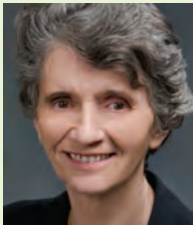




John Newsom-Davis



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is Emeritus Professor of Neuroimmunology at Oxford University. In the 1970s she helped John Newsom-Davis to establish the Neurosciences Group at the Royal Free Hospital, which then moved to the Weatherall Institute in Oxford. Since his retirement in 1998 she has led the Neuroimmunology Group, which is now exploring the whole spectrum of antibody-mediated diseases of the nervous system.

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John Newsom-Davis, MD, FRS, 1932-2007

John Newsom-Davis was a great deal more than a neurologist, of course; he was one of the very few UK clinician scientists of the 1970s and 1980s, and as such had an enormous influence on many who were to come. Here, as well as summarising briefly his achievements, I shall try to draw together some of the aspects of John's early professional life which helped to shape the person that we all admired. Some of the details (given in quotes below) are taken from a transcript of an interview that John gave to the American Neurological Association in 2003, and I am indebted to them and to Barbara Sommer who interviewed him.

John was born the older of twins by a few minutes (his twin sister and older sister are both alive and well). He had a rather conventional middle-class upbringing, but he often admitted that he did not enjoy boarding school (the inference being that he was bullied – probably because he was slight in build and did not enjoy the more macho sports). A much more positive influence was undoubtedly the time he spent in the RAF as a national serviceman (an obligatory two-year stint in one of HM's forces) since he was one of a select few who were trained as pilots. As a result he got his 'wings' in 1953 and flew Meteors for a short period before he left the RAF. Meanwhile, he became interested in psychiatry and decided to become a doctor (like his maternal grandfather). He had already been offered a place at Pembroke College Cambridge to read English, but this decision meant that he had to go to a crammer to achieve the necessary higher certificates (A levels) before they would allow him to change to Natural Sciences.

From a relatively undistinguished time in Cambridge he moved to the Middlesex Hospital for his clinical training and it was there that he was particularly influenced by two eminent neurologists: "the first was Dr Michael Kremer, a neurologist who was extraordinarily sharp and who had a remarkable flair for diagnosis, (though it was not always possible – for a medical student – to follow the thought processes by which he reached the right conclusion). But one of his axioms was 'If you can't make the diagnosis, take the history again' – valuable advice that is as relevant now as it was then. The other neurologist who taught me at that time was Professor Roger Gilliatt who had a joint appointment between the Middlesex Hospital and Queen Square. He was a very powerful figure, and a pretty daunting one for a medical student." It was these two who he subsequently acknowledged as the most important in determining his future career.

He could never understand why, when it came to house-job applications, he was selected for the Professorial Unit at the Middlesex under Prof Moran Campbell but considered that privilege as another major career influence and deeply valued Moran's support thereafter. "He himself was passion-

ately interested in research, and a great teacher and I reckon I owe my career to him. He remained immensely supportive through my early career, and I co-authored a monograph with him and Emilio Agostoni, 'The Respiratory Muscles: Mechanics and Neural Control' while I was still a junior doctor."

From that position it was straightforward to be appointed to the Gilliatt and Kramer firm and he was all set for a successful career in Neurology until Gilliatt decided that John was "too old" for neurology and would be more suited to a less demanding specialty! Nevertheless, after a spell at the Brompton where he developed an interest in the neural control of respiration, he started research with Tom Sears at Queen Square looking at the sensation of respiration which he presented as his MD – winning the Queen Square neurology prize. As a result, he was appointed as a junior resident, working for Sean McArdle and Dennis Williams among others, and ending up as Resident Medical Officer.

During his time in training, he found the investigative aspects of academic medicine as appealing, if not more so, as the clinical aspects, and the supervision and encouragement of these great neurologists was crucial. In fact, it was Moran Campbell who was the willing guinea pig in a highly irregular experiment which demonstrated that the sensation of breathlessness did not occur if the individual was paralysed with curare! John became very interested in hiccough, and both John and Tom Sears frequently stuck microelectrodes into their own or the other's intercostals or diaphragm muscles – leading, on one occasion, to John suffering a pneumothorax that he famously described as a cold fish flapping around in his chest – fortunately it resolved spontaneously.

In order to pursue his blossoming commitment to research he joined Fred Plum in New York who was one of the world authorities on the neurology of breathing. He was, perhaps like Roger Gilliatt, a tough boss but "he was a fantastic teacher, hugely knowledgeable, and an excellent clinician" and remained a life-long friend. Returning to Queen Square as a consultant, John began to study the activity of muscle spindles in response to stretch in human intercostal muscles, obtaining them from patients undergoing thoractomies at the London Chest Hospital or undergoing thymectomies at Queen Square.

This was when the switch to myasthenia occurred as John related, "it was in about 1973, and came about in this way. Sir Bernard Katz, the Nobel Prize winner, and Ricardo Miledi who worked with him in the Department of Biophysics, University College, London, were world authorities on the neuromuscular junction and had become interested in myasthenia. They wanted to obtain human intercostal muscle to count the number of acetylcholine receptors using radio-labeled alpha-Bungarotoxin.

Ricardo Miledi knew Tom Sears, my ex-supervisor, who put him in touch with me". John started providing Katz and Miledi with muscle biopsies for the neuromuscular junction and myasthenia studies but he continued to work on the muscle spindles for another couple of years. However, during this time news from the USA highlighted three seminal findings. First, an experimental form of myasthenia could be induced by immunisation against purified (fish) acetylcholine receptors; second, the acetylcholine receptors were reduced in MG muscle (sadly, similar work by Miledi was still in progress at this time and was not, therefore, published until 1978); and thirdly, there were antibodies to AChRs in MG sera. All of these findings pointed to a pathogenic role for the antibodies but the final proof came from two very simple but elegant experiments. In 1975 Toyka et al demonstrated the passive transfer of MG to mice by injection of purified MG IgG, and in 1977 John, Tony Pinching and Keith Peters demonstrated that removal of the circulating antibodies by plasma exchange led to marked improvements. These developments and many others relevant to the field are summarised elsewhere (Vincent Nat Reviews Immunology 2002).

Thereafter John turned most of his attention to myasthenia, recognising the emerging field of neuroimmunology and taking an evening course in immunology at the Middlesex Hospital in order to be better prepared for the future. He started a research group at the Royal Free Hospital recruiting myself (from UCL where I had done much of the myasthenia muscle work) and then Bethan Lang, Nick Willcox and David Beeson over the next eight years, which grew into a very active and multi-disciplinary team. It was at this point that he began to apply his investigative bent towards clinical diseases – recognising that Lambert Eaton myasthenic syndrome (LEMS), which had already been investigated physiologically and morphologically by Ed Lambert and Andrew Engel at the Mayo Clinic – was likely also to be antibody mediated. Plasma exchange was effective and Bethan Lang spent months injecting purified IgG into mice which Dennis Wray (recently retired as Professor of Physiology in Leeds) showed had neuromuscular junction defects. Similarly we showed that seronegative MG was also antibody-mediated even though at that stage we had no idea about the nature of the target antigens – that took another 15 years and is still on-going!

When John was appointed in 1987 to the Action Research Chair of Neurology, 16 of us moved from the Royal Free Hospital to the Institute of Molecular Medicine (now Weatherall Institute) in Oxford, as well as neurophysiologist Kerry Mills and anaesthetist Laurie Loh to the Radcliffe Infirmary. There he attracted some excellent clinical fellows from the Commonwealth as well as the UK and continued to lead the research group in myasthenia, concentrating mainly on the more tricky areas of thymic pathology, T cell specificity

and potential therapies with Nick Willcox and the team. David Beeson started cloning the acetylcholine receptor genes, mutations in which he subsequently discovered in genetic forms of myasthenia. During this period John spent much of his time in the Radcliffe Infirmary Clinical Neurology Department, where he affiliated Margaret Esiri to a Readership in Neuropathology and established Peter Rothwell and Paul Matthews in positions from which they have both achieved great success. But there was never any doubt in our minds that he was happiest when he could shed the dark suit, don the cords, and join us in the Institute. We heard rumours that he could be quite severe in the clinics, but only once managed to get him to lose his cool in the lab.

Curiously, perhaps the most important development was the most serendipitous as it turns out. This was the discovery of VGKC antibodies in acquired neuromyotonia or Isaacs' disease. John approached the condition in a typically thorough manner. It appeared to be very uncommon but he had just seen his first case on a visit to Athens. He did a medline search and found that some cases were associated with penicillamine treatment, thymomas and/or myasthenia. This was sufficient evidence that it was likely to be autoimmune, so he brought the patient to Oxford for plasma exchange. There was a reduction in the frequency of spontaneous bursts on the EMG (demonstrated by Kerry Mills) and the patient's symptoms were markedly improved. More plasma exchanges and passive transfer experiments confirmed that this was an antibody-mediated disease. He hypothesised that the target was a VGKC since these channels are responsible for modulating neurotransmitter release which is increased in neuromyotonia. The neurotoxin dendrotoxin, that produces rather similar physiological features in experimental animals, was radioactively labeled and used to provide a radioimmuno-precipitation assay for the antibodies. What was not clear at the time is that the antibodies are not necessarily against the VGKCs themselves but can be against other proteins that are part of the membrane complexes that hold the VGKCs in place at the nodes of Ranvier (see my Update). If we hadn't used a rather crude brain preparation of VGKCs and, instead, as one would now, expressed the VGKCs in a cell line using molecular techniques, we would probably not have detected the antibodies in many of the patients! But as a result of the use of simple unsophisticated techniques, one of the legacies of John's career is the major interest in antibody-mediated CNS disease that has followed the work on neuromyotonia.

Quite rightly, John was noted for his modesty, lack of pretentiousness, his carefully conceived but effortlessly given lectures, his ability to enthuse individual doctors at early stages of their careers, and to act as a mentor and role model thereafter. Much of this continued when he retired formally from Oxford

in 1998, took over the Editorship of *Brain*, and began to plan the thymectomy trial that NIH, eventually, funded and which is now led by Gil Wolfe in Dallas. In this phase of his very productive life, perhaps more than in any other, he was able to influence younger colleagues and, in particular, patients worldwide. A remarkable conversationist with an excellent (and highly enviable) memory for faces, names and facts, he was loved by far more people than most of us can remember even knowing. When he died so tragically in a RTA in August 2007 literally hundreds of emails reached us from all over the world – almost everyone said "John was such a good friend". There aren't so many eminent men or women of whom that can be said. ♦

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