nature, including disease, became central to the new endeavour. Experimentation in the manner of Galen was revived.[2]

Huge advances followed in the next century. The achievements of Vesalius, Falloppius and Fabricius (William Harvey's teacher) became widely known and students came from all over Europe to study at Padua. The new approach culminated in Harvey's discovery of the circulation of the blood, published in 1628, which in its turn was profoundly influential. In the words of the great German physiologist Albrecht von Haller in 1754:

> *The publication of Dr Harvey's great discovery to the world, soon excited a spirit of emulation and empowered all the European professors of anatomy to trace the steps thereof, both in living and dead subjects ... the consequences of which were very considerable anatomical discoveries ...*[9]

Turning specifically to ideas about nerve function, Vesalius in 1542 reiterated Galen's view that nerves function because of the animal spirits; he conjectured that the spirits were distributed by the nerves and '… may be regarded as the busy attendants and messengers of the brain'.[10]

Thomas Willis, somewhat more than a century later, took the same view, although unlike Vesalius he thought that the animal spirits were transmitted in the nerves downwards as well as upwards, thereby providing the basis for both movement and sensation.[11] But there was a problem about transport. Neither Vesalius nor Willis could find evidence that the nerves were hollow, though Vesalius later concluded that they were; Willis continued to believe that they were 'like an Indian [sugar] cane'.

About this time Descartes put forward a more complex view in his attempt to explain reflex action.[12] He supposed that fine fibrils passing up within tubules within the nerve fibres opened trapdoors in the ventricles, allowing animal spirits to flow through and impinge on the pineal where perception occurred.

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Fig 1. Cardinal Bessarion and two members of the Scuola della Carità in prayer with the Bessarion Reliquary. Gentile Bellini c.1472. Photo © The National Gallery, London.

The mobile pineal then redirected the spirits back down the specific tubules to the muscles of the stimulated part. The demonstration by Steno in 1669 that the pineal was fixed effectively disposed of this hypothesis.[13]

But this was not the end of mechanical ideas of nerve action. Isaac Newton in the early 18th century, invoking his principle of a universally distributed aether, thought that sensation was mediated by vibrations in aether within the nerves.[14] It was a popular view and for a time received support from many, including the distinguished physician and influential Fellow of the Royal College of Physicians (RCP), Richard Mead.[3] By the mid-18th century, however, powerful arguments were being brought against it, notably by von Haller, on the grounds that nerves are soft and since there is no tension in them they cannot effectively transmit vibrations.[15] David Hartley's solution was to suppose that the contents of the nerve fibres could behave like a fluid and support vibrations by virtue of the presence of 'infinitesimal' particles within the nerve fibres which 'were subject to the powers of attraction and repulsion'.[16]

The vis nervosa *and confirmation of the electrical hypothesis*

Von Haller considered carefully the nature of the agent of nerve action. He termed it noncommittally the *vis nervosa,* an expression which remained in use until just over a century ago. Having rejected Newton's vibratory conjecture he considered the possibility that it might be electrical. This idea, which had been discussed in 1733 by Stephen Hales,[17] the English clergyman and natural philosopher who first measured blood pressure, arose in the context of the growing interest at the time in electrical phenomena in general and animal electricity in particular. Electric fish had been depicted by the ancient Egyptians and Greeks, and the Roman physician Scriborius Largus in the 4th century AD had recommended the numbing effects of the live fish as a treatment for headache, gout and anal prolapse.[18,19] Von Haller concluded that the agent of nerve action was not electrical, an argument based on his observation that a ligature tied round a nerve gave rise to paralysis. If the 'nervous fluid' were electrical (he wrote), it would bypass the ligature and cause the muscle to contract. He concluded that it was 'watery, of a lymphatic or albuminous nature' and that it was transmitted in tubes within the nerve fibres, which he had not seen but deduced must be there. He seems to have been unaware that Anthony van Leeuwenhoek thought he had seen them, although he may have been describing axons.[20] Wrisberg, on the other hand, in an annotation in the 1786 translation of Haller's *First lines of physiology*[21] supported the electrical hypothesis, and had thought for some time that the matter would soon be resolved, perhaps by Alexander Monro of Edinburgh. Monro, however, concluded that the agent of nerve action was not electrical.[22] Then, in 1773, Walsh demonstrated for the first time that the shock of the fish *Torpedo* was electrical by noting that it produced the same sensation as the newly invented 'Leyden Phial' (a capacitor capable of delivering a strong shock) when a circuit was made up of an electric fish and four observers holding hands; the sensation was still experienced if a metal conductor, but not sealing wax or glass, was introduced.[23] This delightful manifestation of the friendly relations which existed between gentlemen of those times interested in science is further exemplified by Walsh providing John Hunter with a *Torpedo* specimen for anatomical study. His paper describing the structure of the electric organ follows Walsh's in the *Philosophical Transactions of the Royal Society*.[24] Hunter concluded that it was well suited to '[form] manage and store the electric fluid'.

With all this discussion it was not surprising that in 1791 Luigi Galvani's publication of his *De Viribus Electricitatis in Motu Musculari Commentarius* (translated as C*ommentary on the effect of electricity on muscular motion*) caused a considerable stir.[25] It is a delightful book, combining a clear account of his thinking and experiments, mostly on frogs, and the circumstances in which they were performed. He made a good case for the existence of intrinsic animal electricity and showed clearly that it was identical with atmospheric electricity and 'artificial' electricity produced by rubbing amber. His answer to another of von Haller's objections to electricity being the agent of nerve action, namely that the 'electrical fluid' would diffuse away through the good conducting medium provided by the tissues, was that the oily covering of the nerves visible under the microscope (what we now call myelin) would '… prevent the effusion and dissipation of the electric fluid'. It was soon clear that animal electricity was a general phenomenon. Galvani showed that electrical phenomena existed in the nerves and muscles of sheep and his nephew, Giovanni Aldini, went further and concluded that they were also present in man – as we may conclude from the title of his book *An account of the Galvanic experiments performed by John Aldini on the body of a malefactor executed at Newgate, January 17th 1803.*[26] An expanded version, including macabre illustrations of experiments on guillotined criminals, a cow and a dog, was published the following year in Paris.[27]

But there was still argument. One of Galvani's experiments involved hanging dissected frogs from a bronze hook through the spinal cord on iron railings outside his house. When the hook touched the railing the frog twitched. Alessandro Volta, who had initially accepted Galvani's views about intrinsic animal electricity, later rejected them, concluding that the essential fact was the dissimilarity of the metals in this and other experiments performed by Galvani. Von Humboldt repeated both Galvani's and Volta's experiments and concluded that Galvani, however, had been right.[28]

Interest in Galvani's work nevertheless declined. But in the 1830s Carlo Matteucci (a worker characterised by EGT Liddell as exhibiting more industry than insight[30]) provided a convincing demonstration of the intrinsic nature of animal electricity by showing that it was possible to stimulate a muscle to contract when its nerve was laid on another actively contracting muscle.

The next important step was taken in Florence in 1827 when Leopold Nobili, using his astatic galvanometer, showed that it was possible to detect a flow of current up the body of a flayed frog from muscles towards the spinal cord.[29] It was therefore disappointing that Matteucci and Longet in 1844 using this same

instrument were unable to detect a current in the nerve.[30] It soon became clear however that the instrument was simply not sensitive enough. The problem was rectified by du Bois-Reymond, the Geneva born physiologist working in Müller's laboratory, who, with a much improved instrument, detected an electrical change (which he termed the negative variation) accompanying activity in nerve and muscle.[30]

An aspect of nervous action that had perplexed investigators from the middle of the 18th century was its speed. Wildly different estimates were given. Haller guessed that it was '9,000 feet a minute', although figures as high as '57,600 million feet in a second' were proposed.[30] Hermann von Helmholtz settled the matter in 1850 with his convincing measurements of the velocity of conduction in frog motor nerve. This was clearly recognised as an important achievement since it was communicated to the Academy of Science in Berlin in January 1850,[31] and just 2 months later to that in Paris by no lesser a figure than von Humboldt.[32] The velocity can be calculated from the data in the first paper as 25.00–42.50 m/s.[20,33] In the French paper, Helmholtz gave the velocity as 43 m/s and noted that it was influenced by temperature. By 1870, Baxt had measured the velocity in motor nerves of man to be 30–35 m/s.[34]

It was clear, as Liddell has pointed out, that the electricity in nerves was unlike that in a wire and that new concepts were needed to account for it. They began to appear in the early 20th century with Bernstein's membrane hypothesis,[35,36] and culminated in the ionic hypothesis of Hodgkin and Huxley,[37] for which they were awarded the Nobel Prize in 1963. As a footnote it is interesting to record that a belief in the existence of some other force in nerve that drove the impulse lingered into the 1930s. Sir Andrew Huxley recently drew my attention to the correspondence in 1937 between Sir Alan Hodgkin and Joseph Erlanger (then the doyen of nerve physiologists)[38] in which it is clear that Erlanger did not accept Hodgkin's evidence that the impulse advances by local circuits; if it does not, something else must drive it.

The central nervous system

It was implicit in much of the early writing that what happened in the periphery also happened centrally. The first demonstration came with the work of Richard Caton who reported in the *British Medical Journal* in 1875 that by using a galvanometer it was possible in rabbits and monkeys to detect 'feeble currents of varying direction … when the electrodes are placed on two points of the external surface, or one electrode on the grey matter and one on the surface of the skull'.[39] This, in fact, was the first recording of the electroencephalogram. Caton was funded by the British Medical Association and chose to demonstrate his discovery at its annual general meeting. It must have been a spectacular occasion, not least because of the sheer size of the galvanometer scale. The working of the galvanometer depends on two sets of fundamental principles. The first are the laws of magnetism laid out in the book *De Magnete* by a former President of the RCP, Sir William Gilbert.[40] It was this book, published in 1600, that inspired Galileo's work on magnetism and led him to describe Gilbert as the founder of the experimental method of science.[41] The second set of principles are those of electromagnetism, which Oersted of Copenhagen had discovered in 1820. He showed that a magnetic needle suspended inside a coil is deflected when a current flows. In order to amplify very small currents it was customary to attach a mirror to the suspending thread. A beam of light shone on the mirror and was reflected on to a graduated scale on the wall, which on this occasion 'was some eight or nine feet in length'. Conduction in spinal tracts was soon afterwards demonstrated by Gotch and Horsley using the capillary electrometer.[42] Their photographic record is the first published of conduction in the central nervous system, the velocity of which they measured at 39.5 m/s.

Thus, by the end of the 19th century it had been established that the agent of nerve action in brain, cord and peripheral nerve, which Galen, Vesalius and Willis had called the animal spirits and von Haller the *vis nervosa*, was indeed electrical in nature.

Abnormal conduction

So far I have considered what might be termed good impulses – the impulses that mediate the functions of the normal nervous system. What about bad impulses – those that determine the clinical manifestations of disease in the nervous system? That there would be bad impulses was suggested by Galvani, who in the last chapter of the *Commentary* concluded that paralysis is due to perturbations of animal electricity, although his interpretation of the mechanism by which they do so still depended on the humoral theory of Galen.

By the mid-19th century, with the convincing demonstration that the agent of nerve action was electrical, Galvani's conjecture seemed increasingly likely. Acceptance, however, was not universal. Vulpian, professor of medicine at the University of Paris, in his 1866 *Lectures on the general and comparative physiology of the nervous system*,[43] paid tribute to Helmholtz yet concluded that unlike many physiologists, he was still not persuaded that the electrical phenomena of nerves and muscles and the manifestations of their activity were identical. In particular, he was concerned about the implications of the neurotrophic functions of nerves, which were by then fairly well known. In his classical 1850 experiment in which he cut the glossopharyngeal and hypoglossal nerves of the frog, Augustus Waller had shown that the nerve fibres distal to the section broke up. From this observation he deduced what became known as the second law of Waller, ie that the nerve cell body acts as a 'trophic centre' to maintain viability of the nerve fibre.[44] For this discovery Waller was awarded medals from the Academy of Medicine in Paris and the Royal Society in London.

Neurological deficit

Vulpian's reservations were not shared by his younger colleague Jean-Martin Charcot, who in his classical account of disseminated

sclerosis published just 2 years later says of the characteristic tremor:

> *... the long persistence of the axis cylinders deprived of medullary sheathing, in the midst of the foci of sclerosis, probably plays an important part here. Transmission of voluntary impulses would still proceed by means of the denuded axis cylinders, but it would be carried on irregularly, in a broken or jerky manner and would thus produce the oscillations which disturb the due execution of the voluntary movements.*[45]

Here Charcot is clearly evoking bad impulses as an explanation for bad movements. In a later lecture on compression of the spinal cord he attributes the loss of function to the demyelination and degeneration he observed at post-mortem.[46] Early in the 20th century, Gordon Holmes, when pathologist at the National Hospital Queen Square, made similar observations and addressed explicitly their physiological implications.[47] His remarkably prescient conclusion was that demyelination must produce conduction block and 'that the presence of the myeline [sic] sheaths is necessary for the functions of the tract fibres of the cord as conducting strands'. Denny-Brown, investigating peripheral nerve injury experimentally during the Second World War, reached the same conclusion for locally compressed peripheral nerve.[48] But in the 1950s there had still not been any direct recording of impulses at the site of damage and no demonstration of the way in which the impulses were bad.

AK McIntyre, Professor of Physiology at the University of Otago at that time who had worked in Cambridge after the War, appreciated the relevance that such information would have for both physiology and for the understanding of the pathophysiology of multiple sclerosis. He proposed a series of experiments on peripheral nerve that revealed that normal conduction changed abruptly at the site of a focal demyelinating lesion: the prodromal positivity of the compound action potential was greatly enhanced as the negative component disappeared, signalling complete conduction block. Records from single fibres showed that surviving impulses were conducted at a reduced velocity.[49] The same changes were soon found in demyelination in the spinal cord.[50] In the latter experiments it also emerged that the damaged fibres were unable to conduct trains of impulses faithfully; as a result conduction was indeed jerky as Charcot had supposed (though the explanation of the tremor is of course rather more complex).

Mechanisms of recovery

Hippocrates knew that recovery occurred, and indeed his aphorisms contain prognostic guidance.[1] Gordon Holmes recognised that the integrity of the axons in the demyelinated area, whether in multiple sclerosis or in the compressed cord, is the key to recovery, writing that:

> *The anatomical integrity of the axis-cylinder and its trophic cell remain unaffected, and [therefore] reparative processes would be consequently possible. That such return of function may occur has been frequently observed in the rapid recovery of power and sensation that follow the removal of tumours and the draining of tubercular abscesses which have produced symptoms of compression paraplegia.*[47]

But it was another 80 years before the three mechanisms were demonstrated. First, there is remyelination, which was believed not to occur in the central nervous system until it was demonstrated experimentally by Richard and Mary Bunge in 1961,[51] and found by Lassmann,[52] Prineas and Connell[53] and others in multiple sclerosis in the next two decades. An illustration in a paper by Babinski,[54] who was working in Charcot's laboratory, suggests that he had probably seen it in the 1870s but had not recognised it as such. That the new sheaths are effective in restoring reliable conduction was shown by Kenneth Smith in the 1980s.[55]

The second recovery mechanism was discovered by Bostock and Sears in peripheral nerve in 1976.[56] They showed that the demyelinated axon can acquire the ability to conduct continuously like an unmyelinated axon and that at least sometimes the process is efficient enough to restore conduction through and beyond a demyelinated region. Hodgkin and Huxley had shown that conduction of the nerve impulse depends on an inward flux of sodium ions through what they termed 'pores' (and what were later christened 'channels' by Hille[57]) – they could not see them but deduced that they must exist, rather as von Haller deduced the existence of tubules in nerve to transport the *vis nervosa*. But, unlike von Haller, Hodgkin and Huxley were right. In the 1970s the number, size, distribution and properties of sodium (and other) channels were established in peripheral and central nerve fibres using a range of physiological, pharmacological and biochemical techniques.[57] They were visualised by electron microscopy, and as predicted sodium channels were found to be concentrated at nodes and sparse in internodes where the axons are normally covered by myelin.[58] The key to recovery of conduction was found in 1991 when JD England showed that new sodium channels are formed in the demyelinated axon.[59] Conduction in these circumstances is an order of magnitude slower than in the normally myelinated portions of the same fibre. Herein lies the explanation of the delayed evoked potentials which, after they were discovered in 1972, quickly provided a powerful diagnostic tool for multiple sclerosis.[60,61] Evidence that similar recovery mechanisms are involved in this human disease was provided in the 1990s by Moll *et al*,[62] who observed a marked increase in sodium channel density in demyelinated lesions in which axons survived. It has recently become clear that though sodium channels are likely to play a central role in recovery, the changes in axon channels in response to demyelination are more complex than at first they seemed. Some may actually be harmful in ways that might be manipulable pharmacologically to limit damage and enhance recovery.[63,64]

We have seen how conduction block leads to neurological deficit in demyelinating disease and that recovery from symptoms produced in this way depends on restoration of conduction. But there is still something of a problem. This brings me to the third mechanism contributing to recovery of function. Normal function in the nervous system depends on the precisely

timed arrival of impulses at their proper destinations. Yet apparently normal vision is possible with partial conduction block and conduction times thrice normal. Moreover, given that the extent of demyelination is often different even in nearby fibres, it can be predicted that the temporal pattern of information being transmitted along the damaged pathways will be grossly distorted – a conjecture confirmed experimentally.[49,50] These observations suggest that somehow the central nervous system can adapt so that it can make effective use of a disorganised input. How it does so remained a mystery until the beginning of the 21st century and the exploitation of functional nuclear magnetic resonance (NMR) imaging.

Using this technique, David Werring working with Alan Thompson and David Miller in the NMR Unit at Queen Square took a first step towards elucidating the mechanism by asking a simpler question: 'Are there differences in the way in which the brain processes visual signals from a normal eye as compared with those from an eye in which vision has recovered after an attack of demyelinating optic neuritis?' He found that there are.[65] Stimulating in a simple way a normal eye in a healthy individual or the unaffected eye in a patient with optic neuritis leads to activation confined to the primary visual cortex (Fig 2). In contrast, stimulation of a recovered eye activates widely distributed cortical areas with visual connections. That such changes are important in recovery is shown by Ahmed Toosy's serial study of optic neuritis from onset.[66] A comparable extension of cortical activation in association with recovery of motor function has been demonstrated after stroke[67] and involvement of motor pathways in multiple sclerosis,[68] suggesting that this process may be a general one.

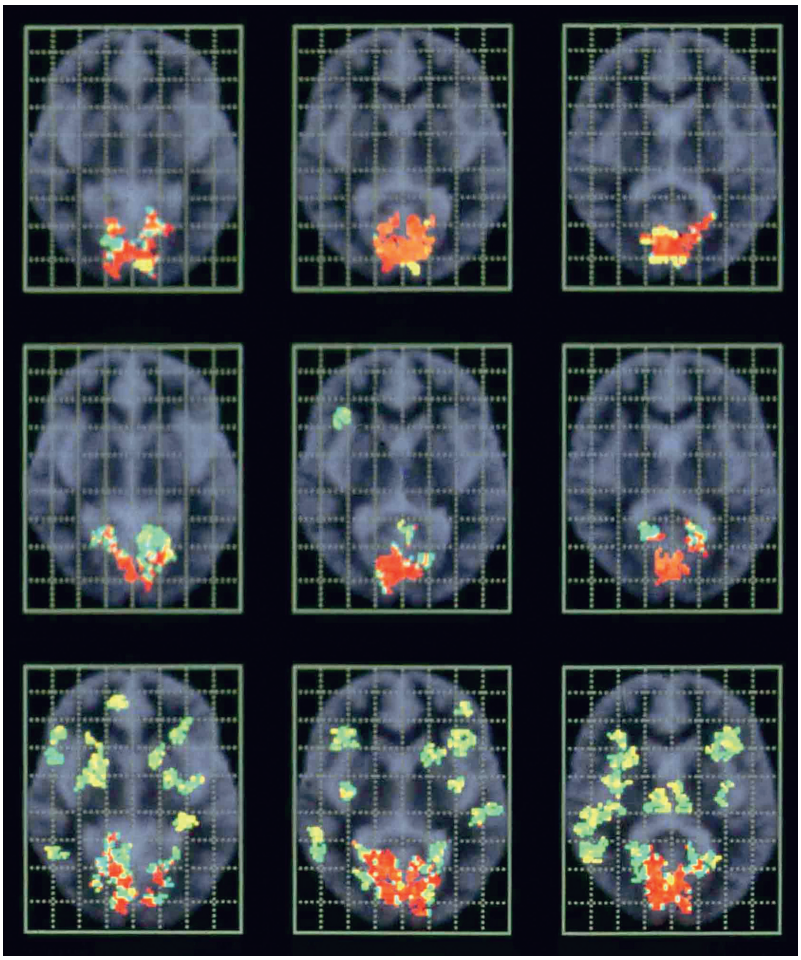

Fig 2. Brain activation maps from seven control subjects and seven patients who had recovered from optic neuritis. In the control group (a) only the primary visual cortex is activated. In the patient group (unaffected eye, b) there is a single additional focus of activation in the right insula-claustrum. In the patient group (affected eye, c) 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. Reproduced with modification from Werring *et al*.[65]

This survey of how symptoms are produced and recovery takes place has dealt only with some of the most obvious: loss of function and its return. But we should note that the techniques that in the second half of the 20th century permitted the elucidation of these mechanisms have also shed light on other symptoms such as paraesthesiae, seizures and perceptual dysfunction.[69]

Conclusion

I have come to the end of a 2,500 year journey tracing the attempts of physicians to explain loss of function and recovery after brain damage. We have seen how understanding progressed as physicians developed explanations of the phenomena they observed on the basis of their understanding of the mechanism of nervous action. Animal spirits were succeeded by the *vis nervosa* which in turn was superseded by electricity. In the 20th century, each generation witnessed a deepening of understanding to more fundamental levels. Later in the century there were practical consequences, eg in improved methods of diagnosis. At the beginning of the 21st century, our expanding knowledge of repair mechanisms and their regulation at the systems, cellular, membrane and now molecular levels is such that while much remains to be done there are real prospects that we may soon be able to intervene as Galvani hoped, and through our grasp of the 'concealed properties [of nerve and muscle] be able more surely to heal their diseases'.[25]

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Concise Guidelines Series

These Concise Gudelines are from a series of brief evidence based guidelines to good practice produced under the auspices of the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians in conjunction with the specialist societies. It is intended that the guidelines will enable quick, informed decisions to be made on the management of disorders that are not usually covered by the major guideline producers.

Series Editor Lynne Turner-Stokes FRCP

Use of antidepressant medication in adults undergoing recovery and rehabilitation following acquired brain injury – National guidelines

Developed jointly by the British Society of Rehabilitation Medicine, the British Geriatrics Society and the Royal College of Physicians Clinical Effectiveness and Evaluation Unit

Depression is increasingly recognised as a common sequel to brain injury and the use of antidepressant medication in this context has increased markedly over recent years. However, these drugs are not without side effects – some of them serious – and they should not be used without proper evaluation and monitoring, to guide clinicians working with people who have brain injury of any cause (ie stroke, trauma, anoxia, infection etc). The guidance covers screening and assessment of depression in the context of brain injury; issues to consider and discuss with the patient and family/carer before starting treatment, and proper treatment planning and evaluation – including planned withdrawal at the end of the treatment. Also included are assessment tools, a checklist for management of depression following acquired brain injury and specially written information for patients and their families and carers.

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HIV testing for patients attending general medical services – National guidelines

Produced by the Clinical Effectiveness and Evaluation Unit in collaboration with the British Association for Sexual Health and HIV, with input from the Department of Health's Expert Advisory Group on AIDS

The National Strategy for Sexual Health and HIV aims to reduce the prevalence of undiagnosed HIV infection. While this will have both individual and public health benefits, it will also require more testing outside the specialist genitourinary medicine departments, including testing in general medical settings. There is therefore a need to ensure standardisation of practice, regardless of context, which these guidelines will help address.

They have been designed for physicians in the general medical specialties, as well as those working in primary care, and surgical and other specialties. Formulated by an expert group and strongly evidence based, they offer guidance on when and how to test and on issues of consent and feedback. The appendices include the text for a leaflet in the form of questions and answers which may be offered to patients before the test, and a summary of the insurance issues that are likely to affect patients following a diagnosis of HIV. (The patient leaflet is also included as a separate laminate sheet for ease of photocopying and distribution.)

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Produced by the Clinical Effectiveness & Evaluation Unit at the Royal College of Physicians

Botulinum Toxin (BTX) is a powerful neurotoxin that blocks cholinergic transmission at the neuromuscular junction. Injected into spastic muscles it produces localised paralysis of the selected muscle(s). Judiciously applied, it can reduce muscle overactivity, while maintaining the strength in other muscles. BTX has the potential to be extremely useful, but it is expensive and there remains an underlying danger in the doses that may be required. The guidelines cover patient selection, the appropriate dosage, and the necessary follow-up procedures and documentation.

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