‘Acetylcholine receptors and end-plate electrophysiology in myasthenia gravis’ by Y Ito, R Miledi, A Vincent and J Newsom-Davis. From the Department of Biophysics, University College London, Gower Street, London WC1E 6BT and the Batten Unit, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG (Brain 1978: 101; 345–68); with ‘The Lambert-Eaton myasthenic syndrome’ by JH O’Neill, NMF Murray and J Newsom-Davis. From the National Hospital for Nervous Diseases, Queen Square, and the Department of Neurological Science, Royal Free Hospital School of Medicine, London (Brain 1988: 111; 577–96); and ‘Immunological associations of acquired neuromyotonia (Isaacs’ syndrome). Report of five cases and literature review’. By John Newsom-Davis and Kerry R Mills. Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford, UK (Brain 1993: 116; 453–69)

John Newsom-Davis published 12 original articles in Brain. Many dealt with autoimmunity in disorders of the neuromuscular junction or peripheral nerve. Together this work provided a foundation for knowledge on disorders resulting from autoantibodies directed at the acetylcholine receptor, pre-synaptic calcium channels, and peripheral nerve potassium channels. In 1978, Newsom-Davis and colleagues ask: is the defect in myasthenia gravis pre- or post-synaptic? Previous recordings of miniature end-plate potentials and the response to repetitive firing suggest reduced amounts of pre-synaptic acetylcholine released in individual quanta; but, conversely, studies using radioactively labelled α-bungarotoxin indicate fewer functional post-synaptic acetylcholine receptors. This ambiguity needs to be resolved. But one thing is clear. Myasthenia gravis is an autoimmune disease: patients have antibody directed against the acetylcholine receptor; and passive transfer of their serum induces a transient defect of neuromuscular transmission in mice. Now John Newsom-Davis and colleagues report their findings on pre- and post-synaptic function in intercostal muscle removed at thymectomy from 20 patients with myasthenia gravis. The diagnosis is established clinically; and by both a positive response to intravenous edrophonium and the presence, in 13 of 14 patients tested, of anti-acetylcholine receptor antibody. Clinical severity varies amongst the patients; and seven are known to have a thymoma. No patient has taken anti-cholinesterases in the preoperative period; but four are on low-dose alternate day prednisolone. Control muscle is taken from patients undergoing thoracotomy for a variety of reasons. Riccardo Miledi has already confirmed that exposure to α-bungarotoxin leads to rapid and irreversible decline in muscle twitch tension and size, but not frequency, of the miniature end-plate potential. Taken with retained sensitivity of the muscle to direct electrical stimulation, the evidence favours an effect of α-bungarotoxin on acetylcholine receptors. But is the small size of the miniature end-plate potential due to fewer ion channels opening in response to binding of acetylcholine with its receptor or an alteration in amplitude of the elementary event that follows the opening of each individual channel?

With Sir Bernard Katz a normal value for the elementary event of 0.3–0.4 μV at 25°C has previously been established; myasthenic end-plates are less sensitive but, once induced, have an equivalent amplitude and time-course of the elementary event (Fig. 1). I^125-α-bungarotoxin binding is confounded by non-specific decoration of elements other than the end-plate—tendons and muscle fibres themselves—making it necessary to dissect out the region of interest. But after subtracting the background and counting the number of muscle fibres in the preparation, an estimate of the number of α-bungarotoxin binding sites—that is, the number of acetylcholine receptors—can be made, once saturation has been achieved: 0.49 × 10^7 in myasthenic muscle compared with 1.57 × 10^7 in controls (Fig. 2). The distribution of miniature end-plate potentials and the number of acetylcholine receptors in samples of myasthenic muscle are both skewed downwards compared with controls. However, these electrophysiological and pharmacological characteristics do not correlate with clinical severity. As for other features, myasthenic end-plates show replacement of the usual clustering of cholinesterase by a more diffuse and less dense pattern; but neither the morphological appearances of the individual fibres nor any loss of teradotoxin sensitivity suggest that myasthenia gravis is characterized by chronic partial denervation. Taken together it seems reasonable to conclude that the essential characteristic of myasthenic muscle is a reduction in the number of normally active potentials from around 3000 to 1000 per end-plate compared to controls which, with the reduced binding of I^125-α-bungarotoxin, must reflect a reduced number of acetylcholine receptors, sufficient to account for the decreased effect of each quantum and altered sensitivity to acetylcholine. John Newsom-Davis and colleagues do not consider that their observations might reflect a reduction in size or morphology of the post-synaptic membrane; nor are their findings likely due to altered configuration of the myasthenic acetylcholine receptor.
They cannot add to the literature on whether their electrophysiological and pharmacological findings, and the apparent increase in acetylcholine seen in some samples of myasthenic muscle, are confounded by chronic exposure to anti-cholinesterases. Although not strictly part of the current story, the authors rehearse the emerging evidence that myasthenia gravis results from autoimmune injury of the acetylcholine receptor. Be that as it may, their study has shown that the principal abnormality in myasthenia gravis is post-synaptic and characterized by reduction in the number and density, but probably not the functional properties, of acetylcholine receptors active at the neuromuscular junction. The extent to which the defect of transmission results from pharmacological block, destruction of membrane containing acetylcholine receptors or increase in degradation of acetylcholine remains unclear. Probably, all three play a part.

Ten years later, John Newsom-Davis—now based in Oxford and writing with John O’Neill (a visiting trainee from Australia) and Nick Murray, consultant neurophysiologist at the National Hospital—reviews 50 cases of the Lambert–Eaton myasthenic syndrome. Here the abnormally small resting compound action potential that increases progressively during high-frequency repetitive supramaximal nerve stimulation or following a period of maximum tetanic voluntary muscle contraction is attributed to a pre-synaptic defect in which the quanta of acetylcholine released...
by each nerve impulse are reduced. They describe the clinical, electrophysiological and immunological features in a large group of patients seen by John Newsom-Davis between 1978 and 1986 in the light of recent evidence implicating autoimmune mechanisms that target voltage-gated calcium channels. Twenty-five cases are paraneoplastic, almost all with small cell carcinoma of the lung in smokers, occasionally more than one neoplasm being detected; and 25 have no evidence for malignancy even after extensive investigation at presentation and with follow-up for between 5 and 10 years. Males predominate; and age at onset varies between 17 and 79 years, no patient aged <30 having an associated carcinoma. Symptoms of neuromuscular disease and the diagnosis of Lambert–Eaton myasthenic syndrome often precede discovery of the tumour by up to one year. This usually presents as respiratory symptoms or signs but the tumour may come to attention through a variety of other paraneoplastic syndromes—cerebellar degeneration, inappropriate secretion of anti-diuretic hormone, skin hyper-pigmentation, Cushing’s disease, finger clubbing or gynaecomastia. A past personal or family history of another autoimmune disease is often present: 34% of all patients have organ-specific disorders and in nine others there is another immunologically mediated condition. Presenting with fatiguable leg or generalized weakness, aching muscles, autonomic symptoms and drooping of the eyelids in most cases, the wrong diagnosis is made initially in a high proportion of cases (46%), the usual error being confusion with myasthenia gravis; and it is not diagnosed in 78% of cases for organ-specific and non-specific antibodies, respectively. The edrophonium test often yields ambiguous results; and muscle biopsy is equally unrewarding. Neurophysiological studies are usually diagnostic: a low compound muscle action potential (3.7 SD ± 3.4 mV in cases compared with 16.2 SD ± 3.8 mV in controls: Fig. 3), not distinguishing carcinoma associated from non-paraneoplastic cases and tending to reduce with disease duration; increasing with 15 s voluntary muscle contraction (by 890%) or 20 Hz repetitive stimulation (by 854%); and with abnormal jitter and/or blocking in all cases undergoing this investigation. As expected, the prognosis is poor in the patients with small cell carcinoma—most dying at a median duration of 8.5 months from tumour detection—whereas the majority of the non-paraneoplastic cases have survived for up to 14 years from diagnosis.

In discussing their findings, John Newsom-Davis and colleagues assemble the argument based on several lines of evidence that small cell lung carcinoma cells, probably of neural crest origin and staining with the neuroectodermal marker UJ13A, express voltage-gated calcium channels; and that serum from patients with Lambert–Eaton syndrome inhibits the K+ stimulated Ca2+ flux. Successful treatment of the tumour (when possible) is associated with improvement or remission in the symptoms of neuromuscular disease. ‘This suggest(s) that the primary autoantibody response in SLCC [small cell lung carcinoma]…is…to VGCCs [voltage-gated calcium channels] on the cancer cells, cross reactivity of the antibody with similar VGCC determinants at motor nerve terminals leading to the neurological syndrome’. From the clinical perspective, in the context of fatiguable muscle weakness, the Lambert–Eaton myasthenic syndrome is suggested by the relative absence of cranial nerve signs apart from bilateral ptosis; dysautonomia, especially a dry mouth; muscle pain; decreased or absent reflexes with post-tetanic potentiation; a confusing response to intravenous edrophonium; and no detectable anti-acetylcholine receptor antibody. For a patient first presenting with Lambert–Eaton syndrome the risk of having a small cell carcinoma is ~60%, dropping over the next 2 years and being negligible thereafter. That said, <5% of patients with a small cell carcinoma develop symptoms of the Lambert–Eaton myasthenic syndrome. A non-paraneoplastic basis for the Lambert–Eaton syndrome is suggested by the presence of serum auto-antibodies. Nothing else distinguishes the two groups of patients. ‘Thus this disease is homogenous in its clinical expression [and] has more than one triggering factor: in about 60% of cases this appears...
to be SLCC [small cell lung carcinoma] while in the remainder the factor(s) are unknown.’

Acquired neuromyotonia is the third autoimmune disorder of nerve and the neuromuscular junction in which the pathogenesis was illuminated by John Newsom-Davis and colleagues. Presenting with weakness and muscle cramps on activity, slow relaxation, slightly enlarged muscles and excessive sweating—sometimes in association with peripheral neuropathy, or hallucinations and altered behaviour indicating involvement of the central nervous system—it has been variously designated as ‘undulating myokymia’ or ‘neuromyotonia’. The electrophysiological features are typically bursts of doublet, triplet or continuous unit discharges at a frequency of between 40 and 200 per second (Fig. 4), fibrillation potentials (<100 μV, representing the discharge of single muscle fibres) and fasciculations (single motor unit potentials firing at low and irregular frequencies), or ‘continuous muscle fibre activity’ unaffected by sleep or general anaesthesia and complete proximal nerve block but abolished by curare. Neuromyotonia mainly differs from the muscle activity that may complicate radiation injury of the brachial plexus, pontine demyelination (facial myokymia), or rattlesnake envenomation and the ‘cramp-fasciculation syndrome’ in its irregularity; and it is quite unlike the ‘stiff-man syndrome’ in which abnormal muscle activity disappears during sleep and lacks the high-frequency burst discharges. Although ‘the cause of acquired neuromyotonia is not yet established’, John Newsom-Davis is again on the immunological trail through having treated one patient successfully with plasma exchange, and shown that his serum enhances the resistance to d-tubocurarine at the neuromuscular junction in the in vitro phrenic nerve—diaphragm preparation. Now, with his colleague Kerry Mills (consultant neurophysiologist in Oxford), the plan is to assess the evidence for an autoimmune aetiology in this and four other cases and through review of the published literature. A Greek army officer develops exercise-induced muscle cramps in the legs 1 month after injuring his foot and receiving an anti-tetanus injection; his muscles relax slowly following voluntary contraction and electrophysiological studies of his arm—spontaneous activity, response to peripheral nerve block, and the effect of curare—show all the features of acquired neuromyotonia. These abnormalities partially reverse and he improves clinically after a course of plasma exchange followed by immunosuppression with corticosteroids and...
azathioprine. A 25-year-old male has to abandon football and tennis because of exercise-induced muscle twitching in the calves which spreads to many other muscles; and he sweats excessively. His grip relaxes slowly; electrophysiological studies show typical discharges and no response to peripheral nerve block. These abnormalities and all his symptoms improve following two courses of plasma exchange. A male aged 43 years has a 2-year history of generalized exercise-induced muscle cramps and sweating; examination shows widespread fasciculation. Each feature of acquired neuromyotonia is present on electrophysiological investigation, and he has a peripheral neuropathy. There is a modest response to serial courses of plasma exchange and treatment with prednisolone and azathioprine (Fig. 5). A 20-year-old experiences difficulty in releasing his hand-grip and leg cramps on exercise; examination shows muscle weakness and fasciculation after sustained contraction. Discharges typical of acquired neuromyotonia, increasing with voluntary activity, and fasciculations are present on muscle sampling. His symptoms are adequately controlled with phenytoin. A 47-year-old nurse complains of progressive weakness in the limbs and cramps especially in the ribcage; examination reveals occasional fasciculations and she has abnormal discharges, persisting after nerve block but abolished by d-tubocurarine, on muscle sampling. Her symptoms are adequately controlled on baclofen (20 mg daily).

The neurophysiological features indicate that the discharges of acquired neuromyotonia are generated mainly from the terminal portion of peripheral nerve although more proximal sites may be implicated; and there does seem to be an association with acquired inflammatory peripheral neuropathy. As for clues to the autoimmune nature of the disorder, a suspicious number of reported cases have had a thymoma, often with clinical features of myasthenia gravis or the presence of anti-acetylcholine receptor antibodies. As with myasthenia gravis, there are cases apparently induced by treatment with penicillamine. And neuromyotonia has been reported in association with cancer suggesting a paraneoplastic disease mechanism. But particularly persuasive in arguing for an autoimmune basis is the high frequency of a past personal or family history of autoimmunity in the five newly described cases and the presence in three of oligoclonal bands in the cerebrospinal fluid. The response to plasma exchange and immunosuppression is strongly suggestive. What might be the immunological mechanism? Work from Oxford has already shown that the physiological abnormalities of acquired neuromyotonia can be passively transferred using serum from an affected individual: ‘it appears highly unlikely that the pathogenic antibodies are acting at post-synaptic acetylcholine receptors...rather, the results suggest [interference] with ion channels that normally regulate nerve excitability. The most likely target would seem to be K⁺ channels. Their down regulation by antibody would result in an increase in quantal content (by prolonging the action potential) and in the occurrence of repetitive discharges, as is observed with the K⁺ channel 4-aminopyridine.’ Since these channels are located at nerve terminals and the nodes of Ranvier, antibodies that have crossed the blood-nerve barrier may be present—consistent with the presence of oligoclonal bands. But confirmation of the insightful prediction that potassium channel antibodies are present in acquired neuromyotonia and in cases conforming to the syndrome described by Augustin Marie Morvan (De la chorée fibrillaire. Gazette Hebdomadaire de Médecine et de Chirurgie 1890: 37; 173–200), representing a third neuroimmunological scalp for John Newsom-Davis and his colleagues, lay ahead.

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